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The Official Journal of the
Italian Society for the Study of Hemostasis and Thrombosis
SISET
Società Italiana per lo Studio dell'Emostasi e della Trombosi

BLEEDING, THROMBOSIS AND VASCULAR BIOLOGY

XXIX Congresso Nazionale SISET

Roma | 28-31 ottobre 2026

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Bleeding, Thrombosis and Vascular Biology

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Il **XXIX Congresso Nazionale della Società Italiana per lo Studio dell'Emostasi e della Trombosi (SISET)** si terrà a Roma dal 28 al 31 ottobre 2026. Si tratta di un importante evento scientifico organizzato da SISET, società che conta circa 1000 membri provenienti dalle aree specialistiche mediche, biologiche e biotecnologiche e che condividono l'interesse per le patologie tromboemboliche ed emorragiche.

Le malattie tromboemboliche (arteriose e venose) costituiscono la principale causa di mortalità e morbilità nei paesi occidentali. Pertanto, la loro diagnosi, prevenzione e trattamento, sono oggetto di continui studi e i progressi in questo campo della medicina sono stati negli ultimi anni rapidi e sempre in evoluzione. In particolare, lo sviluppo di nuovi farmaci ha offerto importanti vantaggi nella prevenzione dell'ictus e nella terapia del tromboembolismo venoso e il loro impiego in altri tipi di patologie quali i tumori e sono tuttora oggetto di studio.

Le malattie emorragiche congenite (quali ad esempio l'emofilia, la malattia di von Willebrand, le piastrinopatie) e acquisite (piastrinopenia immune, da cirrosi epatica, coagulopatia da consumo) costituiscono una importante sfida diagnostica e terapeutica anche per gli specialisti del settore e richiedono un costante aggiornamento. Anche in questo ambito, importanti, nuove prospettive terapeutiche si sono affacciate all'orizzonte e stanno cambiando radicalmente il modo di gestire soprattutto i pazienti affetti da emofilia, che rappresenta la patologia emorragica congenita più impegnativa nelle sue forme più gravi.

Le problematiche trombotiche ed emorragiche verranno approfondite sia dal punto di vista fisiopatologico che dal punto di vista clinico; sarà inoltre data particolare attenzione alle tematiche della salute della donna e del bambino, e alla gestione di situazioni complesse quali la contemporanea presenza di rischio trombotico ed emorragico in un medesimo scenario clinico.

Il Congresso SISET rappresenta una grande occasione per tutti i ricercatori italiani di incontrarsi e presentare gli ultimi risultati degli studi clinici e di ricerca di base che sono condotti nei centri universitari e ospedalieri del nostro Paese. Verranno presentati i prodotti della ricerca più avanzata nel settore attraverso **sessioni di comunicazioni orali e poster**, selezionando le migliori comunicazioni che saranno esposte in seduta plenaria. Il Congresso offrirà l'opportunità del più ampio aggiornamento sulle principali tematiche nel campo delle patologie tromboemboliche ed emorragiche, che sarà presentato dai più affermati esperti italiani del settore in **16 Sessioni educazionali e di esame dello "state of the art"**, con argomenti incentrati su ricerca di base, biologia vascolare, medicina clinica, e di laboratorio. Gli aspetti educazionali saranno arricchiti anche da **4 Simposi congiunti** in cui SISET si confronterà su temi di comune interesse con relatori identificati da altre Società Scientifiche attive nel settore delle patologie trombotiche ed emorragiche (AICE, FADOI, FCSA, SIAPAV, SIC, SIMI, SIMTI, SISA). Nel programma è anche previsto un Simposio inaugurale dedicato alla tematica "Fattori ambientali e rischio trombotico" e un Simposio Presidenziale, che affronterà il tema dell'evoluzione dei paradigmi molecolari e funzionali nella gestione dei disordini dell'emostasi e della trombosi. In entrambi i Simposi parteciperanno prestigiosi esperti nazionali e internazionali per offrire letture magistrali di altissimo livello. Sarà prevista anche una **Sessione "SISET Giovani"**, gestita dal Gruppo di Studio Giovani e dedicata all'ottimizzazione dei percorsi decisionali tra appropriatezza diagnostica e gestione delle complicanze tromboemorragiche nella pratica clinica.

Essendo l'emostasi, per sua natura, trasversale a tutte le discipline mediche il Congresso è rivolto a tutti coloro che svolgono attività di ricerca e/o assistenziale (ematologi, internisti, cardiologi, neurologi, pneumologi, rianimatori, chirurghi, ginecologi).

Giancarlo Castaman
Presidente SISET



The **XXIX National Congress of the Italian Society for the Study of Hemostasis and Thrombosis (SISET)** will be held in Rome from October 28 to 31, 2026. This is an important scientific event organized by SISET, a society that counts approximately 1000 members from medical, biological, and biotechnological specialties who share an interest in thromboembolic and hemorrhagic disorders.

Thromboembolic diseases (arterial and venous) are the leading cause of mortality and morbidity in Western countries. Therefore, their diagnosis, prevention, and treatment are the subject of continuous studies, and the progress in this field of medicine has been rapid and ever-evolving in recent years. In particular, the development of new drugs has offered significant advantages in the prevention of stroke and the treatment of venous thromboembolism, and their use in other types of pathologies such as cancers is still under study.

Congenital bleeding disorders (such as hemophilia, von Willebrand disease, and thrombocytopathies) and acquired disorders (immune thrombocytopenia, liver cirrhosis, consumptive coagulopathy) represent a significant diagnostic and therapeutic challenge even for specialists in the field and require constant updates. Even in this field, important new therapeutic perspectives have emerged on the horizon and are radically changing the way we manage patients with hemophilia, which represents the most challenging congenital bleeding disorder in its most severe forms.

Thrombotic and hemorrhagic issues will be explored both from a pathophysiological and clinical perspective; particular attention will also be given to issues related to women's and children's health, and to the management of complex situations such as the simultaneous presence of thrombotic and hemorrhagic risk in the same clinical scenario.

The SISET Congress represents a great opportunity for all Italian researchers to meet and present the latest results of clinical and basic research studies conducted in the university and hospital centers of our country. The most advanced research products in the field will be presented through **oral communication and poster sessions**, selecting the best communications to be displayed in a plenary session. The Congress will offer the opportunity for the most comprehensive update on the main topics in the field of thromboembolic and hemorrhagic diseases, which will be presented by the most established Italian experts in the field in **16 educational sessions and "state of the art"** reviews, with topics focused on basic research, vascular biology, clinical medicine, and laboratory work. The educational aspects will also be enriched by **4 joint symposia** in which SISET will engage in discussions on topics of common interest with speakers identified from other scientific societies active in the field of thrombotic and hemorrhagic disorders (AICE, FADOI, FCSA, SIAPAV, SIC, SIMI, SIMTI, SISA).

The program also includes an inaugural symposium dedicated to the topic "Environmental Factors and Thrombotic Risk" and a Presidential Symposium, which will address the evolution of molecular and functional paradigms in the management of hemostatic and thrombotic disorders. In both Symposia, prestigious national and international experts will participate to offer high-level keynote lectures. There will also be a **"SISET Young" Session**, managed by the Young Study Group and dedicated to optimizing decision-making pathways between diagnostic appropriateness and the management of thromboembolic complications in clinical practice.

Since hemostasis, by its very nature, is transversal to all medical disciplines, the Congress is aimed at all those who engage in research and/or care activities (hematologists, internists, cardiologists, neurologists, pulmonologists, intensivists, surgeons, gynecologists).

Giancarlo Castaman
President of SISET

XXIX Congresso Nazionale SISET

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ORAL COMMUNICATIONS



XXIX CONGRESSO NAZIONALE SISET
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ABSTRACT N. CO001

DERIVATION AND VALIDATION OF THE BLEEPE SCORE FOR RISK STRATIFICATION OF MAJOR BLEEDING IN PATIENTS WITH ACUTE PULMONARY EMBOLISM

M.C. Vedovati[1], L. Cimini[1], V. Valeriano[2], I. Montenovo[1], A. Murgia[3], L. Pierpaoli[4], G. Tratar[5], S. Zaccaroni[6], A. Bongarzoni[7], A. Vinci[1], A. Mavri[5], L. Martinelli[8], G. Pepe[9], S. Cozzio[10], C. Becattini[1]

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Background and Aims. Major bleeding (MB) is the most feared complication of anticoagulant treatment in patients with acute pulmonary embolism (PE). Existing bleeding risk scores showed a modest performance, especially for predicting short-term MB. The aim of this study in patients with acute PE was to develop and validate a risk score for MB at 30-day during anticoagulation: the BLEEPE score.

Methods. Data from prospective cohorts of patients with acute PE were merged in a collaborative database. Potential predictors (univariate p-value ≤ 0.1) for MB within 30 days were evaluated in a multivariable Cox regression model. Candidate predictors were identified and scored based on clinical relevance and β-coefficient and used to derive the BLEEPE score. The score was internally validated by bootstrap and externally validated in the COPE study population (NCT03631810). The performance of the BLEEPE score was assessed by discrimination (c-statistics), sensitivity, specificity, positive and negative predictive value (NPV).

Results. Age>65 years, prior MB, syncope, and hemoglobin<11 g/dl were identified as independent predictors of MB in the derivation cohort: incidences of MB in the high and low-risk groups were 7.9% and 1.1%, respectively (HR 7.59, 3.29-17.51) (Table). Incidences in the validation cohort were 6.9% and 1.6%, respectively (HR 4.48, 95% CI 3.39-6.46). C-statistics in derivation and validation cohorts were 0.735 and 0.680, respectively. The NPV was 99% in the derivation and 98% in the validation cohort.

Conclusions. The BLEEPE score showed a good accuracy and discrimination for 30-day MB in patients with acute PE. The simple parameters included in the BLEEPE score could help to implement strategies for personalized management in this population.

Table: 30-day major bleeding risk stratification in patients with acute pulmonary embolism according to the BLEEPE score

	BLEEPE risk group (cut-off)	MB according to risk group n (%)	HR (95% CI)	c-statistics (95% CI)	SE (95% CI)	SP (95% CI)	PPV (95% CI)	NPV (95% CI)
Derivation cohort (1108 patients)	High (≥2)	18 (7.9%)	7.59 (3.29-17.51)	0.735 (0.631-0.839)	69 (66-72)	78 (75-80)	8 (6-10)	99 (98-99)
	Low (0-1)	8 (1.1%)						
Validation cohort (5213 patients)	High (≥2)	96 (6.9%)	4.48 (3.39-6.46)	0.680 (0.635-0.725)	62 (60-62)	74 (73-76)	7 (6-8)	98 (98-99)
	Low (0-1)	60 (1.6%)						

HR=hazard ratio, MB=major bleeding, NPV=negative predictive value, PPV=positive predictive value, SE=sensitivity, SP=specificity

ABSTRACT N. CO002

RETROSPECTIVE LONGITUDINAL ASSESSMENT OF JOINT HEALTH AND QUALITY OF LIFE IN ADOLESCENT AND ADULT PATIENTS AFFECTED BY MODERATE OR SEVERE HAEMOPHILIA A WITH OR WITHOUT INHIBITOR SWITCHING FROM INTRAVENOUS FVIII TREATMENT TO SUBCUTANEOUS PROPHYLAXIS WITH EMICIZUMAB

S. Ceglie[1], R. Gualtierotti[1|2], S. Arcudi[1], A. Ciavarella[1], S.M. Siboni[1], F. Peyvandi[1|2]

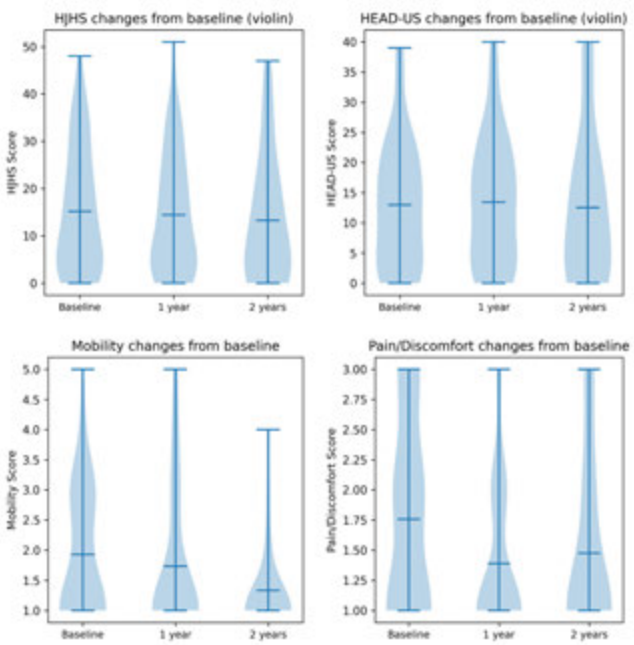
[1]Centro Emofilia e Trombosi Angelo Bianchi Bonomi, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milano, Italy; [2]Dipartimento di Fisiopatologia Medico-Chirurgica e dei Trapianti, Università degli Studi di Milano, Milano, Italy

Background and Aims. Joint damage and impaired quality of life (QoL) remain major long-term complications in patients with haemophilia A (HA). Real-world longitudinal data after switching to emicizumab prophylaxis are limited. The aim of our study is to evaluate longitudinal changes in joint health and QoL in moderate/severe HA patients switching to emicizumab.

Methods. Among 101 patients switching from FVIII to emicizumab at our centre, 41 underwent systematic joint health assessment (between 2020 and 2024), at baseline, 1 year after the switch, and after 2 years (n=21). Joint health was assessed using Hemophilia Joint Health Score (HJHS) and Hemophilic Early Arthropathy Detection with Ultrasound (HEAD-US) score, QoL with EuroQol-5 Dimensions-5 Levels (EQ-5D-5L) questionnaire and EuroQol Visual Analogue Scale (EQ-VAS). The Anualized Bleeding Ratio (ABR) was recorded. Changes between −1 and +1 point in HEAD-US were considered stable, ≥2-point variation indicated improvement or worsening. Continuous variables are reported as median (IQR/range). Fisher's exact test compared worsening in target vs non-target joints. QoL changes were analysed with Wilcoxon and Friedman tests ($p<0.05$).

Results. HEAD-US score remained mostly stable from baseline (median 12, IQR 3-19) to 1 (14, IQR 4-20) and 2 years (11, IQR 2-18). For HJHS, 32/41 patients (78.0%) were stable or improved at 1 year, and 15/21 (73.7%) showed stability or improvement at 2 years. EQ-VAS remained stable. EQ-5D-5L showed significant improvements in pain/discomfort ($p=0.024$) and mobility ($p=0.030$) (Figure). To provide a joint-level perspective, 224 joints were evaluated at 1 year and 106 at 2 years, with stability in HEAD-US score predominating (>95% unchanged at 1 year and similarly high rates at 2 years). At 1 year, worsening occurred only in 6/103 target joints compared with 1/121 non-target joints (OR 7.42, $p=0.050$); at 2 years, worsening was observed in 3/39 target joints versus 1/67 non-target joints (OR 5.5, $p=0.14$). From baseline to 1 year, patients with an ABR of 0 increased (16/41 vs 22/41; risk difference RD 15%), whereas the proportion of patients with ABR ≥ 3 decreased (10/41 vs 5/41 RD 12%).

Conclusions. In our cohort of HA patients switching to emicizumab, joint health was preserved. Most joints remained stable, with limited worsening mainly involving target joints. Improvements in pain/discomfort and mobility further support the clinical benefit of emicizumab beyond structural outcomes.



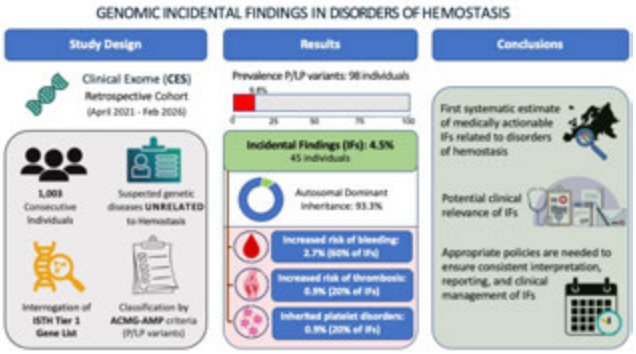
ABSTRACT N. CO003

GENOMIC INCIDENTAL FINDINGS IN DISORDERS OF HEMOSTASIS

M. D'Apolito, G. D'Andrea, G.P. Palladino, C. Ceccarini, G. Cordisco, A. Leccese, I. Adipietro, P. Stanziale, M. Margaglione, R. Santacroce

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Clinical exome sequencing (CES) is widely used for the diagnosis of rare genetic diseases and may incidentally reveal variants unrelated to the primary testing indication but with potential clinical relevance. Data on incidental findings (IFs) related to inherited thrombotic, bleeding, and platelet disorders are currently lacking. We retrospectively analyzed 1,003 consecutive individuals referred for CES between April 2021 and February 2026 for suspected genetic conditions unrelated to disorders of hemostasis. Genomic data were interrogated for variants within the 99 genes included in the International Society on Thrombosis and Haemostasis (ISTH) TIER1 gene list. Pathogenicity was assessed according to ACMG-AMP criteria using multiple annotation tools and databases. Overall, 98 individuals (9.8%) carried at least one pathogenic or likely pathogenic variant in genes associated with thrombotic, bleeding, or platelet disorders. Among these, 45 individuals showed variants classified as IFs with potentially medically actionable phenotypes unrelated to the testing indication, corresponding to an overall rate of 4.5%. Most IFs were associated with autosomal dominant conditions (93.3%). Predisposition to bleeding was identified in 2.7% of individuals (60.0%), whereas IFs conferring susceptibility to thrombosis and inherited platelet disorders were each detected in 0.9% of the cohort (20.0% each). These findings provide the first systematic estimate of medically actionable IFs related to disorders of hemostasis in a large CES cohort tested for unrelated indications. The results highlight the potential clinical relevance of such variants and underscore the importance of appropriate policies for the interpretation, reporting, and clinical management of incidental genomic findings.





A NOVEL GENETIC CLASSIFICATION OF INHIBITOR RISK FOR F8 NONSENSE MUTATIONS BASED ON IMMUNOGENIC PROFILING OF RIBOSOMAL READTHROUGH

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Background and aims. Among F8 mutation types, Premature Termination Codon (PTC) lead to the synthesis of truncated endogenous factor VIII (eFVIII) and display a wide variation of inhibitor risk after administration of therapeutic FVIII (tFVIII), lowering the performance of clinical risk prediction models. Translational readthrough (RT), which overrides PTCs and incorporates predictable amino acids subsets, produces traces of eFVIII full-length FVIII including missense and wild-type molecules (WT-RT). In line with data obtained for F8 missense variants, we hypothesized that higher affinity of the administered tFVIII than eFVIII counterpart to MHCII molecules may increase immunological response, and that the RT output may modulate the inhibitor risk.

Methods. To provide a new classification of PTC based on RT susceptibility and inhibitor formation, F8 genotypes, inhibitor status and predictable RT output, were investigated in 1048 patients (PTCs, n=335), recorded in the EAHAD database. These data were integrated with expression studies of a wide panel (n=43) of FVIII PTCs fused with Gaussia Luciferase (FVIII-GL). The predicted RT output without WT formation, based on PTCs type (UGA, Trp; UAG, Gln/Tyr, UAA, Tyr/ Gln), were tested using in silico NetMHCII tool, which calculates binding affinity between eFVIII missense peptides arising from RT and molecules MHC class II allowing comparisons across different HLA alleles. Affinity of RT missense-deriving peptides (eFVIII) was compared with that of the corresponding WT counterpart (t-FVIII).

Results. Wild-type FVIII molecules (WT-RT), which would re-incorporate the WT residue and reduce inhibitor development risk, was i) lower in patients with than without inhibitors (p=0.022), ii) not predicted in patients with recurrent PTCs detected in at least three inhibitor-positive cases (n=136, p=0.0001), and iii) much lower (12%) for FVIII light chain PTCs, highly associated with inhibitor development than for the heavy chain (25.2%) and B-domain (27.4%). Comparison of RT output arising from FVIII-GL PTCs in vitro expression, did not show a quantitative difference between WT-RT positive (mixture of WT and missense variants) and negative (missense variants only) groups, further supporting the presence of WT-RT molecules as a determinant of decreased inhibitor risk. Conversely, for F8 PTCs without WT formation (n=297), mean differences in affinity between MHCII molecules and novel missense peptides were higher for missense variants predicted in patients with than without inhibitors (p<0.0001), and increased for PTCs present in more than one patient with inhibitor. A comprehensive in silico analysis of Single Nucleotide Variants in the entire F8 coding sequence, consisting of prediction of WT-RT or differential affinity of FVIII missense peptides (classified as predictable PTCs), revealed that naturally occurring PTCs have a higher inherent potential to produce WT-RT (31%) compared with predictable PTCs (22%, p=0.001), potentially increasing inhibitor risk associated to these latter.

Conclusions. Our data provide a new classification of PTCs based on genetic features that, based on predicted RT output and immunogenicity, could be exploited to improve estimate of individual PTC-related inhibitor risk in HLA genotyped patients.



HEPATIC ENDOTHELIUM AS A SAFE AND DURABLE TARGET FOR LENTIVIRAL GENE THERAPY OF HEMOPHILIA A

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Background and Aims. Hemophilia A (HA) is a bleeding disorder caused by mutations in the F8 gene, leading to reduced/absent activity of factor VIII (FVIII). Current FVIII replacement therapies are limited by inhibitor development and the need for lifelong treatment. Gene therapy has recently reshaped the therapeutic landscape, with EMA and FDA approval of AAV based hepatocyte directed approaches for severe HA. However, clinical data show a progressive decline in FVIII expression over time. In addition, recent preclinical studies in mice suggest that supraphysiological FVIII production in hepatocytes may activate the unfolded protein response (UPR) and endoplasmic reticulum (ER) stress, contributing to this loss of efficacy. Since liver sinusoidal endothelial cells (LSECs) are the main physiological source of FVIII, they represent an attractive target for gene correction. In our preclinical studies, FVIII expression in LSECs using a lentiviral vector (LV) under the control of the LSEC-specific Stabilin2 promoter resulted in stable correction of the bleeding phenotype in a mouse model, with sustained FVIII activity and no inhibitor formation. Aim of this study was to assess whether LV-directed FVIII expression in LSECs could affect liver homeostasis and tissue integrity over time when gene therapy is applied to hemophilic newborns and adult mice.

Methods. Neonatal and adult HA mice were injected with lentiviral vector (LV) encoding FVIII under the LSEC-specific Stabilin2 (STAB2) promoter. Phenotypic correction has been assessed by aPTT and anti-FVIII ELISA assays, while liver integrity was evaluated by histology and immunofluorescence before and after an additional endothelial damage induced with monocrotaline (MCT, 150mg/kg). To determine whether FVIII expression in LSECs activates endoplasmic reticulum (ER) stress pathways, unfolded protein response (UPR) markers (BIP, XBP1s, ATF4, CHOP) were quantified by qRT PCR and western blot at short and long term timepoints after LV administration.

Results. In both neonatal and adult HA mice, LV.STAB2 FVIII achieved stable FVIII activity and maintained constant expression even after MCT induced endothelial damage, with vector integration profiles remaining comparable between LV and LV+MCT groups. To assess whether FVIII expression in LSECs affects liver homeostasis, we evaluated ER stress and tissue integrity. Adult HA mice injected with LV.STAB2-FVIII showed constant FVIII activity throughout follow up without inhibitors. Untreated HA mice exhibited elevated hepatic UPR markers, suggesting baseline ER stress associated with the disease. In contrast, LSEC specific FVIII expression significantly reduced UPR marker expression, restoring levels closer to WT. Histological and immunofluorescence analyses showed preserved liver architecture, absence of inflammatory infiltrates, and no evidence of endothelial or parenchymal injury, supporting the safety of LSEC directed gene therapy.

Conclusions. LSEC-targeted FVIII gene therapy provides efficient and sustained correction of the hemophilic phenotype without inducing cellular stress or compromising liver integrity. These findings support the feasibility of LSEC-targeted FVIII gene therapy as a safe and durable strategy to maintain long-term FVIII activity while preserving liver homeostasis



PREVALENCE OF GASTROINTESTINAL BLEEDING IN GLANZMANN THROMBASTHENIA PATIENTS: RESULTS OF A WORLDWIDE SURVEY

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Background and Aims. Bleeding manifestations in Glanzmann Thrombasthenia (GT) are typically moderate-to-severe mucocutaneous hemorrhages, post-partum and post-surgical bleeding. Although gastrointestinal bleeding (GIB) is part of mucocutaneous hemorrhages, its prevalence and severity have not been systematically investigated in GT. GIB represents a clinically relevant complication due to the frequent delayed diagnosis, leading to significant blood loss, therapeutic challenges, and the need for repeated hospitalizations and transfusions. A potential underlying cause of occult GIB is gastrointestinal angiodysplasia (GIA), a vascular malformation associated with abnormal neoangiogenesis. GIA-related bleeding is frequent in von Willebrand disease, but it has not been explored in GT, in which it could reflect an impairment of integrin-B3 role in endothelial physiology. We aimed to assess the prevalence, severity, and current management of GIB, as well as its association with GIA, in a large international cohort of GT patients through a retrospective, international, multicenter survey.

Methods. A survey, supported by EHA and ISTH, was conducted across specialized centers managing patients with GT. All adult and pediatric patients with a confirmed diagnosis of GT or ITGA2B/ITGB3-related thrombocytopenia were included. GT diagnosis had to be based on genetic analysis and/or typical laboratory findings. A standardized, anonymized case report form (CRF) had to be completed for each GT patient followed at the participating centers, regardless of the presence or not of GIB. The CRF captured demographic and clinical data, detailed characteristics of the GIB episodes and treatment approaches.

Results. We enrolled 479 patients: 232 with ITGA2B variants, 125 with ITGB3 variants, and 122 with variant unknown. 252 were type I GT, 60 type II, 36 type III, 73 had ITGA2B/ITGB3-RT and 44 were not classified. 194 GIB episodes in 166 GT patients were reported. 34.1% of GT patients had at least one GIB (0.1%/year in the general population). Of the 166 patients with GIB, 68.7% were type I GT, 9.7% type II, 6% type III, 3.6% ITGA2B/ITGB3-RT, 12% not classified. The ISTH-BAT bleeding score (BS) was higher in patients with GIB than in those without (17.98±8 vs 12.8±10.1; $p<0.0001$). Among the overall GT population 6% had GIA (0.8% in the general population). The percentage of patients with GIB was similar in ITGA2B-mutated and ITGB3-mutated patients, while GIA was more frequent among ITGB3-mutated patients, although not significantly. GIB was more severe in ITGB3-mutated patients, in fact they experienced more bleeding episodes (3-10 in their life) and with a higher frequency (3-4 times/month). Red blood cell transfusions were the most frequently used treatment (58.7%), followed by platelet transfusions and antifibrinolytic agents; 34.6% of patients received combined treatments. DDAVP had the highest success rate, followed by combined treatments and argon plasma coagulation.

Conclusions. GIB is a frequent and clinically relevant complication in GT, often severe and associated with a high incidence of GIA. GT patients carrying ITGB3 variants seem to suffer more frequent and severe GIB. GIB carries a serious and often recurrent bleeding burden to GT patients These findings support the need of systematic screening of GIB in GT patients and urge studies on the targeted prevention and management of this bleeding complication.

ABSTRACT N. CO007

TPO-RECEPTOR AGONISTS AS INDEPENDENT RISK FACTOR FOR VTE IN ITP PATIENTS WITH PERSISTENT APL POSITIVITY

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Background and Aims. The presence of antiphospholipid antibodies (aPL) and exposure to thrombopoietin receptor agonists (TPO-RAs) may increase thrombotic risk in patients with immune thrombocytopenia (ITP). This study aimed to identify predictors of thrombotic events (TEs) in ITP patients with persistent aPL positivity.

Methods. We conducted a retrospective observational study including 56 consecutive ITP patients with persistent aPL positivity. Clinical, laboratory, and treatment data were collected. aPL testing included lupus anticoagulant (LA), anticardiolipin (aCL) IgG/IgM, and anti-β2 glycoprotein I (aβ2GPI) IgG/IgM. A high-risk aPL profile was defined according to ACR/EULAR 2023 criteria (LA positivity, high-titer single positivity, or double/triple positivity). Thrombosis-free survival (t-EFS) was defined as the time from ITP diagnosis to the first thrombotic event or last follow-up. Statistical analyses included univariate and multivariate logistic regression to identify predictors of thrombosis. Time-to-event analysis was performed using the Kaplan–Meier method, censoring patients without events at last follow-up. Odds ratios (OR), adjusted ORs (aOR), and 95% confidence intervals (CI) were calculated. A p-value <0.05 was considered statistically significant.

Results. Median age at diagnosis was 37 years (range 10–81); 44 patients (78.6%) were female. All patients were persistently aPL-positive: 32 (57.1%) had single positivity, 16 (28.6%) double, and 8 (14.3%) triple positivity. A high-risk aPL profile was observed in 47 patients (83.9%), of whom 26 (55.3%) received primary antithrombotic prophylaxis (low-dose aspirin or clopidogrel). Twenty patients (35.7%) had concomitant autoimmune diseases, and 32 (57.1%) had cardiovascular comorbidities. Antirheumatic therapy was administered in 24 patients (42.9%), mainly hydroxychloroquine. Fifteen patients (26.8%) experienced a total of 20 thrombotic events: 12 venous and 4 arterial. Median platelet count at thrombosis was 72,000/μL (range 30,000–298,000).Eleven patients (19.6%) received TPO-RAs; among them, 6 (54.5%) developed venous thromboembolism (VTE) during treatment, corresponding to an incidence rate of 15.6 events per 100 patient-years. Kaplan–Meier analysis showed significantly reduced thrombosis-free survival in patients exposed to TPO-RAs (p=0.032). In univariate analysis, TPO-RA exposure was associated with increased thrombotic risk (OR 6.94; 95% CI 1.58–30.43; p=0.01), whereas antiplatelet prophylaxis (OR 0.20; 95% CI 0.048–0.799; p=0.02) and female sex (OR 0.26; 95% CI 0.07–0.99; p=0.048) were protective. In multivariate analysis, TPO-RA exposure remained an independent risk factor (aOR 6.98; 95% CI 1.36–35.78; p=0.02), while antiplatelet therapy retained a protective effect (aOR 0.20; 95% CI 0.04–0.97; p=0.046). Female sex was no longer significant (p=0.42). Other variables, including age, aGAPSS score, and aPL profile, were not associated with thrombosis.

Conclusions. TPO-RA therapy appears to significantly increase the risk of VTE in ITP patients with persistent aPL positivity, whereas antiplatelet prophylaxis may reduce this risk. These findings support systematic aPL screening at ITP diagnosis and careful risk assessment before initiating TPO-RA therapy. Prospective studies are warranted to confirm these results.

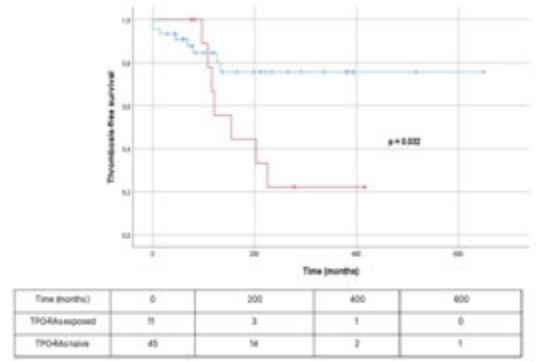


Figure 1. Kaplan-Meier curves showing time from diagnosis to first thrombotic event, stratified by TPO-RA exposure. Patients receiving TPO-RAs (red line) had a significantly higher risk of thrombosis compared with non-exposed patients (blue line) (p=0.032).



ALLOSTATIC LOAD AND THE RISK OF ARTERIAL AND VENOUS VASCULAR EVENTS: A PROSPECTIVE ANALYSIS FROM THE MOLI-SANI STUDY

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Background and Aims. Allostatic load (AL) reflects cumulative multisystem biological dysregulation induced by chronic exposure to stressors and has emerged as an integrative marker of chronic physiological burden. However, prospective evidence on whether AL captures long-term risk across both arterial and venous vascular outcomes remains limited. We therefore aimed to evaluate the association between AL and mortality, cardiovascular disease (CVD), and venous thromboembolism (VTE) in a large prospective cohort.

Methods. We analyzed 22,255 participants from the Moli-sani study, a population-based cohort in Italy (aged ≥35 years, 52% women), apparently free of cardiovascular disease (CVD) and venous thromboembolism (VTE) at baseline (2005-2010). Outcomes included all-cause and CVD mortality, as well as fatal and non-fatal CVD, coronary heart disease (CHD), stroke subtypes, and unprovoked VTE. AL was computed as the sum of standardized (z-score) biomarkers across multiple physiological systems, with inversion of protective markers and equal weighting. Variables included cardiovascular (systolic and diastolic blood pressure, heart rate), inflammatory/immune (C-reactive protein, fibrinogen, white blood cell count, albumin [inverted], glycoprotein acetyls), metabolic (HDL cholesterol [inverted], total cholesterol, triglycerides, glucose, body mass index, waist-to-hip ratio, insulin, lipoprotein(a), apolipoprotein B), respiratory (FEV1 and FVC [both inverted]) and renal markers (creatinine, cystatin C). Higher values of AL index indicated greater biological dysregulation; the index was categorized into quartiles. Cox proportional hazards models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs), adjusting for demographic, socioeconomic and lifestyle factors.

Results. Median follow-up ranged from 13 to 15 years across outcomes. During follow-up, 2,831 deaths and 1,555 incident arterial and venous vascular events were recorded, as reported in the Table. Participants in the highest global AL index quartile, compared with those in the lowest one, had an increased hazard of all-cause mortality (HR 1.43; 95% CI 1.24-1.64) and cardiovascular mortality (HR 1.80; 95% CI 1.35-2.41). A strong graded association was observed for fatal and non-fatal CVD (HR 3.14; 95% CI 2.53-3.90), with the strongest effect observed for coronary heart disease (HR 4.54; 95% CI 3.45-5.98). Associations with overall cerebrovascular outcomes were weaker than those observed for CHD, although participants in the highest versus lowest AL index quartile still showed an almost twofold higher hazard of fatal and non-fatal ischemic stroke (HR 1.92; 95% CI 1.15-3.20). This adverse association extended beyond arterial outcomes to venous thrombotic events, with higher AL index being associated with more than a twofold higher risk of fatal and non-fatal unprovoked venous thromboembolism (HR 2.25; 95% CI 1.11-4.54).

Conclusions. In this large population-based prospective cohort, a higher global AL index was associated with an excess hazard of all-cause and cardiovascular mortality and major arterial cardiovascular events, particularly CHD. The association also extended to unprovoked VTE. A cumulative multisystem biological dysregulation may capture long-term vascular vulnerability beyond traditional arterial outcomes and may represent an integrative marker for risk stratification.

Table. Hazard ratios and 95% confidence intervals for mortality and cardiovascular outcomes according to quartiles of allostatic load in the Moli-sani study (n = 22,255).

	Quartiles of allostatic load			
	Q1	Q2	Q3	Q4
Range of AL	-29.55 to -6.17	-6.17 to -0.01	-0.01 to 5.97	5.97 to 93.69
N of participants	5,563	5,564	5,564	5,564
Total mortality, 2,831 events				
Incidence rate per 10,000 person-years	30.3 (26.8-34.3)	62.2 (57.0-67.8)	95.2 (88.7-102.2)	166.5 (157.6-175.8)
Multivariable model	Ref.	0.99 (0.85-1.15)	1.11 (0.96-1.28)	1.43 (1.24-1.64)
CVD mortality, 928 events				
Incidence rate per 10,000 person-years	6.3 (4.8-8.3)	19.4 (16.6-22.7)	30.5 (26.9-34.5)	60.2 (55.0-65.9)
Multivariable model	Ref.	1.28 (0.94-1.75)	1.35 (1.00-1.83)	1.80 (1.35-2.41)
Fatal and non-fatal CVD, 1,447 events				
Incidence rate per 10,000 person-years	14.1 (11.6-17.1)	38.7 (34.4-43.6)	60.4 (54.9-66.5)	98.1 (90.9-106.0)
Multivariable model	Ref.	1.74 (1.39-2.19)	2.25 (1.80-2.81)	3.14 (2.53-3.90)
Fatal and non-fatal CHD, 1,036 events				
Incidence rate per 10,000 person-years	8.4 (6.5-10.8)	26.4 (22.8-30.4)	44.3 (39.6-49.5)	71.7 (65.5-78.4)
Multivariable model	Ref.	2.11 (1.58-2.82)	3.08 (2.33-4.07)	4.54 (3.45-5.98)
Fatal and non-fatal stroke, 443 events				
Incidence rate per 10,000 person-years	5.8 (4.3-7.8)	12.6 (10.3-15.5)	17.3 (14.5-20.7)	27.3 (23.6-31.5)
Multivariable model	Ref.	1.17 (0.81-1.70)	1.16 (0.81-1.67)	1.34 (0.94-1.90)
Fatal and non-fatal ischemic stroke, 235 events				
Incidence rate per 10,000 person-years	2.6 (1.7-4.1)	6.2 (4.7-8.4)	8.4 (6.5-10.9)	16.2 (13.4-19.5)
Multivariable model	Ref.	1.33 (0.77-2.28)	1.33 (0.78-2.26)	1.92 (1.15-3.20)
Fatal and non-fatal haemorrhagic stroke, 126 events				
Incidence rate per 10,000 person-years	2.1 (1.2-3.4)	4.0 (2.8-5.8)	5.2 (3.8-7.2)	6.5 (4.9-8.7)
Multivariable model	Ref.	1.15 (0.61-2.17)	1.12 (0.60-2.09)	1.06 (0.57-1.99)
Fatal and non-fatal unprovoked venous thromboembolism, 108 events				
Incidence rate per 10,000 person-years	1.5 (0.8-2.7)	3.3 (2.2-5.0)	4.2 (2.9-6.0)	6.3 (4.6-8.5)
Multivariable model	Ref.	1.60 (0.78-3.31)	1.76 (0.86-3.60)	2.25 (1.11-4.54)

Multivariable model was adjusted for age, sex, education, housing, smoking, history of cancer, leisure-time physical activity, Mediterranean Diet score without alcohol consumption, energy intake and alcohol drinking patterns (categorical).



EVALUATION OF A NON-LABORATORY CARDIOVASCULAR RISK SCORE ADAPTED FOR RURAL TANZANIA

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Background and Aims. Cardiovascular diseases represent a growing health challenge in low-resource settings, where access to laboratory testing is often limited. In rural Tanzania, this constrains the use of standard risk prediction tools and delays preventive care. This study aimed to assess the feasibility and utility of a simplified non-laboratory cardiovascular risk score adapted from a previously validated model. The primary objective was to evaluate its application within a district-level noncommunicable disease program, while describing score components, temporal trends, and potential impact on cardiovascular outcomes.

Methods. A longitudinal observational study was conducted from March 2019 to September 2023 in a rural referral hospital. Adults aged 25–74 years with hypertension or type 2 diabetes mellitus were enrolled. The risk score included age, sex, smoking status, systolic blood pressure, body mass index, diabetes history, and capillary fasting glucose. Assessments were performed at baseline and every six months. Analyses included descriptive statistics and estimation of changes in risk score over time, alongside projected reductions in cardiovascular events.

Results. A total of 1,284 participants were included. The tool enabled immediate risk stratification and facilitated early identification of previously undiagnosed diabetes mellitus. The average risk score decreased by 1.54% (95% CI: −1.98% to −1.10%) at 54 months, corresponding to an estimated 10.2 (95% CI: −13.1 to −7.3) avoided fatal and non-fatal cardiovascular events. Significant reductions in systolic blood pressure (−18.7 mmHg) and fasting glucose (−3.6 mmol/L) were observed at 54 months, along with a decrease in body mass index (−1.7 kg/m²). No differences emerged by distance from the hospital or insurance status.

Conclusions. This simplified risk score is a feasible, low-cost approach for cardiovascular risk assessment in resource-limited settings. Its use may support earlier intervention, strengthen preventive strategies, and enhance patient engagement and local awareness.



MAPPING HEMOSTATIC BIOMARKER EXPRESSION ACROSS CANCER TYPES AND STAGES WITHIN THE HYPERCAN COHORT

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Background and Aims. Systemic hypercoagulability is a recognized hallmark of malignancy. Growing evidence suggests that markers of hemostatic activation may serve as surrogates for tumor aggressiveness and prognosis, other than thrombosis; however, a comprehensive characterization of this "hemostatic signature" within an inflammatory milieu across large prospective cohorts remains limited. This study aims to evaluate tumor-specific procoagulant profiles within a large, prospective, multicenter cohort of patients diagnosed with common solid malignancies.

Methods. We analyzed 4,292 patients from the HYPERCAN study (NCT02622815) with newly diagnosed non-small cell lung (NSCLC), gastric (GC), colorectal (CRC), and breast cancer (BC). Plasma samples were collected at diagnosis to assess thrombin generation (TG_CAT), D-dimer, fibrinogen, and prothrombin fragment 1+2 (F1+2). All participants provided informed consent, and data were analyzed using SPSS 21.0.

Results. Metastatic disease was predominant in the NSCLC (67%), GC (53%), and CRC (47%) cohorts, whereas 75% of the BC cohort consisted of high-risk surgically resected patients. Fibrinogen levels were significantly elevated in metastatic cases compared with resected cases across all tumor types ($p < 0.001$), with the highest concentrations observed in metastatic NSCLC. Notably, CRC exhibited a stage-dependent, stepwise increase in fibrinogen (348 to 444 mg/dL; $p < 0.05$). While FVIII was consistently higher in metastatic groups (except GC), D-dimer peaks were most pronounced in metastatic GC and NSCLC ($p < 0.002$). Although F1+2 effectively differentiated metastatic from localized disease in NSCLC, GC, and BC ($p < 0.05$), it showed no discriminatory power in CRC. Finally, the highest TG-Peak and ETP values were found in BC and NSCLC; in the latter, TG values positively correlated with disease burden, significantly distinguishing metastatic from resected patients ($p < 0.003$).

Conclusions. These data demonstrate that cancer-associated hypercoagulability is a heterogeneous, tumor-specific hallmark rather than a uniform systemic event. While fibrinogen and D-dimer remain robust indicators of metastatic progression—particularly in NSCLC and GC—the sensitivity of markers like F1+2 and TG varies by histotype. These findings underscore the necessity of tailored hemostatic profiling to better understand biological heterogeneity and improve risk stratification across diverse malignancies.



GENERATION OF A TARGETING NON-BLOCKING TISSUE FACTOR ANTIBODY FOR SAFE AND EFFICACIOUS CANCER TREATMENTS

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Background and Aims. Tissue factor (TF) is overexpressed in approximately 80% of human malignancies and is associated with poor prognosis, making it an attractive target for cancer immunotherapy. Tisotumab vedotin (TV), a TF-targeting antibody–drug conjugate, has been approved for the treatment of recurrent or metastatic cervical cancer. However, its clinical benefit remains modest, with a limited improvement in overall survival compared to standard chemotherapy, and its use is complicated by significant adverse events, including severe hemorrhage. Given that TF is the primary initiator of the extrinsic coagulation cascade through complex formation with Factor VIIa (FVIIa), therapeutic strategies that interfere with TF/FVIIa activity may compromise hemostatic balance. Therefore, our aim is to develop TF-targeted therapies that inhibit tumor progression while preserving physiological coagulation.

Methods. Monoclonal anti-TF antibodies were generated using hybridoma technology. Forty clones were screened and compared with tisotumab for binding affinity, avidity, and ability to interfere with TF/FVIIa-mediated coagulation. Binding was assessed by ELISA and flow cytometry, while avidity was evaluated using a urea-based ELISA dissociation assay. Functional blockade of TF activity was determined by prothrombin time (PT) assays and measurement of Factor Xa generation. Epitope competition assays were performed by ELISA to determine whether selected clones shared binding epitopes with tisotumab. For in vivo evaluation, murine Lewis lung carcinoma cells were engineered to express human TF and implanted into mice to assess therapeutic efficacy and safety.

Results. One clone demonstrating strong binding to TF with minimal interference in TF/FVIIa-mediated coagulation was selected for further characterization. Competitive binding assays showed that its interaction with TF was not affected by the presence of tisotumab, indicating recognition of a distinct epitope. In the preclinical model, treatment with the selected anti-TF antibody resulted in significant tumor growth control without evidence of hemorrhagic complications. The antibody was subsequently humanized to enable translational development. Additionally, luciferase-based reporter assays demonstrated that our anti-TF antibody modulates transforming growth factor (TGF)-β signaling, a key pathway driving tumor progression and metastatic dissemination.

Conclusions. We generated and humanized a monoclonal anti-TF antibody that selectively targets TF without disrupting its physiological role in hemostasis. This antibody represents a promising platform for the development of next-generation TF-targeted therapeutics, including bispecific antibodies, T-cell engagers, CAR T-cell therapies, and antibody–-drug conjugates. Our approach aims to exploit TF as a tumor-associated antigen while minimizing the risk of coagulation-related adverse events, thereby advancing the design of safer and more effective TF-based cancer immunotherapies.

ABSTRACT N. CO012

LONG TERM RISK OF RECURRENT VENOUS THROMBOEMBOLISM IN ADULT PATIENTS WITH ACTIVE CANCER AND FIRST CATHETER-RELATED UPPER EXTREMITY DEEP VEIN THROMBOSIS AFTER DISCONTINUATION OF ANTICOAGULANT TREATMENTS AND LINE REMOVAL: A RETROSPECTIVE MULTI-CENTER COHORT STUDY – CANCER-CRT STUDY

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Background and Aims. Central venous catheters (CVCs) are commonly used in patients with cancer, mainly for the administration of cancer treatments. Catheter-associated upper extremity deep vein thrombosis (UEDVT), also known as catheter-related thrombosis (CRT), is a common complication of CVCs. The available evidence reports rates of symptomatic VTE of 7% over 3 months in patients with active cancer and a new CVC. Current clinical guidelines recommend therapeutic anticoagulation for at least 3 months and as long as the catheter is in place. Evidence on the long-term risk of recurrent venous thromboembolism (VTE) after catheter removal and after treatment discontinuation in patients with ongoing active cancer is scarce, and significant heterogeneity in therapeutic approach after the initial 3-month duration is frequently observed in clinical practice. Our study aims to assess the incidence of recurrent VTE following a first CRT in patients with active cancer who discontinued anticoagulation after completion of at least 3 months of treatment and after line removal.

Methods. This is a retrospective multi-center cohort study of adult patients with cancer who have been diagnosed with CRT from Jan 2019 to Dec 2023. Inclusion criteria were discontinuation of anticoagulation, catheter removal, and persistent active cancer. We excluded patients with concomitant other sites VTE, history of VTE, and an indication for long-term anticoagulation (e.g., atrial fibrillation). The minimum duration of follow-up was 90 days after anticoagulant treatment discontinuation. The primary outcome was recurrent VTE. Secondary outcomes included major bleeding events, clinically relevant non-major bleeding events, and all-cause mortality. Assuming a 3% annual rate of recurrent events (corresponding to the observed risk of recurrent events after a first episode of VTE provoked by a transient risk factor in the general population), a calculated sample size of 250 patients would yield an expected one-sided 95% upper confidence bound within 5% (corrected calculation 4.8% evaluated considering normal approximation). Outcomes were calculated as point-estimate risks at 90 days. Kaplan-Meier method was used to estimate the cumulative probability of recurrent VTE, bleeding, and mortality among the overall population.

Results. While recruitment is ongoing, we here report the results of the analysis of 117 patients from 5 Italian hospitals. Baseline characteristics and treatment details are described in Table 1. At 90 days after treatment discontinuation, 2 recurrent VTEs (1.7%) occurred. After a median follow-up of 2 years, the cumulative incidence rate was 2.6 (6 events) per 100 patient/years (95%CI 1.2-5.8). Recurrent VTEs were represented by one pulmonary embolism and five UEDVTs, most of them (n:3) related to a new catheter placement, and two incidentally diagnosed. No major bleeding events were observed. Mortality rate was 6.9 per 100 patient/years (95%CI 4.2-11.3), all events related to the underlying malignancy.

Conclusions. Our preliminary results showed that recurrent VTE after anticoagulation discontinuation was relatively low, suggesting that the presence of active cancer alone should not warrant long-term anticoagulation in this setting. Results from a larger sample will be presented at the congress.

Table 1. Baseline characteristics, anticoagulation, and follow-up details

	STUDY POPULATION (N=117)
Age, years (mean, SD)	55.5 (14.1)
Female sex, n (%)	77 (65.8)
Weight, kg (mean, SD)	68.9 (15.4)
Concomitant CKD (CrCl <60 mL/min), n (%)	9 (7.7)
Concomitant antiplatelet use, n (%)	6 (5.1)
Khorana score >=2, n (%)	34 (29.1)*
Tumor type, n (%)	
- Hematological	36 (32.5)
- Breast	31 (26.5)
- Endometrial OI	18 (15.4)
- Lung	5 (4.3)
- Pancreas	5 (4.3)
- Others	20 (17.1)
Metastatic (solid), n (%)	33 (33.7)
Absence of additional provoking factors (e.g. hospitalization, surgery, etc.)	78 (66.7)
Diagnostic method, n (%)	
- Doppler US	102 (87.2)
- CT scan	15 (12.8)
Catheter type, n (%)	
- PICC	66 (56.1)
- CVC	21 (18.0)
- Midline	20 (17.1)
- Port-A-Cath	8 (6.8)
Deep vein involved, n (%)	
- Axillary	77 (65.8)
- Subclavian	65 (55.5)
- Brachial	44 (37.6)
- Jugular	30 (25.6)
- Anonymous	3 (2.6)
- Superior cava	2 (1.7)
Concomitant SVT, n (%)	39 (33.3)
Type of anticoagulation, n (%)	
- LMWH	54 (46.1)
- Fondaparinux	3 (2.6)
- DOAC	64 (54.7)
- Apixaban	19 (16.2)
- Edoxaban	28 (24.8)
- Rivaroxaban	12 (10.3)
- LMWH followed by DOAC or VKA	4 (3.4)
Dose of anticoagulation, n (%)	
- Therapeutic	115 (98.3)
- Prophylactic	2 (1.7)
Duration of anticoagulation, days (median, IQR)	183 (98-296)
Time interval from diagnosis to start of anticoagulation, days (median, IQR)	1 (1-1)
Time interval from catheter removal to stop of anticoagulation, days (median, IQR)	90 (45-185)
Follow-up duration, years (median, IQR)	2.0 (1.0-2.8)

*Information missing in 9 patients.

Legend: CKD, chronic kidney disease; CrCl, creatinine clearance; CT, computed tomography; CVC, central venous catheter; DOAC, direct oral anticoagulant; GI, gastrointestinal; IQR, interquartile range; LMWH, low-molecular-weight heparin; PICC, peripherally inserted central catheter; SVT, superficial vein thrombosis; US, ultrasonography; VKA, vitamin K antagonist.



INDICATIONS AND OUTCOMES OF OPTIONAL INFERIOR CAVA FILTERS IN CANCER-ASSOCIATED THROMBOSIS AND IN NON CANCER PATENTS WITH VENOUS THROMBOEMBOLISM

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Introduction. Inferior vena cava filters (IVCF) are an option in patients with acute venous thromboembolism (VTE) with a coexisting absolute contraindication to anticoagulation to reduce the risk of fatal pulmonary embolism. Cancer patients are at high risk of both VTE, bleeding and death and the benefits of IVCF insertion in cancer-associated thrombosis (CAT) are uncertain.

Objectives. to investigate the indications for optional IVCF, their retrieval rates and complications in patients with CAT compared to cancer-free patients with VTE.

Design. retrospective cohort study in two tertiary care hospitals.

Participants. consecutive patients diagnosed with symptomatic VTE and undergoing optional IVCF placement from 2018 and 2022 and a follow-up of two years.

Primary outcome measures. IVCF retrieval rates and complications, thromboembolic complications and short (within 30 days) and long term (24 months) all-cause mortality.

Results. 334 patients (171 women - 53%, median age 75.5 years) were included. IVCF was inserted pre-operatively in 156 patients (47%) of whom 107 (68%) had CAT. Non pre-operative IVCF was inserted in 178 patients of whom 74 (41%) had CAT, 136 (76%) had major bleeding and 41 (12.3%) were at high bleeding risk. IVFC was removed in 135 patients (40.4%), with a similar rate of filter thrombosis (13.5% vs. 10.4%; p=0.73) and removal (41% vs 46%; p=0.9) among cancer and cancer free patients. VTE recurrence or progression was similar between cancer and non cancer patients (13% vs 12%) over 24 months. Non pre-operative IVCF was associated with a higher mortality rate at 30 days after IVCF insertion both in CAT and cancer free patients. All cause mortality between 31 days and 24 months after filter insertion was higher in cancer than non cancer patients (p=0.0001).

Conclusions. Thrombotic complications after IVCF insertion were similar in CAT and non-cancer patients. Short term mortality was higher after non pre-operative than after pre-operative filter insertion in both CAT and cancer free patients. However, patients with CAT had a higher long term all-cause mortality, regardless of IVCF indication and removal.

ABSTRACT N. CO014

INCIDENCE OF NEW OR RECURRENT MALIGNANCY AFTER SUPERFICIAL VEIN THROMBOSIS: A SYSTEMATIC REVIEW AND META-ANALYSIS

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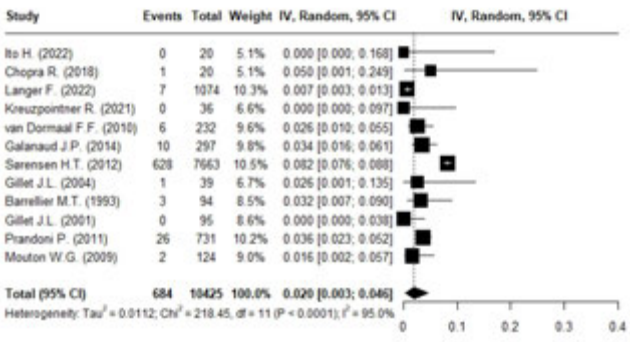
Background. superficial vein thrombosis (SVT) has been associated with occult malignancy, but the risk magnitude and the timing of cancer diagnosis remain uncertain. Consequently, the role of cancer screening after SVT is not well defined.

Aims. To estimate the cumulative incidence of new or recurrent malignancy after SVT, and to explore its potential clinical implications through estimation of the number needed to screen (NNS).

Methods. A systematic review and meta-analysis were conducted according to PRISMA 2020 guidelines. Four major databases were searched from inception to November 2025. Studies enrolling adult patients with SVT and reporting incident or recurrent cancer during follow-up of ≥6 months were included. A random effects meta-analysis of proportions was performed using inverse-variance methods with Freeman– Tukey double arcsine transformation. Heterogeneity was evaluated according to I^2. Among others, a prespecified sensitivity analysis restricted to studies with 12-month follow-up was conducted. NNS estimates were indirectly derived using the obtained pooled incidence of cancer and the published sensitivities of common screening tests, under best-case and more realistic uptake scenarios.

Results. Twelve studies including 10,425 patients with SVT were included. In the main analysis, the pooled cumulative incidence of new or recurrent malignancy was 2.0% (95% CI 0.3–4.6), with substantial heterogeneity (I^2 = 95%). (Figure 1) Sensitivity analyses yielded consistent results. Restriction to studies reporting 12-month follow-up showed a pooled incidence of 1.2% (95% CI 0.3–2.5). Subgroup analyses based on screening strategies did not demonstrate statistically significant differences between systematically and non-systematically screened cohorts. Based on pooled incidence estimates, best-case NNS ranged from approximately 99 to 153 depending on cancer type. When adjusted for test sensitivity and assuming 80% screening uptake, realistic NNS values substantially increased Contrast CT thorax/abdomen protocol yielded far lower realistic NNS of 71.

Conclusions. The cumulative incidence of new or recurrent cancer diagnosis after SVT was not negligible. Although this risk may be clinically relevant, indirect NNS estimates of routine systematic cancer screening after SVT in unselected patients is unlikely to be efficient. A routine CT-scan strategy focusing on high-risk subgroups may be feasible





EVOLUTION OF ANTICOAGULANT THERAPY FOR CANCER-ASSOCIATED THROMBOSIS: THE START2 REGISTRY ONCO-VTE LONGITUDINAL STUDY

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Background. Managing anticoagulant therapy in cancer-associated thrombosis (CAT) remains a clinical challenge, balanced between the heightened risks of recurrent venous thromboembolism (VTE) and major bleeding. The START2 Registry ONCO-VTE provides prospective, real-world evidence from patients with active malignancies, tracking the transition of clinical practice toward direct oral anticoagulants (DOACs).

Objectives. This study characterizes the CAT patient population and assesses temporal changes in prescription trends and clinical outcomes by comparing two distinct enrollment windows: January 2022–April 2024 (Group 1) and April 2024–December 2025 (Group 2).

Methods. Data from 333 patients (extracted as of Dec. 18, 2025) were analyzed. Group 1 comprised 270 patients, while Group 2 included 63 patients enrolled via the REDCap platform. Primary endpoints focused on anticoagulant selection, VTE recurrence, major bleeding events, and all-cause mortality.

Results. The median age of the cohort was 69 years (29% aged ≥75). Over a median follow-up of 12 months (14 months for Group 1; 6 months for Group 2), solid tumors—primarily lung (18%) and colorectal (13%)—were the most prevalent. Deep vein thrombosis was the leading index event (52%), with 35% of all events being incidentally detected. Comorbidities such as hypertension (47%) and cardiovascular disease (11%) were frequent. A clear shift in treatment was observed: DOAC use rose from 59% in Group 1 to 64% in Group 2, while parenteral anticoagulant use (LMWH/Fondaparinux) declined from nearly 40% to 34%. Across the full cohort, VTE recurrence and major bleeding occurred in 7.5% and 6.6% of patients, respectively. In a balanced subgroup analysis (≥6 months follow-up, n=227), Group 2 showed a significant reduction in major bleeding compared to Group 1 (7.1% vs. 11.2%), despite similar VTE recurrence rates (7.1% vs. 8.1%).

Conclusions. Analysis of the START2 ONCO-VTE registry highlights a growing preference for DOACs in real-world oncology. This evolution in prescribing patterns is associated with a significant reduction in major bleeding events without loss of antithrombotic protection. These results suggest that modern management strategies provide a high degree of safety and efficacy, even within this fragile patient population.



PLATELET HYPERREACTIVITY AND PROCOAGULANT PHENOTYPE IN ESSENTIAL THROMBOCYTHEMIA: INSIGHTS FROM ADVANCED PLATELET FUNCTION TESTING

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Backgrounds and aims. Essential thrombocythemia (ET) is a myeloproliferative neoplasm (MPN) that increases the risk of vascular events. Enhanced platelet activation is involved in pathogenesis of thrombosis in ET and the hallmark of thrombotic prevention is the use of the antiplatelet agent aspirin. Aim of the study was to identify platelet phenotype and innovative applicable laboratory approaches to improve risk scores and eventually prognostic value in ET patients.

Methods. In blood samples from patients with TE (n=40,15M, age:65±16 years) and healthy volunteers (n=47,18M, age:45±18 years) we assessed: i)percent maximal aggregation (MA) in platelet-rich plasma in response to agonists; ii)the activation of αIIbβ3 (defined as % platelets positive to PAC1 antibody binding); iii)thrombogenicity of whole blood using the Thrombosis Formation Analysis System (T-TAS) which measures platelet thrombus formation (PL chip) or fibrin formation (AR chip) mimicking the coagulation process under shear forces, both expressed as area under curve (AUC). Informed consent was obtained and the study was approved by Territorial Ethics Committee.

Results. ET patients, if compared to healthy subjects, showed increased aggregability, specifically to ADP (2.5μM) (63±7 vs 40±5, p=0.016) and thrombin receptor-activating peptide-6 (TRAP-6, 5μM) (44±8 vs 6±2, p=0.016). About 20% of on aspirin patients showed MA to arachidonic acid (1mmol/l) higher than 20%, thus indicating an incomplete effect of aspirin. If compared to healthy subjects (0.50±0.07) a decrease of PAC-1 binding was evident in platelets from ET patients both in the absence (0.16±0.03, p<0.001) and presence (0.31±0.03, p=0.04) of aspirin treatment. AUC values of PL T-TAS positively correlated with aggregations to 2.5μM ADP (r=0.524,p=0.015), 4mg/L collagen (r=0.517, p=0.016), and 5μM epinephrine (r=0.395, p=0.017) whereas AUC values of AR T-TAS inversely correlated with PAC-1 expression (r=0.664, p=0.018).

Conclusions. Collectively, these results indicate that platelets from ET patients show increased activation and aggregability even when exposed to aspirin. Furthermore, the reduced expression of active αIIbβ3a in a significant subset of platelets likely mirrors their procoagulant phenotype. Because ET management relies on risk stratification, our data also suggest that T-TAS could represent a reliable screening test for platelet function and coagulation by helping to identify the hypercoagulable state in ET.



LIFE'S SIMPLE 7 FOR CARDIOVASCULAR HEALTH IS ASSOCIATED WITH LOWER CANCER RISK IN THE MOLI-SANI STUDY

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Background and Aims. Cardiovascular disease and cancer share several modifiable risk factors and possibly common biological pathways, as proposed by the “common soil” hypothesis. Life’s Simple 7 (LS7) is a composite metric of cardiovascular health encompassing behavioural and biological factors. While higher adherence to LS7 is consistently associated with reduced cardiovascular morbidity and mortality, evidence on its relationship with cancer risk remains limited and inconsistent. This study sought to investigate the association between adherence to LS7 and overall and site-specific cancer incidence, and explore the potential biological mechanisms underpinning this relationship in a large Italian population-based prospective cohort.

Methods. We longitudinally analysed data on 21,689 apparently cancer-free participants from the Moli-sani Study cohort (baseline 2005-2010). The LS7 metric includes smoking, physical activity, diet, body mass index, blood pressure, total blood cholesterol, and glucose. Each ideal metric was assigned 2 points, with total scores ranging from 0 to 14. Shared biological risk factors (i.e., inflammatory markers, renal markers and resting heart rate) were evaluated as potential mediators. Cox proportional hazards models were used to estimate hazard ratios and 95% confidence intervals for cancer risk associated with a 1-point increase in LS7, adjusting for established risk factors.

Results. Over a median follow-up of 13.1 years, 1,303 incident cancer cases were documented. Each 1-point increase in LS7 was associated with a 5% reduction in overall cancer incidence (HR=0.95; 95%CI 0.92–0.98), with similar associations observed in men and women. Inverse associations were observed for lung (HR=0.86; 95%CI 0.80–0.93) and pancreatic cancer (HR=0.89; 95%CI 0.79–1.00), as well as for colorectal cancer in men only (HR=0.92; 95%CI 0.86–0.99). Mediation analyses indicated that inflammatory markers and resting heart rate together accounted for approximately 20% of the association between LS7 and cancer incidence.

Conclusions. Higher adherence to LS7 is associated with a lower risk of incident cancer in this adult population-based cohort. The partial mediation by inflammation and resting heart rate suggests that shared systemic and physiological processes may contribute to the observed relationship, supporting the “common soil” hypothesis. Optimising cardiovascular health should be introduced as part of integrated strategies for cancer prevention. The present study was performed in the context of the Fondazione Umberto Veronesi ETS—IRCCS Neuromed framework agreement.

ABSTRACT N. CO018

THE MOLI-SANI RISK SCORE, A MEASURE OF MODIFIABLE CARDIOVASCULAR RISK, PREDICTS NON-CARDIOVASCULAR MORTALITY AND SELECTED CANCERS, BUT NOT NEURODEGENERATIVE DISEASES

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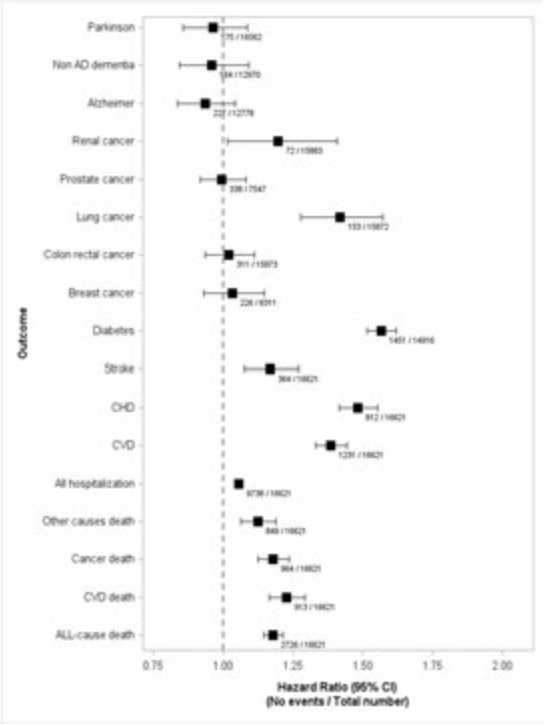
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Background and aims. The Moli-sani Risk Score (MRS) is a weighted score developed in the Moli-sani Study to quantify the overall burden of modifiable cardiovascular risk by combining 9 modifiable factors, including smoking, adherence to Mediterranean diet, blood lipids (triglycerides, LDL and HDL-cholesterol, blood pressure, glucose, adiposity and physical activity. Although originally developed for cardiovascular disease (CVD), it is unclear whether this measure of global modifiable CVD risk may also identify susceptibility to major non-CVD outcomes. We therefore examined the association of the MRS with mortality, hospitalization, cancer and neurodegenerative outcomes in then Moli-sani cohort.

Methods. We analyzed 16,621 men and women aged ≥45 years from the adult general population-based Moli-sani Study. Median follow-up ranged from 12 to 15 years across outcomes. Outcomes included all-cause, CVD, cancer and other-cause mortality; all-cause hospitalization; CVD, coronary heart disease (CHD), stroke and diabetes; breast, colorectal, lung, prostate and renal cancer; Alzheimer's disease, non-Alzheimer dementia and Parkinson's disease. Participants with the corresponding condition at baseline were excluded from each specific analysis. Competing risks were handled within outcome macro-areas by censoring at the first competing event in the same domain, and cause-specific Cox models were used. For interpretability, the MRS was originally rescaled so that 1 MRS point corresponds approximately to the cardiovascular risk associated with 1 additional year of age. Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated for a 5-point increase in MRS, that is, for an increment slightly smaller than 1 SD in our analytic sample.

Results. As shown in the Figure, higher MRS was associated with all-cause mortality (HR 1.18; 95%CI 1.14–1.21; Figure), cancer mortality (1.18; 1.13–1.24), other-cause mortality (1.12; 1.06–1.19), and all-cause hospitalization (1.06; 1.04–1.07). Among site-specific cancers, associations emerged for lung cancer (1.42; 1.28–1.57) and renal cancer (1.20; 1.02–1.41), but not for breast (1.03; 0.93–1.15), colorectal (1.02; 0.94–1.11) or prostate cancer (1.00; 0.92–1.08). No association was observed with neurodegenerative disorders, including Alzheimer's disease, non-Alzheimer dementia and Parkinson's disease (Figure). As expected for a score designed to capture global modifiable cardiovascular risk, MRS was also associated with CVD mortality (1.23; 1.17–1.29), CVD incidence (1.39; 1.33–1.44), CHD (1.48; 1.41–1.55), stroke (1.17; 1.08–1.27), and type 2 diabetes (1.57; 1.51–1.62). Sex-stratified analyses showed broadly similar findings in men and women.

Conclusions. In this large general-population cohort, the MRS, a score of modifiable factors contributing to cardiovascular risk, was associated not only with cardiovascular outcomes, but also with non-CVD mortality, all-cause hospitalization and selected cancers. By contrast, no association emerged with neurodegenerative diseases. These findings suggest that the MRS captures a broader modifiable risk profile extending beyond CVD, although not across all non-CVD clinical outcomes.



ABSTRACT N. CO019

THE COMPLEX INTERACTION BETWEEN THE SECRETOR AND ABO BLOOD GROUP GENOTYPES DETERMINES LARGE DIFFERENCES IN FACTOR VIII LEVELS AMONG SEVERE AORTIC STENOSIS PATIENTS

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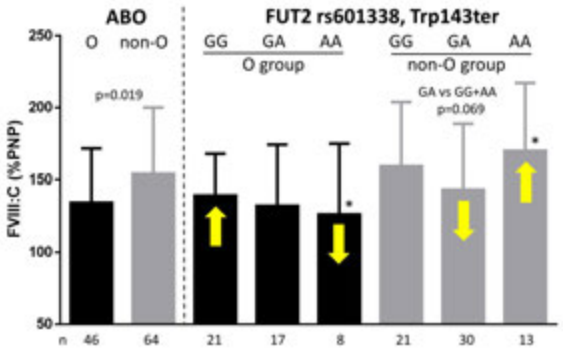
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Background and Aims. More than 100 SNPs across dozens of loci have been reported to influence plasma factor VIII (FVIII) and/or von Willebrand factor (VWF) levels. Among these, several FVIII/VWF clearance receptor genes display a role in combination with the ABO locus, a main determinant of these plasma phenotypes. We reported that selected lectin (ASGR2 and CLEC4M) and low-density lipoprotein receptor (LDLR) cell receptor genotypes differentially modulate the ABO blood group influence on FVIII levels in severe aortic stenosis (SAS), which alters VWF conformation through turbulent blood flow. We aimed at investigating the impact on FVIII levels of the interaction between genotypes encoding the ABO blood groups and genotypes responsible for ABO(H) glycan secretion in plasma (α 1,2 fucosyltransferase, FUT2/Secretor gene).

Methods. This observational study was performed within the angiographically-controlled cardiovascular cohort of Verona Heart Study. SAS patients (n=110, 59±12 years) undergoing angiography before heart valve surgery were selected. All the patients had the aortic valve area < 1.0 cm2 or the trans-valvular pressure mean gradient ≥ 40 mm Hg or peak aortic jet velocity ≥ 4 m/s by transthoracic echocardiography. SAS patients were genotyped and categorized for O and non-O blood groups (ABO), and for a frequent FUT2 SNP (rs601338G/A, MAF=0.48) that abolishes (Trp143ter) secretion (non-secretor blood group status). The association of combined genotypes with FVIII activity levels (% PNP) was investigated by t-test. Results (figure 1): FVIII levels (mean±SD), which showed high intragroup variability, were 20% lower (p=0.019) in patients with the O (n=46, 134.5±37.1) than non-O (n=64, 154.1±45.9) blood groups. Whereas in the O group the highest FVIII levels were observed among the Secretor homozygotes (O FUT2 GG, n=21, 139.4±28.6), in the non-O group were observed in the non-Secretor homozygotes (non-O FUT2 AA, n=13, 170.0±47.1). Differently, the O FUT2 AA genotype was associated to the lowest levels (n=8, 126.4±48.5, range 75-219). Consequently, the non-Secretor FUT2 AA genotype increases intragroup FVIII level variance by predicting the highest FVIII levels in the non-O and the lowest in the O group, with 43% mean differences (p=0.061, Mann Whitney test). Among non-O patients, the FUT2 GA heterozygotes, predicting a Secretor phenotype, displayed the lowest levels (n=30, 143.5±45.3), which produced a trend for significant intragroup differences (GA vs GG+AA, p=0.069, Mann Whitney test) and similar FVIII levels in non-O FUT2 GA and O FUT2 GG (139.4±28.6) subgroups. This suggests that ABO/Secretor genotype combinations contribute to abolish the expected ABO effects. The unexpected FVIII-lowering effect of ABO/FUT2 GA was similar to that previously observed for the non-lectin LDLR r688C/T genotypes (CT n=32, 147.3±41.3).

Conclusions. The interaction between the FUT2 Trp143ter null genotypes and ABO groups profoundly influences FVIII activity levels, potentially by clearance mechanisms. The genotype-driven large differences among groups i) may have clinical implication for SAS, characterized by either prothrombotic or bleeding diathesis, the latter also favored by the often concomitant anticoagulant therapies and ii) contribute to interpret the high inter-patient level variability. These observations deserve investigation in larger cohorts of patients, to confirm and better quantify the size of potentially remarkable effects.

FVIII activity levels (mean±SD) in severe aortic stenosis patients grouped for ABO and α 1,2 fucosyltransferase (FUT2/Secretor) genotypes.



FVIII-increasing/lowering effects in genotype combinations are indicated by the arrows. *Comparison between O FUT2 AA and non-O FUT2 AA groups, p=0.061



LEFT ATRIAL ENLARGEMENT AS A MARKER OF ADVERSE CLINICAL OUTCOMES: PRELIMINARY RESULTS OF A PROSPECTIVE COHORT STUDY

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Background and Aims. Left atrial enlargement (LAE) is a cardiac structural abnormality which signals adverse cardiovascular remodelling in response to chronic pressure and/or volume overload. LAE may be easily measured and graded with transthoracic echocardiography (TTE) using the left atrial volume index (LAVi), as suggested by current cardiac imaging guidelines, and has been linked to adverse cardiovascular outcomes. We have previously described a statistically significant association between LAE and 1-year cerebrovascular events in subjects without atrial fibrillation (AF) and ongoing anticoagulation. With this study, we aimed to assess the association between LAE and short-term all-cause mortality.

Methods. We carried out a prospective cohort study across three teaching hospitals in Milan, Italy (Bassini, Niguarda, San Paolo), including consecutive adults undergoing TTE between 2012 and 2023. Patients with a history of AF or receiving anticoagulants (for any indication) were excluded from the analysis. LAE was categorized using the LAVi as absent (≤34 mL/m2), mild (>34 and ≤41 mL/m2), moderate (>41 and ≤48 mL/m2), or severe (>48 mL/m2). The primary outcome was all-cause mortality within 1 year of the index echocardiogram. Multivariate logistic regression models were used to evaluate the independent association of LAE with 1-year all-cause mortality.

Results. We included 56,512 subjects with a median age of 67 years (47% female). Three thousand five hundred eighty-five subjects (6.3%) died within 1 year of the index TTE. In the multivariate analysis, all categories of LAE were associated with 1-year all-cause mortality compared with no LAE (mild: OR 1.5, 95% CI 1.4-1.7; moderate: OR 1.8, 95% CI 1.6-2.0; severe: OR 2.4, 95% CI 2.1-2.6). This association was independent of other clinically meaningful covariates, including age, diabetes mellitus, heart failure, left ventricular dysfunction, prior stroke and cardioactive treatments (including antiplatelet agents and statins). The association between LAE and all-cause mortality was evident also across low-risk subgroups, such as subjects ≤65 years of age (mild LAE vs normal LAVi: 2.2, 95% CI 1.7-2.8; moderate LAE vs normal LAVi: 3.1, 95% CI 2.2-4.4; severe LAE vs normal LAVi: 4.4, 95% CI 3.3-5.9), with no hypertension (mild LAE vs normal LAVi: 2.4, 95% CI 2.0-2.8; moderate LAE vs normal LAVi: 4.0, 95% CI 3.3-4.8; severe LAE vs normal LAVi: 6.3, 95% CI 5.4-7.4) and with no diabetes (mild LAE vs normal LAVi: 2.2, 95% CI 2.0-2.4; moderate LAE vs normal LAVi: 3.1, 95% CI 2.7-3.6; severe LAE vs normal LAVi: 5.1, 95% CI 4.6-5.6).

Conclusions. Our preliminary results suggest that, in subjects without AF and ongoing anticoagulation, LAE is significantly associated with short-term all-cause mortality. The increase in effect size with increasing degrees of LAE suggests the existence of a causal relationship between the two phenomena. The association between LAE and all-cause mortality was evident also in subjects nominally at low cardiovascular risk, suggesting that LAE may be an early indicator of frailty and poor prognosis in this subject population.



TIME COURSE OF LP(A) LEVELS AFTER ACUTE CORONARY SYNDROME: A LONGITUDINAL STUDY

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Background and Aims. Lipoprotein (a) [Lp(a)] is a well-established, independent, atherosclerotic cardiovascular risk factor. Several studies have demonstrated its prognostic value, alongside traditional risk factors, in patients with acute myocardial infarction (AMI), contributing to improved risk stratification and therapeutic management. Lp(a) levels vary markedly across populations, whereas in each individual they are largely determined by genetics of *LPA* gene, encoding apolipoprotein (a), and are minimally influenced by other factors: for this reason, current guidelines recommend measuring serum Lp(a) at least once in a lifetime. However, emerging evidence suggests that certain clinical conditions, such as acute inflammatory states, may alter Lp(a) concentrations due to the interference with acute phase responders such as interleukin (IL)-6. This raises the question of whether Lp(a) measurement should be reassessed in these scenarios. Therefore, we conducted a longitudinal study assessing Lp(a) concentrations in patients with AMI who were followed for up to one year after the acute event.

Methods. We analysed Lp(a) concentration in serum or plasma samples of 288 patients, admitted to the coronary units of the six hospitals of the Florence health district between 2008 and 2010, enrolled in the frame of the Florence Acute Myocardial Infarction (AMI-Florence 2) registry, using a particle enhanced immunoturbidimetric assay on Cobas c 311 platform (Roche). Serum and plasma samples were stored at -80°C until analysis.

Results. The study cohort included 218 men and 70 women with a median age of 69 years (IQR 59–77). Lp(a) concentrations were first assessed at admission for the acute event (T0), showing a median value of 32.5 (11.0–82.8) nmol/L. Follow-up measurements were performed when available: at T1 (2.2±1.2 months, n=100) with a median Lp(a) of 14 (5–43) nmol/L, at T2 (6.5±1.0 months, n=196) with a median of 19.0 (5.0–49.5) nmol/L, and at T3 (12.6±1.6 months, n=203) with a median of 15 (5–48) nmol/L. Overall, Lp(a) levels showed a statistically significant decrease from the acute phase to all subsequent follow-up time points ($p<0.001$). At T3, in 62/203 (30.5%) patients tested we observed a reduction of at least 25 nmol/L. Stratifying patients according to Lp(a) levels above or below 125 nmol/L (50 mg/dL), we observed a progressive decline in the proportion of individuals classified in the high risk category from T0 to T3. By the 12 month follow up, 22 patients who initially presented with above threshold values had shifted to below threshold levels, an evolution that may meaningfully influence clinical risk stratification and long term management. When examining the cohort by sex, we also confirmed a well established pattern: women consistently exhibited significantly higher Lp(a) concentrations than men at T0 and T1 ($p=0.036$ and $p=0.038$, respectively), a difference that remained evident, though not significant, at the other time points.

Conclusions. Our data demonstrate that Lp(a) levels are significantly affected by the acute phase in patients with an acute myocardial infarction, as levels drop significantly over the months following AMI. Reassessment during follow-up may therefore be necessary to ensure more accurate risk stratification in this clinical setting.



SUBOPTIMAL MEDITERRANEAN DIET ADHERENCE IN VASCULAR PREVENTION: BASELINE FINDINGS FROM THE NEUROMED CENTER OF THE CV-PREVITAL STUDY

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Background and aims. The Mediterranean diet is a modifiable component of cardiovascular prevention and may influence vascular risk through favorable effects on inflammation, oxidative stress, lipid profile and platelet function. However, adherence to this dietary pattern is declining even in Mediterranean countries. In a context of primary cardiovascular prevention, identifying subjects with poorer adherence may help recognize groups less exposed to a potentially protective dietary profile. We examined Mediterranean diet adherence and its main sociodemographic and clinical correlates in adults recruited by the IRCCS Neuromed center within the CV-PREVITAL study.

Methods. This baseline analysis included 1,542 individuals (men and women aged ≥45 years), apparently free of previous cardiovascular disease, recruited by the IRCCS Neuromed center as part of the multi-center, nationwide CV-PREVITAL study. Adherence to the Mediterranean diet was assessed using the 14-item Mediterranean Diet Adherence Screener (MEDAS), with scores ranging from 0 to 14. Low, intermediate or high adherence were defined as scores ranging between 0–5, 6–9 and ≥10, respectively. Multivariable linear regression was used to estimate the association of demographic, socioeconomic and clinical characteristics with the 14-MEDAS score. Models were adjusted for age, sex, residence, housing, education, occupation, marital status, body mass index and major clinical conditions.

Results. Mean age was 57.7 years (SD 8.5), and 55.6% of participants were women. 72% of participants had an intermediate 14-MEDAS score (between 6 and 9), whereas 16% had lower adherence and 12% had higher adherence. In multivariable analyses, men had a lower 14-MEDAS score than women (β=-0.37; 95%CI -0.57 to -0.17). Compared with participants aged 45–54 years, adherence was higher among those aged 55–64 years (β=0.51; 95%CI 0.29 to 0.72) and ≥65 years (β=0.59; 95%CI 0.33 to 0.86). Urban residence was associated with lower adherence compared with rural residence (β=-0.20; 95%CI -0.39 to -0.01). Separated/divorced participants (β=-0.36; 95%CI -0.71 to -0.02) and widowed participants (β=-0.47; 95%CI -0.91 to -0.03) had lower scores than married or cohabiting individuals. Among clinical factors, hypercholesterolemia was associated with higher adherence (β=0.21; 95%CI 0.01 to 0.41), whereas a history of cancer was associated with lower adherence (β=-0.41; 95%CI -0.78 to -0.05). Neither education, nor occupation, or diabetes, or hypertension or body mass index was independently associated with the 14-MEDAS score.

Conclusions. In this Southern Italian subgroup recruited by the IRCCS Neuromed center within the CV-PREVITAL study, higher adherence to the Mediterranean diet was quite uncommon. Lower adherence clustered in men, younger adults, urban residents and individuals not living in a couple. In the setting of primary vascular prevention, the latter groups may represent priority targets for tailored nutritional counselling and digitally supported interventions aimed at improving modifiable cardiovascular and thrombo-inflammatory risk profiles.



STILL FAR FROM TARGET: REAL-WORLD LDL-CHOLESTEROL CONTROL, THERAPY USE AND SEX DIFFERENCES IN TUSCANY

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Background. Achieving low-density lipoprotein cholesterol (LDL-C) targets is a cornerstone of cardiovascular prevention, yet real-world data consistently show suboptimal control. We evaluated LDL-C target attainment, lipid-lowering therapy (LLT) use, adherence, and persistence in a large real-world population from Tuscany (Italy), with a specific focus on sex differences and temporal trends.

Methods. Administrative health databases and laboratory records were linked to identify individuals aged ≥45 years in Tuscany between 2019 and 2023. Patients were classified into cardiovascular risk categories according to contemporary European guidelines, with corresponding LDL-C targets. LDL-C target attainment, LLT consumption (expressed as defined daily doses, DDD/1,000 inhabitants/day), adherence, and 1-year persistence were analyzed overall, by risk class, and by sex.

Results. Among the Tuscan population, only 31% underwent at least one LDL-C measurement in 2023. Of 778,680 classified patients, 35.1% achieved their LDL-C target in 2023, compared with 11.6% in 2019–2021. Despite improvement, 64.9% remained above target, particularly in very high and extreme risk groups. LDL-C target attainment increased across all risk categories but remained low in very high-risk patients (22.7%). LLT consumption rose from 103 to 130.9 DDD/1,000 inhabitants/day between 2019 and 2023, driven mainly by increased use of statins, statin–ezetimibe combinations, and PCSK9 inhibitors. Adherence and persistence improved over time, with a reduction in low adherence (−9.2%) and an increase in high adherence (+5.2%). Women showed lower overall adherence than men but experienced the greatest improvement in adherence and 1-year persistence over time.

Conclusions. In this large real-world population, most individuals remain far from LDL-C targets despite encouraging temporal improvements. Increased LLT use, better adherence, and the introduction of combination therapy and PCSK9 inhibitors have contributed to progress. However, substantial gaps persist, particularly in high-risk patients and in women. Structured follow-up, early intensification of therapy, and targeted strategies to reduce sex disparities are essential to further improve LDL-C control.



THE ROLE OF BLOOD CLOTTING AND ENDOTHELIAL ACTIVATION IN THE STRATIFICATION OF BLEEDING AND THROMBOTIC RISK OF ATRIAL FIBRILLATION ON ORAL ANTICOAGULANT THERAPY: INSIGHTS FROM THE STRAT-AF 2 STUDY

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Background. Atrial fibrillation (AF) is associated with a prothrombotic *milieu* characterized by activation of coagulation and endothelial dysfunction, as indicated by increased D-dimer and von Willebrand factor levels. However, the relation between blood clotting activation, endothelial activation and neuroimaging-based markers remains to be completely understood.

Objectives. Aim of the present study was to evaluate the association between blood clotting activation, endothelial dysfunction and the neuroimaging markers evaluated by CT scan in the STRATAF-2 population.

Methods. The STRAT-AF 2 is a prospective observational extension of the STRAT-AF study, including a *de novo* cohort of anticoagulated patients with atrial fibrillation aged ≥ 65 years who underwent baseline and 1-year follow-up brain computed tomography (CT) (n=100). Neuroimaging assessment included the Van Swieten scale on CT for white matter lesions, identification of lacunes (≤15 mm), and cortical atrophy grading using the Pasquier scale. Medial temporal lobe atrophy (MTA) was evaluated on coronal CT images. Overall small vessel disease burden was estimated by the SVD score (0–3). TC cohort patients were followed for at least 1 year.

Results. At baseline, a moderate-to-severe leukoencephalopathy was associated with higher D-dimer levels compared with absent or mild white matter changes (p=0.024), and this association persisted at 12 months (p=0.046). Similarly, the presence of lacunar infarcts was associated with higher D-dimer levels both at baseline (p=0.022) and at follow-up (p=0.049). Neither D-dimer nor von Willebrand factor levels were associated with non-lacunar infarcts. Higher D-dimer levels were also associated with cortical atrophy (p=0.029) and severe MTA (p=0.016) at baseline, with consistent associations at 12 months (p=0.016 and p=0.004, respectively). Moreover, D-dimer levels were positively associated with increasing SVD burden, with higher levels observed in patients with three SVD features both at baseline (p=0.026) and follow-up (p=0.005). No significant association between neuroimaging markers by CT and von Willebrand factor levels was found. In multivariable logistic regression analysis adjusted for age, sex, CHA_2DS_2-VASc, HAS-BLED, and type of anticoagulant, D-dimer levels were significantly and positively associated with the presence of lacunar infarcts at baseline [OR (95% CI)| 3.3 (1.1–10.7), p=0.046]. D-dimer levels were also significantly associated with cortical atrophy at 12-month follow-up [OR (95% CI)| 3.0 (1.1–8.9), p=0.044].

Conclusions. These findings indicate that D-dimer, but not von Willebrand factor, is consistently associated with CT markers of cerebral small vessel disease in anticoagulated AF patients. Overall, coagulation activation may play a key role in the pathophysiology of lacunar damage and brain structural changes, supporting its potential use in risk stratification.

ABSTRACT N. CO025

HEPHAESTUS: A DIGITAL ATLAS FOR TRAINING AND STANDARDIZATION OF JOINT POINT-OF-CARE ULTRASOUND IN HEMOPHILIC ARTHROPATHY

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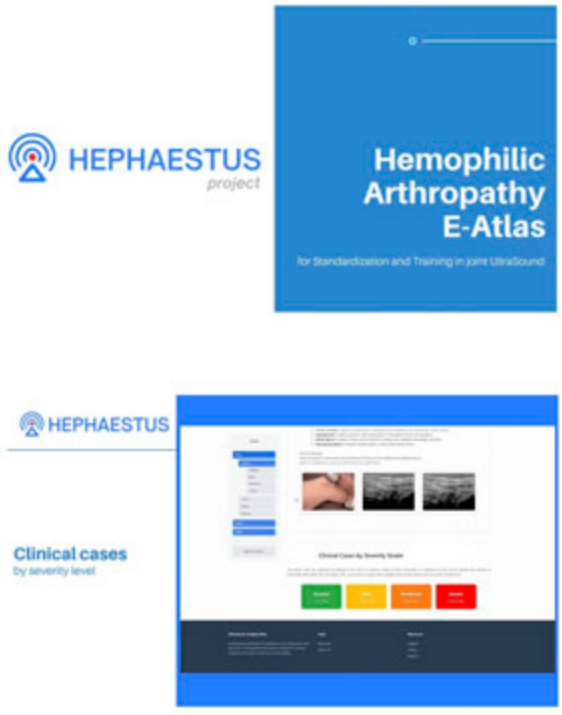
Background. Medical imaging plays a central role in hemophilia care, particularly for evaluating joint involvement and detecting bleeding-related damage. Point-of-care ultrasound (POCUS) represents a non-invasive, accessible tool for early diagnosis and longitudinal monitoring of hemophilic arthropathy. However, its widespread clinical implementation remains limited by the lack of structured training programs and standardized protocols for image acquisition and interpretation. Although several ultrasound scoring systems and guidelines have been proposed, dedicated digital resources are still needed to support systematic education and harmonization of practice.

Aims. The HEmoPHilic Arthropathy E-atlas for Standardization and Training in joint UltraSound (HEPHAESTUS) project was developed to address these unmet needs by providing a comprehensive, evidence-based training platform for joint POCUS.

Methods. A web-based educational atlas was designed through collaboration between clinicians, radiologists, and computer science experts. The platform integrates current international recommendations for standardized ultrasound assessment of the three joints most commonly affected in hemophilia: elbows, knees, and ankles. High-quality ultrasound images and video recordings were collected from patients with different ages, disease severities, and stages of arthropathy. All materials were reviewed, annotated, and validated by experienced operators.

Results. The platform includes a curated collection of representative cases, ranging from early synovial hypertrophy to advanced osteochondral damage. Content is organized within a structured learning environment comprising theoretical tutorials, more than 60 case-based examples, and progressive selfassessment modules with expert feedback. Interactive tools enable users to compare their own interpretations with validated reference annotations, facilitating both guided instruction and independent learning. The system supports repeated practice, standardized reporting, and continuous skill development.

Conclusions. The HEPHAESTUS digital atlas represents an innovative educational resource aimed at improving training and standardization of joint POCUS in hemophilia care. A pilot evaluation involving hematologists, physiotherapists, and radiologists will assess usability, feasibility, and educational impact. By promoting consistent image acquisition and interpretation, this platform may reduce inter-operator variability, enhance diagnostic accuracy, and support earlier detection and monitoring of joint disease. Wider dissemination of this tool has the potential to foster international collaboration and strengthen the integration of POCUS into routine hemophilia management, ultimately contributing to improved longterm outcomes for people with hemophilia.



ABSTRACT N. CO026

LIVER FIBROSIS, STEATOSIS AND SUBCLINICAL ATHEROSCLEROSIS IN PATIENTS WITH HEMOPHILIA: A CROSS-SECTIONAL STUDY

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Background and Aims. Metabolic dysfunction–associated steatotic liver disease (MASLD) is increasingly recognized as a driver of cardiovascular risk beyond traditional factors. At the same time, patients with hemophilia (PWH) are aging and accumulating metabolic comorbidities such as obesity, hypertension and dyslipidemia, and are therefore no longer protected from arterial disease. However, liver involvement in this population is heterogeneous and often reflects a complex interplay between metabolic dysfunction and previous viral infections. As a result, it remains unclear whether liver fibrosis and steatosis truly identify patients at increased cardiovascular risk in hemophilia. This study aimed to explore the relationship between liver fibrosis, steatosis and subclinical atherosclerosis in a cohort of PWH.

Methods. We report an interim analysis of a cross-sectional study evaluating liver health in (PWH). Liver fibrosis was assessed and graded from F0 to F4, while liver steatosis was evaluated and graded from S0 to S3. Subclinical atherosclerosis was assessed and recorded as present or absent. Clinical data included age, hemophilia type and severity, viral history (HCV, HBV, HIV), liver enzymes, platelet count, FIB-4, and traditional cardiovascular risk factors. Fibrosis and steatosis were analyzed as both ordinal variables and clinically relevant categories. Associations with atherosclerosis were assessed using non-parametric tests and contingency-table analyses.

Results. A total of 49 patients with hemophilia were included (median age 55 years). Baseline characteristics of the study population are summarized in Table 1. Subclinical atherosclerosis was detected in 8/45 patients (16.3%). Liver fibrosis was generally mild, with significant fibrosis (F2–F4) observed in 6/49 patients (12.2%). Steatosis was present in 21/41 patients (51.2%), with moderate-to-severe steatosis (S2–S3) in 11/41 (26.8%). No significant association was found between fibrosis stage and the presence of atherosclerosis (p=0,524). Similarly, steatosis was not associated with atherosclerosis (p=0,389). Traditional cardiovascular risk factors were common, with hypertension in 42.8%, dyslipidemia in 32.6%, and active or previous smoking in 71.4% of patients. Atherosclerosis was more frequently observed in patients with a higher burden of cardiovascular risk factors (p=0,043). Number of cardiovascular risk factors showed a trend toward association with atherosclerosis (OR 2.22, 95% CI 0.94–5.22; p=0.068).

Conclusions. In this cohort of patients with hemophilia, liver fibrosis and steatosis were not associated with subclinical atherosclerosis. Cardiovascular risk appears to be mainly driven by traditional risk factors rather than liver-related parameters. These findings highlight the complex and heterogeneous nature of liver disease in this population and warrant further investigation in larger cohorts.

	Overall population (n.49)	Without atherosclerosis (n. 37)	With atherosclerosis (n.8)
Age, years [IQR]	55 [48-63]	54 [48-64]	57 [48-61]
Type of Hemophilia, n (%)			
HA	45 (91.8)	34 (94.4)	6 (75)
HB	4 (8.2)	2 (5.6)	2 (25)
Severe	30 (61.2)	22 (61.1)	6 (75)
BMI, kg/m² [IQR]	24.9 [23.3-27.8]	25.5 [24.0-28.3]	23.6 [21.8-26.2]
Number of cardiovascular risk factors, n (%)			
0	7 (14.3)	4 (11.1)	-
1	15 (30.6)	12 (33.3)	1 (12.5)
2	14 (28.6)	11 (30.6)	3 (37.5)
3	11 (22.4)	8 (22.2)	3 (37.5)
4	2 (4.1)	1 (2.8)	1 (12.5)
Cardiovascular risk factors, n (%)			
Obesity	5 (10.2)	5 (13.9)	-
Arterial hypertension	21 (42.8)	15 (41.7)	5 (62.5)
Dyslipidemia	16 (32.6)	11 (30.6)	5 (62.5)
Active or previous smoke	35 (71.4)	11 (30.6)	7 (87.5)
Diabetes	3 (6.1)	1 (2.8)	2 (25.0)
Other comorbidities, n (%)			
Active cancer	3 (6.1)	2 (5.6)	1 (12.5)
Rheumatological diseases	4 (8.2)	3 (8.3)	1 (12.5)
Venous thromboembolism	2 (4.1)	1 (2.8)	1 (12.5)
Mild thrombophilia	5 (10.2)	5 (13.9)	0
HCV, n (%)			
Active	2 (4.1)	1 (2.8)	1 (12.5)
Eradicated	30 (61.2)	24 (66.7)	4 (50.0)
FIB-4 score, [IQR]	1.43 [0.97-1.97]	1.48 [1.00-1.97]	1.42 [0.82-1.76]
Liver stiffness [LSM], KPa[IQR]	5.2 [4.3-6.4]	5.1 [4.3-6.3]	5.3 [4.5-6.3]
Severity of stiffness, n (%)			
F0	19 (38.8)	14 (38.9)	3 (37.5)
F1	24 (49.0)	17 (47.2)	4 (50.0)
F2	4 (8.2)	3 (8.3)	1 (12.5)
F3	1 (2.0)	1 (2.8)	-
F4	1 (2.0)	1 (2.8)	-
Steatosis [CAP], dB/m [IQR]	247 [204-284]	249 [217-293]	263 [190-297]
Severity of steatosis, n (%)			
S0	22 (51.2)	15 (41.7)	2 (33.3)
S1	10 (23.3)	8 (22.2)	2 (33.3)
S2	-	-	-
S3	11 (25.6)	9 (25.0)	2 (33.3)

Table 1. Clinical, hepatic and cardiovascular characteristics of the study population stratified by subclinical atherosclerosis; data are presented as median [interquartile range] or number (%); cardiovascular risk factors include obesity, arterial hypertension, dyslipidemia, diabetes and active or previous smoking; liver fibrosis was assessed by liver stiffness measurement (F0–F4) and steatosis by controlled attenuation parameter (S0–S3); abbreviations: IQR, interquartile range; HA, hemophilia A; HB, hemophilia B; BMI, body mass index; HCV, hepatitis C virus; FIB-4, fibrosis-4 index; LSM, liver stiffness measurement; CAP, controlled attenuation parameter.

ABSTRACT N. CO027

PREIMPLANTATION GENETIC TESTING IN FAMILIES AT RISK OF HEMOPHILIA: RESULTS FROM A SINGLE CENTRE

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Background and aims. Preimplantation genetic testing for monogenic diseases (PGT-M) is a reliable and safe reproductive option for couples at high risk of transmitting inherited genetic disorders. It is a well-established diagnostic procedure that involves the biopsy and analysis of embryonic cells, either blastomeres at the cleavage stage or trophectoderm cells at the blastocyst stage, allowing the detection of monogenic disorders prior to embryo transfer. This approach allows couples at risk of transmitting a genetic disease to avoid invasive prenatal diagnosis and the potential interruption of the pregnancy in case of an affected male fetus, often representing a more acceptable option for most couples. We report a ten-year single-centre PGT-M experience in families at risk of hemophilia, an X-linked recessive bleeding disorder caused by gene variants in *F8* or *F9* genes.

Methods. Following a multidisciplinary consultation involving a geneticist, gynecologist, psychologist and hematologist, a pre-clinical PGT work-up was performed for couples in which the female was a carrier of hemophilia A or B. To reduce the risk of bleeding episodes during oocyte pickup, specific hemostatic management was administered to carriers with low levels of coagulant activity. Intracytoplasmic sperm injection (ICSI) was used to generate embryos. Blastocysts on days 5–7 were biopsied for genetic testing, and subsequently cryopreserved by vitrification. Informative polymorphic short tandem repeat (STR) markers were used for linkage analysis, either alone or in combination with the familial pathogenic variant detection using a multiplex PCR approach. Embryos identified as unaffected were suitable for transfer one at a time, while affected embryos remained cryopreserved.

Results. A total of 23 couples contacted the centre for information on the PGT-M program, of whom 19 underwent multidisciplinary counselling and pre-clinical PGT work-up (Table 1). In two cases, the analysed STR markers were not informative, and therefore the embryo testing was not feasible. Two additional couples discontinued the process for personal reasons. Overall, 15 couples, eleven with hemophilia A and four with hemophilia B, proceeded with PGT-M cycles. Following ICSI, 69 embryos (47 tested for hemophilia A and 22 for hemophilia B) were biopsied and genetically characterized. A conclusive genetic diagnosis was obtained for 58 embryos (84%), 43 of which were classified as unaffected embryos suitable for transfer. Twenty-six vitrified embryos were transferred, resulting in 13 pregnancies (50% implantation rate per transfer), leading to eight live births (live birth rate of 31%), four miscarriages and one therapeutic abortion (Table 1). Prenatal diagnosis by chorionic villus sampling, performed in three cases, confirmed the PGT-M results. Amplification failure occurred in nine cases, eight of which were successfully re-biopsied and genetically characterized. Allele drop-out was observed in two embryos and recombination in one embryo.

Conclusions. Our ten-year experience shows that PGT-M represents a transformative advancement in reproductive medicine, enabling the avoidance of transmitting hereditary diseases through early genetic testing, reducing the risk of affected pregnancies and alleviating the emotional burden linked to therapeutic abortion.

Table 1. Characteristics of couples undergoing multidisciplinary counselling and data from embryo biopsies analysed.

	HA	HB	TOT
Couples (Total)	18	5	23
Couples requiring information only	3	1	4
Couples counseled	15	4	19
Couples discontinued PGT program	2	0	2
Couples with negative preclinical PGT work-up	2	0	2
Couples underwent PGT cycles	11	4	15
Embryos byopsied and analyzed	47	22	69
Embryos diagnosed (%)	41 (87%)	17 (77%)	58 (84%)
Trasferable embrios	30	12	42
Untrasferable embrios	10	5	15
Embryos with allele recombination	1	0	1
Embryos no diagnosed§	4	5	9
Embryos rebiopsied	4	4	8^
Embryos diagnosed (%)	4 (100%)	4 (100%)	8 (100%)
Inconclusive analysis°	2	0	2
Embryo transfer	19	7	26
Positive hCG test	9	4	13
Implantation rate (per ET) (%)	9	4	13 (50%)
Clinical pregnancies	7	1	8
Live births	6	2	8
Female	5	0	5
Male	1	2	3
Miscarriages	2	2	4
Termination of pregnancy	0	1	1
Prenatal diagnosis	1	2	3
Embryos still remain cryopreserved	28	14	42

§ Amplification failed for all markers and for specific gene variant
° Allele-drop out
^ One embryo did not survive thawing for second biopsy



ASSOCIATION BETWEEN BONE MARROW EDEMA AND JOINT PAIN IN HEMOPHILIC ARTHROPATHY: A RETROSPECTIVE SINGLE-CENTER STUDY

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Background. Bone marrow edema (BME) on magnetic resonance imaging (MRI) is a common finding in osteoarthritis and may reflect osteochondral damage or micro-fractures. However, its presence in hemophilic arthropathy and its relationship with joint pain is often overlooked.

Aims. To assess the prevalence of BME in haemophilic joints of consecutive patients undergoing MRI for different reasons and to evaluate its association with joint pain, age and global joint health scores.

Methods. We retrospectively reviewed 55 joint MRI examinations performed between 2013 and 2024 in 32 persons with haemophilia. For each examination we recorded the presence/absence of BME, joint involved, BME grade, age, Haemophilia Joint Health Score (HJHS), Haemophilia Early Arthropathy Detection with Ultrasound (HEAD-US), home treatment category, indications for MRI, presence and type of pain (acute spontaneous, acute post-traumatic or chronic), and prosthesis status.

Results. BME was present in 35/55 joints (63.6%). Median age at MRI was 37.1 years in joints with BME and 32.6 years without (p = 0.56). Patients with joints with BME had higher HJHS (median 13 vs 5; p = 0.03) and HEAD-US scores (median 11.5 vs 3; p = 0.001). Pain was reported in 14/35 (40%) joints with BME and 2/20 (10%) without BME; Fisher's exact test showed a significant association (p = 0.03) between pain and BME. Among painful joints, acute spontaneous pain predominated in the BME group (11 vs 2 cases), whereas post-traumatic pain was uncommon (2 vs 0) and only one case of chronic pain was observed. Most joints with BME were ankles and elbows, and severe grades of edema were seen in 40% of BME joints. Home therapy was heterogeneous: FVIII standard (48.6%), FVIII EHL (8.6%), FIX EHL (11.4%), Emicizumab (14.3%), Concizumab (2.9%), DDAVP (5%) and other regimens.

Conclusions. In this cohort, BME was frequent and associated with higher HJHS and HEAD-US scores. A significant association was found between BME and joint pain, particularly spontaneous acute pain. These findings suggest that BME contributes to symptomatic arthropathy. Prospective studies are needed to clarify the clinical and prognostic significance of BME in persons with hemophilia

ABSTRACT N. CO029

REAL WORLD EVALUATION OF A NOVEL PATIENT CENTERED OUTCOME INDICATOR TO SUPPORT VALUE BASED HEALTHCARE DECISION-MAKING IN HEMOPHILIA A IN ITALY: THE HEMPROVE NON-INTERVENTIONAL STUDY

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Background and Aims. Existing outcome and care quality indicators for haemophilia A have limitations in capturing the impact of the evolving treatment landscape, highlighting the need for novel clinician- and patient-reported outcome indicators (PROIs). By reflecting health status from the patient's perspective, PROIs provide essential insights that support value-based healthcare and data-driven decision-making. Within this context, the VBH2 project introduced a set of composite indicators to assess care value in haemophilia, including a composite PROI integrating the Brief Pain Inventory (BPI) Short Form, which assesses pain severity and its impact on daily life, and the Haemophilia Activities List (HAL)/Pediatric HAL (PedHAL), which evaluate mobility and physical activity in adults and children/teenagers. The HemPROve study aims to assess the composite PROI in a real-world setting, by describing the distribution of the utility and relative scores among Italian patients with severe haemophilia A and by exploring its association with clinical characteristics.

Methods. HemPROve is a non-interventional, multicenter, cross-sectional study enrolling patients aged ≥6 years with severe haemophilia A (FVIII <1%), without inhibitors, and receiving prophylactic treatment according to routine clinical practice. Patients were consecutively enrolled across 13 Italian haemophilia centers. Data collection started in March 2025 and was completed in December 2025. Final study results are expected by July 2026. All data were collected at a single time point, including administration of the BPI and HAL/PedHAL instruments. The composite PROI will be calculated in accordance with the developers' instructions, assigning an age-specific utility score to the relevant health state identifier, derived from the combined levels of the constituent PRO domains [Table 1]. In parallel, potential modifiers will be explored among patients' collected socio-demographic and clinical characteristics, including: age at enrolment; educational level; comorbidities requiring pharmacological treatment; Haemophilia Joint Health Score (HJHS); type of prophylaxis administered at enrolment (i.e., FVIII standard half-life, FVIII prolonged half-life, non-replacement therapies), with relative treatment administration frequency and duration up to enrolment; and the number of treated bleeds in the last 24 weeks prior to enrolment.

Results. A total of 128 patients have been enrolled across the following age classes (years): 6-13, n=31; 14-35, n=42; 36-65, n=44; >65, n=11. The study is expected to provide valuable insights into patients' health-state levels and utility scores as defined by the composite PROI, to explore its applicability in haemophilia A, and to identify factors associated with variability in PROI scores.

Conclusions. Implementation of the new PROI provides a patient-centered framework that supports clinical decision-making and optimizes achievable outcomes in haemophilia A. HemPROve is funded by Roche S.p.A. Italy.

Table 1. Composite Patient-Reported Outcome Indicator (PROI): health states and utilities associated

Health state ID	BPI Short Form		HAL/PedHAL	Utilities by age groups (years)			
	Pain Severity (mean score level)	Pain impact on daily life (mean score level)	(normalized score level)	6-13	14-35	36-65	>65
1	0-3	0-3	>90	10	10	10	10
2	0-3	0-3	65-90	7	7	7	8
3	0-3	0-3	<65	5	6	6	6
4	0-3	4-7	>90	6	7	7	8
5	0-3	4-7	65-90	5	5	6	7
6	0-3	4-7	<65	5	5	5	6
7	0-3	8-10	>90	5	6	6	7
8	0-3	8-10	65-90	4	5	5	6
9	0-3	8-10	<65	4	5	5	5
10	4-7	0-3	>90	6	7	7	8
11	4-7	0-3	65-90	5	6	6	6
12	4-7	0-3	<65	5	5	5	6
13	4-7	4-7	>90	5	6	6	7
14	4-7	4-7	65-90	4	5	5.5	6
15	4-7	4-7	<65	4	5	5	5
16	4-7	8-10	>90	4	5	5	6
17	4-7	8-10	65-90	3	4	5	5
18	4-7	8-10	<65	3	3	4	5
19	8-10	0-3	>90	4	5	5	5
20	8-10	0-3	65-90	2	4	5	5
21	8-10	0-3	<65	2	3	3	5
22	8-10	4-7	>90	3	4	5	6
23	8-10	4-7	65-90	2	4	5	5
24	8-10	4-7	<65	1	2	3	4
25	8-10	8-10	>90	2	3	4	5
26	8-10	8-10	65-90	1	2	3	4
27	8-10	8-10	<65	0	0	0	0

Source: Cortesi PA et al., Haemophilia. 2024 Mar;30(2):437-48. doi: 10.1111/hae.14943.
The Health state ID 1 represents the best patient's conditions, while ID 27 the worst ones. A higher Utility score represents a more desirable health state from a societal perspective.
BPI: Brief Pain Inventory (Copyright 1991 Charles S. Cleeland, PhD. Pain Research Group).
HAL: Haemophilia Activities List (Copyright Van Genderen et al., 2005, UMC Utrecht). PedHAL: Paediatric Haemophilia Activities List Parents' and Children's/Teenagers' versions (Copyright Van Creveldkliniek, University Medical Center Utrecht).

ABSTRACT N. CO030

MILD HEMOPHILIA A AND JOINT HEALTH IN REAL LIFE: IS THAT AN EMERGING ISSUE? A SINGLE CENTER EXPERIENCE

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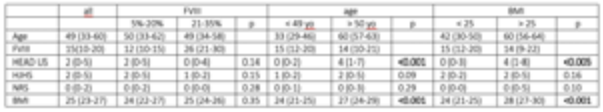
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Background and aims. Mild hemophilia A (mHA), defined by factor VIII levels between 0.05 and 0.40 IU/mL, is characterized by sporadic bleeds that rarely lead to symptomatic arthropathy. However, definition of mHA includes different bleeding phenotypes with manifestations that can widely vary between patients, and data concerning the extent on joint damage in mHA are limited. The aim of this study is to investigate joint status in our cohort of mHA patients, in order to detect any significant sign of arthropathy and to explore any relationship between joint health and FVIII levels, body mass index (BMI) and age. Furthermore, we perform a quality of life (QoL) assessment in order to detect any impairment health related.

Methods. Patients with FVIII between 0.05 and 0.35IU/ml and between 18 and 65 years old referred in our center in 2025 were included. For each patient elbows, knees and ankles were evaluated by HJHS (Hemophilia Joint Health Score) and by musculoskeletal ultrasound according to HEAD US (Hemophilia Early Arthropathy Detection with Ultrasound) protocol. Data regarding FVIII basal value, BMI and pain (according to NRS scale) were also collected. Variables were analyzed for the entire cohort and splitted according to age (< 49 yo and > 50 yo) and FVIII levels (form 0.05UI/ml to 0.20IU/ml and from 0.21IU/ml to 35IU/ml). EQ-5D-3L, SF36 and IPAQ questionnaires were administered to explore QoL and physical activity.

Results. Of the 96 mHA patients treated at our center, 42 hemophilia patients fulfilled inclusion criteria and were enrolled in the study. Results are reported in table 1. We globally found low joint health scores; median HEAD US was 2 (IQR 0-5), median HJHS was 2 (IQR 0-5). However, only 15 (36%) patients had no joint damage (HEAD US=0), 27 (64%) had at least one joint with a HEAD-US (table 1). No differences were found in HEAD US and HJHS according to FVIII, nevertheless we found that for elderly patients and for whom with higher BMI there is a statistically significant increase in HEAD-US. 20 patients fulfilled all QoL questionnaires: 14/20 (70%) patients showed no impairment in QoL, 6/20 (30%) expressed discomfort related to musculoskeletal criticalities. In the IPAQ evaluation, 15/20 (75%) patients were classified as quite or very active and 5/20 (25%) inactive. Despite low sample size, we observed a correlation trend between high HJHS and worse QoL perception. No correlation between QoL and FVIII levels, HEAD US, age or BMI were found.

Conclusions. Our data suggest that mHA patients show overall better joint status compared to severe or moderate HA patients, without any differences according to severity FVIII deficiency. No correlation between HJHS and others variables was detected, in contrast we found a significant correlation between HEAD US and age and BMI, identifying these two parameters as risk factors for early arthropathy development. mHA patients showed overall good QoL, with only critical issue represented by pain and/or musculoskeletal impairment, suggesting that the disease burden is related to articular health rather than the disease itself. In conclusion, ultrasound joints alterations, even in the absence of clinical sign of arthropathy, should be routinely investigated in mHA patients in order to prevent or detect any reversible damage, that can occur especially in adulthood and in overweight patients and can affect QoL.



ABSTRACT N. CO031

PREEMPTIVE RITUXIMAB IN ADAMTS13 RELAPSE DURING CLINICAL REMISSION OF IMMUNE THROMBOTIC THROMBOCYTOPENIC PURPURA: A MULTICENTER ITALIAN STUDY

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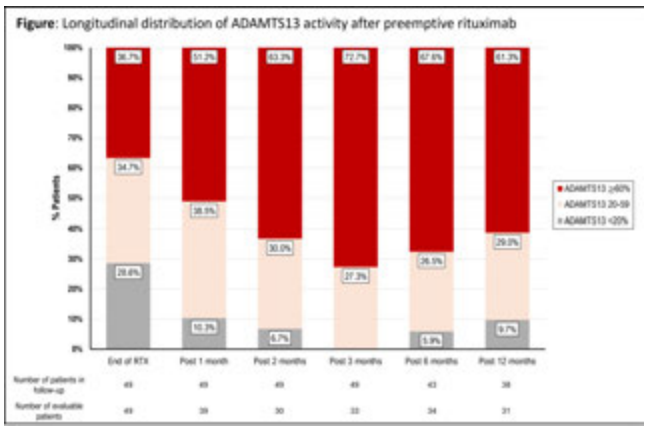
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Background And Aims. Immune thrombotic thrombocytopenic purpura (iTTP) is a rare hematologic disorder caused by immune-mediated ADAMTS13 deficiency. ADAMTS13 activity monitoring during remission enables early detection of biochemical relapse (ADAMTS13 activity <20% without hemolysis, anemia or thrombocytopenia). In this setting, preemptive rituximab (RTX) is recommended, but real world data are limited. The aim of this study was to evaluate the effectiveness of preemtive RTX in iTTP with biochemical relapse and to identify predictors of relapse, including ADAMT13 activity kinetics.

Methods. We performed an observational study across nine Italian hematology centers including iTTP patients (pts) treated with RTX for biochemical relapse. ADAMTS13 response was defined as activity ≥20% in two consecutive evaluations; ADAMTS13 complete response (CR) as ≥ lower limit of normal, corresponding to ≥60% in our laboratory (Cuker A et al.Blood 2021). Predictors of biochemical relapse included: prior RTX or caplacizumab use, prior clinical relapse, RTX dose and 12-months ADAMTS13 kinetics.

Results. Forty-nine pts were included; 22 had prior RTX and 24 caplacizumab. At biochemical relapse, median age was 48.8 years; median ADAMTS13 activity and inhibitor were 3% (IQR 0.5–7.1) and 1.8 BU/mL (IQR 0.9–5.4). RTX was used standard dose (375 mg/m² weekly x4 or x6) in 46pts (93.9%); 3pts received a lower flat dose (200 mg x4). Median follow up was 33.6 months (mos); 5 infections occurred. Forty-six pts (93.9%) achieved ADAMTS13 response, including 36 (73.5%) CR. Median ADAMTS13 activity increased progressively during follow up: 50% (IQR 24.5–82.1) at fourth RTX; 60% (IQR 34–89.4) after 1 mo; 76% (IQR 55.7–88) after 3 mos; 79.5% (IQR 54–96) after 6 mos; and 78% (IQR 43–92.9) after 12 mos (Figure). Median time to best response was 5.0mos. Twenty responders (43.5%) experienced a second biochemical relapse (n.18, 90% after ≥1 year from RTX, median 34.8 mos). Prior RTX exposure (OR 3.67, p=0.047) and clinical relapses (OR 4.2, p=0.002) were associated with higher relapse risk. RTX retreatment was given in 19pts, with 18 responders. One clinical relapse occurred in a non responder. Overall, 21pts experienced a biochemical/clinical relapse or failed to achieve response ≥1 year from RTX. Failure to achieve a complete ADAMTS13 response within 1 year was associated with a significantly higher risk of non-response or subsequent clinical or biochemical relapse (p=0.001).

Conclusions. Preemptive RTX is effective in iTTP pts with biochemical relapse, with no clinical relapses observed in responders. Pts with a refractory/relapsing disease are at higher relapse risk after preemptive RTX. Early ADAMTS13 activity dynamics identify pts who may benefit from intensified preemptive therapy, reinforcing the value of systematic ADAMTS13 monitoring.



ABSTRACT N. CO032

VENOUS THROMBOEMBOLISM IN ACUTE IMMUNE MEDIATED THROMBOTIC THROMBOCYTOPENIC PURPURA, A SINGLE-CENTER RETROSPECTIVE COHORT STUDY

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Background and Aims. immune-mediated thrombotic thrombocytopenic purpura (iTTP) is a rare and life-threatening disorder caused by a severe deficiency of the von Willebrand factor–cleaving metalloprotease ADAMTS13, due to anti-ADAMTS13 autoantibodies, leading to microvascular thrombosis in arterioles and capillaries. Venous thromboembolism (VTE) may complicate acute iTTP, and its management is challenging because of the frequent coexistence of bleeding manifestations, thrombocytopenia, and routinary use of caplacizumab. Moreover, evidence regarding the occurrence of VTE in acute iTTP is limited, making the assessment of thrombotic risk in these patients challenging. The aim of this study was to describe the prevalence and characteristics of VTE events during acute iTTP in clinical practice.

Methods. we conducted a single-center retrospective cohort study including all patients admitted to our Department between November 2008 and March 2026 with a diagnosis of first episode or relapsed iTTP. Diagnosis was confirmed by measurement of ADAMTS13 activity and inhibitor titer. For each episode, demographic, clinical, and laboratory data were collected, including age, length of hospitalization, ICU admission, neurological, cardiac, and renal involvement, and use of caplacizumab, antiplatelet agents, or anticoagulants during the episode, as reported in the table. The use of Doppler ultrasonography for VTE diagnosis was also recorded. The occurrence of deep vein thrombosis (DVT) in typical or atypical sites, superficial venous thrombosis (SVT), and pulmonary embolism (PE) was documented.

Results. a total of 65 iTTP episodes in 47 patients (30 females, 17 males) were identified. Fourteen VTE events were recorded, occurring across 11 iTTP episodes (16.9%) and affecting 11 distinct patients. In three episodes, two VTE events occurred; while no patient experienced VTE in more than one episode. SVT was documented in 2 episodes (3%), whereas DVT occurred in 9 episodes (13.8%), including cases with multiple events. No PE was observed. All thrombotic events were asymptomatic; all but one were catheter-related, and none were fatal. VTE was diagnosed at a median of 6 days (IQR 5–16) after hospital admission. Eight patients with VTE had at least one risk factor, and 3 had multiple risk factors (5 were active smokers, 2 were obese, 1 had a prior PE, 1 carried a heterozygous prothrombin variant, 1 had a family history of VTE, and 1 was receiving oral estrogen–progestin therapy). Cardiac involvement and ICU admission were significantly more frequent in iTTP episodes complicated by VTE compared with those without VTE. No statistically significant differences were observed for other variables (Table 1). However, VTE-related iTTP episodes were characterized by a higher median age and a greater frequency of neurological and renal involvement.

Conclusions. these findings indicate a clinically relevant risk of VTE in patients with iTTP, Notably, the true incidence is likely underestimated, as these events are predominantly asymptomatic; on this basis, we advocate for more intensive ultrasound surveillance. Furthermore, we believe it is important to implement preventive strategies; in particular, we suggest the prompt removal of central venous catheters when no longer needed, and the use of pharmacological thromboprophylaxis, when the platelet count allows, in patients of advanced age, with multiple risk factors, or with multiple/severe organ involvement.

	iTTP episode with VTE	iTTP episode without VTE	p
Age	56 (IQR: 38-69; range 27-74)	46 (IQR: 35-54; range 20-71)	0.09
Type of TTP event			
First event	7(63.6%)	33 (61.2%)	1.0
Relapse	4 (36.4%)	21 (38.8%)	
Hospitalization days	17 (IQR: 13-26)	46 (IQR: 9-23)	0.26
ICU admission	7 (63.6%)	14 (25.9%)	0.03
Clinical			
Neurological	8 (72.7%)	23 (42.6%)	0.35
Cardiological	10 (90.9%)	22 (40.7%)	0.03
Renal	5 (45.5%)	12 (22.2%)	0.14
PEX procedures	6 (IQR: 6-8)	7(IQR: 5-13)	0.29
Caplacizumab	7 (63.6%)	18 (33.3%)	0.09
Antithrombosis			
Anti-platelet	1 (9.0%)*	38 (70.3%)	-
Anticoagulant therapy	4 (36.3%)*	8 (15.3%)	
None	5 (45.5%)*	9 (16.7%)	
Ultrasound performed	11 (100%)	7 (12.9%)	-

**at time of first VTE*

ABSTRACT N. CO033

THE BURDEN OF CEREBRAL SMALL VESSEL DISEASE AND GLOBAL CORTICAL ATROPHY IN PATIENTS WITH IMMUNE-MEDIATED THROMBOTIC THROMBOCYTOPENIC PURPURA DURING REMISSION

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Background and aims. Immune-mediated thrombotic thrombocytopenic purpura (iTTP) can lead to long-term sequelae related to acute microvascular brain injury. Cerebral small vessel disease (cSVD) reflects chronic small vessels dysfunction and is a risk factor for stroke and cognitive decline. Global cortical atrophy (GCA) is a diffuse cortical brain loss reflecting neurodegeneration and/or vascular injury. Both are detectable on brain magnetic resonance (MRI). Data on the prevalence of cSVD and GCA in iTTP survivors are limited. To assess the prevalence of cSVD and GCA in iTTP patients during clinical remission.

Methods. Fifty-seven iTTP patients underwent a brain MRI at least 12 months after the last acute episode. cSVD burden was scored (0–4) based on lacunes, cerebral microbleeds (CMB), white-matter hyperintensities (WMH), and enlarged perivascular spaces (EPVS). GCA was graded 0 to 3 using the Pasquier scale. Associations between iTTP and cSVD/GCA were evaluated using binary and ordinal logistic regression with age adjustment. The associations of cSVD/GCA with cardiovascular risk factors, iTTP history, and ADAMTS13 activity were also explored.

Results. iTTP patients had a median age of 57 years, with hypertension as the most prevalent cardiovascular risk factor (Table 1). cSVD was detected in 49% of iTTP patients vs 27% of controls, and moderate burden (score≥2) in 19% vs none. In iTTP, the most frequent lesions were CMB, WMH, and lacunes. cSVD scores were higher in iTTP vs controls (ordinal OR 3.04, 95%CI 1.11-8.36), after age-adjustment: OR 2.90, 95%CI 0.93-9.02. In analyses restricted to non-hypertensive participants, the case-control difference was less pronounced. GCA was significantly higher in iTTP than controls (age-adjusted logistic regression OR 12.27, 95%CI 2.07–72.89; ordinal logistic regression OR 15.87, 95%CI 2.60-96.72). cSVD and GCA were not significantly associated with other cardiovascular risk factors, time from first-event, neurological symptoms at iTTP onset, number of relapses, or time with ADAMTS13-activity below 50%.

Conclusions. iTTP patients during remission showed an increased prevalence of cSVD and GCA, and hypertension may contribute to cSVD burden. Optimizing modifiable risk factors may mitigate long-term neurological sequelae.

	iTTP (n=57)	Controls (n=26)
Female sex, n (%)	42 (74)	20 (77)
Age, years, median (IQR)	57 (47 - 63)	50 (42 - 57)
Caucasian ethnicity, n (%)	53 (93)	26 (100)
Cardiovascular risk factors		
BMI1, kg/m2, median (IQR)	26 (24 - 29)	25 (22-26)
Obesity1, n (%)	12 (22)	3 (12.5)
Hypertension2, n (%)	26 (46)	0 (0)
Hyperlipidemia2, n (%)	26 (46)	8 (32)
Diabetes mellitus2, n (%)	3 (5)	1 (4)
Smoking3, n (%)	25 (44)	5 (21)
Positive CVD family history4, n (%)	13 (23)	13 (54)
Other autoimmune disease, n (%)	15 (26)	0
Cardioaspirine therapy, n (%)	16 (28)	-
TTP-related variables		
First iTTP event, n (%)	36 (63)	-
Number of events, median (range)	2 (1-14)	
Time to MRI from first event, years, median (IQR)	7 (1-12)	-
Neurological involvement at first event, n (%)	46 (81)	-
ADAMTS13-related variables5		
Timepoints, median (IQR)	18 (12-32)	-
Follow-up years, median (IQR)	5 (2-10)	-
Percentage of time < 20%, median (IQR)	9 (4-20)	-
Percentage of time 20-50%, median (IQR)	13 (2-31)	-
Percentage of time >50%, median (IQR)	70 (46-86)	-

1Available in all cases and in 24 of 26 controls.
2Available in all cases and in 25 of 26 controls.
3Available in 56 of 57 cases and in 24 of 26 controls.
4 Available in 54 of 57 cases and in 24 of 26 controls.
5 Percent time in ADAMTS13 activity ranges was calculated using linear interpolation between consecutive measurements, summing the duration (days) spent at <20%, 20-50%, and >50%, and dividing by the total observation time up to the MRI date.
Abbreviations: BMI, body mass index; CVD, cardiovascular disease; IQR interquartile range; TTP, thrombotic thrombocytopenic purpura.

ABSTRACT N. CO034

VALIDATION OF A MICROFLUIDIC PLATFORM FOR HEMOSTASIS EVALUATION UNDER FLOW CONDITIONS: FROM PATHOGENETIC MECHANISMS TO THERAPEUTIC MONITORING

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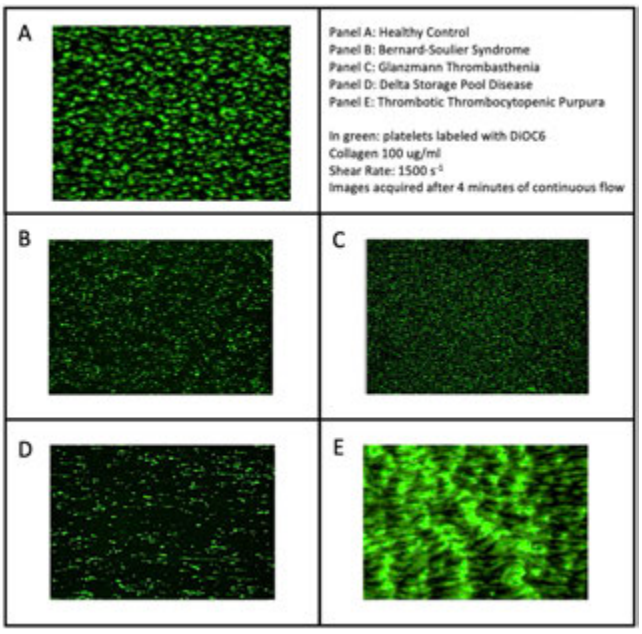
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Background and Aims. Conventional static assays for primary hemostasis evaluation fail to incorporate the crucial role of vascular hemodynamics. The development of strictly controlled in vitro systems capable of replicating physiological and pathological shear stress is required to overcome these limitations and accurately investigate congenital and acquired platelet disorders. The aim of the current study is to develop, validate on a healthy cohort, and preliminarily evaluate a microfluidic assay designed for the functional study of hemostasis, the dissection of pathogenetic mechanisms, and potential ex vivo therapeutic monitoring.

Methods. A microfluidic system was engineered for whole blood perfusion over functionalized surfaces to simulate venous and arterial shear rates via fluorescence microscopy. Specifically, microchannels were coated with collagen at two different concentrations (10 and 100 µg/mL) and blood was perfused at shear rates of 300 s^{-1} and 1500 s^{-1}. Method validation was performed on 40 healthy donors to establish reference ranges, quantifying parameters such as fluorescence intensity, surface coverage, thrombi area and number, with a customized MATLAB algorithm. The platform was subsequently applied to whole blood samples from patients with alreday known hemostatic defects: Glanzmann Thrombasthenia (GT), Bernard-Soulier Syndrome (BSS), delta-storage pool deficiency (delta-SPD), and Thrombotic Thrombocytopenic Purpura (TTP).

Results. Validation in the 40 healthy subjects demonstrated high intra- and inter-assay reproducibility, with an intraclass correlation coefficient >0.75 in most of the measured parameters, establishing stable quantitative profiles for platelet adhesion and aggregation. In preliminary testing, the device successfully discriminated pathological phenotypes under specific flow conditions (Figure 1, Panels A-E: representative fluorescence microscopy images of healthy control vs. pathological samples). Specifically, GT samples showed preserved primary adhesion to the substrate but a complete absence of three-dimensional thrombus formation. In contrast, BSS samples exhibited a severe defect in primary adhesion, which was markedly exacerbated at the higher shear rate of 1500 s^{-1}. Samples from delta-SPD patients displayed normal initial adhesion followed by impaired stability and early disaggregation of the secondary thrombus. At contrary, patients with TTP showed severe platelet hyper-reactivity, resulting in massive microthrombi formation predominantly at 1500 s^{-1}.

Conclusions. The proposed microfluidic assay constitutes a translational tool for the pathophysiological investigation of primary hemostasis and provides a rationale for its use in pharmacological monitoring. However, methodological limitations persist: the assay requires qualified personnel and demands rigorous pre-analytical standardization.





THE ROLE OF INFLAMMATORY BIOMARKERS IN IMMUNE THROMBOTIC THROMBOCYTOPENIC PURPURA

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Background and Aims. Current iTTP treatment with therapeutic plasma exchange (TPE), immunosuppression (IS), and caplacizumab has dramatically reduced the mortality rate to <10%, although the clinical severity of each acute episode remains unpredictable. While ADAMTS13 deficiency is central to iTTP pathogenesis, growing evidence implicates systemic inflammation and NETosis as contributor mechanisms of disease development and prognosis. We aim to investigate the role of biomarkers of NETosis (citrullinated H3 histone, H3Cit) and inflammation (IL-1B, IL-2, IL-6, IL-10, and TNF-α) at iTTP onset and during treatment.

Methods. Six patients (50% female; median age: 57 years, range 20–79) newly diagnosed with acute iTTP were enrolled. Plasma samples were collected at baseline (T0), and on days 6 (T6), 9 (T9), and 15 (T15) following diagnosis. ADAMTS13 activity, anti-ADAMTS13 antibodies and H3Cit were assessed by ELISA, while TNF-α and interleukin levels were quantified by multiplex assay. Clinical data and treatments were recorded. Forty subjects served as controls for inflammatory biomarkers.

Results. At onset, all patients presented neurological symptoms of different severity (2 cases of ischemic stroke). Relevant comorbidities included HIV infection, myelodysplastic syndrome (MDS), and autoimmune disorders. All patients received daily TPE, IS, and caplacizumab. Hematological remission was achieved in all patients, in a median time of 3 days, except for the patient with MDS who reached a stable platelet count >20 $\times 10^9$/L by day 9. Platelets' rise correlated with LDH reduction (p=0.001). Median time to ADAMTS13 >20% was 8 days. At T0, H3Cit and TNF-α were significantly increased in iTTP patients compared to controls (p=0.004). During treatment, a significant decrease in H3Cit (p=0.0018) and TNF-α (p=0.015) plasma levels was observed over the different time points. Specifically, H3Cit levels markedly decreased from T0 (5.90 ng/mL) to T6 (1.32)(p=0.017), T9 (0.55)(p=0.009), and T15 (0.69)(p=0.016). TNF-α also significantly declined from baseline to T9 (14.83 vs 4.90 pg/mL, p=0.035). Furthermore, a significant correlation was found between the decrease of TNF-α levels and anti-ADAMTS13 antibodies (r=0.783; p<0.001). Interestingly, patients who received caplacizumab within 2 days of diagnosis (n=3) had significantly lower post-treatment TNF-α levels (4.6 vs 7.2, p=0.009) and showed a trend toward lower IL-6 levels (2.4 vs 7.3) compared to those who initiated treatment later (n=3). No correlation between inflammatory biomarkers and indicators of clinical severity (i.e., LDH level, serum troponin and major neurological symptoms) was seen, were a positive correlation between anti-ADAMTS13 antibody titers and levels of H3Cit (p=0.028), IL-1B (p=0.023), IL-2 (p=0.013), and IL-6 (p=0.015) at baseline was observed.

Conclusions. During iTTP treatment, a significant reduction in H3Cit and TNF-α was observed in parallel with hematological response, pointing to a role of these biomarkers as indicators of NET-driven inflammation and immune activation. The positive correlation between TNF-α and anti-ADAMTS13 antibodies further supports the link between inflammation and the autoimmune process. This preliminary observation suggests that early initiation of caplacizumab may be associated with reduced inflammation. Further studies, including more severe iTTP cases, will help to clarify the role of inflammation and NETosis on disease severity and prognosis.

ABSTRACT N. CO036

NEUROCOGNITIVE ASSESSMENT OF IMMUNE-MEDIATED THROMBOTIC THROMBOCYTOPENIC PURPURA PATIENTS USING A COMPREHENSIVE TEST BATTERY IN A CROSS-SECTIONAL MRI-INTEGRATED STUDY

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Background and aims. Immune-mediated thrombotic thrombocytopenic purpura (iTTP) patients frequently report cognitive impairment during clinical remission, but magnetic resonance (MRI) findings linking cognitive impairment to cerebral small vessel disease (cSVD) MRI markers, are limited. To characterize cognitive test abnormalities in iTTP patients and evaluate their associations with MRI markers of cSVD.

Methods. Fifty-one iTTP patients in clinical remission followed at our outpatient clinic (at least 12 months after the last acute episode) underwent a standardized neuropsychological assessment covering global cognitive function, attention, logical deductive reasoning, language, memory, prefrontal function, along with brain MRI. Scores were standardized using Italian age and education adjusted norms and compared with population references using one-sample t-tests. Domain impairment was defined as at least one abnormal test per domain. cSVD was assessed both as individual MRI markers (lacunes, cerebral microbleeds [CMB], white-matter hyperintensities [WMH], and enlarged perivascular spaces [EPVS]), and as a composite total cSVD score (0-4). The association with iTTP-related variables were also explored.

Results. iTTP patients were mostly female (76%) with a median age of 58 years (Table 1). iTTP-patients showed preserved global cognition but selective deficits compared with the general population in working memory (digit Span forward and backward) and prefrontal function tests (cognitive estimates errors/bizarreness, Tower of London-accuracy). After adjustment for age and hypertension, memory impairment was associated with CMB (adjusted OR 8, 95%CI 1.5-44.1; p=0.02), and language impairment with lacunes (adjusted OR 8.7, 95%CI 1.1-70.7; p=0.04). The percentage of patients with at least 1 impaired domain increased with cSVD severity (cSVD≥2: 82% vs cSVD=1: 75% vs cSVD=0: 66%). No associations were observed between domain impairment and iTTP-related variables such as the number of relapses, time from the first acute episode, or ADAMTS13-activity levels throughout the observation time.

Conclusions. The prevalence of domain-specific deficits was higher in iTTP-patients compared with the general Italian population. CMB and lacunes were associated with memory and language impairment, whereas the composite cSVD score showed no consistent domain-specific associations, suggesting that individual cSVD markers may be more informative than total cSVD burden for neurocognitive vulnerability.

iTTP (n=51)	
Female sex, n (%)	39 (76)
Age, years, median (IQR)	58 (47 - 63)
Caucasian ethnicity, n (%)	48 (94)
Hypertension, n (%)	25 (49)
TTP-related variables	
First iTTP event, n (%)	34 (67)
Number of iTTP events, median (range)	1 (1-14)
Time to MRI from first event, years, median (IQR)	5 (2-10)
Neurological involvement at first event, n (%)	41 (80)
ADAMTS13-related variables1	
Timepoints, median (IQR)	20 (12-33)
Follow-up years, median (IQR)	5 (2-10)
Percentage of time < 20%, median (IQR)	9 (4-20)
Percentage of time 20-50%, median (IQR)	15 (2-32)
Percentage of time >50%, median (IQR)	66 (44-83)
Neuroimaging biomarkers	
Cerebral microbleeds, n (%)	16 (28)
High-grade WMH, n (%)	12 (21)
Lacunes, n (%)	9 (16)
High EPVS burden BG, n (%)	6 (11)
Total cSVD score, n (%)	
0	26 (51)
1	15 (29)
2	7 (14)
3	2 (4)
4	1 (2)
cSVD burden	
0	26 (51)
Low (1)	15 (29)
Moderate-high (2-4)	10 (20)

1Percent time in ADAMTS13 activity ranges was calculated using linear interpolation between consecutive measurements, summing the duration (days) spent at <20%, 20-50%, and >50%, and dividing by the total observation time up to the MRI date.
Abbreviations: BG, basal ganglia; cSVD cerebral small vessel disease; EPVS, enlarged perivascular space; IQR, interquartile range; iTTP, immune-mediated thrombotic thrombocytopenic purpura; WMH white matter hyperintensities.

ABSTRACT N. CO037

PERFORMANCE OF A QUALITATIVE POINT-OF-CARE TEST IN PATIENTS EXPERIENCING ACUTE THROMBOEMBOLIC OR MAJOR BLEEDING EVENTS TREATED WITH DOACS: THE T-BLEEDOAC MULTICENTER PROSPECTIVE COHORT STUDY

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Background and Aims. Management of acute thromboembolic or hemorrhagic events occurring during treatment with direct oral anticoagulants (DOACs) is challenging. Point-of-care tests to detect DOAC levels have been developed, but their role in emergency situations is poorly defined. The aim of the study was to evaluate the performance of a urinary, qualitative, strip test in comparison to plasma measurement to detect clinically relevant DOAC levels in patients with acute thromboembolism or major bleeding (MB) while on treatment with these agents.

Methods. Patients admitted to the Emergency Department for acute thromboembolism or MB while on treatment with full-dose DOACs were included in a multicenter, prospective, cohort study provided urine and blood samples were collected within 60 minutes of each other. Performance of DOAC dipstick (separate pads for factor Xa and thrombin inhibitor) to detect DOAC plasma levels≥30 ng/mL was assessed. DOAC plasma levels were assessed by drug-calibrated chromogenic assays or diluted thrombin time.

Results. Of 232 patients enrolled in the study, 189 were included in the analysis (43 excluded as in 42 samples were collected beyond 60 minutes of each other, 1 DOAC plasma level was unavailable), 61 admitted for acute thromboembolic event, and 128 for MB. One-hundred-seventy-two patients were treated with an anti-Xa inhibitor (76 apixaban, 55 rivaroxaban, 41 edoxaban) and 17 with dabigatran. Creatinine clearance<30ml/min was found in 22.2% of patients: 26.6% vs 13.1% (p=0.038) of those with index MB or thromboembolic event, respectively. In the overall study population, the diagnostic performance of the urinary DOAC dipstick was good (accuracy 89.9% and 97.9% for anti-Xa and anti-IIa pads, respectively). Similar findings were observed across subgroups: accuracy was 88.5% and 90.6% for antiXa pads, 100% and 96.9% for anti-IIa pads, in the thromboembolic and MB populations, respectively (Table).

Conclusions. Urinary DOAC dipstick showed a good performance in detecting clinically relevant DOAC exposure in patients with acute thrombotic or bleeding events, with better profile for anti-IIa. Management studies are needed to assess the role of this test in clinical practice.

Table: Performance of urinary DOAC dipstick

	Pad	SE, % (95% CI)	SP, % (95% CI)	PPV, % (95% CI)	NPV, % (95% CI)	Accuracy, % (95% CI)	Diagnostic odds ratio (95% CI)
Overall (n=189)	Anti-Xa	94.0 (89.4-96.8)	73.7 (66.7-79.7)	93.4 (88.6-96.4)	75.7 (68.8-81.5)	89.9 (84.8-93.5)	44.2 (16.5-118.6)
	Anti-IIa	81.3 (74.8-86.4)	99.4 (96.6-100.0)	92.9 (88.0-95.9)	98.3 (94.9-99.5)	97.9 (94.7-99.2)	745.3 (72.3-7678.4)
Thromboembolic event (n=61)	Anti-Xa	93.3 (83.1-97.8)	75.0 (62.0-84.8)	91.3 (80.6-96.6)	80.0 (67.4-88.7)	88.5 (78.2-94.3)	42.0 (8.2-214.1)
	Anti-IIa	100 (92.6-100.0)	100 (92.6-100.0)	100 (92.6-100)	100 (92.6-100)	100 (94.1-100)	n.e.
Major bleeding (n=128)	Anti-Xa	94.3 (88.4-97.5)	72.7 (64.0-80.0)	94.3 (88.4-97.5)	72.7 (64.0-80.0)	90.6 (84.3-94.6)	44.4 (12.8-154.9)
	Anti-IIa	72.7 (64.0-80.0)	99.1 (95.0-99.9)	88.9 (81.8-93.5)	97.5 (92.5-99.3)	96.9 (92.2-98.8)	309.3 (28.8-3321.9)
Ischemic or hemorrhagic stroke (n=97)	Anti-Xa	93.6 (86.2-97.3)	73.7 (63.6-81.9)	93.6 (86.2-97.3)	73.7 (63.6-81.9)	89.7 (82.1-94.3)	40.9 (10.4-160.1)
	Anti-IIa	100 (95.3-100)	100 (95.3-100)	100 (95.3-100)	100 (95.3-100)	100 (96.2-100)	n.e.

n.e.=not estimable
CI=confidence interval; SE=sensitivity; SP=specificity; NPV= negative predictive value; PPV=positive predictive value.

ABSTRACT N. CO038

PROGNOSTIC PERFORMANCE OF BLEEDING SEVERITY CLASSIFICATIONS IN HOSPITALIZED PATIENTS WITH GASTROINTESTINAL BLEEDING ON DIRECT ORAL ANTICOAGULANTS

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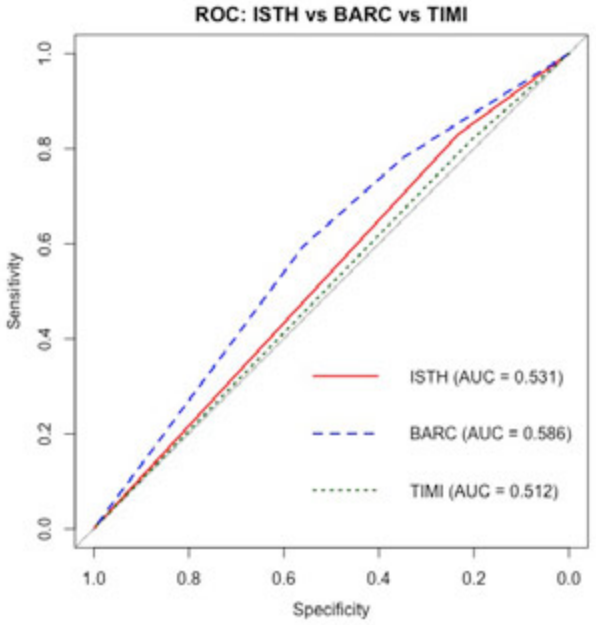
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Background and Aims. Bleeding severity classifications, such as the International Society on Thrombosis and Haemostasis (ISTH), Bleeding Academic Research Consortium (BARC), and Thrombolysis in Myocardial Infarction (TIMI), are widely used to categorize hemorrhagic events in patients receiving direct oral anticoagulants (DOACs). However, their prognostic relevance in patients hospitalized for gastrointestinal bleeding (GIB) remains unclear. Our aim was to evaluate the prognostic performance of current bleeding severity classifications in patients hospitalized for GIB in DOAC therapy.

Methods. We conducted an observational study including consecutive patients hospitalized for GIB while on DOAC therapy. Bleeding severity was classified according to ISTH, BARC, and TIMI criteria. The primary outcome was all-cause mortality at 90 days. Binary logistic regression models were used to assess the association between bleeding severity and mortality. Discriminative performance was evaluated using the area under the receiver operating characteristic curve (AUC) with 95% confidence intervals (CIs), and overall model performance and clinical utility were assessed using the Brier score and Decision Curve analysis (DCA).

Results. A total of 377 patients were included, with a median age of 84 years, of which 85.6% were aged ≥75 years and most patients had multiple comorbidities. Ninety-day mortality was 16.7%. Overall discrimination for 90-day mortality was limited for all bleeding classifications. Comparatively, BARC demonstrated higher prognostic discrimination, with an AUC of 0.59 (95% CI 0.52–0.66), versus 0.54 (95% CI 0.49–0.59) for ISTH and 0.51 (95% CI 0.46–0.57) for TIMI. BARC also showed a slightly better overall performance and a greater net clinical benefit across a clinically relevant range of risk thresholds.

Conclusions. In our cohort of patients hospitalized for GIB while receiving DOAC therapy, bleeding severity classifications according to ISTH, BARC, and TIMI demonstrated limited prognostic performance for 90-day mortality. Among the evaluated scores, BARC demonstrated comparatively better prognostic performance and clinical utility than ISTH and TIMI. Bleeding severity scores, although useful for event classification, have limited value as standalone prognostic tools in this clinical setting.



ABSTRACT N. CO039

CLINICAL SAFETY AND MONITORING OF APIXABAN IN HEMODIALYSIS PATIENTS: A PROSPECTIVE STUDY

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Background and Aims. The use of direct oral anticoagulants (DOACs) in patients with end-stage renal disease (ESRD) on dialysis remains controversial due to bleeding concerns. Dialysis patients have been excluded from randomized clinical trials, and data in this setting are limited. Among DOACs, apixaban appears to have the most favorable profile in this population. We aimed to describe our clinical experience with apixaban in hemodialysis patients, focusing on drug levels, safety, and clinical outcomes.

Methods. We conducted a prospective analysis of hemodialysis patients receiving apixaban 2.5 mg twice daily for atrial fibrillation (AF) or venous thromboembolism (VTE). Apixaban plasma levels (via anti-Xa calibrated assay) were measured at trough (12 hours after drug administration) and peak (4 hours after drug administration) on dialysis days and, when feasible, on non-dialysis days after 10–15 days of treatment. Data included demographic and clinical characteristics, indication for anticoagulation, hemoglobin, and renal function. At follow-up visits scheduled every 6 months, bleeding events (major and clinically relevant non-major, according to ISTH criteria), thrombotic and cardioembolic events, and all-cause mortality were recorded.

Results. Between February 2025 and April 2026, 8 patients (F/M 6/2) were included; median age was 77 years (IQR 68–81). Four patients had AF and 4 VTE. On dialysis days, apixaban levels measured after a median of 12 days from treatment initiation were within the therapeutic range at trough in 6 patients (75%) and at peak in 3 (37.5%); in the remaining patients, levels were slightly elevated. Measurements on non-dialysis days (3 patients) were within range in two (both peak and trough) and slightly increased in one. Laboratory parameters and apixaban levels are reported in Table 1. During a median follow-up of 6 months (IQR 3–7), one major bleeding event occurred (hematemesis with a hemoglobin drop of 2.0 g/dL due to a gastric polyp) in a patient with prior VKA-related bleeding. The incidence rate of bleeding in our cohort was 0.27 events/person-year (IC95%: 0.07 – 1.49 events/person-year). No cardioembolic or thromboembolic events were observed. One death occurred, unrelated to cardioembolic or thromboembolic events or bleeding.

Conclusions. In this small cohort of hemodialysis patients, apixaban appeared safe and effective. Plasma levels were mostly within the therapeutic range, suggesting that, with careful monitoring, apixaban may represent a viable option in this complex clinical setting. Larger studies are needed to confirm pur findings in this high-risk population.

	Pt. 1	Pt 2	Pt 3	Pt 4	Pt 5	Pt. 6	Pt. 7	Pt. 8	Median (IQR)	Therapeutic range
Age (years)	93	67	69	67	85	77	81	77	77 (69 – 81)	-
Sex (M/F)	F	F	F	M	F	F	M	F		-
VTE/AF	AF	AF	TEV	TEV	AF	AF	TEV	TEV		-
Months FU in DOAC	3	6	14	7	8	3	1	5	6 (3 – 7)	-
Hb (g/dL)	9.1	11.5	11.4	11.4	11.4	11.0	12	14.2	11.4 (11.3 – 11.8)	-
Creatinine (mg/dL)	7.5	8	10	10	7.56	5.82	3.5	7.44	7.5 (7 – 8.5)	-
Urea (mg/dL)	80	194	167	102	148	143	90	148	144 (99 – 152)	-
Apixaban dialysis trough (ng/mL)	96.8	139	33	43	166	68	46	49	59 (45 – 107)	**11 – 90 ng/mL**
Apixaban dialysis peak (ng/mL)	211	184	193	77	209	69	**96**	85	140 (83 – 197)	**30 – 153 ng/mL**
Apixaban no-dialysis trough (ng/mL)	-	-	104	58	-	47	-	-	-	**11 – 90 ng/mL**
Apixaban no-dialysis peak (ng/mL)	-	-	176	74	-	73	-	-	-	**30 – 153 ng/mL**
VTE/cardioembolism	0	0	0	0	0	0	0	0	-	-
Bleeding	0	0	0	0	1	0	0	0	-	-
Death	1	0	0	0	0	0	0	0	-	-



MAJOR BLEEDING IN PATIENTS WITH ACUTE PULMONARY EMBOLISM: RESULTS FROM THE COPE STUDY

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Background. In patients with acute pulmonary embolism (PE), major bleeding (MB) is the counterbalance for anticoagulant and thrombolytic treatment. We aimed to assess independent predictors of MB, evaluate the performance of available bleeding risk scores, and identify cluster-phenotypes in patients with acute PE from a prospective, multicentre study.

Methods. The primary outcome was MB defined according to ISTH criteria occurring during 30-day follow-up. MBs were classified as early (<7 days) and late (≥7 days) based on days from PE diagnosis.

Results. Among 5,213 patients with acute PE, 159 had MB (3.1%), 78 as early and 81 as late events. MB occurred in 12.9% and 2.5% of patients treated vs. not treated with thrombolysis. Active cancer, previous bleeding, dementia, anemia, syncope, and thrombolysis were independent predictors of early MB and of MB at 30 days; active cancer, previous bleeding and anemia were independent predictors of late MB. Four patient-phenotypes were identified; phenotype#1= previous VTE/estrogen users, #2= unprovoked PE, #3= cancer patients, #4= fragile patients with comorbidities. The risk of MB was lower in the previous VTE (#1) cluster-phenotype in comparison to the others, with a trend toward increased risk from phenotype #1 to #4. Performance of phenotypes to predict MB at 30-days was similar to that of PE-SARD, BACS and VTE-Bleed.

Conclusions. In patients with acute PE, risk factors for early and late MB within 30 days differ. Compared to stratification strategies that solely based on bleeding predictors, phenotyping appears to offer similar accuracy in identifying patients at risk for MB.

ABSTRACT N. CO041

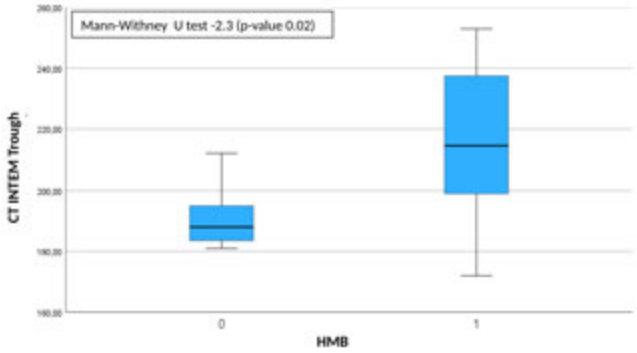
GLOBAL COAGULATION ASSESSMENT FOR THE RISK OF HEAVY MENSTRUAL BLEEDING IN WOMEN ON ORAL ANTICOAGULANT THERAPY – COHMBO STUDY

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Background. Heavy menstrual bleeding (HMB) is a primary side effect in women starting direct oral anticoagulants (DOACs). Defining predictors and management protocols for DOAC-related HMB remains a clinical challenge.
Aims. To assess HMB incidence and to evaluate coagulation parameters, viscoelastic profiles and iron and gynecological status in women starting DOAC.
Methods. This prospective study included women who started DOAC. Menstrual loss was measured via PBAC, pre DOAC and post DOAC (mean value months 1-2 after DOAC start). HMB was defined as PBAC >100, severe HMB as PBAC>150. Uterine dimensions and iron status were recorded after at least 2 menstrual cycles in DOAC. Coagulation was assessed via ROTEM at trough and peak (after 2h) of DOAC assumption. Parametric and non-parametric tests were used (Wilcoxon paired test, Mann Whitney, Spearman's correlation). Ethical approval and informed consent were obtained.

Results. To date, 28 women were enrolled (8 rivaroxaban, 8 apixaban, 10 edoxaban and 2 dabigatran), median age was 35 years. PBAC increased from a median of 89.0 pre to 166 post DOAC (Z- test -2.2, p-value 0.02). Negligible effect size for the change in the menses duration. HMB occurred in 20 (71.4%) and severe HMB in 17 (61%) women, and has been reported with all four DOAC. At trough, iron deficiency was present in 25% of women (ferritin <15.0 ng/mL). Uterine measurements showed no significant correlation with bleeding severity. INTEM CT(sec) at trough is significantly different between women with HMB and women without, U test -2.3, p-value 0.02 (Figure 1).
Conclusions. High incidence of HMB was observed after DOAC initiation and it has been reported with all four DOAC. Bleeding severity is associated with a longer time of clot formation at trough (CT) rather than uterine size or systemic bleeding history. Enrollment is still ongoing. The study is supported by institutional funding.





BLEEDING RISK IN PATIENTS RECEIVING CONCURRENT TREATMENT WITH DIRECT ORAL ANTICOAGULANTS AND CORTICOSTEROIDS: A SYSTEMATIC REVIEW

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Background and Aims. Direct oral anticoagulants (DOACs) and corticosteroids are frequently co-prescribed in clinical practice. While both drug classes independently increase bleeding risk, the impact of their concomitant use remains unclear. The aim of this study was to systematically review the literature on bleeding outcomes associated with concomitant DOAC and corticosteroid therapy.

Methods. We conducted a systematic review following PRISMA guidelines. PubMed, Web of Science, and Scopus were searched for studies reporting bleeding in patients receiving both DOACs and corticosteroids. Cumulative incidences of any bleeding and major bleeding (MB) were estimated using a random-effects model, and study quality assessed using the Newcastle–Ottawa Scale and the Cochrane RoB2. Subgroup analyses were performed for patients treated for atrial fibrillation (AF) and venous thromboembolism (VTE).

Results. Ten studies including 87,256 patients were included. The weighted cumulative incidence of any bleeding was 7.1% (95% CI 4.2–11.7%), and of MB 6.6% (95% CI 6.2–7.0%). Heterogeneity was high for any bleeding in the overall and in the AF populations, likely reflecting differences in patient characteristics, corticosteroid exposure, follow-up duration, and study design, whereas heterogeneity was minimal in the VTE subgroup. Variability in bleeding definitions, limited reporting of corticosteroid dose and duration, and absence of stratification by DOAC type/dose or bleeding site further contributed to differences in observed incidences.

Conclusions. Concomitant DOAC and corticosteroid therapy is associated with a nonnegligible risk of bleeding. Clinicians should carefully evaluate the risk–benefit profile, monitor patients closely, and consider preventive strategies. Future studies are needed to improve risk characterization in this common clinical scenario.



LONG TERM TREATMENT WITH VITAMIN K ANTAGONIST IN PEDIATRIC PATIENTS WITH PROSTHETIC HEART VALVE: THE BERGAMO EXPERIENCE

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Background and aims. Children with mechanical heart valve (MV) replacement require lifelong vitamin K antagonist (VKA) treatment in order to prevent systemic embolism; however the anticoagulation treatment predisposes patients to a substantial risk of bleeding. Clinical data on long term follow up in pediatric setting are lacking. The aim of this study is to retrospectively analyze the safety of long term VKA treatment in MV implanted children, from infancy to adolescence, at our centre.

Methods. We describe the characteristics and outcome, in terms of major bleeding and thromboembolic events, of our cohort of 8 pediatric patients with mechanical prosthetic heart valve. All patients used a point-of-care device for the determination of INR (International Normalized Ratio). INR levels were tested weekly or every two weeks. The Rosendaal method was used to calculate the Time in Therapeutic Range (TTR).

Results. Eight children (2 female and 6 male) underwent MV implantation from 2013 to 2024; the median age at the time of data collection was 9 (2-14) and the median follow up was 5 years (2-12). In 4 patients the valvular heart disease is part of a systemic syndrome (Down, Mucopolysaccharidosis, Myhre, VACTERL syndrome); the valve replacement involved the mitral valve in 5 cases, the aortic valve alone in 2 patients, and double replacement (aortic and pulmonary) in 1 patient. The mechanical valve implanted were all bileaflet valves made in pyrolytic carbon: the valves placed in the aortic position were all St.Jude Medical (SJM), whereas the prostheses implanted in the mitral position were the SJM in one case (the surgical intervention performed in 2013) and Sorin CarboMedics in the other ones. Warfarin was the VKA anticoagulant used by all patients; 6 of them used tablets and 2 the galenic preparation. Therapeutic range INR differed according to the valve position, between 2.5 and 3.5 for the mitral valves (except for 1 patient, between 2.5 and 3), between 2.5 and 3 for 1 aortic valve and the double valve replacement; and between 2 and 3 for the last aortic valve. The width of the range was 0.5 for 3 patients and 1 for the other 5; the narrow width is associated with worse TTR. The median TTR was 54.5% (0-89.2%), and in 50% of cases was >65%, which shows good compliance for the anticoagulant therapy. One exception was a patient in early childhood who reported the worst TTR. A total of 5 hemorrhagic events occurred during follow-up in half of the patients: 3 minor bleeds and 2 major gastrointestinal bleedings: these 2 events occurred in patients with mitral valve replacement and INR range 2.5-3.5. Temporary stop of oral anticoagulation was done. Both patients were less than 10 years old when the event occurred. With a total follow up of 47 person-years the incidence rate of major bleeding was 4,2% per year, while described warfarin-related major bleeding rates in pediatrics are from 0,5% to 1,7% per year. No patient had thromboembolic complications.

Conclusions. Anticoagulant treatment in pediatric patients with mechanical heart valve replacement is effective in preventing thromboembolic events but some concerns remains about safety. Improvement in surgical tecniques and materials and a constant interest in pediatric care are desirable.



QUALITY AND SAFETY OF VITAMIN K ANTAGONIST TREATMENT IN PEDIATRIC PATIENTS: A RETROSPECTIVE CLINICAL AUDIT FROM A SINGLE CENTRE

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Background and aims. The knowledge of quality and safety of vitamin K antagonists in pediatric patients is limited. In children the time-in-therapeutic-range (TTR) achievement has been reported between 39% and 81%, while warfarin-related major bleeding rates ranging from 0.5% to 1.7% per year.

Methods. A retrospective clinical audit has been conducted to evaluate the characteristics and rates of bleeding in long term follow up and identify possible hemorrhagic risk factors. All patients used a point-of-care device for INR determination. The TTR is calculated using the Rosendaal method. TTR > 65% has been considered optimal. Major bleeding refers to the ISTH definition. Patients are in anticoagulation for mechanical valve replacement (group A, 8 patients), other post-surgical congenital cardiopathies, mainly Fontan surgery (group B, 48 patients) and thrombotic disease (group C, 3 patients). Grade 1,2 and 3 types of bleeding according to the CTCAE classification occurred in our population. No grade 4 and 5 events were observed. We evaluated: age, suboptimal TTR, indication for anticoagulation in relation to quality of INR control and type of bleeding. Among grade 3 bleeds, only two could be classified as major. Associations between categorical variables were assessed using Pearson's chi-square test. All statistical analyses were performed using SPSS version 21.0 (IBM Corporation), and a two-tailed p-value < 0.05 was considered statistically significant.

Results. Included were 59 consecutive patients (45 male, 14 female, median age 11), actively in follow up at our outpatient service for vitamin K antagonists (VKA) monitoring. Median duration of follow up was 6 years (range 10-0.5). Median TTR percentage was 63.3% and mean value 65.1%. Nine patients received pediatric formulations of warfarin; 3 patients received acenocumarol while 47 commercial tablets of warfarin. There were 8 cases with at least one grade 1 bleeding event, 8 cases with grade 2 and 8 with grade 3 bleeding events. With a total follow-up of 375 person-years, the incidence rate of all hemorrhagic events was 0.064 per person-year (6.4% per year). Major bleeding events rate was 0.005 per person-year (0.5% per year). No significant correlation has been found between TTR and age; grade 1 and grade 2 bleeding and age, non-optimal TTR, type of indication; grade 3 events and age, non-optimal TTR. Group B indication correlates to less probability of grade 3 bleeding (p=0.014), while patients with prosthetic heart valve replacement have higher risk of grade 3 bleedings (P=0.034) despite a median TTR of 83%.

Conclusions. Our data confirm good INR control when considering TTR and incidence of major bleeding among pediatric patients. Among all types of haemorrhage, the highest risk of events requiring medical intervention was observed in patients with mechanical prosthetic heart valve.

ABSTRACT N. CO045

BEYOND THE VISIBLE: LIPOPROTEIN(A) AS A SILENT DRIVER OF RETINAL VASCULAR DAMAGE

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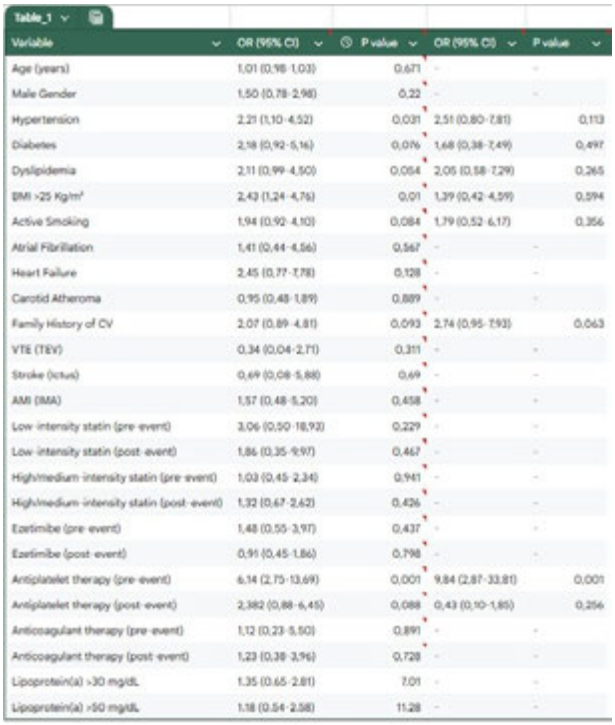
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Background and Aims. Retinal vein occlusion (RVO) is a major cause of vision loss. Recent evidence suggests RVO aligns more closely with an arterial rather than a venous phenotype, sparking interest in Lipoprotein(a) [Lp(a)] as a potential driver of vascular inflammation and impaired fibrinolysis. However, conclusive evidence remains limited. The aim of this retrospective observational study was to evaluate the interplay between traditional cardiovascular risk factors and Lp(a) levels in affecting the incidence of major cardiovascular events (MACE) in patients followed-up after a RVO.

Methods. We included in the analysis 250 patients (111 females, 139 males; median age 62 years) with RVO (BRVO/CRVO) referred to the Atherothrombosis Center of Florence between 2001 and 2026. Lp(a) serum concentrations were measured in a subgroup of 172 patients. Lipid-lowering and antithrombotic therapies were documented both pre- and post-event, with a specific focus on antiplatelet therapy prior to RVO recurrence. Median follow up was 12 months.

Results. Hypertension and dyslipidemia were the most prevalent risk factors. Elevated Lp(a) levels ≥30 mg/dL and >50 mg/dL were present in 45.3% and 30.2% of cases, respectively. In the younger cohort (<55 years), males exhibited higher Lp(a) concentrations than females: mean 39.1 mg/dL (median: 24.5; IQR: 61.3) vs 31.3 mg/dL (median: 14.8; IQR: 32.2). Conversely, older females (≥55 years) showed the highest overall concentrations: mean 48.3 mg/dL (median: 33.6; IQR: 49.7), compared to older males: mean 42.0 mg/dL (median: 19.6; IQR: 54.4). No statistical significance was found between CRVO and BRVO subtypes (p>0.05). RVO recurrence was observed in 19/47 patients (40.4%) with Lp(a) levels ≥30 mg/dL, notably, 13/47 (27.7%) presented values >50 mg/dL, while 59.6% and 72.3% of recurrent patients remained below the 30 and 50 mg/dL thresholds, respectively. At multivariate analysis (Table 1), the only independent predictor od recurrence was the “pre-event antiplatelet therapy” (OR 9.84, 95% CI 2.87–33.81; p<0.001), whereas hypertension and BMI >25 kg/m^2 did not confirm the independent role demonstrated at univariate analysish. Lp(a) levels did not correlate with recurrence (p=0.421. During a median follow-up of 12 months (range: 1–240), five MACE were recorded (2 MI, 3 strokes). Notably, 80% of these events occurred in patients with comorbidities and already on antithrombotic therapy, underscoring the high vulnerability of the cohort despite standard treatment.

Conclusions. RVO should be regarded not as an isolated ocular event, but as a clinical manifestation of a compromised systemic vascular and metabolic profile. While post-event therapy is typically intensified, the high recurrence rate among patients already on antiplatelets (p<0.001) highlights a "residual risk" that standard treatments fail to neutralize, necessitating stricter metabolic control and long-term monitoring. In this context, Lp(a) emerges as a pivotal biomarker for risk stratification: while its rise in women is age-dependent (post-menopausal), in younger males it identifies high-risk genetic phenotypes often overlooked by traditional assessments. Screening for Lp(a) is therefore essential to implement aggressive primary and secondary prevention strategies on modifiable factors, especially in younger cohorts, while awaiting targeted Lp(a)-lowering therapies.



Variable	OR (95% CI)	P value	OR (95% CI)	P value
Age (years)	1,01 (0,98-1,03)	0,671		
Male Gender	1,50 (0,78-2,98)	0,22		
Hypertension	2,21 (1,10-4,52)	0,031	2,51 (0,80-7,81)	0,113
Diabetes	2,18 (0,92-5,16)	0,076	1,68 (0,38-7,49)	0,497
Dyslipidemia	2,11 (0,99-4,50)	0,054	2,05 (0,58-7,29)	0,265
BMI >25 Kg/m^2	2,43 (1,24-4,76)	0,01	1,39 (0,42-4,59)	0,594
Active Smoking	1,94 (0,92-4,10)	0,084	1,79 (0,52-6,17)	0,356
Atrial Fibrillation	1,41 (0,44-4,56)	0,567		
Heart Failure	2,45 (0,77-7,78)	0,128		
Carotid Atheroma	0,95 (0,48-1,89)	0,889		
Family History of CV	2,07 (0,89-4,81)	0,093	2,74 (0,95-7,93)	0,063
VTE (TEV)	0,34 (0,04-2,71)	0,311		
Stroke (Ictus)	0,69 (0,08-5,88)	0,69		
AMI (IMA)	1,57 (0,48-5,20)	0,458		
Low intensity statin (pre event)	3,06 (0,50-18,93)	0,229		
Low intensity statin (post event)	1,86 (0,35-9,97)	0,467		
High/medium intensity statin (pre event)	1,03 (0,45-2,34)	0,941		
High/medium intensity statin (post event)	1,32 (0,67-2,62)	0,426		
Ezetimibe (pre event)	1,48 (0,55-3,97)	0,437		
Ezetimibe (post event)	0,91 (0,45-1,86)	0,798		
Antiplatelet therapy (pre event)	6,14 (2,75-13,69)	0,001	9,84 (2,87-33,81)	0,001
Antiplatelet therapy (post event)	2,382 (0,88-6,45)	0,088	0,43 (0,10-1,85)	0,256
Anticoagulant therapy (pre event)	1,12 (0,23-5,50)	0,891		
Anticoagulant therapy (post event)	1,23 (0,38-3,96)	0,728		
Lipoprotein(a) >30 mg/dL	1,35 (0,65-2,81)	7,01		
Lipoprotein(a) >50 mg/dL	1,18 (0,54-2,58)	11,28		

ABSTRACT N. CO046

BLEEDING RISK FACTOR–BASED PHENOTYPES AND THEIR ASSOCIATION WITH MORTALITY AND HEMORRHAGIC OUTCOMES IN ATRIAL FIBRILLATION

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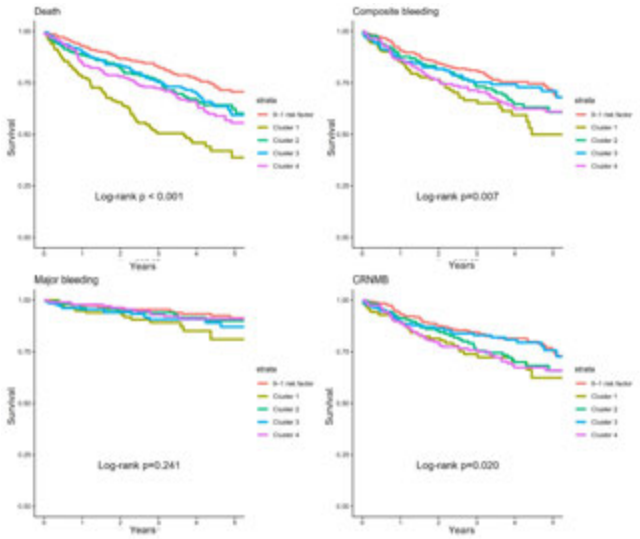
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Background and aims. In patients with atrial fibrillation (AF), multiple bleeding risk factors are well established. However, whether these factors cluster into distinct clinical phenotypes and how these phenotypes relate to mortality and bleeding outcomes remains unclear.

Methods. This prospective observational study included consecutive patients with AF who initiated Non-vitamin K oral anticoagulants (NOACs) therapy between 2013 and 2018. Bleeding risk factors were defined a priori based on clinical relevance and literature evidence and included age >75 years, previous bleeding, chronic kidney disease (CKD), cirrhosis, systolic blood pressure >140 mmHg (uncontrolled hypertension), concomitant antiplatelet therapy, NSAID use, and alcohol abuse. These variables were collected at baseline, and patients were stratified into a low-risk group (0–1 risk factors) and a higher-risk group (≥2 risk factors). Unsupervised clustering using latent class analysis (LCA) was applied to the higher-risk group to identify distinct bleeding risk phenotypes. Associations with primary outcomes (all-cause mortality and composite bleeding) and secondary outcomes (major bleeding and clinically relevant non-major bleeding [CRNMB] according to the ISTH definition) were evaluated using Kaplan–Meier analysis and Cox proportional hazards models.

Results. Overall, 1,039 patients were included (age 75.2±9.6 years, 56.8% female), of whom 316 (30.4%) were classified as low risk. Among the 723 (69.6%) patients in the higher-risk group, four distinct clusters were identified. Cluster 1 represented a frail phenotype, characterized by a high burden of bleeding risk factors, including advanced age, previous bleeding, CKD, and high fall risk. Cluster 2 was defined by alcohol abuse. Cluster 3 was characterized by a high prevalence of NSAID and antiplatelet use. Cluster 4 was characterized by uncontrolled hypertension. After a median follow-up of 1,539 days (IQR 1,124–1,863), 336 (32.3%) deaths and 277 (26.6%) composite bleeding events occurred. Compared with the low-risk group, all clusters showed an increased risk of all-cause mortality, with the highest risk observed in Cluster 1 (HR 2.99, 95% CI 2.17–4.12) (Figure 1). For composite bleeding, Cluster 1 (HR 1.87, 95% CI 1.30–2.69) and Cluster 4 (HR 1.49, 95% CI 1.06–2.10) were significantly associated with increased risk, whereas the association for Cluster 2 was borderline (HR 1.39, 95% CI 0.97–1.99) and not significant for Cluster 3 (Figure 1). Among secondary outcomes, Cluster 1 remained associated with an increased risk of both major bleeding (HR 2.03, 95% CI 1.04–3.95) and CRNMB (HR 1.79, 95% CI 1.18–2.72) (Figure 1). Cluster 2 and 4 showed an increased risk of CRNMB (HR 1.49, 95%CI 1.00-2.22 and HR 1.62, 95% CI 1.11–2.36, respectively), whereas associations for Clusters 3 were not significant (Figure 1).

Conclusions. Bleeding risk factors cluster into distinct clinical phenotypes associated with different risks of mortality and haemorrhagic outcomes.



ABSTRACT N. CO047

OXIDATIVE STRESS–RELATED PLATELET HO-1 AND MICRORNA MODULATION IN PATIENTS WITH TYPE 2 DIABETES MELLITUS UNDER ASPIRIN THERAPY

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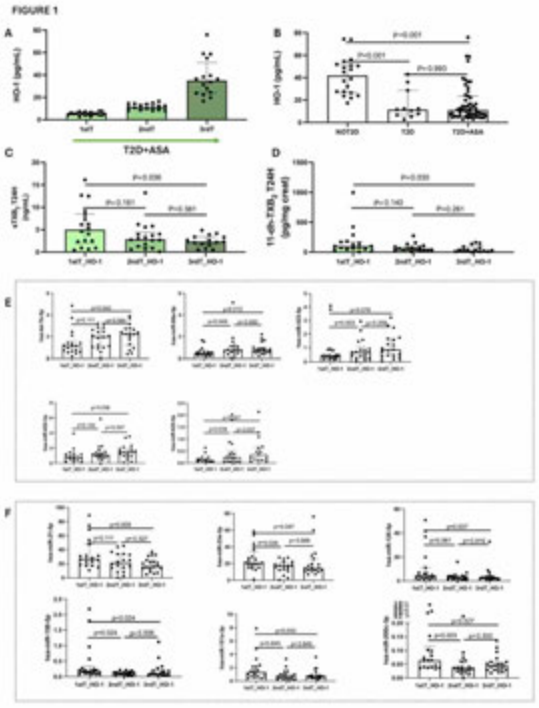
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Background and Aims. Patients with type 2 diabetes mellitus (T2D) exhibit enhanced platelet reactivity and an increased risk of atherothrombotic events. Although low-dose acetylsalicylic acid (ASA) irreversibly inhibits cyclooxygenase-1, a substantial proportion of patients with T2D show a suboptimal antiplatelet response. Oxidative stress has been proposed as a key mechanism underlying this variability. The aim of this study was to investigate the relationship between oxidative stress–related pathways, platelet function, and ASA responsiveness in patients with T2D, focusing on platelet heme oxygenase-1 (HO-1) and platelet-associated microRNAs (miRNAs).

Methods. Patients with T2D receiving chronic ASA therapy (T2D+ASA, n = 55), patients with T2D not receiving ASA (T2D, n = 11), and subjects without T2D (NOT2D, n = 20) were enrolled. Chronic ASA therapy consisted of 100 mg/day for at least one month. Blood and urine samples were collected for platelet isolation and biochemical analyses. Patients in the T2D+ASA group were stratified into tertiles according to platelet HO-1 levels Figure 1A. Platelet miRNA expression profiles were identified by next-generation sequencing and validated by real-time PCR. KEGG pathway enrichment analysis was performed on differentially expressed platelet-associated miRNAs.

Results. Platelet HO-1 levels differed significantly among groups. Patients with T2D, regardless of ASA treatment, exhibited significantly lower platelet HO-1 levels compared with NOT2D subjects (both $P < 0.001$), Figure 1B. Among T2D+ASA patients, lower platelet HO-1 levels were associated with higher levels of markers of platelet activation, including serum thromboxane B_2 (first vs third tertile, $P = 0.036$) and urinary 11-dehydro-thromboxane B_2 ($P = 0.030$), Figure 1C-D. A total of 62 platelet-associated miRNAs were identified. Reduced expression of hsa-let-7b-5p, hsa-miR-98-5p, hsa-miR-423-5p, hsa-miR-652-3p and hsa-miR-625-5p, and increased expression of hsa-miR-21-5p, hsa-miR-23a-3p, hsa-miR-126-5p, hsa-miR-150-5p, hsa-miR-151a-3p and hsa-miR-200c-3p were observed in patients with lower HO-1 levels, Figure 1E-F. KEGG analysis revealed enrichment of pathways related to platelet activation, fluid shear stress and atherosclerosis.

Conclusions. Patients with T2D exhibit reduced platelet HO-1 levels independently of chronic low-dose ASA therapy, indicating a persistent impairment of platelet antioxidant capacity that may contribute to enhanced platelet reactivity and reduced responsiveness to antiplatelet treatment. In this clinical context, lower HO-1 levels are associated with a reduced expression of regulatory let-7 family members, including hsa-let-7b-5p and hsa-miR-98-5p, suggesting a failure of compensatory mechanisms linking platelet miRNAs to redox-sensitive pathways, potentially due to insufficient repression of the HMOX1 transcriptional inhibitor Bach1. Consistently, platelet-associated miRNA profiling and KEGG pathway analysis indicate that low HO-1 levels are associated with a less adaptive modulation of platelet activation and platelet–vascular signaling pathways, which may translate into suboptimal antiplatelet responses and an increased risk of atherothrombotic events.





PREDICTORS OF FIRST THROMBOTIC EVENTS AFTER MECHANICAL VALVE REPLACEMENT FOR RHEUMATIC HEART DISEASE: A RETROSPECTIVE COHORT STUDY FROM SALAM CENTRE FOR CARDIAC SURGERY - SUDAN

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Background and aims. Rheumatic heart disease (RHD) is endemic in sub-Saharan Africa. In advanced disease, valve replacement is a therapeutic option. In young patients, mechanical valves are often preferred because of their durability. However, they require lifelong anticoagulation with vitamin K antagonists (VKAs), with dose adjustment based on close laboratory monitoring to prevent prosthetic valve thrombosis (PVT) and thromboembolism. Aim of the study is the identification of peri-operative and early follow-up predictors of the first thrombotic event after valve replacement in patients with RHD.

Methods. In this retrospective cohort study, we included all consecutive patients who underwent mechanical valve replacement surgery from 1 July 2018 to 31 December 2021. All patients were followed at the Salam Centre Anticoagulation Clinic. The observation period ended on 28 February 2023. Collected variables included sex, age at surgery, country/region of origin, NYHA class and cardiac rhythm at admission, BMI, comorbidities (hypertension and diabetes), pre-operative white blood cell count, haemoglobin, platelet count, and eosinophil count, type and brand/model of implanted valve, left ventricular ejection fraction at discharge, discharge medical therapy, and time in therapeutic range (TTR) during the first 6 months after warfarin initiation. The primary outcome was the first objectively documented thrombotic event after surgery.

Results. A total of 41 first thrombotic events were recorded during follow-up. All events were arterial, 31 PVT and 10 ischaemic strokes. Compared with patients who did not develop thrombosis (n=712), those who developed thrombosis (n=41) did not differ significantly in sex, age at surgery, country or region of origin, type of surgery, comorbidities, NYHA class, cardiac rhythm at admission, left ventricular ejection fraction at discharge, discharge medical therapy, or mean TTR during the first 6 months after warfarin initiation. Among patients undergoing mitral valve replacement, valve type distribution differed significantly between groups (p=0.045), with a higher proportion of Carbomedics valves in the thrombosis group. Patients who developed thrombosis also had higher pre-operative white blood cell counts (7.6 [6.5–9.4] vs 6.6 [5.2–8.4], p=0.01) and higher eosinophil counts (260 [130–580] vs 130 [50–260], p<0.01). Consistently, eosinophilia was more frequent in the thrombosis group at all thresholds examined: ≥350/µL (39.0% vs 17.3%, p=0.001), ≥500/µL (29.3% vs 11.4%, p=0.002), and ≥1500/µL (7.3% vs 0.8%, p=0.01). In the multivariable Cox proportional hazards model, higher pre-operative eosinophil count was independently associated with an increased risk of a first thrombotic event: each increase of 100 cells/µL was associated with a 13% higher hazard (HR 1.13, 95% CI 1.09–1.18; p<0.001). NYHA class IV at admission was also associated with a higher hazard compared with NYHA class I (HR 3.87, 95% CI 1.05–14.29; p=0.042).

Conclusions. Higher pre-operative eosinophil count was consistently associated with subsequent thrombotic events after mechanical valve replacement. This finding suggests that eosinophilia may identify a subgroup of patients with a pro-thrombotic or pro-inflammatory profile who may require closer peri-operative assessment and follow-up. The underlying causes of eosinophilia warrant further investigation, including evaluation for parasitic infection where clinically appropriate.

ABSTRACT N. CO049

RANDOMIZED CONTROLLED TRIAL TO IDENTIFY THE OPTIMAL SCHEME OF HEPARIN FOR TREATMENT OF DEEP VEIN THROMBOSIS IN PREGNANCY

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Background. Venous thromboembolism (VTE) is a major cause of maternal morbidity and mortality worldwide. Low-molecular-weight heparin (LMWH) is the recommended treatment for pregnancy-associated deep vein thrombosis (DVT), yet evidence guiding optimal dose intensity and duration during pregnancy is limited and largely extrapolated from non-pregnant populations. Prolonged administration of full-dose LMWH twice daily is effective but burdensome and may increase bleeding risk, particularly in the peripartum period. Whether anticoagulant intensity can be safely reduced after an initial phase of full treatment remains uncertain.

Aims. The APRICOT study (Adapt hePaRin In pregnanCy-assOciated vTe) aims to assess whether a reduced-dose LMWH regimen is non-inferior to standard full-dose LMWH in preventing recurrent VTE and whether it improves safety with respect to bleeding complications in pregnant women with acute DVT.

Methods. APRICOT is a multicenter, randomized, open-label, controlled, non-inferiority trial (EUCT: 2025-521566-10-00). Pregnant women aged ≥18 years with a first objectively confirmed proximal DVT occurring between 5 and 30 weeks of gestation will be eligible. The study will be conducted in accordance with the Declaration of Helsinki and Good Clinical Practice and will require authorization from the National Ethics Committee and local Institutional Review Boards. All participants will provide written informed consent prior to enrollment. All women will receive initial therapeutic LMWH at a dose of 100 U/kg every 12 hours for six weeks. Thereafter, participants will be randomized 1:1 to continue full-dose LMWH or to switch to a reduced-dose regimen (65–75% of the full therapeutic dose administered once daily) until delivery and for six weeks postpartum. Randomization will be centralized and web-based, stratified by center. Patients will be followed throughout pregnancy and up to 8–12 weeks after delivery. The primary efficacy endpoint is recurrent VTE, defined as symptomatic DVT or pulmonary embolism. The primary safety endpoint is major bleeding according to ISTH criteria. Secondary endpoints include VTE extension and clinically relevant non-major bleeding. All outcomes will be adjudicated by an independent blinded central committee. A minimum sample size of 96 women provides 80% power to demonstrate non-inferiority with a 10% margin.

Conclusions. APRICOT addresses a critical evidence gap in the management of pregnancy-associated DVT and may inform safer, more individualized, and less burdensome anticoagulant strategies during pregnancy



ABSTRACT N. CO050

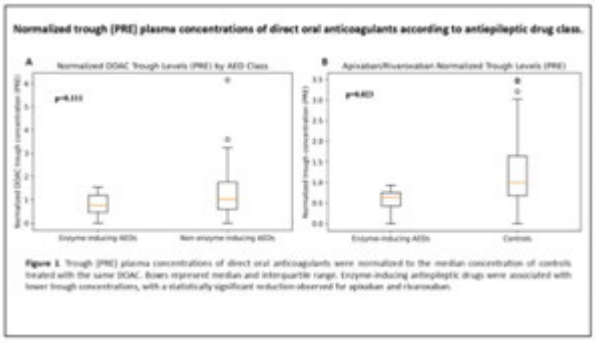
INTERACTION BETWEEN DIRECT ORAL ANTICOAGULANTS AND ANTIEPILEPTIC DRUGS: A MULTICENTER OBSERVATIONAL STUDY

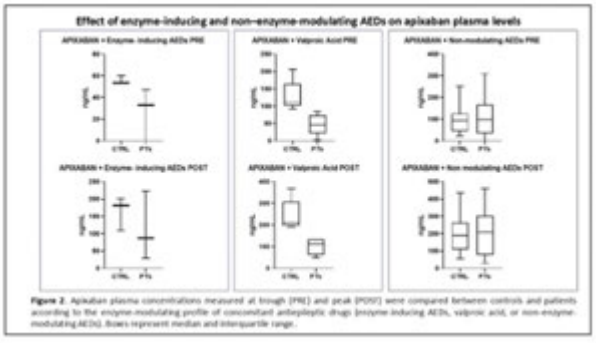
A. Lipari[1], S. Sorrentino[1], M. De Siati[1], L. D'Innocenzo[1], A. Ferretti[1], D. Menichelli[2], V. Cammisotto[2], P. Pignatelli[2], G. Ragna[3], M.C. Vedovati[3], C. Becattini[3], G. Frisullo[4], V. Forte[5], T. Pirozzi[1], L. Di Gennaro[1], M. Basso[1], E. De Candia[1]

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Background. Direct oral anticoagulants (DOACs) are widely used for stroke prevention in non-valvular atrial fibrillation and for venous thromboembolism. Their pharmacokinetics depend on P-glycoprotein (P-gp) transport and, variably, on cytochrome P450 3A4 (CYP3A4) metabolism. Enzyme-inducing antiepileptic drugs (AEDs) may reduce DOAC plasma concentrations and potentially impair efficacy.
Aims. To evaluate the effect of enzyme-inducing and non–enzyme-inducing AEDs on DOAC plasma concentrations.
Methods. This prospective, observational, multicenter study enrolled outpatients receiving DOACs for atrial fibrillation or venous thromboembolism, with (cases) or without (controls) concomitant AED therapy. DOAC plasma concentrations were measured at trough (PRE) and peak (POST, ~2 h after intake) after ≥2 4 weeks of stable treatment. Apixaban, rivaroxaban, and edoxaban were measured using anti–-factor Xa assays, and dabigatran using a thrombin time–based assay. Analyses were performed by individual DOAC. Normalized concentrations (case value/median of age- and sex-matched controls receiving the same DOAC) were used to account for inter-drug variability. AEDs were classified as enzyme-inducing (carbamazepine, oxcarbamazepin, fenobarbital) or non–enzyme-inducing (levetiracetam, gabapentin, pregabalin, lamotrigine, clonazepam, lacosamide). Given its enzyme-inhibiting properties, valproic acid was analyzed separately from other AEDs.

Results. A total of 328 patients (76 cases, 252 controls) were included, with similar baseline characteristics. Overall PRE and POST DOAC concentrations did not differ between cases and controls. Normalized trough concentrations across all DOACs showed a non-significant trend toward lower levels in patients receiving enzyme-inducing AEDs (Fig1A). In analyses restricted to apixaban and rivaroxaban, normalized trough concentrations were significantly reduced in patients treated with enzyme-inducing AEDs compared with controls (Fig1B), whereas peak concentrations were unaffected. On the contrary, non-enzyme inducing AEDs did not affect trough concentration of apixaban and rivaroxaban. Quite surprisingly, valproic acid induced reduced trough concentrations of apixaban and rivaroxaban.
Conclusions. While overall DOAC plasma concentrations were not affected by concomitant AED therapy, enzyme inducing AEDs were associated with reduced trough levels of apixaban and rivaroxaban. These findings support a CYP3A4/P-gp–mediated interaction and underscore the need for careful DOAC selection or the use of non–enzyme-inducing AEDs in patients receiving DOACs.





ABSTRACT N. CO051

PROTEIN S HEERLEN AND OTHER PROS1 GENE VARIANTS IN PROTEIN S-DEFICIENT PATIENTS: A SINGLE-CENTER STUDY

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Background and Aims. Diagnosing protein S (PS) deficiency is challenging due to varied functional defects and diagnostic assays, highlighting the importance of genetic characterization of the PROS1 gene. The clinical significance of the Heerlen (Ser501Pro) variant remains unclear. This study aimed to determine the frequency of coding-region variants in individuals with PS deficiency and assess their correlation with PS phenotype and thrombotic risk.

Methods. We analyzed 55 subjects with persistently reduced free PS levels (<65%) and no identifiable causes of acquired deficiency. Free PS was measured using immunological methods. Genetic analysis of peripheral blood DNA was conducted with next-generation sequencing to detect germline PROS1 variants. Variants were annotated, classified by established criteria, and correlated with biochemical and clinical data.

Results. The cohort comprised 34 females (61.8%) and 21 males (38.2%), with a mean free PS level of 41.6% (range 7–65%). Thrombotic events occurred in 38.2% of subjects (venous n=17; arterial n=4). The median age at first event was 49 years (range 17–88), with recurrence in 9.1%. Family history revealed both PS deficiency and venous thromboembolism (VTE) in 21.8% of patients, VTE alone in 18.1%, and asymptomatic PS deficiency in 21.8%. Free PS levels did not differ significantly between patients with and without VTE (41.1% vs 42.4%, p = 0.7469). No mutations were found in 27 patients (49.1%, group A), of whom 40.7% had VTE and 29.6% had a family history of VTE. Thirteen patients (23.6%, group B) carried the Heerlen variant; 7.6% had VTE and 30.7% had a family history of VTE. Fifteen patients (27.3%, group C) carried other PROS1 variants; 33.3% had VTE and 60% had a family history of VTE. Detected variants included Arg330Trp (n=3, two families), Gly357Arg (n=2, unrelated), and single cases (3.6% each) of Ala525Val, Pro667Leu, Glu360Lys, Ala557Val, Ile591Met, Arg316His, Glu437Lys, Tyr332Ter, Gln563Ter, and Ile546MetfsTer16. Median free PS levels were 48% in groups A (range 7-64%) and B (range 25-65%), and 35% (range in group C (10-53%) (group C vs A or B, p < 0.001) (Figure). Patients with truncating variants (frameshift and nonsense mutations) (n=3) had lower free PS levels (median 12%, range 10–16), indicating a severe loss-of-function effect.

Conclusions. PS-deficient subjects without coding-sequence variants or with the Heerlen variant had significantly higher free PS levels than carriers of other PROS1 variants. Additionally, carriers of Heerlen variant had a low rate of VTE. Amino acid substitutions were identified in only about half of patients with free PS deficiency, suggesting that other defects may involve non-coding mutations or copy number variations affecting PROS1 expression.

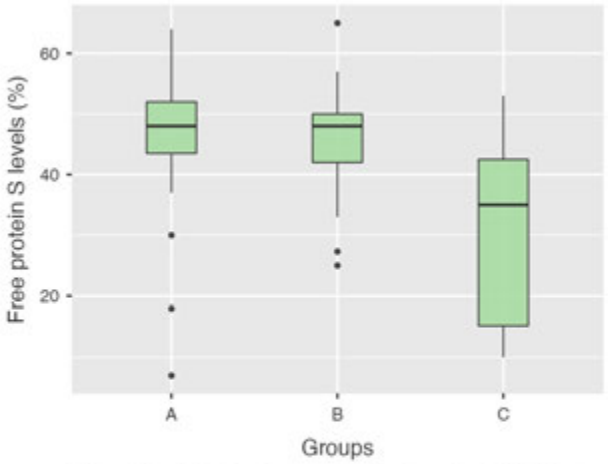


Figure. Free PS levels among patients without PROS gene variants (group A), with PS Heerlen (group B) and with other PS variants (group C).



INCREMENTAL PROGNOSTIC VALUE OF ECHOCARDIOGRAPHIC MARKERS OF RIGHT VENTRICULAR FUNCTION IN ACUTE PULMONARY EMBOLISM: AN INDIVIDUAL PATIENT DATA ANALYSIS

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Background. Right ventricular (RV) dysfunction is a major determinant of early mortality in acute pulmonary embolism (PE). Among parameters at echocardiography,tricuspid annular plane systolic excursion (TAPSE) reflects RV systolic function, whereas systolic pulmonary artery pressure (PASP) estimates RV afterload. The TAPSE/PASP ratio, a surrogate of RV–pulmonary artery coupling, has been proposed as a prognostic marker, but its incremental value remains uncertain.

Purpose. To evaluate the prognostic performance of TAPSE/PASP in acute PE and its incremental value beyond TAPSE and clinical risk stratification.

Methods. We performed an individual patient data meta-analysis including 16 observational studies including patients with confirmed acute PE (PROSPERO CRD4202238420). Studies reporting both TAPSE and PASP were included in the present analysis. The primary outcome was short-term all-cause mortality (in-hospital or within 30 days). TAPSE/PASP, TAPSE and PASP were analyzed as continuous variables using generalized linear mixed-effects models with random intercept for study. Discrimination was assessed by area under the curve (AUC). A sensitivity analysis was performed in hemodynamically stable patients with simplified Pulmonary Embolism Severity Index (sPESI) ≥1.

Results. A total of 2,682 patients (four studies) were included (51.3% women); 43.9% had sPESI ≥1 and 212 were hemodynamically unstable. Short-term mortality occurred in 201 patients (7.5%). TAPSE/PASP was associated with mortality (OR 0.25 per 0.1 increase; 95% CI 0.13–0.49), consistently after adjustment for hemodynamic instability (adjusted OR 0.44; 95% CI 0.23–0.85) and for sPESI (OR 0.41; 95% CI 0.21–0.79). The association was not confirmed in intermediate-risk patients (OR 0.79; 95% CI 0.40–1.57). TAPSE values were independently associated with mortality (OR 0.93 per 1-mm increase; 95% CI 0.90–0.95), whereas PASP was not. When added separately to sPESI, TAPSE improved discrimination (AUC 0.707 vs 0.669; ΔAUC +0.038, p<0.001), whereas TAPSE/PASP yielded only a modest increase (AUC 0.690; ΔAUC +0.021, p=0.028).

Conclusions. In acute PE, TAPSE is a robust prognostic marker. The TAPSE/PASP ratio, although associated with mortality, does not provide meaningful incremental value beyond TAPSE and established clinical risk stratification.



PROGNOSTIC IMPACT OF RIGHT VENTRICULAR DYSFUNCTION AND HYPOXEMIA IN HEMODYNAMICALLY STABLE ACUTE PULMONARY EMBOLISM: AN INDIVIDUAL PATIENT DATA META-ANALYSIS

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Background. In hemodynamically stable acute pulmonary embolism (PE), right ventricular dysfunction (RVD) is a key determinant of early risk. Hypoxemia at presentation is common and may reflect ventilation–perfusion mismatch or the worsening of pre-existing respiratory failure due to non-PE causes . Whether hypoxemia adds prognostic information beyond RVD remains uncertain.

Purpose. The aim of this study was to evaluate the independent and combined associations of RVD and hypoxemia with short-term mortality in acute PE.

Methods. We conducted an individual patient data meta-analysis of observational studies including adults with objectively confirmed acute PE (PROSPERO CRD4202238420). Respiratory insufficiency was defined as oxygen saturation <90% on room air at presentation. The primary outcome was short-term all-cause mortality (in-hospital or ≤30 days); secondary outcome was PE-related mortality. Mixed-effects logistic regression models with random intercept for study were used. Patients were classified into three groups: neither condition, either RVD or hypoxemia alone, and both conditions. An interaction term assessed effect modification.

Results. The analysis included 2,218 patients from six studies. Overall, 52.6% had neither condition, 36.4% had one, and 11.0% had both. Short-term all-cause mortality increased progressively across groups (4.5%, 7.8%, and 11.1%). Compared with patients without either condition, the odds of death were higher in those with one condition (OR 1.88, 95% CI 1.29–2.76) and highest in those with both (OR 2.68, 95% CI 1.64–4.37). In the subset with data on PE-related mortality (n=1,844), mortality rose from 1.9% (reference) to 4.0% (OR 2.39, 95% CI 1.30–4.39) and to 7.2%(OR 4.36, 95% CI 2.17–8.75) in the three groups, respectively. Among haemodynamically stable patients (n=2,152), the associations remained consistent (neither condition=reference, one condition: OR 1.86, 95% CI 1.25–2.77; both: OR 2.25, 95% CI 1.31–3.88). Similar results were observed for PE-related mortality. No significant interaction was detected (p=0.43 for all-cause; p=0.67 for PE-related mortality), indicating additive rather than synergistic effects.

Conclusions. In hemodynamically stable acute PE, hypoxemia identifies a clinically meaningful subgroup at increased short-term risk, particularly when combined with RVD. Mortality exceeded 11% in patients presenting with both conditions despite initial stability. Integrating oxygenation status with cardiac imaging markers may refine early risk stratification and support closer monitoring or timely therapeutic escalation.



ULTRA-PROCESSED FOOD CONSUMPTION IS ASSOCIATED WITH AN INCREASED RISK OF UNPROVOKED VENOUS THROMBOEMBOLISM IN THE MOLI-SANI STUDY

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Background and Aims. Ultra-processed foods (UPFs) are industrial formulations typically made from food-derived substances and additives, with little or no intact whole foods. The consumption of UPFs has been increasingly linked to adverse cardiometabolic outcomes, yet its association with unprovoked venous thromboembolism (VTE) remains poorly investigated. This study examined the relationship between UPF intake and the incidence of VTE in the Moli-sani Study cohort, a large population-based prospective study conducted in Southern Italy (enrollment 2005-2010).

Methods. A total of 20,987 men and women free of a personal history of thromboembolic events at baseline were included. Dietary intake was assessed using a validated food frequency questionnaire, and foods were classified according to the Nova system, which groups foods into four categories based on the extent and purpose of processing. UPF consumption was expressed as the proportion of total food intake by weight. Overall diet quality was evaluated using the Mediterranean Diet Score (MDS). Incident VTE events, including deep vein thrombosis and pulmonary embolism, were identified through Hospital Discharge Records, mortality registry data, and clinical records; validated cases derived from clinical charts (n=107), mortality registry data (n=2), and hospital discharge records (n=6). The association between UPF intake and incident VTE was examined using multivariable Cox proportional hazards models, adjusting for established risk factors.

Results. During a median follow-up of 13.1 years, 115 incident VTE events were documented. Higher UPF consumption was associated with more than a twofold increased risk of incident VTE (HR = 2.33; 95% CI: 1.32–4.12 for Q4 vs. Q1). Further adjustment for the MDS did not substantially alter this association (HR = 2.06; 95% CI: 1.14–3.70). The relationship was consistent across sexes (HR = 3.02; 95% CI: 1.36–6.72 in men, and HR = 2.00; 95% CI: 0.89–4.49 in women; p for difference = 0.23).

Conclusions. Findings from a large population-based cohort suggest that high UPF consumption may represent a modifiable risk factor for unprovoked venous thromboembolism, independent of overall diet quality. This finding raises the possibility that non-nutritional factors (e.g., plastic contaminants, food additives) may play a direct role. Further studies are warranted to confirm these findings and to elucidate the underlying biological mechanisms.



COMPARISON OF VISCOELASTIC COAGULATION MONITOR AND ROTATIONAL THROMBOELASTOMETRY FOR HAEMOSTATIC PHENOTYPING AND OUTCOME PREDICTION IN SEPSIS

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Background and Aims. Sepsis is a leading cause of morbidity and mortality worldwide and sepsis-induced coagulopathy encompasses a complex spectrum ranging from hypercoagulable to hypocoagulable states, significantly influencing patient outcomes. Viscoelastic testing, including rotational thromboelastometry (ROTEM) and the novel Viscoelastic Coagulation Monitor (VCM), enables rapid bedside hemostatic profiling. This study evaluates the diagnostic performance of VCM compared to ROTEM and assessed its utility in identifying phenotypes associated with septic shock and clinical outcomes.

Methods. Adult patients with sepsis or septic shock (Sepsis-3 criteria) admitted to our Internal Medicine Unit from May 2024 to February 2026, were included. ROTEM and VCM were performed within 48 hours of diagnosis. Patients were classified as normocoagulable, hypocoagulable (≥2 hypocoagulable parameters in EXTEM or INTEM) or hypercoagulable (≥2 hypercoagulable parameters in EXTEM or INTEM) based on parameters in EXTEM/INTEM and VCM traces. Primary endpoints included 28-day mortality, thrombotic events, major bleedings. The cohort was stratified according to septic shock. Demographic, laboratory data and clinical outcomes were collected. Group comparisons were performed using non-parametric analysis and Spearman's correlation.

Results. A total of 89 patients were included; 19 (21.8%) developed septic shock. VCM and ROTEM demonstrated strong correlation for maximum clot firmness (MCF) and moderate correlation for clotting time (CT), while no correlation was observed for alpha-angle (Table 1). Based on ROTEM, 28/89 (31.5%) patients were hypercoagulable, 5/89 (5.6%) hypocoagulable, and 56/89 (62.9%) normocoagulable. VCM showed strong agreement with ROTEM in detecting coagulation phenotypes, with high correlation with ROTEM INTEM ($r=0.60$, $p<0.0001$) and EXTEM ($r=0.55$, $p<0.0001$). Hypercoagulable patients exhibited higher platelet counts (269 vs 159×10^9/L, $p<0.001$) and creatinine (224 vs 158 µmol/L, $p<0.001$). Hypocoagulable patients faced significantly higher 28-day mortality compared to hypercoagulable patients (80.0% vs 25.0%; $p=0.009$). Notably, in septic shock, VCM identified prolonged CT (459 vs 396 s, $p=0.015$) and higher 45-minute lysis (LI45) index (98% vs 96%, $p=0.015$), whereas ROTEM parameters showed no significant differences.

Conclusions. VCM shows robust analytical agreement with ROTEM for haemostatic phenotyping in sepsis. Furthermore, VCM may offer superior sensitivity to ROTEM in detecting specific coagulopathic changes associated with septic shock. Hypocoagulability remains a potent predictor of poor clinical outcomes in this population, highlighting the need for its early detection to identify patients at higher clinical risk.

Table 1

VCM Parameter	ROTEM Parameter	ρ (Spearman)	p-value
CT	CT INTEM	0.39	**0.0001**
	CT EXTEM	0.31	**0.0001**
MCF	MCF EXTEM	0.79	**<0.0001**
	MCF INTEM	0.84	**<0.0001**
	MCF FIBTEM	0.49	**<0.0001**
Alpha	Alpha angle		n.s.

ABSTRACT N. CO056

URINARY MARKERS OF PLATELET ACTIVATION AND OXIDATIVE STRESS IN ATHEROSCLEROTIC CARDIOVASCULAR DISEASE IN TYPE 2 DIABETES

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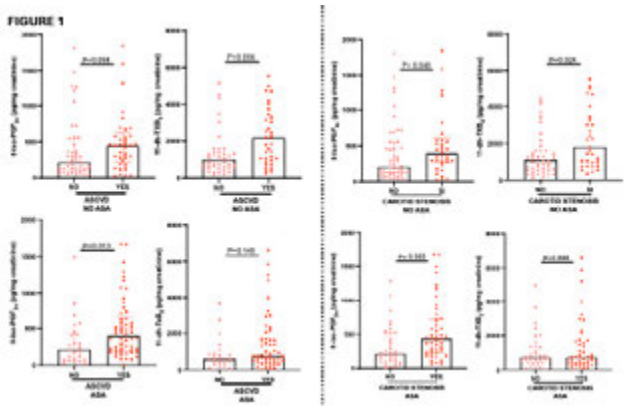
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Background and Aims. In patients with type 2 diabetes (T2D), atherosclerotic cardiovascular disease (ASCVD) is characterized by enhanced platelet activation and increased oxidative stress, both of which contribute to thrombotic risk and disease progression. Carotid artery stenosis represents a clinically relevant manifestation of systemic atherosclerosis and is included among ASCVD conditions. However, the relative contribution of platelet activation and oxidative stress to atherosclerotic burden in patients with T2D remains incompletely defined. This study aimed at investigating urinary markers of platelet activation and oxidative stress—11-dehydro-thromboxane B_2 (11-dh-TXB_2) and 8-iso-prostaglandin $F_2\alpha$ (8-iso-$PGF_2\alpha$)—in T2D patients with or without ASCVD, including those with carotid artery stenosis ≥50%.

Methods. Urine samples were collected from 179 patients with T2D, with (n=84) or without (n=95) aspirin (ASA) therapy. Urinary levels of 11-dh-TXB_2 and 8-iso-$PGF_2\alpha$ were measured by enzyme immunoassay (EIA) following chromatography-based prostaglandin extraction. Patients were stratified according to the presence of ASCVD (n=98 with ASCVD) and carotid artery stenosis ≥50% (n=84 with carotid stenosis ≥50%).

Results. Patients with ASCVD showed higher urinary levels of 8-iso-$PGF_2\alpha$ compared with those without ASCVD, both among patients not receiving ASA therapy (P = 0.058) and among those receiving ASA therapy (P = 0.013), indicating increased oxidative stress in subjects with established atherosclerotic disease. When carotid artery stenosis ≥50% was considered, 8-iso-$PGF_2\alpha$ levels remained significantly higher in patients not receiving ASA therapy (P = 0.048), whereas no significant difference was observed among ASA-treated patients (P = 0.140), supporting an association between oxidative stress and advanced atherosclerotic burden. Urinary 11-dh-TXB_2 levels were significantly higher in patients with ASCVD only among those not receiving ASA therapy (P = 0.006), while no significant difference was observed in patients on ASA therapy (P = 0.140). Similarly, patients with carotid artery stenosis ≥50% showed significantly higher 11-dh-TXB_2 levels only in the absence of ASA therapy (P = 0.024), with no difference among ASA-treated patients (P = 0.898). Urinary levels of 8-iso-$PGF_2\alpha$ and 11-dh-TXB_2 were directly correlated (rho=0.565, <0.001), further confirming the close interplay between oxidative stress and platelet activation in patients with T2D.

Conclusions. In patients with T2D, oxidative stress—as reflected by increased urinary 8-iso-$PGF_2\alpha$—is significantly associated with the presence of ASCVD, including carotid artery stenosis ≥50%. Aspirin therapy effectively attenuates platelet activation, as indicated by the lack of association between urinary 11-dh-TXB_2 and atherosclerotic burden in ASA-treated patients. These results highlight oxidative stress as a key mechanism underlying residual cardiovascular risk in diabetes and suggest that urinary oxidative stress markers may represent a useful tool for identifying patients with advanced atherosclerotic disease.



ABSTRACT N. CO057

THROMBOPOIETIN-PLATELET AXIS IN METABOLIC-ASSOCIATED STEATOTIC LIVER DISEASE

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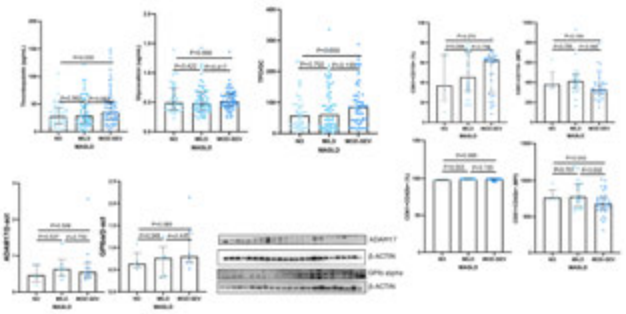
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Background and Aims. Metabolic-associated steatotic liver disease (MASLD) is characterized by systemic alterations involving the liver–platelet axis. Experimental evidence has demonstrated that platelets actively contribute to NASH development and progression to hepatocellular carcinoma, particularly through GPIbα-mediated inflammatory pathways. In parallel, the liver plays a central role in regulating platelet homeostasis by controlling both thrombopoietin (TPO) production and platelet clearance, supporting a bidirectional interaction between liver function and platelet biology. Thrombopoietin (TPO) regulates platelet production through its receptor CD110, while glycocalicin (GC), generated by ADAM17-mediated cleavage of the platelet receptor GPIbα, reflects platelet clearance. In this context, alterations in the TPO–GPIbα axis may represent a link between hepatic dysfunction and platelet-driven inflammation. However, the clinical relevance of these pathways, including the role of the TPO/GC balance in MASLD severity, remains poorly defined. This study aimed to investigate the association between MASLD severity and circulating levels of TPO, GC, and the TPO/GC ratio, as well as platelet expression of CD110, GPIbα, and ADAM17.

Methods. A total of 171 subjects were enrolled. They were stratified according to the presence of MASLD [without (NO) (n=42), mild MASLD (MILD) (n=64), and moderate–severe MASLD (MOD–SEV) (n=65)]. Plasma levels of TPO and GC were measured and used to calculate the TPO/GC ratio. Platelet surface expression of CD110 and GPIbα was assessed by flow cytometry, while total platelet expression of GPIbα and ADAM17 was evaluated by Western blot. Group differences were analyzed using appropriate statistical methods.

Results. Plasma TPO levels were significantly increased in subjects with moderate–severe MASLD compared with those without MASLD (MOD–SEV vs NO, P = 0.030), showing a progressive increase with disease severity; a trend was also observed when comparing MOD–SEV with MILD (P = 0.093). Plasma GC levels did not differ significantly among groups. Consequently, the TPO/GC ratio was higher in patients with moderate–severe MASLD, reaching borderline statistical significance versus controls (MOD–SEV vs NO, P = 0.050), suggesting a shift of the TPO–GPIbα axis toward increased TPO availability (Figure). The percentage of platelets expressing the TPO receptor (%CD110: MOD–SEV vs NO, P = 0.070; MILD vs NO, P = 0.094) and GPIbα (MOD–SEV vs NO, P = 0.095; MILD vs NO, P = 0.003) showed a trend toward higher values in MASLD subjects compared with controls. Conversely, the mean fluorescence intensity (MFI) of both receptors was reduced in moderate–-severe MASLD (MFI CD110: MOD–SEV vs MILD, P = 0.068; MFI GPIbα: MOD–SEV vs NO, P = 0.043; MOD–SEV vs MILD, P = 0.042), indicating receptor redistribution or remodeling (Figure). Platelet ADAM17 expression did not differ significantly among groups, whereas total GPIbα expression assessed by Western blot showed a trend toward increased levels in moderate–severe MASLD (MOD–SEV vs NO, P = 0.065) (Figure).

Conclusions. MASLD severity is associated with progressive dysregulation of the thrombopoietin–platelet axis, characterized by increased circulating TPO. Increased platelet expression of GPIbα may contribute to the enhanced thrombopoiesis in advanced disease, supporting sustained platelet production and survival. These changes occur in the absence of significant ADAM17-mediated shedding, indicating functional platelet adaptation rather than overt activation. Overall, the TPO/CD110–GPIbα axis emerges as a candidate biomarker of disease severity and a mechanistic contributor to MASLD progression.



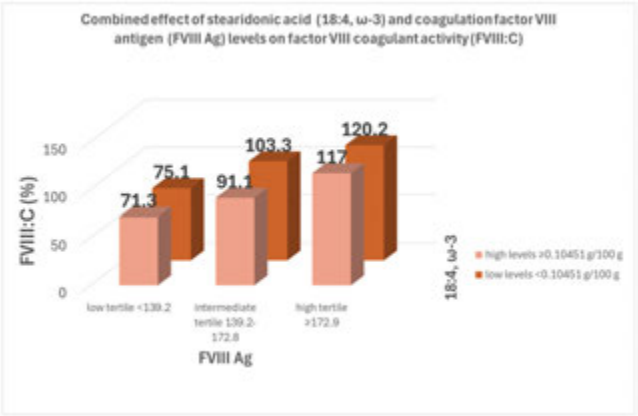
ABSTRACT N. CO058

ELEVATED PLASMA LEVELS OF OMEGA-3 STEARIDONIC ACID ARE ASSOCIATED WITH DECREASED FACTOR VIII COAGULANT ACTIVITY INDEPENDENTLY OF FACTOR VIII ANTIGEN AND VON WILLEBRAND FACTOR LEVELS: PRELIMINARY RESULTS FROM AN ANGIOGRAPHICALLY-CONTROLLED CARDIOVASCULAR COHORT STUDY

N. Osti[1], G. Musuraca[1], A. Castagna[2], M. Spizzo[2], P. Pattini[2], G. Mango[2], M. Baroni[3], B. Lunghi[3], G. Poli[4], C. Brocco[1], C. Angheben[1], M. Grusse[5], P. Van Dreden[5], A. Anesi[1], G. Lippi[3], M. Del Greco[1], S. Friso[2], A. Ferro[1], F. Bernardi[3], N. Martinelli[2]

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Background and Aims. Although research evidence indicates that lipid binding affects blood clotting, there is still debate about how plasma fatty acids (FA) may influence the coagulation cascade. In this study we aimed to assess the relationships between plasma FAs and biomarkers of coagulation factor VIII (FVIII) pathway in a single-center cohort of clinically stable subjects undergoing elective coronary angiography, with or without coronary artery disease (CAD).
Methods. Plasma FAs concentrations were measured by gas-chromatography method. FVIII coagulant activity (FVIII:C) was determined by one-stage clotting assay. FVIII antigen (FVIII Ag), von Willebrand factor (vWF Ag), and binding capacity of VWF for FVIII (VWF:FVIIIB) were measured by ELISA. Individuals receiving anticoagulant therapy were excluded from the analysis, along with those who experienced any acute illness within the preceding month.
Results. Data were available for 376 subjects (males 75.8 %; mean age 68.2±9.8 years, 68 with normal coronary arteries, 46 with coronary lesions with stenosis <50%, and 262 with coronary lesions with stenosis ≥50%). Among all the FAs evaluated, only stearidonic acid (18:4, ω-3) showed a significant correlation with FVIII:C (R=-0.180, P<0.001), which remained significant after adjustment for sex, age, CAD diagnosis, body mass index, renal function, high-sensitivity C-reactive protein, total and HDL cholesterol, triglycerides, FVIII Ag, VWF Ag, and VWF:FVIIIB. In the final linear regression model stearidonic acid (standardized beta coefficient=-0.167, P<0.001), FVIII Ag (standardized beta coefficient=0.483, P<0.001), and VWF Ag (standardized beta coefficient=0.122, P=0.043) were predictors of FVIII:C variability. Plasma concentration of stearidonic acid was not correlated with FVIII Ag, VWF Ag, or VWF:FVIIIB levels. Stratification of the study population according to stearidonic acid and FVIII Ag levels further supported their additive effect on FVIII:C (Figure 1). Consistently, stearidonic acid was also inversely correlated with peak of thrombin at thrombin generation assay (R=-0.112, P=0.030) and in a linear regression model adjusted for all the above-mentioned variables, both stearidonic acid (standardized beta coefficient=-0.153, P=0.004) and FVIII Ag (standardized beta coefficient=0.169, P=0.032) remained predictors of peak of thrombin.
Conclusions. Plasma concentration of stearidonic acid may negatively modulate the activity of FVIII independently of FVIII and VWF antigen levels, thereby indicating a possible anticoagulant function for this ω-3 FA.





EXTRACELLULAR VESICLES AS BIOMARKERS IN FAMILIAL HYPERCHOLESTEROLAEMIA TREATED WITH EVINACUMAB

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Introduction and Aims. Familial hypercholesterolaemia (FH) is an inherited autosomal dominant disorder caused by the presence of variants in the genes that regulate low-density lipoprotein (LDL). Chronic elevation of LDL-cholesterol (LDL-C) levels predisposes patients to an increased cardiovascular risk. Growing evidence suggests that extracellular vesicles (EVs) contribute to vascular dysfunction, inflammation and atherogenesis through paracrine mechanisms and may reflect ongoing pathological processes in cardiovascular disease. The introduction of Evinacumab represents a novel therapeutic strategy for LDL-C reduction. This study aims to evaluate EVs in FH patients, in order to explore their potential role as biomarkers of disease activity and of the therapeutic response to Evinacumab treatment.

Methods. Seven patients with FH (4 males, 3 females; age range 9-83 years) and fifteen healthy age- and sex-matched controls were enrolled. Plasma EVs were isolated from platelet-poor plasma. EVs were quantified (absolute count, expressed as events/µL) and characterized using CytoFLEX flow cytometry at baseline and monthly for six months following initiation of Evinacumab treatment. Instrument standardization and size-based gating were performed using fluorescent polystyrene Gigamix beads (FSC and SSC), establishing an EV detection range of 0.1–0.9µm. EVs integrity was assessed using calcein-AM, membrane labelling was performed with a lipophilic dye and apoptotic EVs were identified by Annexin V staining. EV subpopulations were defined based on cell-specific surface markers: platelets ($CD41^+$, $CD62P^+$), leukocytes ($CD45^+$), monocytes ($CD14^+$), erythrocytes ($CD235a^+$), endothelial cells ($CD62E^+$), and apolipoprotein B–positive ($ApoB^+$).

Results. FH patients exhibited significantly higher levels of total EVs (lipophilic dye^+/calcein-AM^+/Annexin-V^+) and increased concentrations of $CD41^+$, $CD62P^+$, $CD45^+$, $CD235a^+$, $CD62E^+$, and $ApoB^+$ EVs compared with healthy controls ($p \leq 0.005$ for $CD41^+$ and $CD235a^+$; $p \leq 0.0001$ for all other subtypes). Evinacumab treatment was associated with a progressive reduction in endothelial, platelet and inflammatory EVs reaching statistical significance between the second to fifth treatment administrations ($p \leq 0.001$ vs baseline). $ApoB^+$ EV levels showed a significant decrease after the fourth infusion ($p \leq 0.001$).

Conclusions. Evinacumab treatment was associated with a reduction in endothelial- and ApoB-derived EVs and a partial decrease in inflammatory and platelet-derived EVs, suggesting an improvement in vascular and inflammatory status that was not fully normalized. These findings indicate a benefical effect of therapy in FH patients. Longitudinal studies are warranted to assess the durability of these effects. Overall, EVs may represent dynamic biomarkers of disease activity and therapeutic response in FH.



LP(A) AND CARDIOVASCULAR RISK IN FAMILIAL HYPERCHOLESTEROLEMIA

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Background and aims. Familial hypercholesterolemia (FH) is a genetic disorder marked by high low-density lipoprotein cholesterol (LDL-C) levels, mainly caused by mutations in *LDLR, APOB, PCSK9* or *LDLRAP1* genes. FH patients show a higher risk of adverse cardiovascular events than the general population, due to the alteration of lipid profile that causes atherosclerosis. An independent and mostly genetically determined atherosclerotic risk factor is lipoprotein (a) [Lp(a)]. Elevated Lp(a) levels have been demonstrated as a causal risk factor for coronary heart disease (CHD), aortic stenosis and ischemic stroke. A recent (2025) meta-analysis of 27,658 participants enrolled in 6 placebo-controlled statin trials demonstrates the independent and additive nature of Lp(a) and LDL-C levels for atherosclerotic cardiovascular disease (ASCVD) risk, and that LDL-C lowering does not fully offset Lp(a)-mediated risk. The aim of this study was to evaluate the contribution of Lp(a) serum levels in cardiovascular manifestations in Italian FH patients of a referral Center.

Methods. We analyzed 121 patients with possible/probable/definite FH using Dutch Lipid Clinic Network score diagnostic criteria. A targeted 57 genes panel (including genes involved in lipid metabolism and dyslipidaemias), was evaluated through a high throughput sequencing (HTS) technology, using MiSeq Illumina platform. The pathogenicity of *LDLR* variants was evaluated according to the American College of Medical Genetics guidelines. Lp(a) levels were measured by an immunonephelometric method (LPAX IMMAGE, Beckman Coulter). Continuous variables were expressed as median (interquartile range).

Results. Our cohort was characterized by 91 adults and 30 pediatrics with median Lp(a) levels of 271.0 (85.0-1050.0) and 172.0 (56.5-829.5) mg/L, respectively. In adult population, 21/91 (23.1%) patients showed CHD events and 26/91 (28.6%) manifested both CHD or peripheral vascular events, while no events were registered in the pediatric population. In adult patients presenting cardiovascular manifestation, both coronary and/or peripheral, we observed higher median levels of Lp(a) with respect to patients not affected by these clinical complications [717.0 (233.2-1232.5) vs 229.0 (78.0-949.0) mg/L, p=0.02]. Among adults, HTS analysis allowed to identify 29 patients with at least one likely pathogenic/ pathogenic variant in *LDLR* gene, group defined as *LDLR*-positive (*LDLR*+). The remaining 62 patients were mutation-negative (*LDLR*-) or carried only benign/likely benign/uncertain significance variants in this gene. Among *LDLR*+ group, in subjects with CHD and/or peripheral vascular events (10/29=34.4%) higher levels of Lp(a) with respect to subjects without events were reported [257.5 (56.2-787.0) vs 89.0 (28.0-235.0) mg/L, p=0.09]. Among *LDLR*-, patients exhibiting CHD and/or peripheral vascular events (16/62=25.8%) showed significantly higher Lp(a) levels than the event-negative group [981.0 (396.7-1795.0) vs 286.0 (89.5-1095.0) mg/L, p=0.02].

Conclusions. Our data support the contribution of Lp(a) to the higher prevalence of cardiovascular manifestations in FH clinical phenotype, in particular in patients not showing a monogenic causative mutations. This study strengthens the importance of including Lp(a) in the cardiovascular risk assessment of patients also in the FH clinical setting, to better stratify cardiovascular risk and to improve the therapeutic management.



IMMUNOFLUORESCENCE MICROSCOPY REVEALS PLATELET- AND RED BLOOD CELL ALTERATIONS AS MORPHOLOGICAL BIOMARKERS IN MYELOPROLIFERATIVE NEOPLASMS

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Myeloproliferative neoplasms (MPN) are clonal hematologic disorders characterized by heterogeneous clinical manifestations and variable prognosis, with thrombotic complications representing one of the most frequent and severe outcomes. Early diagnosis can be challenging, especially in patients presenting with nonspecific symptoms or isolated thrombotic events. In a previous work, we identified in a subset of MPN patients morphological abnormalities detectable by immunofluorescence microscopy on peripheral blood smears, namely reduced platelet alpha granule content and the presence of aggregates in red blood cells consisting of the cytoskeletal protein non-muscular myosin IIA (NMMIIA). The present study (DRKS-ID: DRKS00032588) aimed to validate these findings in an independent cohort and to assess the diagnostic performance of immunofluorescence microscopy in distinguishing MPN patients from healthy individuals based solely on morphological criteria. We enrolled 147 MPN patients and 99 healthy controls, age- and sex-matched. Standard peripheral blood smears were stained using primary and secondary antibodies and analysed by immunofluorescence microscopy. Two independent observers, blinded for subject identity and clinical information, evaluated all samples. Among the MPN patients, 65 (44%) had polycythemia vera, 27 (18%) essential thrombocythemia, and 46 (32%) primary myelofibrosis. Red blood cell aggregates of NMMIIA were observed in 103 out of 147 patients (70%), co-occurring with reduced platelet alpha granule expression in 55% of cases. An additional 8% (12/147) of patients exhibited isolated alpha granule deficiency. In contrast, these alterations were uncommon among healthy controls: NMMIIA aggregates were detected in only 6% and alpha granule deficiency in 4%. Based on these findings, immunofluorescence microscopy demonstrated a sensitivity of 70.1% (95% CI: 62.7–77.5%) for identifying MPN through the presence of NMMIIA aggregates, and a specificity of 95.9% (95% CI: 88.2–98.7%) for detecting MPN through alpha granule deficiency. When both alterations co-occurred, specificity increased to 100%. These results confirm that the combination of NMMIIA aggregates in erythrocytes and diminished platelet alpha granule content represents a morphologic signature of MPN. Assessing these patterns by immunofluorescence microscopy can provide a useful, adjunctive diagnostic tool, supporting clinicians in identifying patients who warrant further evaluation for MPN—particularly in cases of unexplained thrombosis or subtle hematologic abnormalities.

ABSTRACT N. CO062

REDUCED-DOSE DOACS IN EXTENDED TREATMENT OF CANCER-ASSOCIATED THROMBOSIS (RED-CAT): INTERIM ANALYSIS FROM A MULTICENTER RETROSPECTIVE OBSERVATIONAL STUDY (COORDINATING CENTER DATA)

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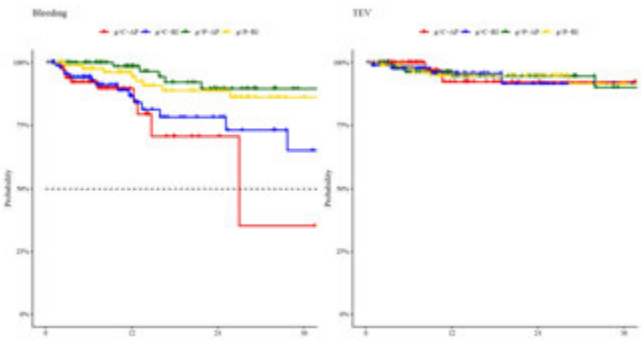
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Background and Aims. The risk of venous thromboembolism (VTE) in cancer patients is increased by 4-7-fold compared to the general population; guidelines recommend continuation of anticoagulation beyond 6 months in patients with VTE and active cancer. The API-CAT trial demonstrated the non-inferiority of apixaban 2.5 mg twice daily (BID) vs 5 mg BID in preventing VTE recurrence with a reduced risk of bleeding. The ReD-CAT study aims to confirm these findings in a real-world setting and extend them to rivaroxaban. The primary endpoint is VTE recurrence with reduced--dose DOACs versus full-dose; secondary endpoints include bleeding events and comparison between apixaban and rivaroxaban.

Methods. This is a multicenter retrospective study conducted across 6 Hemostasis Centers in Piedmont, Italy, with ethics committee approval. Data on 2233 patients treated with rivaroxaban or apixaban from March 2017 to February 2026 were analyzed, extracted from the AIFA registry of the coordinating center; among these, 569 cancer patients were identified, of whom 247 met the inclusion criteria (age ≥18 years, proximal VTE and/or non-subsegmental pulmonary embolism, ≥6 months of full-dose anticoagulation, active malignancy, no disease progression). Data were collected from electronic records. Patients were stratified into four cohorts by DOAC type and dose used for secondary prophylaxis: apixaban 5 mg BID (C-AP) or 2.5 mg BID (P-AP) and rivaroxaban 20/15 mg once daily (C-RI) or 10 mg once daily (P-RI). Group comparisons were performed using a descriptive-comparative approach; safety (bleeding) and efficacy (VTE recurrence) endpoints were assessed using Kaplan–Meier estimates of cumulative incidence over time.

Results. 334 exposures were analyzed: 67 C-AP, 93 C-RI, 87 P-AP, 87 P-RI. Median follow-up was 13 months (8.4 in C-AP; 10 in C-RI; 17.7 in P-AP; 23.1 in P-RI). Baseline characteristics (age, sex, weight, prothrombotic and bleeding risk factors, disease stage, and duration of anticoagulation prior to enrollment) were well balanced across groups. In terms of safety, cumulative bleeding incidence was higher in full-dose groups (C-AP: 10% at 12 months and 65% at 30–36 months; C-RI: 13% and 35%, respectively) compared to reduced-dose groups (P-AP: 1.5% at 12 months and 10% at 30–36 months; P-RI: 5.5% and 14%, respectively). Ten major bleeding events (out of 37 total) were recorded, 6 of which occurred in the C-AP group. Regarding efficacy, cumulative VTE recurrence was comparable across groups: at 12 months C-AP 8%, C-RI 4%, P-AP 4%, P-RI 5% and remained <10% at 36 months in all cohorts. *(Figure 1)*

Conclusions. This represents the first real-world head-to--head study comparing rivaroxaban and apixaban in cancer patients with VTE. Reduced-dose apixaban showed an improved safety profile compared to full-dose, consistent with the API-CAT trial, with comparable findings for rivaroxaban. Overall, while efficacy was comparable across all groups, safety emerged as the main clinical discriminator, with reduced-dose regimens providing the best balance between thrombotic prevention and bleeding risk over a follow-up of up to 36 months. Among full-dose regimens, a trend toward lower bleeding risk was observed with rivaroxaban compared to apixaban. Despite the retrospective design, the good balance of cohorts and consistency with existing literature support the reliability of these findings. Results will be further strengthened with data from the remaining centers.



ABSTRACT N. CO063

NEUTROPHIL-TO-LYMPHOCYTE RATIO AS A POTENTIAL PREDICTOR OF THROMBOSIS IN CLASSICAL HODGKIN LYMPHOMA: AN EXPLORATORY ANALYSIS

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Background and Aims. The neutrophil-to-lymphocyte ratio (NLR) is a simple inflammatory biomarker associated with prognosis and cancer-associated thrombosis (CAT). This study aimed to evaluate NLR as a predictor of CAT in patients with classic Hodgkin lymphoma (cHL)

Methods. We retrospectively evaluated adult patients (>18 years) diagnosed and treated for cHL between 2017 and 2020 at our institution and included in the "Thro-HL" multicenter study. Patients receiving anticoagulation for any indication were excluded. All suspected thrombotic events (TE) were confirmed by imaging. Thrombotic event-free survival (t-EFS) was defined as the time from diagnosis to the occurrence of thrombosis or last follow-up. Receiver operating characteristic (ROC) curve analysis was used to determine the optimal NLR cut-off for predicting TE. Associations between dichotomized NLR, established clinical risk scores (Khorana, Throly, Thro-HL), and TE were assessed using Pearson's Chi-square test. Time-to-event analyses were performed using Cox proportional hazards regression. A multivariable backward stepwise Cox model was used to assess the independent predictive value of NLR beyond clinical scores. Statistical significance was set at $p<0.05$.

Results. A total of 90 patients were included. Forty-eight patients (53.3%) were male and 42 (46.7%) female. Median age at diagnosis was 42 years (range 18-85). Disease stage was early favorable in 11.1%, early unfavorable in 38.9%, and advanced in 50%. Median NLR at diagnosis was 4 (range 0.4–21.2). Khorana score was intermediate in 82.2% and high in 15.6% (2.2% not assessable, NA). Throly score was low in 15.6%, intermediate in 62.2%, and high in 21.1% (1.1% NA). Thro-HL score was low in 44.4%, intermediate in 33.3%, and high in 21.1% (1.1% NA). Eighteen patients (20%) experienced venous TE (VTEs), no arterial events were reported. Median observed t-EFS was 22.2 months (range 0.1-49.2). Median follow up was 28.3 months (range 1.3-50.3). All patients were alive at last follow up. ROC analysis identified NLR >3.9 as the optimal cut-off for predicting TE (AUC 0.633; sensitivity 72.2%; specificity 54.3%). In univariate analysis, elevated NLR (p=0.045), Khorana score (p=0.046), Throly score (p=0.01), and Thro-HL score (p=0.008) were all significantly associated with TE. In univariate Cox regression, the Khorana high-risk category was associated with increased risk compared with intermediate risk (HR 2.99, 95% CI 1.03–8.62, p=0.043). The Throly score showed an overall significant association (p=0.015), with a non-significant trend for high-risk patients (HR 6.96, 95% CI 0.87–55.69, p=0.067). The Thro-HL score demonstrated a strong association with thrombosis (p=0.010), with significantly higher risk in the high-risk group (HR 7.33, 95% CI 1.94–27.67, p=0.003). NLR >3.9 was associated with a trend toward increased risk (HR 2.62, 95% CI 0.93–7.35, p=0.067). In multivariable analysis, only the Thro-HL score remained independently associated with thrombotic risk, while NLR and the other scores were not retained.

Conclusions. NLR showed a trend toward association with CAT in cHL, but it was not independently predictive after adjustment for established clinical risk models. Yet it should be assessed in larger cohorts to determine whether NLR may complement existing tools for thrombotic risk stratification in this population.

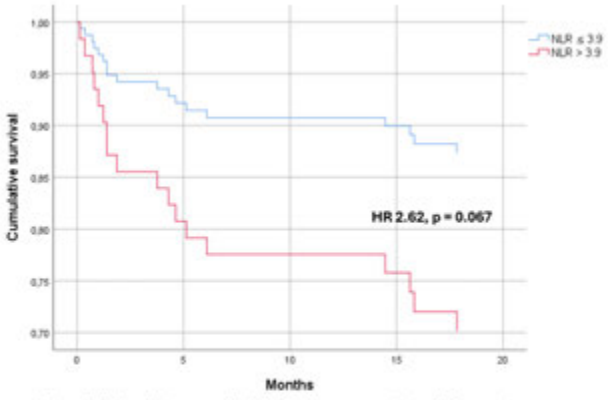


Figure 1. Kaplan–Meier curves for thrombotic events according to NLR categories (cut-off 3.9). Patients with NLR > 3.9 showed a higher incidence of thrombotic events compared to those with NLR ≤ 3.9. In univariable Cox regression analysis, NLR > 3.9 was associated with a non-significant trend toward increased thrombotic risk (HR 2.62, 95% CI 0.93–7.35, p = 0.067).

ABSTRACT N. CO064

THROMBOTIC AND BLEEDING EVENTS IN PATIENTS WITH VASCULAR INVASION BY ADVANCED HEPATOCELLULAR CARCINOMA: A SYSTEMATIC REVIEW

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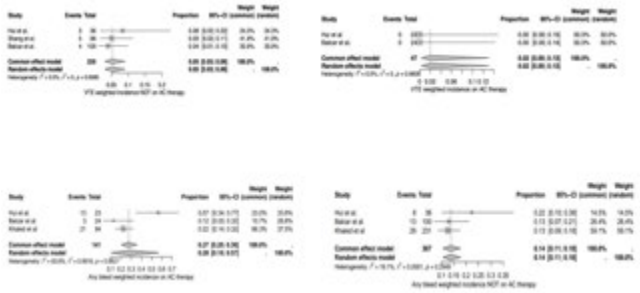
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Background. The role of anticoagulation in advanced hepatocellular carcinoma (HCC) with macrovascular invasion remains uncertain. While anticoagulation may be associated with a lower incidence of venous thromboembolism (VTE), it may also increase bleeding risk, particularly in patients with portal hypertension.

Methods. We conducted a systematic review of studies reporting thrombotic and bleeding outcomes in anticoagulated (AC) versus non-anticoagulated (NOT AC) adults patients with advanced HCC and vascular invasion. Pooled weighted incidences were calculated, and risk of bias was assessed with the Newcastle–Ottawa Scale.

Results. Four retrospective cohort studies (n=608; 142 AC, 466 NOT AC) were included. VTE incidence was low overall and numerically lower in AC patients (2.0%) compared with NOT AC patients (5.3%). In contrast, bleeding events were more frequent in the AC group (28.1% vs 13.8%), with higher rates of both major (MB) and clinically relevant non-major bleeding (CRNMB), particularly in the largest cohort. Mortality was high across studies and primarily driven by tumor progression. No pooled effect estimates were calculated due to sparse data and heterogeneity.

Conclusions. Available evidence indicates a numerically lower VTE incidence was observed in anticoagulated patients, alongside a higher incidence of bleeding events in patients with advanced HCC and vascular invasion. Given the limited and heterogeneous evidence, the net clinical benefit remains uncertain. Prospective studies are urgently needed to better define patient selection in this high-risk population.





THROMBOTIC RISK IS NOT UNIFORM ACROSS APHERESIS SETTINGS: INSIGHTS FROM CAR-T LYMPHOCYTAPHERESIS AND AUTOLOGOUS STEM CELL COLLECTION

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Background. Pericatheter thrombosis (PCT) is a recognised complication of large-bore venous catheters used for cell collection. An incidence of approximately 1.8% has been reported for Mahurkar catheters in peripheral blood stem cell collection. Data in patients undergoing lymphocytapheresis for CAR-T therapy are limited. This study evaluates PCT in this setting and compares thrombotic events with those observed in autologous stem cell collection.

Methods. A retrospective single-centre analysis included 62 patients undergoing CAR-T lymphocytapheresis with a Mahurkar catheter (September 2019–October 2025). During the same period, 127 patients underwent autologous stem cell collection; 62 required a Mahurkar catheter, and a subset of 21 with comparable diseases was analysed. Within the CAR-T cohort, analyses compared (1) PCT vs non-PCT and (2) any thrombosis vs no thrombosis. A third analysis compared CAR-T and autologous cohorts. Continuous variables were analysed with Student's t-test and categorical variables with chi-square or Fisher's exact test.

Results. In the CAR-T cohort, PCT occurred in 5/62 patients (8%) and 13/62 (21%) developed overall thrombosis. No variable was significantly associated with PCT, although platelet count showed a borderline trend ($p = 0.061$). Procedural difficulty was more frequent in PCT cases (66% vs 18%), without statistical significance. In the autologous cohort, no PCT was observed (0/21), while 2 patients (9.5%) developed thrombosis at non-catheter sites. Compared to the autologous cohort, CAR-T patients showed lower platelet count ($p < 0.0001$), haemoglobin ($p = 0.0276$), and differences in white blood cell count ($p = 0.045$). Disease status also differed significantly, with all autologous patients in partial or complete response ($p < 0.001$).

Conclusions. PCT was more frequent in CAR-T lymphocytapheresis than in autologous stem cell collection. This difference appears to reflect underlying patient characteristics rather than procedural factors. CAR-T patients represent a distinct population with more advanced disease and altered haematological profiles. Thrombotic risk should not be considered uniform across apheresis settings, supporting tailored risk assessment and preventive strategies.

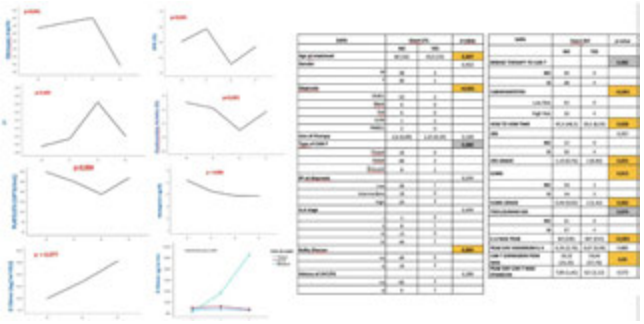
ABSTRACT N. CO066

COAGULOPATHY IN CAR T CELL-TREATED PATIENTS WITH LYMPHOPROLIFERATIVE DISORDERS: A RETROSPECTIVE, SINGLE-CENTER OBSERVATIONAL STUDY

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CAR-T therapy improves outcomes in relapsed/refractory lymphoid malignancies but can cause coagulopathy. Massive cytokine release leads to endothelial injury, platelet activation, excess thrombin, and reduced fibrinolysis, inducing an initial hypercoagulable state. Clinically, it causes bleeding, thrombosis, and sometimes DIC (Disseminated Intravascular Coagulopathy), with frequent laboratory abnormalities. Aim was to evaluate, in a retrospective single-center cohort of patients with lymphoproliferative disorders treated with CAR-T cells, the incidence of post infusion thrombotic and hemorrhagic events (within 60 days of discharge) and changes in major coagulation parameters. Additionally, we analyzed cases of overt DIC and identified predictive risk factors using univariate analysis. For each patient treated with CAR T therapy, laboratory, epidemiological, and clinical data were collected. Laboratory data included coagulation parameters (prothrombin activity, PT, aPTT, fibrinogen, D-dimer, ATIII, Hb, and PLT count), whose temporal variations were assessed at four timepoints: pre- and postlymphodepletion (t0, t1), acute phase (t2) and subacute phase (t3); the parameters were stratified for each type of CAR-T product used. Epidemiological variables included: age and sex. Clinical data included: diagnosis, line of therapy, type of CAR-T, International Prognostic Index (IPI) at diagnosis, Ann Arbor (A.A.) stage, bulky disease, history of DVT/PE, bridging therapy, CAR-HEMATOTOX score, vein-to-vein time, occurrence and grade of CRS and ICANS, use of tocilizumab, IL-6 levels, and CART cell expansion kinetics. Statistical analysis used descriptive statistics, repeated-measures ANOVA, and SPSS ($p < 0.05$). Between November 2020 and August 2025, a total of 72 patients with lymphoproliferative disorders treated with CAR-T therapy were included. Severe hemorrhagic events were rare (1 out of 72 pt, 1.3%), whereas thrombotic events occurred in 4.1% of cases (3 out of 72 pt). Analysis of coagulation parameters showed significant temporal variations in PT, fibrinogen, prothrombin activity, ATIII, PLT, and Hb while aPTT did not demonstrate significant changes. D-dimer was significant only in patients treated with brexucabtagene autoleucel. Overt DIC was observed in 5.5% of patients (4 out of 72 pt), with additional subclinical cases (3 out of 72 pt, 4.1%). The Overall incidence of coagulation abnormalities was 9.6%. Mortality rate associated with overt DIC was 1 out of 4 pt (25%). Factors associated with overt-DIC included age, diagnosis, bulky disease, CAR-HEMATOTOX score, vein-tovein time, severity of CRS/ICANS, IL-6 serum levels, and CAR-T cell expansion ($p<0.05$). No significant association with DIC was observed for IPI, A.A. stage, presence of CRS, or prior thrombotic history. Bridging therapy and tocilizumab use, although not significantly associated, showed a trend toward potential significance. Thrombotic events often occur after discharge, indicating a need for prolonged anticoagulant prophylaxis. Hemostasis shows a biphasic pattern: early inflammation with high fibrinogen and PT changes, followed by consumption with low fibrinogen and ATIII. Overt DIC (5.5%) carries high mortality. Risk factors include young age, Brexu-cel use, bulky disease, high CAR-HEMATOTOX score, short vein--to-vein time, severe CRS/ICANS, high IL-6 serum level, and strong CAR-T expansion. Future approaches should target inflammation and endothelial protection.



ABSTRACT N. CO067

ELUCIDATING THE EVIL RELATIONSHIP OF METABOLIC DYSFUNCTION–ASSOCIATED FATTY LIVER DISEASE WITH CARDIOVASCULAR COMORBIDITIES: THE COMPLEX INTERPLAY AMONG HYPERCOAGULABILITY, INFLAMMATION AND LIVER FIBROSIS

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Background and aims. Metabolic dysfunction–associated steatotic liver disease (MASLD) is highly prevalent and is associated with increased cardiovascular (CV) morbidity and mortality. We aimed to evaluate the relationship between liver fibrosis and early CV damage, hypercoagulability, and systemic inflammation in a cohort of MASLD patients.

Methods. Consecutive patients with MASLD were enrolled and stratified according to liver fibrosis severity assessed by transient elastography. The primary endpoint was the presence of a prothrombotic/hemostatic imbalance in patients with advanced fibrosis, assessed through an extensive hemostatic work-up including viscoelastic testing, procoagulant factors, natural anticoagulants (protein C/protein S/antithrombin), fibrinolysis markers (plasminogen, PAI-1), and platelet function testing in whole blood and platelet-rich plasma. Secondary endpoints included subclinical vascular damage assessed by ankle–brachial index and vascular ultrasound (carotid IMT/plaque and aortic diameter), as well as systemic inflammatory markers. All multivariable models were adjusted for age, sex, BMI, hypertension and diabetes.

Results. Overall, 615 MASLD patients were included (median age 62 [52–69] years; median BMI 29 [26–32] kg/m^2; 62.1% male); 49 (7.9%) had advanced fibrosis (F3–F4) on transient elastography (538 F0–F2; 28 missing) (Table 1). Advanced fibrosis was associated with higher systolic blood pressure independent of hypertension status (p=0.019) and with higher LDL-C levels (adjusted p=0.0004). From a hemostatic perspective, advanced fibrosis was associated with a significant shift toward a prothrombotic/rebalanced state. Specifically, platelet count was reduced (157 vs 183×10^9/L, p<0.001), together with lower levels of natural anticoagulants, including protein C activity (119% vs 132%, p<0.001), protein C antigen (105% vs 118%, p=0.002), and antithrombin (92% vs 102%, p<0.001). Conversely, procoagulant factors were increased, with higher fibrinogen (398 vs 357 mg/dL, p=0.005) and factor VIII activity (155% vs 139%, p=0.02) (Table 1). Whole blood ROTEM parameters and platelet function testing did not show major differences across fibrosis stages. Despite these hemostatic alterations, fibrosis severity was not independently associated with subclinical atherosclerosis. The prevalence of atherosclerotic plaques was higher in advanced fibrosis (48.8% vs 35.4%), but this association was not significant after adjustment (OR 0.99, 95% CI 0.80–1.22; p=0.915), with age, sex, hypertension, and diabetes remaining the main predictors.

Conclusions. Advanced fibrosis in MASLD is associated with a significant hemostatic shift characterized by reduced natural anticoagulants and increased procoagulant factors, suggesting early progression toward a rebalanced but potentially prothrombotic state. These alterations occur independently of changes in whole-blood coagulation assays. These alterations occur independently of changes in whole-blood coagulation assays and are not directly linked to subclinical atherosclerosis, which appears to be mainly driven by traditional CV risk factors.

Table 1. Key clinical, vascular and hemostatic characteristics of MASLD patients according to fibrosis severity

Variable	F0–F2	F3–F4	p-value
Demographics / cardiometabolic profile			
N	538	49	
Age, years (median [IQR])	61 [51-68]	65 [54-69]	0.04
Male sex, n (%)	333 (61.8)	33 (67.3)	ns
BMI, kg/m^2 (median [IQR])	29 [26-32]	33 [29-35]	<0.001
Diabetes mellitus, n (%)	145 (26.9)	26 (53)	<0.001
Arterial hypertension, n (%)	296 (55)	38 (77.5)	0.007
Systolic blood pressure, mmHg (median [IQR])	130 [120-140]	135 [128-150]	0.03
LDL-C (median [IQR])	97 [62-118]	113 [79-136]	0.04
Subclinical vascular damage			
Any atherosclerotic plaque (yes), n (%)	187 (35.4)	23 (48.8)	0.08
Hemostatic profile			
Platelet count, ×10^9/L (median [IQR])	183 [155-212]	157 [126-177]	<0.001
Fibrinogen, mg/dL (median [IQR])	357 [311-399]	398 [353-453]	0.005
Factor VIII activity, % (median [IQR])	139 [110-173]	155 [124-193]	0.02
Protein C activity, % (median [IQR])	132 [117-150]	119 [103-138]	<0.001
Protein C antigen, % (median [IQR])	118 [102-136]	105 [87-129]	0.002
Antithrombin, % (median [IQR])	102 [94-111]	92 [87-98]	<0.001
PAI-1 antigen (median [IQR])	29.8 [20.5-42.9]	34 [21.8-47.8]	ns
ROTEM			
EXTEM-MCF, mm (median [IQR])	65 [62-68]	62 [59-67]	ns
FIBTEM-MCF, mm (median [IQR])	16 [14-20]	17 [15-20]	ns
Inflammatory markers			
hs-CRP (median [IQR])	1.17 [0.61-2.38]	1.93 [0.73-4.24]	ns
CRP (median [IQR])	2.3 [0.81-4.8]	5.6 [1.7-53]	ns

BMI, body mass index; CRP, C-reactive protein; hs-CRP, high-sensitivity C-reactive protein; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol; MCF, maximum clot firmness; ns, not significant; PAI-1, plasminogen activator inhibitor-1; ROTEM, rotational thromboelastometry

ABSTRACT N. CO068

FACTORS AFFECTING SPONTANEOUS PLATELET AGGREGATION IN HEALTHY SUBJECTS AND PATIENTS WITH STABLE CORONARY ARTERY DISEASE

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[1]Laboratorio di emostasi e trombosi, Dipartimento di Scienze della Salute, Università degli Studi di Milano, Divisione di Medicina Generale II, ASST Santi Paolo e Carlo, Italy; [2]National Medical Research Center of Cardiology, Ministry of Health of the Russian Federation, Moscow, Russia; [3]Fondazione Arianna Anticoagulazione, Bologna, Italy

Background and Aims. Platelets of some subjects aggregate in light transmission aggregometer (LTA) in absence of exogenous agonists ("spontaneous platelet aggregation", SPA), reflecting "platelet hyper-reactivity". Two prospective studies showed that SPA predicts the risk of cardiovascular events in healthy subjects and recurrent coronary events and mortality patients with myocardial infarction. However, its clinical use has been limited by concerns that it represents an *in vitro* artifact, especially in consideration of the fact that it is detectable in platelet-rich plasma (PRP) anticoagulated in citrate but not in hirudin. We aimed to compare SPA in patients with stable coronary artery disease (CAD, cases) and control subjects, using different anticoagulants and aggregometers: LTA and the more sensitive Optical Density Fluctuations Aggregometer (ODFA), which can detect small aggregates of 2-3 platelets.

Methods. SPA was measured in citrate-PRP and hirudin-PRP from age- and sex-matched 139 controls and 102 cases, using both LTA and ODFA. Citrate-PRP was also tested after aspirin (100 µM) addition to inhibit potential thromboxane-A2 synthesis in a low-Ca^{2+} medium. Reproducibility of SPA was assessed in a second session, after at least two weeks, in a subset of subjects. All procedures adhered to international recommendations to minimize in vitro platelet activation.

Results. Citrate-PRP. SPA was higher in cases than controls with both LTA and ODFA, in presence and absence of added aspirin (Fig. 1). Using tertile stratification of data obtained in controls, the frequency of cases was lower in the first tertile and higher in the third tertile, compared to controls: LTA, 33% controls *vs* 21% cases in first tertile, X^2=4.58, P=0.032, 33% controls *vs* 45% cases in third tertile, X^2=3.59, P=0.058; ODFA 33% controls *vs* 22% cases in first tertile, X^2=3.52, P= 0.061, 33% controls *vs* 50%, cases in third tertile, X^2=6.72, P=0.009. The SPA phenotype was reproducible in 73% of subjects in the first tertile and 88% in the third tertile (LTA) and 58% in the first tertile and 83% in the third tertile (ODFA). Hirudin-PRP. A very low extent of SPA was detected by LTA only in 4 subjects in each group, while it was measurable in most subjects by ODFA, although its extent was much lower than in citrate-PRP (Fig. 1). At variance with citrate-PRP, there was no difference in the extent of SPA between cases and controls, suggesting that citrate-sensitive variables account for the observed difference between cases and controls. It is known that platelet aggregation in citrate-PRP is inversely related to hematocrit levels. However, hematocrit was not responsible for the observed difference in SPA, because it was similar in controls and cases (39.3% *vs* 40,2%, P=0.548). We found that agonists that induce platelet aggregation by binding to Gi-coupled receptors (ADP in presence of P2Y1 antagonist, epinephrine and sulprostone, a PGE2 analogue) induced platelet aggregation (LTA) in citrate-PRP, but not in hirudin-PRP, thus perfectly mimicking the results obtained with SPA and raising the hypothesis that a hyper-functional platelet Gi pathway regulates SPA in CAD patients.

Conclusions. SPA is more frequent and pronounced in CAD patients than in controls when assessed in citrate-PRP, but not in hirudin-PRP. Citrate likely unmasks platelet Gi signalling that is responsible for SPA and may be hyper-functional in CAD patients.

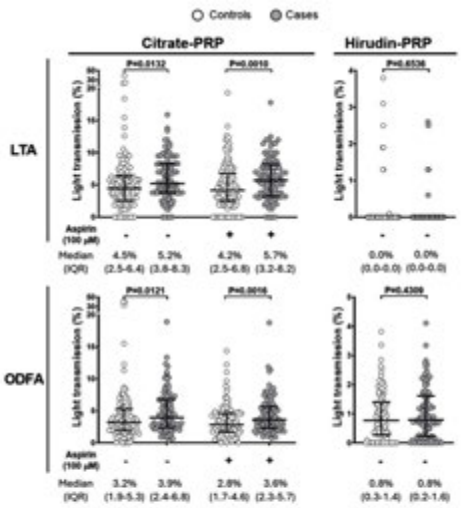


Figure 1. Comparison of SPA measurements by LTA and ODFA in citrate-PRP and hirudin-PRP
Citrate-PRP was analysed in absence (139 controls and 102 cases for LTA; 137 controls and 101 cases for ODFA) and presence of aspirin (100 µM) (132 controls and 102 cases for LTA; 129 controls and 100 cases for ODFA). Hirudin-PRP (128 controls and 97 cases for LTA; 123 controls and 98 cases for ODFA) was analysed without aspirin only. In all experiments, PRP was stirred at 1,000 rpm at 37°C for 6 minutes and analysed by LTA or ODFA without addition of exogenous platelet agonists. Changes in light transmission were interpreted as due to SPA. Data are presented as medians with interquartile ranges (IQR). Statistical comparisons were performed using the Wilcoxon test.

ABSTRACT N. CO069

POLYSTYRENE NANOPLASTICS PRIME PLATELETS TO DRIVE PRO-INFLAMMATORY AND PRO-FIBROTIC ACTIVATION OF CARDIAC FIBROBLASTS

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Background and Aims. Nanoplastics (NPs) are emerging environmental contaminants with potential cardiovascular effects, but their impact on platelet activation and cardiac remodeling remains poorly defined. Atrial fibrosis is a key mechanism underlying atrial fibrillation (AF), driven by fibroblast transition to a pro-fibrotic phenotype. Platelets contribute to thrombo-inflammation and may infiltrate atrial tissue, modulating fibroblast phenotype. We investigated whether polystyrene NPs (PS-NPs, 50 nm) induce platelet activation in vitro and in vivo and enhance platelet-fibroblast crosstalk, promoting pro-inflammatory and pro-fibrotic signaling.

Methods. PS-NPs were administered intravenously in C57BL/6 mice, and serum thromboxane B_2 (TXB_2) was measured after 5 days as an index of platelet activation. Human isolated platelets were incubated with 50 nm PS-NPs (20 or 200 µg/mL) for 1 and 18 h at 37 °C under rotational conditions and assessed for TXB_2 generation and P-selectin membrane translocation. Washed human platelets were exposed to fluorescent Dragon Green-labelled particles, and platelet-derived extracellular vesicles (EVs) release and NPs incorporation into EVs were evaluated. Human atrial fibroblasts (HCF) were incubated for 24 h with platelet releasate obtained following platelet-NP interaction to assess effects on cytokine production and Snail expression.

Results. Single-dose i.v PS-NP administration (20 or 200 µg/mL) in C57BL/6 mice increased TXB_2 generation after 5 days (2.15- and 2.21-fold vs. baseline, $p<0.01$). Consistently, human platelets exposed to PS-NPs (20 or 200 µg/mL) for 1 and18h, showed a concentration-dependent significant increase of TXB_2 levels, even in the absence of platelet agonists. PS-NP exposure also significantly enhanced P-selectin surface expression at the highest concentration ($p < 0.05$). Exposure to PS-NPs did not significantly affect platelet-derived EVs release at 1 h or 18 h. However, the percentage of NP-positive EVs increased from ~45% to ~80% (20 vs. 200 µg/mL; $p < 0.01$), suggesting interaction and/or incorporation into EVs. To investigate functional consequences of platelet activation induced by PS-NPs, HCF cells were treated with platelet releasate collected after platelet incubation with PS-NP. After 24h, releasate from PS-NP unexposed platelets significantly upregulated the expression of inflammatory and remodeling markers, including interleukin (IL)-1α, IL-6, and IL-1β, as well as the fibroblast activation marker Snail. Notably, exposure of HCFs to releasate from PS-NP–treated platelets further enhanced the expression of inflammatory cytokines and Snail, with the strongest induction observed with releasate from platelets exposed to 200 µg/mL PS-NPs, indicating an additional effect of PS-NPs on platelet activation that translates into amplified fibroblast responses.

Conclusions. PS-NPs promote platelet activation and enhance platelet–fibroblast crosstalk, amplifying thrombo-inflammatory and pro-remodeling signaling. Although EVs release was unchanged, the increase in NP-positive EVs suggests their incorporation into EVs and a potential role in their systemic distribution. By priming platelets toward a more reactive phenotype, PS-NPs may contribute to atrial remodeling, supporting their role as an underrecognized modulator of cardiovascular pathophysiology.

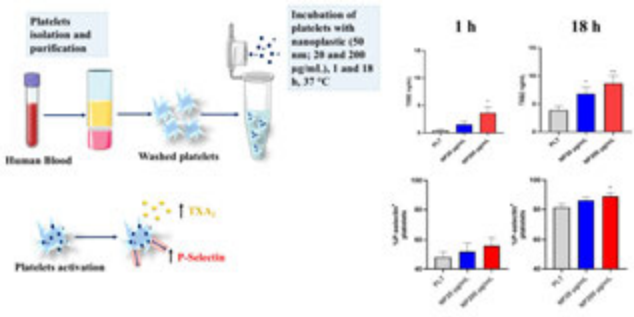


Figure 1 In the absence of platelet agonists, exposure to PS-NPs (50 nm; 20–200 µg/mL) induced a time and concentration-dependent increase in TXB_2 generation and P-selectin exposure in washed human platelets at 1 h and 18 h. * $P < 0.05$ and ** $P < 0.01$ for NP exposed platelets vs. control PLT.



PLASMIN GENERATION AND ITS INTERPLAY WITH COAGULATION AND FIBRINOLYSIS IN ATRIAL FIBRILLATION: IMPACT OF ANTICOAGULANT THERAPY

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Background and Aims. Atrial fibrillation (AF) is one of the most common cardiac arrhythmias in clinical practice. Evidence shows an impaired balance between clot formation and fibrinolysis in AF, characterized by a prothrombotic and hypofibrinolytic state with dysregulated plasmin generation. This study aimed to evaluate plasmin generation (PG) and its relationships with markers of fibrinolysis (clot lysis time, CLT) and coagulation (thrombin generation, TG) in patients with AF.

Methods. The STRAT-AF study, an observational prospective study, enrolled 180 AF patients referred for anticoagulant management. A total of 159 with complete laboratory data were included in the final analysis. Among them, 31.5% were treated with vitamin K antagonists (VKA) and 68.5% with direct oral anticoagulants (DOAC). Citrated whole blood was centrifuged (4000 x g, 15 min), with an additional centrifugation step for TG assays; PG and TG were measured using a fluorometer (Fluoroscan Ascent). Parameters included lag time, time to peak (ttPeak), peak, and endogenous plasmin or thrombin potential (EPP/ETP). CLT was assessed in the presence of tissue factor and tPA, monitoring absorbance at 405 nm.

Results. Non-parametric analysis showed a significant positive association between PG lag time and CLT (rho= 0.163; p = 0.043). Conversely, significant negative correlations were found betweenand both EPP (rho= −0.207; p = 0.010) and PG peak (rho= −0.178; p = 0.027). Significant correlations were also observed between PG and TG: PG lag time correlated with TG lag time (rho = 0.300; p < 0.001) and TG ttPeak (rho = 0.254; p = 0.001); PG ttPeak correlated with TG lag time (rho = 0.229; p = 0.004); and PG and TG ttPeak values were also associated (rho = 0.195; p = 0.014). When stratified by anticoagulant therapy, DOAC-treated patients showed longer PG lag time [9.15 (4.30–32.57) vs 8.15 (3.3–14.52); p = 0.171] and significantly longer PG ttPeak [18.85 (1.07–37.67) vs 12.95 (6.52–19.65); p = 0.008] compared with VKA-treated patients. Among DOACs, dabigatran was associated with significantly higher lag time, peak, and ttPeak values compared with other DOACs. At logistic regression analysis, after the adjustment for age, sex, CHA2DS2-VASc and type of anticoagulant therapy, reduced plasmin generation, as reflected by lower ETP-PG and peak-PG, was associated with the occurrence of non-lacunar infarction at 1-year follow-up [OR (95% CI): 0.17 (0.05-0.61p=0.007].

Conclusions. These findings highlight a close interplay between fibrinolysis and coagulation in AF. Delayed plasmin generation is associated with a hypofibrinolytic state, while increased plasmin activity promotes faster clot lysis. Anticoagulant therapy influences fibrinolytic profiles, with DOACs -particularly dabigatran-associated with delayed plasmin activation compared with VKAs. Overall, both anticoagulant type and fibrinolytic balance contribute to the hemostatic profile in AF and may favor the formation of more stable, lysis-resistant thrombi, as suggested by the inverse association between non-lacunar infarcts and plasmin generation.

ABSTRACT N. CO071

ATRIAL FIBRILLATION, CEREBRAL SMALL VESSEL DISEASE AND GENDER MEDICINE: FOCUS ON BIOMARKERS AND NEUROIMAGING

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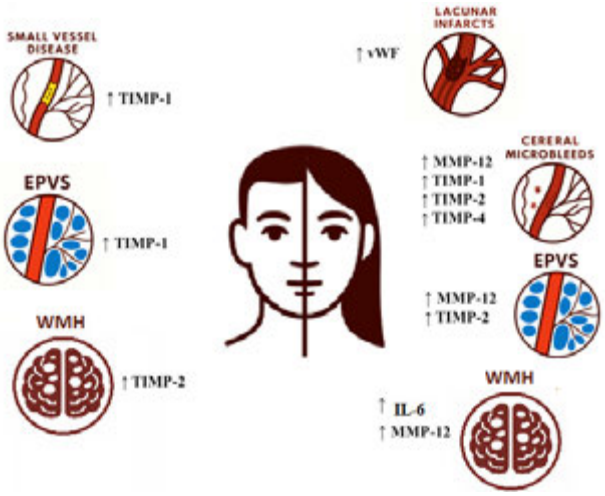
Background. Atrial fibrillation (AF) is the most common supraventricular arrythmia and one of the most commonly encountered heart conditions in clinical practice. Emerging evidence suggests a significant role of inflammation, endothelial disfunction and extracellular matrix (ECM) remodeling in the pathogenesis of AF. Population studies have also suggested an association between AF and cerebral small vessel disease (CSVD) with growing evidence indicating that the burden of certain markers of CSVD is greater in women. However, the association between female sex and CSVD remains poorly understood.

Objectives. The main outcome of the study was thus to investigate the role of gender in the association between circulating biomarkers and the progression of CSVD in AF patients undergoing oral anticoagulant therapy.

Methods. The Strat-AF study is an observational, prospective, single-center, hospital-based study enrolling elderly patients with AF. Results refer to 170 patients (60 women and 110 men). Recruited patients are evaluated by means of a comprehensive protocol, with clinical, cerebral magnetic resonance imaging (MRI) and circulating biomarkers assessment.

Results. At multivariate logistic regression analysis adjusted for age, CHA2DS2-VASc HAS-BLED and type of anticoagulant, independent predictors were: high levels of vWF for the presence of lacunar infarcts in women [OR 95% CI 3,24 (1,23-8,55), p=0.018]; high levels of TIMP-1 for having at least one sign of SVD at the SVD score in men [OR 95% CI 7,25 (2.18-24.15), p=0.001]; high levels of MMP-12, TIMP-1, TIMP-2 and TIMP-4 for the presence of CMB in women [OR 95% CI 7,76 (1,60-37,69), p=0,021; OR 95% CI 1,90 (1,02-3,52), p=0,042; OR 95% CI 2,46 (1,27 4,80), p=0,008 e OR 95% CI 2,36 (1,12-4,95), p=0,023, rispectively]; high levels of TIMP-1 for the presence of bgEPVS in men [OR 95% CI 2,20 (1,11-4,38), p=0,025] and high levels of MMP-12 and TIMP-2 for the presence of bgEPVS in women [OR 95% CI 2,57 (1,22-5,93), p=0,027 and OR 95% CI 2,15 (1,03-4,53), p=0,043, respectively]; elevated IL-6 and MMP-2, levels for the presence the presence of white matter hyperintensities in women [OR 10.65 (1.31–86.67), p = 0.027; OR 3.36 (1.23–9.15), p = 0.018, respectively]; elevated TIMP-1 levels for the presence the presence of white matter hyperintensities in men [OR 2.10 (1.08–4.08), p = 0.030].

Conclusions. These results from the Strat-AF study demonstrated that a complete biohumoral and instrumental assessment can jointly identify female patients with AF at higher risk of SVD. These findings pave the way for the implementation of clinical protocols incorporating brain MRI and circulating biomarkers as potential innovative tools for an increasingly refined – and sex-specific – stratification of cardiovascular risk in AF patients undergoing oral anticoagulant therapy.





PERSISTENT ENDOTHELIAL THROMBOINFLAMMATORY PHENOTYPE IN PATENT FORAMEN OVALE: EVIDENCE FROM PATIENT-DERIVED ENDOTHELIAL COLONY-FORMING CELLS

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Background and Aims. Patent foramen ovale (PFO) is increasingly recognized as a condition associated with thromboinflammatory milieu, particularly in patients with migraine with aura. Beyond platelet activation, endothelial dysfunction may represent a contributor to this prothrombotic state. Endothelial colony-forming cells (ECFCs), as patient-derived endothelial progenitors retaining donor-specific characteristics, provide a valuable model to investigate endothelial thrombogenicity and vascular adaptation in PFO. We aimed to characterize the endothelial procoagulant phenotype, response to physiological shear stress and transcriptional changes associated with PFO closure in ECFCs from PFO patients.

Methods. ECFCs were isolated from peripheral blood of 35 PFO patients before closure (T0) and 6 months after closure (T1), and from 25 healthy subjects (HS). Intracellular Tissue Factor (TF) and Tissue Factor Pathway Inhibitor (TFPI) expression were evaluated by flow cytometry and ELISA. Functional procoagulant activity was assessed by CAT. To investigate endothelial mechanoadaptation, ECFCs were exposed to high laminar shear stress (HLSS), and the expression of genes involved in endothelial homeostasis, vascular tone, inflammation, and coagulation (e.g. KLF2, KLF4, NOS3, EDN1, HMGB1, and TF) was quantified. RNA sequencing was performed to compare endothelial profiles before and after PFO closure.

Results. ECFCs derived from PFO patients displayed a clear procoagulant phenotype. TF expression was significantly increased at baseline compared with HS and decreased after PFO closure, supporting a direct association between PFO and endothelial prothrombotic activation. Consistently, the TF/TFPI balance was shifted toward a procoagulant state in patients, with an increased TF/TFPI ratio and enhanced thrombin-generating capacity. A greater proportion of ECFC lines from PFO patients generated measurable thrombin compared with HS, and this functional procoagulant tendency persisted after closure, suggesting only partial restoration of endothelial hemostatic balance. Under HLSS, healthy ECFCs activated a physiological mechanoprotective program characterized by induction of flow-responsive genes. In contrast, ECFCs from PFO patients showed an impaired adaptive response, with reduced induction of shear-responsive protective mediators, particularly KLF4, and persistence of pro-inflammatory and procoagulant signals, including TF and HMGB1. Transcriptomic analysis revealed that PFO closure induced partial endothelial reprogramming, with downregulation of pathways associated with coagulation, platelet interaction, and inflammatory activation, together with upregulation of pathways involved in vascular repair, tissue remodeling, and immune regulation.

Conclusions. PFO is associated with a distinct endothelial thromboinflammatory phenotype characterized by enhanced TF-driven procoagulant activity and impaired adaptation to physiological shear stress. PFO closure partially restores endothelial homeostasis, but residual prothrombotic features persist, suggesting that endothelial dysfunction may represent a component of the thromboinflammatory burden associated with PFO. These findings identify the endothelium as an active contributor to PFO-associated thrombogenicity and a potential target for biological stratification and therapeutic intervention. Funding: M6C2I2.1_PNRR_NEXT_GENERATION_EU, PNRR-MAD-2022-12376277, CUP-B43C22001110008 Clinical trial: NCT06046508



THROMBIN GENERATION PROFILE IN ELDERLY PATIENTS WITH ATRIAL FIBRILLATION: IMPACT OF ORAL ANTICOAGULANT TYPE

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Background and Aims. Atrial fibrillation (AF) is the most common cardiac arrhythmia and is associated with an increased risk of thromboembolic events. Oral anticoagulants, including direct oral anticoagulants (DOACs) and vitamin K antagonists (VKAs), represent the cornerstone of treatment, with DOACs largely replacing VKAs due to a more favorable safety profile. Previous data from our group suggest differential effects of these therapies on hemostatic parameters. This study aimed to evaluate thrombin generation (TG) and fibrinolytic markers in AF patients, according to the type of oral anticoagulant, to better characterize their impact on the hemostatic profile.

Methods. STRAT-AF is a prospective, observational, single-center study enrolling patients aged >65 years with AF on oral anticoagulation. A total of 170 patients were included. Thrombin generation was assessed on platelet-poor plasma using calibrated automated thrombography (CAT) in the absence (TM−) and presence (TM+) of thrombomodulin. TG parameters included lag time, time to peak, peak thrombin, endogenous thrombin potential (ETP), and ETP ratio (ETP TM+/ETP TM−). Fibrinolytic markers included plasminogen activator inhibitor-1 (PAI-1) and clot lysis time (CLT).

Results. Mean age was 77.7±6.8 years; 34.7% were female and 69.4% were on DOACs. Patients on dabigatran showed significantly prolonged lag time compared with factor Xa inhibitors and VKAs [19.7 vs 8.3 vs 8.3; p=0.008], and longer time to peak compared with VKAs [31.5 vs 13.1; p=0.012]. ETP ratio was higher in VKAs compared with both DOAC groups (p=0.004). CLT was significantly prolonged in patients on factor Xa inhibitors compared with VKAs and dabigatran [59.13 (45.35-75.58) vs 51.33 (41.60-58.96) vs 48.86 (42.66-59.31); p=0.026]. At multivariate analysis, age (OR 1.05; 95% CI 1.00-1.11; p=0.038), dabigatran therapy (OR 3.23; 95% CI 1.11-9.38; p=0.031) and statin use (OR 2.19; 95% CI 1.03-4.65; p=0.041) were identified as independent predictors for a prolonged lag time. Both factor Xa inhibitors (OR 0.388; 95% CI 0.183-0.820; p=0.013) and dabigatran (OR 0.332; 95% CI 0.134-0.820; p=0.017) were associated with lower ETP ratios compared to VKAs. Increasing age was inversely associated with high ETP ratio (OR 0.937; 95% CI 0.891–0.986; p=0.013).

Conclusions. These findings provide evidence of the differential effects of DOACs and VKAs on the hemostatic profile of elderly AF patients. Overall, dabigatran causes prolonged TG kinetics, which is consistent with its mechanism as a direct thrombin inhibitor. Incorporating these parameters into existing risk assessment models could represent a valuable tool for a comprehensive characterization of the hemostatic profile in AF patients, potentially supporting more targeted therapeutic strategies.



WHOLE-BLOOD COAGULATION AND PLATELET DYNAMICS IDENTIFY DIFFERENTIAL PROTHROMBOTIC STATES IN RHEUMATOID ARTHRITIS PATIENTS TREATED WITH JAK OR TNFα INHIBITORS

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Background and Aims. Rheumatoid arthritis (RA) is a chronic inflammatory disorder characterized not only by joint involvement but also by systemic manifestations, including a prothrombotic state driven by persistent inflammation. This condition is associated with increased activation of the coagulation cascade, impaired fibrinolysis, and heightened platelet activation, ultimately contributing to an elevated risk of venous thromboembolism. In recent years, post hoc analyses of randomized clinical trials and real-world safety data have raised concerns about a potentially different thrombotic risk profile between patients treated with Janus kinase inhibitors (JAKi) and those receiving tumor necrosis factor inhibitors (TNFi). Nevertheless, the precise effects of these therapeutic strategies on global coagulation dynamics in whole blood, as well as on platelet function, remain incompletely understood and warrant further investigation. The aim of this study was to compare viscoelastic coagulation properties and platelet reactivity among RA patients treated with JAK inhibitors or TNF inhibitors, and to evaluate differences relative to healthy control subjects (HC), in order to better characterize treatment-related prothrombotic profiles.

Methods. This was a single-centre observational study including RA patients receiving stable treatment with either JAKi or TNFi for at least three months. All participants underwent assessment of coagulation and platelet function using whole-blood rotational thromboelastometry (ROTEM®) and impedance aggregometry (MULTIPLATE®). The primary endpoints were the evaluation of: (a) whole-blood thrombogenic potential, assessed through viscoelastic clot parameters, and (b) platelet reactivity in response to specific agonists. Multivariable linear regression models were applied to adjust for potential confounders, including age, body mass index (BMI), natural logarithm-transformed Simplified Disease Activity Index (SDAI), treatment group, and ln-transformed prednisone dose.

Results. A total of 61 RA patients (30 receiving JAKi and 31 receiving TNFi) and 34 healthy controls were included in the analysis. Compared with healthy individuals, RA patients demonstrated significantly increased maximum clot firmness (MCF) across all ROTEM assays, including INTEM (63.4±4.0 vs 57.2±4.1 mm), EXTEM (66.2±4.1 vs 55.9±4.7 mm), and FIBTEM (15.7±3.6 vs 12.4±3.7 mm), with all comparisons reaching statistical significance ($p<0.001$). In addition, platelet aggregation responses were significantly enhanced in RA patients across all tested pathways ($p<0.001$). In multivariable analyses, treatment with JAK inhibitors, compared with TNF inhibitors, was independently associated with higher EXTEM MCF (β=2.32, 95% CI 0.42–4.23; p=0.018) and FIBTEM MCF (β=1.72, 95% CI 0.07–3.37; p=0.041). Furthermore, prednisone dose emerged as an independent predictor of increased INTEM and EXTEM MCF, while disease activity, as measured by SDAI, was independently associated with enhanced ADP-induced platelet aggregation (β=11.34, 95% CI 4.31–18.37; p=0.002).

Conclusions. RA is associated with a prothrombotic phenotype characterized by increased clot firmness and heightened platelet reactivity. Treatment with JAK inhibitors appears to be independently associated with greater viscoelastic clot strength compared with TNF inhibitors. Additionally, systemic inflammation and glucocorticoid exposure represent key determinants of coagulation activation and platelet hyperreactivity, underscoring their central role in shaping thrombotic risk in this patient population.

ABSTRACT N. CO075

PLATELET ACTIVATION PROFILE IN RELAPSING-REMITTING MULTIPLE SCLEROSIS AND ITS RELATIONSHIP WITH NEURONAL AND ASTROGLIAL BIOMARKERS

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Background and Aims. Multiple sclerosis (MS) is a chronic inflammatory and neurodegenerative disease involving complex immune-nervous system interactions. Beyond their role in hemostasis, platelets contribute to inflammation and immune responses. This study aimed to investigate platelet phenotype in relapsing-remitting MS (RRMS) patients and its association with biomarkers of neuronal damage and astroglial activation.

Methods. Citrated-blood was collected from 49 RRMS patients and 41 control subjects. ADP (2 µM)-induced platelet aggregation, ATP secretion and dense granule content (ATP and ADP) were assessed in platelet-rich plasma (PRP) using lumiaggregometry. Platelet activation markers, such as P-selectin expression, GPIIb/IIIa activation (PAC-1 binding), platelet-monocyte (PMAs), platelet-granulocyte (PGAs) and platelet-lymphocyte (PLAs) aggregates were evaluated by flow cytometry, along with platelet procoagulant markers (tissue factor expression and phosphatidylserine exposure) and reactive oxygen species (ROS) generation. Serum neurofilament light chain (sNfL) and glial fibrillary acidic protein (sGFAP) were measured by SIMOA technology as markers of neuronal damage and astroglial activation, respectively.

Results. ADP (2 µM)-induced platelet aggregation and ATP secretion did not differ between RRMS patients and CTRL [82% (61-89) *vs* 76% (52-90), P=0.5022; 0.2 nmol/10^8 platelets (0.0-0.4) *vs* 0.1 nmol/10^8 platelets (0.0-0.4), P=0.4702, respectively]. However, ADP content in platelet dense granule was reduced in RRMS patients, resulting in an increased ATP/ADP ratio compared with controls (Figure 1A-B). Markers of platelet activation, including P-selectin expression, PAC-1 binding, PMAs, PGAs and PLAs were all significantly increased in RRMS patients (Figure 1C-G). In contrast, tissue factor (TF) expression, phosphatidylserine exposure (lactadherin binding) and ROS generation were not increased in RRMS patients compared to controls [3.7% (1.9-5.3) *vs* 2.8% (1.8-3.8), P=0.1108; 0.4% (0.3-0.4) *vs* 0.6% (0.3-0.8), P=0.0424; 5.8% (4.0-11) *vs* 10% (4.8-15), P=0.1591, respectively]. Notably, both biomarkers, sNfL and sGFAP, positively correlated with PMAs (sNfL: r=0.342, P=0.026; sGFAP: r=0.311, P=0.045) and PGAs (sNfL: r=0.546, P<0.001; sGFAP: r=0.315, P=0.042), but not with P-selectin expression (sNfL: r=0.0127, P=0.423; sGFAP: r=0.225, P=0.151) or PAC-1 binding (sNfL: r=0.192, P=0.223; sGFAP: r=0.131, P=0.408).

Conclusions. Patelets from RRMS patients show preserved agonist-induced functional responses but a distinct activated phenotype, characterized by altered dense-granule nucleotide content and increased platelet–leukocyte aggregate formation, without evidence of enhanced platelet procoagulant activity. The association of sNfL and sGFAP with PMAs and PGAs suggests that platelet-immune cell interactions, rather than isolated platelet activation, may be linked to neuronal and astroglial injury in RRMS. These findings support platelet-leukocyte aggregates as potential biomarkers of thrombo-inflammatory disease activity and as possible targets for strategies aimed at modulating platelet-immune crosstalk in MS.

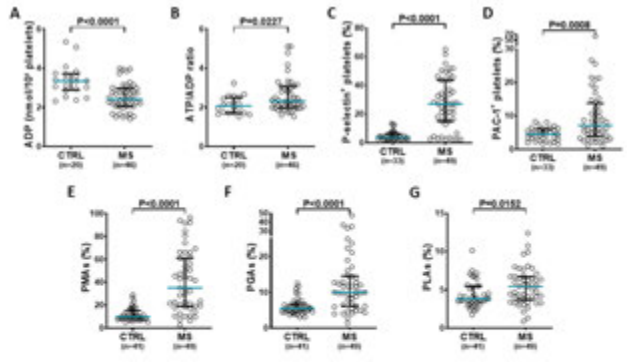


Figure 1. Platelet profile in relapsing-remitting multiple sclerosis patients RRMS) and control subjects (CTRL). Dense granule content was evaluated (**A**) ADP (nmol/10^8 platelets) and (**B**) ATP/ADP ratio. Flow cytometry analysis was performed to evaluate (**C**) P-selectin expression, (**D**) PAC-1 binding (GPIIb/IIIa activation), (**E**) platelet-monocyte aggregates (PMAs), (**F**) platelet-granulocyte aggregates (PGAs) and (**G**) platelet-lymphocyte aggregates (PLAs). Each dot represents an individual subject; horizontal blue lines indicate medians ± interquartile range. Statistical analysis was performed using unpaired t-test or Mann–Whitney test, as appropriate.

ABSTRACT N. CO076

ASSOCIATION OF MATRIX METALLOPROTEINASE 2 PLASMA LEVELS WITH CARDIOVASCULAR EVENTS IN PATIENTS WITH ATRIAL FIBRILLATION: A NESTED CASE CONTROL STUDY FROM THE ATHERO-AF COHORT

D. Menichelli[1], E. Falcinelli[2], P. Pignatelli[3], R. Carnevale[4|5], A. D'Amico[4], F. Violi[2], P. Gresele[2], D. Pastori[4|5], F. Paciullo[6]

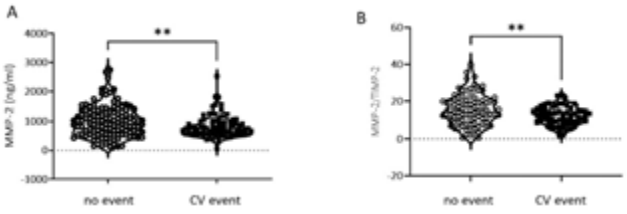
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Background and Aims. Atrial fibrillation (AF) is associated with increased cardiovascular (CV) morbidity and mortality. In addition to cardioembolic stroke, patients with AF are exposed to a significant burden of adverse CV outcomes, including myocardial infarction, peripheral arterial ischemic events, heart failure progression and CV death. This has led to the definition of a residual CV risk not fully mitigated by anticoagulation alone. Growing evidence suggests that vascular inflammation, endothelial dysfunction and cardiac structural remodeling may contribute to this risk. Matrix metalloproteinases (MMPs) are a heterogeneous family of zinc-dependent proteolytic enzymes involved in extracellular matrix turnover and vascular remodeling. Among them, MMP-2 has been implicated in endothelial function, smooth muscle cell migration and atherosclerotic plaque evolution, and has been proposed as a biomarker of CV risk. MMPs appear to be involved in atrial structural remodeling and fibrosis in AF, processes associated with arrhythmia persistence and disease progression. Aim of the present study was to investigate the association between circulating levels of MMP-2 and major adverse CV events (MACE) in AF patients.

Methods. We conducted a nested case-control analysis within the ATHERO-AF study, a prospective observational cohort study of patients with non-valvular atrial fibrillation. Plasma levels of MMP-2 and of its selective endogenous inhibitor, tissue inhibitor of metalloproteinase-2 (TIMP-2), were measured using standardized laboratory techniques. Patients who experienced major adverse cardiovascular events (MACE) during follow-up were compared with event-free controls matched for relevant clinical characteristics. MACE included ischemic stroke or transient ischemic attack (TIA), acute myocardial infarction (AMI) and CV death. Clinical data, comorbidities and ongoing antithrombotic therapies were systematically recorded.

Results. A total of 211 patients with AF were included in the analysis, of whom 86 experienced at least one MACE event and 125 remained event-free during follow-up. Overall, 103 MACE were documented: 29 TIA or ischemic stroke (28.15%), 36 AMI (34.95%) and 38 CV deaths (36.9%). Patients who developed CV events exhibited significantly lower plasma levels of MMP-2 compared with controls (Fig. 1). Low MMP-2 levels were associated with MACE (χ^2: 11.6; $p<0.01$) and, in particular, with ischemic stroke (χ^2: 4.9; $p<0.05$). No significant differences were observed with respect to TIMP-2 levels.

Conclusions. Reduced circulating MMP-2 levels are associated with an increased risk of adverse CV outcomes in patients with chronic atrial fibrillation, independently of anticoagulant therapy. MMP-2 is involved in atrial remodeling and fibrosis, processes linked to an increased risk of cardioembolic stroke, and reduced MMP-2 activity may disrupt extracellular matrix homeostasis, promoting myocardial fibrosis and cardiac dysfunction. These findings support a potential protective role of MMP-2 in CV homeostasis and highlight the interplay between vascular remodeling, inflammation and thrombosis in AF. Further prospective studies are warranted to clarify the mechanistic role of MMP-2 and evaluate its utility as biomarker for residual CV risk stratification in non-valvular atrial fibrillation. Fig.1 (A) MMP-2 plasma levels and (B) MMP-2/TIMP-2 ratio in NVAF patients with or without MACE.





PLATELET MIR-144-5P REGULATES COX-1/2 EXPRESSION AND MODULATES ASPIRIN RESPONSE IN PATIENTS WITH CARDIOMETABOLIC RISK

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Background and Aims. Interindividual variability in response to low-dose aspirin (ASA) contributes to residual platelet activation and thrombotic risk. Platelet microRNAs (miRNAs) may modulate ASA pharmacodynamics, but mechanistic insights remain limited. To investigate whether platelet miR-144-5p regulates cyclooxygenase (COX)-1/2 expression and modulates ASA response in cardiometabolic patients.

Methods. Two hundred ASA-treated patients were stratified into tertiles of serum thromboxane B_2 ($sTXB_2$) slope, an ex vivo marker of COX-1 recovery. Platelet and extracellular vesicle miR-144-5p levels were quantified by RT-qPCR and correlated with biochemical and clinical variables. Functional studies were performed in megakaryocytic (DAMI) and endothelial (HUVEC) cells transfected with miR-144-5p mimics or inhibitors to assess COX-1/2 regulation.

Results. Patients with poor ASA response (3rd tertile of $sTXB_2$ slope) exhibited reduced platelet miR-144-5p ($p=0.027$) and higher COX-1 mRNA/protein levels ($p\leq0.027$), whereas miR-144-5p was enriched in platelet-derived extracellular vesicles. Platelet miR-144-5p was inversely correlated with $sTXB_2$ ($\rho=-0.235$, $p=0.007$) and COX-1/2 mRNA expression. In DAMI (human megakaryocyte) cells, ASA exposure upregulated miR-144-5p cells; in addition, miR-144-5p overexpression suppressed, and inhibition enhanced, COX-1 protein levels. Similar effects were observed in HUVECs, where miR-144-5p downregulated both COX-1 and COX-2. Among our patients, platelet miR-144-5p were lower in those with obesity, dyslipidemia, and metabolic dysfunction-associated steatotic liver disease, conditions known to affect aspirin response.

Conclusions. Platelet miR-144-5p directly regulates COX-1/2 expression and contributes to interindividual variability in ASA response. Low platelet miR-144-5p identifies patients with accelerated COX-1 recovery and residual thromboxane generation, providing a mechanistic basis for precision antiplatelet therapy and potential miRNA-targeted interventions.



METABOLOMIC AND LIPOPROTEOMIC MODULATION FOLLOWING INCLISIRAN TREATMENT IN DYSLIPIDEMIC PATIENTS

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Background and Aims. Inclisiran is a subcutaneously administrated synthetic small interfering RNA directed against proprotein convertase subtilisin–kexin type 9, leading to sustained low-density lipoprotein cholesterol (LDL-C) reduction with a twice-yearly dosing regimen. While its lipid-lowering efficacy is well established, its broader metabolic effects remain incompletely characterized. Metabolomics refers to the comprehensive analysis of small-molecule metabolites reflecting systemic biochemical activity, whereas lipoproteomics focuses on the detailed characterization of lipoprotein particles and their subclasses, providing deeper insight into lipid transport and cardiovascular risk. This study aimed to comprehensively evaluate serum metabolomic and lipoproteomic changes in patients with dyslipidemia before and after inclisiran treatment using an integrated nuclear magnetic resonance (NMR)-based approach.

Methods. This observational single-center study included 69 patients with dyslipidemia treated with inclisiran in routine clinical practice. Fasting serum samples were collected at baseline and three months after treatment initiation. A total of 30 metabolites and 112 lipoprotein-related parameters were quantified using NMR spectroscopy. Paired comparisons between time points were performed using the Wilcoxon signed-rank test with false discovery rate correction. Clustering based on lipoprotein changes was conducted using the KODAMA algorithm to identify distinct response patterns.

Results. Inclisiran treatment was associated with extensive and coherent reductions in lipoprotein-related parameters. Seventy-four lipoprotein variables showed significant changes. Reductions were observed across LDL, IDL, and VLDL subclasses, while some HDL-related parameters were increased. In contrast, the global metabolomic profile remained largely unchanged; trimethylamine-N-oxide (TMAO) was the only metabolite significantly increased at follow-up. KODAMA clustering identified three patient groups with heterogeneous responses. Two groups demonstrated marked lipoprotein reductions, particularly those with higher baseline LDL-related parameters, whereas one group exhibited minimal changes. Baseline TMAO levels were lower in the group with the most pronounced lipid response and increased at follow-up, potentially reflecting changes in concomitant lipid-lowering therapy rather than a direct effect of inclisiran.

Conclusions. Inclisiran induces a broad and consistent improvement in lipoprotein profiles, extending beyond LDL-C reduction, while exerting only minimal effects on the global metabolomic landscape. These findings reinforce the highly specific lipid-lowering mechanism of inclisiran and underscore inter-individual variability in treatment response, particularly in the context of concomitant lipid-lowering therapies.



FVIII DEFICIENCY COMPROMISES IN VITRO OSTEOBLASTS MINERALIZATION AND THEIR SECRETOME PROFILE

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Background and Aims. Hemophilia A (HA) is frequently associated with reduced bone mineral density and skeletal fragility, indicating a role for factor VIII (FVIII) in bone homeostasis. Emerging evidence suggests that FVIII may directly regulate osteoblast function. However, the underlying mechanisms remain poorly understood. This study investigated the effects of FVIII, von Willebrand factor (vWF), and the FVIII/vWF combination on osteoblast mineralization and explored FVIII-dependent changes in the osteoblast secretome.

Methods. Primary osteoblast precursors were isolated from 3-week-old HA and wild-type (wt) mice and cultured under osteogenic conditions. During differentiation, the cultures were supplemented with increasing concentrations of recombinant FVIII (Nuwiq®), vWF, or the FVIII/vWF combination. Calcium deposition was assessed by Alizarin Red S staining. For secretome analysis, culture supernatants of HA and wt osteoblasts maintained for 48 hours were collected, and proteins were identified using Proteome Discoverer.

Results. FVIII supplementation significantly increased calcium deposition in a dose-dependent manner in both HA and wt osteoblasts, with 10ng/ml able restoring the mineralization deficit observed in untreated HA osteoblasts. In contrast, physiological concentrations of vWF selectively enhanced mineralization in HA osteoblasts, with no significant effect in wt cultures. Treatment with the FVIII/vWF complex increased calcium deposition exclusively in HA osteoblasts and only at hypophysiological concentrations (20ng/ml FVIII – 1mg/ml vWF). Secretome profiling revealed a reduced secretion of several proteins in HA compared with wt osteoblasts, while FVIII supplementation restored a wt-like secretome profile. Enrichment analysis identified pathways related to extracellular matrix organization, cell adhesion, wound healing, and skeletal development; among these, fibronectin and several collagen isoforms were particularly affected by FVIII deficiency.

Conclusions. FVIII deficiency impairs osteoblast mineralization and secretory function, leading to altered ECM organization and reduced metabolic activity. These findings support a direct, non-hemostatic role for FVIII in osteoblast biology and indicate that VWF may modulate osteoblast activity under conditions of FVIII deficiency, Collectively, these data suggest that FVIII replacement therapy may contribute to improved bone integrity in patients with HA.



INVESTIGATING MECHANISMS OF ACQUIRED VON WILLEBRAND SYNDROME ACROSS HEMATOLOGICAL DISEASES: THE CONTRIBUTION OF INTRAPLATELET VWF

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Background. Acquired von Willebrand syndrome (AVWS) is a rare bleeding disorder due to reduced or dysfunctional von Willebrand factor (VWF) in patients without a personal or family bleeding history. It is commonly associated with myeloproliferative neoplasms (MPNs) and lymphoproliferative disorders (LPDs). The contribution of platelet VWF stores is less defined.

Aims. To characterize AVWS phenotypes in a single-center cohort, focusing on intraplatelet VWF.

Methods. We retrospectively included AVWS patients diagnosed between April 2014 and March 2025. Bleeding severity was assessed by ISTH-BAT. Testing included FVIII:C, VWF:Ag, VWF:GPIbR, VWF:RCo, VWF:CB, VWF propeptide (VWFpp), and multimer analysis. In a subset, intraplatelet VWF:Ag and GPIbR activity were measured in platelet lysates from citrate blood and expressed as IU/10^9 platelets.

Results. Among 140 patients, 106 (76%) had MPNs and 26 (19%) LPDs. At least one bleeding symptom occurred in 70%, and clinically significant bleeding in 24%, more frequent/severe in LPDs (58%; mainly mucocutaneous and gastrointestinal) than in MPNs (13%). LPDs showed severe functional defects, marked high-molecular-weight multimer loss, and elevated VWFpp/VWF:Ag ratio (median 6.7), consistent with accelerated clearance; anti-VWF antibodies were detected in 30% of tested LPDs/autoimmune cases. MPNs displayed mild high-molecular-weight multimer reduction and normal clearance (median VWFpp/VWF:Ag 1.0), with an inverse correlation between platelet count and multimer depletion (ρ=-0.48, $p<0.001$). Bleeding severity correlated inversely with VWF:GPIbR in LPDs (ρ=-0.50, $p=0.02$) and with VWF:RCo in MPNs. Intraplatelet assays were available for 38 patients (31 MPNs, 7 LPDs): MPNs had reduced intraplatelet VWF:Ag 0.18 IU/10^9 (IQR 0.14–0.21; reference 0.22–0.60) and intraplatelet GPIbR 0.14 IU/10^9 (0.09–0.16; reference 0.15–0.58), whereas LPDs showed higher values (VWF:Ag 0.31, 0.20–0.38; GPIbR 0.25, 0.24–0.30).

Conclusions. AVWS shows two main patterns: immune/clearance-driven in LPDs and platelet-mediated in MPNs. In MPN-associated AVWS, plasma VWF:Ag may be preserved, yet reduced intraplatelet VWF suggests partial depletion of megakaryocyte/platelet VWF stores, potentially reflecting altered synthesis or sustained release. This challenges the assumption that MPN-related AVWS is confined to plasma functional defects and points to a dual endothelial and megakaryocyte/platelet contribution to the bleeding phenotype in some patients. Integrating intraplatelet VWF with plasma assays and multimer analysis may refine mechanistic phenotyping and support targeted management.



RESTORATION OF CEREBRAL MICROVASCULAR STRUCTURE AND FUNCTION IN HEMOPHILIA A MICE THROUGH FVIII GENE THERAPY

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Background and Aims. Hemophilia A (HA) is an X-linked bleeding disorder caused by factor VIII (FVIII) deficiency. Although spontaneous intracranial hemorrhage represents a severe complication, the underlying mechanisms remain unclear. Increasing evidence suggests that FVIII may contribute to endothelial cell homeostasis, raising the possibility that vascular defects in HA extend beyond impaired coagulation. This study aimed to characterize structural and functional alterations of the cerebral microvasculature in HA and to specifically investigate intrinsic defects of brain microvascular endothelial cells (BMECs), as well as their correction following FVIII gene therapy.

Methods. Brains were collected from HA, wild-type (WT), and HA mice treated with a lentiviral vector expressing FVIII under the Stab2 promoter (LV-Stab2-FVIII-HA) at 8, 12, and 24 weeks of age. Microvascular density and vessel length were quantified by mCD31 immunofluorescence. Vascular permeability was assessed in vivo at 8 weeks using fluorescent dextrans (4 and 150 kDa) under basal conditions and after DMSO-induced stress, with extravasation measured at 5, 10, and 15 minutes. BMECs isolated from HA and WT mice were analyzed in vitro for proliferation and migration using wound healing assays.

Results. HA mice showed significantly reduced microvascular density and shorter vessel length compared to WT at all time points, indicating persistent cerebrovascular impairment. FVIII gene therapy induced a robust and sustained improvement of the vascular phenotype at all analyzed time points, with both vessel density and length markedly increased compared to untreated HA mice. Although these parameters did not fully reach WT levels, the differences between HA-LV-FVIII and WT mice were no longer statistically significant, indicating a substantial functional rescue by gene therapy for FVIII. Baseline permeability did not differ between groups; however, DMSO-induced stress caused a marked increase in dextran extravasation in HA mice at all time points, while WT vessels remained stable. Importantly, HA-derived BMECs exhibited significantly reduced proliferative capacity and impaired migratory ability compared to WT-BMECs, demonstrating an intrinsic endothelial dysfunction consistent with the in vivo phenotype.

Conclusions. HA is associated with both structural defects and increased stress susceptibility of the cerebral microvasculature. The impaired proliferation and migration of HA-BMECs indicate a cell-autonomous endothelial dysfunction that likely contributes to vascular fragility. Restoration of FVIII expression via gene therapy rescues vascular architecture, supporting a direct role of FVIII in maintaining BMEC function and cerebrovascular integrity beyond its role in coagulation.



IN SILICO ANALYSIS THROUGH A NEW-GENERATED FACTOR VIII MODEL SUPPORTS TOLERANCE OF B DOMAIN TO MULTIPLE AMINO ACID SUBSTITUTIONS LIMITING THE LOCAL IMPACT OF MISSENSE VARIANTS

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Background and Aims. Missense variants represent a relevant cause of factor VIII (FVIII) deficiency in haemophilia A (HA). Intriguingly, a very few HA-associated missense variants, particularly those associated with severe phenotypes, are reported in B domain that, among FVIII domains, remains the least characterized and structurally unresolved. Here, to provide insights into the impact of multiple amino acid substitutions in B domain at a single-residue scale, we performed systematic in-silico analyses through a new-generated FVIII model ($FVIII_{IT}$) with assembled B domain.
Methods. Generation of the $FVIII_{IT}$ model by the I-TASSER tool, and in-silico analysis through DDmut and REVEL tools.
Results. The integrated inspection of HA databases indicate that HA-associated missense variants are mainly reported in FVIII A1-A2-A3-C1-C2 (hereafter referred as A1-C2) domains, as indicated by the local (A1-A3, 77%; C1-C2, 20%) distribution in comparison with B domain (3%). In particular, missense variants associated with severe phenotypes in B domain are the least represented, as also highlighted by their relative frequency normalized per domain size (A1-C2, 0.36-0.49, mean 0.45; B, 0.02). To extensively and systematically dissect the impact of amino acid substitutions in B domain, the new-generated $FVIII_{IT}$ model was first validated for resolved A1-C2 domains towards reference structures by alanine scanning, then extended to B domain and in correlation with REVEL scores, which showed a minor impact in B domain. Noticeably, a mutational scanning taking advantage of DDmut/REVEL at a single-residue scale on all possible single-nucleotide changes resulting in missense variants (>6,0000 for B domain) showed significant differences ($p<0.0001$) between B and A1-C2 domains, with high-percentage (~90%) of B-domain value localization in favourable score ranges corresponding to neutral variants. Single-nucleotide changes are also associated with the clinically relevant nonsense mutations causing premature termination codons (PTCs), whose suppression by the so-called translational readthrough (TRT) may result in the synthesis of full-length proteins bearing amino acid substitutions, with pathophysiological implications even for inhibitor susceptibility. Analysis of TRT-deriving missense variants from either possible (n=2439) or HA-associated (n=1094) PTCs revealed favourable values ($p<0.0001$) for B-domain variants. Noticeably, scores for B-domain missense variants remained significant even by analysis of those arising from possible (n=457) or HA (n=190) PTCs at which TRT-mediated re-insertion of the original amino acid is not predicted. This favourable output for B domain included TRT-deriving missense variants at tryptophan residues, where missense changes are expected to be detrimental as indicated by their high association with severe phenotypes in A1-C2 domains, whereas among the very few number of HA-associated B-domain missense variants no Trp missense changes have been reported as causative of HA. Moreover, our extensive analysis was further validated in association with experimentally obtained data.
Conclusions. Altogether, these original insights, obtained by rational in-silico analyses through the new-generated $FVIII_{IT}$ model, strongly support tolerance of B domain to multiple amino acid changes and support potential underestimation of HA-associated B-domain missense variants due to limited local impact of amino acid substitutions.

ABSTRACT N. CO083

IN VITRO CORRECTION OF SEVERE FACTOR V DEFICIENCY USING A NOVEL PLASMA-DERIVED FV CONCENTRATE: A WHOLE BLOOD THROMBIN GENERATION STUDY

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Background and Aims. Severe factor V (FV) deficiency is a rare bleeding disorder currently managed with fresh frozen plasma. A novel plasma-derived FV concentrate has been developed as a targeted potential replacement therapy. We evaluated the *in vitro* ability of this concentrate to restore global hemostatic function in patients with severe FV deficiency using the whole blood thrombin generation assay.
Methods. Whole blood samples from 10 patients with severe FV deficiency were spiked *in vitro* with increasing FV concentrations (0%, 25%, 50%, and 100%). Due to limited sample availability, 2 patients were not tested at 25%. Thrombin generation was assessed in whole blood using 1 pM tissue factor, without addition of exogenous phospholipids, by measuring lag time, peak thrombin, and endogenous thrombin potential (ETP). In addition, viscoelastic testing by rotational thromboelastometry (ROTEM; INTEM, EXTEM, FIBTEM) was performed. Statistical analysis was performed using a mixed-effects model (REML), followed by Dunnett's multiple comparisons test versus baseline (0%). Healthy control samples were used to define the interquartile range, which served as reference for lag time, peak thrombin, and ETP.
Results. FV supplementation significantly affected all thrombin generation parameters. Lag time was reduced (F(1.003, 8.361)=20.06, p=0.0018), with all concentrations showing shorter lag time compared to baseline (25%, p=0.0059; 50%, p=0.0032; 100%, p=0.0027). Peak thrombin was increased (F(1.576, 13.13)=17.96, p=0.0003), with differences versus baseline at all concentrations (25%, p=0.0126; 50%, p=0.0026; 100%, p=0.0037). ETP showed significant increases at 50% (p=0.0006) and 100% (p=0.0009), while the increase at 25% did not reach statistical significance (p=0.0624). As shown in Figure 1A-B, at baseline lag time was prolonged in all patients and returned within the interquartile range of healthy controls in all cases already at 25% FV. In contrast, peak thrombin was normal or increased in half of cases (Figure 1C), while ETP was within or above the interquartile range of healthy controls in most patients (Figure 1D); in the five patients with low baseline peak thrombin values, levels at 25% FV exceeded the interquartile range of healthy controls (Figure 1C). Consistently, ROTEM showed prolonged clotting times at baseline. Both INTEM and EXTEM-clotting time normalized after FV supplementation at 25% in most patients, although a minority required 50% FV to reach normal values. Parameters reflecting clot propagation and strength were largely within the normal range at baseline and FV supplementation had no relevant effect.
Conclusions. Whole blood thrombin generation and ROTEM suggest that delayed coagulation initiation is the predominant functional abnormality in severe FV deficiency, while thrombin and fibrin-generating capacity is variably preserved. In our study, the novel plasma-derived FV concentrate effectively corrected this defect, restoring lag and clotting times within the interquartile range of healthy controls already at 25% FV. These findings support the potential clinical utility of whole blood thrombin generation as a global assay to evaluate treatment response.

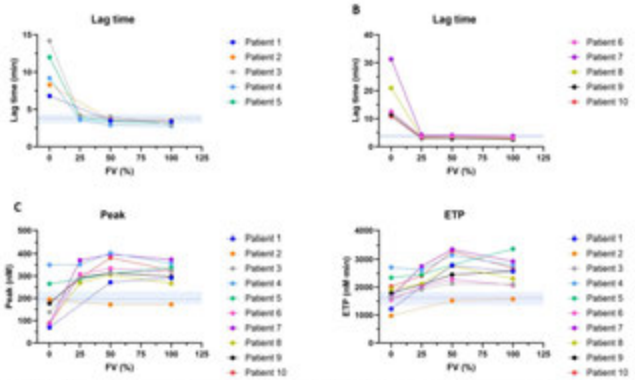


Figure 1. Effect of a novel plasma-derived factor V (FV) concentrate on whole blood thrombin generation parameters in patients with severe FV deficiency. (A–B) Lag time, (C) peak thrombin, and (D) endogenous thrombin potential (ETP) at FV concentrations of 0%, 25%, 50%, and 100% following supplementation with the FV concentrate in individual patients (n=10). Patients 1-5 are shown in panel A and patients 6-10 in panel B for lag time; panels C and D include all patients. Each line represents an individual patient. The dashed horizontal line indicates the median, and the shaded area the interquartile range, of healthy controls. Dashed lines for patients 1 and 2 indicate missing data at 25% FV.



NEW INSIGHTS INTO HEMOPHILIA A: FACTOR VIII–INTEGRIN B1 PATHWAY AS KEY REGULATOR OF ENDOTHELIAL CELL FUNCTION

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Background and Aims. Factor VIII (FVIII) is a well-known coagulation factor, and its deficiency causes hemophilia A (HA). Beyond its canonical role in coagulation, FVIII has emerged as a regulator of endothelial cell (EC) biology. However, the molecular mechanisms by which FVIII exert direct effects on EC function remain poorly defined, and the endothelial receptor mediating FVIII-dependent signaling, vascular integrity, and metabolism are still under investigation. The aim of the study is to identify the endothelial surface receptor that binds FVIII and to map the downstream signaling pathways regulating EC function and vascular homeostasis.

Methods. Blood outgrowth ECs (BOECs) from HA patients and healthy donors were isolated. FVIII expression in HA-BOECs was restored either by lentiviral vector transduction with a B-domain deleted FVIII (LV-FVIII) or by recombinant FVIII (rhFVIII) treatment. Proteomic profiling of healthy, HA and LV-FVIII HA-BOECs were assessed. Ligand-receptor interactions were investigated using Flow-TriCEPS technology, co-immunoprecipitation, and immunofluorescence. Functional assays included angiogenesis, migration, permeability, 3D vessel-on-chip models, mitochondrial respirometry, and proliferation. The role of integrin β1 signaling was assessed by shRNA-mediated knockdown and downstream FAK inhibition.

Results. Co immunoprecipitation, colocalization, and shRNA mediated knockdown studies identified integrin β1 as a key endothelial surface receptor mediating FVIII binding. Engagement of the FVIII– integrin β1 activated intracellular FAK/Src signaling, which was essential for FVIII driven angiogenesis, migration, and barrier stabilization. In 3D vessel on chip models, FVIII–integrin β1 signaling restored vascular integrity and network formation in HA BOECs, whereas integrin β1 silencing abolished these effects. Proteomic profiling revealed dysregulation of pathways related to angiogenesis, extracellular matrix organization, and mitochondrial metabolism in HA-BOECs, all normalized by FVIII reintroduction. Consistently, HA BOECs displayed impaired mitochondrial respiration, ATP production, and reserve respiratory capacity, which were rescued by FVIII in an integrin β1 dependent manner. FVIII deficiency significantly impaired endothelial proliferation, which was restored by either FVIII replacement therapy or gene transfer. However, FVIII signaling was not rescued in HA-BOECs following integrin β1 silencing, supporting the existence of a functional FVIII–integrin β1 signaling axis.

Conclusions. FVIII functions as a ligand for integrin β1 on ECs, activating FAK dependent signaling that governs vascular integrity, proliferation, angiogenesis, and mitochondrial activity. This newly defined FVIII–integrin β1 axis is critical for endothelial homeostasis and provides a mechanistic explanation for endothelial dysfunction in hemophilia A, highlighting novel therapeutic opportunities beyond hemostasis.



GENE REGULATION OF THE HYPERACTIVE FIX PADUA VARIANT VIA DCAS9-KRAB TO MODULATE THROMBOPHILIA

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Background and Aims. Thrombophilia is characterized by an increased risk of venous thromboembolism due to a hypercoagulable state resulting from inherited or acquired alterations in coagulation or fibrinolysis. Among genetic variants, factor IX (FIX) R384L (FIX Padua) is associated with markedly increased FIX activity and a consequent elevated thrombotic risk. To modulate FIX expression and activity in carriers of the FIX Padua variant, CRISPR/dCas9-KRAB–mediated transcriptional repression represents a reversible and dynamic epigenetic strategy with the potential to decrease thrombotic risk. This study aimed to evaluate CRISPR/dCas9-KRAB–Mediated Modulation of the Factor IX Padua variant expression in an "*ex vivo*" model of human hepatocyte-like cells (HLCs) derived from a variant carrier.

Methods. Peripheral blood stem cells were isolated from a thrombophilia patient carrying the FIX Padua variant and reprogrammed into induced pluripotent stem cells (iPSCs). Clonal iPSC lines were established and pluripotency was confirmed by the expression of Oct4, Sox2, Klf4, Nanog. Gene modulation was performed using CRISPR/dCas9-KRAB technology. iPSCs were subsequently differentiated into HLCs, using a previously optimised protocol. FIX expression was assessed by immunofluorescence analysis (IF).

Results. iPSCs exhibited alkaline phosphatase activity and expressed pluripotency markers, as confirmed by IF. Upon differentiation, HLCs expressed cytokeratin 18, as demonstrated by IF and real time qPCR. FIX expression in patient-derived HLCs was assessed before and after CRISPR/dCas9-KRAB–mediated repression. Prior to editing, HLCs showed high FIX expression levels, which were significantly reduced by approximately 40% following CRISPR/dCas9-KRAB modulation, as quantified by mean fluorescence intensity.

Conclusions. This study demonstrates that CRISPR/dCas9-KRAB–mediated transcriptional repression effectively modulates the expression of a hyperactive coagulation factor in an "*ex vivo*" model derived from a carrier of the FIX Padua. This reversible epigenetic approach enables precise regulation of FIX levels without introducing permanent genomic alterations. The observed reduction in FIX expression in edited HLCs supports the potential of this strategy to mitigate prothrombotic risk. Overall, these findings highlight CRISPR/dCas9-KRAB–based gene regulation as a promising approach for personalized therapies for inherited thrombophilia.

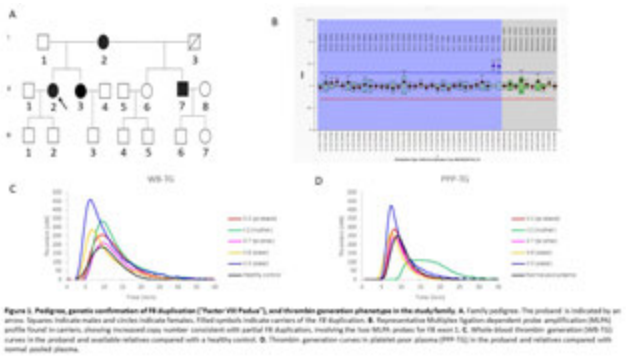
ABSTRACT N. CO086

CLINICAL AND GENETIC CHARACTERIZATION OF A NEW FAMILY CARRYING THE “FACTOR VIII PADUA” F8 DUPLICATION

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Background and aims. Elevated factor VIII (FVIII) levels represent a strong risk factor for venous thromboembolism (VTE), yet the underlying genetic determinants remain incompletely defined.
Aims. To report a clinical case of recurrent VTE associated with a partial F8 gene duplication, and to describe the thrombotic phenotype within the family through pedigree analysis.
Methods. Clinical history and pedigree were collected in the proband and relatives. FVIII clotting activity and FVIII antigen were measured using routine assays. F8 copy number variation was assessed by multiplex ligation-dependent probe amplification (MLPA). Whole-blood thrombin generation (WB-TG) was performed in available subjects under basal conditions and after addition of 20 nM thrombomodulin (TM), measuring lag time, endogenous thrombin potential (ETP), peak thrombin, and TM-mediated inhibition. Platelet-poor plasma (PPP)-TG was assessed in parallel.
Results. The proband (II-2, female, 50 years) experienced recurrent deep vein thrombosis, with first onset at 17 years during oral contraceptive use. The pedigree (Figure 1-A) revealed additional thrombotic manifestations among first-degree relatives, including VTE in the mother (I-2, female, 82 years) and in a male sibling (II-7, 60 years), both in the absence of major transient risk factors. Another carrier (II-3, female, 42 years) developed superficial vein thrombosis in the context of COVID-19 infection, whereas one tested relative (II-6, female, 56 years) had no history of thrombotic events. Standard thrombophilia screening was negative in all tested individuals. However, markedly elevated FVIII levels were consistently observed in all carriers, with FVIII:C ranging from 457% to 498% and FVIII:Ag from 465% to 550%, while the non-carrier relative showed substantially lower levels (FVIII:C 201%, FVIII:Ag 175%). MLPA and further genetic characterization confirmed the duplication of the proximal portion of the F8 gene (promoter, exon 1, and a large part of intron 1, identified as “Factor VIII Padua”) in all affected subjects (Figure 1-B), whereas one unaffected tested relative (II-6, female, 56 years) had no history of VTE, lower FVIII levels, and wild type MLPA. At the time of evaluation, most affected individuals were receiving anticoagulant therapy (edoxaban 60 mg or rivaroxaban 10 mg), with the exception of one carrier (II-3). WB-TG demonstrated a hypercoagulable profile in all tested carriers, with minimal TM-mediated inhibition in the only carrier not receiving anticoagulant therapy (II-3; ETP ratio 0.92) (Figure 1-C). In contrast, PPP-TG showed a hypercoagulable phenotype only in the untreated carrier (II-3) (Figure 1-D). Notably, the PPP-TG ETP ratio was increased in three carriers (0.80, 0.88 and 0.78), further supporting reduced TM sensitivity in plasma.
Conclusions. This report adds a new thrombophilic family carrying the “Factor VIII Padua” (F8 duplication) variant to the limited number of families described to date. The combination of extreme FVIII elevation, MLPA confirmation, and thrombin generation evidence supports a consistent FVIII--driven prothrombotic phenotype.





PLATELET ACTIVATION AND THROMBOSIS IN PATIENTS WITH FACTOR V LEIDEN MUTATION: A CROSS SECTIONAL STUDY

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Background. Factor V Leiden (FVL) is the most common inherited thrombophilia and a well-established risk factor for venous thromboembolism (VTE). Beyond its role in venous thrombosis, emerging evidence suggests that FVL may contribute to arterial thrombotic events through enhanced thrombin generation and platelet activation. We aimed to characterize the prothrombotic profile of FVL carriers by assessing biomarkers of platelet and coagulation pathway activation.

Methods. We conducted a preliminary cross-sectional study including 50 patients with genetically confirmed heterozygous or homozygous FVL mutation and previous VTE, compared with 50 age- and sex-matched individuals with prior VTE but no detectable inherited thrombophilic mutations. Blood samples were collected for measurement of soluble P-selectin (sP-selectin), soluble CD40 ligand (sCD40L), and prothrombin fragment 1+2 (F1+2) as markers of platelet activation and thrombin generation. Clinical and laboratory characteristics were recorded for all participants.

Results. Preliminary analyses showed that patients carrying FVL exhibited significantly higher levels of platelet activation markers, including sP-selectin and sCD40L, compared with the reference group. Similarly, F1+2 levels were increased in FVL carriers, indicating enhanced thrombin generation. These findings suggest that FVL is associated with a persistent prothrombotic state characterized by concomitant platelet hyperreactivity and activation of the coagulation cascade, despite ongoing anticoagulant therapy in a proportion of patients.

Conclusions. FVL mutation is associated with enhanced platelet activation and hypercoagulability, supporting a broader thrombotic phenotype beyond activated protein C resistance. These findings may contribute to improved thrombotic risk stratification in FVL carriers.



LONG-TERM EXPOSURE TO AIR POLLUTION AND RISK OF INCIDENT VENOUS THROMBOEMBOLISM: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Background and Aims. Long-term exposure to ambient air pollution was linked to arterial cardiovascular disease. Evidence regarding its association with venous thromboembolism (VTE) remains less clearly established. A systematic review with meta-analysis is needed to summarize the knowledge and identify key research gaps.
Methods. Embase, MEDLINE and Pubmed were searched for studies published in English up to June 30th, 2025 without time restrictions. Inclusion criteria were observational studies on adults (18+ years old) evaluating the association between exposure to outdoor air pollutants and VTE incidence, including deep vein thrombosis (DVT), pulmonary embolism (PE), and VTE at unusual sites. Risk of bias was assessed using the ROBINS-E checklist. Hazard ratios (HRs) with 95% confidence intervals (CIs), expressed for 10 µg/m3 increase in pollutants, were pooled using a random effects approach. Exposures included PM2.5, PM10, nitrogen dioxide (NO2), and ozone (O3). Heterogeneity was evaluated using the I2 statistic. The study protocol was registered (PROSPERO-ID:CRD420251071570).
Results. We identified 11 studies (7 cohorts, 2 case-control and 2 case-cross over; 4 USA, 4 Europe and 3 Asia) comprising 4,718,128 individuals published between 2008 and 2024. The meta-analytical HRs for PM2.5 (9 studies: 6 VTE, 2 DVT, 1 PE) and PM10 (10 studies; 7 VTE, 1 DVT, 2 PE) were 1.13 (95%CI:1.04-1.22) and 1.17 (1.02-1.34), respectively; estimates were consistent across studies reporting composite VTE vs. DVT or PE. For both pollutants, heterogeneity was substantial (I2>0.90). Leave-one-out validation attenuated the risk increase for PM2.5 to 1.07 (1.03-1.12) after excluding one study on a high-risk MEDICARE population. Kendall's tau tests for funnel plot asymmetry revealed no publication bias (p-values>0.60). NO2 and O3 contributed with 3 studies each, all with HRs larger than one and most statistically significant.
Conclusions. Long-term exposure to air pollutants, in particular to particulate matter, is an emerging risk factor for the incidence of VTE



LONG-TERM RISK OF VENOUS THROMBOEMBOLISM IN AUTOIMMUNE HEMOLYTIC ANEMIA: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Background and aims. Autoimmune hemolytic anemia (AIHA) is increasingly recognized as a systemic prothrombotic condition; however, the long-term magnitude of venous thromboembolism (VTE) risk across diverse epidemiologic settings remains insufficiently defined. Although individual investigations have reported elevated rates of deep vein thrombosis and pulmonary embolism in AIHA, an integrated assessment quantifying both absolute and relative risk has been lacking. The aim of this study was to systematically evaluate the long-term risk of VTE in adults with AIHA compared with non-AIHA populations and to derive clinically relevant absolute risk estimates that may inform thrombosis prevention and risk stratification strategies.

Methods. A systematic search of MEDLINE and Embase identified observational cohort, case-control, and registry studies enrolling adults (≥18 years) with warm AIHA or cold agglutinin disease that reported VTE outcomes relative to comparator groups. Two independent reviewers performed study selection, data extraction, and quality appraisal according to PRISMA and Cochrane guidance. Random-effects models generated pooled risk ratios (RRs), cumulative incidence estimates, and absolute risk measures including attributable risk, attributable fraction among the exposed (AFE), population attributable fraction, and number needed to harm (NNH). Heterogeneity, sensitivity analyses, and publication bias were comprehensively assessed.

Results. Seven studies comprising 10,484,989 adults (8,652 with AIHA) and up to 44 years of follow-up were included. AIHA was associated with a 2.9-fold increased VTE risk versus controls (RR 2.9; 95% CI 1.9–4.4; P < .0001). The pooled cumulative incidence of VTE was 6.0% (95% CI 4.5–7.5%) in AIHA and 2.9% (95% CI 1.3–4.4%) in non-AIHA groups. The attributable risk was 3.6% (95% CI 2.7–4.6%), and the AFE was 65% (95% CI 58–72%), indicating that nearly two-thirds of VTE events among exposed individuals are directly attributable to AIHA. The NNH was 27 (95% CI 20–34). Results were consistent across sensitivity analyses, with no significant publication bias.

Conclusions. This comprehensive meta-analysis establishes AIHA as a clinically significant long-term prothrombotic disorder, conferring markedly increased absolute and relative VTE risks. These findings support incorporating routine VTE risk assessment, intensified monitoring during hemolytic activity, and consideration of targeted thromboprophylaxis into contemporary AIHA management. Future guidelines should explicitly address VTE prevention in autoimmune hemolysis.



DIRECT ORAL ANTICOAGULANTS IN THE SECONDARY PREVENTION OF VENOUS THROMBOEMBOLISM IN PATIENTS WITH SEVERE INHERITED THROMBOPHILIA: A REAL-WORLD MULTICENTER STUDY

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Introduction. The role of direct oral anticoagulants (DOACs) in the management of patients with venous thromboembolism (VTE) and severe inherited thrombophilia is controversial.

Aims. To evaluate effectiveness and safety of DOACs in VTE patients with severe thrombophilia.

Patients and methods. Consecutive patients with a history of VTE and severe thrombophilia [AT, PS, PC deficiency, FV Leiden (FVL) homozygosis, FIIG20210A homozygosis, combined heterozygosis of FVL+ FIIG20210A, and homocystinuria], referred between March 2014 and November 2025 to five tertiary thrombosis centres were included. All patients were treated with DOACs for at least 3 months. Each patient underwent follow-up every 3 months.

Results. A total of 100 patients were included. During follow-up, three recurrent VTE events (3%) occurred, corresponding to an incidence rate of 0.49 events per 100 patient-years (95% CI 0.10–1.43). No recurrences were observed within the first 3 months of treatment. Notably, recurrent events occurred in the presence of major transient prothrombotic conditions (pregnancy or active cancer). No major bleeding events were recorded. Minor bleeding occurred in 3% of patients, and clinically relevant non-major bleeding in 1%.

Conclusions. In this multicenter real-world cohort of patients with severe inherited thrombophilia, long-term DOAC therapy was associated with a low recurrence rate and a favourable safety profile. These findings provide clinically relevant reassurance supporting the use of DOACs for secondary prevention of VTE in carefully selected patients with severe inherited thrombophilia.



DOWNREGULATION OF MARKERS OF PLATELET ACTIVATION, PLATELET TURNOVER AND PLATELET DESIALYLATION IN GOOD RESPONDERS TO FIRST-LINE TREATMENT(S) FOR IMMUNE THROMBOCYTOPENIA

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Background and Aims. In immune thrombocytopenia (ITP), thrombocytopenia is the result of immune-mediated accelerated platelet clearance and impaired megakaryopoiesis. Evidence suggests that the pathogenic mechanisms of ITP may be heterogeneous across patients and modulated by treatment. Flow cytometry (FC) platelet profiling may help identify residual pathogenic pathways and support mechanism-based treatment tailoring. With this study, we aimed to investigate FC platelet markers in recipients of first-line ITP treatment(s).

Methods. We included adult ITP patients followed up at the Haematology outpatient clinic of hospital San Paolo, Milan, sampled before and after ITP-specific first-line treatment (high-dose corticosteroids and/or intravenous immunoglobulin, IVIG), administered as per current clinical guidelines. Post-treatment samples were obtained at least 14 days after the start of corticosteroids and 3 days after the start of IVIG. For this analysis, patients were classified as good responders, responders and poor responders based on their post-treatment platelet counts (≥100x10^9/L, 50-99x10^9/L and ≤49x10^9L, respectively). We evaluated markers of circulating activated platelets [surface p-selectin expression, platelet-monocyte and platelet-granulocyte aggregates (P-MAs, PGAs)], platelet turnover (reticulated platelets) and platelet desialylation (platelet β-galactose exposure) through FC. The cut-off was the 95th centile of 20 healthy subjects. This project was funded by the Italian Ministry of Health (SG-2021-12375578).

Results. Thirty-two patients were enrolled in this study (20 females). All patients had been treated with ITP-directed first-line treatment(s). Based on their post-treatment platelet counts, 14 patients were classified as good responders, 8 as responders, and 10 as poor responders. With regards to markers of circulating activated platelets, the highest proportion of patients with p-selectin positive platelets was found in the poor response group (5/10, 50%) compared to the response (2/8, 25%) and good response (0/13, 0%) groups (poor responders vs good responders, p=0.01). Similar trends were observed for PMAs [6/10 (60%), 3/8 (38%) and 3/13 (23%)], PGAs [7/10 (70%), 3/8 (38%) and 5/13 (38%)], increased reticulated platelets [3/10 (30%), 2/8 (25%) and 0/13 (0%)] and platelet desialylation [2/7 (29%), 1/6 (17%) and 1/11 (9%)] in poor responders, responders and good responders, respectively. Ten patients had samples drawn before and after treatment, all with post-treatment platelet counts ≥50x10^9/L. The proportions of patients with increased reticulated platelets [pre- vs post-treatment: 4/9 (44%) vs 0/10 (0%), p=0.03], p-selectin positive platelets [3/7 (43%) vs 0/9 (0%), p=0.06], PGAs [8/10 (80%) vs 4/9 (44%), p=0.17], PMAs [9/10 (90%) vs 2/9 (22%), p=0.01] and platelet desialylation [5/8 (63%) vs 1/9 (11%), p=0.05] declined post-treatment.

Conclusions. In the examined cohort, there was an overall trend towards the improvement of FC markers of platelet turnover, activation and desialylation in good responders to ITP-directed first-line treatment, suggesting that the successful downregulation of ITP pathogenic mechanisms may be measurable. Persistent abnormalities in these markers may help identify residual mechanisms of thrombocytopenia and guide personalized treatment escalation in ITP.

ABSTRACT N. CO092

FOSTAMATINIB IN CHRONIC IMMUNE THROMBOCYTOPENIA: A REAL-WORLD MONOCENTRIC EXPERIENCE

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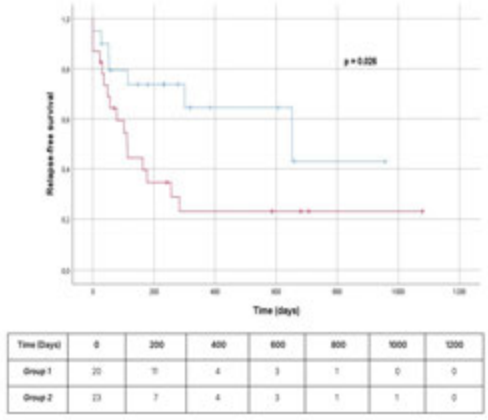
Background and aims. Fostamatinib, an inhibitor of spleen tyrosine kinase, has become a valuable therapeutic option for chronic ITP, as a second or subsequent line of treatment. Our analysis aims to evaluate its efficacy and safety in the real-world setting.

Methods. We retrospectively analyzed 43 consecutive adult patients (> 18 years) with chronic ITP treated with fostamatinib in our center. Efficacy was evaluated as time to treatment failure (TTF); data were censored for patients who did not relapse until the last follow-up or who discontinued treatment for reasons other than loss of efficacy. Clinical response was categorized according to the international consensus criteria by Rodeghiero et al. (2009). Safety was assessed by monitoring treatment-emergent adverse events, with a focus on infections, arterial hypertension, diarrhea and thrombotic events. Infections were defined severe if they required hospitalization. Patients were stratified by therapy line in Group 1 (1-2 prior treatment lines) and Group 2 (≥ 3 prior treatment lines). Statistical analysis was performed with SPSS26 using Kaplan-Meier curves and the Log-Rank test. Statistical significance was set at $p < 0.05$.

Results. Thirty patients (69.8%) were female, 13 (30.2%) male. Prior to fostamatinib, patients had received a median of 4 therapy lines (range 2-12). All patients had been previously treated with corticosteroids (100%), while 21 (48.8%) received eltrombopag, 15 (34.9%) rituximab, 13 (30.2%) romiplostim, 8 (18.6%) avatrombopag, 6 (14.0%) splenectomy, 5 (11.6%) azathioprine and 1 (2.3%) cyclosporine A. Twenty-three patients (53.4%) had a concomitant autoimmune diathesis, including Hashimoto thyroiditis (18.6%), antiphospholipid antibodies persistent positivity (9.3%), antiphospholipid syndrome (7%), systemic lupus erythematosus (7%), multiple sclerosis (4.7%), common variable immunodeficiency (2.3%), Crohn disease (2.3%) and Raynaud phenomenon (2.3%). Seven patients (16.3%) had previous thrombosis. Median age at fostamatinib start was 55 years (range 25-80). The median duration of fostamatinib treatment was 282 days (range 26-1319). The overall response rate (ORR) was 90.7%, with a complete response rate (CR) of 67.4%. Thirty-five patients (81.4%) received concomitant ITP treatments (15 corticosteroids, 12 TPO-RAs+corticosteroids, 6 TPO-RAs, 2 rituximab+corticosteroids). Twelve patients (27.9%) discontinued fostamatinib due to non-response or loss of response and two patients (4.7%) due to diarrhea; one patient (2.3%) tapered and discontinued fostamatinib maintaining a response of therapy. No patients discontinued treatment due to arterial hypertension. No thrombotic events were reported. Severe infections occurred in 2 patients (4.7%), none of which led to permanent drug discontinuation. Kaplan-Meier analysis showed that therapy line is a significant predictor of response durability. Patients in Group 1 achieved a significantly longer median TTF compared to Group 2 (not reached vs. 112 days) (Log-Rank p=0.026) (Figure 1).

Conclusions. Fostamatinib proved to be safe and effective in our monocentric experience with a median follow up of about 10 months (16/43 patients with a drug exposure more than a year). The use of fostamatinib as second/third line of treatment led to a significantly more durable response, supporting its early use in the ITP treatment algorithm.

Figure 1. Time to Treatment Failure (TTF) according to line of therapy.



Patients of *Group 1* (1-2 prior treatment lines) showed a significantly longer median TTF compared to patients of *Group 2* (≥ 3 prior treatment lines) (not reached vs. 112 days; Log-Rank p=0.026). Censure was applied for patients who did not relapse until the last follow-up or who discontinued treatment, for reasons other than loss of

ABSTRACT N. CO093

PROGNOSTIC ROLE OF ANTIPLATELET ANTIBODY TESTING IN IMMUNE THROMBOCYTOPENIA

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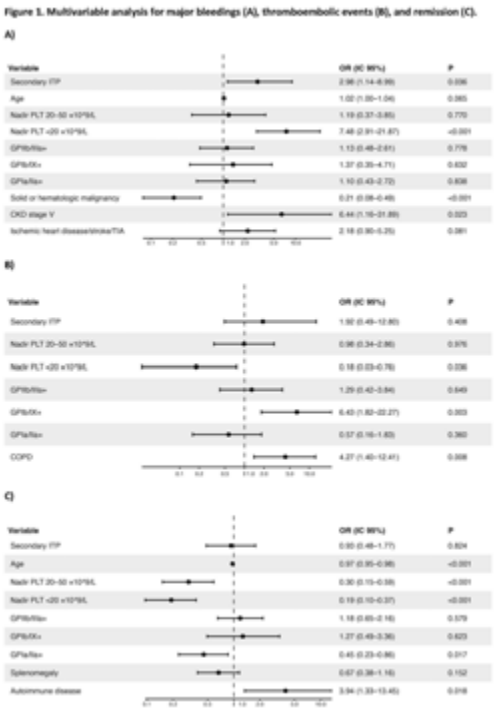
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Background and Aims. Antiplatelet antibody (APA) testing is considered an adjunct laboratory tool in the diagnosis of immune thrombocytopenia (ITP). The prognostic role of APA testing remains undefined. We aimed to assess the prognostic value of APAs in patients with ITP.

Methods. We conducted a retrospective study including patients referred for APA testing using the glycoprotein-specific indirect MAIPA assay (anti-GpIIb/IIIa, anti-GpIa/IIa and anti-GpIb/IX) and subsequently diagnosed with ITP (February 2023-October 2025) at our center. Study outcomes were major bleeding (MBs), defined as moderate-to-severe bleeding according to the ISTH bleeding assessment tool, and thromboembolic events (TEs), defined as one among objectively confirmed acute coronary syndrome, ischemic stroke or TIA, proximal deep vein thrombosis, unusual site thrombosis, or pulmonary embolism, occurring within 30 days from the onset of acute thrombocytopenia. Remission was defined as a platelet count >100,000/μL for at least one month.

Results. A total of 336 patients with ITP diagnosis were included, 75 with primary and 261 secondary ITP. APAs were detected in 37.3% of primary and 47.1% of secondary ITP patients. One, two, and three positive APAs were detected in 22.7%, 10.7%, and 4.0% of primary ITP and in 24.9%, 17.2%, and 5.0% of secondary ITP, respectively. The most prevalent APA was anti-GpIIb/IIIa (35.1%), followed by anti-GpIa/IIa (27.1%) and anti-GpIb/IX (8.0%). MBs occurred in 46 patients (13.7%), TEs in 21 (6.2%), and remission in 170 (50.6%). No association was found between MBs and the presence, number, or type of APAs. Anti-GpIb/IX positivity was independently associated with TEs (OR 6.43, 95% CI 1.82–22.27; p=0.003). APAs were independently associated with lower odds of remission (OR 0.54, 95% CI 0.32–0.91; p=0.021), mainly driven by anti-GpIa/IIa (OR 0.45, 95% CI 0.23–0.86; p=0.017).

Conclusions. In our cohort of ITP patients, indirect MAIPA-based APA positivity—particularly anti-GpIa/IIa—was associated with reduced probability of remission but not with the risk of MB. The observed association between anti-GpIb/IX antibodies and TEs warrants confirmation in further studies.





ASSESSMENT OF THE MINIMAL EFFECTIVE DOSE OF AVATROMBOPAG IN IMMUNE THROMBOCYTOPENIA: A SINGLE-CENTER REAL-WORLD STUDY

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Background and Aims. Avatrombopag, a second-generation thrombopoietin receptor agonist (TPO-RA), represents an effective treatment option for chronic immune thrombocytopenia (ITP). In clinical practice, its use is increasingly embedded in a personalized treatment strategy, in which dosing is progressively adjusted to the individual patient in order to optimize platelet count control while minimizing the risk of adverse events and toxicity. In this context, defining the minimal effective dose plays a central role within a tailored approach to ITP management. The aim of this study was to evaluate the minimal maintenance dose of avatrombopag required to sustain a platelet count >50,000/µL, while also analyzing clinical characteristics, treatment response, and safety profile.

Methods. We retrospectively analyzed 37 patients treated at our center with avatrombopag (26 females, 11 males), either currently on therapy or previously exposed to the drug. Median age was 47 years (range 19–86). At diagnosis, median platelet count was 10,000/µL, with bleeding manifestations in 56% of patients. Patients had received a median of 3 prior lines of therapy; all had been treated with first-line corticosteroids and 78.38% with intravenous immunoglobulins (IVIG). Twenty-seven patients had received a prior TPO-RA, and among them, 24 underwent a direct switch to avatrombopag. Reasons for switching included lack or loss of response in 62.5% of cases, significant platelet count fluctuations in 8.33%, adverse events in 8.33%, and patient preference for a better tolerability profile.We assessed time to response, number of dose adjustments, minimal effective maintenance dose, and safety outcomes.

Results. During follow-up, a median of 3 dose adjustments was required before reaching a stable effective dose capable of maintaining platelet counts >50,000/µL. In 5 patients (13.5%), temporary treatment interruption due to thrombocytosis during the tapering phase was required, with subsequent reintroduction of therapy. The median stable maintenance dose of avatrombopag was 50 mg/week, associated with a median platelet count of 151,000/µL.At the time of analysis, 25 patients (67.6%) remained on active treatment, while 12 (32.4%) had permanently discontinued therapy. Among these, the median dose at discontinuation was 210 mg/week, with a median platelet count of 21,500/µL. Reasons for discontinuation included loss or lack of response in 6 cases (50%), marked platelet count fluctuations in 4 cases (33.3%), one major adverse event (NSTEMI, 8.3%), and achievement of sustained off-treatment response (SROT, 8.3%).Regarding safety, 14 patients (37.8%) experienced treatment-related adverse events, including thrombocytosis in 5/37 patients (13.5%), thrombotic events (NSTEMI) in 1/37 (2.7%), platelet count fluctuations in 4/37 (10.8%), hepatotoxicity in 3/37 (8.1%), bleeding events in 2/37 (5.4%), and asthenia in 1/37 (2.7%)

Conclusions. In our real-world experience, avatrombopag confirms its effectiveness as a rapid-acting treatment for chronic ITP. The variability in maintenance dose highlights the need for a highly individualized approach, in which the minimal effective dose is often lower than the initial dosing regimen. Dose tapering represents a key step in clinical practice, transforming ITP management into a truly tailored model in which both efficacy and safety are optimized on a patient-specific basis.

ABSTRACT N. CO095

IMMATURE PLATELET FRACTION PREDICTS CLINICAL INSTABILITY IN CHRONIC IMMUNE THROMBOCYTOPENIA: PRELIMINARY RESULTS FROM THE PLATE-RET STUDY

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Background. Effective management of Immune Thrombocytopenia (ITP) is hindered by the lack of biomarkers reflecting disease activity and predicting clinical course. The utility of indexes of platelet turnover and thrombopoietic drive, such as immature platelet fraction (IPF) and Thrombopoietin (TPO), in adult ITP remains undefined.
Aims. To evaluate IPF and TPO in adult ITP patients compared to healthy controls (HC) and their predictive value for 6 months outcomes.
Methods. The PLATE-RET study is an ongoing monocentric observational study enrolling adult ITP patients and matched HC. IPF% were measured via Sysmex XN-9000 analyzer. Serum TPO was measured by ELISA. A subset of persistent/chronic patients were followed for 6 months. A Composite Adverse Outcome (CAO) was defined as: active bleeding (WHO>0), platelet count drop >40%, rescue therapy/dose escalation. Statistics included Mann-Whitney U-test and logistic regression. Informed consent was obtained; the study was approved by the local Ethics Committee.
Results. We enrolled 80 ITP patients (median age 56 years; females 58.8%) and 29 HC. Patients exhibited higher IPF% (11.3% vs 7.0%, p<0.001) and TPO (84.0pg/mL vs 63.9pg/mL; p=0.001) than HC. Stratification revealed that IPF levels were significantly higher in patients with platelet count <50x10^9/L compared to >50x10^9/L (20.7% vs 9.15%; p<.001), while TPO was higher in patients in therapy (94.3pg/mL vs 60.5pg/mL; p=0.002) (Figure, Panel A and B). In the longitudinal cohort of persistent/chronic patients (n=46), 56.5% experienced the CAO. In univariate logistic regression, higher baseline IPF% significantly predicted the occurrence of CAO (OR 1.11 per unit increase, 95%CI 1.03–1.19). In multivariate analysis, high IPF remained an independent predictor of instability in patients on active therapy, after adjusting for platelet count (Figure, Panel C), whereas TPO levels showed no prognostic value (p=0.355).
Conclusions. Adult ITP is characterized by significantly higher IPF and moderately higher TPO levels compared to HC. High baseline IPF predicts clinical instability at 6 months in patients on therapy, whereas TPO lacks prognostic value. This identifies a high-risk subgroup where elevated IPF may warrant closer monitoring.

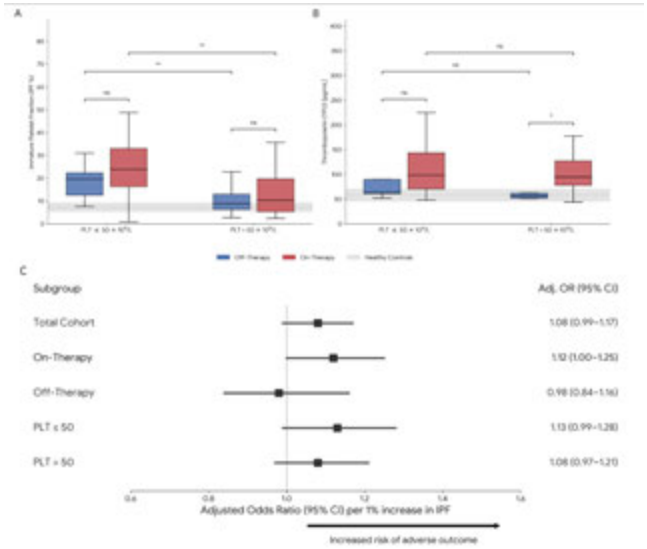


Figure. Assessment of thrombopoietic profile by platelet count (A) and therapy status (B). (C) Forest plot showing the risk of adverse clinical outcomes associated with IPF increase.

ABSTRACT N. CO096

WHEN THE BODY SAYS 'NO': CHRONIC RELATIONAL STRESS AND IMMUNE THROMBOCYTOPENIA—TOWARD AN INTEGRATED PSYCHONEUROIMMUNOLOGICAL MODEL

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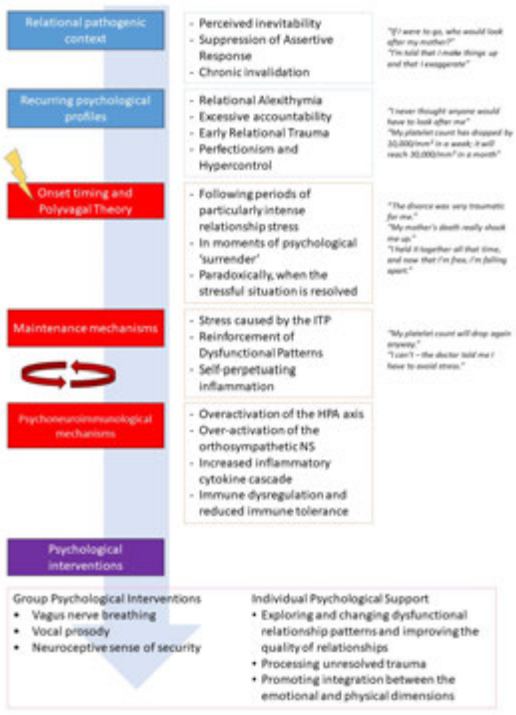
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Background. Immune thrombocytopenia (ITP) is an autoimmune disorder. These diseases have a biological, environmental, and psychosocial factors interact in shaping clinical expression. Chronic stress, may act as a significant modulator of immune function, yet its role in ITP is insufficiently explored. Emerging evidence from psychoneuroendocrineimmunology (PNEI) suggests that unresolved relational trauma and chronic emotional dysregulation may leave measurable biological traces, contributing to immune imbalance.

Methods. "Living under the Sword of Damocles" is a psychosocial support program designed for ITP patients and caregivers. Core activities include online/in-person group sessions and individual psychotherapy if someone were to express the need. Within these settings, a qualitative analysis of patients' narratives was conducted. An integrated theoretical framework combining PNEI and polyvagal theory was applied to explore, qualitatively, the connections between relational experiences, autonomic regulation, and immune function.

Results. Recurring patterns emerged across participants, including: perceived inescapability within significant relationships; chronic suppression of assertive responses, persistent emotional invalidation. These conditions were frequently rooted in early relational experiences and reinforced over time, contributing to maladaptive coping styles (hyper-responsibility, alexithymia, and over-control). From a neurophysiological perspective, these patterns are associated with sustained activation of the hypothalamic–pituitary–adrenal axis and dysregulation of the autonomic nervous system, particularly reduced ventral vagal tone and oscillations between sympathetic hyperarousal and dorsal vagal shutdown. Such alterations may promote increased production of pro-inflammatory cytokines and impairment of immune tolerance mechanisms, facilitating autoimmune responses. Notably, ITP onset was often temporally associated with critical relational events, periods of coping exhaustion, or phases following stress resolution (the "let-down effect"). Patients frequently described a sense of "embodied conflict," where unexpressed emotions and inhibited defensive responses appeared to manifest somatically. Additionally, the disease itself may contribute to the maintenance of dysfunctional relational dynamics through secondary gain mechanisms, reinforcing patterns of inescapability and reduced assertiveness.

Conclusions. These findings suggest that chronic relational stress may represent a relevant cofactor in the modulation and clinical expression of ITP. We propose that rethinking the pathogenesis of immune-mediated diseases through a biopsychosocial lens constitutes not only an innovative perspective but also a potential strength in understanding disease variability and outcomes. In this model, immune dysregulation reflects not only biological vulnerability but also the cumulative impact of relational experiences on neurophysiological systems. We believe that medical management and structured psychological interventions is particularly valuable: while pharmacological treatment remains essential, the addition of interventions targeting autonomic regulation, emotional awareness, trauma processing, and assertiveness development may enhance overall disease management. This multidisciplinary collaboration between physicians and psychologists supports a more comprehensive and person-centred model of care. GA/LR equally drafted the text





IMPACT OF THE 2023 ACR/EULAR ANTIPHOSPHOLIPID SYNDROME CRITERIA IN 1200 WOMEN WITH PRIOR OBSTETRIC ANTIPHOSPHOLIPID SYNDROME

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Background and aims. The 2023 ACR/EULAR classification criteria for antiphospholipid syndrome (APS) were developed to improve specificity, but concerns have emerged regarding their sensitivity, particularly in obstetric APS (OAPS). This study aimed to assess the impact of the new criteria in a large, well-characterized cohort of women previously classified with OAPS according to the Sydney criteria, and to explore potential clinical implications of reclassification.

Methods. We analysed 1,200 women included in the EU-ROAPS registry who fulfilled the 2006 Sydney classification criteria for obstetric APS. These cases were re-evaluated using the 2023 ACR/EULAR criteria, focusing on obstetric clinical manifestations (domain 4) and laboratory features (domain 8). The cohort included patients from 30 tertiary centres across Europe and Argentina. Descriptive analyses were performed to determine the proportion of patients remaining classifiable under the new framework and to identify the main factors driving exclusion.

Results. Application of the 2023 ACR/EULAR criteria led to a substantial reduction in classifiable cases. Based on clinical criteria alone, 68% of women were excluded, primarily due to the lower weighting of recurrent pregnancy loss and fetal death. Additional exclusions occurred when applying laboratory constraints, including reduced consideration of isolated IgM positivity and the introduction of fixed antibody thresholds. Overall, only 256 out of 1,200 women (21.3%) remained classifiable as OAPS. The main drivers of reclassification were the stringent scoring system in the obstetric domain, the non-cumulative nature of clinical items, and restrictive laboratory definitions.

Conclusions. In this large multicentre cohort, the 2023 ACR/EULAR criteria markedly reduced the number of women classified with obstetric APS compared with the Sydney criteria. While increased specificity may benefit research homogeneity, the significant loss of sensitivity raises concerns about under-recognition of clinically relevant disease. These findings highlight the need for careful clinical judgement and further prospective studies to refine classification strategies and ensure that patients at risk are not overlooked.

ABSTRACT N. CO098

ANTI-B2GPI AND ANTI-PS/PT ANTIBODIES, AND THEIR COMBINATION, EXERT A DISTINCT PLATELET ACTIVATION PROFILE

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Background and Aims. Antiphospholipid syndrome (APS) is a systemic autoimmune disorder characterized by venous and arterial thrombosis in the presence of antiphospholipid antibodies. Platelets are increasingly recognized as key cellular effectors in APS, contributing not only to thrombus formation but also to amplification of thrombo-inflammatory and procoagulant pathways. Recent evidence has shown that total IgG from high-risk APS patients can induce a platelet procoagulant profile, characterized by increased P-selectin, activated integrin αIIbβ3 and tissue factor (TF) expression. Besides anti-β2GPI antibodies, anti-phosphatidylserine/prothrombin (PS/PT) antibodies are frequently detected in high-risk APS profiles. However, the relative contribution of these antibody specificities to platelet activation remain incompletely defined. The aim of this study was therefore to compare the individual effect of anti-β2GPI and anti-PS/PT antibodies on platelet phenotype.

Methods. Immunoaffinity-purified anti-β2GPI or anti-PS/PT IgG or total IgG from tetra-positive APS patients were used to investigate platelet activation markers in whole blood by flow cytometry. 10µl of WB (4x10^6 platelets) were incubated for 30 minutes at RT with 50µl of anti-β2GPI or anti-PS/PT IgG (1.25-2.5 µg/ml according to each single IgG concentration). To evaluate the impact of IL-6 (100 pg/ml) and/or Calcium (5mM) on platelet activation, healthy subject (NHS) blood was stimulated with IL-6 or calcium plus anti-β2GPI or anti-PS/PT IgG at RT for 30 minutes. Samples were then labelled with specific mAb for P-selectin, aGPIIbIIIa and TF and analyzed by flow cytometry.

Results. Purified anti-β2GPI and anti-PS/PT IgG fractions obtained from 4 APS patients were characterized for antigen specificity, isotype, lupus anticoagulant activity and antibody titer (Figure 1A). When tested in whole blood from healthy subjects, anti-β2GPI IgG showed limited ability to induce classical platelet activation markers (P-selectin and activated GPIIb/IIIa) when added alone. However, in the presence of IL-6, anti-β2GPI IgG induced P-selectin and activated GPIIb/IIIa expression. These findings suggest that inflammatory priming is required to fully unmask the platelet-activating potential of anti-β2GPI antibodies. In contrast, anti-β2GPI IgG were able to induce platelet TF expression even in the absence of IL-6, with a further increase under inflammatory stimulation, indicating a direct contribution of these antibodies to the acquisition of a platelet procoagulant phenotype (Figure 1B). By contrast, anti-PS/PT IgG did not induce a significative increase in platelet TF expression in the presence of calcium, either alone or in combination with IL-6, with values remaining largely comparable to controls (Figure 1C). Consistently, total IgG from high-risk APS patients induced a marked increase in TFpos-platelets compared with unstimulated whole blood and NHS IgG suggesting that the effect is likely driven by anti-β2GPI IgG (Figure 1D).

Conclusions. Anti-β2GPI and anti-PS/PT IgG both contribute to platelet activation with distinct effects. Anti-β2GPI antibodies are primarily involved in TF induction, whereas both antibody specificities may support platelet activation in an inflammatory context. These data provide further insight into the cellular mechanisms underlying thrombosis in high-risk APS patients and support the concept that different antiphospholipid antibody specificities cooperate in shaping a platelet-driven thrombophilic phenotype.

A)

Patients	IgG anti-β2GPI (µ/mL)	IgG anti-β2GPI ELISA (U)	LA	IgG aPS/PT (µg/mL)	IgG aPS/PT ELISA (U)	LA
# 1	56	100	+	25	152	++
# 2	30	29	+	22	130	++
# 3	89	194	+	55	250	+++
# 4	49	141	+	22	110	++

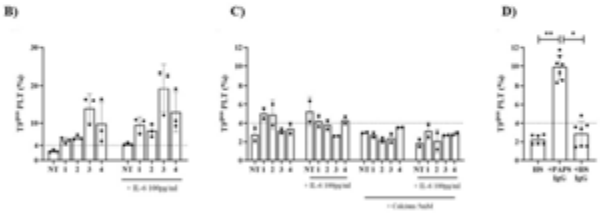


Figure: (A) Characterization of anti-β2GPI and aPS/PT IgG obtained from 4 tetra-positive APS patients. Effect of a.p. anti-b2GPI **(B)** and anti-PS/PT **(C)** IgG on NHS platelet TF-expression. Effect of APS or NHS total IgG on NHS platelet TF-expression **(D).** Dotted lines show the normal cut-off values. Values are reported as mean ± SD. * p< 0.05; **< 0.01.



OPTIMIZING CUT-OFFS FOR LUPUS ANTICOAGULANT TESTING: EVIDENCE FROM A MULTICENTER REGIONAL STUDY

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Background. Antiphospholipid syndrome requires a multidisciplinary approach, and despite similar analytical platforms across Tuscany, harmonization is needed to ensure diagnostic consistency. Accurate lupus anticoagulant (LAC) testing depends on minimizing clinical and laboratory variability, including standardized diagnostic algorithms, normalization methods, cut-off definition, and interpretative criteria. In this context, a regional working group was established in Tuscany in 2025 to promote harmonization of LAC testing and management.

Aims. To identify and compare optimal cut-offs for the LAC diagnostic algorithm using data from the Tuscany Regional Working Group on Hemostasis and Thrombosis.

Methods. Citrated plasma samples were collected from blood donors at hospital and university transfusion centers across Tuscany (October–December 2025). Donors were not on anticoagulant therapy and had no known atherothrombotic or autoimmune diseases. Samples were tested using a standardized LAC panel, including Silica Clotting Time (SCT) and Dilute Russell's Viper Venom Time (dRVVT) assays (screening, mixing, confirmatory) (Werfen, Italy). Analyses were performed on ACL TOP analyzers (Werfen, Italy). Results were expressed as ratios normalized to normal pooled plasma (NPP). Cut-offs were defined as the 99th percentile according to ISTH guidelines. Outliers were identified using CLSI criteria (values >1.5×IQR).

Results. A total of 198 samples (110 males, 88 females; mean age 42 years) were analyzed. Initial cut-offs (99th percentile) were: SCT screening 1.20, SCT mixing 1.10, SCT NTR 1.23; dRVVT screening 1.23, mixing 1.14, NTR 1.22. After exclusion of 9 outliers, SCT cut-offs remained unchanged, whereas dRVVT screening and NTR slightly decreased (1.19 and 1.21, respectively). In 98 AF patients from Careggi University Hospital, LAC positivity using previous (>1.2) and study-derived cut-offs showed 92.9% concordance (91/98) and 7.2% discordance, with excellent agreement (κ=0.85, $p<0.001$). No significant differences in clinical-laboratory characteristics were observed, except for lower anti-β2GPI IgG levels in discordant cases.

Conclusions. LAC standardization remains challenging, with the mixing test representing a critical step influenced by NPP quality. Standardized reference materials and collaborative initiatives may reduce variability, improve reproducibility, and enhance harmonization of LAC diagnostics.



ANTIPHOSPHATIDYLSERINE–PROTHROMBIN ANTIBODIES IN ANTIPHOSPHOLIPID SYNDROME: CLINICAL ASSOCIATIONS AND DIAGNOSTIC GAPS MAPPED BY A SCOPING REVIEW

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Background and Aims. Antiphospholipid syndrome (APS) is a systemic autoimmune thromboinflammatory disorder characterized by thrombosis and/or pregnancy morbidity in association with antiphospholipid antibodies (aPL). As no single laboratory test serves as a diagnostic gold standard, non-criteria antibodies such as antiphosphatidylserine–prothrombin (aPS/PT) have been proposed to complement conventional testing, though their clinical utility remains inconsistently reported. This scoping review mapped the clinical and laboratory relevance of aPS/PT in APS, including seronegative APS, while identifying diagnostic gaps, methodological heterogeneity, and key uncertainties.

Methods. A scoping review was conducted in accordance with PRISMA-ScR guidance and prospectively registered on the Open Science Framework (OSF; doi:10.17605/OSF.IO/FSJ8Z). A systematic search of PubMed, Scopus, Embase, and Web of Science identified 1,540 records using predefined strategies. After removal of 1,080 duplicates, title/abstract screening, and full-text review, 58 studies were selected for data extraction. Screening was performed using the Rayyan software. Data were extracted using a structured electronic form and synthesized descriptively.

Results. A total of fifty-eight studies were incorporated, predominantly single-centre (53 out of 58) and retrospective (34/58), spanning 1988–2023. The majority examined IgG and IgM aPS/PT (52/58), exhibiting considerable geographic and methodological heterogeneity. Only fourteen studies distinctly distinguished primary antiphospholipid syndrome (APS), secondary APS, non-APS, and disease controls, whereas most investigations depended on mixed or outcome-driven cohorts. Commercial assays were predominant (42 out of 58), primarily from Werfen; however, cut-off definitions varied considerably, even within identical kit types. Persistence and titers of aPS/PT were infrequently evaluated. Lupus anticoagulant was assessed in fifty-five studies employing diverse methodologies. Among thirty-five studies assessing concordance, aPS/PT demonstrated a positive correlation with lupus anticoagulant in thirty-one, although multivariable adjustment was uncommon. Associations with thrombosis and pregnancy morbidity were frequently reported but lacked consistent definitions and analytical approaches.

Conclusions. aPS/PT demonstrates a reproducible trend toward association with APS-related laboratory and clinical outcomes; however, marked heterogeneity in cohort definitions, patient selection, assay platforms, cut-off determination, and limited multivariable analyses underscores substantial scope for methodological harmonization and standardized statistical approaches to improve confidence in interpreting this widely discussed non-criteria antibody.



PLATELET ACTIVATION AND THROMBOGENICITY IN ANTI-PHOSPHOLIPID ANTIBODY-POSITIVE SUBJECTS: AN INTEGRATED TGA AND T-TAS ANALYSIS

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Background and Aims. Antiphospholipid syndrome (APS) is characterized by the presence of antiphospholipid antibodies (aPL) and is associated with an increased risk of thrombotic events and pregnancy morbidity. However, risk stratification in aPL-positive subjects, particularly in those without prior clinical manifestations, remains challenging. This study aimed to evaluate platelet phenotype and thrombogenicity as potentially valuable tools for the identification and thrombotic risk stratification of patients with aPL.
Methods. Thirty-two patients (16 males, age: 50±17, n=11 on warfarin, n=8 on aspirin) with aPL positivity (n=17 APS, n=10 with thrombocytopenia) was compared with age- and sex-matched healthy controls (n=40). Platelet aggregation was assessed by light transmission aggregometry and expressed as percentage of maximal aggregation (%MA). Platelet activation markers (CD62P and PAC-1) were evaluated by flow cytometry as mean fluorescence intensity (MFI). Global hemostatic potential was assessed using thrombin generation assay (TGA) and total thrombus-formation analysis system (T-TAS), a microchip-based flow chamber evaluating platelet thrombus formation (PL chip) and whole-blood thrombogenicity (AR chip).
Results. Platelets from patients showed: i) reduced aggregability to 5µmol/l ADP (57±6 vs 72±4, p=0.045), 4 mg/l collagen (46±6 vs 85±4, p<0.01), 5µmol/l epinephrine (35±6 vs 66±7, p=0.02), arachidonic acid (35±7 vs 69±5, p<0.001); ii) increased basal CD62 expression (14±2 vs 6±0.4, p<0.001) and reduced binding to PAC-1 in response to 5µmol/l ADP (65±4 vs 80±2, p=0.02) and 1µmol/l TRAP-6 (0.74 ±0.15 vs 1.3 ±0.25, p=0.05). Patients also showed altered TGA profiles characterized by prolonged lag time (tLAG: 9.6±0.7 vs 6.2±0.5 min, p=0.005.) and reduced thrombin production (PEAK:273±23 vs 3872 ±636 nm/l, p<0.03) more evident in patients with thetra positivity to aPL, and by altered T-TAS profiles: AUC-PL:186±34 vs 362±11(p<0.001) and AUC-AR: 944±138 vs 1362±25 (p=0.01). These alterations were found independently of anti- aggregant or anti-coagulant therapy. Strong correlations between T-TAS and TGA parameters were also found.
Conclusions. APS and aPL-positive subjects exhibit significant alterations in platelet activation and coagulation profiles. Platelets show reduced aggregability, increased expression of the activation marker CD62, and reduced PAC-1 binding, likely reflecting a shift toward a procoagulant phenotype. The positive correlation between thrombin generation parameters and T-TAS suggests that these two assays capture, at least in part, the same pathophysiological axis: the overall capacity to generate thrombin and to support thrombus formation and stability. For this reason, T-TAS may be a valuable tool to identify different aPL profiles can underlie different prothrombotic states.



VARIABILITY IN ANTIPHOSPHOLIPID ANTIBODY TESTING AND TREATMENT STRATEGIES IN OBSTETRIC ANTIPHOSPHOLIPID SYNDROME: RESULTS FROM THE OAPS-CARE SURVEY, ON BEHALF OF THE EUROPEAN FORUM ON ANTIPHOSPHOLIPID ANTIBODIES

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Background and aims. Obstetric antiphospholipid syndrome (OAPS) is a major cause of pregnancy morbidity characterized by placental insufficiency, fetal loss, and recurrent miscarriage in association with persistent antiphospholipid antibodies (aPL). Despite international classification criteria and therapeutic recommendations, substantial variability remains in real-world practice. To address this gap, the Obstetric Antiphospholipid Syndrome: Clinical Assessment and Reproductive Evaluation (OAPS-CARE) survey was developed within the European Forum on Antiphospholipid Antibodies framework to document international, real-world practices for assessing and managing OAPS.

Methods. The OAPS-CARE study was designed as an international, cross-sectional, internet-based survey to assess current clinical practices in the diagnosis and management of OAPS. The survey was formulated by a multidisciplinary steering committee comprising rheumatologists, internists, obstetricians, and clinical immunologists with specialized knowledge on APS and pregnancy morbidity. The 60-item questionnaire addressed definitions of obstetric morbidity, indications, timing, interpretation of aPL testing, use of classification criteria, and treatment strategies across pregnancy scenarios

Results. A total of 152 clinicians from 24 countries participated, of whom 123 (81%) completed the survey. The majority were rheumatologists (46.3%) and obstetricians/gynecologists (22.0%), mostly practicing in tertiary care centers. Recurrent miscarriage (93.5%), placental insufficiency (65.9%), and preeclampsia (56.1%) were the most frequently associated obstetric manifestations. Although lupus anticoagulant (98.2%), anticardiolipin (96.3%), and anti-β2-glycoprotein I antibodies (89.9%) were widely tested, variability emerged in timing, interpretation, and repeat testing practices. While most respondents recommended low-dose aspirin plus low-molecular-weight heparin in confirmed OAPS, management strategies diverged substantially between double/single aPL positivity and non-criteria scenarios. Adjunctive therapies, such as hydroxychloroquine, were inconsistently administered. In cases of refractory OAPS and high-risk pregnancies most clinicians prefer to escalate treatment rather than continue the same regimen. Nearly half (46.1%) of practitioners would increase to therapeutic-dose LMWH plus LDA, while almost two-thirds (64.7%) would add HCQ from preconception, making HCQ the most recommended adjunctive strategy.

Conclusions. Our findings indicate that contemporary OAPS management operates in a hybrid space between classification-driven precision and phenotype-driven pragmatism. The predominance of small effect sizes across many comparisons indicates encouraging international alignment; however, the consistent variability in lower-risk and refractory scenarios reveals areas where guidance remains insufficiently operationalized. Future international recommendations should (i) harmonize obstetric definitions, (ii) standardize laboratory thresholds across assay platforms, and (iii) formalize risk-adapted escalation pathways integrating antibody profile, obstetric phenotype, and prior treatment response.



DIAGNOSTIC VALUE OF PLATELET GRANULE CONTENT AND RELEASE IN PATIENTS WITH INHERITED PLATELET FUNCTION DISORDERS WITH NORMAL PLATELET AGGREGATION

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Background and Aims. Inherited platelet function disorders (IPFD) are a heterogeneous group of rare bleeding disorders characterized by dysfunctional platelets. Establishing a definitive diagnosis of IPFD is crucial not only for providing personalized treatment and accurate prognostic assessment, but also for genetic counseling and family screening. This is particularly important for IPFDs associated with a high risk of bleeding and linked to potentially severe syndromic manifestations. However, the diagnosis of IPFD is complex and requires first-, second-, and third-level laboratory tests. The "gold standard" test for the diagnosis of IPFD is light transmission aggregometry. However, this method may lack sensitivity in detecting platelet α- and/or δ-granules content and/or release defects, thereby limiting their identification. The ISTH guidelines for IPFD diagnosis recommend the evaluation of platelet granule release and content as a first- and second-line tests, respectively (PMID: 25403439). However, an international survey showed that fewer than 50% of specialized laboratories assess platelet granule content and/or release tests during the diagnostic work-flow of a suspected IPFD, and, when they do it only as a second-line test (PMID: 24976115). Our aim was to explore the diagnostic value of assessing platelet α- and δ-granules content and/or release as first-line laboratory investigations in patients with IPFD but normal platelet aggregation.

Methods. We enrolled 39 patients with 11 different forms of IPFD diagnosed according to strict laboratory criteria and we performed the following first- and second-level diagnostic tests: light transmission aggregometry, platelet α-granule content and release (P-selectin expression by flow cytometry, and β-thromboglobulin content and release by ELISA), platelet δ-granule content and release (mepacrine uptake and release by flow cytometry, and ATP content and release by lumi-aggregometry)

Results. 26% of the enrolled patients (10 over 39), despite having a diagnosis of IPFD, exhibited normal platelet aggregation, and in particular: 5 patients with primary secretion defect, 2 with α/δ-granule defect, 2 with Hermansky Pudlak syndrome, 1 with familial platelet disorder predisposing to myeloid malignancies. Of the patients with normal platelet aggregation 40% showed defective α -granule content and 70% defective release. Moreover, 40% showed defective δ -granule content and 70% defective release. Overall, 70% showed defective content of α- or δ-granules and 100% defective release. Therefore, 100% of patients with normal platelet aggregation had a defect of α- or δ-granules. Measurement of β-thromboglobulin release detected more defects than assessment of P-selectin expression (70% vs 35% of patients). Results were comparable for assessment of mepacrine and ATP content and release (content: 40% vs 44%; release: 80% vs 70%).

Conclusions. Relying exclusively on light transmission aggregometry for the identification of IPFD may lead to overlooking the diagnosis of a non-negligible proportion of patients who can instead be identified through laboratory assays evaluating platelet α- or δ-granules release. The assessment of platelet granules should therefore be systematically included as first-line diagnostic test for suspected IPFD. Moreover, a test different from P-selectin expression may be advisable as alternative or additional test for the detection of α-granule defects.



PERIOPERATIVE BLEEDING IN CHILDREN WITH LOW VON WILLEBRAND FACTOR UNDERGOING ENT SURGERY: A 15-YEAR SINGLE-CENTRE EXPERIENCE

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Background and aims. Low von Willebrand factor is a borderline haemostatic condition with uncertain perioperative significance in children. ENT surgery represents a clinically relevant model, as bleeding risk may reflect both systemic haemostatic impairment and local surgical and fibrinolytic mechanisms. We aimed to evaluate the incidence, timing and predictors of perioperative bleeding in children with low VWF undergoing ENT surgery, and to compare outcomes with a large cohort of healthy paediatric controls. We conducted a retrospective single-centre study including 120 children with low VWF undergoing ENT surgery and 1,136 healthy paediatric controls.

Methods. Cohorts were derived from institutional databases collected over partially non-overlapping time periods.Collected variables included age, sex, type of surgery, personal and family bleeding history, ISTH-BAT score (available in a subset), VWF:RCo, VWF:Ag, FVIII, aPTT ratio and platelet function analyser (PFA) closure times.The primary outcome was intra-/post-operative bleeding, classified as early (0–48 h), late (G7–13) or not defined. Continuous variables were analysed using the Mann–Whitney U test and categorical variables using Fisher's exact test.

Results. The low VWF cohort (n=120) was comparable to controls for age and sex. Baseline clinical bleeding features were more prevalent in low VWF patients (personal bleeding 17.5% vs 3.9%, $p<0.001$; family history 17.5% vs 1.1%, $p<0.001$). Perioperative bleeding occurred in 25.0% of low VWF patients and 28.3% of controls ($p=0.521$). Major bleeding occurred in 5.8% vs 3.0% ($p=0.103$). Among classified events, major bleeding was more frequent in low VWF patients (26.9% vs 10.6%, $p=0.023$). Within the low VWF cohort, no baseline clinical or laboratory parameter predicted bleeding, including age, sex, type of surgery, personal bleeding history, family history, ISTH-BAT score, VWF:RCo, VWF:Ag, FVIII and PFA closure times (all $p>0.1$). The only parameter associated with bleeding was a lower aPTT ratio in bleeders (1.09 vs 1.15; $p=0.014$), with a stronger association observed in major bleeding, although its direction is not biologically intuitive. Bleeding events showed a bimodal temporal distribution: 70.0% occurred within 48 h, 23.3% between G7–13 and 6.7% were not defined.

Conclusions. Children with low VWF undergoing ENT surgery display a clinically relevant rate of perioperative bleeding; however, overall bleeding rates are not significantly different from those observed in healthy paediatric controls. Despite a higher prevalence of baseline bleeding phenotype, no clinical or laboratory parameter reliably predicted surgical bleeding, suggesting a multifactorial mechanism not captured by standard haemostatic assessment. A shift towards more severe bleeding among classified events and a bimodal temporal pattern support the coexistence of systemic and local mechanisms. Differences in cohort collection periods and potential heterogeneity in bleeding reporting should be considered when interpreting comparisons.

ABSTRACT N. CO105

THALIDOMIDE FOR RECURRENT GASTROINTESTINAL BLEEDING IN RARE BLEEDING DISORDERS AND VENOUS MALFORMATIONS: A MONOCENTRIC EXPERIENCE

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Background and Aims. Recurrent gastrointestinal (GI) bleeding due to angiodysplasia or venous malformations represents a major therapeutic challenge, particularly in patients with underlying congenital or acquired bleeding disorders. Endoscopic and haemostatic treatments often achieve only transient benefit, while long-term pharmacologic options remain limited. Thalidomide, an anti-angiogenic agent, has shown efficacy in refractory gastrointestinal angiodysplasia in randomized controlled trials and meta-analyses; however, these studies were conducted in patients without systemic bleeding disorders. Consequently, real-world data on the use of thalidomide in ultra-rare bleeding disorders associated with angiodysplasias remain scarce. To evaluate the efficacy, safety, and clinical patterns of response to thalidomide in a monocentric cohort of patients with recurrent GI bleeding associated with rare bleeding disorders and angiodysplasias or vascular malformations.

Methods. We retrospectively analysed seven patients treated with oral thalidomide (50–150 mg/day) for recurrent GI bleeding unresponsive or only partially responsive to endoscopic therapy and standard haemostatic approaches. Diagnoses included acquired von Willebrand disease (AVWD), type 2B von Willebrand disease (vWD), Glanzmann thrombasthenia (GT), and Blue Rubber Bleb Nevus Syndrome (BRBNS). All patients had documented GI bleeding from angiodysplasias or from multiple venous malformations located mainly in the submucosa of the gastrointestinal tract (BRBNS). Outcomes included haemoglobin (Hb) stability, transfusion requirements, hospitalizations, recurrence of overt bleeding, treatment adherence, and adverse events.

Results. Five patients achieved sustained clinical benefit, with marked reduction of GI bleeding relapses, stabilization or improvement of Hb levels, and discontinuation or de-escalation of transfusions, IVIg, octreotide, and/or vWF/FVIII concentrate support (fig. 1). Dose–response and adherence emerged as key determinants of efficacy, particularly in type 2B vWD and one AVWD patient. The BRBNS patient achieved complete bleeding control with low-dose thalidomide (50 mg/day) (fig. 2). A type 2B vWD patient with refractory jejunal angiodysplasia-related bleeding achieved sustained bleeding control with thalidomide 50 mg/day, with no need for further transfusions and hospitalizations discontinuation of octreotide, and reduction of vWF/FVIII concentrate support over approximately 5–6 months of follow-up. Conversely, the GT patient experienced only a transient improvement, followed by recurrent bleeding and significant toxicity, limiting long-term treatment (Fig 2). Adverse events included dose-dependent peripheral neuropathy, mild paresthesias, fatigue, constipation, and one case of suspected bone marrow suppression, in line with previously reported safety profiles.

Conclusions. In this small monocentric cohort, thalidomide provided meaningful and, in several cases, sustained control of recurrent GI bleeding in AVWD, type 2B vWD, and BRBNS, whereas efficacy was transitory in GT. These findings extend randomized trial evidence to ultra-rare bleeding conditions and support the use of thalidomide as a second-line, symptom-targeted option in carefully selected patients with bleeding disorders and recurrent GIBs, provided that toxicity is closely monitored and adherence maintained. Larger real-world studies are needed to better define optimal dosing, treatment duration, and long-term safety.



Figure 1: Clinical outcomes before and during thalidomide therapy in seven patients with recurrent gastrointestinal bleeding associated with rare bleeding disorders and gastrointestinal vascular lesions. The table shows transfusion requirements, mean haemoglobin levels, and concomitant therapies before and during treatment, highlighting reduced transfusion needs, improved haemoglobin stability in most patients, and de-escalation of supportive therapies in responders.

Patient	Diagnosis	Treatment's lenght	Thalidomide's dose	Response	Side effects
Case #1	AvWD	30 months	50 mg/die	Complete response	None
Case #2	AvWD	24 months	from 50 mg/48h to 50 mg/die	Complete response	Paresthesias
Case #3	AvWD	24 months	from 50 mg/48h to 50 mg/die	Complete response/dose-dependent	Lower limb pain
Case #4	vWD 2B	22 months	from 50 mg/die to 100 mg/die	Partial response limited to first 18 months	None
Case #5	GT	24 months	from 50 mg/die to 100 mg/die	Partial response limited to first 6 months	Mental confusion Walking instability Paresthesias Neutropenia
Case #6	BRBNS	11 months	50 mg/die	Complete response	None
Case #7	vWD 2B	6 months	50 mg/die	Complete response	Paresthesias Fatigue

Figure 2: Summary of thalidomide dosing, treatment duration, clinical response, and adverse events in six patients, showing sustained benefit in most disorders except GT, and variable toxicity profiles.

ABSTRACT N. CO106

ENDOTHELIAL DYSFUNCTION AS A POSSIBLE ADDITIONAL DRIVER OF BLEEDING IN HERMANSKY–PUDLAK SYNDROME

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Background and aims. Hermansky-Pudlak syndrome (HPS) is an inherited multisystem disorder caused by a defect of lysosome-related organelles, like delta granules in platelets and Weibel Palade Bodies (WPB) in endothelial cells (EC). All HPS subtypes manifest oculocutaneous albinism (OCA) and bleeding, while recurrent infections due to neutropenia and/or immunodeficiency may develop only in patients with HPS types 2, 9 or 10 and pulmonary fibrosis in patients with HPS types 1, 2, or 4 (PMID: 23171219). Additionally, patients with HPS-1 and HPS-4 may manifest granulomatous colitis (PMID: 40387003). Most of the studies exploring the molecular mechanisms involved in the pathogenesis of HPS investigated melanosomes, alveolar epithelial cells and platelet delta granules but little is known about ECs. We aimed to investigate endothelial function in different subtypes of HPS, specifically in HPS-1, HPS-2, HPS-3, and HPS-6; exploring the hypothesis that the bleeding phenotype of patients with HPS may not only be due to the well-known platelet defect but also to a defect of endothelial cells.

Methods. Endothelial colony forming cells (ECFC) were generated from peripheral whole blood of one HPS patient from each subtype considered in the study (HPS-1, HPS-2, HPS-3, and HPS-6) and from four age and sex matched healthy controls. ECFC were characterized morphologically and for EC surface markers by flow cytometry. WPB were quantified by immunofluorescence. EC migration was assessed by the transwell migration assay towards 10% FBS, and results are reported as fold change of covered lower filter surface respect to control. Angiogenesis was evaluated by the Matrigel tube formation assay and quantified as total tube length, total tube number and total branching points. Apoptosis was assessed using the Caspase-Glo 3/7 assay.

Results. ECFCs, from passage three, expressed all EC markers (CD31, CD309, CD146) and were negative for leukocyte (CD45) and monocyte (CD14) markers. WPBs were significantly reduced in ECFCs from all HPS subtypes and showed a disorganized structure in all subtypes, except in HPS2 in which, although reduced, they maintained a normal structure (Fig.1A). Impaired ECFC migration was observed in HPS-1, HPS-3 and HPS-6 but not in HPS-2 (Fig.1B). Similarly, defective angiogenesis was observed with HPS-1, HPS-3 and HPS-6 ECFC, but not with HPS-2 ECFC (Fig.1C). Finally, only HPS-2 ECFCs showed increased apoptosis (Fig.1D).

Conclusions. ECFCs from all the HPS subtypes we studied showed reduced number of WPB, while an altered structure was observed in HPS-1, HPS-3 and HPS-6 ECFCs. These results were associated with defective EC migration and angiogenetic activity in all subtypes, except HPS-2, that however showed increased apoptosis. Our results suggest that endothelial dysfunction may play a role in the bleeding phenotype of HPS patients. Further studies are warranted to explore possible endothelial drug targets for restoring endothelial function in HPS with the aim of attaining a personalized therapeutic approach.

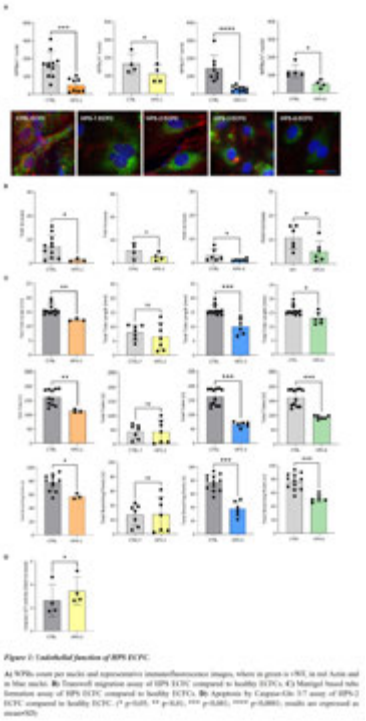


Figure 1: Endothelial function of HPS ECFC.

A) WPBs count per nuclei and representative immunofluorescence images, where in green is vWF, in red Actin and in blue nuclei. B) Transwell migration assay of HPS ECFC compared to healthy ECFCs. C) Matrigel based tube formation assay of HPS ECFC compared to healthy ECFCs. D) Apoptosis by Caspase-Glo 3/7 assay of HPS-2 ECFC compared to healthy ECFC. (* $p \leq 0.05$, ** $p \leq 0.01$, *** $p \leq 0.001$, **** $p \leq 0.0001$; results are expressed as mean±SD).



PREGNANCY IN A YOUNG WOMAN WITH SEVERE THROMBOCYTOPENIA ASSOCIATED WITH GNE GENE MUTATION

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Background. The GNE gene encodes UDP-N-acetylglucosamine 2-epimerase/N-acetylmannosamine kinase, a rate-limiting enzyme involved in the biosynthesis of sialic acid. Pathogenic GNE variants can cause GNE-related thrombocytopenia and/or myopathy. The clinical management of pregnant patients with a GNE gene mutation is not defined, nor are the risks and methods for minimising bleedings associated with this condition, especially during childbirth.

Case Report. We report of a young woman with a homozygous GNE mutation (p.Gly590Arg) presenting with severe thrombocytopenia and a moderate muco-cutaneous haemorrhagic syndrome, with some major haemorrhages (epistaxis since childhood and heavy menstrual bleedings) (ISTH-BAT: 13). Thrombocytopenia was evident from the first days of life (6–10 × 10^9 platelets/L) and had previously been misdiagnosed as immune thrombocytopenia. Standard treatments for immune thrombocytopenia were ineffective, with the exception of eltrombopag, which elicited a prompt increase in circulating platelets (30 to 60 × 10^9 platelets/L). Haemorrhagic phenotype improved over the years. At 21 years of age, the patient became pregnant while not receiving any pharmacological treatment. No change in haemorrhagic diathesis was observed and clinical monitoring was therefore decied during the first two trimesters of pregancy. The mean platelet count during pregnancy ranged 11 to 34 × 10^9/L. Pregnancy was complicated by gestational diabetes. To minimise the risk of delivery-related haemorrhage, eltrombopag (25 mg/day) was initiated at 34 weeks of gestation, resulting in an increase in platelet count to 47–51 × 10^9/L without any adverse event. The management of delivery was decided on a multidisciplinary basis (platelet transfusion, use of tranexamic acid and rFVIIa in the event of severe bleeding were recommended). Labour was induced at 38 weeks and delivery occurred without haemorrhagic or thrombotic complications in either the mother or the new born. Eltrombopag withdrawal during puerperium and lactation was followed by a prompt reduction in circulating platelets (27 × 10^9 platelets/L) with 76% immature platelet fraction. The assessment of platelet phenotype and function by flow cytometry revealed increased expression of activated GPIIb/IIIa, reduced GPIbα and increased binding of Annexin V (procoagulant platelets) in resting platelets, as well as a diminished response to platelet agonists (both secretion and glycoprotein expression).

Conclusions. Eltrombopag, administered in this case of GNE-related thrombocytopenia before the pregnancy and during the third gestational trimester, was both effective and safe. To our knowledge, this is the first report describing the use of eltrombopag in a patient with GNE-related thrombocytopenia. The present case and our findings indicate that thrombocytopenia is associated with indices of elevated platelet turnover, and platelet activation, which may contribute to platelet removal and may partly justify the discrepancy between severely reduced platelet counts and relatively mild bleeding symptoms. Further studies are needed better characterize the observed platelet functional abnormalities and the basis of clinical heterogeneity in this rare condition.

ABSTRACT N. CO108

MECHANOCHEMICAL REPROGRAMMING OF VWF–GPIB INTERACTIONS UNCOUPLES AFFINITY FROM AVIDITY AND LINKS THROMBOCYTOPENIA TO ANGIODYSPLASIA IN TYPE 2B VON WILLEBRAND DISEASE

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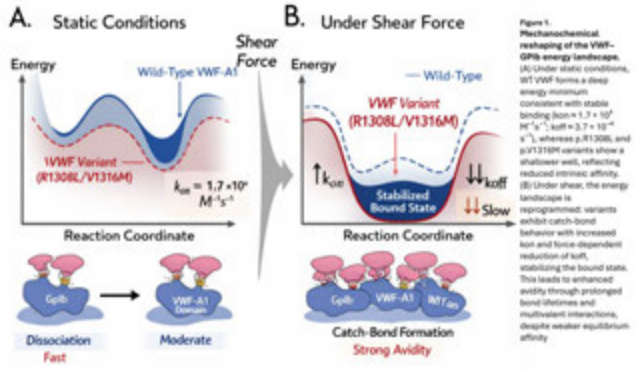
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Background and Aims. Gain-of-function variants of the von Willebrand factor (VWF) A1 domain, including p.R1308L and p.V1316M, are associated with enhanced platelet binding via glycoprotein Ib (GpIb), and high incidence of angiodysplasia lesions, as shown by two clinical cases herein described. Here, we combine structural interface analysis with thermodynamic and kinetic considerations to investigate the possible mechanisms responsible for these phenomena.

Methods. The combined use of I-TASSER, HADDOCK v2.4 and Prodigy programs allowed getting structural and energetic details of the complexes between WT, p.R1308L, and p.V1316M VWF variants and GpIb-A1 domain.

Results. The results showed comparable binding free energies between these VWF species, and even slightly reduced equilibrium affinity for p.V1316M relative to wild type (WT). Structural metrics reveals a redistribution of interfacial contacts toward a compact, high-density interaction core for the p.V1316M and p.R1308L variants. This configuration for the p.V1316M variant reduces geometric constraints for binding, enhancing association rates (kon), while promoting force-dependent stabilization through catch-bond behavior. We propose that the two variants shift the interaction from thermodynamic to kinetic and mechanical control, thereby increasing effective avidity under physiological shear (Fig.1). Molecular modeling of WT-, p.R1308L-, and p.V1316M-VWF variants with angiopoietin-2 showed that the latter are characterized by significant lower affinity for the angiopoietin-2, which, being less buffered by VWF2B, contribute to formation of angiodyplasia lesions.

Conclusions. These findings highlight the limitations of static ΔG predictions in mechanosensitive systems and provide a unified framework for understanding gain-of-function VWF variants and their angiodysplastic potential.



THE ROLE OF SELECTED *LDLR* AND *LRP1* VARIANTS IN MODULATING LDL AND FVIII LEVELS IN METABOLIC SYNDROME

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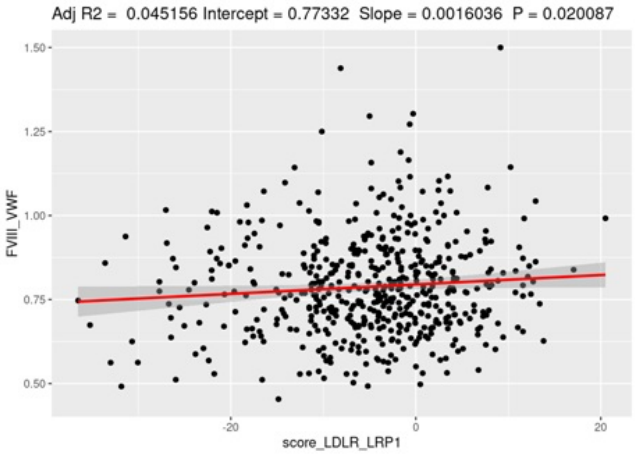
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Background and Aims. Low-density lipoprotein receptor (LDLR) and LDLR-Related Protein 1 (LRP1) showed a synergistic activity in modulating the clearance of coagulation factor VIII (FVIII). As a result, high FVIII coagulant activity levels (FVIII:C>150 IU/dL) were observed in carriers of *LDLR* variants. The combination of high FVIII levels with high FVIII:C/Von Willebrand Factor antigen (VWF:Ag) ratio (>1.5) suggests a reduced FVIII clearance. To date, data on the effect of these variants in metabolic syndrome are scarce. This study aims to evaluate the impact of *LDLR* and *LRP1* variants on plasma levels of (1) low-density lipoprotein-cholesterol (LDL-c), (2) FVIII and FVIII:C/VWF:Ag in patients with metabolic syndrome.

Methods. Blood donors aged 40-65 with metabolic syndrome were consecutively enrolled from July 2019 to July 2021 in the frame of the Liver BIoBank Lombardia gEnomic (Liver-Bible) cohort. A list of 65 variants (61 in *LDLR* and 4 in *LRP1*) associated with cholesterol levels, coronary artery disease, or body mass index (BMI) were selected from the GWAS Catalog (https://www.ebi.ac.uk/gwas/). Among these, 54 variants were extracted from the Liver-Bible genome-wide association study. Linkage disequilibrium r2 was calculated using Plink and 28 tag variants were selected (r2>0.8). Association analyses were performed by linear regression models. Potential effect modifiers [e.g. age, sex, ABO blood group, C-reactive protein (CRP), BMI, glycated haemoglobin (HbA1c)] have been taken into account.

Results. A total of 1,190 subjects were eligible for aim (1), 574 for aim (2). After adjusting for age, sex and BMI, three variants (rs688, rs10422256 and rs6511721) were found associated with higher LDL-c levels. No association between analysed variants and FVIII levels was found. The variant rs74257940 was associated with higher FVIII:C/VWF:Ag ratio. A LDLR-LRP1 weighted polygenic score (PGS), calculated using the beta coefficients obtained from the association with LDL-c levels, correlated with higher FVIII:C/VWF:Ag ratio (Figure).

Conclusions. Among the 28 analysed *LDLR* and *LRP1* variants, three *LDLR* variants (rs688, rs10422256 and rs6511721) were associated with increased LDL-c levels in a cohort of subjects with metabolic syndrome. The developed polygenic score resulted to be associated with higher FVIII:C/VWF:Ag ratio, suggesting a potential role of the selected variants in reducing FVIII clearance.



ABSTRACT N. CO110

FLOW-BASED WHOLE-BLOOD THROMBUS PROFILING DISCRIMINATES ANTITHROMBOTIC DRUG EFFECTS AND UNCOVERS PLATELET-DEPENDENT COAGULATION DEFECTS AFTER CARDIOPULMONARY BYPASS

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Background and Aims. Conventional coagulation tests and viscoelastic assays assess isolated enzymatic pathways or fibrin-weighted clot mechanics and often fail to capture thrombus formation as a dynamic process arising from platelet–coagulation interactions under flow. Most methods also rely on exogenous activators or inhibitors that may alter physiological responses. These limitations are relevant in complex settings such as cardiopulmonary bypass (CPB), where coagulopathy is multifactorial and not fully reflected by routine assays. We evaluated a flow-based whole-blood approach to quantify integrated thrombus formation under native conditions and assess its sensitivity to antithrombotic therapies and CPB-related hemostatic alterations.

Methods. Whole blood from healthy donors (n=62), patients on antiplatelet therapy (ASA n=24; $P2Y_{12}$ inhibitors n=11; DAPT n=32), anticoagulants (DOACs n=18; VKAs n=12), and CPB patients (Pre-CPB n=21; Post-CPB t_0 (immediately after protamine infusion) n=5; Post-CPB ICU (within ≈ 1.5h from protamine) n=21) was analyzed. Pre-CPB patients received low-dose aspirin (75–100 mg/day). Recalcified citrated blood was perfused over collagen at arterial shear ($\dot{\gamma}$=300 s^{-1}) without exogenous activators or inhibitors. Dual-channel epifluorescence imaging enabled real-time quantification of platelet aggregation and fibrin(ogen) formation. Time-series of integrated density (ID) were modeled to derive pseudo-volumes (AUC ID) for platelets, fibrin(ogen), and total thrombus. Platelet aggregate size was assessed at early (50–100 s) and late (200–450 s) phases; fibrin lag time was assessed by Kaplan–Meier analysis.

Results. The assay resolved distinct pharmacodynamic signatures. ASA reduced fibrin(ogen) and total thrombus more than platelet signal, whereas $P2Y_{12}$ inhibition markedly impaired platelet-dependent thrombus growth; DAPT showed the strongest inhibition. Anticoagulants mainly reduced fibrin(ogen) and total thrombus, with greater suppression in VKAs at higher INR. In CPB patients (Table 1), platelet (−66%), fibrin(ogen) (−71%), and total thrombus (−70%) pseudo-volumes were markedly reduced at ICU despite near-normal INR and aPTT. Early platelet adhesion (50–100 s) was preserved, indicating intact initial interaction with collagen. In contrast, aggregate growth was impaired in the late phase (200–450 s), when thrombin normally amplifies platelet recruitment and fibrin formation. Consistently, fibrin lag time was prolonged (219→332 s). These findings indicate that, despite preserved adhesion, insufficient development of a platelet-dependent procoagulant surface limits thrombin generation, resulting in reduced fibrin formation and smaller thrombus structures.

Conclusions. Flow-based whole-blood thrombus profiling discriminates functional signatures of anticoagulant and antiplatelet therapies and identifies a platelet-dependent coagulation defect after CPB not detected by conventional assays. The dissociation between preserved early adhesion and impaired thrombus growth reflects defective support of thrombin generation during the propagation phase of coagulation. By integrating platelet and fibrin dynamics under physiological flow without exogenous substances, this approach provides a mechanistic assessment of hemostatic function and may improve identification of clinically relevant bleeding risk in complex settings.

Table 1. Flow-Dependent Thrombus Parameters Before and After Cardiopulmonary Bypass

Parameter	Statistic	Pre-CPB (ASA) (n=21)	Post-CPB ICU (n=21)	Δ vs pre-CPB	Interpretation
INR	Range	1.00–1.41	1.03–1.76	Minimal change	Plasma pathways preserved
aPTT ratio	Range	0.80–1.39	0.76–1.67	No consistent prolongation	Intrinsic pathway preserved
Platelet AUC ID [×10⁶]	Mean ± SD	3.06 ± 1.56	1.04 ± 0.70	↓ 66%	Reduced platelet contribution under flow
Fibrin(ogen) AUC ID [×10⁶]	Mean ± SD	3.33 ± 1.47	0.96 ± 0.78	↓ 71%	Reduced thrombin-driven fibrin formation
Aggregate Size at 50 s (µm²)	Mean ± SD	17.7 ± 14.1	13.4 ± 5.6	↓ 24% (ns)	Initial adhesion preserved
Aggregate Size at 100 s (µm²)	Mean ± SD	13.3 ± 3.2	13.0 ± 4.5	↓ 2% (ns)	Early adhesion preserved
Aggregate Size at 200 s (µm²)	Mean ± SD	32.2 ± 9.9	18.6 ± 7.0	↓ 42%	Impaired thrombin-independent consolidation
Aggregate Size at 450 s (µm²)	Mean ± SD	131.7 ± 80.4	55.9 ± 37.0	↓ 58%	Reduced thrombus expansion
Fibrin Lag Time (s)	Median (K–M)	219	332	↑ 52%	Delayed thrombin onset
Total Thrombus AUC ID [×10⁶]	Mean ± SD	6.37 ± 2.72	1.94 ± 1.41	↓ 70%	Markedly reduced global thrombus capacity

ABSTRACT N. CO111

ROLE OF CONSTITUTIVE ENDOTHELIAL DYSFUNCTION IN THE PATHOGENESIS OF UNPROVOKED VENOUS THROMBOEMBOLISM: CHARACTERIZATION OF ENDOTHELIAL COLONY-FORMING CELLS AND ASSOCIATION WITH RISK OF RECURRENCE

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Background. Venous thromboembolism (VTE) can be associated with provoking factors, either major (defining provoked events, pVTE) or minor (defining weakly provoked events, wpVTE). Nonetheless, up to 40-50 % of VTE cases occur in absence of known triggering factors (unprovoked events, uVTE) and show high risk of recurrence. Since endothelial dysfunction (ED) plays a crucial role in triggering thrombus formation, possible presence of constitutive endothelial alterations deserves to be investigated in uVTE patients. In this regard, endothelial colony-forming cells (ECFCs) represent a valuable tool to study patient-specific endothelium.

Aims. To investigate the presence of alterations in ECFCs of VTE patients, thus identifying endothelium perturbation(s) involved in uVTE pathogenesis and recurrence risk.

Methods. ECFCs were isolated from 123 patients– classified as uVTE (n=28), wpVTE (n=58), pVTE (n=37) - and 58 matched healthy donors (HDs). Three months after the acute event, patients were evaluated. for clinical predictors of VTE recurrence and underwent peripheral blood sampling for ECFC isolation. ED was assessed by analyzing (i) platelet deposition and fibrin formation through thrombogenesis assay; (ii) thrombin formation through thrombin generation assay (TGA) on ECFCs; (iii) ECFC iexpression of adhesion molecules and pro-coagulant and anti-coagulant proteins; (iv) soluble forms of adhesion molecules in ECFC supernatant and plasma. The project was funded by the Italian Ministry of Health (GR-2018-12365520).

Results. In thrombogenesis assays, uVTE-ECFCs supported increased platelet deposition compared with HD ($p<0.05$), with no differences in fibrin formation. This pro-adhesive phenotype was associated with increased ECFC expression of ICAM-1 and PECAM-1 versus HD ($p<0.05$) and higher VCAM-1 versus HD and provoked VTE ($p<0.01$), paralleled by increased sICAM-1 and sPECAM-1 in ECFC supernatants and selective plasma sICAM-1 increase in uVTE. TGA showed faster and greater thrombin generation in uVTE versus HD and pVTE ($p<0.05$–0.01). Consistently, uVTE-ECFCs displayed increased tissue factor (TF) and reduced thrombomodulin (TM) expression, resulting in a higher TF/TM ratio ($p<0.01$). Overall, ED-related features were predominantly observed in the uVTE group, which also clustered with a higher risk of VTE recurrence based on clinical predictors (Table).

Conclusions. uVTE patients display a distinct ED phenotype and the highest recurrence risk, suggesting that ED may contribute to uVTE pathogenesis and represent a relevant feature for clinical risk stratification.



ABSTRACT N. CO112

LIPOPROTEIN(A) PLASMA LEVELS AND COAGULATION BIOMARKERS: RESULTS FROM A COMPREHENSIVE LABORATORY ASSESSMENT IN AN ANGIOGRAPHICALLY-CONTROLLED CARDIOVASCULAR COHORT

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Background and Aims. Lipoprotein(a) [Lp(a)] is a causal risk factor for coronary artery disease (CAD), with proposed prothrombotic properties in addition to its proatherogenic effects. However, the association between Lp(a) and coagulation remains controversial so far. This study examined this relationship in subjects with or without angiographically documented CAD.

Methods. Plasma levels of Lp(a) and coagulation biomarkers were assessed in clinically stable subjects undergoing elective coronary angiography. Subjects taking any anticoagulant therapy were excluded. The coagulation panel included coagulant activities of factors II, V, VII, VIII, IX, X, XI and XII, von Willebrand Factor Antigen (vWF:Ag), factor VII-antithrombin (FVIIa-AT) complex, total Tissue Factor Pathway Inhibitor (TFPI) and thrombin generation assay (TGA). Lp(a) threshold values were defined according to the European Atherosclerosis Society consensus statement: normal <30 mg/dL, intermediate 30-50 mg/dL, and high >50 mg/dL.

Results. Complete laboratory data were available for 383 subjects (males 75.3%; mean age 68.2±9.7 years): 65 subjects had normal coronary arteries (CAD-free group), 51 subjects had coronary lesions with stenosis <50% (CAD-borderline group), and 267 subjects had coronary lesions with stenosis ≥50% (CAD group). Only a modest yet significant increase in coagulant activity of FV (FV:C) from low to high Lp(a) plasma levels was found (Table I). In linear regression models, high Lp(a) levels remained significantly associated with FV:C after adjustment for potential confounders including sex, age, CAD diagnosis, body mass index, renal function, ApoB, ApoA-I, triglycerides, and coagulant activities of the other coagulation factors. No difference was observed for all the other coagulant activities, neither vWF:Ag, FVII-a-AT complex, total TFPI plasma levels nor TGA parameters. FV:C showed a progressive increase from low to high Lp(a) plasma levels also within the CAD group (p=0.034), and even if not statistically significant, presented the same trend also within the CAD free group.

Conclusions. In this pilot study, no major contribution of Lp(a) plasma levels was detected in modulating coagulation phenotype. High Lp(a) plasma levels were associated with only a mild increase of FV:C.

Table I: Coagulant activity of individual coagulation factors, concentration of activated factor VII-antithrombin (FVIIa-AT) complex, total tissue factor pathway inhibitor (TFPI), thrombin generation parameters and von Willebrand factor antigen (vWF:Ag) and according to Lp(a) plasma levels.

	Lp(a) <30 mg/dL (n = 256)	Lp(a) 30-50 mg/dL (n = 45)	Lp(a) >50 mg/dL (n = 82)	p *
FII:C (%)	90.1 ± 11.9	88.4 ± 13.9	91.3 ± 13.0	0.618
FV:C (%)	84.3 ± 18.7	86.8 ± 16.5	90.1 ± 18.7	0.010
FVII:C (%)	88.9 (86.2-91.7)	87.3 (81.0-94.2)	93.8 (89.7-98.1)	0.125
FVIII:C (%)	98.5 (94.7-102.4)	95.8 (88.2-104.1)	98.0 (90.5-106.1)	0.828
FIX:C (%)	117.5 ± 19.6	111.7 ± 19.8	114.7 ± 19.3	0.149
FX:C (%)	96.3 (94.3-98.3)	89.7 (84.9-94.7)	94.2 (90.8-97.8)	0.143
FXI:C (%)	104.1 ± 19.5	99.6 ± 21.6	102.9 ± 19.1	0.442
FXII:C (%)	102.3 ± 24.8	93.8 ± 27.7	100.6 ± 25.8	0.371
FVIIa-AT (pM)	103.1 (97.1-109.4)	107.0 (92.9-123.2)	112.9 (100.9-124.9)	0.160
Total TFPI (ng/mL)	65.3 ± 13.3	65.2 ± 15.6	70.0 ± 17.0	0.056
Lag time (min)	3.95 (3.86-4.05)	3.94 (3.86-4.20)	3.96 (3.80-4.13)	0.930
ETP (nM * min)	969 (933-1007)	1013 (920-1116)	952 (870-1041)	0.820
Peak (nM)	153 (145-160)	153 (136-171)	144 (129-160)	0.334
Time to peak (min)	7.62 (7.47-7.77)	7.67 (7.28-8.06)	7.77 (7.51-8.04)	0.346
MRI (nM/min)	42.3 (39.3-45.5)	41.4 (35.5-48.4)	38.5 (33.5-44.4)	0.227
vWF:Ag (IU/dL)	136.3 ± 43.3	141.4 ± 43.0	140.5 ± 49.3	0.802

ETP: endogenous thrombin potential; MRI: mean rate index
* : by ANOVA with polynomial contrasts for linear trend

ABSTRACT N. CO113

AN OBSERVATIONAL STUDY ON THE EFFECT OF HEMODIALYSIS MEMBRANES ON ENDOGENOUS THROMBIN POTENTIAL IN END STAGE RENAL DISEASE PATIENTS

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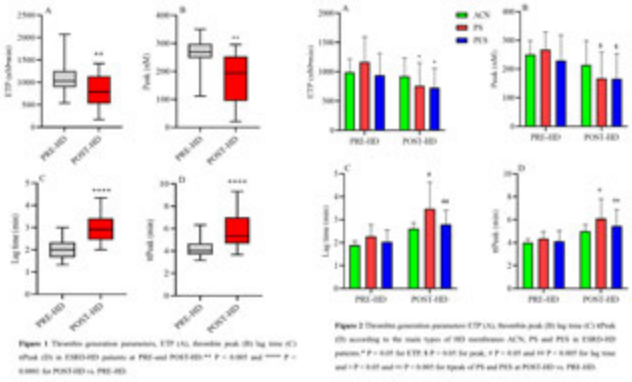
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Background and Aims. Cardiovascular disease and thrombosis are the leading cause of death in chronic kidney disease (CKD) patients. The end stage renal disease patients undergoing hemodialysis (ESRD-HD) are predisposed to hemostatic dysfunction, also due to HD membrane bioincompatibility. In this study, we aimed to evaluate thrombin generation potential in patients at different stages of CKD, including ESRD-HD patients. Furthermore, in HD patients, we compared thrombin generation parameters in pre-hemodialysis (PRE-HD) vs. post-hemodialysis (POST-HD). We also focused on the impact of different HD membranes and vascular access on thrombin generation parameters in ESRD-HD patients.

Methods. In this prospective observational study, we recruited 61 patients at different stages of CKD: 31 patients at stages I to V and 30 at ESRD-HD; we also evaluated 6 healthy controls. Thrombin generation by calibrated automated thrombin assay was evaluated in different classes of CKD and ESRD-HD; then, thrombin generation as well as total extracellular vesicles (EVs), platelets, endothelium and leukocyte derived microparticles (MPs) by flow-cytometry were evaluated at PRE-HD and POST-HD in ESRD-HD patients.

Results. Patients with CKD stages III, IV, V and ESRD-HD patients exhibited significantly lower endogenous thrombin potential (ETP) than control group, suggesting a reducing trend in thrombin generation potential along with decreasing renal function. Moreover in ESRD-HD patients, a significant decrease in ETP (829.4±348.5 vs. 1083±342.7 nM•min; $p < 0.005$) and peak thrombin generation (185.5±84.14 vs. 257.7±55.40 nM; $p < 0.005$) together with a prolonged lag time (3.02±0.66 vs. 2.06±0.45 min; $p < 0.0001$) and time to peak (ttpeak) (5.86 ±1.57 vs. 4.25 ± 0.72 min; $p < 0.0001$) were observed at POST-HD compared to PRE-HD, indicating a lower thrombin generation potential after dialysis. The flow-cytometric analysis identified a clear split into two groups, with some patients showing a significant reduction in total EVs, platelets, endothelium and leukocyte derived MPs and activated platelets MPs at POST-HD compared with PRE-HD and others showing a significant increase at POST-HD than PRE-HD, suggesting the variation in clinical characteristics of the patients and types of HD membrane might affect the EVs release. At an exploratory analysis, we observed a significant reduction in ETP and thrombin peak, consistently with a prolonged lag time and ttpeak, in patients treated with polysulfone-based (PS) and polyethersulfone-based (PES) HD membranes at POST-HD than PRE-HD, whereas patients on heparin-coated acrylonitrile membrane (ACN) showed no significant difference in thrombin generation parameters between PRE-HD and POST-HD. ESRD-HD patients with arteriovenous fistula access showed significantly lower thrombin generation parameters at POST-HD than PRE-HD.

Conclusions. Overall, these findings indicate lower thrombin generation parameters in patients with ESRD-HD compared with other CKD groups suggesting a higher risk of bleeding of this population, particularly after HD, when thrombin generation further decreases. The alteration in thrombin generation potential in this population could be in part due to variation in HD membrane and vascular access type.



ANTI-PS/PT IGM IDENTIFIES AN ANTIGEN-DEFINED SUBSET WITHIN LUPUS ANTICOAGULANT POSITIVITY ASSOCIATED WITH THROMBOTIC PHENOTYPE

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Background and Aims. Interpretation of isolated lupus anticoagulant (LAC) positivity remains challenging because LAC represents a functional coagulation abnormality rather than an antigen-defined immune response. Anti-phosphatidylserine/prothrombin (aPS/PT) antibodies have been proposed as non-criteria antiphospholipid antibodies that may refine serological characterization of LAC-positive patients. The study aims to determine whether aPS/PT antibodies identify antigen-defined subgroups associated with thrombotic phenotype among consecutive patients undergoing antiphospholipid antibody testing.

Methods. We performed a retrospective two-center observational study including 131 consecutive adult patients referred for antiphospholipid antibody evaluation (Fig. 1). All underwent testing for LAC, anticardiolipin antibodies, anti-β2-glycoprotein I antibodies, and aPS/PT antibodies. Because antibody testing was performed after clinical events, thrombosis was analyzed as a historical clinical phenotype. Associations were assessed using stratified comparisons and logistic regression adjusted for age, sex, smoking status, and hypertension.

Results. A history of objectively confirmed thrombosis was present in 72.1% of patients. aPS/PT IgM levels correlated with LAC activity measured by dRVVT ratio. Patients positive for LAC and aPS/PT IgM but negative for anticardiolipin and anti-β2-glycoprotein I antibodies had significantly higher odds of prior thrombosis compared with the reference serological profile (adjusted OR 11.2; 95% CI 2.5–50.8; p = 0.002).

Conclusions. In this selected tertiary referral cohort enriched for thrombotic disease, aPS/PT IgM identified a biologically and clinically distinct subset within LAC-positive patients associated with prior thrombosis. These findings support further prospective evaluation of aPS/PT testing for refinement of heterogeneous LAC positivity.

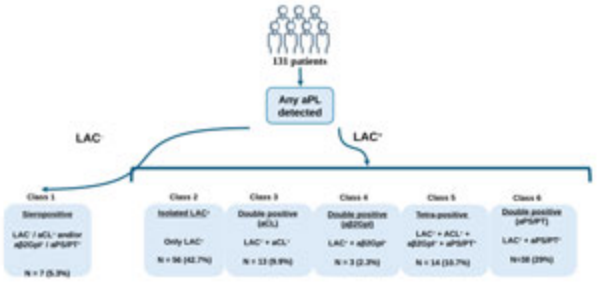


Figure 1

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POSTER



ABSTRACT N. PO001

EMERGENCY DEPARTMENT MANAGEMENT OF PULMONARY EMBOLISM IN CANCER PATIENTS: PROGNOSTIC STRATIFICATION AND OUTCOMES

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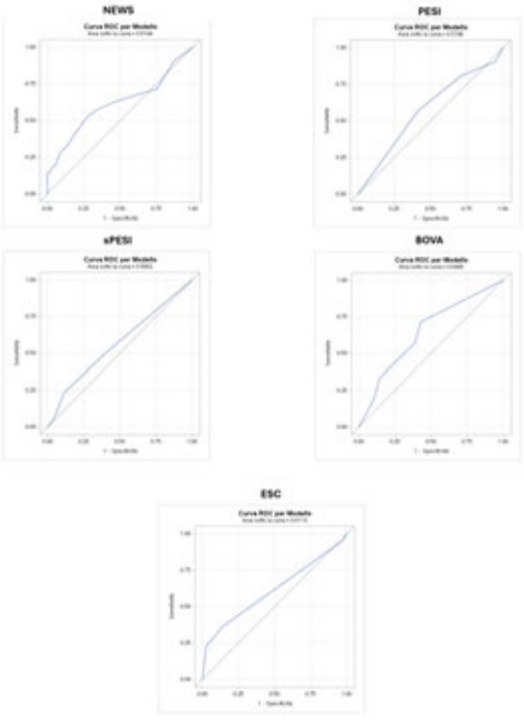
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Background and Aims. Cancer-associated pulmonary embolism (PE) represents a clinically complex condition, characterized by increased short-term mortality, competing thrombotic and bleeding risks. The performance of several risk stratification tools for PE in patients with active cancer remains uncertain, since cancer-related factors may independently affect clinical outcomes. This study aimed to describe management and short-term outcomes of patients with acute PE and active cancer admitted to the Emergency Department (ED) of the Ospedale di Circolo, ASST Sette Laghi, Varese, and to evaluate the prognostic performance of commonly used risk scores in this population.

Methods. We conducted a retrospective observational cohort study including consecutive adult patients diagnosed with acute PE after ED admission between July 2021 and January 2026. Patients were identified through ICD-9 codes and data were collected from hospital discharge letters, laboratory and imaging reports. Only patients with active cancer were included. Demographic data, cancer site and stage, active treatment, presenting symptoms, markers of right ventricle dysfunction (RVD), hospital pathway and outcomes were recorded. A composite outcome of mortality, major bleeding and recurrent venous thromboembolism (VTE) within 30 days was considered. Prognostic performance of PESI, sPESI, ESC and AHA risk classes, BOVA score and NEWS2 was assessed by ROC curve analysis.

Results. Ninety-nine patients were included. The mean age was 69.2 years (SD 11.1). The most frequent cancer sites were lung (23.2%), colorectal (11.1%) and breast (8.1%). Metastatic disease was present in 38.4% of patients and 55.6% were receiving chemotherapy at PE diagnosis. At diagnosis 63 patients were symptomatic, whereas 36 patients were referred to ED after incidentally found PE at CT scans performed for cancer follow-up. PE was limited to subsegmental arteries in 6 (6.1%) of patients, whereas it involved lobar arteries in 71 (71.7%) of patients. Elevated troponin levels were present in 39.4%, while RVD was detected in 16.2%. Thirty-one (31.3%) patients were discharged home from ED after a mean of 26.3 hours and early followed-up at the Thrombosis and Haemostasis Center, whereas 66 (66.7%) patients were admitted, mainly to Oncology, Internal Medicine or Emergency Medicine wards. No recurrent VTE was observed within 30 days. Six patients experienced major bleeding (6,1%). Thirty-day mortality was 13,1% (13/99). The composite outcome occurred in 2 (2%) patients discharged home from ED (no patient died) and in 17 (17.2%) patients admitted to hospital wards (p=0,0289). All cancer patients has sPESI ≥1 by definition. According to ESC classification, AHA classification, Bova score, NEWS2 score 96 (97%), 87 (87.9%), 18 (18.2%), and 38 (38.4%) patients were classified not at low-risk of short-term adverse outcome, respectively. ROC curves and AUC are presented in Figure.

Conclusions. In patients with acute PE and active cancer, short-term adverse outcomes were frequent. Conventional PE risk scores showed only moderate prognostic performance, suggesting that standard stratification may not fully capture cancer-related vulnerability. Updated analyses on the expanded database are needed to confirm these findings and to integrate cancer-specific variables into PE risk assessment.





VENOUS THROMBOEMBOLISM IN PATIENTS WITH FACTOR VII DEFICIENCY: A CASE SERIES AND REVIEW OF THE LITERATURE

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Background. Factor VII (FVII) deficiency is an autosomal bleeding disorder characterized by a wide spectrum of clinical presentations, ranging from asymptomatic states to life-threatening bleeding, with poor correlation between laboratory and clinical phenotypes. Information about the occurrence and management of venous thromboembolism (VTE) in patients with FVII deficiency is scanty, being heterogeneously described in case reports and small series.
Methods. We report 4 cases (3 recurrent) and review of English language literature (1990-2025) on VTE in patients with FVII deficiency.
Results. Case 1. A 64-yr old man (FVII 20%) had recurrent unprovoked VTE (pulmonary embolism, PE; 8 years later, lower limb superficial/deep vein thrombosis, SVT/DVT); persistent mild thrombocytosis led to detect JAK2 V617F mutation and diagnose an unclassifiable myeloproliferative neoplasm. Direct oral anticoagulants were administered for both events. Case 2. A 64-yr old woman (FVII 12%) developed bilateral PE with lower limb DVT after surgery for endometrial adenocarcinoma on replacement therapy with low-dose recombinant FVIIa. She was treated with low--molecular-weight heparin (LMWH, 75% of therapeutic dose) for 6 months. Cases 3-4. A 38-yr woman (FVII 35%) developed an upper limb SVT after surgery and one year later massive PE with DVT after ankle fracture despite heparin prophylaxis. She was treated with intravenous unfractionated heparin (UFH), followed by LMWH and long-term dabigatran (110 mg twice daily). Her brother had 2 lower limb DVT following air travel and later an unprovoked PE. Thrombophilia screening was negative in the 2 siblings. No bleeding complications occurred during anticoagulation in these 4 patients, who did not show significant bleeding tendency. Missense F7 variants were detected in all patients. The literature review identified 87 potentially relevant papers. After excluding reports on different topics or with insufficient data, 22 articles were retrieved, reporting 33 patients experiencing 45 VTE episodes (11 patients >1 event), most DVT and/or PE and including 7 VT at unusual sites. FVII levels were <5% and >20% in 9 (27%) and 8 (24%) subjects, respectively. No relevant bleeding history was reported in 17 patients (51%). Only 5 events were apparently unprovoked. Fourteen VTE episodes (31%) occurred after surgery, on replacement treatment (rFVIIa, plasmaderived FVII, fresh frozen plasma) in 12 cases. Five VTE occurred in cancer patients, 6 were associated with pregnancy or oral contraceptives. Congenital/acquired thrombophilia was found in 5 patients (one with recurrent VTE). In 17 events more than one triggering/risk factors were identifiable. Data about treatment were available for 30 VTE. UFH or LMWH were used in most patients, some received low-dose warfarin or more recently apixaban, often with shorter duration of treatment. In 2 patients vena cava filters were placed. Bleeding complications (2 severe) occurred in 5 cases (16%).
Conclusions. VTE may occurr in patients with FVII deficiency, particularly in subjects with milder factor reductions/clinical phenotype. In most cases established predisposing/risk factors are found. The role for possible specific genetic variants or co-inherited factors, suggested by cases of recurrent VTE and/or family history, deserves further investigations. In most cases anticoagulation is safely and effectively used, type and duration of treatment aiming at minimizing bleeding risk.



CATHETER-RELATED THROMBOSIS IN CANCER PATIENTS: A RETROSPECTIVE REAL-WORLD STUDY

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Background. Catheter-related thrombosis (CRT) is one of the most frequent and clinically relevant complications of central venous access in cancer patients, driven by cancer-associated hypercoagulability and device-related factors. The increasing use of central venous catheters (CVCs) and peripherally inserted central catheters (PICCs) for the administration of chemotherapy and supportive treatments has heightened awareness on CRT as a major component of cancer- associated venous thromboembolism (VTE). CRT may lead to serious clinical consequences including pulmonary embolism, treatment delays, loss of venous access and reduced quality of life.

Aims. the aim of this study was to evaluate the treatments and complications of CRT in cancer patients. We report the experience of a hub hospital, from catheter placement through follow-up after the primary event.

Methods. we retrospectively collected data from oncological patients diagnosed with CRT between 2023 and 2025 at the Angiology Unit of Angelo Hospital in Venezia-Mestre. All 649 enrolled patients had placed a venous catheter for chemotherapy at the hospital's Pain Management Unit. Most patients were evaluated at the thrombosis diagnosis and at 1 and 3 months after diagnosis.

Results. CRT developed in 89 of oncologic patients (13.7%) who underwent venous catheter placement. No significant differences in CRT incidence were observed according to tumor type (hematologic vs. solid). Affected patients had a median age of 66 years; 48.3% were male. Overall, 10.8% of patients (8/74) died. Patients treated with direct oral anticoagulants (DOACs) had a significantly higher bleeding risk compared with those receiving low-molecular-weight heparin (LMWH) (50% vs. 8.1%, p 0.007). In detail, 4 patients developed bleeding episodes, of which 1 minor bleeding (epistaxis) and 3 major bleeding (melena and unspecified anemia). Of 66 patients with a low-intermediate Khorana score, 28 discontinued anticoagulation after chemotherapy cessation, without waiting 3 months. 7/8 patients with Khorana score ≥3 continued anticoagulation post-chemotherapy. CRT recurred in 4/69 patients (5.8%), all during ongoing chemotherapy. Three of the four patients had a Khorana score of 0 in the 3 rd month follow-up and therefore did not receive thromboprophylaxis. One had disease progression at the 3 rd month and continued reduced-dose DOAC at the recurrence. Recurrence and complications were comparable to published literature.

Conclusions. CRT is a frequent complication in cancer patients, and treatment with LMWH is a better choice than DOACs. A close integration of expertise in Angiology, Pain Management, and Oncology unit enables a personalized approach to complex oncology patients. This multidisciplinary strategy may facilitate the early diagnosis of cancer-related thrombosis (CRT) and potentially reduce the risk of recurrence and mortality.



SEX-RELATED DIFFERENCES AND PREDICTORS OF MORTALITY IN MAJOR ORTHOPEDIC SURGERY: INSIGHTS FROM THE ORTHO-START REGISTRY

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Background. Sex-related differences in outcomes after major orthopedic surgery remain under-investigated, and the prognostic relevance of a history of venous thromboembolism (VTE) is unclear.

Aims. To investigate sex-related differences in clinical characteristics, peri-operative management, and postoperative outcomes.

Methods. The ORTHO-START registry is a prospective, multicenter study including 1,077 consecutive adults undergoing major orthopedic surgery (elective hip/knee arthroplasty or urgent hip fracture repair) across six Italian centers between July 2018 and March 2022. Baseline characteristics, perioperative complications, and antithrombotic therapy were collected. The primary outcome was all-cause mortality at 24 months; secondary outcomes were thromboembolic and bleeding events. Multivariable logistic regression identified predictors of mortality.

Results. Women represented 72.3% (n = 775) of the cohort and were older than men (80.6 ± 10.0 vs. 76.2 ± 13.0 years, p < 0.001). Urgent procedures comprised 65.6% (n = 706) of surgeries, predominantly involving women (n = 542). At 24 months, mortality was higher in men (31% vs. 18%, p = 0.018). Table shows factors predicting mortality at univariate analysis and multivariable logistic analysis. Independent predictors of mortality included male sex (OR 2.6, 95% CI 1.8–4.0), older age, lower BMI, urgent surgery (OR 7.2, 95% CI 4.1–12.4), and prior VTE (OR 5.7, 95% CI 1.4–23.9). Causes of death were known for 160/210 (76.2%): neurological complications were most frequent (25%), followed by cardiovascular disease (21.3%) and immobility-related causes (14.4%); pulmonary embolism accounted for 1.3% of deaths. Thrombotic and hemorrhagic events occurred in both sexes without significant differences.

Conclusions. Male sex and a history of VTE are independent predictors of long-term mortality following major orthopedic surgery. Incorporating these factors into preoperative risk assessment may improve management and postoperative outcomes.

Table. Predictors of mortality

Panel a. Univariate analysis

Variable	OR	95%CI
Male Sex	2.64	1.73-4.02
Age	1.06	1.03-1.08
BMI	0.95	0.90-0.99
Hb	0.90	0.82-0.99
Active cancer	4.08	1.36-12.22
Previous VTE	6.25	1.23-33.77
Urgent surgery	4.87	2.60-9.11

Panel b. Logistic regression

Variable	OR	95%CI
Male Sex	2.40	1.60-3.70
Age	1.07	1.05-1.09
Previous VTE	5.02	1.10-23.72
Urgent surgery	5.20	2.93-9.22

Hb: Hemoglobin; BMI: Body Mass Index; VTE: Venous Thromboembolism

ABSTRACT N. PO005

EXTENDED ANTICOAGULATION WITH DOACS IN PATIENTS AFFECTED BY HEMATOLOGIC MALIGNANCIES AND VENOUS THROMBOEMBOLISM: DOES LOW DOSE FIT ALL?

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Background and Aims. Data on the extended treatment of venous thromboembolism (VTE) in the oncohematologic patients is lacking. The aim of our monocentric retrospective analysis was to evaluate the efficacy and safety in secondary prophylaxis of two different Direct Oral Anticoagulants (DOACs) treatment strategies (full-dose/low-dose) in onco-hematologic patients, based on the persistence of complete venous occlusion.

Methods. We included adult oncohematologic patients with objectively confirmed VTE and at least 12 months of follow-up from the start of DOAC treatment. During the acute-phase of VTE treatment (first 3-6 months), the patients were treated with therapeutic dose of anticoagulants. In the extended therapy, the patients were treated with full-dose DOAC in case of persistent complete thrombosis and with low-dose DOAC in case of partial or complete vein recanalization and active cancer. Follow-up visits were scheduled every three months and included monitoring for bleeding (B-AEs) and thrombotic adverse events (T-AEs). Imaging with doppler ultrasound or computed tomography was performed every six months as per institutional policy, or earlier if recurrence was suspected. B-AEs were classified according to the ISTH criteria.

Results. Patients' characteristics and AEs are summarized in Table 1. Fourteen bleeding events (87.5%) occurred during full-dose treatment (1 major [severe metrorrhagia] and 13 CRNM) and 2 (12.5%) during low-dose treatment (1 major [cerebral hemorrhage], 1 CRNM). The 13 CRNM events during full-dose included 10 gastrointestinal bleedings, 1 epistaxis, 1 mild metrorrhagia and 1 hematuria associated with bladder catheter placement. The CRNM event during low-dose was a conjunctival bleeding. During extended phase, the incidence rates of B-AEs were 9.9 per 100 patient-years for full-dose therapy and 0.8 per 100 patient-years for low-dose therapy. Nine patients (6.1%) experienced recurrent thrombosis during extended therapy with DOACs, including 6 (66.7%) on full-dose and 3 (33.3%) on low-dose. During extended phase, the incidence rates of T-AEs were 4.3 versus 1.3 per 100 patient-years, respectively. During follow-up, five patients experienced a platelet count reduction between 50×10^9/L and 100×10^9/L, while none had counts below 50×10^9/L.

Conclusions. Despite the indication bias inherent in this retrospective design, our findings suggest that in onco-hematologic patients, full-dose therapy may be appropriate for those with persistent complete venous occlusion due to a higher baseline risk of recurrence, which appears to remain significant over time: the higher incidence rate of T-AEs during full dose DOAC in the extended treatment could be accounted to a higher thrombotic risk associated with no vein recanalization. De-escalation to reduced-dose DOACs after vein recanalization appeared to reduce the incidence of bleeding events, particularly CRNM B-AEs.



Patients' characteristics	N (%)*
Sex	
Male	78 (52.7)
Female	70 (47.3)
Age (years at thrombosis) – Median (range)	65.3 (18.9-90.9)
Type of VTE	
Typical site	96 (64.9)
Atypical site	47 (31.7)
PICC-related	5 (3.4)
Onco-hematologic disease	
MPN	61 (41.2)
Lymphoma	55 (37.2)
MM	17 (11.5)
PNH ± Aplastic anemia	8 (5.4)
AL	4 (2.7)
MDS	3 (2)
Acute treatment of VTE	
DOACs	119 (80.5)
Apixaban	59 (39.9)
Edoxaban	38 (25.7)
Rivaroxaban	22 (14.9)
VKA	29 (19.5)
DOACs dosage during extended treatment of VTE	
Full dose DOACs	29 (19.5)
Full dose DOACs → low dose DOACs†	97 (65.4)
Low dose DOACs	22 (15.1)
Duration of extended treatment of VTE (months) – Median (range)	35.3 (12.8-119.4)
Duration of full dose DOACs (months) during extended treatment of VTE* – Median (range)	13.4 (0.1-125.4)
Time from full dose to low dose DOACs (months) during extended treatment of VTE* – Median (range)	12.2 (0.5-100.1)
Duration of low dose DOACs (months) during extended treatment of VTE*– Median (range)	24.2 (1.3-109.4)
Bleeding adverse events (full dose DOACs vs low dose DOACs) – Rate per 100 patient-years	
Major	0.7 vs 0.4
CRNM	9.2 vs 0.4
Thrombotic adverse events – Rate per 100 patient-years	
During full dose DOACs	4.3
During low dose DOACs	1.3

VTE: venous thromboembolism, PICC: peripherally inserted central catheter, MPN: myeloproliferative neoplasm, MM: multiple myeloma, PNH: paroxysmal nocturnal hemoglobinuria, AL: acute leukemia, MDS: myelodysplastic neoplasm, LMWH: low molecular weight heparin, DOACs: direct oral anticoagulants, VKA: vitamin K antagonists, CRNM: clinically relevant non major bleedings.

*If not otherwise specified.

†Patients were switched to low dose after partial or complete vein recanalization and persistence of active cancer.

*If applicable.

ABSTRACT N. PO006

FLOW-MEDIATED DILATION AND ECFC DERIVED ENDOTHELIAL DYSFUNCTION IN VENOUS THROMBOEMBOLISM

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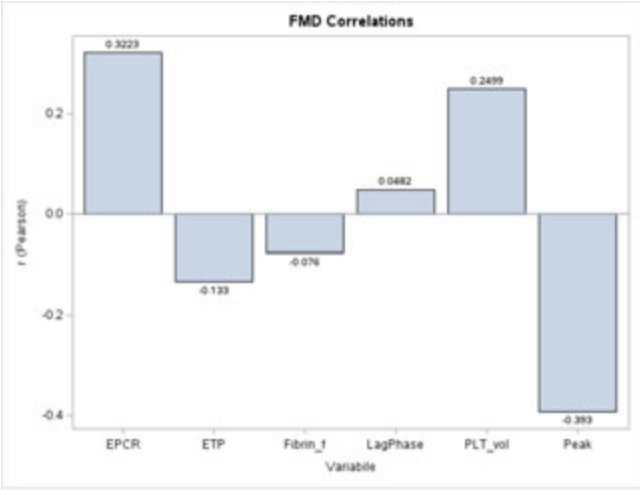
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Background and aims. Venous thromboembolism (VTE) is a major cause of cardiovascular morbidity and mortality worldwide. VTE may develop in the presence of major transient risk factors (provoked VTE, pVTE) or minor predisposing conditions (weakly provoked VTE, wpVTE); nevertheless, nearly 40–50% of events arise without any recognizable trigger (unprovoked VTE, uVTE) and are associated with an increased likelihood of recurrence. Endothelial dysfunction (ED) plays a central role in thrombus formation, and its evaluation may provide important insights into the pathophysiology and recurrence risk of VTE. In this context, flow-mediated dilation (FMD) represents a valuable tool to assess vascular endothelial function. The aim of this study is to evaluate the presence of ED in VTE patients through FMD measurement and to investigate the relationship between FMD and putative markers of constitutive ED identified by studying endothelial colony-forming cells (ECFCs)

Methods. This is a substudy of a wider project on ED, funded by the Italian Ministry of Health (GR-2018-12365520). Three months after the acute event, patients underwent peripheral blood sampling for ECFC isolation. ED was assessed by analyzing (i) platelet deposition and fibrin formation through thrombogenesis assay and (ii) thrombin formation through thrombin generation assay (TGA) on ECFCs, along with additional assays described in the main report. For the purpose of this substudy, patients also underwent FMD assessment on the brachial artery according to standardized methodology. Briefly, after at least 10 minutes of supine rest, baseline brachial artery diameter (BAD) was measured by high-resolution ultrasound. A sphygmomanometer cuff positioned on the forearm was then inflated to supra-systolic pressure for 5 minutes to induce ischemia. After cuff deflation, reactive hyperaemia was obtained and the maximal post-deflation brachial artery diameter was recorded within 60–90 seconds. FMD was expressed as the percentage change from baseline diameter. The relationship between markers of ED, assessed by FMD and by ECFC characterization, was explored through correlation analyses, using Spearman's rho (Sr) coefficients.

Results. A total of 26 patients with VTE—classified as uVTE (n=9), wpVTE (n=11), and pVTE (n=6)— were included in the study. Mean age was 47.7 years (SD 10.2), 15 (57.7%) were male and mean body mass index (BMI) was 26.6 kg/m^2 (SD 5.3). FMD showed a mean value of 8.2% (SD 6.3), ranging from 2.0% to 25.9%. The mean absolute change in BAD was 0.03 cm (SD 0.02, min 0.01 max 0.09 cm). No statistically significant associations emerged between FMD values and some thrombin generation parameters, including Lag phase (Sr=0.048, p=0.849) and endogenous thrombin potential (Sr=-0.133, p=0.598), whereas an inverse trend was found between FMD and peak thrombin generation (Sr=-0.393, p=0.107). With regards to the thrombogenesis assay, no significant correlation was observed between FMD and platelet volume deposition (Sr= 0.250, p=0.333) or fibrin formation (Sr=-0.076, p = 0.771)

Conclusions. Given the limited sample size, the study was likely underpowered to detect associations. Although the relationship between peak thrombin generation and FMD did not reach statistical significance, it may reflect a biologically plausible link between endothelial dysfunction and a prothrombotic phenotype. These results should be considered hypothesis-generating and warrant confirmation in larger cohorts.





OUTCOMES OF PATIENTS WITH JAK2V617F VAF ≤2% EVALUATED FOR SUSPECTED MYELOPROLIFERATIVE NEOPLASMS

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Detection of the JAK2V617F mutation is central to the diagnosis of myeloproliferative neoplasms (MPNs). In clinical practice, a variant allele frequency (VAF) >2% is considered unequivocally positive and is also used to define clonal hematopoiesis of indeterminate potential (CHIP). Current WHO/ICC recommendations advocate the use of highly sensitive methods to detect JAK2V617F when the VAF is below 1%. However, interpretation of low-level JAK2V617F positivity remains challenging, as the mutation can be detected in individuals without hematologic disease and no validated diagnostic cut-off for MPNs has been established.To investigate the clinical and molecular characteristics of patients referred for suspected MPN with a JAK2V617F VAF <2%. Fifty-five patients evaluated for erythrocytosis (n=31) or thrombocytosis (n=24) and harboring a JAK2V617F VAF <2% were included. Median age was 64 years (range: 15–86). JAK2V617F analysis was performed on granulocyte DNA at diagnostic suspicion using quantitative PCR (ipsogenR JAK2MutaQuantR, limit of detection 0.0014%). At referral, median JAK2V617F VAF was 0.354% (range: 0.02–1.975), significantly higher in patients with thrombocytosis than in those with erythrocytosis (0.451% vs 0.25%, p=0.047). Median erythropoietin level was 5.4 mU/mL (range: 1–16.8), with 51% of erythrocytosis cases showing subnormal levels. None of the patients met diagnostic criteria for MPN at the time of the initial JAK2 assessment. Among patients with erythrocytosis, 4 (12.9%) were subsequently diagnosed with polycythemia vera and 1 with prefibrotic myelofibrosis. Median hematocrit was 50.2%, ten patients required phlebotomy, and two received cytoreductive therapy. Among patients with thrombocytosis, 7 (22.5%) were diagnosed with essential thrombocythemia; CALR mutations were identified in three cases, all fulfilling ET criteria. Median platelet count was 564 × 109/L, and three patients received cytoreductive treatment. The median time from first quantitative JAK2 assessment to MPN diagnosis was 21.1 months. Patients who later developed MPN had a higher median VAF at baseline compared with those who did not (0.532% vs 0.24%, p=0.02). Sequential samples available in 27 patients confirmed persistence of JAK2V617F with stable VAF <2% over a median follow-up of 31.7 months. The median time from first quantitative JAK2 assessment to MPN diagnosis was 21.1 months. Patients who later developed MPN had a higher median VAF at baseline compared with those who did not (0.532% vs 0.24%, p=0.02). Sequential samples available in 27 patients confirmed persistence of JAK2V617F with stable VAF <2% over a median follow-up of 31.7 months. The median time from first quantitative JAK2 assessment to MPN diagnosis was 21.1 months. Patients who later developed MPN had a higher median VAF at baseline compared with those who did not (0.532% vs 0.24%, p=0.02). Sequential samples available in 27 patients confirmed persistence of JAK2V617F with stable VAF <2% over a median follow-up of 31.7 months.Overall, 17 patients (30.9%) experienced thrombotic events, occurring a median of 4.3 months after molecular testing. Thrombotic rates were similar in patients with and without subsequent MPN diagnosis (25% vs 32.5%, p=0.57). However, patients with thrombosis had a significantly higher median JAK2V617F VAF than those without events (0.44% vs 0.23%, p=0.038).

ABSTRACT N. PO008

HISTORY OF CANCER IN VTE PATIENTS WITH AND WITHOUT HEREDITARY THROMBOPHILIA: A SINGLE CENTER COHORT STUDY

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Background and Aims. Hypercoagulability is a well-recognized feature of cancer and may play a role in tumor development and progression. Hereditary thrombophilia confers a lifelong predisposition to thrombosis, yet its relationship with cancer risk remains uncertain. This study aims to compare the prevalence of cancer among patients with venous thromboembolism (VTE) with and without hereditary thrombophilia.

Methods. Consecutive patients with a history of venous thromboembolism (VTE) who underwent hereditary thrombophilia testing were enrolled. Patients were classified into three groups: no thrombophilia, mild thrombophilia, and severe thrombophilia (n = 200 each). The primary outcome was a history of cancer, defined as any solid or hematological malignancy diagnosed at any time. Age at first VTE was used as age at inclusion. Prevalence ratios (PRs) for cancer were estimated using Poisson regression with a log link and robust standard errors, adjusted for age and sex. Incident post-VTE cancer was analyzed after excluding pre-VTE cancer cases, using Cox regression adjusted for age and sex.

Results. Cancer prevalence was 12.5% (25/200) in patients without thrombophilia, 14.0% (28/200) in those with mild thrombophilia, and 11.0% (22/200) in those with severe thrombophilia. Adjusted Poisson regression showed no association between thrombophilia status and overall cancer prevalence (mild vs no thrombophilia: PR 1.31, 95% CI 0.74–2.32, p = 0.362; severe vs no thrombophilia: PR 1.06, 95% CI 0.59–1.91, p = 0.839), while increasing age was independently associated with cancer (p = 0.001). Pre-VTE cancer prevalence was 9.0% (18/200) in patients without thrombophilia, 2.5% (5/200) in mild thrombophilia, and 6.5% (13/200) in severe thrombophilia. However, thrombophilia was not independently associated with pre-VTE cancer after adjustment for age and sex (overall p = 0.212). In sensitivity analyses based on thrombophilia subtypes, an overall association between subtype and pre-VTE cancer was observed (p = 0.041), mainly driven by protein C deficiency (PR 2.19 vs no thrombophilia; p = 0.032). Median age at cancer diagnosis was 64.5 [54.0–73.0] years in patients without thrombophilia, 61.5 [53.5–69.0] in mild thrombophilia, and 58.0 [47.0–66.8] in severe thrombophilia. Incident cancer occurred in 6.9% (39/564) over 5,722 person-years (0.68 per 100 person-years, 95% CI 0.47–0.90), with no association with thrombophilia in adjusted Cox regression, while age remained an independent risk factor.

Conclusions. In VTE patients, hereditary thrombophilia was not independently associated with overall cancer prevalence. Cancer risk was mainly driven by age. Subtype analyses suggested a possible signal for protein C deficiency and pre-VTE cancer, but this finding requires confirmation.

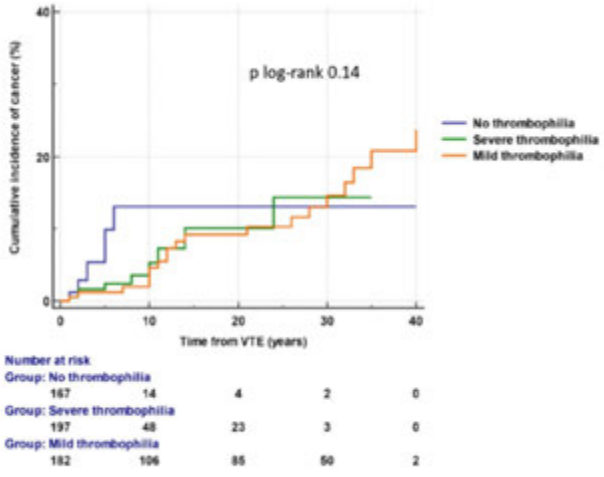


Figure 1. Cumulative incidence of cancer after index VTE according to hereditary thrombophilia status

ABSTRACT N. PO009

THROMBOPHILIA AND ASSISTED REPRODUCTIVE TECHNOLOGY: PRELIMINARY RESULTS FROM A SINGLE CENTER RETROSPECTIVE COHORT STUDY

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Background and Aims. Pregnancy is characterized by physiological changes, including a hypercoagulable state that reduces hemorrhagic risk at delivery. In the presence of inherited or acquired thrombophilia, this adaptation may increase the risk of venous thromboembolism (VTE) as well as maternal–fetal complications such as recurrent miscarriage, preeclampsia, and intrauterine growth restriction. Thrombophilias have also been investigated in relation to embryo implantation failure and adverse outcomes in assisted reproductive technology (ART), although their etiopathogenetic role remains unclear. Evidence regarding anticoagulant therapy in women undergoing ART is heterogeneous and no consensus on management has been established. This study aimed to evaluate reproductive outcomes in relation to antithrombotic therapy (low-molecular-weight heparin [LMWH] and/or acetylsalicylic acid [ASA]) by analyzing: (1) implantation rate, (2) clinical pregnancy and miscarriage rates, and (3) live birth rate. A secondary aim was to compare our findings with the existing literature to improve multidisciplinary management.

Materials and Methods. A single-center retrospective cohort study was conducted on 22 women undergoing ART for infertility or recurrent pregnancy loss at the Internal Medicine B outpatient clinic of AOUI Verona between 2024 and 2025. Selective screening for inherited and acquired thrombophilia was performed. Patients received LMWH and/or ASA, or no antithrombotic therapy, starting from embryo transfer.

Results. The 22 women were stratified into 3 groups: Group A, negative thrombophilia screening or thrombophilia not assessed (n = 12); Group B, low-risk inherited thrombophilia (n = 6), including 3 women heterozygous for the Factor II (G20210A) mutation and 3 heterozygous for Factor V Leiden; and Group C, obstetric antiphospholipid syndrome (OAPS) (n = 4). In Group A, 6 women received LMWH alone or in combination with ASA, with favorable clinical outcomes (pregnancy or live birth) in 5 cases (83.3%). In Group B, 5 patients received LMWH alone or in combination with ASA, resulting in 2 pregnancies (40%). In Group C, all 4 women were treated with combined LMWH and ASA, with 3 pregnancies achieved (75%). Overall, 15 women received LMWH (alone or in combination with ASA), whereas 7 remained untreated(Figure 1). The best outcomes in terms of implantation, clinical pregnancy, and live birth rates were observed in patients treated with LMWH, with or without ASA, with an overall benefit in 66% of cases. In contrast, untreated patients or those receiving ASA alone predominantly experienced implantation failure or early pregnancy loss.

Conclusions. These findings are consistent with the literature, confirming a significant benefit of combined LMWH and ASA in patients with OAPS, with implantation, clinical pregnancy, and live birth rates of 75%. In low-risk inherited thrombophilia, the benefit appears limited (40% clinical pregnancy rate). The high success rate in thrombophilia-negative or untested patients treated with LMWH (± ASA) may be related to the pleiotropic and anti-inflammatory effects of heparin. Overall, anticoagulant therapy may be beneficial regardless of thrombophilia status, with favorable outcomes in 66% of cases. The main limitations of this study include the small sample size and the absence of high-risk inherited thrombophilia. Larger prospective studies are needed to confirm these findings and to better guide clinical management.

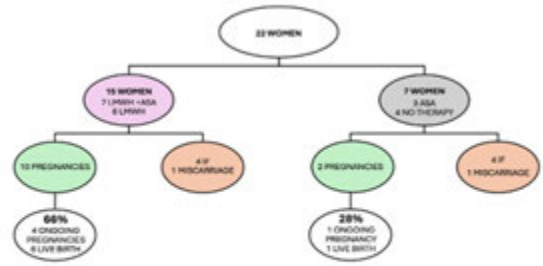


Figure 1. *Reproductive outcomes according to antithrombotic treatment independent of thrombophilia status.*



D-DIMER TESTING BEYOND THROMBOSIS: A LABORATORY AUDIT OF TEST UTILIZATION, APPROPRIATENESS AND INTERPRETIVE CHALLENGES

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Background. D-dimer is a high-sensitivity biomarker central to diagnostic algorithms for venous thromboembolism (VTE). However, its low specificity—particularly in elderly and hospitalized patients—limits clinical utility when not integrated with pre-test probability assessment. Inappropriate test utilization may generate diagnostic ambiguity and unnecessary downstream imaging.

Objectives. To evaluate real-world patterns of D-dimer utilization and identify predictors of guideline-adherent testing, focusing on implications for diagnostic stewardship.

Methods. We conducted a retrospective observational study including all consecutive D-dimer requests over a 12-month period at a tertiary care hospital. Appropriateness was defined according to established indications (suspected VTE, acute aortic syndrome, disseminated intravascular coagulation). Demographic, laboratory, and clinical discharge data were collected. Multivariable logistic regression was performed to identify independent predictors of appropriate test use.

Results. A total of 519 D-dimer requests were analyzed. Only a minority met predefined appropriateness criteria, indicating substantial overuse in routine practice. D-dimer levels were elevated in the majority of cases, while values below the conventional 0.5 mg/L FEU cut-off were uncommon. At multivariable analysis, increasing age was independently associated with a lower likelihood of appropriate test utilization (OR 0.98 per year; 95% CI 0.97–0.996; p=0.011), whereas sex was not significantly associated with appropriateness.

Conclusions. In real-world hospital settings, D-dimer testing is frequently performed outside structured diagnostic pathways. Given its high sensitivity but limited specificity—-particularly in elderly populations—its indiscriminate use may reduce diagnostic efficiency. Strengthening laboratory–-clinician integration and implementing diagnostic stewardship strategies, including age-adjusted thresholds and contextualized reporting, may improve appropriateness and reduce unnecessary downstream investigations.



A TWO CENTERS REAL-WORLD EXPERIENCE WITH ANTI-XA DIRECT ORAL ANTICOAGULANTS IN CANCER PATIENTS WITH UNUSUAL SITE VEIN THROMBOSIS

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Background and aims. Unusual-site venous thrombosis (USVT) refers to the occurrence of venous thromboembolism (VTE) in atypical sites, such as the upper extremities, splanchnic (portal, mesenteric, hepatic, splenic, gonadal, renal) and cerebral veins. Cancer is one of the most frequent predisposing conditions for USVT. However, evidence supporting the use of direct oral anticoagulants (DOACs) in these settings remains limited, as pivotal clinical trials on DOACs typically excluded patients with USVT. We aimed to evaluate the safety and efficacy of DOACs in active cancer patients affected by USVT referred to our two centers for congenital bleeding and thrombotic disorders.

Methods. We evaluated 28 consecutive patients with active malignancy and USVT (16 females and 12 males, median age 62.3 years) referred to our centers between January 2023 and January 2026. Thrombosis sites included: 8 (28.6%) splenoportal axis, 4 (14.3%) inferior vena cava, 1 (3.6%) renal vein, 1 (3.6%) ovarian vein, and 14 (50%) upper limb venous thrombosis. Nine patients (32.1%) had onco-hematological diseases (Multiple Myeloma, Non-Hodgkin Lymphoma, Hodgkin Lymphoma) and 19 (67.9%) had solid tumors. All patients received initial parenteral anticoagulation for at least 15 days before transitioning to a DOAC (Apixaban 64.3%, Rivaroxaban 7.1%, or Edoxaban 28.6%) at full or reduced doses according to label criteria.

Results. Over a median follow-up of 7 months, follow-up imaging was performed at 3 and 6 months. No major bleeding occurred. One patient (Non-Hodgkin Lymphoma) experienced an ISTH clinically relevant non-major bleeding (CRNMB), manifesting as mild anemia during chemotherapy; DOAC was switched to prophylactic low-molecular-weight heparin after 5 months of full-dose treatment. Two patients discontinued anticoagulation due to cancer remission. Regarding radiological outcomes, 15 patients showed persistent thrombosis, while 13 initially achieved complete recanalization. Among the latter, 2 patients subsequently experienced an ipsilateral thrombotic recurrence during treatment (one of which was associated with the initiation of Lenalidomide), while the remaining 11 maintained complete recanalization. Anticoagulation was continued in all patients with persistent or recurrent disease due to active malignancy. Finally, seven patients died due to cancer progression (3 from the recanalization group and 4 from the persistent thrombosis group).

Conclusions. Our real-world data suggest that DOACs are a viable and safe therapeutic option for patients with active malignancy and venous thrombosis at atypical sites (USVT). In our cohort, both recurrent thrombotic events and bleeding complications appear to be clinically acceptable, supporting the use of these agents in a complex oncological setting. However, the high prevalence of persistent thrombosis observed during follow-up confirms that active cancer remains a significant risk factor for impaired radiological recanalization. These findings highlight the necessity of personalized anticoagulant strategies and rigorous monitoring, tailored to the patient’s specific oncological profile, treatment burden, and evolving clinical status.



RECURRENT CENTRAL RETINAL VEIN THROMBOSIS IN A PATIENT WITH MILD HEMOPHILIA A AND HETEROZYGOSITY FOR THE PROTHROMBIN G20210A VARIANT

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Background. Hemophilia A is an X-linked inherited bleeding disorder caused by a deficiency of coagulation factor VIII (FVIII), leading to impaired hemostasis. It is classified as severe (<1% FVIII activity), moderate (1–5%), or mild (>5–40%). In mild forms, bleeding is often limited to trauma or invasive procedures, resulting in delayed diagnosis. Treatment consists of FVIII replacement therapy, administered on demand or prophylactically in severe cases. Despite its hemorrhagic nature, rare thrombotic events have been described in hemophilia A, particularly in the presence of additional risk factors or hemostatic treatments, suggesting a complex balance between bleeding and thrombosis.

Case Report. We report the case of a 62-year-old man with mild hemophilia A and a history of significant post-traumatic and post-surgical bleeding. He had a previously treated and eradicated hepatitis C virus infection. The patient was managed with on-demand recombinant FVIII (Beriate). At the time of the first event (2022), he was not receiving FVIII therapy. He presented to the Emergency Department with acute visual loss in the left eye. Laboratory testing excluded acquired thrombophilia; however, genetic analysis revealed heterozygosity for the prothrombin G20210A variant. Fluorescein angiography showed retinal hemorrhages with hypofluorescent areas consistent with central retinal vein occlusion (CRVO). Due to the bleeding risk, anticoagulation was not initiated. The patient was treated with intravitreal anti-VEGF injections, achieving complete visual recovery. In March 2024, he returned with blurred vision in the same eye. Fluorescein angiography confirmed a recurrent CRVO, similar to the previous episode. He again received intravitreal anti-VEGF therapy and low-dose antiplatelet treatment. Further evaluation showed mildly elevated LDL cholesterol (66 mg/dL; target <55 mg/dL), and ezetimibe therapy was started. Thrombophilia screening revealed Protein S 93%, Antithrombin 89%, APC resistance ratio 0.95, Factor V 97%, and FVIII 13.7%. Carotid Doppler ultrasound showed normal findings, and coronary CT angiography excluded significant coronary artery disease.

Conclusions. This case describes recurrent central retinal vein thrombosis in a patient with mild hemophilia A, occurring in the absence of replacement therapy. The coexistence of a congenital bleeding disorder and a prothrombotic genetic variant (prothrombin G20210A) highlights the complexity of hemostatic balance. Although hemophilia is primarily a bleeding disorder, thrombotic events may occur when additional risk factors are present. Improved life expectancy in hemophilia patients has led to an increasing overlap with age-related cardiovascular risk profiles. The traditional view that hypocoagulability protects against thrombosis is no longer universally valid, emphasizing the need for individualized risk assessment



COMPLEX COAGULATION PROFILE IN ALG8-CDG: EXPANDING CLINICAL RECOGNITION OF A RARE DISORDER

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Congenital disorders of glycosylation (CDG) comprise a rapidly expanding group of metabolic diseases caused by genetic defects affecting glycoprotein synthesis. CDGs are clinically and genetically heterogeneous, and to date, approximately 100 types have been identified, with over 700 patients reported worldwide. ALG8-CDG (OMIM #608104) is one of the rarer CDG subtypes that is caused by variants in the ALG8 gene which encodes glucosyltransferase 2 (dolylyl-phosphateglucose 1-mannose 9-N acetylglucosamine glucosyltransferase). Fewer than 30 patients have been reported in the literature. It affects an early step in protein glycosylation and is generally associated with a poor prognosis. Patients with ALG8-CDG typically present with highly consistent clinical features, including neonatal onset, and a fatal outcome within the first year of life may occur. Early distinguishing features include multisystem involvement, dysmorphic features, neurological symptoms, and cataracts in approximately 50% of cases. Currently, no curative treatment is available for ALG8-CDG; however, establishing a molecular diagnosis is essential for family counseling and prenatal diagnosis. We report the case of a 2-year-old girl who presented with delayed psychomotor development, language delay, and febrile seizures. She exhibited axial hypotonia at birth. Laboratory investigations repeatedly demonstrated a complex deficiency of hemostatic factors (aPTT ratio: 1.44; antithrombin: 40%; protein C: 28%; factor IX: 14%; factor XI: 45.4%). In addition, she carried the FII A20210G variant in the heterozygous state. Her parents were asymptomatic and showed no abnormalities of hemostatic factors. Whole-exome sequencing revealed compound heterozygosity in the ALG8 gene: c.685C>T (p.Arg229*) and c.206C>T (p.Pro69Leu). In silico tools predicted these variants to be deleterious; the former is classified as pathogenic (ACMG criteria: PVS1, PM2, PP5), while the latter is considered likely pathogenic (ACMG criteria: PM3, PP3, PP5). We describe a new case of ALG8-CDG that further expands current knowledge of this very rare autosomal recessive disorder and confirms the presence of a complex coagulation profile, likely related to hepatic involvement. These features represent a significant challenge for the clinical management of ALG8-CDG.



DETERGENT AND GANGLIOSIDE GM1-BINDING PROPERTIES OF PLATELET FACTOR 4 AS ASSESSED BY CHARGE-SHIFT ELECTROPHORESIS

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Background and Aims. platelet factor 4 (PF4) is a 7.8 kDa chemokine comprising 70 amino acids. Three anti-parallel β-sheets defining a hydrophobic region characterise the N-terminus; two pairs of contiguous oxidizable lysine residues defining a β-helix with amphiphilic properties characterised the carboxyl-terminus. During coagulation, the positively charged moieties of PF4 bind with high affinity to the negatively charged heparan sulphate (HS) and glycosaminoglycans (GAGs) neutralising their anticoagulant effect. Herein we detailed the amphiphilic and HS and ganglioside GM1-binding properties of PF4 and their possible modification after oxidation and nitration.
Methods. charge-shift electrophoresis (CSE) (1% agarose gels (0.05 M glycine/NaOH, 0.1 M NaCl, pH 9.0) in the presence of: 1) a detergent mix of composed of neutral TritonX-100 (TX100) and anionic deoxycholate (DOC) and in the presence of 2) the cationic detergent cetyltrimethylammonium bromide (CTAB); in vitro oxidation with 1mM 4-hydroxy-2-nonenal and in vitro nitration with 60 μM peroxynitrite (ONOO-).
Results. 1) PF4 shifted markedly in the presence of TX-100 plus DOC, indicating its ability to participate in the formation of mixed micelles with TX-100 and DOC compared to TX-100 alone or no detergent at all. 2) In the presence of TX-100 plus CTAB, PF4 exhibited no cathodic shift. The incorporation of Sudan Black B proved that mixed micelles of TX-100/DOC and TX-100-CTAB were formed under the conditions employed. However, the anodic shift of PF4 in the presence of DOC, with unaltered migration in the presence of CTAB are testimony to the electrostatic nature of the interaction of PF4 with DOC, with no participation of PF4 in the formation of mixed detergent micelles. 3) The migration of PF4 was shifted to the anod also in the presence of ganglioside GM1 at concentrations from 0.33 to 1.33 mg/mL, exceeding the GM1 critical micellar concentration. The formation of GM1 micelles was also documented by the SBB incorporation. GM1 binding to PF4 was dose-dependent, reaching saturation at the GM1:PF4 ratio of 1.2:1 by mass, or 23:1 on a molar basis. The formation of GM1 micelles with multiple negative charges was indispensable for shifting PF4 toward the anod, since the interaction of PF4 with the sole GM1 pentasaccharide mojety was unable to cause the same effect. 4) By the same CSE methodology in the absence of detergents, but with the addition of either HS or chondroitin sulfate (CS), PF4 shifted to the anode more markedly than in the presence of DOC and GM1; in addition, the PF4-CS complexes were highly poly-dispersed compared to the PF4-HS complexes. 5) In vitro oxidation with 1 mM 4-hydroxy-2-nonenal or nitration with 60 μM peroxynitrite (ONOO-) made PF4 undetectable in the agarose gels, likely due to aggregation/precipitation in the reaction vials.
Conclusions. we document the ability of PF4 to establish electrostatic interactions with negatively charged amphiphilic molecules, such as the negatively charged surfactant DOC and ganglioside GM1, as well as polyanionic polysaccharides. This is relevant in physiological PF4 interactions with the annular lipid shells that are in contact with the hydrophobic surfaces and support the structural stability and functions of integral membrane proteins, such as HS proteoglycans expressed on endothelial cells and activated platelets, perlecan and chemokine receptor CXCR3B at the surface of endothelial cells. The destabilization of PF4 upon reaction with 4-hydroxy-2-nonenal and peroxynitrite indicates that in the course of oxidative and nitrative stress occurring in inflammation the physiologic functions of PF4 could be lost.

ABSTRACT N. PO015

OSA *VS.* CHA FOR RPFVIII MEASURE: STILL AN ISSUE?

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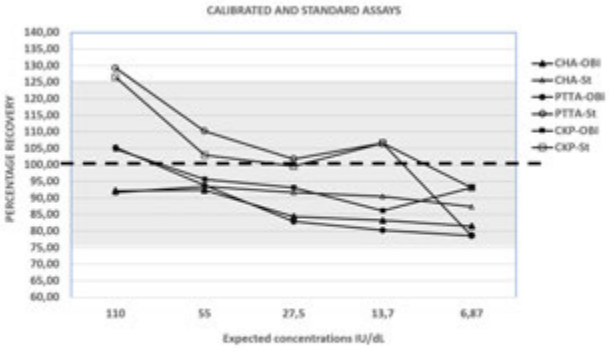
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Background and Aims. Acquired Hemophilia A (AHA) management requires accurate monitoring of susoctocog alfa (rpFVIII, Obizur®), a recombinant porcine FVIII. However, significant methodological challenges persist: chromogenic assays (CHA) have been reported to underestimate rpFVIII activity compared with one-stage assays (OSA), which have traditionally guided clinical management. In addition, discrepancies between spiked and in vivo studies have been described, further complicating interpretation. Data on the performance of Stago reagents in this setting remain limited. As a result, clinicians relying on Stago platforms may face uncertainty in result interpretation and dose optimization. This study aims to evaluate the performance of Stago OSA and CHA reagents for susoctocog alpha measurement.

Methods. The analytical performance of Stago reagents for the measurement of susoctocog alfa was evaluated using a standardized dilution protocol: The susoctocog alfa calibrator, provided by Takeda, served as the primary standard. The calibrator was analyzed both undiluted and at four serial dilutions (1:2, 1:4, 1:10, 1:20) prepared using FVIII-deficient plasma (Stago). Based on the certified potency of the calibrator, the expected FVIII activity levels were defined as 110, 55, 27.5, 13.75, and 6.87 IU/dL. For standard clotting assays, Unicalibrator® (Stago) was utilized as the reference plasma to establish the standard curves All measurements were performed on the STA R Max3® (Stago) automated coagulation analyzer using three different methodological approaches: two OSAs (CK-Prest®, utilizing kaolin as the surface activator, and PTT-A®, utilizing silica as the surface activator) and one CHA (TriniCHROM®). All reagents and deficient plasmas were stored and handled in strict accordance with the manufacturer's instructions Two distinct calibration strategies were employed: Each dilution level was analyzed in five replicates to ensure statistical robustness and assess intra-assay precision. The same dilution series was analyzed against a dedicated calibration curve established using the susoctocog alfa (Obizur) calibrator itself. We first compared the performance of the OSA against the CHA based solely on measurements derived from the Obizur-calibrated curve. Subsequently, we compared the activity levels measured using the standard calibration curve with those obtained using the Obizur-specific calibration curve to identify potential recovery shifts or method-dependent biases. Results were expressed as percentage recovery relative to the expected theoretical activity to evaluate the accuracy and consistency of each reagent across different calibration models.

Results. All analytical methods and reagents tested demonstrated high repeatability across all concentrations and experimental conditions. When the assays were calibrated specifically using the Obizur (susoctocog alfa) calibrator, all reagents showed high concordance with each other and closely matched the certified expected values. In contrast, when using a standard calibration curve, the two OSAs (kaolin-based and silica-based) consistently yielded activity levels that were slightly higher than those produced by the CHA. Despite this divergence, the measured values remained robust, falling almost entirely within the clinically acceptable range of ±25% of the expected theoretical activity.

Conclusions. Our results demonstrate that OSA and CHA Stago reagents provide high precision and accuracy for the measurement of rpFVIII, also without a product-specific calibration. However, as this study was conducted using spiked samples, these findings must be confirmed in a clinical setting. Further studies on plasma samples from patients with AHA treated with rpFVIII are necessary to validate these analytical performances in the presence of real-world biological variables and inhibitors



Filled symbols: Assays calibrated with the Obizur® -specific calibrator.
Empty symbols: Assays performed using a standard calibration curve (Unicalibrator ®).
CKP: CK Prest® (kaolin-based one-stage assay); PTTA: PTT-A® (silica-based one-stage assay); CHA: TriniChrom® (chromogenic assay)
The dashed line indicates 100% recovery, while the shaded area represents the ±25% clinical acceptability range



TOLL-LIKE RECEPTOR 4-MEDIATED ENDOTHELIAL DYSFUNCTION VIA NOX2 ACTIVATION IN COVID-19

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Background. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection is associated with endothelial dysfunction. Multiple pathophysiological mechanisms have been proposed, including direct endothelial infection and indirect injury mediated by systemic inflammation. However, alternative receptors involved in SARS-CoV-2–induced endothelial damage remain to be fully elucidated. We hypothesized that the SARS-CoV-2 Spike protein contributes to endothelial dysfunction via Toll-like receptor 4 (TLR4)-mediated oxidative stress.

Methods. We studied 20 patients with SARS-CoV-2 infection. Endothelial function was assessed by flow-mediated dilation (FMD). Serum levels of Spike protein and TNF-α were measured. In vitro, human umbilical vein endothelial cells (HUVECs) were incubated with recombinant Spike protein, TNF-α, or both, in the presence or absence of specific inhibitors of TLR4, NOX2, $p47^{phox}$, PKC, and ACE2. Markers of endothelial activation (NO bioavailability, endothelin-1) and oxidative stress (H_2O_2, sNOX2-dp, $p47^{phox}$ phosphorylation) were evaluated.

Results. Compared with controls, COVID-19 patients exhibited significantly reduced FMD. Linear regression analysis in the overall population showed that FMD inversely correlated with serum Spike protein and TNF-α levels. A significant positive correlation between TNF-α and Spike protein was also observed. In vitro, S protein (250 and 500 ng/mL) reduced nitric oxide (NO) bioavailability and significantly increased endothelin-1 levels compared with unstimulated HUVECs. These effects were attenuated by TLR4 or $p47^{phox}$ inhibition, whereas ACE2 inhibition (DX600) had no impact. Mechanistically, S protein increased H_2O_2 production, sNOX2-dp levels, $p47^{phox}$, and PKC phosphorylation in a dose-dependent manner. NOX2 activation and $p47^{phox}$ phosphorylation were reduced by TLR4 or $p47^{phox}$ inhibitors, while ACE2 inhibition did not affect S protein–induced oxidative stress. Exposure of HUVECs to TNF-α alone, at concentrations comparable to those observed in patients, or to S protein alone induced endothelial activation and oxidative stress. Co-incubation with TNF-α and S protein further amplified these effects, which were significantly reduced by inhibition of TLR4, S protein, TNF-α, or $p47^{phox.}$

Conclusions. The Spike protein directly induces endothelial oxidative stress and dysfunction through a TLR4–NOX2–$p47^{phox}$ signaling pathway, independently of ACE2. TNF-α synergistically enhances these effects. These findings identify TLR4-mediated signaling as a key mechanism underlying COVID-19–related vascular damage and suggest potential therapeutic targets to prevent thrombotic complications.



BEYOND IONIC STRENGTH: ANION EFFECTS ON FIBRIN CLOT FORMATION, STRUCTURE, AND MECHANICAL PROPERTIES

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Background and Aims. The role of anions in protein aggregation and gelation has long been underestimated and commonly interpreted as arising from direct macromolecule–anion interactions or from simple ionic strength effects. However, growing evidence across several protein classes, as well as in non-protein systems, supports a more general underlying mechanism. These effects correlate with the position of anions in the Hofmeister series, which reflects their physico-chemical properties and their ability to influence water structure. Within this framework, anions range from kosmotropes—including polyvalent (sulfate, phosphate, carbonate) and monovalent (fluoride, bicarbonate) species—to monovalent chaotropes (chloride, bromide, nitrate, iodide). This perspective is particularly relevant for fibrinogen, whose conversion into fibrin represents a sol–gel phase transition that underlies the final step of the coagulation cascade. This study investigates how anions modulate fibrin clot formation, structure, and functional properties, providing insight into their contribution to haemostasis and thrombosis.

Methods. Fibrin clots were prepared from desalted, purified human fibrinogen (0.085–0.50mg/mL) and thrombin (0.01–0.1U/mL) in presence of sodium salts (50–500mM) and calcium chloride (0–5mM), pH 7.5. Anion-dependent effects on clot structure and viscoelastic properties were evaluated using turbidity, confocal microscopy, and microrheology. Maximum absorbance (A_{MAX}), derived from turbidity measurements, was used as an indicator of the gel's final macroscopic structure. Fractal dimension and lacunarity, obtained from confocal microscopy image analysis, were used as quantitative descriptors of network spatial density and heterogeneity, respectively. Chloride was used as a reference anion due to its central position in the Hofmeister series and its biological abundance.

Results. At physiological concentration, A_{MAX} in turbidity experiments was 0.072±0.004 for chloride. Monovalent kosmotropes increased A_{MAX} to 0.236±0.042 ($p<0.0001$), whereas polyvalent kosmotropes and chaotropes decreased it to 0.006±0.004 ($p=0.0126$) and 0.006±0.005 ($p=0.0051$), respectively. This was reflected in confocal imaging, where chloride generated the most organized and homogenous network structure, as reflected by the highest fractal dimension (1.796±0.004) and lowest lacunarity (0.299±0.013). Changing anions induced differences in fibrin clot architecture, including fiber diameter, network density and connectivity, pore distribution, and spatial heterogeneity. Polyvalent and monovalent kosmotropes reduced fractal dimension to 1.766±0.028 ($p=0.0230$) and 1.719±0.015 ($p<0.0001$), respectively, and monovalent kosmotropes increased lacunarity significantly to 0.445±0.116 ($p=0.0076$). Chloride resulted in the stiffest clots, exhibiting the highest storage modulus (G') at 10Hz (2.327±0.676 Pa), whereas all other anions significantly reduced it by approximately 85% ($p<0.0001$), thereby decreasing clot strength.

Conclusions. Progression along the Hofmeister series yields distinct fibrin clots at the same concentration, reflecting each anion's physico-chemical profile and revealing effects beyond simple ionic strength contributions. These findings highlight the importance of the anionic environment during clot formation, as alterations in anion composition, common in many thrombosis-associated conditions, can significantly reshape clot structure, mechanical properties, and function.



IS VESSEL-ON-CHIP COMPLEXITY WORTH IT? A QUANTITATIVE COMPARISON OF SIMPLIFIED AND COMPLEX HIGH-FIDELITY VASCULAR MODELS

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Background and Aims. Endothelial cells (ECs) are highly sensitive to biophysical and biochemical cues, including extracellular matrix (ECM) composition, vessel geometry, and shear stress. Vessel-on-Chip (VoC) platforms are widely used to study vascular biology, yet they differ substantially in structural complexity and physiological relevance. Cylindrical collagen-based microvessels closely replicate native vessel geometry and matrix conditions but involve technically demanding fabrication. Conversely, endothelialized PDMS microchannels are easier to fabricate and handle, despite their square geometry and rigid, non-physiological substrates. Although both are used extensively, few studies directly compare these architectures. This study aims to perform a controlled, side-by-side comparison of these two VoC models, systematically evaluating fabrication robustness, success rates, and the ability of the endothelial monolayer to respond to inflammation and shear stress.

Methods. Two VoC architectures were compared: (i) a cylindrical lumen (160 µm diameter) within a 3D collagen-I hydrogel formed by needle templating, and (ii) a square PDMS microchannel (170 × 170 µm) fabricated via soft lithography. Both models were seeded with human umbilical vein endothelial cells (HUVECs). PDMS channels were directly used as lumens for cell seeding after fibronectin coating, whereas hydrogel vessels required additional steps for gelation and lumen formation. Fabrication success rate and lumen geometry were quantified in both systems. Endothelial confluency, morphology, and junctional integrity were assessed by confocal microscopy using VE-cadherin staining. Inflammatory activation was evaluated via E-selectin expression. Shear stress response was analysed by measuring cell spreading, elongation, and F-actin organization under flow compared to static controls.

Results. The PDMS model demonstrated superior robustness and reproducibility, with a 100% fabrication success rate (usable lumens) and 75% of devices reaching the experimental endpoint, compared to 68% fabrication success and only 30% endpoint survival for the hydrogel model. Furthermore, the PDMS model required a significantly shorter preparation time (3 days vs. 1 week) and less operator expertise. Both models provided reliable endothelial responses to inflammatory stimuli, characterized by E-selectin expression ($p<0.01$ in PDMS channels), junctional destabilization ($p<0.01$) and partial cells loss. Response to shear flow was successfully quantified in the PDMS model, where ECs showed increased spreading ($p<0.05$) and elongation while preserving barrier integrity. Moreover, perfusion induced a shift from cortical to cytoplasmic F-actin, consistent with stress fiber formation and alignment under flow.

Conclusions. This study highlights a key trade-off between physiological relevance and experimental practicality. While collagen-based microvessels better replicate native conditions, PDMS microchannels provide greater consistency, robustness, and scalability. These findings indicate that increased biomimicry does not necessarily translate to improved experimental performance. Instead, model selection should be guided by the specific biological question and the required level of throughput and reproducibility.

ABSTRACT N. PO019

LONGITUDINAL COAGULATION PROFILING BY THROMBIN GENERATION AND CIRCULATING MICROVESISCLES OF INDIVIDUALS UNDERGOING GENDER-AFFIRMING HORMONE THERAPY

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Background and aims. Transgender individuals may have an increased thrombotic risk related to gender-affirming hormone therapy (GAHT). We aimed to investigate longitudinal GAHT-related changes in coagulation and explore mechanisms underlying hypercoagulability.

Methods. Prospective longitudinal study enrolling adult transgender individuals initiating GAHT. Blood samples were collected at baseline and follow-up up to 24 months. Hemostatic profiling included procoagulant factors, natural anticoagulants, global assays, thrombin generation (PPP, calibrated automated thrombogram), and large extracellular vesicles (MVs) by flow cytometry. Clinical events were recorded.

Results. The cohort included 44 Assigned Male at Birth (AMAB) and 52 Assigned Female at Birth (AFAB) participants. Over follow-up, AMAB individuals showed a progressive procoagulant shift. Factor VIII increased significantly over time; p for trend=0.04). Natural anticoagulant pathways significantly changed, with longitudinal variations in free protein S antigen (p=0.03), protein S activity (p=0.02), and antithrombin (p=0.009). Thrombin generation increased, with shortening of lag time (p=0.005) and marked increases in peak thrombin (p<0.001), ETP (p=0.04), and ETP ratio (p=0.005). Consistently, ROTEM showed faster clot initiation with shortening of EXTEM-CT (p<0.001) (Table 1). In AFAB individuals, factor VIII and fibrinogen did not significantly change. Protein C activity decreased over time (p=0.01), while free protein S antigen (p=0.05), protein S activity (p=0.03), and antithrombin (p=0.02) showed longitudinal variations. TG lag time decreased (p=0.005) and peak thrombin increased (p<0.001), whereas ETP and ETP ratio remained unchanged. On ROTEM, clot propagation was impaired, as indicated by increased INTEM-CFT (p<0.001) and EXTEM-CFT (p=0.002), along with reduced INTEM-MCF (p=0.04) (Table 1). In AMAB participants, total circulating Annexin V+ MVs significantly increased over follow-up (p for trend=0.0009), while erythrocyte-derived MVs (Annexin V+ CD235a+) decreased over follow-up (p=0.0156), with lower levels already evident at 3 months and persisting up to 24 months. In AFAB, platelet-derived MVs (Annexin V+ CD41+CD62P+) varied over follow-up (p=0.0146), suggesting time-dependent modulation after testosterone initiation, with early changes at 3 months (Table1).

Conclusions. GAHT induces sex-specific coagulation changes. AMAB develop a progressive procoagulant phenotype with increased thrombin generation and faster clot initiation, while AFAB show a distinct profile involving thrombin peak and clot propagation, accompanied by MV modulation. These findings support different mechanisms of GAHT-related hypercoagulability.

Table 1. Longitudinal trend of coagulation parameters in AMAB e AFAB subjects undergoing GAHT

Parameter	Baseline	3 months	6 months	12 months	24 months	p for trend
Thrombin generation AMAB						
TG lag time, min	3.6 [3.0–4.3]	3.5 [3.4–3.7]	3.4 [3.2–3.7]	3.1 [2.7–3.6]	3.1 [2.9–3.2]	0.005
TG peak thrombin, nM	227 [158–248]	257 [242–286]	271 [237–290]	265 [249–309]	316 [286–341]	<0.001
TG ETP, nM·min	1266 [1183–1540]	1352 [1265–1598]	1406 [1237–1702]	1459 [1278–1578]	1468 [1421–1580]	0.04
TG ETP ratio	0.61 [0.54–0.80]	0.76 [0.57–0.83]	0.77 [0.66–0.83]	0.83 [0.68–0.87]	0.84 [0.70–0.88]	0.005
Thromboelastometry (ROTEM) AMAB						
EXTEM-CT	79 [75–81]	77 [72–78]	64 [61–72]	63 [59–70]	57 [55–64]	<0.001
Extracellular vesicles (EVs) AMAB						
Total Annexin V+ EVs (Calcein+ Annexin V+ events), n/µL	1963 [1612–2423]	1882 [1476–2289]	1844 [1556–2189]	2048 [1637–2503]	2522 [2293–2911]	0.009
Erythrocyte-derived MVs (Annexin V+ CD235a+), n/µL	2349 [2074–2909]	1846 [1665–2359]	2060 [1699–2277]	1904 [1456–2222]	2150 [1963–2683]	0.0162
Thrombin generation AFAB						
TG lag time, min	3.3 [3.1–3.8]	3.5 [3.1–3.9]	3.5 [3.3–3.8]	3.4 [3.0–4.2]	3.1 [2.8–3.2]	0.005
TG peak thrombin, nM	252 [214–260]	246 [226–290]	255 [207–280]	255 [201–290]	278 [251–306]	<0.001
TG ETP, nM·min	1339 [1183–1506]	1331 [1062–1471]	1306 [1164–1519]	1333 [1193–1494]	1302 [1206–1448]	ns
TG ETP ratio	0.68 [0.53–0.84]	0.64 [0.46–0.86]	0.61 [0.48–0.86]	0.68 [0.53–0.79]	0.66 [0.59–0.77]	ns
Thromboelastometry (ROTEM) AFAB						
INTEM-MCF	66 [64–69]	64 [61–67]	64 [58–69]	61 [59–64]	63 [60–65]	0.04
INTEM-CFT	60 [50–65]	71 [61–80]	83 [72–97]	96 [82–109]	72 [64–82]	<0.001
EXTEM-CFT	70 [65–74]	80 [74–85]	90 [73–121]	95 [89–106]	73 [62–89]	0.002
Extracellular vesicles (EVs)						
Platelet-derived MVs (Annexin V+ CD41+CD62P+), n/µL	434 [367-620]		269 [211–654]	553 [327–719]	396 [309–511]	501 [399–741]	0.0146

AMAB, assigned male at birth; CT, clotting time; ETP, endogenous thrombin potential; EXTEM, extrinsically activated thromboelastometry test; GAHT, gender-affirming hormone therapy; IQR, interquartile range; ns, not significant; ROTEM, rotational thromboelastometry; TG, thrombin generation; MVs, microvesicles.

ABSTRACT N. PO020

EXTRACELLULAR VESICLE PROFILES REFLECT THROMBO-INFLAMMATORY ACTIVATION AND ARE ASSOCIATED WITH CLINICAL OUTCOMES IN LIVER CIRRHOSIS

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Background and aims. Cirrhosis is characterized by progressive immune dysregulation, endothelial dysfunction, and haemostatic imbalance. Circulating extracellular vesicles (EVs) have emerged as potential biomarkers reflecting these pathophysiological processes. We aimed to determine whether EVs mirror disease severity and predict liver-related outcomes in cirrhosis.

Methods. In this prospective single-centre study, patients with compensated, stable decompensated, or acutely decompensated cirrhosis were enrolled. A group of 32 healthy controls was included. EVs were isolated from platelet-poor plasma and quantified by flow cytometry to characterize platelet-, endothelial-, anticoagulant-, immune-, hepatocyte-, and fibrosis- derived EVs. Primary endpoints were first hepatic decompensation in compensated cirrhosis and a composite of further decompensation, acute-on-chronic liver failure, or liver-related mortality in acutely decompensated cirrhosis. Associations were analysed using Fine-Gray competing-risk models.

Results. We included 228 patients, including 75 compensated, 44 stable decompensated, and 109 acutely decompensated. Median follow-up was 418 days. EV profiling showed progressive increases in total, platelet-derived, endothelial-, immune-derived, and fibrosis- associated EVs across Child–Pugh stages, indicating increasing thrombo-inflammatory and endothelial activation. First hepatic decompensation occurred in 7 patients with compensated cirrhosis and was associated with higher MELD and Child–Pugh scores, alcohol-related aetiology, and lower platelet count. In univariate competing-risk analyses, higher levels of several EV subpopulations were associated with first decompensation, but these associations disappeared after adjustment for MELD. Among patients with decompensated cirrhosis, 36 developed further decompensation, ACLF, or liver-related death; higher CRP levels were associated with these events, whereas no EV subpopulation could predict the composite outcome.

Conclusions. Circulating EVs reflect cirrhosis severity and progressive thrombo- inflammatory, endothelial, and pro-fibrotic alterations, supporting their role as markers of underlying pathophysiological processes. However, EVs were not independently associated with clinical outcomes and therefore have limited value for prognostic stratification.

Table 1 Circulating MVs across disease severity

Variable (MV subset)	Healthy controls	Child–Pugh A	Child–Pugh B	Child–Pugh C	P overall
Total MVs (Calcein)	3867 (3407–4362)	4582 (3803–5380)	5579 (4069–6289)	5830 (4832–7234)	<0.001
Platelet MVs (CD41⁺)	3085 (2654–3715)	3447 (2544–4447)	4117 (3076–5587)	4631 (2971–6337)	<0.001
Activated platelet MVs (CD41⁺CD62P⁺)	822 (574–1005)	600 (452–928)	830 (549–1204)	966 (617–1483)	<0.001
Activated endothelium (CD62E⁺)	1311 (833–1550)	808 (530–1169)	1016 (703–1427)	1141 (733–1754)	<0.001
Activated endothelium + TF (CD62E⁺TF⁺)	272 (211–320)	4 (2–9)	5 (2–10)	10 (4–22)	<0.001
Monocytes/Macrophages (CD45⁺)	3610 (2895–4740)	3589 (2466–4280)	4240 (3191–5475)	4776 (3612–6198)	<0.001
Monocytes/Macrophages (CD45⁺CD14⁺)	2716 (2118–3560)	2501 (1790–3067)	2979 (2255–3911)	3376 (2692–4351)	<0.001
Angiogenesis/HCC (CD105⁺)	3134 (2568–3988)	3842 (2697–4948)	4229 (3588–5561)	4729 (3775–6175)	<0.001
Angiogenesis/HCC (CD147⁺)	2174 (1879–2681)	3161 (2597–4238)	4197 (3187–5282)	4381 (3419–5974)	<0.001
Angiogenesis/HCC (CD105⁺CD147⁺)	1525 (1346–1913)	2017 (1515–2546)	2636 (2051–3377)	2868 (2127–3862)	<0.001
Hepatocyte damage (CK18⁺)	121 (97–195)	154 (69–265)	186 (111–270)	190 (133–328)	0.011
Hepatocyte damage + TF (CK18⁺TF⁺)	113 (90–194)	58 (37–91)	65 (46–90)	67 (47–96)	<0.001
T-lymphocytes (CD11a⁺)	2110 (1733–2550)	2964 (2150–3716)	3494 (2771–4402)	3962 (3166–5045)	<0.001
T-lymphocytes (CD11a⁺CD4⁺)	529 (410–662)	602 (428–797)	719 (525–953)	878 (683–1107)	<0.001
Endothelial cells (CD144⁺)	2594 (2303–2994)	3672 (2486–4180)	3988 (3043–5105)	4885 (3731–5760)	<0.001
Endothelial cells + VEGFR2 (CD144⁺VEGFR2⁺)	1397 (1245–1619)	2055 (1356–2410)	2755 (2074–3282)	3025 (2354–3842)	<0.001
EPCR⁺ endothelial MVs (EPCR)	974 (831–1298)	752 (481–960)	906 (573–1222)	1010 (718–1384)	<0.001
Thrombomodulin⁺ endothelial MVs (CD141⁺)	1358 (1185–1516)	19 (10–61)	26 (14–55)	42 (19–83)	<0.001
Anticoagulant endothelial MVs (CD141⁺EPCR⁺)	325 (288–481)	7 (2–30)	14 (7–31)	19 (7–41)	<0.001

MVs: microvesicles; TF: tissue factor; EPCR: endothelial protein C receptor; HCC: hepatocellular carcinoma; VEGFR: vascular endothelial growth factor receptor

ABSTRACT N. PO021

PLATELETS MATTER: THROMBIN GENERATION IN PLATELET-RICH PLASMA VERSUS PLATELET-POOR-PLASMA UNDER NON-REPLACEMENT THERAPIES IN HAEMOPHILIA

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Background and aims. Non-replacement therapies have transformed the management of Hemophilia A (HA) and B (HB). Emicizumab (Emz) is a subcutaneously administered, recombinant, humanized bispecific monoclonal antibody that mimics the function of missing activated FVIII (FVIIIa), thereby restoring activation of FX, downstream thrombin generation, and propagation of the coagulation cascade. Concizumab (Concz) is an anti–tissue factor pathway inhibitor (TFPI) monoclonal antibody that enhances thrombin generation by inhibiting the TFPI anticoagulant pathway, thus compensating for the deficiency of both FVIII and FIX. While their mechanism of action is well established, their potential interaction with cellular components of coagulation, such as platelets, remains poorly characterized. Platelets play a crucial role in coagulation by providing a procoagulant phospholipid surface and amplifying thrombin generation; however, their contribution in patients receiving non-replacement therapies has not been fully elucidated. This study aimed to assess whether platelets contribute to hemostatic potential in patients treated with Emz or Concz by comparing thrombin generation assay (TGA) parameters in platelet-rich plasma (PRP) and platelet-poor plasma (PPP).

Methods. Among 21 patients on Emz prophylaxis and 2 patients on Concz prophylaxis (in Novo Nordisk study NCT04082429) followed at our Centre, blood sampling was obtained from 15 patients with severe HA, with and without inhibitors, on stable Emz prophylaxis, and 2 patients receiving Concz (one with severe HA and one with severe HB). Thrombin generation was evaluated in both PRP and PPP using the ST Genesia® (Stago, Asnières-sur-Seine, France): frozen PPP samples were analyzed using the standard protocol. PRP samples were analyzed within 2 hours of collection using an in-house validated protocol. The following parameters were recorded: Lag Time, Peak Height, Time to Peak, Endogenous Thrombin Potential (ETP), Velocity Index, and Start Tail. PRP and PPP results were compared to evaluate the impact of platelets on thrombin generation.

Results. Six samples were excluded due to instrument malfunction. A comparison of the results obtained in PRP and PPP in the 11 evaluable patients is shown in Table 1. A consistent trend was observed across all pts: in PRP, there was an increase in Lag Time, Time to Peak, ETP and Start Tail, and a decrease in Velocity Index; instead, Peak Height did not demonstrate a uniform trend across all pts. However, no appreciable differences in the thrombin generation profile were observed between patients treated with Concz and those treated with Emz.

Conclusions. A consistent difference between PPP- and PRP-based TGA was observed across all patients. Specifically, PRP curves exhibited a delayed onset of thrombin generation and a prolonged time to peak, alongside a higher total amount of thrombin generated and greater endogenous thrombin potential. These findings suggest that PRP-based TGA may provide a more comprehensive assessment of the hemostatic profile in patients receiving non-replacement therapies, capturing the contribution of platelet-dependent coagulation processes.

Increase or decrease between PPP and PRP			
Parameter	Emicizumab (Hemophilia A)	Concizumab (Hemophilia A)	Concizumab (Hemophilia B)
Lag Time	+151,80%	+133,19%	+109,06%
Peak Height	+19,53%	-0,62%	-46,81%
Time to Peak	+126,33%	+82,30%	+137,88%
ETP	+51,00%	+27,97%	+43,67%
Velocity Index	-33,49%	-62,73%	-82,04%
Start Tail	+33,47%	+43,94%	+157,67%



ARTIFICIAL INTELLIGENCE–ASSISTED PREDICTION OF THROMBOTIC AND HEMORRHAGIC COMPLICATIONS IN PATIENTS TREATED WITH VITAMIN K ANTAGONISTS: A RETROSPECTIVE EXPLORATORY STUDY

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Background and Aims. Vitamin K antagonist (VKA) therapy remains widely used but is burdened by a substantial risk of thrombotic and hemorrhagic complications. Despite the availability of standardized international coagulation parameters, individualized therapeutic ranges, dedicated anticoagulation management software, and specialized anticoagulation clinics, adverse events continue to represent a major clinical challenge. Artificial intelligence (AI) tools, particularly large language models, may offer new opportunities for risk prediction. This study evaluated whether an AI chatbot, when guided by structured prompts, could predict thrombotic or hemorrhagic events in patients treated with VKAs.

Methods. We retrospectively analyzed 17 patients (4 males, 13 females; mean age 77.1 years, range 58–95) receiving VKA therapy who experienced thrombotic or bleeding complications. Sixteen patients were treated with warfarin and one with acenocoumarol. Indications for anticoagulation included atrial fibrillation (n=7), mechanical heart valve (n=4), deep vein thrombosis (n=5), and pulmonary embolism (n=1). A total of 19 adverse events were recorded: 10 hemorrhagic (7 intracranial, 3 gastrointestinal) and 9 thrombotic (5 ischemic strokes, 1 transient ischemic attack, 2 superficial venous thromboses, 1 myocardial infarction). One patient experienced both event types, and one had two thrombotic events. The mean time from therapy initiation to the adverse event was 4017.3 days, longer for thrombotic events (4972.5 days) than for hemorrhagic events (3157.6 days). Relevant comorbidities included erosive gastritis (n=1), renal insufficiency (n=3), and antiphospholipid antibody syndrome (APS) (n=1) among bleeding cases; APS (n=2) and malignancy (n=1) among thrombotic cases. CHATGPT® was instructed to predict the likelihood of thrombotic or hemorrhagic complications in a hypothetical population with identical demographic and clinical characteristics, including indication for anticoagulation, VKA type, and comorbidities, without disclosing that events had already occurred. Event timing was categorized into four intervals (0–5, 5–10, 10–15, >15 years). Prediction accuracy was assessed by comparing the AI assigned risk category—high (≥15%), intermediate (8–14.9%), or low (<8%)—with the actual occurrence of events within the corresponding time interval. These thresholds were derived from 5 year conversions of established bleeding risk models (HAS BLED, ORBIT, warfarin specific models) and applied uniformly to both bleeding and thrombotic outcomes.

Results. CHATGPT predictions demonstrated high or very high concordance in 12 of 19 cases (63.1%), intermediate concordance in 6 cases (31.6%), and poor concordance in only 1 case (5.3%). Overall, predictions were fully correct in 14 events and partially correct in 4, yielding an overall reliability of 94.7%.

Conclusions. This exploratory analysis suggests that AI based chatbots may achieve a high degree of accuracy in predicting thrombotic and hemorrhagic complications in patients treated with VKAs. Although preliminary and limited by the small sample size, these findings support the potential role of AI tools in enhancing individualized risk stratification. Larger prospective studies, including healthy control groups and more diverse clinical profiles, are warranted to refine predictive performance and to integrate AI assisted risk assessment into routine anticoagulation management.



CLOPIDOGREL USE IN ANTIPLATELET MANAGEMENT OF ESSENTIAL THROMBOCYTHEMIA (TECLA STUDY): DESIGN AND FEASIBILITY OF A SINGLE-CENTRE STUDY

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Background. Essential Thrombocythemia (ET) is characterized by enhanced platelet generation and high risk of both arterial and venous thrombosis, as the leading cause of morbidity and mortality. Thus, chronic low-dose aspirin is recommended for primary and secondary thrombosis prevention. In ET, the accelerated platelet turnover has been shown to reduce the stability and degree of platelet inhibition by standard low dose aspirin given once-daily, due to the increased daily regeneration of the drug's target. Clopidogrel, a thienopyridine prodrug, given once-daily is used in case of aspirin allergy or intolerance, for primary and secondary thrombosis prophylaxis in ET patients. Similar to aspirin, clopidogrel active metabolite acts irreversibly, and its target is the P2Y12, ADP receptor. Whether clopidogrel given once-daily can produce a steady and optimal 24-hour inhibition of platelets is currently unknown Our study has different aims: 1. Measure the degree of platelet inhibition in patients affected by ET receiving clopidogrel and in a non-ET population with an indication for clopidogrel therapy due to cardiovascular disorders; 2) to compare the capacity of two different platelet function methods to detect the pharmacodynamics of clopidogrel ex vivo.

Methods. A total of 25 adult patients with Essential Thrombocythemia (ET) and 25 age- and sex-matched non-ET patients on standard clopidogrel (75 mg) once-daily will be enrolled. All patients will be instructed to take the clopidogrel tablet always at breakfast time, for 7-10 days. ADP-induced platelet aggregation in whole blood (Verify Now-P2Y12) and in platelet-rich plasma will be measured. At the morning routine visit a blood sample will be collected 24 hours after the last intake of clopidogrel for platelet aggregation testing.

Results. This study has received the approval of the Local Ethical Committee. The first patient was studied on 31th March 2026. At present, 16 patients gave their informed consent.

Conclusions. This study will verify the hypothesis that the same mechanisms reducing aspirin responsiveness in ET patients may also contribute to a reduced ADP induced platelet inhibition under standard clopidogrel 75 mg OD.

ABSTRACT N. PO024

IMPLEMENTATION OF 4PL SIGMOIDAL REGRESSION FOR FACTOR VIII INHIBITOR QUANTIFICATION IN ACQUIRED HEMOPHILIA

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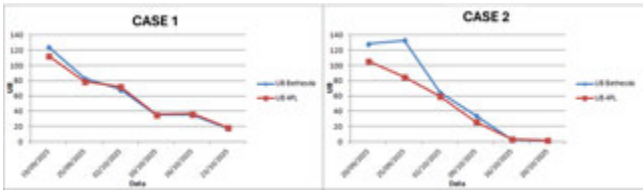
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Background and Aims. The quantification of Factor VIII (FVIII) inhibitors is critical for managing patients with hemophilia. The standard Nijmegen-Bethesda assay relies on a theoretical linear-logarithmic relationship where 1 Bethesda Unit (BU) is defined as the amount of inhibitor neutralizing 50% of FVIII activity. While this model is effective for Type 1 inhibitors (typically alloantibodies in congenital hemophilia), it often fails to accurately represent Type 2 inhibitors (typically autoantibodies in acquired hemophilia). Type 2 inhibitors exhibit complex, non-linear kinetics and incomplete FVIII neutralization, leading to potential underestimation or overestimation of titers when using the standard formula. In this work, we evaluate the accuracy of the 4-Parameter Logistic (4PL) sigmoidal regression model compared to the traditional Bethesda method in quantifying inhibitors for patients with acquired hemophilia, across different kinetic profiles.

Methods. We analyzed longitudinal data from two clinical cases of acquired hemophilia. Inhibitor titers were initially calculated using the traditional Nijmegen-Bethesda formula based on the dilution closest to 50% residual activity (RA). These results were compared against a new calculation method using 4PL sigmoidal regression. The 4PL model creates a "best fit" curve by considering all serial dilutions, governed by specific biological constraints: Top fixed at 100%, Bottom ≥0 and optimized Hillslope and LogEC50. The inhibitor titer in BU was derived as 2logEC50. Statistical accuracy was assessed by calculating the sum of squared errors (SSE) between measured and predicted RA values and by evaluating the consistency of the clinical trend.

Results. In Case 1, the inhibitor showed a more linear behavior in the 25-75% RA range. In the initial sample, the 4PL method yielded 112.3 BU compared to 124.4 BU with the traditional method (SSE = 17.9), showing relatively good alignment. Throughout the observation period, the results of both methods remained closely aligned, indicating that the traditional calculation is reliable for linear kinetics. However, Case 2 demonstrated the limitations of the traditional assay: multiple dilutions clustered around 50% RA, making validation difficult. For the initial sample, the traditional method estimated 128.6 BU, while the 4PL model provided a more mathematically robust estimate of 105.5 BU. When examining the entire period for the second case, the traditional method showed high volatility (e.g., an inconsistent jump from 128.6 to 133.0 BU between two consecutive samples), whereas the 4PL model (moving from 105.5 to 85.1 BU) reflected a more consistent biological trend that aligned with the clinical course.

Conclusions. We demonstrate that kinetic profiles of FVIII autoantibodies frequently deviate from the ideal theoretical model of the Nijmegen-Bethesda assay. While the traditional method is simple and reliable for inhibitors following linear kinetics, it lacks accuracy when dealing with the non-linear neutralization typical of acquired hemophilia. The 4PL sigmoidal regression provides a superior fit for raw laboratory data, minimizing errors by integrating information from all dilutions rather than a single data point. Implementing 4PL regression in the clinical laboratory setting offers a more accurate, standardized, and reproducible approach to monitoring inhibitor titers, ultimately improving therapeutic decision-making in complex hemophilia cases.



ABSTRACT N. PO025

CHARACTERIZATION OF PLATELET DYSFUNCTION IN NOONAN SYNDROME PATIENTS

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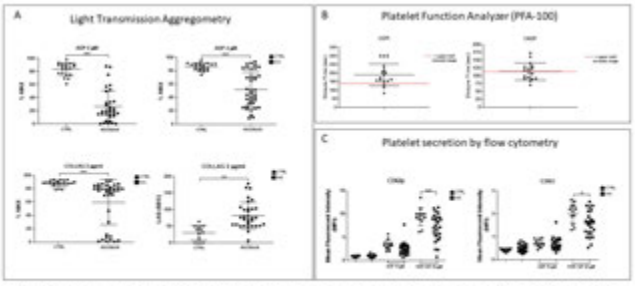
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Background and aims. Noonan syndrome (NS) is a RASopathy characterized by dysregulation of the Ras/MAPK pathway and frequently associated with bleeding diathesis. Although hemostatic abnormalities are reported in the majority of patients, the underlying mechanisms remain incompletely defined, particularly with regard to platelet function. Preliminary evidence suggests a high prevalence of platelet defects, but their functional characterization and pathway involvement are still poorly delineated. This study aimed to refine the platelet dysfunction phenotype in NS by integrating aggregation and secretion data.

Methods. In this case–control monocentric study, 29 NS patients were compared with 20 age-matched healthy controls at a single center. Bleeding tendency was assessed using the ISTH-BAT score. Standard coagulation parameters (PT, aPTT, fibrinogen, platelet count) were evaluated. Platelet function was investigated by light transmission aggregometry (LTA) using adenosine diphosphate (ADP), collagen, epinephrine, arachidonic acid (AA), and PAR1-activating peptide (PAR1-AP). Maximal aggregation (MA, %) and collagen lag phase (LP, sec) were recorded. Platelet secretion was assessed by flow cytometry through CD63 and CD62p expression after stimulation. Platelet Function Analyzer (PFA-100) closure times were available in a subset of patients.

Results. An abnormal ISTH-BAT score (>3) was observed in 24% of NS patients. PT, fibrinogen levels, and platelet count were comparable between groups, whereas prolonged aPTT was detected in 30% of patients. LTA revealed a consistent and pathway-specific impairment of platelet aggregation. ADP-induced responses were markedly reduced, with MA <60% in 91.6% and 79% of patients at 2 µM and 4 µM, respectively. Collagen-induced aggregation was also impaired, with MA <75% in 42% and prolonged LP (>50 sec) in 87% of patients. Impaired responses were also observed with epinephrine (MA <60% at 180 sec in 87% NS) and PAR1-AP (MA <75% in 45.8% NS). In contrast, AA-induced aggregation was largely preserved, suggesting selective pathway involvement rather than a global defect. Flow cytometry confirmed a secretion defect, with reduced CD63 and CD62p expression after PAR1-AP stimulation. Prolonged PFA-CEPI and PFA-ADP closure times were observed in 82% and 47% of tested patients, respectively.

Conclusions. This study demonstrates that the majority of patients with NS exhibit platelet dysfunction, characterized by impaired aggregation responses to ADP, collagen, and thrombin receptor stimulation, and associated with defective granule secretion. Platelet dysfunction may be detected by prolonged PFA-CEPI closure time. These findings underscore the importance of identifying and characterizing platelet abnormalities in NS patients to optimize the management of bleeding symptoms and to guide hemostatic support during surgical or invasive procedures.



ABSTRACT N. PO026

AUTOSOMAL DOMINANT *ITGA2B* AND *ITGB3* VARIANTS EXPAND THE PHENOTYPIC SPECTRUM OF AIIBB3-RELATED PLATELET DISORDERS

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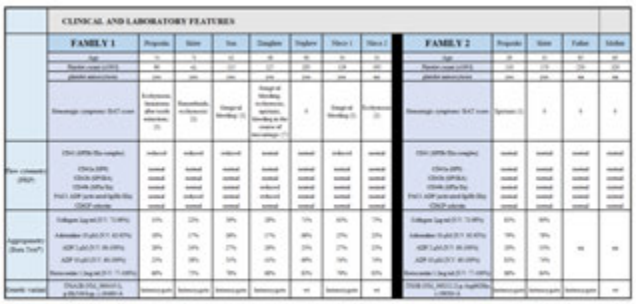
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Background and Aims. Autosomal dominant thrombocytopenias caused by heterozygous *ITGA2B* and *ITGB3* pathogenic variants are increasingly recognized as a distinct entity from classical Glanzmann thrombasthenia (GT). These disorders typically present with mild thrombocytopenia, variable platelet function defects, and heterogeneous bleeding severity. However, given their rarity, they remain poorly defined from a clinical, biochemical, and genetic perspective. We aim to describe the clinical, laboratory, and molecular features of two previously unreported heterozygous variants in *ITGA2B* and *ITGB3* genes identified in two unrelated families with autosomal dominant inheritance.

Methods. Affected individuals underwent standardized bleeding assessment using ISTH Bleeding Assessment Tool (BAT), platelet count followed by aggregation studies, performed on platelet-rich plasma using the Born method (Chronolog). Flow cytometric analysis of αIIbβ3 expression was conducted assessing CD41a expression and PAC-1 binding following ADP stimulation. Genetic analysis was performed in the proband using targeted next-generation sequencing. Identified variants were validated and tested for segregation in available family members by Sanger sequencing. Variant pathogenicity was assessed according to ACMG criteria. Reference transcripts were NM_000419.5 (*ITGA2B*) and NM_000212.3 (*ITGB3*). Structural impact was evaluated by in silico modelling.

Results. Among Family 1 carriers (5/7 individuals), the heterozygous *ITGA2B* p.Gly549Asp (c.1646G>A) (Class 4) variant co-segregated with mild thrombocytopenia and mucocutaneous bleeding. The proband showed mildly reduced platelet count (~96×10^9/L), anisocytosis, and occasional macrothrombocytes. BAT scores ranged from 1 to 7 among the carriers. Platelet aggregation was partially impaired, and above normal range in response to ADP, collagen, and epinephrine, while ristocetin-induced aggregation was preserved (Table 1). Flow cytometry revealed reduced CD41a expression and impaired PAC-1 activation after ADP stimulation. In silico structural modelling suggested destabilization of the extracellular αIIb domain (Table 1). In Family 2, the heterozygous *ITGB3* p.Arg662His (c.1985G>A)(Class 4) variant, affecting the same residue as the Sra alloantigen, previously associated with neonatal alloimmune thrombocytopenia, was identified in the proband, his sister, and father (3/4 individuals). The proband exhibited mild thrombocytopenia (~100×10^9/L), a BAT score of 1, normal platelet aggregation, and normal αIIbβ3 surface expression, consistent with a very mild or subclinical phenotype with variable expressivity.

Conclusions. These findings expand the spectrum of αIIbβ3-related autosomal dominant platelet disorders and highlight significant gene- and variant-specific phenotypic variability. Recognition of these often subtle and heterogeneous presentations is essential for accurate molecular diagnosis and appropriate genetic counselling. The contrasting phenotypes observed between the two families further suggest a continuum of disease severity ranging from functional impairment to near-normal platelet function despite thrombocytopenia depending on a variant-specific effect on αIIbβ3 expression and activation. These observations also underscore the importance of including *ITGA2B* and *ITGB3* in diagnostic workflows for inherited thrombocytopenias, particularly in cases with mild or atypical phenotypes that may be misdiagnosed as other platelet disorders.



ABSTRACT N. PO027

IGFBP-6 REGULATES PLATELET PROCOAGULANT ACTIVITY AT THE INTERFACE BETWEEN INFLAMMATION AND COAGULATION

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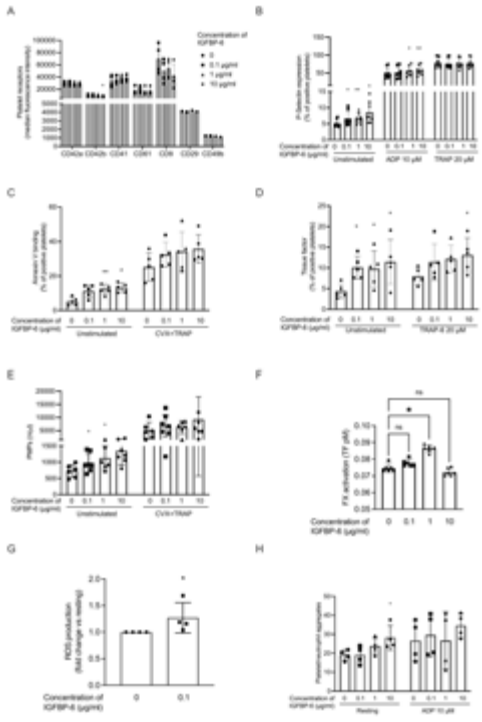
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Background and Aims. Insulin-like growth factor binding protein-6 (IGFBP-6) is a multifunctional protein expressed in several immune and stromal cell types that plays key roles in inflammation and tissue repair. We previously described its role in fibrosis, showing that IGFBP-6 promotes immune cell chemotaxis, reactive oxygen species (ROS) production, and fibroblast activation. However, IGFBP-6 also reduces vascular inflammation and atherosclerosis. Platelets, beyond their canonical hemostatic function, actively participate in thrombo-inflammatory conditions in particular through a specialized subpopulation expressing procoagulant activity. No studies so far have explored the role of IGFBP-6 in regulating platelet activation. We aimed to study whether IGFBP-6 modulates platelet activation and procoagulant activity.

Methods. Spatial proteomics of blood cell antigens was carried out by molecular pixelation. Platelet rich plasma was incubated with IGFBP-6 at three different concentrations (0.1 – 1 – 10 ug/ml). Expression of the major platelet glycoproteins, platelet P-Selectin expression and aIIbb3 activation were assessed by flow cytometry. Procoagulant platelets were detected by measuring phosphatidylserine (PS) exposure and tissue factor (TF) expression by flow cytometry. Platelet extracellular vescicles (EVs) were counted in the supernatants of platelets stimulated with collagen and thrombin by flow cytometry, morphological gate was set using a mix of fluorescent beads of varied diameters. Platelet-leukocyte aggregates were assessed by flow cytometry. ROS production by platelets was assessed by flow cytometry using the H2DCFDA fluorescent probe.

Results. Spatial proteomics revealed decreased CD41 expression after incubation of a leukocyte–platelet suspension with IGFBP-6 while the pre-incubation of platelet rich plasma (PRP) with IGFBP-6 did not affect the expression of the main platelet receptors, except for a slight decrease in GPIba (Figure 1A). Incubation with IGFBP-6 determined also an increase of P-Selectin expression (Figure 1B). IGFBP-6 induced an increase in Annexin V binding, indicating an enhanced exposure of procoagulant phosphatidylserine on the platelet surface (Figure 1C). Consistently, tissue factor expression was increased (Figure 1D), together with a higher release of extracellular vesicles in the supernatant (Figure 1E).Finally, IGFBP-6 significantly increased platelet-dependent FXa generation, thereby enhancing the procoagulant activity of platelets (Figure 1F). Pre-incubation with IGFBP-6 increased ROS levels in platelets (Figure 1G), consistent with a cellular stress response known to favor the development of the procoagulant platelet phenotype. Finally, we observed a significant increase of platelet-neutrophil aggregates (Figure 1H).

Conclusions. Our findings identify IGFBP-6 as a novel regulator of platelet procoagulant activity, supporting a model in which IGFBP-6, at concentrations similar to those found at sites of inflammation, contributes to the fine-tuning of the platelet thromboinflammatory responses. Pre-incubation with IGFBP-6 increased ROS levels in platelets, consistent with a cellular stress response known to favor the development of the procoagulant platelet phenotype. By enhancing platelet–neutrophil crosstalk, IGFBP-6 may contribute to the amplification of thromboinflammatory responses at sites of vascular injury or inflammation.





SUSTAINED RESPONSE OFF TREATMENT IN ITP PATIENTS TREATED WITH TPO-RA: A SINGLE-CENTER EXPERIENCE

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Background and Aims. The introduction of thrombopoietin receptor agonists (TPO-RAs) has significantly improved response rates in patients with immune thrombocytopenia (ITP). In a subset of patients, a sustained response can be achieved despite progressive dose reduction and even after treatment discontinuation, defined as sustained response off treatment (SROT). We analyzed patients from our center who achieved SROT, evaluating response duration, tapering strategies, and relapse rates, with the aim of contributing to process standardization.

Methods. Seventeen patients (9 males, 8 females) were included, with a median age at diagnosis of 63 years (range 21–73). Before TPO-RA initiation, 12/17 patients (70.6%) had received one prior treatment line, 3/17 (17.6%) two lines, and 2/17 (11.8%) ≥3 lines. TPO-RAs were started within 3 months from diagnosis in 2/17 patients, during the persistent phase in 5/17, and in the chronic phase in 10/17. Six patients received eltrombopag, ten romiplostim, and one avatrombopag.

Results. Median duration of TPO-RA therapy was 24 months (range 3–79), with a median peak platelet count of 308×10^9/L. Tapering was performed over a median of 12 months; median platelet count at tapering initiation was 223.5×10^9/L, with a nadir of 119×10^9/L during dose reduction. In 2/17 patients, treatment was discontinued without tapering due to adverse events; both maintained SROT for more than 10 years. Median dose at discontinuation was 25 mg/week for eltrombopag, 0.065 mL/week for romiplostim, and 10 mg/week for avatrombopag. Median platelet count at discontinuation was 139×10^9/L. Median follow-up after discontinuation was 53 months. Relapse occurred in 4/17 patients: two were successfully treated with corticosteroids, while two resumed TPO-RA therapy; one of these regained SROT after a second tapering attempt, while the other remains on treatment.

Conclusions. SROT is an achievable goal in a subset of ITP patients treated with TPO-RAs, with relevant clinical and psychological impact, although relapse may occur in a minority of cases. Our monocentric experience is consistent with available literature and supports the need for standardized tapering strategies. Data on avatrombopag remain limited, and further studies are warranted to identify predictive factors for SROT



IMPACT OF HEPATOCELLULAR CARCINOMA ON CIRCULATING RETICULATED PLATELETS IN PATIENTS WITH AND WITHOUT LIVER CIRRHOSIS

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Background and Aims. Reticulated platelets (RePLTs) are bigger and more reactive platelets with an increased RNA content. In liver cirrhosis, increased platelet turnover leads to the release of these “emergency platelets'', which would counteract bleeding events. However, their role in hepatocellular carcinoma (HCC) remains unclear. The aim of this study is to evaluate RePLT levels and platelet activation in HCC patients with and without cirrhosis.

Methods. Sixty subjects were prospectively enrolled into four groups: healthy controls (CTRL), cirrhosis without HCC (cirrhosis+ HCC-), HCC on a healthy liver (cirrhosis- HCC+), and HCC on cirrhosis (cirrhosis+ HCC+). Exclusion criteria were advanced liver disease (Child-Pugh B/C), portal vein thrombosis and antiplatelet therapy. RePLTs were defined through CD41 and SYTO-13 positivity in the morphological gate set between the 3 µm and 10 µm beads population diameter using flow cytometry and their activation was evaluated by phosphatidylserine and P-selectin exposure across different reticulation strata (low/high/very-high). Multivariable linear regression assessed the independent association between HCC and RePLTs. Repeated-measures ANOVA tested the effect of reticulation and group interaction.

Results. Sixty subjects were included: CTRL (n = 28), cirrhosis+ HCC- (n = 16), cirrhosis- HCC+ (n = 5), and cirrhosis+ HCC+ (n = 11). RePLTs were lower in HCC (median: 4.02% in CTRL, 3.76% in cirrhosis+ HCC-, 1.98% in cirrhosis- HCC+, and 1.55% in cirrhosis+ HCC+; p = 0.004). In a multivariable linear regression, HCC was independently associated with reduced RePLTs (coefficient -2.51%; 95% CI -4.55 to -0.46; p = 0.018). Both phosphatidylserine and P-selectin increased significantly with increasing reticulation ($p < 0.001$ for both). The increase across reticulation strata differed by group for both markers ($p < 0.001$ for both), showing blunted activation in HCC groups. Specifically, in the three reticulation strata, phosphatidylserine increased from 1.07%, 8.29% and 46.0% in CTRL and 0.57%, 11.5% and 68.6% in cirrhosis+ HCC–, with smaller increases in cirrhosis– HCC+ (2.54%, 2.83% and 7.27%) and cirrhosis+ HCC+ (4.74%, 7.54% and 20%). Similarly, P-selectin increased from 3.02%, 29.6% to 93.7% in CTRL and 3.63%, 45.6% to 96.6% in cirrhosis+ HCC–, versus more limited increases in cirrhosis– HCC+ (1.29%, 2.38% to 15.6%) and cirrhosis+ HCC+ (1.59%, 5.01% to 35.3%).

Conclusions. HCC is independently associated with decreased levels of circulating RePLTs. HCC patients exhibited reduced platelet activation as reticulation increases, as demonstrated by significant reticulation-by-group interactions for both phosphatidylserine and P-selectin. Further studies are needed to elucidate the underlying mechanisms and clinical relevance.

ABSTRACT N. PO030

PLATELET AGGREGOMETRY AS POTENTIAL TOOL TO EVALUATE ANTI-PLATELET RESPONSE IN MYELOPROLIFERATIVE NEOPLASMS: COMPARISON OF DIFFERENT TECHNIQUES AND INITIAL RESULTS

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Background and aims. Myeloproliferative neoplasms (MPNs) are clonal hematopoietic stem cell disorders associated with increased thrombotic risk. The prothrombotic phenotype of MPNs is multifactorial, involving not only an increased mass of circulating cells, but also qualitative alterations in their activation and function. Interactions among blood cells, endothelium, and coagulation promote a hypercoagulable state in which activated platelets play a central role. Low-dose acetylsalicylic acid (ASA) is a cornerstone of thromboprophylaxis in MPNs, but its antiplatelet effect has been reported to be heterogeneous, possibly due to increased platelet turnover and/or expanded platelet mass. Available data on ASA effect in MPN often lack healthy controls, ASA-naïve patients, baseline aggregometry or comparison of different techniques. This study aimed to compare multiple electrode aggregometry (MEA) and light transmission aggregometry (LTA) in assessing platelet function in MPN patients and controls, before and during ASA therapy.
Methods. Nineteen patients with MPN (15 Essential Thrombocythemia, 4 Polycythemia Vera; 6 M, 13 F; median age at diagnosis 39 y) diagnosed and followed in our Department, were enrolled. Platelet function was assessed using both MEA (Multiplate®) and LTA (CN3000). MEA included TRAP, ADP, and ASPI tests, while LTA was performed using ADP, collagen, arachidonic acid, ristocetin, and adrenaline as agonists. All assays were conducted both before and during ASA therapy. Results were compared with 19 couples of non-MPN subjects (22 males, 16 females; median age 68 years) matched for sex, age, and platelet count; half of them were on ASA therapy for other indications and the other half was ASA-naïve.
Results. In the absence of ASA, MPN patients showed significantly higher baseline platelet aggregation compared with non-MPN across all agonists, as assessed by both MEA and LTA. During ASA therapy, MPN patients had higher residual platelet aggregation than non-MPN when assessed by MEA using the ASPI test (median 59 vs 13, $p<0.001$; Figure 1), whereas no significant differences were observed with other MEA assays or with LTA across all agonists. To reduce bias connected to significant differences in platelet count, an ASA/non-ASA aggregation ratio was calculated for every MPN patient and couple of controls, for each test and agonist. This ratio was significantly higher in MPN patients in the ASPI test (0.5 vs 0.2, $p=0.011$), while no relevant differences were observed with other MEA parameters or with LTA.
Conclusions. Our study shows that MPNs exhibit increased platelet aggregation compared with controls both at baseline and during antiplatelet therapy. Both MEA and LTA can detect this hyper-aggregation in not treated/naïve patients. During ASA, only MEA, particularly the ASPI test, was able to identify residual aggregation, while this heterogeneous pharmacodynamic response seems to be not captured by LTA. To reduce thrombocytosis-related bias, we calculated the ASA/non-ASA ratio both for MPN and controls. Comparison of the ratios confirmed a persistent higher aggregation in MPN patients. For clinical purposes, MEA may represent a potential tool to evaluate the effect of ASA in MPN patients leading to individualized antiplatelet management, including dose adjustment or alternative regimens, with the ultimate goal of improving thrombotic risk prevention in this high-risk population.

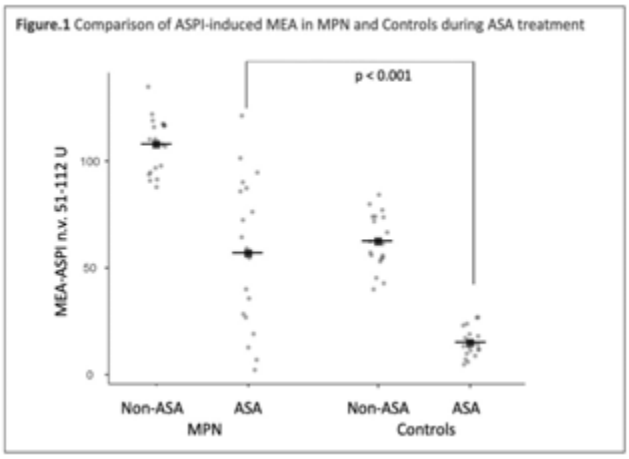


Figure.1 Comparison of ASPI-induced MEA in MPN and Controls during ASA treatment

ABSTRACT N. PO031

IMBALANCE OF PLATELET PRODUCTION AND DESTRUCTION IN PREECLAMPSIA

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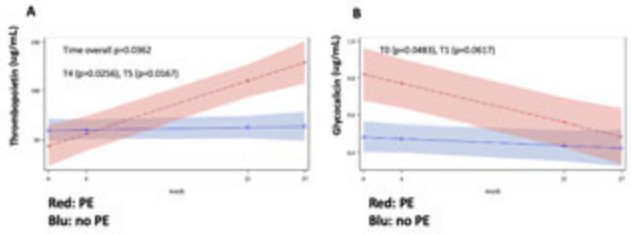
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Background and aims. Preeclampsia (PE) is characterized by endothelial dysfunction and platelet involvement, with increasing evidence pointing to altered platelet turnover. Enhanced platelet consumption may trigger compensatory production, leading to measurable changes in circulating biomarkers. Thrombopoietin (TPO) reflects platelet production, while glycocalicin (GC) indicates platelet destruction. Thiazole orange (TO) identifies immature, reticulated platelets and provides insight into bone marrow response and platelet activity. This study aimed to investigate longitudinal changes in TPO, GC, and TO in high-risk pregnancies treated with low-dose aspirin (ASA), to better characterize platelet turnover and its relationship with PE development.

Methods. This observational study included 25 high-risk pregnant women on ASA and 12 controls with uncomplicated pregnancies. Blood samples were collected at baseline (T0), 21 gestational weeks (T4), and 27 gestational weeks (T5). Platelet-related biomarkers TPO and GC, indicating platelet production and destruction, respectively; and TO were measured longitudinally.

Results. Late onset PE occurred in 6/25 (24%) high-risk women and in none of the controls, while there was no case of early onset disease. Within the high-risk group, TPO and GC levels remained relatively stable in women without events, whereas in women who developed PE, TPO levels increased and were linked to disease onset (overall p=0.036), with more notable differences at T4–T5 (weeks 21 and 27); conversely, GC levels were higher at baseline (p=0.048) and decreased over time in women who developed PE. Using the latest PE risk algorithm, clinical stratification showed high sensitivity and NPV (both 1.00) but low specificity (0.39) and PPV (0.24). Adding baseline glycocalicin improved prediction, with higher thresholds (≥0.80) markedly increasing specificity (0.95) and PPV (0.80), supporting a two-step algorithm–biomarker approach.

Conclusions. Preeclampsia is characterized by a dynamic imbalance in platelet turnover, with early alterations in glycocalicin and subsequent increases in TPO, suggesting temporally distinct changes in platelet destruction and production. While the current PE risk algorithm shows excellent rule-out performance, its limited specificity may be improved by incorporating platelet biomarkers. In particular, baseline glycocalicin enhances risk stratification at higher thresholds, supporting a combined algorithm–biomarker approach for identifying high-risk women despite aspirin prophylaxis.



ABSTRACT N. PO032

INHIBITION OF PLATELET ACTIVATION BY SMALL MOLECULE SYNTHETIC AGONISTS OF THE BILE ACID RECEPTOR: A NOVEL APPROACH TO ANTIPLATELET THERAPY

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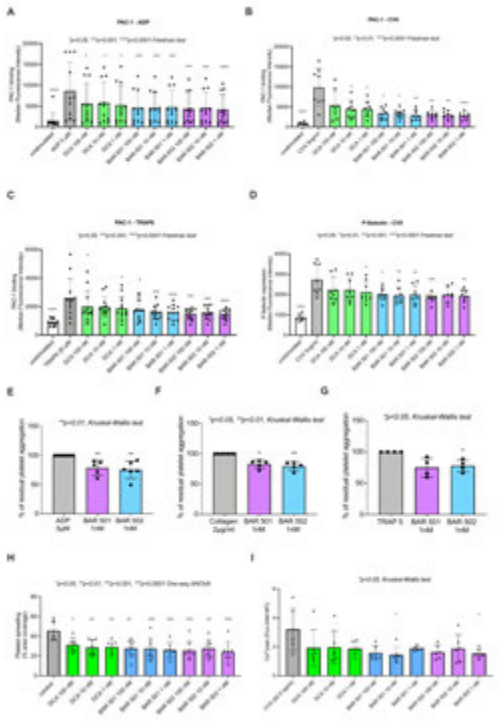
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Background and Aims. Bile acid receptors regulate lipid, glucose and energy metabolism especially in the liver, but they also play a key role as signaling molecules in other processes such as inflammation and immune modulation. Platelets express the two main bile acid receptors: the farnesoid X receptor (FXR) and the Takeda G-protein- coupled receptor 5 (TGR5) and it has been reported that bile acids inhibit platelet activation in vitro and in vivo (PMID:27758768, PMID: 38968449). Indeed deoxycholic acid (DCA), a natural bile acid, acts as a down-regulator of platelet activation acting on TGR5. Moreover, circulating DCA is decreased in patients with coronary artery disease (CAD), a condition associated with increased platelet activation (PMID: 40217125), suggesting that TGR5 signaling may act as a negative modulator for platelets in vivo. Our aim was to investigate the effects of two small molecule synthetic agonists of TGR5, BAR501 and BAR502, currently in clinical development for the treatment of chronic inflammatory bowel diseases (IBD), on platelet function in order to explore whether they may represent potential innovative therapeutic candidates for cardiovascular disease.

Methods. Platelet rich plasma (PRP) from healthy controls was pre-incubated with DCA and the synthetic TGR5 agonists BAR501 and BAR502 (1 to 100 nM) for 30 minutes, then platelet activation was triggered by convulxin (CVX, 5 ng/ml), ADP (5 M) or TRAP-6 (20 M), and assessed by the measurement of P-selectin expression and αIIbβ3 activation by flow cytometry and platelet aggregation by light transmission aggregometry. Platelet spreading on fibrinogen was assessed by immunofluorescence. To investigate on the signaling involved, intracellular Ca^{2+} mobilization was assessed by flow cytometry.

Results. αIIbβ3 activation in response to CVX, ADP and TRAP-6 was reduced by pre-incubation with the synthetic TGR5 agonists BAR501 and BAR502 as well as with the natural bile acid DCA (Figure 1 A-C). Also P-selectin expression in response to CVX was decreased by DCA, BAR501 and BAR502 (Figure 1 D). Accordingly, BAR501 and BAR502, at the dose of 1 nM, significantly reduced platelet aggregation in response to ADP, collagen and TRAP-6 (Figure 1 E-G). All these molecules also decreased platelet spreading on fibrinogen (Figure 1 H). Ca^{2+} mobilization was reduced upon incubation with BAR501 and BAR502 (Figure 1 I).

Conclusions. Activation of TGR5 by physiological concentrations of DCA or by the two synthetic agonists BAR501 and BAR502 at their EC50 markedly suppresses key platelet responses, including platelet activation, adhesion and aggregation. The mechanism of action involves the decreased intracellular Ca^{2+} increase upon agonist stimulation. Our findings highlight TGR5 as a novel pharmacological target for platelet inhibition and support the development of synthetic agonists, such as BAR501 and BAR502, as potential antiplatelet strategies for cardiovascular disease.





PLATELET COUNT AND PERIPROCEDURAL MAJOR BLEEDING IN CIRRHOTIC PATIENTS UNDERGOING INVASIVE PROCEDURES: INDIVIDUAL PATIENT DATA META-ANALYSIS

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Background and Aims. Cirrhotic patients have a fragile hemostatic balance, which can be perturbed by invasive procedures. Thrombocytopenia is often feared because of the risk of periprocedural bleeding and some guidelines recommend platelet transfusion for counts below $50x10^9$/L. However, evidence supporting this practice remains conflicting. We performed an individual patient data meta-analysis to evaluate the impact of the platelet count on periprocedural bleeding in cirrhotic patients undergoing invasive procedures.

Methods. We searched Medline and Embase for randomized controlled trials and prospective and cohort studies published between 2010 and 2021 using a pre-defined research string. We included studies in English reporting on periprocedural major bleeding (ISTH definition) and post-procedural mortality in adult patients with cirrhosis undergoing laparotomic, laparoscopic or percutaneous procedures. Patients undergoing endoscopic or endovascular procedures and those receiving thrombopoietin receptor agonists were excluded. Eligible procedures were classified as high- or low-bleeding risk according to predefined criteria. Individual patient data (including platelet counts) were requested from study authors. The primary outcome of this study was the prevalence of periprocedural major bleeding.

Results. Of 585 retrieved citations, we included 9 studies, resulting in 2747 cirrhotic patients who underwent a total of 3136 eligible procedures. Eligible patients were stratified based on their platelet counts: less than $50x10^9$/L (n=394), 50 to $99x10^9$/L (n=969), and $100x10^9$/L or more (n=1384). Of the eligible procedures, 2135 (68%) were classified at high bleeding risk. Overall, the prevalence of periprocedural major bleeding was 8% (243/3136). Stratifying patients by platelet count, the prevalence of periprocedural major bleeding was 8% (34/416) in patients with counts $<50x10^9$/L, 9% (94/1102) in patients with counts between 50 and $99x10^9$/L and 7% (115/1618) in patients with counts ≥100 $x10^9$/L, with no statistically significant differences across the groups (p=0.37). Stratifying the procedures based on their inherent bleeding risk, periprocedural major bleeding was significantly more prevalent in high-risk procedures (11%, 224/2135) than in low-risk procedures (2%, 19/1001) (p<0.001). The prevalence of major bleeding related to high-risk procedures did not significantly differ across platelet count groups (p=0.16). Periprocedural major bleeding occurred in 8 of 85 (9%) patients who received prophylactic platelet transfusions and in 103 of 2020 (5%) patients who did not, with no statistically significant differences between transfused and non-transfused patients (p=0.14) nor across platelet count groups (transfused and non-transfused patients: p=0.94 and p=0.40, respectively).

Conclusions. The results of this individual patient data meta-analysis show that cirrhotic patients' platelet counts and prophylactic platelet transfusion practices were not associated with the rates of periprocedural major bleeding. The type of invasive procedure and its inherent bleeding risk emerged as the clinical covariates most strongly associated with the occurrence of major bleeding, suggesting that bleeding risk assessment should be based on the procedure type and feasibility of local hemostasis, rather than on platelet counts alone.

ABSTRACT N. PO034

ASSESSMENT OF PLATELET AGGREGATION FOR THE DIAGNOSIS OF INHERITED PLATELET DISORDERS USING A FULLY AUTOMATED COAGULATION ANALYSER: COMPARISON WITH LTA AND MEA

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Background and Aims. Light-transmission aggregometry (LTA) is the gold standard for the diagnosis of inherited platelet-function disorders (IPFD) but it requires skilled personnel and large sample volumes. Recently attempts have been made toward LTA automation to overcome some limitations of manual LTA, allowing the automated selection of agonists and their concentrations. Sysmex CN-6500 is a new haemostasis analyser that performs platelet aggregation with small volume platelet-rich plasma (PRP) (140µl) and automates reagent dilution and aggregation readouts. Aim of our study was to test the agreement between platelet aggregation results obtained with the automated Sysmex CN-6500, manual LTA and multiple electrode aggregometry (MEA) for the study of IPFD.

Methods. Patients aged >18 years and with an IPFD confirmed according to well-defined laboratory and/or molecular genetic criteria were enrolled. A group of 20 healthy subjects with no personal or family history of hemorrhage, with normal platelet aggregation and secretion, and not receiving drug known to interfere with platelet function during the previous 10 days, were used as controls during the same study period to establish the aggregation cut-off. Platelet aggregation was tested in PRP by LTA with the APACT 4 aggregometer (Helena) or with the CN-6500 analyser (Sysmex) and in whole blood with the Multiplate® (Roche) impedance aggregometer using different concentrations of ADP, arachidonic acid, collagen and epinephrine. Correlation between methods was assessed using the Pearson R coefficient and agreement using the Passing-Bablok regression test.

Results. 50 patients (28 females) with a median age of 43 years (95% IC 26-61 years) with various IPFD, including Glanzmann thrombasthenia (10), PT-VWD (2), Filamin A defect (2), TAR (1), FPD/AML (5), TxA2 receptor defect (2), HPS (7), δ-SPD (1), COX-1 like defect (1) and 19 with primary secretion defects were enrolled. The median platelet count in PRP was 260x109/L (95%CI: 176 to 369×109/L). No significant differences in maximal amplitude aggregation were found between manual and automated LTA using all agonists. Passing-Bablok regression analysis showed good agreement between Sysmex CN-6500 and LTA and low agreement with Multiplate (Table 1). Defective aggregation was detected in all the IPFD patients with both manual and automated LTA while MEA failed to identify aggregation abnormalities in 7 patients (6 HPS and 1TxA2 receptor defect). Platelet aggregation testing required 1.1 mL of PRP with the Sysmex CN-6500, 2 mL with manual LTA and 2.4 mL of whole blood with the Multiplate. The turnaround time was approximately 20 minutes for automated LTA, 10 minutes for Multiplate and about 30 minutes for manual LTA.

Conclusions. Automated LTA with the Sysmex CN-6500 provides comparable results to manual LTA in the identification of patients with IPFD, with the advantage of automated serial reagent dilution, smaller total sample volume and shorter turnaround time. Both methods have greater sensibility for IPFD compared with MEA.

Table 1. Passing Bablok regression analysis between Sysmex CN-6500 and the two reference methods. *R= Spearman correlation coefficient; n.d.= not done.*

Agonist	LTA (%)				MEA (AUC)			
	slope	*intercept*	*R*	*p*	*slope*	*intercept*	*R*	*p*
ADP 5µM	0.91	12.8	0.76	<0.0001	385.56	-1299.78	0.66	<0.0001
Collagen 2µg/ml	1.14	-7.51	0.69	<0.0006	232.56	-3347.78	0.76	<0.0001
AA 1mM	11.13	-1.15	0.79	<0.0001	294.38	-5094.71	0.68	<0.0001

ABSTRACT N. PO035

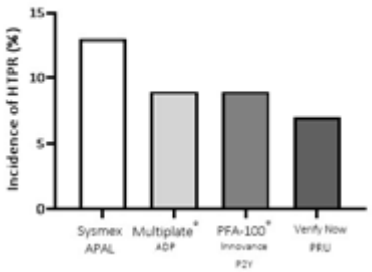
ASSESSMENT OF HIGH-ON-TREATMENT PLATELET REACTIVITY IN PATIENTS ON DUAL ANTIPLATELET THERAPY USING THE FULLY AUTOMATED COAGULATION ANALYZER SYSMEX CN-6500: A COMPARATIVE STUDY WITH THREE POINT-OF-CARE TESTS

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Background and aims. High-on-treatment platelet reactivity (HTPR) in patients on dual antiplatelet therapy (DAPT) with P2Y12-receptor antagonists and aspirin for an acute coronary syndrome (ACS) or a recent carotid artery stent (CAS) has been associated with enhanced adverse cardiovascular events. Platelet function testing may thus be important to monitor antiplatelet therapy in patients at high cardiovascular risk, however different sensitivity across testing methods remains a challenge. Recently, automated light transmission aggregometry (LTA) on a coagulation analyzer (CN-6500 Sysmex) has been developed together with a new aggregation readout (PAL: platelet aggregation level) to assess HTPR in patients on DAPT. Aim of the study was to evaluate residual platelet reactivity in patients on DAPT with aspirin plus P2Y12 inhibitors (e.g., clopidogrel, ticagrelor, prasugrel) comparing the Sysmex CN-6500 with three established point of care (POC) instruments: the PFA-100®, the Multiplate® and the VerifyNowTM.
Methods. Patients with recent ACS or CAS on DAPT were enrolled. The PAL score was calculated by Sysmex CN-6500 on the aggregation waves obtained with ADP 1 and 10 μM (APAL) and compared with the VerifyNow P2Y12 test (PRU), Multiplate using ADP as agonist (U) and PFA-100® using the INNOVANCE® P2Y cartridge. HPTR was defined by results above/below the respective validated cut-off values.
Results. 100 patients (29 females), median age 67 years (95%CI 58-76) on DAPT with ASA 100 mg + Clopidogrel (n=52), Ticagrelor (n=44) or Prasugrel (n=4) were studied. Median platelet count was 198 (95%CI 169-247) × 103/L. A significant correlation was found between the APAL score and the results obtained with the other tests, with higher correlation coefficients for Multiplate-ADP (r= 0.61, p< 0.001) and VerifyNow PRU (r= 0.59, p< 0.001) compared with PFA-100® P2Y (r= −0.57, p< 0.001). In the overall population the prevalence of HTPR varied from 7% to 13%: it was 13% when measured by APAL, 9% by Innovance P2Y-PFA®, 8% by Multiplate-ADP and 7% by the VerifyNow P2Y12 assay, with no statistically significant differences among the assays (Figure 1). DAPT with Ticagrelor was associated with significantly lower rates of HTPR compared to clopidogrel, with HTPR prevalence of 7%-23% for clopidogrel versus 0%-2.2% for ticagrelor. None of the patients treated with prasugrel exhibited HTPR.
Conclusions. The CN-6500 automated coagulation analyzer is a useful tool for detecting HTPR reactivity in patients on DAPT. PAL scores showed good agreement with established POC assays and reliably reflected antiplatelet drug effects. Our study also confirms significant differences in sensitivity to HTPR among different platelet function tests, and their clinical relevance warrants further investigation.

Figure 1. Incidence of HPTR (%) among patients on DAPT (n=100), assessed by different assays.





EVALUATION OF BREAST MILK AS A POTENTIAL MEDIATOR FOR THE TRANSFER OF MATERNAL ANTI-PLATELET ALLOANTIBODIES IN FETAL AND NEONATAL ALLOIMMUNE THROMBOCYTOPENIA

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Background and Objectives. Many studies documented the transmission of anti-platelet antibodies in maternal autoimmune thrombocytopathies. It is unclear whether this also occurs in alloimmune thrombocytopenia. Fetal and Neonatal Alloimmune Thrombocytopenia (FNAIT) is a rare immunological disorder resulting from maternal sensitization against paternal human platelet antigens (HPA) inherited by the fetus. While postnatal management typically focuses on HPA-matched platelet transfusions, the impact of breastfeeding remains a subject of clinical debate. This study aims to investigate whether the excretion of anti-platelet alloantibodies into breast milk may contribute to prolonged or refractory neonatal thrombocytopenia.

Methods. We report a clinical case of a female neonate (39 weeks' gestation, spontaneous delivery) presenting with severe FNAIT-related thrombocytopenia ($21x10^9$/L) and grade III-IV intraventricular hemorrhage. IgG-class alloantibodies were quantified in both maternal and neonatal sera using flow cytometry (DxFLEX platform), yielding values of 2613 and 580 Mean Fluorescence Intensity (MFI), respectively (cutoff: 300 MFI).

Results. Standard therapeutic interventions, including IgG, corticosteroids, and multiple HPA-matched platelet transfusions, failed to maintain stable counts; platelet levels dropped by over 50% within five days post-transfusion (declining from 154-176 to 26-63x10^9/L. Given the ongoing breastfeeding and persistent maternal serum positivity (1800 MFI), breast milk was analyzed following IgG extraction. Testing confirmed the presence of anti-platelet alloantibodies in the milk (552 MFI vs. 173 MFI in the negative control). Following these findings, breastfeeding was restricted to a single daily feed. Within one week, the neonate's platelet count rose from 48 to 80x10^9/L without requiring further transfusions.

Conclusions. This case demonstrates the presence of HPA-specific alloantibodies in breast milk, coinciding with a case of refractory early-onset thrombocytopenia. These findings suggest that the management of breastfeeding in FNAIT should be carefully examinated. Further research is required to determine the clinical significance of milk-derived antibodies versus the persistence of transplacentally acquired maternal IgG.

ABSTRACT N. PO037

TEMPO: A MOBILE HEALTH APPLICATION FOR PERSONALIZED MANAGEMENT OF HEMOPHILIA

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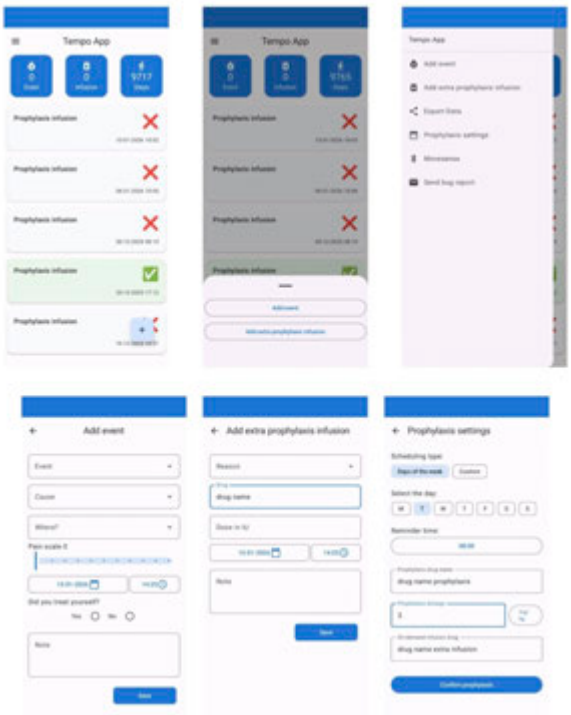
Background. Hemophilia causes recurrent joint bleeding, leading to chronic arthropathy and impaired quality of life. Despite major therapeutic advances, effective management requires sustained self-monitoring and longterm adherence. Digital health tools, including telemedicine, mobile applications, and electronic diaries, may enhance self-management, improve data quality, and support personalized, data-informed clinical care.

Aims. To describe the Tight control of treatment adherence and efficacy by tElemedicine for an improved personalized Management of Patients with hemOphilia (TEMPO) platform, an Android application designed to support patients on prophylaxis through comprehensive treatment tracking, event documentation, and physical activity monitoring.

Methods. TEMPO provides an electronic diary enabling patients to record bleeding episodes and pain events, including anatomical location, cause (spontaneous, post-traumatic, or post-procedural), and pain intensity. The application features a flexible prophylaxis scheduling system with customizable reminders, allowing users to confirm or postpone infusions and to document on-demand treatments with detailed medication information (e.g., drug name and dosage). The application integrates physical activity monitoring through Health Connect (https://developer.android.com/health-and-fitness/health-connect/), collecting data such as daily steps from compatible devices. Climate conditions are recorded as well, without recording location, to preserve the patient's privacy. A subset of patients participates in an extended monitoring protocol using Movesense (https://www.movesense.com/product/movesensesensor-hr/) wearable sensors for inertial data collection during physical activities. All data are synchronized to a secure cloud database and can be exported as CSV files, enabling patients to share information with healthcare providers during clinical visits. A dedicated dashboard for real-time physician follow-up has also been developed.

Results. TEMPO is currently available on the Google Play Store and is undergoing evaluation in a real-world clinical setting involving 25 patients. Preliminary feedback indicates high usability, improved treatment adherence, and increased self-awareness of personal health status. The application supports both Italian and English and is designed for seamless integration into routine clinical practice.

Conclusions. TEMPO aims to overcome the limitations of traditional paper diaries by providing real-time, structured data collection and automated reminders. This digital approach has the potential to improve treatment adherence, reduce recall bias in event reporting, and strengthen patient-clinician communication. In the future, TEMPO-generated data may support physicians and patients in shaping increasingly personalized management strategies for hemophilia.





GLOBAL IMPLEMENTATION AND CLINICAL USE OF POINT-OF-CARE JOINT ULTRASOUND IN HEMOPHILIA: RESULTS FROM AN INTERNATIONAL SURVEY

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Background. Point-of-care joint ultrasound (POCUS) is increasingly recognized as a valuable tool in hemophilia management, enabling rapid assessment of acute joint symptoms and early identification of synovial and osteochondral changes. Despite growing evidence supporting its clinical utility, adoption remains heterogeneous worldwide, largely due to variability in training, infrastructure, and standardization.

Aims. To characterize current practice patterns and unmet needs, the ISTH SSC Subcommittee conducted an international survey endorsed by EAHAD.

Methods. A 38-item questionnaire was developed by an international panel of experts in musculoskeletal ultrasound and hemophilia care and distributed through the ISTH RedCap platform. The survey explored professional background, access to equipment, training, clinical applications, perceived barriers, and follow-up practices. Responses were collected globally and analyzed descriptively.

Results. A total of 185 healthcare professionals from 31 countries completed the survey, including adult hematologists (21%), adult physiotherapists (19%), pediatric hematologists (17%), and pediatric physiotherapists (14%), with representation from additional disciplines. Overall, 71% of respondents reported regular use of POCUS in hemophilia care, while 29% did not routinely employ this modality. The main barriers to implementation were insufficient training or expertise (62%), limited time availability (50%), restricted funding or access to equipment (35% and 22%, respectively), lack of standardized definitions (22%), absence of reimbursement (16%), and uncertainty regarding longitudinal monitoring protocols (15%). POCUS was primarily used to confirm or exclude acute joint bleeding (71%), guide treatment duration during bleed follow-up (59%), assess synovitis (57%), support longitudinal joint surveillance (57%), evaluate painful musculoskeletal episodes (54%), and assist interventional procedures such as joint aspiration (19%). Substantial variability was observed among centers in terms of patient volumes and referral indications.

Conclusions. This international survey demonstrates that POCUS is widely valued and increasingly integrated into hemophilia care, although its implementation remains inconsistent. Major limitations include insufficient structured training, limited resources, and lack of standardized protocols. Addressing these gaps through coordinated educational initiatives, harmonized definitions, and supportive health policies is essential to promote equitable, evidence-based use. These findings represent a foundation for future efforts aimed at standardizing POCUS and improving early, personalized joint management in people with hemophilia.



CLINICAL AND LABORATORY CHARACTERISTICS OF ACQUIRED HEMOPHILIA A: PRELIMINARY RESULTS FROM A RETROSPECTIVE OBSERVATIONAL MONOCENTRIC STUDY

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Background. Acquired hemophilia A (AHA) is a rare autoimmune disorder, characterized by the development of autoantibodies directed against coagulation factor VIII (FVIII), thereby leading to a severe bleeding diathesis. Clinical suspicion and understanding of AHA's features are essential for its effective diagnosis and management.
Aims. To describe the clinical characteristics of AHA patients in a monocentric cohort.
Methods. We conducted a retrospective observational study on a cohort of 39 patients with diagnosis of AHA between 2008 and 2025 at the Hospital of Verona, Italy.
Results. This study included 39 patients (males n=19/49%). The age at diagnosis ranged from 41 to 96 years with a mean age of 77 years. Fifteen subjects (38%) were classified as idiopathic AHA. Malignancy was the most frequent underlying condition in 14 subjects (36%), with 6 cases of cancer of the genitourinary tract, 4 cases of cancer of the gastrointestinal tract, 3 cases of breast cancer, and 1 case of brain tumor. Seven subjects (18%) had concomitant autoimmune disorders. Only one case of postpartum AHA was identified, along with single cases linked to with dermatological disease (bullous pemphigoid) or recent drug administration (clopidogrel). The great majority of patients (n=36/92%) had bleeding at diagnosis. The most frequent hemorrhages involved the mucocutaneous district (n=31/79.4%) and the genitourinary tract (n=4/10%). Only 3 patients (8%) had no significant bleeding and were diagnosed based on the laboratory coagulation tests. The mean hemoglobin level was 8.9±3.8 g/dL and the mean platelet count was 235.000±109.000/mcL. The mean aPTT ratio was 2.64±0.92. The mean FVIII activity level was 5.1±7.7%, with 12 subjects (31%) with FVIII activity <1% and 18 subjects (46%) with FVIII activity 1-5%. The inhibitor titer was 47.1±39.2 Bethesda Units (BU). More than half of the patients (n=22/56%) had a high inhibitor titer (>5 BU).
Conclusions. The data from our cohort align with the existing medical literature. AHA should be suspected especially in the elderly population, either males or females, when there are novel and severe bleeding associated with anotherwise unexplained prolonged aPTT. The development of large registries for AHA could allow for better understanding of this rare and sometimes underdiagnosed disease.

ABSTRACT N. PO040

PHARMACODYNAMIC CHARACTERIZATION OF THROMBIN GENERATION IN SEVERE HEMOPHILIA A PATIENTS ON EMICIZUMAB PROPHYLAXIS: A REAL-WORLD LONGITUDINAL STUDY

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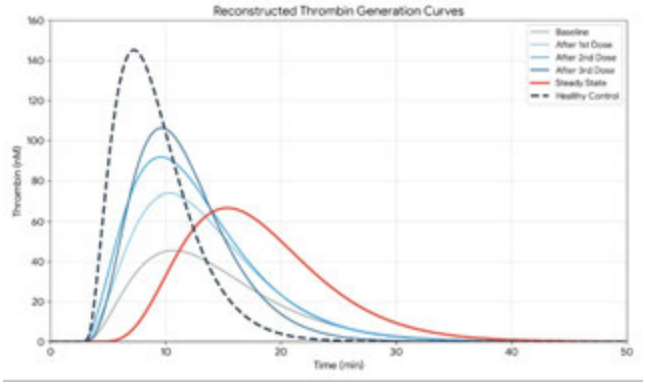
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Background and Aims. Emicizumab, a humanized bispecific antibody mimicking FVIII cofactor activity, has significantly redefined the therapeutic landscape of severe Hemophilia A (HA). However, its constitutive activity leads to profound analytical interference in conventional contact-phase-dependent clotting assays, limiting their clinical utility for monitoring. This study employs the Thrombin Generation Assay (TGA) to investigate global hemostatic remodeling, quantify the restoration of hemostatic potential, and evaluate the correlation between pharmacodynamic parameters and plasma drug concentrations in a real-world setting.

Methods. We studied a cohort of 15 patients with severe HA on Emicizumab, including 4 with high-titer inhibitors. TGA was performed during the loading phase and at steady state using the Calibrated Automated Thrombogram (CAT) on platelet-poor plasma spiked with PPP-Reagent (5 pM TF and 4 µM phospholipids); a dedicated Thrombin Calibrator was used to correct for inner filter effects. Data were compared with: 1) 11 untreated HA patients not receiving Emicizumab and 2) 11 healthy controls. Six kinetic-quantitative parameters (ETP, Peak, Lag Time, ttPeak, Velocity Index, and StartTail) were determined. Statistical analysis included the Wilcoxon signed-rank test for longitudinal comparisons, the Mann-Whitney U-test for independent groups, and Spearman's rank correlation combined with logarithmic regression to model the dose-response relationship with plasma drug levels (measured via modified one-stage clotting assay).

Results. The analysis demonstrates an immediate restoration of the hemostatic potential. Notably, ETP levels reached after the first loading dose were remarkably similar to those observed at steady state (915.41 vs. 936.23 nM·min, p=0.07), providing a laboratory-based rationale for the early discontinuation of FVIII replacement therapy. At steady state, ETP values were statistically comparable to healthy controls (936.23 vs. 1067.34 nM·min, p=0.33), showing a recovery from the severe baseline defect (613.08 nM·min, p<0.01). No significant differences were found between patients with and without inhibitors (p=0.57). A solid dose-response correlation was confirmed between Emicizumab levels and quantitative parameters: ETP (ρ=+0.205, p=0.025) and Peak (ρ=+0.246, p=0.007). Conversely, the kinetic profile remained altered, showing a significant and dosage-independent prolongation of Lag Time, ttPeak, and StartTail (p<0.02).

Conclusions. Emicizumab prophylaxis induces a stable remodeling of the coagulation profile in severe HA. Quantitative parameters, ETP and Peak, show a significant association with plasma drug concentrations, confirming their utility in evaluating the biological response to treatment. The rapid recovery of ETP after the first dose suggests the clinical feasibility of early FVIII replacement therapy discontinuation. Regarding coagulation kinetics, a unique signature with delayed initiation was observed; however, the clinical significance of this kinetic remodeling warrants further investigation. Overall, Emicizumab effectively bridges the native hemostatic gap, providing immediate and predictable protection, Figure 1 Longitudinal Thrombin Generation curves. Reconstructed median curves. Note the rapid ETP restoration after the 1st dose and the specific steady-state kinetic profile (delayed lag time/lower peak).



ABSTRACT N. PO041

VARIABLE CLINICAL RESPONSE TO RECOMBINANT PORCINE FVIII IN ACQUIRED HAEMOPHILIA A: A TWO CASE EXPERIENCE WITH LABORATORY SUPPORTED MONITORING

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Background. Recombinant porcine factor VIII (rpFVIII, Susoctocog α – Obizur®) is used to treat bleeding in patients with Acquired Haemophilia A (AHA). rpFVIII may represent a valid alternative for bleeding control, especially in case of bypassing agents (BPAs) failure. Disadvantages to BPAs include the inability to monitor response with standard laboratory assays, inconsistent haemostatic efficacy and increased thrombotic risk. Susoctocog α allows laboratory monitoring of FVIII activity with calibrated one-stage assays, which may reduce thrombotic risk. However, the response is variable and depends not only on the inhibitor titre (human or porcine), but also on poorly defined pharmacokinetic variables.

Materials and Methods. We collected two cases treated with rpFVIII in June 2025 and January 2026. In the first case, rpFVIII was used for bleeding control in a patient with coronary artery disease and AHA (FVIII 0%, Inhibitor 4.07 BU/mL) who developed severe thrombocytopenia during sepsis (platelets 20 000/mmc). In the second case, rpFVIII was used after BPAs failure to stop femoral arterial bleeding following removal of the embolization introducer in a recently diagnosed AHA patient (FVIII 0.8%, Inhibitor 27.98 BU/mL). Clinical and laboratory findings are summarized in the *Table*. FVIII activity was measured using three assays: one-stage FVIII:C with Actin® (Siemens) calibrated with human plasma; chromogenic FVIII assay (Siemens) calibrated with human plasma; and the reference method for rpFVIII, a one-stage FVIII assay with Actin® FS (Siemens) calibrated with a dedicated Obizur® curve. The anti-porcine FVIII inhibitor was quantified using a mixing Bethesda assay adapted for rpFVIII: patient plasma was heat-inactivated at 56 °C for 45 minutes, mixed 1:1 with Obizur-spiked normal plasma, incubated for 2 hours at 37 °C, and residual FVIII activity measured using the Actin® FS Obizur-calibrated assay.

Results. Bleeding control was achieved in both cases and no adverse events related to rpFVIII were observed. The initial bolus of Susoctocog α was 100 U/kg in both cases with a variable response. In the first case the response was less long-lasting and additional doses were required in the first 24 hours to maintain FVIII >50% (another 100 U/kg in boluses 50–30–20 U/kg). In the second case the response was more prolonged (over 24 hours), without further doses to maintain FVIII >50% and bleeding stop. This difference may be partially explained by the increase in human inhibitor titre (15 BU/mL) during sepsis in the first patient. However, since neither patient developed rpFVIII inhibitors, other factors may underlie these differences (age? pharmacokinetic variables?). The calibrated one-stage FVIII assay (Actin® FS with Obizur calibration) correlated with FVIII:C measured using Actin®, while the chromogenic assay underestimated rpFVIII recovery.

Conclusions. Susoctocog α proved effective and safe in AHA, also at lower than recommended dosage. However, rpFVIII pharmacokinetics can be highly variable and require active laboratory monitoring. Plasma FVIII:C provides an alternative estimation of rpFVIII recovery. A larger case collection could help clarify the heterogeneous response and the factors influencing it (age? rpFVIII inhibitors? pharmacokinetic variables?).

	Case 1				Case 2		
Sex	Female				Female		
Age (Years)	62				76		
Weight (Kg)/Height (cm) Body Mass Index (BMI)	48 Kg/152 cm BMI 20.77				78 Kg/160 cm BMI 30.46		
Cause of AHA	Rheumatoid Arthritis				Autoimmune Thrombocytopenia		
Co-morbidities	Chronic ischemic heart disease, Hypertension and type 2 diabetes mellitus; chronic renal disease (II)				Hypertension, type 2 diabetes mellitus, dyslipidemia; chronic renal disease (III); autoimmune thyroiditis		
Antiplatelet/Anticoagulant at diagnosis	YES Aspirina 100 mg and Ticagrelor 90 mg bis in die				NO		
Bleeding site	Extensive hematoma of the right lower limb complicated by necrotizing fasciitis				Retroperitoneal haematoma and right inguinal haematoma after embolization		
Surgery during AHA	Limb amputation				Inguinal haematoma evacuation		
VIII at diagnosis (%)	0%				0.8%		
Inhibitor Titer (BU/ml)	4.07				27.98		
Therapy before rpFVIII	aPCC/Tranexamic Acid				aPCC/Tranexamic Acid		
Loading dose rpFVIII (UI/kg)	100 U/Kg				100 U/Kg		
Laboratory data	after 1 hour	after 12 hours	after 24 hours	after 48 hours	after 1 hour	after 24 hours	after 72 hours
FVIII chromogenic (%)	85%	21%	32%	4.3%	113%	24%	0.8%
FVIII: C (%)	164%	48%	56%	8.8%	198%	51%	3%
FVIII Obizur® (%)	126%	36%	51%	9%	189%	44%	4.2%
Subsequent doses rpFVIII (UI/Kg)	+ 100 U/Kg in fractionated boluses (50-30-20 U/Kg) in 36 hours for platelets 20 000/mmc				No additional boluses Another bolus 12 days later (100 U/Kg) for rectal bleeding and anemia		
Infusion doses frequency	3				1 dose repeated		
Duration rpFVIII treatment (days)	3 consecutive days				1 days + 1 days		
Immunosuppressive therapy	Corticosteroids/Rituximab				Corticosteroids/Cyclophosphamid		
Transfusion (bags)	3 U				8 U		
Inhibitor rpFVIII (BU/ml)	None				None		
Outcome	Limb amputation				Death from pulmonary sepsis and Candidemia		
VIII Inhibitor Eradication	Yes (66 days from diagnosis)				Yes (42 days from diagnosis)		
Follow up duration	Ongoing (10 months)				70 days		
Therapy	Prednisone 5 mg die				-		



ACQUIRED HEMOPHILIA A AND ANTIPHOSPHOLIPID SYNDROME: CONCURRENCY OR OVERLAPPING?

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Background. Acquired hemophilia A (AHA) is a rare bleeding disorder, with an incidence of 1.5 cases per million per year. It is caused by the development of factor VIII (FVIII) inhibitors and typically presents with recurrent muscular and soft tissues bleeding. Nearly half of AHA cases are considered idiopathic, while the remainder are secondary to autoimmune disorders, malignancies, infections, or pregnancy. Prompt recognition of the condition is essential to manage severe and potentially life-threatening bleeding episodes.

Case report. A 59-year-old patient, with a history of cigarette smoking and mild secondary erythrocytosis, presented to our outpatient clinic, reporting a spontaneous hematoma at right arm. The GP prescribed blood test that showed prolonged aPTTr (Table displays patient's laboratory findings). Second level diagnostic testing confirmed a prolonged aPTTr, that did not correct on mixing test after 2-hour incubation, suggesting the presence of an acquired inhibitor: F VIII was 1.2%, and the anti-FVIII inhibitor 1.7 BU/ml. The diagnosis of AHA was made, and the patient started 1 mg/kg prednisone, plus tranexamic acid. Further testing demonstrated the presence of anti B2GPI IgM and ACL IgM, while LAC was negative, and anti B2GPI IgG and ACL IgG were absent, as well as other autoimmunity tests. Chest x-rays and abdomen ultrasound excluded the presence of malignancies. After 3 weeks of steroid treatment, the patient reached F VIII level of 100%, the hematoma had regressed. Steroid was tapered. Eighty days after the diagnosis, the patient presented to the ER with left arm numbness, dysarthria, left labial fold deviation, and deficit of the VII cranial nerve. The head CT scan and the MRI demonstrated a right-sided ischemic stroke together with chronic cerebral vasculopathy. Having normal FVIII levels, the patient started anti platelet therapy. Further investigations excluded supra-aortic trunks stenosis and arrhythmias, while the presence of anti B2GPI IgM and ACA IgM was confirmed, and the diagnosis of idiopathic antiphospholipid syndrome was made. The antithrombotic therapy was switched to warfarin. A few weeks later, FVIII levels dropped to 24%: steroid therapy was restarted, but only a partial response was achieved; the patient was hence treated with Rituximab (375mg/mq every week for 4 weeks). FVIII levels increased to a full response and steroid was tapered; no effect was described on the antiphospholipid antibodies' titre. During anticoagulation, the patient never experienced hemorrhagic complications.

Conclusions. Cases of concurrent AHA and APS are rare and largely anecdotical , particularly when they are not secondary to malignancies or other autoimmune forms. Both AHA and APS are life-threatening and prone to recurrency if not properly treated. In our patient the two disorders manifested less than 3 months apart and are currently classified as idiopathic. The main challenge in this case lies in balancing the therapeutic approaches and ensuing close clinical monitoring.

Table: patient's laboratory follow-up

	Day 0	Day 30	Day 80	Day 120	Day 180	Day 240	Day 300
	AHA		Stroke, APS	FVIII drop	Rituximab (1st dose)		
aPTTr	3.06	0.96	1.02	2.61	2.06	1.94	1.76
aPTTr mix	1.44						
aPTTr mix 2h	2.02						
PTr	1.03		0.94		2.29	2.57	
Fibrinogen [g/L]			3.11				
F VIII [%]		106	97	24	46	100	125%
F VIII inhibitor [BU]	1.7						
vWF activity [%]	134						
vWF antigen [%]	129						
F IX [%]	105						
F X [%]	112						
F XI [%]	88						
F XII [%]	65						
LAC	Negative		Negative				
ACA IgM [CU]	215		164		132		
ACA IgG [CU]	5.1		2.4		12.1		
Anti-B2GPI IgM [CU]	208		137		121.6		
Anti-B2GPI IgG [CU]	21.3		17.9		19.7		



MULTICENTRE REAL-WORLD EXPERIENCE OF EMICIZUMAB PROPHYLAXIS IN AN ITALIAN COHORT OF 49 CHILDREN WITH SEVERE HEMOPHILIA A - EMIPED STUDY

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Background. Emicizumab prophylaxis is approved for people of all ages with hemophilia A (HA) with and without inhibitors. Efficacy and tolerability of emicizumab have been evaluated in children and adolescents in phase III studies and the HAVEN 7 phase IIIb clinical trial evaluating infants is ongoing. However, real-world data on emicizumab use in children and infants are limited.

Aims. We aim to evaluate the clinical impact in transitioning from substitutive therapy/bypassing agents to emicizumab in HA paediatric Italian population.

Methods. Using a retro-prospective medical record chart review, we conducted a self-control analysis of 49 patients less than 18 years of age from Haemophilia Centers of Turin, Florence and Bari, during equivalent periods of 12 months of factor replacement therapy versus emicizumab prophylaxis. The study was approved by the Ethical Committees of the Centers involved. Statistical comparisons between different groups were made using one-way ANOVA at a significance level of 0.05.

Results. We evaluated 49 male patients (pts) affected by severe HA, 9 with inhibitors (PWI) and 40 without inhibitors (PWoI). Among PWI, 6 pts developed inhibitors in the 12 months before emicizumab, 1 pt was in aPCC prophylaxis and 2 on demand treatment with rFVIIa. Among PWoI, 4 (8.7%) were never treated with substitutive therapy, 12 (26%) were treated on demand and 30 (65.3%), including the ones who developed inhibitors, were on different prophylaxis regimens. Standard half-life FVIII concentrate were used by 33/46 pts (71.7%) and extended half-life by 13/46 pts (28.3%). The median age at the initiation of emicizumab was 4.5 years (range: 2 months–17 years). 9 pts were younger than 1 year. Emicizumab was used to initiate prophylaxis in 16 PWoI, including 4 PUPs, with a median age of 1 year, range 2-12 months. The chosen regimen for prophylaxis after the loading phase was 1.5 mg/kg/7days for 23 pts, 3 mg/kg/14days for 21 pts and 6 mg/kg/28 days for 5 pts. No pts discontinued emicizumab in the first 12 months of therapy. Data about FVIII concentrate consumption were available for 14 PWoI: in the 12 months before emicizumab median consumption was 75.500 U, range 0-316.000 U, mean 102.464 ± 104.473 U; in the 12 months after emicizumab median was 750 U per pt, range 0-14.000 U, mean 3.643 ± 5.059 U. 31/49 pts (63.3%) had at least one bleeding episode in the 12 months before emicizumab versus 17/49 pts (28.6%) in the 12 months after emicizumab (p=0.004). 17/49 pts (34.7%) had at least one access to emergency department and 11/49 pts (22.5%) at least one hospitalization due to bleeding episodes and/or trauma in the 12 months before emicizumab versus 9/49 pts (28.6%, p=0.05) and 1/49 pts (2%, p=0.002), respectively, in the 12 months after emicizumab start. 6/49 pts (12%) had at least one target joint in the 12 months before emicizumab versus 0/49 pts in the 12 months after emicizumab (p=0.01).

Conclusions. In this population of pediatric HA pts with and without inhibitors, emicizumab prophylaxis was safe and effective in reducing bleeding episodes, including joint bleeds, resolving all the target joints. Likewise, hospitalization due to bleeds and trauma was significantly reduced. No adverse events requiring emicizumab discontinuation occurred, including the 9 pts younger than 1 year at emicizumab start.



UPDATING MANAGEMENT OF ACQUIRED HEMOPHILIA A USING EMICIZUMAB: REAL-WORLD OUTCOMES BY A COLLABORATIVE NETWORK OF 3 ITALIAN CENTERS

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Background. Acquired Hemophilia A (AHA) is a rare, life-threatening autoimmune bleeding disorder caused by autoantibodies (inhibitors) against coagulation factor VIII (FVIII). Traditional management focuses on immediate hemostatic treatment for acute bleeding and the eradication of autoantibodies via immunosuppressive therapy (IST). However, patients remain at high risk of severe hemorrhage until complete remission is achieved, and prolonged IST is associated with significant morbidity. Recently, emicizumab—a bispecific monoclonal antibody that mimics FVIII activity by bridging activated factor IX and factor X—has emerged as an innovative approach for AHA. Originally authorized for bleeding prophylaxis in congenital hemophilia (with or without inhibitors), emicizumab may reduce the bleeding burden even in AHA and allow for more flexible IST regimens. In Italy, the drug is currently accessible for this indication under the provisions of Law 648/1996.

Methods. We reviewed a cohort of AHA patients who received emicizumab at the Hemophilia Center of Parma or through consultations at the Centers in Piacenza and Reggio Emilia. Due to the requirement for chromogenic assays with bovine reagents, monitoring of FVIII and inhibitor levels was centralized at the Parma laboratory. Results are reported as means ± 1 standard deviation.

Results. Five patients (3 men, 2 women) were diagnosed with AHA (idiopathic in 3 cases) at mean age of 81±6 years. All but one patient presented with poor prognostic factors, including FVIII:C <1% and/or high inhibitor titers (mean: 47±31 BU/mL). All patients exhibited severe muscle and subcutaneous hematomas and anemia (Hb <7 g/dL in 3 cases); elbow joint bleeding and gastrointestinal hemorrhage were also observed in one patient each. Initial hemostatic treatment with recombinant activated FVIII (rFVIIa) and red blood cell (RBC) transfusions was administered to all patients as needed. Emicizumab was introduced following the loading schedule in this setting (6 mg/kg on day 1, 3 mg/kg on day 2, and 1.5 mg/kg on day 8) after a mean of 17 days of hospitalization. Maintenance doses were administered weekly for 3 weeks in four patients, while one patient was treated for 4 weeks. Compared to the pre-emicizumab phase, the mean RBC transfusion requirement decreased from 7.2±4.9 to 1±0, and mean rFVIIa consumption fell from 124±72 mg to 71±23 mg (with three patients requiring no further administration). Three patients were discharged 7–9 days after initiating emicizumab, continuing with outpatient monitoring. In two cases, emicizumab helped avoid the intensification of IST and inhibitor eradication was achieved after 42–98 days (FVIII >20% reached within 17–45 days). Despite the reduction in bleeding, two patients died due to complications of the underlying condition (acute leukemia) and sepsis, respectively. No adverse events related to emicizumab were observed, including thrombotic or cardiovascular complications.

Conclusions. A collaborative network of centers providing specialized laboratory and clinical expertise facilitated the integration of emicizumab into the management of these poor-prognosis AHA patients. Emicizumab prophylaxis effectively reduced both the clinical bleeding burden and the treatment requirements, enabling earlier discharge and outpatient follow-up in patients without severe IST-related complications or comorbidities.

ABSTRACT N. PO045

FROM PROPHYLAXIS TO ENDOGENOUS CONTROL: A SIX-MONTH REAL-WORLD EXPERIENCE WITH VALOCTOCOGENE ROXAPARVOVEC GENE THERAPY

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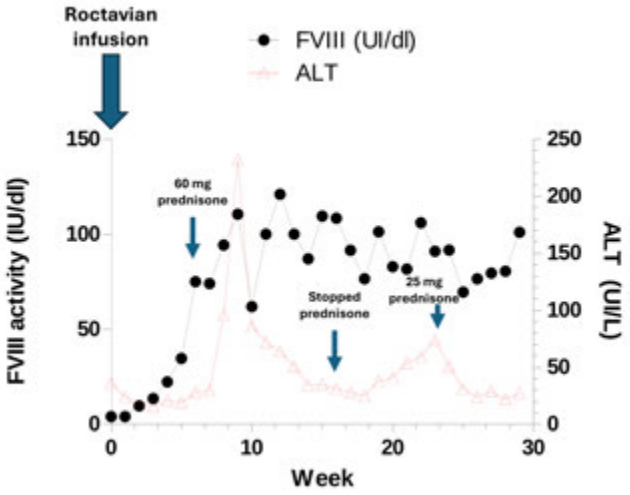
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Background. Severe hemophilia A is an X-linked bleeding disorder characterized by factor VIII (FVIII) activity <1 IU/dL, leading to recurrent bleeding and long-term morbidity. Gene therapy with adeno-associated virus (AAV) vectors, such as valoctocogene roxaparvovec, enables sustained endogenous FVIII expression and reduces treatment burden. In the phase 3 GENEr8-1 trial, this approach significantly reduced bleeding and FVIII use, with alanine aminotransferase (ALT) elevations as the most frequent adverse event . We report a six-month follow-up of a 32-year-old man with severe hemophilia A due to intron 22 inversion.

Methods. The patient had no history of FVIII inhibitors and was on extended half-life FVIII prophylaxis. Baseline liver status was normal (Fibroscan 6.2 kPa). Gene therapy was administered as a single intravenous infusion according to the phase 3 protocol (N Engl J Med 2022;386:1013-25). FVIII prophylaxis was continued for four weeks and discontinued at week 5. Clinical outcomes and liver enzymes were prospectively monitored. ALT elevations were managed with corticosteroids.

Results. Treatment was well tolerated, with no infusion reactions or inhibitor development. FVIII prophylaxis was discontinued at week 5, with no bleeding events thereafter. At week 5, ALT increased (~230 IU/L) and was treated with prednisone 60 mg/day, tapered with normalization by week 16. A second, milder ALT rise at week 24 responded rapidly to prednisone 25 mg/day. This pattern is consistent with trial data, where ALT elevations were common and manageable . The patient reported a major improvement in quality of life, describing for the first time a “hemophilia-free mind.”.

Discussion and Conclusions. This case confirms the efficacy and manageable safety of valoctocogene roxaparvovec in clinical practice. The absence of inhibitors, sustained discontinuation of prophylaxis, and lack of bleeding align with trial results. ALT elevations remain the main safety issue but are controllable with timely corticosteroid therapy. Notably, gene therapy provided substantial psychological benefit, reducing disease burden perception. At six months, this treatment showed a favorable benefit–risk profile and highlights the transformative potential of gene therapy in hemophilia A.



ABSTRACT N. PO046

BLEEDING PHENOTYPE AND PLATELET FUNCTION TESTS IN BERNARD-SOULIER SYNDROME: A CORRELATION STUDY

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Background and Aims. Bernard–Soulier Syndrome (BSS) is a rare autosomal recessive platelet disorder caused by defects of the GPIb-IX-V complex and characterized by a bleeding phenotype that does not always correlate with conventional laboratory findings. The ISTH-BAT provides a standardized method for assessing bleeding; however, its relationship with platelet function in patients with BSS, particularly when evaluated using whole-blood assays, is still not well defined. This study aims to investigate the association between bleeding severity, as measured by the ISTH-BAT score, and platelet function in a cohort of patients with BSS, including individuals with both bleeding and non-bleeding phenotypes.

Methods. Eighteen patients from seven unrelated families with clinical and genetic diagnosis of BSS underwent comprehensive laboratory evaluation. Bleeding tendency was assessed using the ISTH-BAT score. Data on platelet count, size, morphology were acquired. In addition, surface markers expression (CD41A, CD42A, CD42B, CD49B, PAC1, CD62P activated by ADP) were evaluated by platelet immunophenotyping on flow cytometer. Platelet function was assessed in platelet-rich plasma by light transmission aggregometry and in whole blood by using impedance aggregometry (Multiplate®). Whole-blood coagulation was additionally evaluated by rotational thromboelastometry (ROTEM®). Genetic variants were identified by Sanger sequencing.

Results. All patients with BSS (mean age 45 ± 20 years; 9M/9F) had low platelet averaging at 87 ± 45 ×10⁹/L. 13/18 patients manifested haemorrhagic episodes (bleeders group) while 5/18 not having haemorrhagic events were defined as non-bleeders. The ISTH-BAT score was 0 in non-bleeders and >1 in bleeders, with overall values ranging from 0 to 8 and a mean of 3 among bleeders. A significant difference in LTA aggregation between bleeders and non-bleeders was observed in response to collagen (64±24 vs. 81±7%, respectively; p = 0.04) and to Ristocetin (48±28 vs. 73±13%, respectively; p = 0.03). No association was found between the ISTH-BAT score and aggregation assessed by Multiplate®, nor with ROTEM® profiles. Multiplate® and ROTEM® parameters were in the normal range in both groups, except ASPI test, that was reduced in bleeders and non-bleeders (see Table 1). In the PFA-200 test, closure time was prolonged in both COL/EPI and COL/ADP cartridges in both groups; the increase was less pronounced in non-bleeders, although this difference did not reach statistical significance.

Conclusions. Platelet aggregation responses to collagen and Ristocetin are associated with bleeding severity in BSS, whereas platelet count is not. These findings support the variability of laboratory phenotypes in BSS and suggest that platelet function testing may better reflect bleeding risk than platelet count alone. Larger studies are needed to confirm these preliminary observations.

Table 1. Clinical and laboratory characteristics of BSS patients according to bleeding phenotype.

	total	bleeding	non-bleeding	p value*
N. of patients	18	13	5	-
Male, n (%)	9 (50)	6 (46)	3 (60)	0.70
Age°, yrs	45±20	44±18	50±24	0.63
ISTH-BAT score	2±2	3±2	0	-
Plt count, x10⁹/L (r.r. 150-450)	87±45	83±50	98±30	0.50
Immunophenotype, n (%)				
CD41A reduced	0	0	0	-
CD42A reduced	10 (55)	5 (38)	4 (80)	0.11
absent	1 (6)	1 (8)	0	-
CD42B reduced	14 (77)	10 (76)	4 (80)	0.89
absent	1 (6)	1 (8)	0	-
CD49B reduced	1 (6)	1 (8)	0	-
PAC1 ADP reduced	2 (11)	2 (15)	0	-
CD62 ADP reduced	14 (77)	10 (76)	4 (80)	0.89
ROTEM®				
INTEM				
CT, sec (r.r. 139-202)	192±12	192±13	192±12	0.97
MCF, mm (r.r. 55-71)	59±5	60±5	54±4	0.54
EXTEM				
CT, sec (r.r. 48-72)	66±14	67±17	65±3	0.72
MCF, mm (r.r. 54-70)	62±6	62±6	60±4	0.46
FIBTEM				
MCF, mm (r.r. 5-17)	14±5	14±6	13±2	0.48
PFA200, sec				
COL/EPI (r.r. 82-150)	181±65	192±72	154±24	0.14
COL/ADP (r.r. 62-100)	167±73	179±82	157±19	0.12
CN3000, % (r.r. >70)				
ADP2	47±28	43±26	57±30	0.44
ADP10	73±22	68±25	83±3	0.06
COLL	69±22	64±24	81±7	**0.04**
ARA	47±36	43±36	56±35	0.52
EPI	63±25	58±27	77±10	0.06
RISTO	55±27	48±28	73±13	**0.03**
MULTIPLATE®, AUC				
ASPI (r.r. 51-112)	45±22	45±25	43±15	0.87
ADP (r.r. 48 -119)	62±24	62±24	64±22	0.83
TRAP (r.r. 86 -159)	116±22	109±19	133±21	0.09

r.r. reference range, °at the time of blood sample collection, *bleeding vs non bleeding



TRANSIENT IDIOPHATIC ACQUIRED VON WILLEBRAND SYNDROME: A RARE CHALLENGING CONDITION WITH A POSSIBLE RAPIDLY AND FAVOURABLE EVOLUTION

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Background and aims. The acquired von Willebrand syndrome (AvWS) is a rare but probably understimated bleeding disorder characterized by laboratory findings and clinical presentations similiar to those of inherithed von Willebrand disease. However, unlike the inherited disease, AvWS occurs in adults with no personal or family history of bleeding diathesis. Although AvWS is particularly frequent in lymphoproliferative or myeloproliferative disorders, it can also be associated with solid tumors, immunologic and cardiovascular disorders including congenital heart defects, aortic stenosis, and the use of left ventricular assist devices, and other miscellaneous conditions. Various mechanisms are implied in the pathophysiology of AvWS, the majority of them leading to the increased degradation or clearance of circulating vWF. The aim of this abstarct is to demonstrate the significance of follow-up in cases of AvWS without a recognised underlying cause, given the possibility of spontaneous clinical and laboratory resolution of the haemorrhagic condition.

Case report. Considering the aforementioned points, we present a case of a 56 years-old woman that was referred to our centre in 2024 due to multiple episodes of epistaxis and easy bruising. She exhibited negative bleeding histories even in trigger conditions (surgery, childbirth) and no family history of bleeding diathesis. No comorbidities were present at diagnosis and both autoimmune evaluation and cancer screening were negative. One year after diagnosis, a complete clinical and laboratory resolution was observed. As rare disease, the diagnostic process is complex and involves multiple steps, requiring an experienced and specialized laboratory. Despite pathological laboratory results, confirming the acquired nature of this disorder remains a significant diagnostic challenge. The first step routine coagulation tests and vWF screening were performed: factor VIII (FVIII) dosage, VWF Antigen (vWF:Ag), VWF activity (VWF:Ac), VWF ristocetin cofactor activity (VWF:RCo) and collagen binding assay (CBA). Afterwards, dilution and subsequent in vivo recovery test with plasma derived von Willebrand factor concentrate were performed. A genetic test was performed. Dilution and in vivo recovery tests strongly suggested an acquired form. Genetic analysis was inconclusive. One year after diagnosis, no more antibodies were found.

Conclusions. The AvWS is a rare bleeding disorder with a diagnostic work-up and optimal treatment highly individualized. The management remains challenging, particularly when discrepancies arise between laboratory findings and the patient's medical history. For this reason, especially in cases without an underlying cause, it is important to perform close follow-up for the possibility of rapid favorable resolution of the condition.

Parameter	2024	2025
FVIII:C	35%	120%
vWF Antigen (vWF Ag)	33%	90%
vWF Ristocetin Cofactor (vWF RCo)	8%	75%
vWF Collagen Binding Activity (vWF CBA)	22%	70%

ABSTRACT N. PO048

EFFICACY OF RITUXIMAB TREATMENT IN A CASE OF A RELAPSED AND REFRACTORY ACQUIRED VON WILLEBRAND DISEASE SECONDARY TO PRIMARY CUTANEOUS MARGINAL ZONE B-CELL LYMPHOMA

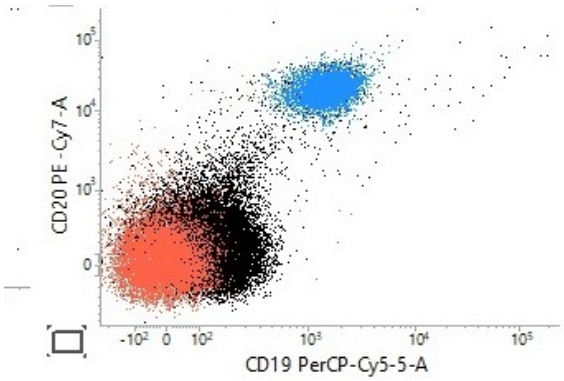
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Background. Acquired von Willebrand disease (AVWD) is a rare disorder of hemostasis characterized by reduced circulating von Willebrand factor (vWF) levels and impaired hemostasis, leading to spontaneous mucocutaneous bleeding manifestations, typically of mild to moderate degree. In AVWD, anti-vWF antibodies (predominantly IgG, and to a lesser extent IgM and IgA) may develop, impairing its hemostatic function by forming immune complexes (Ab–vWF) that accelerate its clearance from the circulation. The production of these antibodies is usually associated with hematologic malignancies and autoimmune diseases.

Case Report. We report the case of a 79-year-old woman who in October 2018 developed bleeding symptoms (spontaneous ecchymoses and mild gingival bleeding), with a negative family history. Coagulation studies showed an aPTT of 39 seconds and normal INR, with factor VIII (FVIII) at 16% and vWF at 14%. A desmopressin test was performed, with no response. The patient was initially diagnosed with congenital von Willebrand disease. At January 2020, a lesion appeared on the right forearm; biopsy led to a diagnosis of primary cutaneous marginal zone B-cell lymphoma stage I, with circulating clonal disease B1 (594/mmc clonal lymphocytes with immunophenotype: CD19+, CD20+, CD5-, CD10-) *[Figure 1]*. The patient started a first-line treatment with anti-CD20 monoclonal antibody rituximab (administered at 375 mg/m² weekly for 4 weeks), achieving complete remission, with resolution of bleeding symptoms. In October 2024, a relapse of the cutaneous lymphoma occurred (with both a skin lesion and circulating clone), along with recurrence of mild bleeding symptoms. Coagulation studies showed INR 0.92, aPTT 42 sec, FVIII 97%, with vWF at 13% and ristocetin cofactor activity (vWF:RCo) at 15%. Given her age at relapse (87 years), she initially received prednisone (0.5 mg/kg for 30 days), without improvement in coagulation parameters (vWF 12% and vWF:RCo 15%). She was therefore retreated with rituximab 375 mg/m² weekly for 4 weeks. At reassessment after 6 weeks, complete remission was again observed, with an INR of 0.96, aPTT of 27 sec, FVIII 117%, vWF 87%, vWF:RCo 44% and complete absence of the circulating clone. The patient is currently in follow up with complete response.

Conclusions. AVWD is a rare condition but should be considered in oncologic patients presenting with new-onset bleeding symptoms. A personalized treatment approach, taking into account the underlying malignancy, should be considered in these patients. In this case, treatment of the B-cell lymphoma with rituximab led to a response also in the coagulopathy, both at the onset and the relapse.





WHOLE-BLOOD THROMBIN GENERATION ASSAY REVEALS HYPERCOAGULABLE STATE IN SICKLE CELL DISEASE IN STEADY STATE AND CORRELATES WITH CLINICAL EVENTS

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Background and Aims. Sickle cell disease (SCD) is a systemic condition characterized by vaso-occlusive crises (VOC), which underlie acute complications and chronic organ damage. The pathophysiology of VOC is multifactorial and includes chronic hypercoagulability. Whole blood thrombin generation (WB-TG) with and without thrombomodulin (TM) enables global and dynamic assessment of coagulation, integrating both plasma factors and cellular components. This study aimed (i) to compare WB-TG parameters in SCD patients in steady state with healthy controls, and (ii) to explore associations between TM-modified WB-TG parameters and laboratory variables and clinical outcomes.

Methods. In this single-center observational study, SCD patients (≥10 years) were enrolled in steady state (no vaso-occlusive crisis, hospitalization, or blood transfusion/exchange within 4 weeks). WB-TG was performed within 4 hours from blood sampling, using TF 1 pM, without added phospholipids, in the absence/presence of TM (20 nM, selected to achieve ~50% inhibition in controls). TG parameters included lag time, time-to-peak, peak thrombin, endogenous thrombin potential (ETP), velocity index, ETP ratio (ETP+TM/ETP), and ETP inhibition (%). Clinical history and standard laboratory data were collected at baseline. Patients were followed for 12 months. Statistical analysis was performed using Mann–Whitney tests for comparisons and exploratory univariate logistic regression for associations with clinical outcomes.

Results. WB-TG was analyzed in 28 SCD patients (median age 19 years) and 21 healthy controls. In steady state, SCD patients showed accelerated thrombin generation kinetics compared to controls: shorter lag time 2.5 [2.4–2.8] vs 3.8 [3.2–4.3] min and time-to-peak 6.3 [5.8–7.1] vs 9.7 [8.3–10.0] min (both p<0.001), higher velocity index 54.4 [44.3–64.8] vs 36.4 [29.3–39.7] nM/min (p<0.001), while ETP and peak thrombin were not significantly different. In presence of TM, SCD patients maintained faster kinetics: shorter lag time+TM 4.2 [3.8–5.4] vs 5.9 [5.2–6.5] min and time-to-peak+TM 7.4 [6.8–7.7] vs 10.2 [9.5–11.5] min (both p<0.001), higher velocity index+TM 49.5 [39.9-60.4] vs 30.6 [24.5-37.6] and higher peak+TM 152.3 [130.9-180.0] vs 117.3 [109.6-132.7] (p=0.034). TM-mediated inhibition was reduced in SCD, indicating TM resistance, as shown by lower ETP inhibition 27.8% [17.6–34.8] vs 46.6% [33.4–52.5] (p=0.018). Lower ETP inhibition was associated with acute clinical events in the previous 12 months: vaso-occlusive crises (p=0.015, OR 0.93, 95% CI 0.87–0.99), acute chest syndromes (p=0.003, OR 0.86, 95% CI 0.76–0.97), and hospitalizations (p=0.015, OR 0.94, 95% CI 0.88–1.00) (Table 1). No significant associations were observed between WB-TG parameters and events over the 12-months follow-up.

Conclusions. In steady state, SCD patients exhibit accelerated thrombin generation kinetics and reduced TM-mediated inhibition, supporting a persistent hypercoagulable phenotype likely related with impaired protein C pathway modulation. The association between TM-modified WB-TG parameters, particularly ETP inhibition, and prior acute clinical events suggests a potential role of this assay in thrombo-inflammatory risk stratification in SCD. Larger prospective studies with longer follow-up are needed to validate these findings and confirm the predictive clinical utility of WB-TG.

Table 1. ETP inhibition according to clinical events in the prior 12 months

Event	Present	Absent	ETP inhibition (%) Event present*	ETP inhibition (%) Event absent*	p value†	OR (95% CI)‡
VOC	18	10	21.3 (IQR 12.9–29.9)	33.6 (IQR 31.7–37.9)	0.015	0.93 (0.87–0.99)
ACS	7	21	11.9 (IQR 2.4–16.6)	30.5 (IQR 24.7–35.2)	0.003	0.86 (0.76–0.97)
Hospitalizations	16	12	21.3 (IQR 10.8–28.6)	33.6 (IQR 29.0–36.1)	0.015	0.94 (0.88–1.00)

* Values are reported as median (interquartile range, IQR).
† p value obtained using Mann–Whitney U test.
‡ Odds ratio from univariable logistic regression (exploratory analysis due to small sample size).
Abbreviations: VOC, vaso-occlusive crisis; ACS, acute chest syndrome; ETP, endogenous thrombin potential.



HEMOSTATIC AND FIBRINOLYTIC PROFILES IN PATIENTS UNDERGOING TAVI: PRELIMINARY RESULTS ON HOMOCYSTEINE, D-DIMER, AND CLOT LYSIS TIME

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Background and aims. Transcatheter Aortic Valve Implantation (TAVI) is the treatment of choice for patients with severe symptomatic aortic stenosis, particularly those with high frailty and multiple comorbidities. Despite its minimally invasive nature, TAVI induces systemic inflammation and mechanical stress, potentially altering haemostatic and fibrinolytic balance during the peri procedural period. The identification of biomarkers capable of predicting thrombotic or haemorrhagic complications remains an unmet clinical need. This study aims to assess peri procedural changes in the coagulation and fibrinolysis profiles of a patient cohort undergoing TAVI. Specifically, we focus on plasma levels of homocysteine, clot lysis time (CLT)—as markers of fibrinolytic potential—and D-dimer levels, to investigate the impact of the procedure on haemostatic activation and the body's capacity for clot resolution.

Methods. This study presents preliminary data from a cohort of 61 patients (mean age 82 ± 4 years; 55.7% female) undergoing TAVI at the AOU Careggi hospital. Plasma levels of homocysteine (HCY), D-dimer (DD), and clot lysis time (CLT) were analysed at two time points: pre-procedure and post-procedure. Between group comparisons were performed using the Mann–Whitney U test, while associations between categorical variables were assessed using the Chi square test. Spearman's rank correlation coefficient was used to explore relationships between biomarkers and clinical variables.

Results. Post procedural homocysteine levels were significantly reduced compared with baseline (median 15.1 µmol/L [IQR 12.9–20.2] vs 14.2 µmol/L [IQR 11.0–17.2]; $p < 0.001$). In contrast, a significant increase in D-dimer levels was observed, rising from a pre-procedural mean of 997ng/mL, IQR 632-1348, to 1508 ng/mL, IQR 962-2416, post-TAVI. CLT values remained relatively stable with a slight upward trend (65 min, IQR 57-77, to 69min, IQR 56-78). Significant Spearman correlations were found between D-dimer levels and both age (rho = 0.27; $p = 0.035$) and homocysteine (rho = 0.33; $p = 0.010$). Contingency tables, where variables were categorized based on specific cut-offs (HCY: Males < 19 µmol/L, Females < 13 µmol/L; CLT: 39–89 min), revealed a strong association between pre- and post-procedural HCY categories ($p < 0.001$), while for CLT, the association between pre- and post-procedural status was also statistically significant ($p = 0.042$).

Conclusions. These preliminary results indicate that TAVI is associated with dynamic and multifaceted alterations in haemostatic and metabolic pathways, extending beyond simple coagulation activation. The observed biomarker variations and their correlations with patient profiles highlight the need for a comprehensive monitoring approach to optimize post-operative management.

ABSTRACT N. PO051

ENDOGENOUS THROMBIN POTENTIAL RATIO AS A PREDICTOR OF BIRTHWEIGHT PERCENTILE IN PREGNANCY

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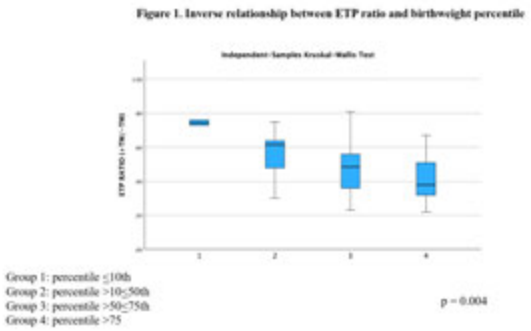
Background. Early identification of pregnancies at risk for placental-mediated adverse outcomes remains challenging, particularly in women with prior obstetric complications, such as small-for-gestational-age (SGA) newborns. Subtle hemostatic alterations in these settings may escape detection by conventional coagulation tests. The thrombin generation assay (TGA) provides an integrated measure of procoagulant–anticoagulant balance and may better reflect coagulation changes related to placental dysfunction.

Aims. The primary aim was to compare first-trimester thrombin generation parameters in women at increased obstetric risk with those of healthy pregnant controls. The secondary aim was to evaluate the association between first-trimester thrombin generation and birthweight percentile at delivery.

Methods. In this prospective observational study, women were enrolled at 5–14 weeks' gestation and followed to delivery. Thirty-one women at increased obstetric risk (history of pregnancy loss or intrauterine fetal death, implantation failure, or previous SGA newborn) were compared with 21 gestational age–matched healthy controls. Twelve cases received prophylactic enoxaparin (4000 IU/day), with sampling ≥12 hours after the last dose. TGA was assessed on platelet-poor plasma using the calibrated automated thrombogram with PPP reagent, with and without thrombomodulin, analyzing peak thrombin, time-to-peak, endogenous thrombin potential (ETP), and ETP ratio

Results. Baseline characteristics were comparable between groups, including age (33.2 ± 4.9 vs 32.2 ± 4.7 years) and body mass index (24.3 ± 4.3 vs 26.1 ± 5.9 kg/m^2), as well as parity, mode of delivery, and neonatal sex. First-trimester thrombin generation parameters did not differ significantly between cases and controls. Mean birthweight was lower in cases than controls (3150 ± 640 g vs 3400 ± 398 g), although not statistically significant. Notably, 10 cases delivered neonates with birthweight <10th percentile, compared with none among controls (p = 0.008). Across the whole cohort, the first-trimester ETP ratio was significantly associated with birthweight percentile. Lower ETP ratios were observed in pregnancies with birthweight <10th percentile compared with ≥10th percentile (0.46 ± 0.14 vs 0.53 ± 0.20), with a progressive increase across higher percentiles (Kruskal–Wallis, p = 0.004) (Figure 1). Enoxaparin use did not modify this association.

Conclusions. First-trimester ETP ratio was associated with fetal growth, supporting the potential role of early global coagulation assessment in identifying pregnancies at risk of SGA neonates.





ABSTRACT N. PO052

VALIDATION OF THROMBIN GENERATION MEASUREMENT IN PLATELET- RICH-PLASMA: EVOLUTION IN THE ST GENESIA® SYSTEM

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Background and Aims. Thrombin generation assay (TGA) represents a promising tool for monitoring novel non-replacement therapies in haemophilia. ST Genesia® system (*Stago, Asnières-sur-Seine, France*) is validated to measure thrombin generation (TG) in platelet poor plasma (PPP) but there is no standardized method available on this platform for testing TG in platelet-rich plasma (PRP). Such a method would enable the investigation of platelet–drug interactions and provide a more comprehensive assessment of the patient's haemostatic function.The aim of this study was to experiment and validate, on ST Genesia system, the technical reliability of TG measurement in PRP, evaluating: intra- and inter-run reproducibility, PRP sample stability over time, effectiveness of normalization by reference plasma, absence of methodological interference from the platelet component, and robustness of the method.

Methods. The procedure required the following materials: PRP Reagent (CAT PRP-Reagent, Stago) that contains relipidated Tissue Factor that allows the initiation of reaction, a home made PPP reference plasma (RefPlasma) prepared from a pool of at least 20 healthy donors, used for result normalisation, analytical variability monitoring, and internal system calibration and the PRP samples under investigation. RefPlasma validation was performed by calculating the intra-run (≥10 replicates) and inter-run (≥3 days) coefficients of variation (CV%), alongside assessment of routine coagulation parameters (PT, aPTT, fibrinogen, AT). PRP sample stability was evaluated by performing TG measurements at three time points: T0 (baseline), T1 (1 hour post T0), and T2 (3 hours post T0).

Results. RefPlasma validation demonstrated acceptable intra-run CV% (10 replicates within a single run) and Inter-run CV% (across 3 runs on separate days) described in Table 1. Routine coagulation parameters (PT, aPTT, fibrinogen, AT) were within normal reference ranges. PRP stability testing revealed a progressive decline in Peak Height, ETP, and Velocity Index from T0 through T2, accompanied by a corresponding increase in Lag Time, Time to Peak, and Start Tail.

Conclusions. With coefficients of variation predominantly below 10%, the RefPlasma demonstrated satisfactory reproducibility both within individual runs and across runs performed on different days. Regarding PRP stability, the progressive reduction of TG parameters (Peak Height, ETP) over time suggests that specimens should be analysed within 3 hours of collection to mitigate pre-analytical degradation. This finding warrants further investigation, particularly concerning the feasibility of test centralisation when processing samples received from external centres. In conclusion, this procedure represents a validated approach for TGA in PRP, enabling a more physiologically relevant evaluation when it is important to have a global assessment of drug-coagulation interactions.

Parameter	CV% INTRA-RUN	CV% INTER-RUN
Lag Time	2.63%	11.74%
Peak Height	2.37%	3.43%
Time to Peak	2.89%	8.07%
ETP	2.65%	2.37%
Vel.Index	6.02%	8.69%
Start Tail	2.91%	5.81%

ABSTRACT N. PO053

PLATELET AGGREGATION AND THROMBIN GENERATION IN MULTIPLE MYELOMA: A PROSPECTIVE STUDY

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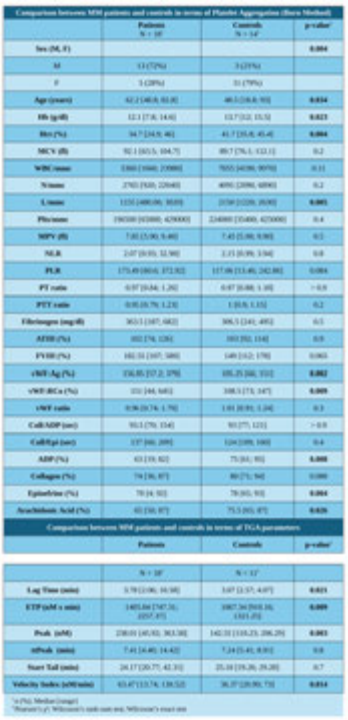
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Background and Aims. Multiple Myeloma (MM) is a plasma cell dyscrasia characterized by the clonal proliferation of plasma cells, which is associated with a significantly increased risk of both thrombotic and hemorrhagic complications. This ongoing prospective observational study aims to characterize platelet function and thrombin generation (TGA) in patients with newly diagnosed MM and to assess the impact of first-line therapy on these parameters.

Methods. To date, eighteen patients with newly diagnosed MM have been enrolled. Platelet function was evaluated using closure time (PFA200) and light transmission aggregometry (Born method) with four agonists: ADP (5 µM), Epinephrine (Epi) (10 µM), Collagen (Coll) (2 µg/ml), and Arachidonic Acid (AA) (1 mM). Thrombin generation (TGA) was assessed using the Calibrated Automated Thrombogram (CAT) assay. Baseline results were compared with historical healthy control cohorts. Intra-patient analysis was performed on 11 patients after four cycles of induction therapy (D-VTd or DRd). Statistical analysis was performed using R software (version 4.4). Comparisons between patients and controls were performed using the Wilcoxon rank-sum test and Pearson's Chi-square test. For paired data the Wilcoxon signed-rank test was employed. Statistical significance was set at $p < 0.05$.

Results. In this interim analysis, at diagnosis, MM patients exhibited significantly lower platelet aggregation compared to controls for ADP (p=0.008), Epinephrine (p=0.004), and Arachidonic Acid (p=0.026). Procoagulant markers were significantly elevated: vWF:Ag (p=0.002) and vWF:RCo (p=0.009), while Factor VIII (p=0.065) showed a trend toward elevation. TGA analysis revealed significantly prolonged Lag Time (p=0.021) and significantly higher ETP (p=0.009), Peak (p=0.003), and Velocity Index (p=0.014) in MM patients (Table 1). Following therapy, most parameters remained stable, showing persistence of high thrombin generation, elevated vWF/FVIII levels, and impaired platelet function. Only Mean Platelet Volume (MPV) showed a significant decrease (7.85 fl vs. 7.30 fl, p=0.024).

Conclusions. This study highlights the coexistence of hypercoagulability and platelet dysfunction in MM. Based on these preliminary results, the reduction of tumor burden and the treatment do not seem to modify the evaluated parameters.





HEMOSTASIS RESTORATION AFTER SPIKE OF FACTOR V CONCENTRATE IN COMMERCIAL FACTOR V-DEPLETED PLASMA

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Background and Aims. Human coagulation Factor V (FV) has a central role as a non enzymatic cofactor within the Prothrombinase Complex, where it markedly accelerates the conversion of prothrombin to thrombin. Congenital FV deficiency (Parahaemophilia) is an uncommon autosomal recessive disorder characterized by decreased functional FV levels which manifests symptoms from mild bleeding to life-threatening haemorrhages. Therapeutic options are limited to Fresh Frozen Plasma (FFP) administration, due to the lack of approved recombinant FV or plasma-derived concentrates. FFP therapy presents significant limitations, including transfusion-related adverse events and potential pathogen transmission. The present study aimed to evaluate the capacity of a novel lyophilized FV preparation to restore the haemostasis function after spike in commercial FV-depleted Plasma.

Methods. Two pilot batches (N1 and N2) were manufactured from human plasma using a multistep purification process combining chromatography and tangential flow ultrafiltration. Biochemical and functional characterization of the FV preparations obtained were performed. Purity and structural integrity were assessed by SDS-PAGE and Western blot analysis. Factor V activity was determined using a clot based functional assay based on a modified prothrombin time. The resulting lyophilized FV preparations were spiked into FV-depleted plasma (provided by Instrumentation Laboratory) at three different dilutions.

Results. Both lyophilized preparations showed FV Potency within the predefined expected range (16-24 IU/mL) of respectively 17,14 IU/mL (N1) and 17,79 IU/mL (N2). SDS-PAGE analysis showed no evidence of activation immediately after production. Three levels of spike (1:20, 1:40 and 1:80) for each preparation were performed in FV-depleted plasma. Potency assays demonstrated effective restoration of the haemostasis within the target range (0,8-1,2; 0,4-0,6; 0,2-0,3 IU/mL respectively for each level of spike).

Conclusions. These preliminary results demonstrate that both lyophilized preparations can restore the haemostasis in FV-depleted plasma. Further studies are required to evaluate long-term stability and safety.

ABSTRACT N. PO055

THROMBIN GENERATION PROFILES IN PATIENTS WITH WILD-TYPE TRANSTHYRETIN AMYLOIDOSIS

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Background and Aims. Thromboembolic events are frequently observed in wild-type transthyretin amyloidosis (ATTRwt), with a reported prevalence ranging from 6% to 28%. The main mechanisms contributing to thrombosis include atrial fibrillation (AF), mechanical atrial dysfunction, and myocardial involvement leading to myopathy. However, thromboembolic complications have also been described in patients who are in sinus rhythm or receiving apparently adequate anticoagulant therapy, suggesting that additional, not yet fully understood, pathophysiological factors may be involved. This study aimed to assess whether hyperactivation of the coagulation system can be detected through thrombin generation (TG) testing in patients with transthyretin amyloidosis.

Methods. A total of 24 patients with ATTRwt (median age 80 years; 17 males and 7 females), all without AF and not receiving anticoagulant therapy, were enrolled. Their results were compared with those of 50 healthy controls matched for age (± 3 years) and sex. Thrombin generation was measured in platelet-poor plasma (PPP) samples, both in the presence and absence of thrombomodulin, using the automated and standardized ST Genesia analyzer (Stago, Asnières-sur-Seine, France) and the STG-ThromboScreen kit, in accordance with the manufacturer's instructions.

Results. Thrombin generation parameters are reported in Table 1. No statistically significant differences were observed between patients and controls across all evaluated parameters. Specifically, lag time (min), endogenous thrombin potential (ETP, nmol/L·min), peak height (nM), time to peak (min), velocity index (nM/min), and start tail (min) were comparable between the two groups, both in assays performed with and without thrombomodulin.

Conclusions. Thrombin generation profiles in patients with ATTRwt appear to be similar to those observed in healthy individuals. These findings suggest that, under the conditions examined, there is no clear evidence of coagulation system hyperactivation detectable by TG. Further studies are warranted to better elucidate the molecular mechanisms underlying potential hypercoagulability and to determine whether TG may serve as a predictive marker of a prothrombotic clinical phenotype.

	ATTRwt patients (n. 24)	Healthy Controls (n. 24)	P value
Sex (male/female)	17/7	17/7	-
Median age (years)	80 (±16)	78 (±14)	-
WB-TG without TM			
Lag time, min	4.2 (3.6-5.4)	4.0 (3.3-4.5)	0.19
ETP, nmol/l*min	1232 (1067-1367)	1399 (1266-1514)	0.09
Peak-height, nM	202 (160-238)	199 (173-243)	0.57
Time-to-peak, min	7.5 (6.1-8.7)	8.3 (6.8-9.2)	0.87
Vel index, nM/min	66.0 (40.6-85.5)	49.3 (36.4-75.5)	0.55
Start tail (min)	23.9 (22.3-27.0)	26.1 (22.8-27.5)	0.70
WB-TG with TM			
Lag time, min	5.1 (4.3-6.2)	4.3 (3.8-5.0)	0.13
ETP, nmol/l*min	396 (175-578)	568 (301-743)	0.10
Peak-height, nM	85 (27-133)	113 (58-137)	0.18
Time-to-peak, min	8.3 (6.8-10.0)	7.3 (6.4-8.3)	0.06
Vel index, nM/min	29.4 (7.2-55.8)	36.9 (18.5-57.7)	0.35
Start tail (min)	22.6 (21.1-25.0)	21.8 (20.5-23.3)	0.15



ABSTRACT N. PO056

SYNERGISTIC EFFECT OF RECOMBINANT FACTOR INFUSION ON THROMBIN GENERATION IN HEMOPHILIA PATIENTS UNDER EMICIZUMAB OR CONCIZUMAB PROPHYLAXIS

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Background and aims. Hemophilia is a deficiency of clotting factor VIII (FVIII) or IX (FIX). Modern prophylaxis includes non-replacement therapies like emicizumab (FVIII-mimetic) and concizumab (anti-TFPI), which enhance thrombin generation assay (TGA). However, managing breakthrough bleeding episodes or surgical procedures remains a challenge, as these clinical scenarios may require concomitant infusion of recombinant factor concentrates. This study evaluated the synergistic effect of factor infusion on TGA in patients receiving emicizumab or concizumab.

Methods. A total of 23 patients (pts) were screened, comprising 21 on emicizumab and 2 on concizumab prophylaxis enrolled in Novo Nordisk study NCT04082429. Among them, only 4 required recombinant factor infusion for breakthrough bleeding or surgery and were thus eligible for this analysis. This subset was categorized by prophylaxis type as follows: Emicizumab Group (n=3): three pts (1 moderate-severe and 2 severe hemophilia A). Clinical indications for factor infusion included major surgery (n=2) and a bleeding event (n=1). Concizumab Group (n=1): one patient (pt) with severe hemophilia B, who was evaluated across three distinct bleeding episodes requiring factor treatment. For each pt, a blood sample was collected within 12 hours following the infusion of recombinant factor administered for the bleeding episode or surgery. TGA was tested in platelet-poor plasma using the ST Genesia® system (Stago, Asnieres-sur-Seine, France) using STG BleedScreen reagent. To establish a baseline for each pt, TGA results were obtained from follow-up samples previously collected and stored during routine monitoring, while the pts were receiving prophylaxis with the non-replacement drug alone.

Results. The percentage changes in thrombin generation (T-G) parameters following factor infusion exhibited a heterogeneous pattern in the emicizumab group (Table 1). Pts 2 and 3 showed the expected procoagulant shift, conversely, Pts 1 demonstrated a paradoxical decline in TG parameters accompanied by an elongation of the StartTail. Notably, in Pts 1, the attainment of a 29% FVIII plasma level post-infusion did not prevent this reduction in thrombin generation potential compared to baseline. Regarding the pt receiving concizumab, a consistent pattern was observed across all three bleeding events, characterized by a rise in Peak Height and a concomitant decrease in ETP and StartTail values.

Conclusions. TGA profiles revealed distinct kinetic patterns: concizumab was associated with a more immediate thrombin peak linked to massive thrombin generation followed by rapid degradation, whereas emicizumab displayed a more gradual upward slope consistent with the drug's mechanism of action. The paradoxical reduction in thrombin generation observed in Pts 1 (Table 1), despite the attainment of a 29% FVIII level, is of particular clinical interest. We hypothesize that this discrepancy could be related to clinical variables, such as the accelerated consumption of clotting factors during major surgery and the concomitant use of heparin, which acts to decelerate thrombin generation. This suggests that TGA provides a comprehensive global hemostatic profile, essential for tailoring personalized prophylaxis and optimizing management during bleeding or surgery. Future implementation of TGA in Platelet-Rich Plasma may further enhance clinical insights by better reflecting physiological conditions and in vivo cellular interactions.

	Emicizumab			Concizumab		
	Patient 1	Patient 2	Patient 3	Patient 4 - bleeding 1	Patient 4 - bleeding 2	Patient 4 - bleeding 3
Peak Height (nM)	-37.7	+29.9	+67.8	+11.3	+23.9	+12.2
ETP (nM.min)	-25.9	+5.7	+11.1	-8.4	-2.5	-1
Start Tail (min)	+27.1	-12.4	-27.3	-16.1	-15.2	-10.4
Total dose of recombinant factor	30 IU/Kg	50 IU/Kg	30 IU/Kg	30 IU/Kg	30 IU/Kg	30 IU/Kg
Factor level after infusion (chromogenic assay)	29.2%	38.7%	19.3%	12.2%	9%	6.6%

Table 1



IS PLATELET FUNCTION TESTING CLINICALLY USEFUL IN PATIENTS WITH CHRONIC SUBDURAL HEMATOMA UNDERGOING NEUROSURGERY WHILE ON ANTIPLATELET THERAPY?

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Background and aims. Patients undergoing neurosurgery are increasingly treated with antiplatelet therapy, which increases bleeding risk and complicates the management of chronic subdural hematoma (CSDH), a condition for which clear guidelines are lacking. Platelet function testing may help optimize the timing of neurosurgical intervention by balancing hemorrhagic and thrombotic risks, given the variability in individual responses to antiplatelet drugs. This study aims to evaluate the safety and clinical utility of platelet reactivity testing in patients undergoing neurosurgical evacuation of CSDH.

Methods. We conducted a case–control study including patients undergoing surgical evacuation of CSDH between 2022 and 2025. Cases were patients on antiplatelet therapy with an urgent surgical indication who showed early normalization of platelet function on reactivity testing (i.e., normalization before the recommended drug withdrawal period). Controls were patients not receiving antiplatelet therapy. Outcomes included early complications (<7 days), and 30-day recurrences.

Results. A total of 333 patients were included: 176 cases and 157 controls. Patients on antiplatelet therapy were older (81.1±7.4 vs 77.0±11.4 years; p<0.001) and had a higher prevalence of hypertension (63.6% vs 48.1%; p=0.004) and diabetes (26.7% vs 12.7%; p=0.02), while other clinical and hematological characteristics were comparable. Among cases, aspirin monotherapy was the most common regimen (70.5%), followed by clopidogrel (23.9%) and combination therapy (~6%). Preoperative platelet inhibition was observed in 34.6% of clopidogrel-treated patients (PRU <208) and 97.8% of aspirin-treated patients (ARU <550). Early normalization of platelet function was achieved in most patients (98% for ARU; 98% for PRU). No significant differences were observed between groups (cases and controls) in early postoperative complications (<7 days) or 30-day recurrence. The incidence of surgical complications at 7 days was similar between groups (p=0.818), as were recurrence rates at 30 days (p=0.698).

Conclusions. Platelet function testing appears to be a safe and potentially useful tool to guide the timing of neurosurgical intervention in CSDH patients receiving antiplatelet therapy. Its use may allow earlier surgery without increasing hemorrhagic or ischemic complications, potentially reducing hospitalization time and improving clinical management.

ABSTRACT N. PO058

IMMUNOMODULATORY EFFECTS OF FOSTAMATINIB IN A PATIENT WITH EVANS SYNDROME, TRIPLE-POSITIVE ANTIPHOSPHOLIPID ANTIBODIES AND RELATED COAGULATION ABNORMALITIES

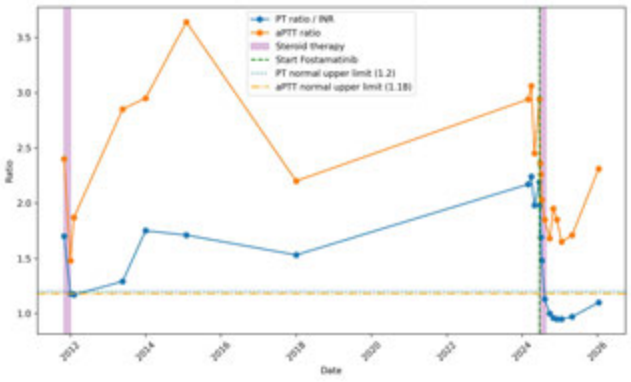
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Background. Fostamatinib is a spleen tyrosine kinase (Syk) inhibitor approved for immune thrombocytopenia, with emerging evidence suggesting a potential role in autoantibody-mediated disorders beyond platelet destruction. The aim of this report is to evaluate the role of fostamatinib in a patient with Evans syndrome, persistent antiphospholipid antibody (aPL) positivity, and laboratory abnormalities in coagulation tests.

Case Report. A 32-year-old man who, in 2011, following an infectious episode, presented with prolonged PT and aPTT associated with Coombs-positive hemolytic anemia. Further investigations showed triple positivity for aPL (lupus anticoagulant, high-titer anticardiolipin and anti-β2GPI antibodies), medium-titer ANA, low C4 with normal C3; infectious screening was negative and past medical history was unremarkable. Steroid therapy was initiated, leading to complete resolution of hemolytic anemia and normalization of hemolysis markers, and was discontinued after two months. PT initially normalized and then showed progressive prolongation from 2013 onward. Concomitantly, thrombocytopenia was observed (nadir 69,000/mmc), along with mild splenomegaly and hilar lymphadenopathy. Bone marrow biopsy showed trilineage hyperplasia and features of hemophagocytosis; PET was negative, with a mild reduction in the CD4/CD8 ratio and no evidence of monoclonal gammopathy. Platelet count subsequently recovered spontaneously and remained stable (>100,000/mmc) for more than 10 years, with progressive normalization of spleen size. aPL remained persistently positive in the absence of thrombotic events; primary prophylaxis with low-dose aspirin was initiated in 2015. Given the persistent prolongation of PT and aPTT, coagulation factor assays showed a concordant reduction of intrinsic pathway factors (VIII, IX, XI, XII), with normal FVII levels. No clinically relevant bleeding events occurred. In 2024, progressive thrombocytopenia recurred, together with the detection of medium-titer anti-prothrombin IgG antibodies. At a platelet nadir of 31,000/mmc, a short course of steroids and fostamatinib was initiated, resulting in platelet recovery; steroids were subsequently discontinued while fostamatinib was continued. Concomitantly, stable normalization of PT, negativization of anti-prothrombin antibodies, and normalization of coagulation factor levels were observed. The temporal trend of coagulation parameters in relation to treatment is shown in *Figure 1*.

Conclusions. Fostamatinib is a spleen tyrosine kinase (Syk) inhibitor with immunomodulatory activity on autoantibody-mediated effector mechanisms. Its effect is predominantly functional rather than serological, as it modulates downstream signaling without directly eliminating autoantibodies. In this context, the present case suggests a potential role for Syk inhibition in modulating aPL-related coagulation abnormalities.





HYPERCOAGULABILITY AND THROMBOTIC RISK IN MODERATE-TO-SEVERE OBSTRUCTIVE SLEEP APNEA: A PROSPECTIVE OBSERVATIONAL STUDY

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Background and Aims. Obstructive sleep apnea (OSA) is a common and clinically significant disorder characterized by recurrent episodes of upper airway obstruction during sleep, leading to intermittent hypoxia and sleep fragmentation. Increasing evidence suggests that OSA may promote a prothrombotic state through several interconnected mechanisms, including oxidative stress, endothelial dysfunction, platelet activation, and alterations in coagulation and fibrinolysis pathways. These changes may contribute to an elevated risk of cardiovascular and thrombotic complications in affected individuals.

Methods. We conducted an observational study involving adult patients (≥18 years) diagnosed with untreated moderate-to-severe OSA, defined by an apnea–hypopnea index (AHI) greater than 15 events per hour. Patients were excluded if they had experienced recent cardiovascular events, had known coagulation disorders, active prothrombotic conditions, or were receiving anticoagulant therapy. For each participant, demographic and clinical characteristics, including body mass index (BMI), were collected. Both routine coagulation tests and more specific hemostatic markers were assessed through blood sampling. Participants were prospectively followed for a period of six months to document the occurrence of thrombotic events. The study group consisted of 41 patients with OSA, who were compared with 41 healthy controls matched for age and sex.

Results. Standard coagulation parameters, including prothrombin time (PT), international normalized ratio (INR), activated partial thromboplastin time (aPTT), as well as fibrinogen, antithrombin, plasminogen, and plasminogen activator inhibitor-1 (PAI-1), showed no significant differences between OSA patients and controls. In contrast, specific procoagulant factors were significantly elevated in the OSA group, including factor VIII ($P = .011$), factor XI ($P < .001$), and the factor VIIa–antithrombin complex ($P = .009$). No significant differences in these markers were observed between patients with moderate versus severe OSA, and no correlation was found between AHI values and the levels of these coagulation factors. During the six-month follow-up period, 17% of patients experienced thrombotic events. These events were associated with higher baseline levels of the identified procoagulant factors.

Conclusions. Moderate-to-severe OSA is associated with a selective increase in specific procoagulant factors, despite largely normal findings in routine coagulation tests. This pattern suggests the presence of a hypercoagulable state that may contribute to an increased risk of thrombotic events. Notably, these hemostatic alterations appear to be independent of OSA severity, indicating that prothrombotic mechanisms are already active even in moderate forms of the disease.



DISCREPANCY IN FACTOR VIII LEVELS AMONG HEMOPHILIA A CARRIERS: ONE-STAGE *VS.* CHROMOGENIC ASSAY

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Background. Hemophilia A (HA) is an X-linked bleeding disorder caused by mutations in the F8 gene. While clinical focus is often on affected males, obligate and symptomatic carriers frequently exhibit reduced Factor VIII (FVIII) activity due to lyonization (X-chromosome inactivation). A significant diagnostic challenge has emerged regarding the "assay discrepancy," where FVIII:C values differ significantly between the One-Stage Clotting Assay (OSA) and the Chromogenic Substrate Assay (CSA). This study investigates the prevalence of this discrepancy in HA carriers and its implications for clinical risk stratification.

Methods. A comparative analysis was performed on a cohort of 16 confirmed F8 mutation carriers. FVIII activity was measured using both OSA (based on the activated partial thromboplastin time - aPTT) and CSA (measuring the rate of Factor Xa generation). Discrepancy was defined as a ratio of CSA/OSA < 0.6 or > 1.6. Genetic sequencing was integrated to correlate specific missense mutations with the observed biochemical phenotypes.

Results. The results demonstrate that 50% of HA carriers manifest a significant discrepancy between the two assays (Table 1). Analysis of FVIII activity levels revealed a unidirectional discrepancy, characterized exclusively by One-Stage Assay (OSA) values significantly exceeding Chromogenic Substrate Assay (CSA) results (OSA > CSA). No instances of the inverse relationship (CSA > OSA) were observed. This systematic overestimation by the OSA potentially obscures diminished biological clotting activity, posing a significant diagnostic risk. Patients harboring a mild bleeding phenotype may be inaccurately classified as having "hemostatically secure" FVIII levels by traditional clotting assays, despite manifesting a functional deficiency in chromogenic quantification. These findings indicate that OSA-only protocols are insufficient for detecting sub-optimal FVIII function in carriers of "discrepancy-prone" mutations. In such cohorts, clinical bleeding scores (ISTH-BAT) often correlate poorly with OSA-derived FVIII levels. Consequently, the CSA appears to more accurately reflect in vivo hemostatic capacity and the stability of the tenase complex.

Conclusions. Relying exclusively on the One-Stage Assay limits the scope of a comprehensive assessment for Hemophilia A carriers, as this methodology may not fully capture the complexities of an individual’s hemostatic profile. The discrepancy between the OSA and the Chromogenic Substrate Assay (CSA) is a tangible biological phenomenon rooted in the molecular stability of Factor VIII and the kinetic integrity of the tenase complex. Consequently, a dual-testing approach is essential for ensuring clinical safety, particularly for symptomatic carriers or those undergoing surgical procedures. This integrated strategy provides a more reliable foundation for personalized prophylactic or on-demand treatment plans, ensuring that clinical decisions are based on the most accurate reflection of in vivo clotting activity.



LONG-TERM HEADACHE IMPROVEMENT WITH VITAMIN K ANTAGONISTS IN PRIMARY AND SECONDARY ANTIPHOSPHOLIPID SYNDROME: 2-YEAR OBSERVATIONAL COHORT

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Background and aims. Headache is a frequent and often disabling manifestation in patients with antiphospholipid syndrome (APS) and in individuals positive for antiphospholipid antibodies (aPL). While previous reports have suggested a potential benefit of anticoagulation on headache symptoms, available evidence remains limited, heterogeneous, and largely retrospective. This study aimed to evaluate the long-term effect of vitamin K antagonists (VKA) on headache outcomes in a well-characterized APS cohort over a 24-month follow-up.

Methods. We conducted a prospective observational cohort study including 26 patients fulfilling ACR/EULAR classification criteria for APS, all presenting with chronic or recurrent headache prior to anticoagulation. Patients received long-term warfarin with therapeutic INR targets. The cohort included predominantly thrombotic APS phenotypes (23 venous events, 3 ischemic strokes), with 18 primary APS and 6 APS secondary to systemic lupus erythematosus. No additional headache-specific treatments were introduced during follow-up. Headache severity and impact were systematically assessed at baseline, 12, and 24 months using validated tools (Numeric Rating Scale [NRS], HIT-6, and MIDAS). Outcomes were categorized as complete resolution, major improvement (≥50% reduction in pain), or no improvement.

Results. At 12 months, complete headache resolution was observed in 8 (30.8%) patients. This proportion increased to 13 patients (50%) at 24 months, with an additional 10 patients (38%) experiencing major improvement. Overall, 88% of patients demonstrated clinically meaningful benefit after two years of VKA therapy. Warfarin was well tolerated, with no unexpected safety concerns. Sustained improvement was observed across both primary and secondary APS subgroups.

Conclusions. This study provides the first longitudinal evidence supporting a significant and sustained improvement of headache symptoms in APS patients treated with vitamin K antagonists. The findings reinforce the hypothesis of a pathogenic link between aPL-related mechanisms and headache, and highlight anticoagulation as a potential therapeutic strategy in selected patients. These results warrant confirmation in controlled prospective trials to better define indications and optimize management strategies.

ABSTRACT N. PO062

AN AUTOMATED LABORATORY ALERT ALGORITHM FOR EARLY IDENTIFICATION OF THROMBOTIC THROMBOCYTOPENIC PURPURA IN THE EMERGENCY SETTING

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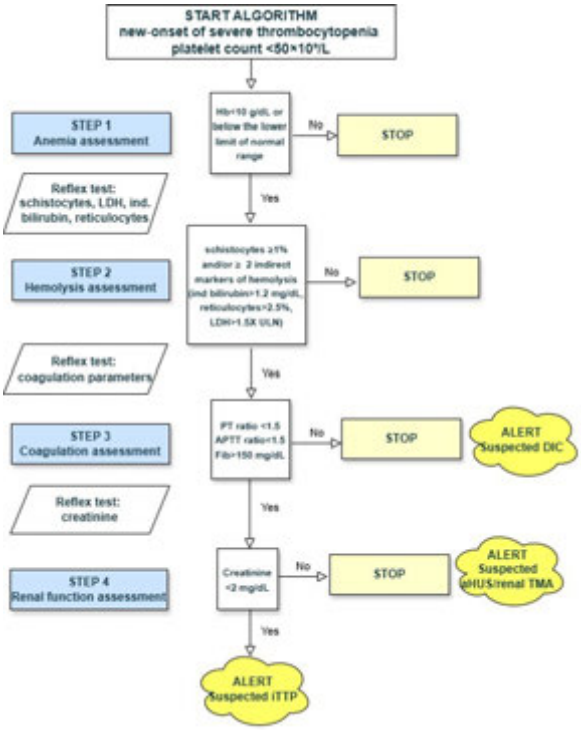
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Background and Aims. Immune thrombotic thrombocytopenic purpura (iTTP) is a life threatening thrombotic microangiopathy requiring rapid recognition and treatment. Clinical presentation is often heterogeneous, and diagnostic delays worsen outcomes. Severe thrombocytopenia and microangiopathic hemolytic anemia (MAHA) are constant laboratory features. No fully automated alert systems for iTTP are currently implemented in emergency practice. We proposed and designed an automated, stepwise laboratory algorithm to support early identification of suspected iTTP.

Methods. We conceptualized a cascade algorithm based on routine emergency tests. Triggered by new onset severe thrombocytopenia (platelet count <50×10⁹/L), the algorithm sequentially evaluates anemia, hemolysis, coagulation and renal function, following the decision pathway illustrated in the accompanying figure. Each step determines whether the process continues or stops, generating specific alerts for suspected iTTP, suspected DIC, or suspected aHUS / renal TMA. All patients diagnosed with TTP between 2023 and 2025 were retrospectively reviewed to assess the algorithm's ability to identify confirmed cases. In addition, emergency admissions over a two year period were examined to estimate the potential operational impact of algorithm activation.

Results. The algorithm correctly identified 10 of 11 patients with confirmed iTTP. The only missed case presented with severe thrombocytopenia and laboratory signs of hemolysis but without anemia, meaning that the algorithm would not have been activated at all, as the first step was not met. In all other cases, the cascade was triggered by thrombocytopenia and MAHA related abnormalities. In the two year emergency cohort (n=249564 patients), the alert would have been triggered in 0.4% of patients (n=998), all of whom presented with both severe thrombocytopenia and anemia, as required by the algorithm. By automatically activating reflex LDH, indirect bilirubin, reticulocyte and schistocyte testing, the algorithm rapidly provides clinicians with all laboratory parameters required for PLASMIC score assessment. Although PLASMIC also includes clinical variables, the algorithm ensures that the laboratory components are delivered immediately, complete and standardized, markedly accelerating the diagnostic workflow. The retrospective operational analysis confirmed that activation frequency remains low, with a limited impact on overall laboratory workload.

Conclusions. A fully automated, stepwise laboratory algorithm based on routine emergency tests may effectively support early identification of suspected iTTP. The missed non anemic presentation highlights the need to evaluate hemolysis markers even in the absence of anemia and to proceed through the diagnostic pathway when hemolysis is documented. This approach strengthens integration between laboratory and clinical workflows, reduces inappropriate ADAMTS13 testing while ensuring complete PLASMIC score assessment, and may facilitate timely initiation of life saving therapies. Prospective validation in a pilot center and evaluation of its impact on diagnostic timing and clinical outcomes are warranted.





EVALUATION OF PLATELET ACTIVATION MARKERS IN PATIENTS WITH THROMBOTIC THROMBOCYTOPENIC PURPURA

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Background and Aims. Thrombotic Thrombocytopenic Purpura (TTP) is a rare disease characterized by deficiency of ADAMTS13, a metalloprotease involved in the cleavage of high-molecular-weight (HMW) multimers of von Willebrand factor (VWF). This process regulates the interaction between VWF and platelet (PLT) membrane receptors, thereby supporting PLT adhesion to the sub endothelium and aggregation. In the onset and progression of TTP, the interaction between VWF and PLT plays a pivotal role. It is known that PLT glycoproteins (Gp), including GpIbα, GpIIb/IIIa, and GpVI, as well as the contents of alpha and dense granules and the ability of PLT to degranulate, contribute to PLT plug formation. In some conditions, these mechanisms may be overexpressed, leading to the development of thrombotic events. In this study, we aimed to investigate the contribution of PLT to the onset of TTP.

Methods. Six patients with acquired TTP associated with the presence of anti-ADAMTS13 antibodies (Abs) were enrolled at the IRCCS CRO of Aviano. Two patients were evaluated during the disease acute phase, while the others during routine follow-up. The diagnostic work-up included assessment of ADAMTS13 activity, anti-ADAMTS13 Abs, VWF levels, and VWF multimer analysis. PLT activation markers were studied using an indirect method at the IRCCS Humanitas Research Hospital. Briefly, two whole-blood samples from healthy donors (HDs) were treated with 1 µM prostaglandin E1 and centrifuged twice at low speed to obtain a PLT pellet. One PLT sample was resuspended in plasma derived from TTP patients (PLT-TTP), while the other in plasma from HDs (PLT-HD), used as an autologous control. We investigated the expression of PLT GpIbα, GpIIb/IIIa, GpVI, P-selectin, PAC-1, mepacrine, and CD63 at steady state and after activation with the agonists ADP 10µM, collagen 5µg/mL, and TRAP 50µM. We also assessed VWF binding to PLT (VWF-PLT) after stimulation with ristocetin, by flow cytometry. Results were analyzed using descriptive statistics, reporting mean values, SEM, and p-values ($p<0.05$).

Results. Patients with TTP showed low levels of ADAMTS13 activity during the acute phase, with an increase during follow-up. Anti-ADAMTS13 Abs were variable, ranging from 2 to 30 IU. Two patients showed increased HMW multimers, which were associated with ADAMTS13 activity below 50%. PLT-TTP appeared more activated than PLT-HD, showing decreased levels of GpIbα, GpIIb/IIIa, GpVI, and mepacrine (42%vs72%, $p=0.02$) at steady state. In contrast, P-selectin expression was increased in PLT-TTP compared with PLT-HD (30% vs 16%, $p=0.03$). Upon stimulation with agonists, these markers were not further upregulated. VWF-PLT binding was not constitutive but was induced by agonist stimulation. It was higher in PLT-TTP than in PLT-HD, reaching 32.6% vs 15.5% upon stimulation with ristocetin.

Conclusions. Our results suggest that PLT from HDs, when exposed to plasma from TTP patients, undergo downregulation of surface Gps, possibly reflecting the shedding of these receptors, together with increased expression of P-selectin, PAC-1, and CD63. Moreover, the reduced mepacrine signal at steady state suggests that PLT are activated and externalize dense granule contents. Overall, these findings indicate that plasma from TTP patients may enhance the activation state of resting platelets. Further studies are needed to confirm these preliminary results during follow-up and in additional patients with TTP who will be enrolled.



CONGENITAL THROMBOTIC THROMBOCYTOPENIC PURPURA: HOW TO MANAGE? - A CASE FROM REAL WORLD

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Introduction. Congenital thrombotic thrombocytopenic purpura (cTTP) is a rare genetic condition also known as Upshaw-Schulman syndrome with an estimated prevalence of 0.5-2.5 cases per million. It is an autosomal recessive disorder caused by pathogenic homozygous or compound heterozygous mutations in the ADAMTS13 gene that result in ADAMTS13 activity <10%. Since its proven safety and efficacy, recombinant ADAMTS13 (rADAMTS13) is functional to treat acute episodes or prophylaxis in cTTP which can be triggered by infections, trauma, pregnancy and major surgery. In this regard, the aim of this paper is to discuss pre and postoperative management of patients with cTTP, throughout monitoring hemolysis indices and administer prophylaxis with rADAMTS13.

Case report. In this paper we discuss the case of a 46 year old female who presented at our center in March 2026 in anticipation of elective surgery of left hemicolectomy and hepatic excision of suspected sigma cancer metastasis. From childhood she suffered from cyclic thrombocytopenia with jaundice, treated by plasma transfusion. In 2016, because of multiple uterine fibroids, she underwent transverse laparotomic uterine myomectomy complicated by massive hemorrhage due to severe thrombocytopenia which required intensive care. Subsequently several episodes of thrombocytopenia non responding to steroids had followed and in 2017 Coombs-negative hemolytic anemia occurred in addition to severe thrombocytopenia, treated with steroids and plasmapheresis, until complete resolution. Diagnostic workup revealed a severe deficiency of ADAMTS13 activity in absence of specific anti-ADAMTS13 antibodies. Therefore she underwent a molecular test resulting in the presence of homozygous biallelic mutation c.4078-2A>G in the ADAMTS13 gene that confirmed cTTP diagnosis. From April 2019 she started prophylaxis with fresh-frozen plasma (FFP) once per month with increased level of platelets and from September 2025 she started treatment with rADAMTS13 at a prophylactic dose of 40 UI/kg body weight (corresponding to 2 vials each one containing 1500 UI) every two weeks without any disease recurrence. As a precautionary measure, one vial of medicine was administered the day before the surgery. Fortunately the surgery was performed without any complications, though we recommended keeping sufficient supplies of rADAMTS13 and FFP to deal with a possible relapse of cTTP. From the day of the surgery the patient was tested for blood count, hemolysis indices and ADAMTS13 activity, every day during the hospitalization and twice per week for the first month after the surgery. According to international guidelines, we decided to perform a vial of rADAMTS13 when ADAMTS13 activity was < 10%. It resulted in an administration of rADAMTS13 every two days for the first week after surgery and one administration per week for the first month after surgery.

Conclusions. cTTP is a very rare genetic condition: scientific literature does not set an optimal level of pre and postoperative ADAMTS13 activity, in fact clinical monitoring and therapeutic management are left up to physician's personal experience. This case report evidences that rADAMTS13 is safe and improves the patient's QoL, especially while undergoing surgery. So if available we suggest intensifying rADAMTS prophylaxis (possibly weekly) and a close monitoring of ADAMTS13 levels which can be lower during the postoperative period.

ABSTRACT N. PO065

PSEUDO-THROMBOTIC THROMBOCYTOPENIC PURPURA DUE TO VITAMIN B12: A SYSTEMATIC REVIEW

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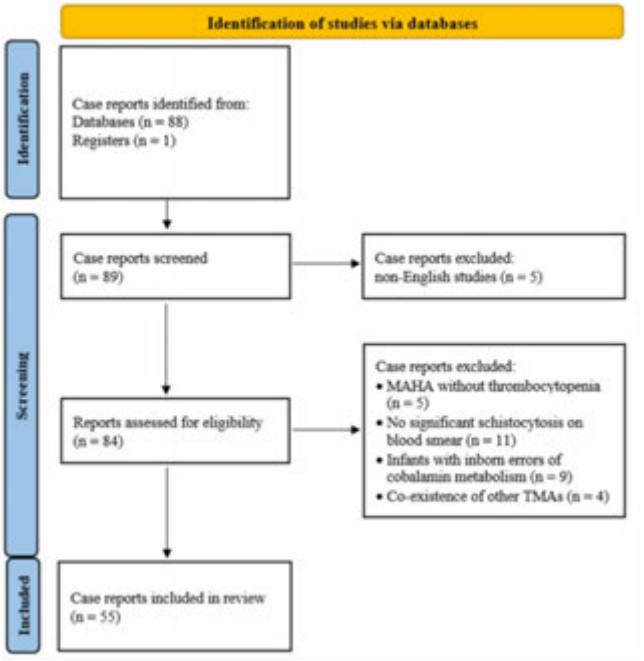
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Background and aims. Vitamin B12 deficiency is known as a "great imitator" of many blood disorders, including thrombotic thrombocytopenic purpura (TTP). This similarity may lead to unnecessary TTP-specific treatments, with inappropriate costs and risks. The clinical features of pseudo-TTP due to vitamin B12 deficiency have mainly been described in case reports and a comprehensive understanding of its overall characteristics remains limited so far. The aim of this study was to evaluate the clinical and laboratory characteristics of patients with pseudo-TTP due to vitamin B12 deficiency.

Methods. Prompted by a case of pseudo-TTP identified at our Institute, we conducted a systematic review of the medical literature following the PRISMA statement. Specifically, we searched PubMed and Scopus from 1977 to 2025, using various keywords related to vitamin B12 deficiency and pseudo-TTP combined with Boolean operators. Finally, 55 cases remained eligible for the analysis (Figure 1).

Results. The study cohort comprised 30 males and 25 females with a mean age of 54±18 years. The most common presenting symptoms were non-specific fatigue and/or dyspnoea (n=44). Neurological symptoms were reported by 12 individuals, including altered mental status, paraesthesia, and gait instability. Bleeding was reported by 11 individuals, predominantly cutaneous (n=7). All the patients had thrombocytopenia and anaemia with altered haemolytic biomarkers and schistocytosis. Thrombocytopenia was mild-to-moderate (mean platelet count: 66,300±30,060/mcL; only 6 patients <30,000/mcL), while anaemia was severe (mean haemoglobin: 5.30±1.54 g/dL) with an unexpected low absolute reticulocyte count (46,200±40,980/mcL; only 3 patients >100,000/mcL). White blood cell counts were slightly low (4,812±2,693/mcL). Mean corpuscular volume (MCV) was substantially elevated (mean MCV: 110±15 fL; only 3 patients <90 fL). The PLASMIC score, when calculable, tended to be high, thus not helping to differentiate pseudo-TTP from real TTP. Many patients awaiting ADAMTS13 activity results, which ultimately ruled out TTP diagnosis, were initially treated with therapies for acquired TTP: plasma exchange (n=24), high-dose corticosteroids (n=16), and caplacizumab (n=3).

Conclusions. Vitamin B12 deficiency should be included in the differential diagnosis of TTP. In suspected conditions of thrombotic microangiopathy where platelet count is not too low, anaemia is marked with macrocytosis, and reticulocytosis is poor or absent, clinicians should raise consideration for vitamin B12 deficiency.



ABSTRACT N. PO066

ONE IN TWO MILLION: A 'DOUBLE-HIT' CASE OF INFRARENAL VENA CAVA AGENESIS AND TRIPLE-POSITIVE ANTIPHOSPHOLIPID SYNDROME

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Background. Inferior vena cava (IVC) agenesis is a rare congenital vascular anomaly, with an estimated prevalence of 0.0005%–1% in the general population. Although frequently asymptomatic, it leads to extensive collateral circulation to compensate for impaired venous return. This chronic blood stasis is a critical anatomical risk factor for deep vein thrombosis (DVT), accounting for up to 5% of idiopathic events in young adults. Antiphospholipid Syndrome (APS) is a systemic autoimmune disease characterized by persistent antiphospholipid antibodies (aPL) associated with thrombosis; its prevalence is estimated at 40-50 cases per 100,000 persons with annual incidence of 1-2 cases per 100,000. Within this spectrum, the even rarer triple-positive phenotype (LAC, anti-cardiolipin, and anti-β2-glycoprotein I) stands out as a potent biochemical driver of thrombosis, carrying the highest risk for recurrence.

Case report. A 33 years old male presented with a massive first DVT involving bilateral femoral veins and the left iliac and popliteal veins. Initial management was challenging; the patient exhibited poor response to therapeutic low--molecular-weight heparin. Clinical stabilization was achieved only after initiating Vitamin K Antagonists (VKA) within the therapeutic INR range (2.0–3.0). Despite optimal treatment, complete recanalization was never achieved. After three years of stable anticoagulation, the patient self-discontinued VKA and suffered a symptomatic recurrence within 24 hours: a superficial vein thrombosis of the right great saphenous vein extending to the saphenofemoral junction. Thrombophilic screening confirmed a high-risk triple--positive APS profile. Simultaneously, a vascular study documented an extensive compensatory network with anomalous anastomoses (apparently arterial-venous). Subsequent abdominal contrast-enhanced CT provided the definitive anatomical explanation: agenesis of the infrarenal IVC and common iliac veins, with prominent collateral circulation involving the superficial system, hypogastric veins, pelvic varicocele, and presacral drainage. Lifelong anticoagulation was indicated. In 2015, the patient was enrolled in the TRAPS study and randomized to the warfarin arm. He has since been maintained on VKA therapy, supplemented by hydroxychloroquine and low-dose aspirin following episodes of amaurosis fugax and the incidental finding of an IgM-kappa monoclonal gammopathy of undetermined significance. Currently, 17 years after the first episode, the patient remains in good clinical standing with good adherence (Time in Therapeutic Range: 90%).

Conclusions. The simultaneous occurrence of infrarenal IVC agenesis and triple-positive APS is an exceptionally rare "double-hit" model of venous thrombosis, estimated to affect fewer than one in two million individuals. This case highlights how a permanent anatomical anomaly inducing chronic stasis can act as a critical trigger in the presence of a potent autoimmune prothrombotic state. The immediate recurrence upon VKA withdrawal underscores the extreme hypercoagulability of this phenotype, which requires an extended multidisciplinary approach to ensure long-term clinical stability.

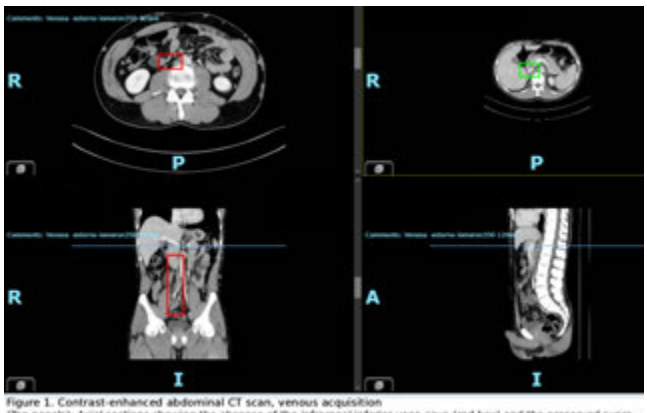


Figure 1. Contrast-enhanced abdominal CT scan, venous acquisition
(Top panels): Axial sections showing the absence of the infrarenal inferior vena cava (red box) and the preserved suprarenal segment of the IVC (green box).
(Bottom panels): Coronal and sagittal reconstructions showing the absence of the infrarenal inferior vena cava (red box)..

ABSTRACT N. PO067

LONG-TERM SAFETY AND EFFECTIVENESS OF VITAMIN K ANTAGONISTS IN PATIENTS WITH ANTIPHOSPHOLIPID ANTIBODIES: A RETROSPECTIVE COHORT ANALYSIS

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Background and Aims. antiphospholipid antibodies significantly increase the risk of thrombotic events, often necessitating prolonged anticoagulation. Although vitamin K antagonists (VKAs) remain the standard of care, their long-term management in this population continues to raise questions regarding safety and therapeutic stability. This study evaluated the course of VKA therapy in patients followed at the Hemostasis and Thrombosis Service of Reggio Calabria, with particular attention to hemorrhagic and thrombotic complications.

Methods. we retrospectively analyzed 67 patients (29 males, 38 females; mean age 58.1 years, range 29–87) receiving VKA therapy (Warfarin n=66, Acenocoumarol n=1). All were treated due to antiphospholipid antibody positivity and associated clinical conditions: 50 had venous thrombosis, 15 arterial thrombosis, and 2 were treated for non-thrombotic disorders. Twenty-seven patients had concomitant autoimmune diseases, and eight had genetic thrombophilia (4 were heterozygous for the prothrombin G20210A mutation and 4 were heterozygous for Factor V Leiden). Clinical characteristics are summarized in Table 1. The mean follow-up duration was 2,744.9 days (range 155–10,882). The mean Time in Therapeutic Range (TTR) during the last six months was 68% (range 27–100%).

Results. a total of 10 complications occurred in 9 of 67 patients (13.4%): 3 thrombotic events (4.5%) (1 superficial and 2 deep vein thrombosis) and 7 hemorrhagic events (10.4%) (2 nosebleeds, 2 metrorrhagias, 1 muscle hematoma, and 1 hemoperitoneum). One patient experienced both event types. The annual incidence rate was 2 complications per 100 patient-years. All events resolved without permanent sequelae; only one case (hemoperitoneum) required hospitalization. Temporary discontinuation of VKA therapy occurred in 7 of 10 events. No fatal outcomes were recorded.

Conclusions. the low annual complication rate, together with a mean TTR exceeding 66%, underscores the safety and effectiveness of VKA therapy when managed by specialized anticoagulation centers. Until direct oral anticoagulants with proven efficacy and safety in antiphospholipid-positive patients become available, VKAs remain a reliable and well-established option for the treatment and prevention of thromboembolism. We also observed that venous thrombosis was more than three times as frequent as arterial thrombosis, supporting routine screening for antiphospholipid antibodies in patients with otherwise unexplained venous thrombotic events.

Table 1: Associated clinical conditions of patients with antiphospholipid antibody positivity

Vein Thrombosis	Patients No.	Arterial Thrombosis	Patients No.
Deep Venous Thrombosis	23	Stroke	9
Pulmonary Embolism	6	Myocardial infarction	4
Deep Vein Thrombosis with Pulmonary Embolism	9	Peripheral arterial embolism	2
Superficial Vein Thrombosis	8	**Total Arterial Thrombosis**	**15**
Retinal Vein Thrombosis	1		
Mesenteric Venous Thrombosis	2	**Other diagnosis**	**Patients No.**
Cerebral Vein Thrombosis	1	Mechanical valve prosthesis	1
Total Vein Thrombosis	**50**	Valvular heart disease	1



ANTIPHOSPHOLIPID ANTIBODIES IN PATIENTS WITH MULTIPLE SCLEROSIS AND MS-LIKE DISEASES: MS OR APS?

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Background. The APS is characterized by arterial and venous thrombosis, recurrent fetal loss, thrombocytopenia, and the presence of anti-phospholipid antibodies (aPL). Currently available commercial tests for aPL include assays for lupus anticoagulants, anti-cardiolipin antibodies, and anti-B2-glycoprotein-1 antibodies. The association between aPL and vascular events is well established. The broad spectrum of neurological manifestations related to aPL includes transient ischemic attack, migraine, recurrent stroke, and multi-infarct states. In addition to these cerebrovascular events, both transverse myelitis and multiple sclerosis-like (MSL) illnesses have been described in APS. Although the pathophysiology is not clear, vascular events such as small strokes in white matter may produce lesions that resemble the demyelinating plaques seen in multiple sclerosis (MS).

Aims. To describe the frequency, clinical, and laboratory features of patients diagnosed with MS or MSL in a large, prospectively followed cohort of aPL positive patients.

Methods. Between 1990 and 1995, patients referred to our Hemostasis Centre (AORN Moscati, AV, Italy) were prospectively evaluated for aPL using questionnaires designed to detect aPL- related symptoms and/or a family history of aPL-related illnesses. Magnetic resonance imaging (MRI) was performed when significant neurological features were present. A subgroup of all patients diagnosed with MS or MSL was identified, and their clinical, laboratory, and imaging findings were reviewed.

Results. Of 322 patients evaluated for aPL-related symptoms or events, 189 (59%) were positive for at least one class of aPL. 26 of 322 patients (8%) had a diagnosis of MS or MSL, either at the initial evaluation or during the study period. 23 of the 26 individuals (88%) tested positive for aPL, while the remaining 3 (12%) tested repeatedly negative. 18 of the 23 patients (78%) had either more than one class of aPL or multiple positive titres. IgM aCL was found in 18 of the 23 patients (78%). Oligoclonal bands were present in 5 patients. Antinuclear antibodies and low complement levels were frequently observed. Blinded MRI readings showed lesions consistent with MS in most cases. Clinically, 7 patients had transverse myelitis, and optic neuritis was present in 8 patients.

Conclusions. A substantial number of aPL-positive patients have a concurrent diagnosis of MS or MSL, frequently presenting with elevated IgM aCL, optic neuritis, and transverse myelitis. APS should be strongly considered as an alternative diagnosis to MS in these patients.



ABSTRACT N. PO069

PERIOPERATIVE CHALLENGES IN ACQUIRED THROMBOTIC THROMBOCYTOPENIC PURPURA DURING CAPLACIZUMAB TREATMENT

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Background. Acquired Thrombotic Thrombocytopenic Purpura (aTTP) is a life-threatening thrombotic microangiopathy caused by autoantibodies to a disintegrin and metallopeptidase with thrombospondin type 1 motif 13 (ADAMTS13), the specific von Willebrand Factor (VWF) cleaving protease. Treatment consists of daily plasma exchange (PEX), Caplacizumab (Capla) and immunosuppressive therapy (steroids +/- rituximab). Capla shortens time to normalization of platelet count and reduces recurrences but increases bleeding risk. VWF activity may be useful to estimate in vivo Capla effect. The management of bleeding during Capla involves discontinuation of the drug and, if necessary, FVIII/VWF concentrate administration. In case of invasive procedure, a 7-days suspension is recommended; in emergency setting, FVIII/VWF concentrate may be considered to correct hemostasis.

Case report. This is a case of a 68 years-old male with relapsing aTTP, presented to the emergency department on March 25 for dark urine and ecchymoses after an infectious episode. His blood test showed severe thrombocytopenia (9.000/ul), undetectable haptoglobin, elevated lactate dehydrogenase and indirect bilirubin. Undetectable ADAMTS13 activity (<0.2%) confirmed aTTP relapse and standard treatment was immediately started (prednisone 1mg/kg/day, daily PEX, Capla 10mg before and after first PEX and 10mg/day from day 1). Given the relapse, rituximab 375mg/sm/week x4 was started on day +4. The therapy led to a rapid normalization of platelet count and hemolysis markers. PEX was discontinued on day +3 (4 sessions in total). The patient was discharged on day +6, with ADAMTS13 activity still undetectable (<0.2%), continuing Capla and prednisone at home. On day +11 (II rituximab) hematologic response was confirmed with low ADAMTS13 activity (0.4%), Capla was continued and III rituximab was scheduled for day +18. On day +15, the patient presented to the emergency department for acute renal colic. Urology consultant confirmed indication for surgical intervention given the size of ureteral stone. Following a multidisciplinary discussion, it was decided to proceed with ureteral stenting, postponing surgery until ADAMTS13 recovery. As the procedure was urgent, it was decided to proceed by administering antihemorrhagic prophylaxis with FVIII/VWF concentrate (Fanhdi). ADAMTS13 activity and VWF activity were 18% and 30% respectively; Fanhdi 25 IU/kg was administered before surgery without bleeding complications. Given the excellent trend in ADAMTS13 activity, Capla was not resumed to reduce post-procedural bleeding risk. ADAMTS13 activity was reassessed on day +19, confirming a complete response (40%) and the definitive Capla discontinuation. Rituximab was performed on day +18 and +25. Definitive surgical treatment was performed in June 2025.

Conclusions. This case provides several insights for optimizing Capla therapy in complex settings: first, FVIII/VWF concentrate proved to be safe and effective in preventing perioperative bleeding during Capla; second, VWF activity may be useful in guiding decisions regarding the dose of FVIII/VWF concentrate to be administered; third, early use of rituximab enabled a rapid increase in ADAMTS13 activity, allowing for early discontinuation of Capla and further reducing the risk of postoperative bleeding. In conclusion, the support of a laboratory capable of rapidly providing reliable tests is essential to optimize the management of these complex scenarios.



INFECTIVE ENDOCARDITIS AND ISCHEMIC CEREBRAL EVENTS IN A PATIENT WITH SYSTEMIC LUPUS ERYTHEMATOSUS AND TRIPLE ANTIPHOSPHOLIPID POSITIVITY: THE ROLE OF ANTICOAGULATION IN PRIMARY PREVENTION

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Background. The management of thrombotic risk in patients with triple positivity for antiphospholipid antibodies in the absence of clinical events remains controversial, particularly in the setting of systemic lupus erythematosus (SLE). The role of anticoagulation for primary prevention is not clearly established, especially in complex clinical scenarios such as infective endocarditis.

Case Report. A 29-year-old woman (52 kg) with a history of SLE and persistently high-titer triple-positive antiphospholipid antibodies, with no prior thrombotic events, was receiving mycophenolate mofetil and low-dose aspirin. She was admitted for infective endocarditis due to methicillin-sensitive Staphylococcus aureus involving the aortic valve. The condition was complicated by multiple ischemic cerebral events affecting the temporo-parietal and right fronto-parietal regions, resulting in right-sided facio-brachio-crural hemiplegia, without evidence of hemorrhagic transformation. Concurrently, septic dissemination to the liver, spleen, and osteo-articular system was documented. Lower limb Doppler ultrasound was negative for thrombosis. The patient underwent mechanical thrombectomy of the right middle cerebral artery, followed by surgical aortic valve replacement with a mechanical prosthesis. She was treated with cefazolin for six weeks. During the perioperative period, immunosuppressive therapy was discontinued, and anticoagulation was initiated with low-molecular-weight heparin, later transitioned to warfarin. Laboratory findings showed mild neutrophilic leukocytosis, normochromic anemia, and persistent high-titer antiphospholipid antibody positivity. The clinical picture was consistent with septic embolization secondary to infective endocarditis rather than a primary thrombotic event related to antiphospholipid syndrome. Although triple positivity represents a high thrombotic risk factor, in the absence of prior thrombotic events it does not constitute a well-established indication for anticoagulation according to current EULAR recommendations. Moreover, anticoagulation does not prevent septic embolic complications and may increase the risk of bleeding during the acute phase. While a concomitant thrombotic component could not be entirely excluded, the predominant mechanism underlying the clinical presentation appears to be infectious and embolic.

Conclusions. This case highlights the need for individualized assessment of both thrombotic and hemorrhagic risk in complex clinical scenarios. It also raises a critical question: could primary thromboprophylaxis with anticoagulants have prevented such severe and disabling events in this patient?



WHEN SJÖGREN'S DISEASE MIMICS TTP

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Introduction. Sjögren's disease is a systemic autoimmune disorder primarily affecting salivary and lacrimal glands, leading to hypofunction. It may occur as a primary condition or in association with other autoimmune diseases, including systemic lupus erythematosus (15%), rheumatoid arthritis (20%), and systemic sclerosis (30%). Key biomarkers include anti-SSA/Ro (most specific), anti-SSB/La, ANA, and rheumatoid factor. Diagnosis relies on a weighted score incorporating symptoms, serology, glandular involvement, Schirmer's test, and salivary flow (1). Although xerophthalmia and xerostomia are common, the disease may involve multiple organs, with complication such as interstitial lung disease and lymphoma, impacting prognosis. Treatment is mainly symptomatic, with immunosuppressive therapy reserved for systemic involvement. Hematologic abnormalities, including cytopenias, may occur and rarely mimic thrombotic thrombocytopenic purpura (TTP), posing diagnostic challenges.

Case Report. A 52-year-old man from Ivory Coast was referred to our Internal Medicine Unit with suspected TTP for therapeutic plasma exchange (PEX). He had presented to another Emergency Department with worsening performance status, hypotension, diffuse xerosis, severe thrombocytopenia (14,000/mm^3), and hemolytic anemia (Hb 6.9 g/dL, LDH 430 U/L), without schistocytes and with normal renal function. Neurological evaluation and brain CT were normal. Based on a PLASMIC score of 7 and reduced ADAMTS13 activity (7%) measured at the referring hospital, corticosteroids and caplacizumab were started. On admission, no neurological, cardiac, or renal involvement was detected. PEX was initiated. However, after two sessions, platelet count remained ~12,000/mm^3 and ADAMTS13 activity normalized (45%), leading to discontinuation of TTP-directed therapy. Repeat testing confirmed ADAMTS13 >40%, with persistent absence of schistocytes and normal haptoglobin. Further workup showed positive direct Coombs test (IgG), ANA 1:640, and high anti-SSA/SSB titers, consistent with Sjögren's disease. Intravenous immunoglobulins (2 g/kg over five days) led to progressive improvement, with platelets >50,000/mm^3 and hemoglobin recovery after transfusion. Despite a negative Schirmer's test, systemic involvement was documented, including submandibular gland edema on CT, diffuse lymphadenopathy, and interstitial lung disease (possible NSIP/UIP pattern) with reduced DLCO (28%). Bone marrow biopsy and and PET imaging excluded lymphoproliferative disease. After cutaneous and hematological improvement (Hb 9.7 g/dL, platelets 125,000/mm^3) he was discharged on tapering prednisone with multidisciplinary follow-up.

Discussion and Conclusions. This case highlights Sjögren's disease presenting with severe hematologic involvement mimicking TTP. Initial findings (thrombocytopenia, hemolytic anemia, reduced ADAMTS13) supported TTP, but normalization of ADAMTS13 without platelet response argued against it. Autoimmune cytopenias, though uncommon in Sjögren's disease, include hemolytic anemia and immune thrombocytopenia (2). Differentiation from thrombotic microangiopathies is essential, as management differs. In this case, response to immunoglobulins supported an autoimmune mechanism. Transient ADAMTS13 reduction may be nonspecific. Integration of clinical evolution and treatment response is crucial to avoid misdiagnosis and inappropriate therapy. 1. Ramos-Casals M, EULAR, Ann Rheum Dis. 2020
2. Liu C, Front Immunol. 2026



DIAGNOSTIC CHALLENGES IN THROMBOTIC MICROANGIOPATHY: A CASE OF ATYPICAL HEMOLYTIC UREMIC SYNDROME

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Background. Atypical hemolytic uremic syndrome (aHUS), also known as complement-mediated HUS, is a form of thrombotic microangiopathy characterized by microangiopathic hemolysis, thrombocytopenia, and acute kidney injury (AKI). When central nervous system (CNS) manifestations occur, it is crucial to establish a differential diagnosis with thrombotic thrombocytopenic purpura (TTP) and typical HUS. We hereby present an illustrative case of aHUS, and the diagnostic workup.

Case Report. A 62-year-old Caucasian man was admitted to the Intensive Care Unit (ICU) with rapidly progressive neurological deterioration and coma. The patient was previously admitted to an Internal Medicine Unit for urinary tract infection; his hospital stay was complicated by an episode of C. difficile infection, and central venous catether-associated thrombosis of the right iliac and left jugular veins. During ICU stay, the patient developed anemia and thrombocytopenia; a spontaneous bleeding in the right kidney occurred, which required embolization, as well as multiple blood and plasma transfusions. Thrombophilia and antiphospholipid antibodies testing were negative. Following cognitive deterioration, a brain MRI was performed, showing no recent ischemic lesions but revealing *symmetric T2 hyperintensity in the anteromedial thalami, mammillary bodies, mesencephalic tegmentum, and posterior columns of the medulla*, findings suggestive of thiamine deficiency encephalopathy, for which pharmacological treatment was initiated. The patient was then transferred to our Unit with persistent thrombocytopenia (platelets 5,000/mm^3) and Coombs-negative microangiopathic hemolytic anemia, consistent with thrombotic microangiopathy (PLASMIC score 5; French score 1). A whole-body CT scan ruled out malignancies; anti-PF4/heparin antibodies were negative, while ADAMTS13 activity was not severely reduced (21%), making TTP less likely. Further testing showed only isolated C3 consumption, in the absence of other microbiological or molecular findings. Given the initial TTP suspicion, the patient underwent plasma exchange, along with supportive care and transfusions as needed. The patient underwent dialysis due to worsening renal function; later, he developed COVID-19 and died due to septic complications.

Conclusions. The clinical overlap between HUS and TTP represents a diagnostic challenge in thrombotic microangiopathy. Microangiopathic hemolytic anemia, thrombocytopenia, AKI and acute CNS involvement are cardinal features of both conditions, yet none is pathognomonic. Although CNS involvement is more frequently observed in TTP, it has been reported in approximately 11% of aHUS cases. In these patients, CNS involvement is the leading cause of death, and most commonly affects the basal ganglia, although other brain regions can also be involved. Imaging findings may include cytotoxic, vasogenic, or mixed edema, sometimes associated with ischemic and/or hemorrhagic lesions, resulting in non-specific pattern. For a timely differential diagnosis, early blood sampling for microbiological (including stool cultures), serological, molecular, and immunological investigations (including ADAMTS13 activity) are essential. The timing of these investigations is crucial, as delayed testing may compromise interpretability, particularly if performed after the initiation of transfusion therapy. Their results play a decisive role in guiding therapeutic decisions and may significantly influence patient outcomes.



ANALYTICAL VARIABILITY IN FIBRINOGEN TESTING REVEALING FIBRINOGEN LONGMONT: A CASE REPORT

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Background. Fibrinogen plays a central role in coagulation, as it is cleaved by thrombin into fibrin, which then assembles into a stable clot through sequential steps of protofibril formation and lateral aggregation. Congenital dysfibrinogenemia is a qualitative fibrinogen disorder caused by structural abnormalities that impair coagulation, with variable clinical presentation. Diagnosis can be challenging due to potential discrepancies between assays, and management depends on the clinical phenotype. Fibrinogen Longmont is a rare congenital dysfibrinogenemia caused by a heterozygous mutation in the Bβ chain (Arg166Cys), leading to the production of structurally abnormal fibrinogen molecules linked by aberrant disulfide bonds. It is typically characterized by a discrepancy between antigenic fibrinogen levels, which may be normal, and reduced functional activity. While early fibrin formation is relatively preserved, defective lateral aggregation impairs clot structure. This variant is associated with heterogeneous clinical and laboratory findings and may be challenging to diagnose due to inconsistencies across coagulation assays.

Case report. We report the case of an adult male was referred for hematological evaluation for isolated thrombocytopenia in the setting of liver disease, with concomitantly reduced antithrombin activity. Routine coagulation tests were within normal limits, whereas Clauss fibrinogen levels were unmeasurable using a bovine thrombin reagent on an optical analyzer. In contrast, Clauss fibrinogen activity was within the normal range when measured with a human thrombin-based reagent on the electromechanical platform, while antigenic fibrinogen levels assessed by an immunoturbidimetric assay on the analyzer were also normal. These findings highlighted marked assay-dependent variability. Given the unusual discrepancy, further investigation was undertaken, raising suspicion of a congenital fibrinogen variant consistent with fibrinogen Longmont, a condition previously associated with differences between analytical methods and thrombin sources. Indeed, DNA sequencing of exon 4 of the FGB gene confirmed that the patient was heterozygous for fibrinogen Longmont, carrying a point mutation identified as FGB NM_000514.4: c.586C>T (p.Arg196Cys).

Conclusions. Fibrinogen Longmont is associated with impaired fibrin polymerization due to defective lateral aggregation, leading to the formation of a translucent clot. In our case, the discrepant fibrinogen results appear to be primarily related to differences in clot detection methods (optical versus electromechanical). The case underscores the importance of employing multiple testing approaches when fibrinogen results are incongruent. This observation highlights the impact of analytical methodology on assay performance and interpretation and supports the added value of molecular analysis, which can be crucial for establishing a definitive diagnosis when functional assays yield inconclusive or unmeasurable results.



DEVELOPMENT OF INNOVATIVE LONG-ACTING FACTOR IX AND FACTOR X VARIANTS VIA CONDITIONAL ALBUMIN FUSION

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Background and Aims. The management of Hemophilia A and B requires therapeutics that combine high hemostatic efficacy with reduced dosing frequency. While extending the half-life of clotting factors is a primary goal, fusion with high molecular weight partners often impairs biological activity. We describe the development of novel fusion proteins for Factor IX (FIX) and an engineered Factor X (FX) variant designed for bypassing activity. This work compares traditional full length QMP-albumin fusions with an innovative approach integrating minimized albumin domains into FIX and FX at strategic activation-sensitive sites. This conditional release mechanism aims to balance long-acting potential with uncompromised efficacy.

Methods. Five novel chimeric proteins were expressed in HEK293 cells: 1) Full length fusions comprising two for engineered bypassing FX variant and one for FIX-Padua variant fused with full-length QMP-albumin; 2) Minimized domain chimeras (one FIX-Padua and one bypassing FX) featuring albumin domains at activation-sensitive sites. Functional characterization included aPTT in FVIII and FIX-deficient plasmas and PT assays in FX-deficient plasma. Western Blot to characterize the proteolytic cleavage of the albumin domains. To predict half-life extension, FcRn binding affinity was evaluated via ELISA and Surface Plasmon Resonance (SPR) to determine kinetic constants.

Results. Preliminary data confirm the functional efficacy of all constructs. The engineered FX variants (full-length and minimized) demonstrated bypassing activity, significantly shortening aPTT in FVIII-deficient plasma compared to wild type controls. PT assays confirmed that albumin domain integration or full-length fusion did not impair native extrinsic FX activation. FIX variants successfully restored the intrinsic pathway in FIX-deficient plasma, with ongoing analyses intended to confirm conditional albumin cleavage upon activation. Finally, ELISA and SPR demonstrated that full-length QMP-albumin fusions retain high pH-dependent affinity for FcRn at pH 5.5 (KD 2-6 nM), comparable to unfused QMP-albumin and efficient release at physiological pH, that strongly supports the potential for an extended plasma half-life through the FcRn-mediated recycling pathway.

Conclusions. Fusing FIX-Padua and bypassing FX variant with albumin domains through cleavage-dependent sites is a promising strategy to enhance pharmacokinetics without compromising procoagulant function. The successful expression and functional performance of these minimized chimeras suggest a novel direction for long-acting hemostatic agents. Further characterization of cleavage efficiency and FcRn-binding kinetics will finalize the profile of these innovative therapeutic candidates.

ABSTRACT N. PO075

HEMOSTATIC AND CARDIOVASCULAR PROFILES IN HEMOPHILIA PATIENTS WITH AND WITHOUT ATHEROSCLEROSIS

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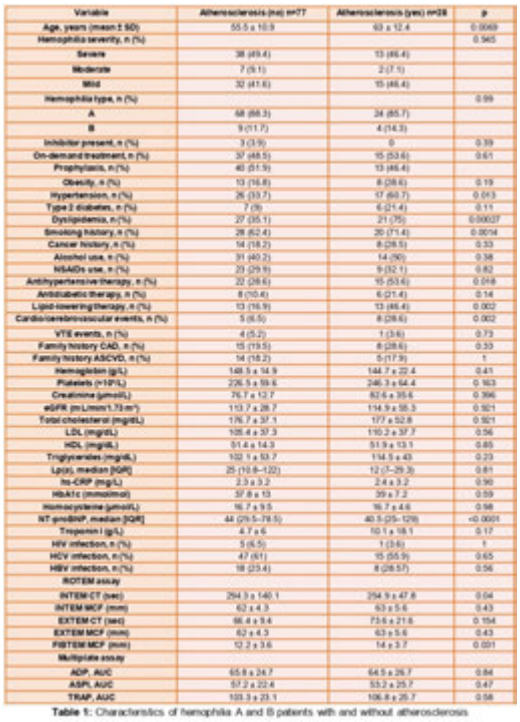
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Background and Aims. Hemophilia is classically characterized by hypocoagulability; however, patients remain susceptible to atherosclerosis due to the presence of conventional cardiovascular risk factors. Data on global hemostasis and platelet function in hemophilia patients with arterial disease are still limited. This study aimed to compare clinical characteristics, laboratory parameters, ROTEM findings, and platelet function between hemophilia patients with and without atherosclerosis, and to explore potential differences in their hemostatic profiles.

Methods. This cross-sectional study included 105 adult patients with hemophilia A and B, of whom 77 had no evidence of atherosclerosis and 28 had atherosclerosis. Atherosclerosis was defined as ≥50% carotid artery stenosis on Doppler ultrasound, the presence of any aortic plaque on imaging, or a pathological ankle–brachial index (ABI ≤ 0.9) consistent with peripheral arterial disease. Clinical history, comorbidities, medications, laboratory parameters, ROTEM, and Multiplate assays were collected. Continuous variables were expressed as mean ± standard deviation or median [IQR], and categorical variables as counts and percentages. Group comparisons were performed using the t-test, Mann–Whitney U test, or chi-square test, with $p < 0.05$ considered statistically significant.

Results. Patients with atherosclerosis were older than those without (63 ± 12.4 vs. 55.5 ± 10.9 years; p = 0.007) and showed a higher prevalence of hypertension (60.7% vs. 33.7%; p = 0.013), dyslipidemia (75% vs. 35%; p < 0.001), use of antihypertensive therapy (53.6% vs. 28.6%; p = 0.018), lipid-lowering therapy (46.4% vs. 16.9%; p = 0.002), and prior cardiovascular or cerebrovascular events (28.6% vs. 6.5%; p = 0.002). No significant differences were observed in hemophilia type or severity, obesity, diabetes, alcohol consumption, or presence of inhibitors. Routine laboratory parameters, including hemoglobin, platelet count, renal function, lipid profile, lipoprotein(a), hs-CRP, and HbA1c, were comparable between groups. NT-proBNP differed significantly between groups but remained within normal ranges. ROTEM analysis showed a shortened INTEM clotting time in patients with atherosclerosis (254.9 ± 47.8 vs. 294.3 ± 140.1 s; p = 0.04) and increased FIBTEM maximum clot firmness (14 ± 3.7 vs. 12.2 ± 3.6 mm; p = 0.031), suggesting subtle procoagulant changes. No significant differences were observed in EXTEM parameters or in Multiplate ADP and ASPI assays, indicating preserved platelet function (Table 1). Kaplan–Meier analysis showed no significant difference in survival between groups (p = 0.93).

Conclusions. Despite their inherent hypocoagulable state, hemophilia patients with atherosclerosis display a cardiovascular risk profile similar to that of the general population. ROTEM analysis suggests early and subtle shifts toward a procoagulant state, characterized by faster clot initiation and increased fibrin-based clot firmness. These findings highlight the importance of comprehensive cardiovascular risk assessment and global hemostasis evaluation in hemophilia patients, and support ROTEM as a sensitive tool for detecting subclinical prothrombotic changes associated with atherosclerosis.



Variable	Atherosclerosis (no) n=77	Atherosclerosis (yes) n=28	p
Age, years (mean ± SD)	55.5 ± 10.9	63 ± 12.4	0.0069
Hemophilia severity, n (%)			0.965
Severe	38 (49.4)	13 (46.4)	
Moderate	7 (9.1)	2 (7.1)	
Mild	32 (41.6)	13 (46.4)	
Hemophilia type, n (%)			0.99
A	68 (88.3)	24 (85.7)	
B	9 (11.7)	4 (14.3)	
Inhibitor present, n (%)	3 (3.9)	0	0.39
On-demand treatment, n (%)	37 (48.5)	15 (53.6)	0.61
Prophylaxis, n (%)	40 (51.9)	13 (46.4)	
Obesity, n (%)	13 (16.8)	8 (28.6)	0.19
Hypertension, n (%)	26 (33.7)	17 (60.7)	0.013
Type 2 diabetes, n (%)	7 (9)	6 (21.4)	0.11
Dyslipidemia, n (%)	27 (35.1)	21 (75)	0.00027
Smoking history, n (%)	28 (62.4)	20 (71.4)	0.0014
Cancer history, n (%)	14 (18.2)	8 (28.5)	0.33
Alcohol use, n (%)	31 (40.2)	14 (50)	0.38
NSAIDs use, n (%)	23 (29.9)	9 (32.1)	0.82
Antihypertensive therapy, n (%)	22 (28.6)	15 (53.6)	0.018
Antidiabetic therapy, n (%)	8 (10.4)	6 (21.4)	0.14
Lipid-lowering therapy, n (%)	13 (16.9)	13 (46.4)	0.002
Cardio/cerebrovascular events, n (%)	5 (6.5)	8 (28.6)	0.002
VTE events, n (%)	4 (5.2)	1 (3.6)	0.73
Family history CAD, n (%)	15 (19.5)	8 (28.6)	0.33
Family history ASCVD, n (%)	14 (18.2)	5 (17.9)	1
Hemoglobin (g/L)	148.5 ± 14.9	144.7 ± 22.4	0.41
Platelets (×10⁹/L)	226.5 ± 59.6	246.3 ± 64.4	0.163
Creatinine (µmol/L)	76.7 ± 12.7	82.6 ± 35.6	0.396
eGFR (mL/min/1.73 m²)	113.7 ± 28.7	114.9 ± 56.3	0.921
Total cholesterol (mg/dL)	176.7 ± 37.1	177 ± 52.8	0.921
LDL (mg/dL)	105.4 ± 37.3	110.2 ± 37.7	0.56
HDL (mg/dL)	51.4 ± 14.3	51.9 ± 13.1	0.85
Triglycerides (mg/dL)	102.1 ± 53.7	114.5 ± 43	0.23
Lp(a), median [IQR]	25 (10.8–120)	12 (7–29.3)	0.61
hs-CRP (mg/L)	2.3 ± 3.2	2.4 ± 3.2	0.90
HbA1c (mmol/mol)	37.8 ± 10	39 ± 7.2	0.59
Homocysteine (µmol/L)	16.7 ± 9.5	16.7 ± 4.6	0.98
NT-proBNP, median [IQR]	44 (20.5–78.5)	40.5 (25–129)	<0.0001
Troponin I (g/L)	4.7 ± 6	10.1 ± 18.1	0.17
HIV infection, n (%)	5 (6.5)	1 (3.6)	1
HCV infection, n (%)	47 (61)	15 (55.9)	0.65
HBV infection, n (%)	18 (23.4)	8 (28.57)	0.56
ROTEM assay			
INTEM-CT (sec)	294.3 ± 140.1	254.9 ± 47.8	0.04
INTEM MCF (mm)	62 ± 4.3	63 ± 5.6	0.43
EXTEM CT (sec)	66.4 ± 9.4	73.6 ± 21.8	0.156
EXTEM MCF (mm)	62 ± 4.3	63 ± 5.6	0.43
FIBTEM MCF (mm)	12.2 ± 3.6	14 ± 3.7	0.031
Multiplate assay			
ADP, AUC	65.8 ± 24.7	64.5 ± 26.7	0.84
ASPI, AUC	57.2 ± 22.4	53.2 ± 25.7	0.47
TRAP, AUC	103.3 ± 23.1	106.8 ± 26.7	0.58

Table 1: Characteristics of hemophilia A and B patients with and without atherosclerosis



ACQUIRED FACTOR V INHIBITOR WITH CONCOMITANT LUPUS ANTICOAGULANT: DIAGNOSTIC PITFALLS AND THERAPEUTIC CHALLENGES

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Background. Acquired Factor V (FV) inhibitors are rare, with an estimated incidence of 0.09 to 0.29 cases per million person-years. Associated with infections, malignancies, or medications, they typically present with unexplained prolongation of Prothrombin Time (PT) and activated Partial Thromboplastin Time (aPTT), while the Thrombin Time (TT) remains normal. Presentation varies from asymptomatic laboratory findings to life-threatening haemorrhage or, paradoxically, thrombosis.

Case report. An 80-year-old male was recently discharged following severe pneumonia. His medical history included hypertension, aortic stenosis, previous myocardial infarction, and peripheral obstructive arterial disease (external iliac artery) treated with clopidogrel. He presented to the Emergency Department with pain and a large ecchymosis on his upper arm. Initial screening showed extreme PT/aPTT prolongation with normal platelets, TT, fibrinogen, and Factor XIII. To investigate the coagulopathy, dRVVT assays revealed a strong lupus anticoagulant (LA) effect (ratio 2.8). To distinguish a "pseudo-deficiency" from a true inhibitor, serial plasma dilutions were performed: all factors normalised at 1:16 except for Factor V, which normalised only at 1:512, confirming a specific high-titre FV inhibitor (initially 445 BU). Basing on the patient's high thrombotic risk and a stable clinical phenotype, initial therapy consisted of prednisone (1 mg/kg/day) without bypassing agents. However, after 7 days, despite a decrease in the inhibitor titre to 177 BU, the patient developed acute abdominal pain. A CT scan revealed an 8 X 6 X 10 cm rectus abdominis haematoma associated with a haemoglobin drop of 2 g/dL. Haemostatic treatment with recombinant activated Factor VII (rFVIIa) at 90 µg/kg was initiated but yielded no clinical benefit or improvement in ROTEM (EXTEM) parameters. Tragically, following rFVIIa administration, the patient suffered a cerebellar stroke, highlighting the severe thrombotic risk in this population. Since FV inhibitors interfere with the prothrombinase complex, often making bypassing agents ineffective, and FV stored in platelet alpha-granules is partially activated and relatively resistant to circulating inhibitors, one unit of platelet concentrate was transfused to allow for urgent embolisation of the inferior epigastric artery. This led to the normalisation of EXTEM, and the procedure was completed without further bleeding. Besides, a pulsed immunosuppressive protocol with a lower cumulative dose of cyclophosphamide, rituximab and steroids (CyDRi) was started. After two weeks of this treatment, the FV inhibitor decreased to 16 BU and the coagulation factors, previously extremely reduced, rose to 40 UI/dl in undiluted plasma.

Conclusions. In cases of unexplained PT/aPTT prolongation with normal TT, FV inhibitors must be considered. When initial assays suggest a multiple factor deficiency, serial plasma dilutions are essential to unmask the specific inhibitor. Clinicians must carefully balance haemorrhagic control with the high risk of thrombosis, particularly when using bypassing agents in vasculopathic patients. Platelet transfusion represents a critical haemostatic bridge when traditional agents fail, enabling high-risk interventional procedures. Finally, this case demonstrates that point-of-care viscoelastic testing (ROTEM) is an invaluable tool in this setting, as it can objectively demonstrate and monitor the immediate haemostatic effect of platelet transfusion, providing real-time guidance for high-risk invasive procedures.

ABSTRACT N. PO077

BALANCING BLEEDING AND THROMBOSIS: SAFETY OF LOW-MOLECULAR-WEIGHT HEPARIN THROMBOPROPHYLAXIS IN PATIENTS WITH HEMOPHILIA UNDERGOING MAJOR SURGERY

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Background and Aims. In patients with hemophilia, the risk of venous thromboembolism (VTE) has historically been considered low. However, in the setting of major surgery, particularly orthopedic and oncologic procedures, this risk may become clinically relevant. Available evidence is limited and sometimes conflicting. The World Federation of Hemophilia guidelines (WFH, 3rd edition) recommend an individualized assessment of both thrombotic and bleeding risk, favoring mechanical thromboprophylaxis and reserving pharmacological prophylaxis for selected cases under adequate factor replacement and in patients without inhibitors. Similarly, the International Society on Thrombosis and Haemostasis (ISTH) highlights the low quality of available evidence and the need for a personalized approach. A recent systematic review reported a low incidence of VTE after major orthopedic surgery, but considerable heterogeneity in thromboprophylaxis use, reflecting the lack of consensus. In this context, we aimed to retrospectively evaluate the safety of pharmacological thromboprophylaxis with low-molecular-weight heparin (LMWH) in patients with hemophilia undergoing major surgery.

Methods. Medical records of 105 patients with moderate/severe hemophilia A or B followed at our center were retrospectively reviewed. Among these, 12 patients undergoing a total of 18 major surgical procedures received postoperative LMWH thromboprophylaxis. Data were verified and integrated through comparison with the rare diseases registry.

Results. All included patients had severe hemophilia A and received perioperative factor replacement therapy. Trough factor levels during the first three postoperative days were ≥14%, and ≥11% thereafter. Patient characteristics, type of surgery, and trough levels are reported in *Table 1*. A single bleeding event occurred in a patient undergoing intestinal reanastomosis for previous rectal adenocarcinoma (previously treated with LMWH prophylaxis without complications), who presented on postoperative day 4 with hematemesis and rectal bleeding, requiring LMWH discontinuation and transfusion support. No other major or minor bleeding events were observed. One patient developed a clinically evident VTE on postoperative day 8 despite LMWH thromboprophylaxis, in the presence of multiple risk factors (high-risk inherited thrombophilia and smoking). No additional clinically evident thromboembolic events were observed.

Conclusions. In a setting of limited and conflicting evidence, all patients underwent individualized assessment of thrombotic and bleeding risk. They received adequate factor replacement therapy and were monitored through factor levels. In this context, LMWH thromboprophylaxis appeared safe in the vast majority of cases. These findings support the feasibility of a personalized approach to pharmacological thromboprophylaxis in patients with hemophilia undergoing major surgery, although prospective studies are warranted to confirm its safety.

Pt	Age at surgery	Preoperative prophylaxis	Additional VTE risk factors	Surgery	VTE	Bleeding	Trough FVIII POD 1-3 (%)	Trough FVIII >POD3 (%)
1.1	60	Replacement	Heterozygous factor V Leiden + homozygous prothrombin polymorphism + smoking	Laparoscopic cholecystectomy + endoscopic bile duct clearance	NO	NO	44	80
1.2	63	Replacement	Heterozygous factor V Leiden + homozygous prothrombin polymorphism + smoking	TKA	YES	NO	59	88
2	65	Replacement	Obesity	THA	NO	NO	100	50
3	50	Replacement	History of PICC-related VTE	Infected TKA removal + debridement + knee arthrodesis with external fixation	NO	NO	55	16
4.1	66	Non-replacement (Emicizumab)	Rectal adenocarcinoma + smoking	Thoracoscopic lung biopsy	NO	NO	45	NA
4.2	60	Replacement	Rectal adenocarcinoma + smoking	Rectal resection for adenocarcinoma with ileostomy	NO	NO	47	20
4.3	61	Replacement	Rectal adenocarcinoma + smoking	Surgical revision for anastomotic leak after rectal resection	NO	NO	24	17
4.4	61	Replacement	Rectal adenocarcinoma + smoking	Intestinal reanastomosis	NO	YES	35	21
5.1	54	Replacement	Klinefelter syndrome	TKA	NO	NO	49	95
5.2	50	Replacement	Klinefelter syndrome	TKA	NO	NO	106	50
6	36	Replacement	NO	TKA	NO	NO	152	160
7	62	Replacement	NO	TKA revision for periprosthetic fracture	NO	NO	58	40
8	41	Replacement	NO	TKA	NO	NO	63	11
9	67	Non-replacement (Emicizumab)	NO	TKA	NO	NO	39	49
10.1	54	Replacement	NO	Patellar tendon repair	NO	NO	14	14
10.2	51	Replacement	NO	THA	NO	NO	84	104
11	28	Replacement	NO	Ischial tuberosity exostosis resection (osteoma)	NO	NO	60	45
12	67	Replacement	NO	THA	NO	NO	63	40

Abbreviations: Pt, patient; VTE, venous thromboembolism; POD: postoperative day; TKA, Total knee arthroplasty; THA, Total hip arthroplasty; NA, not available.

ABSTRACT N. PO078

CARDIOVASCULAR EVENTS AND SUBCLINICAL ATHEROSCLEROSIS IN HEMOPHILIA A AND B PATIENTS: A MULTICENTER COHORT STUDY

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Background and Aims. Advances in hemophilia care have significantly improved life expectancy, thereby increasing exposure to cardiovascular risk. Although hemophilia has traditionally been considered protective against thrombosis, cardiovascular events are increasingly recognized in this population. This study aims to evaluate the prevalence and predictors of cardiovascular events in patients with hemophilia A and B, and to investigate their association with both clinical and subclinical atherosclerosis.

Methods. We conducted a multicenter ambispective observational cohort study including 163 patients aged >40 years with hemophilia A or B (139 hemophilia A; 24 hemophilia B), followed at the Hemophilia Centers of Padua and Castelfranco Veneto, in North-East Italy. Patients were divided into two groups according to the occurrence of clinical events (myocardial infarction, stroke/TIA, and venous thrombosis). Demographic, clinical, laboratory, and treatment-related variables were collected. ROTEM and Multiplate assays were performed. All participants underwent carotid ultrasound, abdominal aorta diameter measurement, and ankle-brachial index (ABI) assessment. Associations with outcomes were evaluated using univariate analyses and multivariable logistic regression models.

Results. A total of 16.6% of patients (27/163) experienced at least one event, which occurred more frequently in patients with mild compared to severe hemophilia (70.4% vs 40.4%; p = 0.0199), with no significant difference between hemophilia A and B (p = 0.545). Patients with events were significantly older than those without (67.8 ± 12.2 vs 55.7 ± 10.7 years; p = 0.001). Patients with events showed a higher prevalence of cardiovascular and metabolic comorbidities, including hypertension (66.6% vs 38.2%; p = 0.01), dyslipidemia (59.3% vs 38.2%; p = 0.04), and cancer (37% vs 13.2%; p = 0.004). In multivariable analysis, events were independently associated with HIV infection (OR 6.51; 95% CI 1.38–30.77), hypertension (OR 3.17; 95% CI 1.31–7.68), and dyslipidemia (OR 2.38; 95% CI 1.02–5.56). Imaging and vascular assessments showed greater carotid plaque thickness, larger abdominal aorta diameter, and a higher prevalence of abnormal ABI (<1) in patients with events (p = 0.006, p = 0.03, and p = 0.001, respectively).Laboratory analyses revealed significantly lower hemoglobin (p = 0.0076) and platelet counts (p = 0.0037) in patients with events. Renal function was also impaired, as indicated by higher creatinine levels (p = 0.0182). In addition, NT-proBNP (p = 0.02) and troponin I (p = 0.004) were significantly increased in patients with events. Thromboelastometry demonstrated a shorter INTEM clotting time in patients with events (p = 0.0037), while platelet function testing showed significantly reduced ASPI AUC (p = 0.03) and TRAP AUC (p = 0.002).Kaplan–Meier analysis showed no significant difference in event-free survival between patients with mild and severe hemophilia (p = 0.94) (Figure 1).

Conclusions. Thrombotic and cardiovascular events occurred in a minority of patients with hemophilia A and B and were more frequent among older individuals, patients with mild disease, and those with HIV infection. Events were associated with traditional cardiovascular risk factors and markers of subclinical atherosclerosis, emphasizing the importance of comprehensive cardiovascular evaluation in this population.

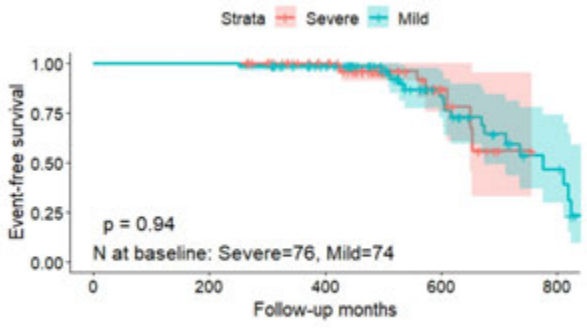


Figure 1: Cardiovascular Event–Free Survival in Severe vs Mild Hemophilia

ABSTRACT N. PO079

PERIOPERATIVE MANAGEMENT OF MILD-TO-MODERATE HEMOPHILIA: A COMPARATIVE STUDY OF EXTENDED HALF-LIFE VERSUS STANDARD HALF-LIFE CONCENTRATES ON CLINICAL OUTCOMES AND FACTOR CONSUMPTION

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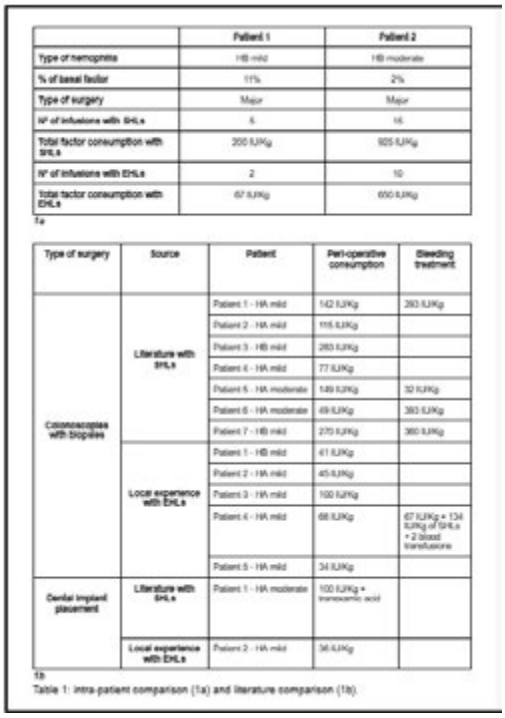
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Background and Aims. In recent years, extended half-life concentrates (EHLs) have become an effective alternative to standard half-life concentrates (SHLs) in hemophilia, offering improved pharmacokinetics and reduced infusion frequency. These features make EHLs particularly attractive for perioperative management. While their efficacy and safety in surgery have been confirmed in severe or moderate-severe hemophilia, evidence remains scarce for mild-to-moderate hemophilia. The aim of this study was to confirm perioperative safety and hemostatic efficacy of EHLs and to evaluate the reduction of factor consumption and number of infusions of EHLs compared to SHLs in patients with mild-to-moderate hemophilia A (HA) or B (HB).

Methods. We retrospectively analyzed 191 patients with mild-to-moderate HA or HB and collected data from 27 EHLs-managed surgeries performed at our center in 22 patients from 2018 to 2026. Fourteen major (52%) and 13 minor (48%) surgeries were performed. Twenty patients (91%) had mild hemophilia and 2 (9%) had moderate hemophilia. Two patients had undergone the same surgery once with SHLs and once with EHLs allowing an intra-patient comparison. We also compared our data with published literature for the same procedures (direct comparison of major surgeries was not possible due to the lack of comparable literature data). Preoperative pharmacokinetic (PK) studies were conducted before 16 procedures (59%) to guide dosing strategies. Mean trough level of 55% (24h) and 31% (72h) were maintained. In two cases of major surgery, the emergency nature of the procedure precluded pharmacokinetic analysis. Regarding patients with HA, 11 procedures were performed using turoctocog alfa pegol, 4 with rurioctocog alfa pegol, 1 with damoctocog alfa pegol. Among patients with HB, nonacog beta pegol was utilized in 6 cases, eftrenonacog alfa and albutrepenonacog alfa in 2 cases each.

Results. In both comparisons we observed a reduction in the number of infusions (Table 1a) and total factor consumption (Table 1a, Table 1b). All 27 surgeries were managed with a single preoperative infusion. Postoperative infusions were administered once daily, whereas the literature reports twice-daily infusions when using SHLs. The sole exception in our cohort was a patient with mild HA undergoing cardiac surgery, who required more frequent infusions within the first 24 hours post-surgery before early transition to a single daily infusion. No patients developed inhibitors; a single bleeding event was due to poor hemostasis.

Conclusions. EHLs appear safe and effective for surgery in mild-to-moderate hemophilia, offering clinical advantages over SHLs across all analyzed populations, particularly in HB. While not statistically significant due to the limited cohort, these findings demonstrate a clinical advantage, despite the absence of baseline factor levels for literature-based cases. For HA, further improvements are expected with the advent of newer molecules.



	Patient 1	Patient 2
Type of hemophilia	HB mild	HB moderate
% of basal factor	11%	2%
Type of surgery	Major	Major
N° of infusions with EHLs	6	16
Total factor consumption with SHLs	300 IU/Kg	925 IU/Kg
N° of infusions with EHLs	2	10
Total factor consumption with EHLs	67 IU/Kg	650 IU/Kg

1a

Type of surgery	Source	Patient	Peri-operative consumption	Bleeding treatment
Colonoscopies with biopsies	Literature with SHLs	Patient 1 - HA mild	142 IU/Kg	283 IU/Kg
		Patient 2 - HA mild	115 IU/Kg	
		Patient 3 - HB mild	283 IU/Kg	
		Patient 4 - HA mild	77 IU/Kg	
		Patient 5 - HA moderate	149 IU/Kg	32 IU/Kg
		Patient 6 - HA moderate	49 IU/Kg	393 IU/Kg
		Patient 7 - HB mild	270 IU/Kg	360 IU/Kg
	Local experience with EHLs	Patient 1 - HB mild	41 IU/Kg	
		Patient 2 - HA mild	45 IU/Kg	
		Patient 3 - HA mild	100 IU/Kg	
		Patient 4 - HA mild	66 IU/Kg	67 IU/Kg + 134 IU/Kg of SHLs + 2 blood transfusions
		Patient 5 - HA mild	34 IU/Kg	
Dental implant placement	Literature with EHLs	Patient 1 - HA moderate	100 IU/Kg + tranexamic acid	
	Local experience with EHLs	Patient 2 - HA mild	36 IU/Kg	

1b

Table 1: intra-patient comparison (1a) and literature comparison (1b).



BEYOND STANDARD COAGULOPATHY: SEVERE FACTOR XIII DEFICIENCY AS THE HARBINGING SIGN OF ACUTE PROMYELOCYTIC LEUKEMIA

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Background. Acute promyelocytic leukemia (APL), representing 10% of AML cases, is characterized by the t(15;17) translocation. Despite cure rates exceeding 90% with ATRA and ATO, early hemorrhagic death remains a critical challenge, occurring in 10–30% of patients. APL coagulopathy is multifactorial, involving DIC and primary hyperfibrinolysis. Malignant promyelocytes trigger these pathways via tissue factor and annexin A2 expression. Furthermore, ATRA-induced ETosis—the release of extracellular chromatin traps (NETs)—exacerbates the condition by discharging potent proteases like elastase. Crucially, these enzymes degrade Factor XIII (FXIII), a transglutaminase vital for fibrin cross-linking. This acquired FXIII deficiency destabilizes hemostasis, significantly contributing to the severe bleeding diathesis. We present an APL case where severe FXIII deficiency and related bleeding preceded the onset of characteristic APL coagulopathy

Case Report. A 12-year-old male with no prior history of bleeding disorders presented to the emergency department with a soft, 15 mm scalp hematoma in the right parietal region, triggered by minor hair pulling. He also reported recent fatigue and low-grade fever. Coagulation tests showed a PT ratio of 1.4, a PTT ratio of 1.15, and fibrinogen levels of 151 mg/dL. Given that the severity of the hemorrhage appeared disproportionate to these mild laboratory abnormalities, Factor XIII (FXIII) levels were assessed, revealing a severe deficiency (7%). No other bleeding manifestations were present. FXIII levels improved following administration of fresh frozen plasma and subsequently normalized with purified FXIII concentrate. Over the following days, the patient developed progressive pancytopenia; peripheral blood and bone marrow investigations led to the diagnosis of acute promyelocytic leukemia (APL).

Conclusions. The coagulopathy associated with acute promyelocytic leukemia (APL) is traditionally attributed to disseminated intravascular coagulation (DIC) and primary hyperfibrinolysis. However, acquired Factor XIII (FXIII) deficiency represents a critical, yet often under-recognized, component of this hemostatic failure. Diagnosing acquired FXIII deficiency is challenging because routine screening tests, such as PT and aPTT, remain normal in cases of isolated deficiency. Therefore, quantitative FXIII activity assays should be prioritized in APL patients presenting with severe or unexplained bleeding. Despite the severity of these mechanisms, current international guidelines—including those from ASH, ELN, EHA, and NCCN—are highly rigorous regarding APL management but do not yet include specific recommendations for FXIII monitoring. Our case highlights a unique clinical scenario where severe acquired FXIII deficiency and its subsequent hemorrhagic manifestations preceded the formal diagnosis of APL and the onset of its characteristic coagulopathy by several days. The early detection of this deficiency allowed for the prompt initiation of replacement therapy with FXIII concentrate, effectively preventing further life-threatening bleeding complications. This observation suggests that proteolytic degradation of FXIII can act as a primary and independent driver of hemorrhage in the earliest stages of the disease. In conclusion, integrating FXIII assessment into the initial diagnostic workup of suspected APL may be crucial for early stabilization and improved clinical outcomes.



FROM VON WILLEBRAND DISEASE TO MILD HEMOPHILIA A AND BACK: THREE ILLUSTRATIVE CASES HIGHLIGHTING THE ROLE OF GENETIC TESTING IN IMPROVING DIAGNOSTIC ACCURACY

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Background. von Willebrand disease (VWD) is an inherited bleeding disorder caused by quantitative or qualitative defects of von Willebrand factor (VWF), often associated with reduced factor VIII (FVIII). Clinical presentation mainly involves mucocutaneous bleeding; VWF activity between 30–50 UI/dl can be classified as "low VWF". Inheritance is autosomal dominant or recessive, depending on subtype. Hemophilia A is an X-linked disorder due to FVIII deficiency; mild forms (FVIII activity 5–40 UI/dl) often present after trauma or surgery. Differential diagnosis between mild hemophilia A and VWD may be challenging, with implications for management and genetic counseling. Genetic testing is not routinely performed in all VWD subtypes but can be useful in selected cases.

Case report. Case 1: a 36-year-old woman was referred during pregnancy for prolonged aPTT. At 16 gestational weeks, FVIII (chromogenic assay) was 49 UI/dl, VWF activity (GP1bM) 69 UI/dl; she reported easy bruising and menorrhagia. Her father had a bleeding history and a reported (undocumented) VWD diagnosis. Postpartum exams showed persistently reduced FVIII (34 UI/dl) with mildly decreased VWF activity and antigen (44 and 51 UI/dl). Genetic analysis included next generation sequencing (NGS) of *VWF* and *F8*, with exonic deletion/duplication analysis, intron 22 and 1 inversion screening, *F8* promoter Sanger sequencing. No pathogenic *VWF* variants were identified, while a heterozygous *F8* promoter c.-257T>G variant, associated with mild hemophilia A, was detected. The variant was confirmed in her father and son (FVIII 43 and 18 UI/dl, normal VWF in both); an obligate carrier sister had FVIII 44UI/dl, normal VWF. X-inactivation in the proband was not markedly skewed. Case 2: a 70-year-old man was referred for reassessment of bleeding risk and management in atrial fibrillation. He was diagnosed with VWD at age 40 based on VWF activity 28–36 UI/dl and post-procedural bleeding. Current evaluation showed normal VWF (activity 94UI/dl, antigen 125 UI/dl) but persistently reduced FVIII (29–36 UI/dl). Genetic testing identified no *VWF* variants and a hemizygous *F8* promoter c.-219C>T variant, causative of mild hemophilia A. He underwent left atrial appendage closure and anticoagulation (dabigatran) with prophylaxis using pegylated recombinant FVIII. His daughter, obligate carrier, had FVIII 57.6 UI/dl and no bleeding phenotype. Case 3: a 20-year-old man was diagnosed with mild hemophilia A based on reduced FVIII activity (25–37 UI/dl) and normal VWF, after prolonged aPTT during presurgical screening, without personal or familiar bleeding history. *F8* testing was negative, while the homozygous *VWF* c.2561G>A (p.Arg854Gln) pathogenetic variant, associated with autosomal recessive type 2N VWD, was identified, leading to diagnostic reclassification.

Conclusions. genetic testing enabled diagnostic reclassification, with relevant implications for clinical management and genetic counseling. In case 1, mildly reduced VWF suggests possible coexisting low VWF, consistent with evidence that up to 50% of such cases lack identifiable variants, potentially contributing to her low FVIII levels, not fully explained by X-inactivation. Notably, *F8* promoter variants are not routinely covered by standard NGS panels, underscoring the importance of targeted analysis in specialized centers. Although still not routinely performed, genetic testing may be decisive in patients with atypical or discordant phenotypes.

ABSTRACT N. PO082

HEMOPHILIA AND LOW BONE MINERAL DENSITY: AN OBSERVATIONAL STUDY

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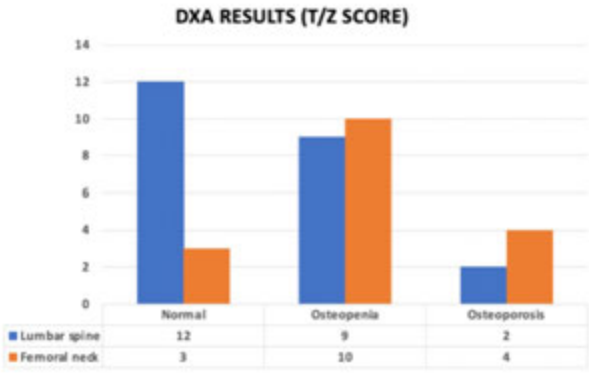
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Background and aims. Hemophilia is a rare X-linked recessive disorder caused by deficiency of factor VIII (FVIII) or IX (FIX). Management focuses on controlling bleeding and preventing joint damage. With improved care, more patients reach adulthood, revealing broader effects beyond hemostasis, including altered bone turnover. This study shows an increased risk of low bone mineral density (BMD) leading to osteopenia/osteoporosis, particularly in cortical bone.

Methods. In this prospective observational study we enrolled 30 hemophilic patients from October 2024 through March 2026, all men, with a mean age of 54. 26 had Hemophilia A, 77% severe (FVIII < 1%), 15% moderate (FVIII 1-5%) and 8% mild (FVIII > 5%). 4 patients had Hemophilia B (75% severe, 25% mild). All the patients except one had undergone to major orthopedic surgeries (25 knee replacements, 2 hip replacements, and 2 other types) and were admitted to our Internal Medicine department around the third post-operative day. The most significant comorbidities and risk factors in the study population were: smoking (25%), obesity (60%), sedentary lifestyle (according to the Global Physical Activity Questionnaire, 95%) and previous HCV infection (75%). The following blood tests were assessed in the entire sample: calcium, phosphorus, magnesium, 25OHVitD, Beta-CTX, total alkaline phosphatase (ALP) and bone alkaline phosphatase (BALP), parathyroid hormone, testosterone and urinary tests: calcium, phosphorus and 24-hour protein. Moreover, 23 and 17 patients in the cohort respectively underwent Dual-Energy X-Ray Absorptiometry (DXA) of the lumbar spine (L1-L4) and femoral bone.

Results. A mean 25OHVitD level of 17 ng/dL was found, indicating severe hypovitaminosis D in 90% of the sample, despite 13% was already receiving supplementation. Age-standardized beta-CTX levels were at the upper limit (0.6 in the group older than 50 and 0.55 in the younger group) suggesting elevated bone turnover. Testosterone levels also showed unusual results, with a mean below the normal range (10 nmol/L), resulting in severe suppression in 60% of the sample. T/Z scores in 23 and 17 DXA respectively of the lumbar spine and femoral bone showed a high presence of osteopenia or osteoporosis in the study group. This finding appears to be more significant for the femoral bone than for the spine. In fact, reduced BMD with osteopenia/osteoporosis was present in 82% of the sample undergone to DXA of the femur compared to 47% of the sample undergone to DXA of the lumbar spine (Figure 1).

Conclusions. Studies show hemophilic patients have lower BMD than general population with a fivefold higher fracture risk. Causes include reduced physical activity, recurrent hemarthrosis and past HIV/HCV treatments. FVIII/FIX deficiency also impairs bone turnover by reducing thrombin and altering osteoclast/osteoblast activity, but also disrupting, together with the cytokine cascade triggered by chronic local inflammation, the RANK/RANKL/OPG pathway involved in bone resorption regulation. The study shows high rate of hypovitaminosis D associated with high bone turnover in this population. Also low testosterone levels contribute to bone loss, representing the main factor involved in osteoporosis in men. Finally, DXA results confirm increased bone fragility, mainly affecting cortical bone. In conclusion, early screening of bone metabolism in hemophilic patients is essential to reduce fracture risk, especially given increasing life expectancy.



ABSTRACT N. PO083

WOMEN AND HEMOPHILIA: ASSESSMENT OF THE BLEEDING PHENOTYPE – ANALYSIS OF THE BRESCIA COHORT

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Background and Aims. Female genetic carriers of hemophilia face an increased risk of bleeding manifestations that have historically been underestimated or correlated with plasma factor levels only. Despite the updated ISTH nomenclature, many symptomatic women and girls remain undiagnosed and lack access to specialized Hemophilia Treatment Centers (HTCs). This work aimed to implement a proactive multidisciplinary screening pathway at the ASST Spedali Civili di Brescia to analyze the clinical, genetic, and phenotypic profiles of a female cohort of obligated and potential genetic carriers of hemophilia A and B, facilitating earlier diagnosis and personalized management.

Methods. A screening protocol was established involving both the Pediatric and Adult HTCs in Brescia. The population (N=33) was stratified according to ISTH definitions into: Women and Girls with Hemophilia (WGH, N=12, factor levels <40 IU/dL) and Hemophilia Carriers (HC, N=14, factor levels ≥40 IU/dL); we added the category of Potential Carriers (PC, N=7), including women and girls who weren't obligated genetic carriers and were waiting for genetic confirmation tests. The bleeding phenotype was assessed using the ISTH-Bleeding Assessment Tool (ISTH-BAT), with a specific focus on Heavy Menstrual Bleeding (HMB). Laboratory testing included coagulation factors VIII and IX (FVIII/FIX) levels determined via one-stage (OSA) and chromogenic substrate (CSA) assays, VWF assays (antigen and activity), an iron status evaluation (serum iron, serum ferritin) and routine hemocoagulative tests (complete blood count, prothrombin time, activated partial thromboplastin time, fibrinogen).

Results. The proactive screening successfully identified eight WGH (66% of the subgroup) previously unknown to the HTC, emphasizing the underdiagnosis of the condition even within known hemophilia families. An abnormal bleeding phenotype (pathological ISTH-BAT and/or HMB) was identified in 24.2% of the total cohort, with higher prevalence in WGH (41.6%) compared to HC (14.2%). Clinical data analysis confirmed that HMB is the most frequent and impactful symptom, accounting for 40% of the total ISTH-BAT variance – occasionally leading to chronic iron deficiency, even in cases with sub-pathological ISTH-BAT scores. In accordance with the published literature, no direct linear correlation was found between FVIII/FIX levels and bleeding severity, suggesting that other factors may influence the phenotype.

Conclusions. A significant percentage of symptomatic carriers remain unrecognized. The lack of a clear correlation between laboratory factor levels and clinical symptoms reinforces the necessity of adopting validated clinical tools like the ISTH-BAT and prioritizing menstrual history in the diagnostic workup. Our findings strengthen the importance of implementing proactive, family-based screening pathways – essential to ensure gender equity in hemophilia care and to prevent hemorrhagic complications during critical life events, such as surgery, menarche, childbirth, or the transition to perimenopause.

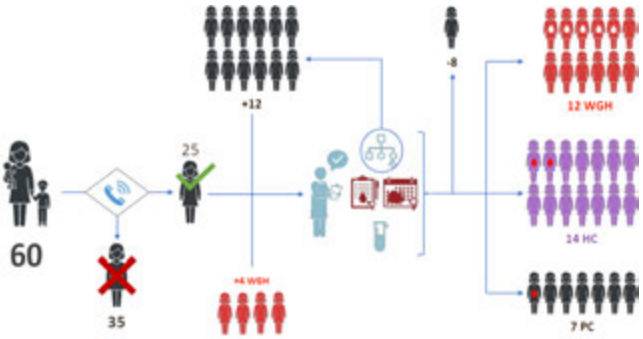


Figure 1. Integrated screening protocol and clinical outcomes infographic
From an initial cohort of 60 mothers of PWH, 25 were enrolled via telephone triage (35 were unavailable/declined). The cohort was supplemented by 12 family members identified through pedigree analysis and 4 previously known cases. The workup included bleeding assessment (ISTH-BAT and/or HMB) and laboratory assays. After 8 patients were lost to follow-up, final stratification identified 12 WGH, 14 HC, and 7 PC. Overall, 8 subjects presented an abnormal bleeding phenotype (symbolized by the drop icon).

Legend
PWH: Patient with Hemophilia; WGH: Women and Girls with Hemophilia; HC: Hemophilia Carriers; PC: Potential Carriers (waiting for genetic confirmation); HMB: Heavy Menstrual Bleeding.



BRIDGING THE CLINICAL CHASM: GENETIC ANALYSIS AS A CONFIRMATORY TOOL IN MISMATCHED GLANZMANN THROMBASTHENIA

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Background and aims. Glanzmann Thrombasthenia (GT) is a rare inherited recessive platelet function disorder caused by quantitative or qualitative defects of the glycoprotein IIb/IIIa (GPIIbIIIa), encoded by the ITGA2B/ITGB3 genes (chromosome 17), resulting in impaired platelet aggregation. Several pathogenic variants have been described, mainly in ITGA2B gene because of its larger size compared with ITGB3; however the associated clinical phenotypes are indistinguishable. We report the case of a 55-year-old woman referred to our centre for recently developed haemorrhagic diathesis: epistaxis, prolonged wound or gum bleeding and easy bruising, but negative bleeding history even in trigger conditions (surgery, pregnancy, delivery), no comorbidities at diagnosis and no family history. This atypical clinical presentation, including late-onset bleeding, raised suspicion for an acquired form. In this way genetic test helped. The aim of this study is to show the usefulness of genetic analysis as a confirmatory step in the diagnostic work-up, particularly when a mismatch exists between laboratory results and medical history.

Methods. Platelet function was assessed by Platelet Function Analyser (PFA-100), Total Thrombus- Formation Analysis System (T-TAS®01) and aggregometry. Absence of GPIIb/IIIa and presence of platelet autoantibodies/alloantibodies were tested by flow cytometry (Beckman Coulter Epics, High Wycombe, UK). Platelet antibody specificity was determined by Enzyme- Linked Immunosorbent Assay (ELISA). Owing to the discrepancy between the medical history and laboratory findings suggestive of congenital GT, molecular genetic analysis was performed.

Results. PFA-100 and T-TAS were elongated. Aggregometry showed a profile consistent with GT. Flow cytometric analysis showed a GPIIb/IIIa expression profile comparable to that observed in a patient with a confirmed diagnosis of GT. No antibodies or associated disease were detected. Genetic testing identified two heterozygous mutations *c.1947-1_1947ins* in ITGA2B gene, never reported in ClinVar, that represents a novel mutation, and another one *c.260G>A* reported only once in the GnomAD database.

Conclusions. Because this disorder is rare and its diagnostic work-up complicated, its management remains challenging, particularly when discrepancies arise between laboratory findings and the patient's medical history. For this reason, it may be important to include molecular genetic analysis not as an exclusive test for specific cases, but as a fundamental tool in the diagnostic process.



ACQUIRED HEMOPHILIA A IN THE SURGICAL PATIENT: DIAGNOSTIC AND THERAPEUTIC COMPLEXITY

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Background. Acquired hemophilia A (AHA) is a rare, potentially life-threatening autoimmune coagulopathy characterized by the presence of autoantibodies directed against factor VIII (FVIII). The disease often arises in complex clinical settings, posing significant diagnostic and therapeutic challenges. Diagnostic delay is common, particularly in patients with concomitant thrombotic risk or those receiving anticoagulant therapy—conditions that may hinder the correct interpretation of coagulation tests.

Case Report. We report the case of an 81-year-old patient with multiple comorbidities (diabetes, ischemic heart disease, a biological prosthetic valve, and peripheral artery disease) on antiplatelet therapy, who underwent emergency surgery for intestinal obstruction complicated by hemoperitoneum and ileal ischemia. Given the high thrombotic risk, heparin prophylaxis was initiated after discontinuation of aspirin. The postoperative course was complicated by diffuse bleeding from surgical sites and subcutaneous tissue, disproportionate to the ongoing antithrombotic therapy, accompanied by severe anemia requiring transfusion. Laboratory tests revealed a prolonged aPTT (65 s), a normal prothrombin time (PT), FVIII activity of 0.7%, and an anti-FVIII inhibitor titer of 5.5 BU, consistent with a diagnosis of AHA. Initial treatment with recombinant activated factor VII (rFVIIa) (subsequently replaced by activated prothrombin complex concentrate), corticosteroids, and cyclophosphamide failed to produce a significant clinical or laboratory response. The patient exhibited persistent bleeding, anemia, and progressive clinical deterioration, requiring continuous transfusion support. Following a decline in renal function, cyclophosphamide was discontinued. During follow-up, an abdominal CT scan revealed a splenic infarction. Suspecting endocarditis involving the prosthetic valve, blood cultures were performed and were positive for Candida spp., indicating fungal sepsis. Given the presence of systemic infection, rituximab was contraindicated, rescue therapy with cyclosporine and intravenous immunoglobulins (IVIG) was initiated resulting in a reduction of the inhibitor (1.19 BU) and an increase in FVIII levels (15%). Despite hematological improvement, the patient died of septic shock.

Conclusions. In patients presenting with bleeding disproportionate to the clinical context, particularly in the postoperative setting, AHA should be strongly considered. Concomitant anticoagulation and an underlying thrombotic risk profile may contribute to diagnostic delays. Therapeutic decisions must be individualized, and aggressive upfront immunosuppressive approaches should be used cautiously in frail patients, as their toxicity and associated infectious risk may limit subsequent treatment options. A multidisciplinary approach is essential to balance hemostatic efficacy with the risks of immunosuppression, as infectious complications represent a critical determinant of prognosis.

ABSTRACT N. PO086

INHERITED PLATELET GPIV DEFICIENCY: FIRST DESCRIPTION OF TWO PATIENTS WITH BLEEDING DIATHESIS

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Background and Aims. Platelet glycoprotein (GP) IV, also known as CD36, is expressed on multiple cell types, where it plays a role in lipid metabolism, immune regulation, and vascular biology. In platelets, GPIV serves as a receptor for thrombospondin-1 and collagen, mediating adhesive interactions and intracellular signaling events regulating platelet activation. Genetic variants in CD36 cause GPIV deficiency, a rare inherited condition. Cd36$^{-/-}$ mice show low bone mass due to defective osteoblast differentiation but not bleeding(1). Despite its involvement in platelet activation, GPIV deficiency in humans has not been associated so far with a bleeding phenotype, and platelet aggregation was generally normal(2). Our aim was to describe two unrelated patients carrying heterozygous CD36 variants associated with markedly reduced platelet GPIV expression and bleeding manifestations.

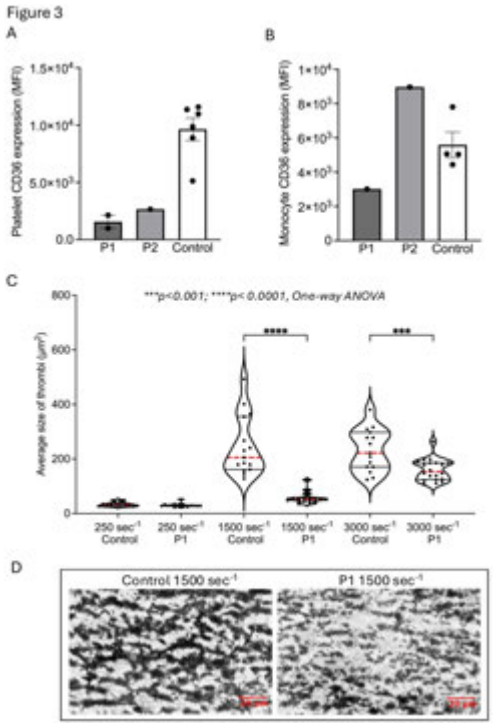
Methods. Platelet aggregation was evaluated by light transmission aggregometry, glycoprotein expression by flow cytometry, and α- and δ-granule content and release by P-selectin expression, β-TG release, mepacrine uptake/release, and ATP secretion by lumiaggregometry. Platelet adhesion to collagen under flow was assessed using a perfusion chamber. Clinical exome sequencing was performed using a capture-based NGS approach.

Results. Patient 1 (P1) was a 22-year-old woman with easy bruising and prolonged bleeding after dental extractions (ISTH-BAT score 5); she previously clinically diagnosed with joint hypermotility but no Ehlers–Danlos syndrome mutations were found. Patient 2 (P2) was a 50-year-old woman with lifelong mucocutaneous bleeding, gynecological bleeding and an ISTH-BAT score of 10; she also had bone-related abnormalities, including osteolipomas. Blood clotting assays, platelet number and volume, LTA and granule secretion were all normal in both patients, but PFA-100 closure time was prolonged in P1 and bleeding time in P2. Flow cytometric analysis showed markedly reduced expression of CD36 in platelets from both patients and also in monocytes from P1 suggesting type I CD36 deficiency in P1 and type II in P2 (Figure 1 A-B). Platelet adhesion to collagen under flow conditions at high shear rates was reduced (Figure 1C). Von Willebrand factor (VWF) values in P1 were slightly reduced (VWF:Ag 54%, normal values 61-152%; VWF:RCo 50%, normal values 58-175%; VWF:CBA 61%, normal values 50-400%) and moderately reduced in P2 (VWF:Ag 57-65%, VWF:RCo 48-61%). Clinical exome sequencing identified two heterozygous frameshift variants in the CD36 gene: the CD36 (NM_001001548.3):c.660_669del (p.Asn220Lysfs*4), Pathogenic, in P1 and the CD36 (NM_001001548.3):c.338_339del (p.Ser113Phefs*20), Likely Pathogenic, in P2. No variants in the VWF gene were observed.

Conclusions. These cases expand the clinical spectrum of inherited GPIV deficiency, suggesting that heterozygous CD36 variants may, in rare instances, be associated with mild to moderate bleeding. The associated collagen- and bone- related features are consistent with the role of CD36 in vascular integrity and skeletal homeostasis. Low levels of VWF in both patients are consistent with emerging genetic evidence showing that loss-of-function mutations in CD36 are associated with lower VWF levels in large population studies(5).

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BEYOND POSITIVITY: THE HIERARCHICAL ROLE OF IMMUNOASSAYS IN HEPARIN INDUCED THROMBOCYTOPENIA

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Background and aims. Heparin induced thrombocytopenia (HIT) is an immune mediated disorder induced by the exposure to heparin with subsequent production of antibodies against heparin-platelet factor 4 (H-PF4) complexes. The diagnosis of HIT is based on a combination of 4T pre-test probability score (4Tscore) and detection of antibodies bound to H-PF4 complexes by immunoassays and, if available, a functional assay. Immunoassays are characterised by ease of performance, wide availability and high sensitivity. Functional assays are the gold standard for HIT diagnosis but these methods are complex, completely manual, requiring washed platelets and more expensive. This analysis aims to investigate the hierarchical role of immunoassays and their integration with the 4Ts score for ruling out HIT.

Methods. We conducted a retrospective analysis, from 2020 to 2026, of 103 patients from Azienda Ospedaliera Molinette with suspected HIT. For each case, the pre-test clinical probability was assessed using the 4Ts score. Laboratory evaluation included immunoassays (ELISA, CLIA, and LIA) and a functional assay (HIPA), used as the reference standard. Agreement between assays was evaluated using concordance rates, and diagnostic performance was assessed by calculating positive predictive value (PPV) and negative predictive value (NPV).

Results. 33 patients out of 103 (32%) were positive to immunoassays. HIPA was performed on only 9 patients; for the remaining 24 patients, it was not possible to carry out HIPA due to a lack of sufficient samples. In the group of 24 patients, clinical management was based solely on the immunoassays results. In the group of 9 patients, the distribution of 4Ts scores showed a predominance of intermediate-risk cases (7), with some patients classified as high probability (2). In the same group Immunoassays demonstrated a higher rate of positivity compared to the functional assay (ELISA 100%, CLIA 78%, LIA 89%), with HIPA positive in approximately half of the cases (67%). Concordance with HIPA was highest for CLIA (88.9%), followed by ELISA and LIA (both 66.7%). CLIA showed a high PPV (85,7%) and a NPV 100%, indicating strong rule-out capability. In contrast, ELISA and LIA showed lower reliability in excluding HIT, with NPV values of 0%.

Conclusions. The results suggest a hierarchical role among immunoassays in HIT diagnosis, with variable diagnostic performance. The integration of immunoassays with an intermediate-to-high 4Ts score may support exclusion of HIT, potentially reducing the need for functional testing. However, functional assays remain essential in cases with discordant or uncertain results.

Comparison	Simple Accordance	Cohen's kappa (k)	Result
ELISA vs HIPA	66,70%	0	absence of variance in the ELISA
CLIA vs HIPA	88,90%	0,73	a real and strong agreement
LIA vs HIPA	66,70%	-0,12	systematic disagreement



INVESTIGATING THE MEAN PLATELET VOLUME OF PATIENTS WITH LIVER CIRRHOSIS AND CHRONIC LIVER DISEASE: A CASE-CONTROL STUDY

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Background and Aims. Haemostasis is rebalanced in patients with liver cirrhosis, but few and contradictory data are available regarding the platelet size. We designed this study to investigate the mean platelet volume (MPV) in patients with liver cirrhosis.

Methods. All patients with liver cirrhosis and chronic liver disease were consecutively enrolled among the outpatients followed up at the Hepatology outpatient clinic of hospital San Paolo (Milan). Control subjects were enrolled among healthcare workers of hospital San Paolo. All subjects had at least one complete blood count (CBC) performed at the laboratory of hospital San Paolo between 2015 and 2020 (normal range for MPV: 9.3-12.6 fL). All CBCs were performed with the same instrument during this time. The primary outcome was the comparison of the MPV in the three groups. Additionally, the MPV was evaluated in cirrhotic patients classified according to their Child-Pugh score at the time of blood withdrawal and history of previous decompensation (which we defined as any among ascites, portosystemic encephalopathy, variceal bleeding, spontaneous bacterial peritonitis and portal vein thrombosis). Finally, in patients with liver cirrhosis, we evaluated the correlations between platelet count and the MELD-Na score at the time of blood withdrawal with the MPV.

Results. We enrolled 60 controls (32 females, median age 47 years, IQR 39-52), 120 patients with chronic liver disease (63 females, 63 years, IQR 53-73) and 120 patients with liver cirrhosis (52 females, 67 years, IQR 56-75). Cirrhotic patients had significantly lower median platelet counts ($122x10^9$/L, IQR 78-175) compared to chronic liver disease patients ($220x10^9$/L, IQR 185-260) and controls ($251x10^9$/L, IQR 226-277) (p<0,0001). Cirrhotic patients' Child-Pugh score was A for 59 subjects, B for 37 and C for 24. Sixty cirrhotic patients (50%) had a history of previous decompensation. The median MPV was significantly higher both in cirrhotic patients (11.3 fL, IQR 10.4-12.3) and chronic liver disease patients (11.0 fL, IQR 10.2-11.8) compared to controls (10.5, IQR 9.9-11.2; p<0.0001 and p=0.01, respectively). The proportion of cirrhotic patients with a MPV higher than the upper limit of the reference range was 13% (95% CI, 8-20), significantly higher compared to controls (0%, 95% CI 0-6, p=0.0072). Neither the median MPV nor the proportion of patients with a MPV higher than the reference range significantly differed across Child-Pugh A, B and C cirrhotic patients. The proportion of cirrhotic patients with a MPV higher than the reference range was non-significantly higher in patients with previous decompensation (20%, 95% CI 11-32 vs 7%, 95% CI 2-16; p=0.0575). There was an inverse correlation between the platelet count and the MPV (r=-0.36, p<0.0001) and a mild direct correlation between the MELD-Na score and the MPV (r=0.21, p=0.02) in cirrhotic patients.

Conclusions. Taken together, our results are in keeping with the notion that increased platelet size signals compensatory platelet production in response to consumption and/or sequestration, but in liver cirrhosis, contrarily to chronic liver disease, the MPV appears to plateau, with less pronounced variations that often fail to reach statistical significance as liver disease progresses. This may reflect the coexistence of pathomechanisms with opposite effects on platelet size, including inflammation, hypersplenism, decline in TPO synthesis, in patients with more advanced disease.



A RISK-ADAPTED, MULTIDISCIPLINARY CONSENSUS FOR ADULT ITP MANAGEMENT: BRIDGING GUIDELINES AND REAL-WORLD PRACTICE

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Background and Aims. Immune thrombocytopenia (ITP) is a rare and heterogeneous immune-mediated disorder characterized by unpredictable bleeding risk, paradoxical thrombotic complications, and significant treatment-related burden. Despite the availability of multiple therapeutic options, real-world management remains highly variable, and optimal sequencing of therapies is still debated. We aimed to develop a multidisciplinary, real-world regional consensus to standardize the management of adult ITP and address current unmet clinical needs.

Methods. A structured narrative review of international guidelines and recent evidence was integrated with real-world clinical experience. Multidisciplinary meetings involving 25 experts from the three Tuscan university centers and affiliated hospital networks were conducted to define key clinical statements. Core domains included diagnosis, treatment thresholds, therapeutic sequencing, management of refractory disease, and patient-centered outcomes. Consensus was reached with a level of agreement >90% for all recommendations, with a focus on lo safety-driven and individualized care.

Results. The consensus highlights persistent unmet needs in ITP, including variability in treatment initiation, risk of overtreatment, and lack of standardized sequencing beyond first-line therapy. A risk-adapted strategy was proposed: observation for asymptomatic patients with platelet counts >30×10^9/L; early treatment for <30×10^9/L and/or bleeding; and individualized decisions in intermediate-risk scenarios. Short-course corticosteroids remain first-line therapy, with IVIg reserved for urgent indications. TPO-RAs are identified as the preferred second-line option due to high response rates (~70–90%) and sustained efficacy, while fostamatinib represents a key alternative in patients with high thrombotic risk. Rituximab is reserved for selected cases requiring treatment-free intervals. Splenectomy is deferred and restricted to highly selected patients. The consensus also emphasizes the emerging role of novel agents (FcRn inhibitors, BTK inhibitors, and B-cell targeted therapies) and combination strategies in refractory disease, as well as the critical impact of fatigue, psychological burden, and long-term treatment exposure on quality of life.

Conclusions. This regional consensus provides a pragmatic, safety-oriented, and future-focused framework for ITP management, integrating current evidence with real-world practice. A high-agreement multidisciplinary approach may reduce variability, optimize treatment sequencing, and better address unmet needs, supporting a shift toward personalized and standard care in ITP.



INCOMPLETE THROMBIN INHIBITION: BIOCHEMICAL AND FUNCTIONAL EVIDENCE OF ADP P2Y1 RECEPTOR DESENSITIZATION IN HUMAN PLATELETS

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Background and Aims. Adenosine diphosphate (ADP) is a key agonist of platelet activation and aggregation through the stimulation of purinergic receptors $P2Y_1$ and $P2Y_{12}$. Tight regulation of ADP-mediated signaling is essential during platelet plug formation. It has recently been demonstrated that the $P2Y_1$ receptor, upon ADP stimulation, can be downregulated through a protein kinase C (PKC)-dependent phosphorylation mechanism, leading to receptor desensitization. First we demonstrated that a prior platelet thrombin activation reduces PLC activation and Calcium mobilization induced by ADP, suggesting a capability of thrombin to densitize P2Y1 receptor. When pre-analytical procedures are not properly followed, ADP responses is lacking. The aim of this study was to investigate whether residual thrombin activity, under such conditions, induces desensitization of platelet $P2Y_1$ signaling pathways in a PKC-dependent manner, thereby to verify if limits ADP induced platelet response.
Methods. Human platelets obtained from sodium citrate-anticoagulated blood were prepared under different agitation conditions (3 times manual inversions vs mild shaking; in presence or absence of hirudin, a thrombin inhibitor). Platelets were stimulated with ADP (0.8, 2, and 4 μM) to assess both platelet aggregation and in washed, aspirin-treated platelets, intracellular calcium mobilization was measured using FURA-2 as a probe. It was also evaluated PKC activity by analyzing the phosphorylation of PKC substrates at baseline (T=0) and after 2 hours (T=2h) by Western blot analysis.
Results. Platelets analyzed 2 hours after blood collection, subjected to mild shaking and not treated with hirudin, showed reduced ADP-induced aggregation, accompanied by a marked attenuation of intracellular calcium mobilization, indicating decreased responsiveness of the $P2Y_1$ receptor. Normal response were observed both in the shaking hirudin treated sample and in samples correctly agitate by inversion. In contrast, PKC shows a slightly activation immediately after the blood sampling that become higher after two hours, in shaking treated platelets. Hirudin treatment showed no PKC activation either immediately or after 2 hours, as well as agitate sample and no treated with hirudin.
Conclusions. Our findings demonstrate that insufficient inhibition of thrombin during platelet preparation induces desensitization of the $P2Y_1$ receptor, leading to reduced platelet responsiveness to ADP. This artefact can be the cause of variability in platelet aggregation results across different laboratories. A thrombin-dependent, PKC-mediated mechanism may represent an additional regulatory pathway limiting platelet activation during sustained stimulation. To the best of our knowledge, this is the first evidence that a thrombin contributing to the prevention of excessive platelet aggregate, similar to the limitation of platelet plug formation endothelial dependent.

ABSTRACT N. PO091

RESPONSE AND CARDIOVASCULAR SAFETY OF FOSTAMATINIB IN CHRONIC IMMUNE THROMBOCYTOPENIA: A REAL WORLD ANALYSIS

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Background and Aims. Real-world evidence on fostamatinib (FST) in immune thrombocytopenia (ITP) has expanded substantially in recent years, with multicentre national experiences from Spain and Italy confirming its effectiveness and safety in routine clinical practice. Additional cohort analyses remain clinically relevant to better define treatment patterns and outcomes in patients with complex biological and clinical features, including autoimmune diathesis and cardiovascular/thrombotic risk. We therefore aimed to describe the characteristics of a real-world cohort of chronic ITP treated with FST, and to assess response rate, time to response, treatment exposure, and cardiovascular safety, while also exploring whether earlier response was associated with longer treatment exposure.

Methods. We retrospectively evaluated 29 patients with chronic ITP treated with FST in a real-world setting, with data cut-off on April 12, 2026. Outcomes of interest included overall response rate, time to response, treatment exposure, and cardiovascular safety. We also explored whether earlier response was associated with longer treatment exposure. Baseline patient and treatment characteristics are reported in Table 1.

Results. Baseline characteristics are summarized in Table 1. Briefly, the cohort showed a median TH2 score of 1, with only 4/29 patients (13.8%) displaying a hemorrhagic-risk profile, while the remainder had a prothrombotic profile; moreover, 18/29 patients (62.1%) had at least one cardiovascular risk factor. Overall response rate was 75.9% (22/29), including 15 complete responses and 7 partial responses, while 7 patients were non-responders. Among responders, median time to response was 15.5 days (IQR 10–42.5; range 3–409), with a median platelet count at response of 160×10^3/mmc. In heavily pretreated patients, overall response rate was 62.5% (5/8). At cut-off, 16 patients were still on treatment, with a median platelet count of 170×10^3/mmc (range 65–328); response was maintained in all but 2 patients who shifted from complete to partial response. No significant association was observed between shorter time to response and longer treatment exposure (Spearman rho=0.37, p=0.091). No new cardiovascular events were observed.

Conclusions. In this real-world chronic ITP cohort, fostamatinib showed high response rates and rapid activity, including in heavily pretreated patients. Outcomes were consistent with published real-world evidence. While early response did not predict longer treatment exposure, fostamatinib delivered meaningful and sustained benefit across this real-world cohort. Particularly reassuring was the absence of new cardiovascular events in a population enriched for cardiovascular risk factors.

Table 1. Baseline population characteristics

Characteristic	Value
Patients, n	29
Female sex, n (%)	21 (72.4)
Male sex, n (%)	8 (27.6)
Median age at diagnosis, years (range)	49 (11–84)
Median prior treatment lines, n	3
Heavily pretreated patients*, n (%)	8 (27.6)
Splenectomized patients, n (%)	7 (24.1)
Autoimmune profile	
Autoimmune diathesis, n (%)	14 (48.3)
Antiphospholipid antibodies positivity, n (%)	5 (17.2)
Cardiovascular/thrombotic profile	
Prior cardiovascular/thrombotic history, n (%)	5 (17.2)
– Ischemic heart disease, n (%)	2 (6.9)
– Deep vein thrombosis, n (%)	2 (6.9)
– Transient ischemic attack, n (%)	1 (3.4)
≥1 cardiovascular risk factor/comorbidity, n (%)	18 (62.1)
– Arterial hypertension, n (%)	11 (37.9)
– Hypercholesterolemia, n (%)	8 (27.6)
– Diabetes mellitus, n (%)	6 (20.7)
– Obesity, n (%)	5 (17.2)
– Smoking, n (%)	3 (10.3)
– Metabolic syndrome, n (%)	1 (3.4)
– Chronic heart failure, n (%)	1 (3.4)
– Chronic venous insufficiency, n (%)	1 (3.4)
– Abdominal aortic ectasia, n (%)	1 (3.4)
– Atrial fibrillation, n (%)	1 (3.4)
– Dilated cardiomyopathy, n (%)	1 (3.4)
TH2 score analysis	
Median TH2 score	1
Hemorrhagic-risk TH2 profile, n (%)	4 (13.8)
Prothrombotic TH2 profile, n (%)	25 (86.2)
Treatment characteristics	
Fostamatinib started for non-response, n (%)	21 (72.4)
Fostamatinib started for platelet count oscillation, n (%)	5 (17.2)
Fostamatinib started for adverse events to prior therapies, n (%)	3 (10.3)
Bridging treatment, n (%)	16 (55.2)

*Heavily pretreated defined as ≥4 prior treatment lines.



HEPARIN-INDUCED THROMBOCYTOPENIA IN A PATIENT WITH GUILLAIN-BARRÉ SYNDROME: A POSSIBLE LINK WITH IMMUNE DYSREGULATION

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Background. Heparin-induced thrombocytopenia (HIT) is a potentially life-threatening immune-mediated adverse reaction caused by antibodies against platelet factor 4 (PF4)-heparin complexes, leading to platelet activation and an increased risk of thrombosis. Conditions associated with systemic immune activation may facilitate antibody formation through immune priming. A retrospective study (2018) reported that patients with HIT were significantly more likely to have a concomitant chronic autoimmune disease compared with those without HIT, suggesting a potential association between immune dysregulation and the development of HIT. Guillain-Barré syndrome (GBS) is an acute immune-mediated neuropathy, typically triggered by infections and characterized by dysregulated immune responses. Although rare, it represents a neurological emergency as a potentially fatal condition.

Case Report. We report an 87-year-old female with post-infectious GBS, occurring 10–14 days after gastroenteritis, with anti-GM1 IgG and anti-GD1a antibody positivity, treated with plasma exchange with good neurological response. According to the Padua Prediction Score, pharmacological thromboprophylaxis was indicated. Low-molecular-weight heparin (enoxaparin 4,000 IU subcutaneously once daily) was administered for five days and discontinued due to an isolated haemoglobin decrease to 8 g/dL (−2 g/dL from baseline), without thrombocytopenia. Anaemia was attributed to ongoing plasma exchange and resolved after completion of treatment and transfusion support. Following treatment completion, a femoral peripherally inserted central catheter (PICC)-related deep vein thrombosis (DVT) was diagnosed and therapeutic-dose enoxaparin was initiated. Platelet counts remained stable (>150×10^9/L), but within 24 hours of therapeutic heparin re-exposure, platelet count dropped to 85×10^9/L (>50% reduction), reaching a nadir of 30×10^9/L over subsequent days. The 4T score indicated high probability for HIT (score 6), prompting immediate discontinuation of heparin and initiation of fondaparinux at therapeutic dose. Anti-PF4/heparin IgG antibodies by ELISA were strongly positive, and a functional platelet activation assay confirmed heparin-dependent platelet activation, consistent with definite HIT. Anticoagulation with fondaparinux was continued. During the acute phase, a further catheter-related upper limb DVT (midline, left arm) occurred. Concomitantly, neurological worsening with suspected cortical hypodensity on brain CT was observed, although its thrombotic nature remained uncertain in the context of GBS.

Conclusions. This case highlights a temporal association between GBS-related immune activation and HIT onset, supporting the hypothesis that immune dysregulation, including acute conditions, may lower the threshold for anti-PF4 antibody development. Plasma exchange may represent a potential confounding factor in platelet count interpretation and, in this case, did not prevent the occurrence of high-titre antibodies, possibly due to ongoing immune activation. These findings highlight the need for increased clinical vigilance and suggest that acute autoimmune states may represent an underrecognized risk context for HIT. Further studies and additional case reports are needed to better define this potential association.



HOW LONG IS TOO LONG? A CASE OF SEVERE PERSISTENT THROMBOCYTOPENIA

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Background. The diagnostic differential of thrombocytopenias is wide. The periodic re-evaluation of the working diagnosis is of crucial importance, especially in the face of poor response to treatment, as 1 in 7 patients suspected of having primary immune thrombocytopenia (ITP) are misdiagnosed.

Case report. A 42-year-old woman was admitted on August 1st, 2025, because of severe new-onset thrombocytopenia ($9x10^9$/L, n.v. 150-350$x10^9$/L) and moderate normocytic anemia (9.2 g/dL, n.v. 12.3-15.3 g/dL). She was symptomatic for fatigue but otherwise in good clinical condition. At the time of admission, haemolysis markers were negative and there were no immature cells or schistocytes on the peripheral blood film. We suspected ITP and started high-dose dexamethasone and intravenous immunoglobulin. Because her platelets remained at critically low levels, we started romiplostim, again with no response. Because of the poor response to ITP-directed therapies, we performed a bone marrow biopsy, which revealed increased megakaryocytes, dismyelopoiesis and MF-1 fibrosis, and ordered a PET-CT, which showed hepatosplenomegaly and multiple metabolically active lymphadenopathies both below and above the diaphragm. We performed an excisional lymph node biopsy on August 18th. In the meantime, the patient's clinical condition quickly worsened. She developed an abrupt increase in inflammatory markers, low-grade fever, nocturnal night sweats, worsening kidney function, a decline in her urine output and subsequent fluid overload, requiring the start of intermittent dialysis. The rapidly evolving clinical picture and the findings from the lymph node biopsy (marked hypervascularity, lymphoid follicle atresia and polyclonal plasmacellular infiltrate) rose the suspicion of TAFRO, a rare and potentially life-threatening form of idiopathic multicentric Castleman disease characterized by thrombocytopenia, anasarca, bone marrow fibrosis, renal dysfunction and organomegaly not associated with HIV, EBV or HHV-8 infection. Flow cytometry (FC) evaluations during florid disease revealed increased p-selectin positive platelets (13%, n.v. <7%), inappropriately low reticulated platelets (7%, n.v. <16%), and increased platelet desyalilation (8%, n.v. <0.2%). From August 22nd, we started treatment with high-dose methylprednisolone, rituximab and the anti-IL6 monoclonal antibody siltuximab. With this course of treatment, the patient's condition improved: her inflammatory markers declined until normalization, she was weaned off dialysis and her constitutional symptoms resolved. Despite this, severe anaemia and thrombocytopenia persisted, with development of intravascular haemolysis (consumed haptoglobin, increased lactate dehydrogenase and reticulocytes) and symptomatic hypertension. Disseminated intravascular coagulation, thrombotic thrombocytopenic purpura and intracranial haemorrhage were ruled out. We suspected a complement-mediated thrombotic microangiopathy (TMA) and administered eculizumab as rescue therapy on September 16th. Unfortunately, the patient died of refractory septic shock on September 23rd.

Conclusions. Our FC findings suggest that, during florid TAFRO, impaired megakakaryopoiesis and platelet desyalilation can contribute to thrombocytopenia. In the described case, the persistence of thrombocytopenia and the onset of neurological symptoms despite the control of the inflammatory syndrome prompted the recognition of a superimposed TMA.

ABSTRACT N. PO094

ARTIFICIAL INTELLIGENCE IN PULMONARY EMBOLISM PHENOTYPING: A SCOPING REVIEW

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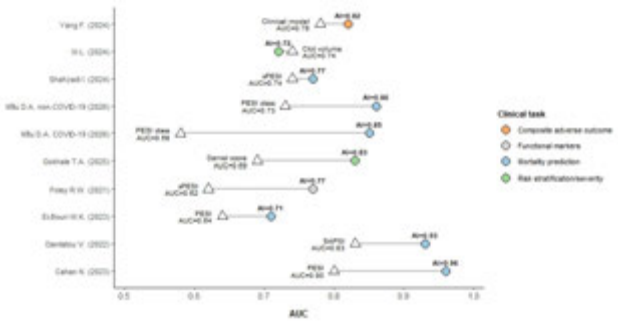
Background. Pulmonary embolism (PE) phenotyping aims to stratify patients according to clinical, radiological, and prognostic features to guide management. Artificial intelligence (AI) tools are increasingly applied to PE for risk stratification and outcome prediction, yet the scope, methodological quality, and clinical applicability of these approaches remain unclear.

Aims. To systematically map the existing literature on the application of AI in PE phenotyping, describe methodological characteristics and performance metrics, and identify gaps in current evidence.

Methods. A scoping review was conducted in accordance with the JBI methodology and the PRISMA-ScR checklist. Eligible studies included adult patients with imaging-confirmed or administratively coded PE and applied AI methods for phenotyping.

Results. After screening 2,074 records, 22 studies met inclusion criteria. Publications increased markedly in recent years, with 17 of the 22 studies published between 2023 and 2025. Reported sample sizes varied widely, ranging from 70 to 6,853. All studies were retrospective, with most conducted at a single center. Traditional machine learning models were used in 14 studies, deep learning approaches in 3, combined deep learning and traditional machine learning in 2, commercial imaging AI in 2, and quantitative imaging plus traditional machine learning in 1; radiomics-based features were used in 4 studies. Imaging-only inputs were most common, followed by clinical/laboratory data and multimodal models. Mortality prediction was the most frequent clinical task, followed by PE risk stratification or severity classification, composite adverse outcome prediction, functional marker assessment, and clot-burden evaluation. AI-derived model performance was most frequently reported using the area under the receiver operating characteristic curve (AUC), with values ranging from 0.63 to 0.97; 6 of 20 studies with reported AUCs achieved an AUC ≥0.90. Direct comparative evaluation against existing clinical or imaging-based scores was available in 9 studies, corresponding to 10 paired comparisons; AI-based models outperformed the comparator in 9 of 10 comparisons (Figure 1). External or temporal validation was conducted in a minority of studies.

Conclusions. This scoping review identified an arising publication trend in AI-phenotyping related articles. The literature is characterized by retrospective designs, frequent single-center cohorts, and substantial heterogeneity in study populations, data sources, and AI methodologies. Most studies focused on mortality prediction or risk stratification, while external validation and multimodal modeling were less frequently performed. Despite promising AI-model prediction capabilities and generally higher AUCs compared with traditional methods, the evidence reveals important methodological limitations, highlighting key research gaps and the need for standardized reporting to support interpretability and clinical implementation.



ABSTRACT N. PO095

HEPARIN-INDUCED THROMBOCYTOPENIA PRESENTING AS A CIRCUIT-TRIGGERED PULMONARY SYNDROME IN HEMODIALYSIS: A CASE REPORT

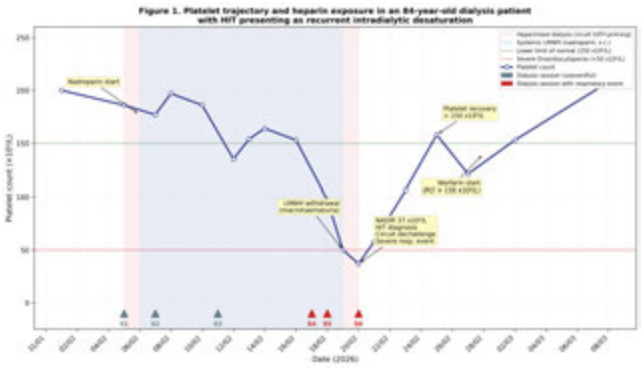
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Background. Heparin-induced thrombocytopenia (HIT) is an immune-mediated prothrombotic disorder caused by antibodies against PF4/heparin complexes, leading to platelet activation and thrombin generation. In hemodialysis (HD), repeated exposure to heparin and extracorporeal circuits increases the risk of HIT. A distinct clinical phenotype, the acute systemic reaction, may occur minutes after heparin exposure and includes dyspnoea, chest symptoms and hemodynamic changes. A pulmonary-predominant form, mimicking pulmonary embolism without detectable thrombosis, has been described. However, cases presenting exclusively as recurrent intradialytic dyspnoea temporally linked to circuit exposure during HD, without macrovascular thrombosis, remain rare, with fewer than 15 reports in the literature.

Case report. An 84-year-old man with bladder cancer was admitted for urosepsis and developed acute kidney injury requiring HD. He was exposed to unfractionated heparin during dialysis and to therapeutic-dose low-molecular-weight heparin for chronic atrial fibrillation. During HD, he developed three recurrent episodes of acute dyspnoea with desaturation occurring within minutes of circuit initiation. Symptoms were severe, unresponsive to bronchodilators and steroids, and required interruption of dialysis and ventilatory support. Notably, all episodes resolved rapidly after circuit disconnection, with no symptoms between sessions. Pulmonary embolism was excluded by CT angiography. The temporal association with dialysis and resolution after dechallenge, in the absence of systemic heparin (previously discontinued due to haematuria), suggested a circuit-triggered mechanism (Fig. 1). HIT was suspected (4Ts score: 8) and confirmed by positive anti-PF4/heparin antibodies. Heparin from the dialysis circuit was discontinued and replaced with regional citrate anticoagulation, after which HD continued without further respiratory events. Due to high bleeding risk, no immediate alternative anticoagulation was started. Vitamin K antagonist therapy was introduced only after platelet recovery. No thrombotic complications occurred.

Conclusions. Dyspnoea should be actively considered as a potential manifestation of HIT in hemodialysis patients, particularly when it occurs acutely after circuit exposure and in association with thrombocytopenia. This case supports the existence of a rare pulmonary HIT phenotype characterized by recurrent intradialytic respiratory symptoms without macrovascular thrombosis. The strict temporal relationship with the extracorporeal circuit may represent a key diagnostic clue, even before laboratory confirmation. The absence of pulmonary embolism on imaging suggests a mechanism of localized platelet activation and microthrombosis rather than embolic disease. This report adds to the limited available literature and is notable for the clear reproducibility of symptoms exclusively during circuit exposure, as well as for the identification of the extracorporeal circuit as the predominant trigger in the absence of systemic heparin. These features strengthen the recognition of this underdiagnosed clinical presentation. Regional citrate anticoagulation represents a safe alternative for dialysis continuation in the acute phase. Moreover, management of anticoagulation after HIT should be individualized, particularly in patients with high bleeding risk, balancing guideline recommendations with clinical context.





IDENTIFICATION OF A NEW VARIANT IN THE *RASGRP2* GENE IN A CHILD WITH SUSPECTED GLANZMANN THROMBASTHENIA

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Introduction. Congenital platelet disorders constitute a heterogeneous group of primary hemostatic defects that are often difficult to diagnose without an integrated approach that includes functional testing. We report the case of a child with suspected Glanzmann thrombasthenia, in whom a novel variant of the *RasGRP2* gene (NM_001098671.2) was identified that cosegregates with the clinical phenotype.

Methods. An 8-year-old boy, presenting with recurrent epistaxis and bruising and without a significant family history, was evaluated at our center. Initial tests showed normal PT and aPTT and impaired platelet function (PFA-100), suggesting a platelet disorder such as Glanzmann's thrombasthenia. However, the absence of aggregation tests and flow cytometric analysis prevented a definitive differential diagnosis. To identify the genetic cause and confirm the suspected diagnosis, clinical exome sequencing (6,600 genes) was performed using the NextSeq 550 platform (Illumina). Bioinformatic analysis included filtering based on allele frequency (<1%), phenotypic correlation, and information from major databases (ClinVar, gnomAD). All relevant variants were confirmed by Sanger sequencing.

Results. Exome sequencing identified a new homozygous missense variant (c.578T>C, p.Leu196Pro) in the *RasGRP2* gene, associated with a rare autosomal recessive hemorrhagic platelet disorder type 18 (OMIM-605577). Both parents are heterozygous carriers of the mutation. The variant is classified as a variant of uncertain significance according to ACMG guidelines, with a pathogenicity score of 4. Several in silico prediction algorithms (CADD, SIFT, PolyPhen-2) suggest a possible pathogenic effect of the variant on the protein. The frequency in the general population is less than 1%. Taken together, these data suggest a possible causal role of the variant in the patient's bleeding phenotype, ruling out a diagnosis of Glanzmann's thrombasthenia.

Discussion/Conclusion. In this study, we identified a new variant in the *RasGRP2* gene that is likely responsible for the patient's bleeding phenotype. The result highlights the importance of clinical exome sequencing as a complementary tool to functional and quantitative tests for an accurate differential diagnosis. An integrated approach allows for an accurate diagnosis and appropriate therapeutic management of patients with suspected congenital platelet disorders.



DETERMINANTS OF PLATELET COUNT IN A LARGE SINGLE TERTIARY CARE COHORT: IMPACT OF AGE, SEX, PLATELET REACTIVITY, CARDIOVASCULAR RISK FACTORS AND ANTIPLATELET THERAPY

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Background and Aims. Platelet count is influenced by age, sex, genetics, and ethnicity. However, the role of cardiovascular risk factors, such as smoking, hypertension, dyslipidaemia, and diabetes, in modulating platelet count remains unclear. In addition, the relationship between platelet count and platelet reactivity, responsiveness to antiplatelet therapy, including the potential role of treatment dose and duration, is still poorly defined. To the best of our knowledge, this is one of the few studies to systematically compare platelet counts in a large cohort stratified by age, sex, and clinical characteristics, thereby addressing important gaps in the current literature.

Methods. Platelet counts were collected from 10,610 patients who underwent light transmission aggregometry at the Policlinico Umberto I Hospital, and were initially analysed according to age (0-14, 15-64, 65-74, and ≥75 years) and sex. After application of inclusion and exclusion criteria, 4451 patients were included and stratified into four groups: healthy volunteers (N=506); controls (N=925), defined as patients with at least one cardiovascular risk factor; aspirin (N=2606) or clopidogrel-treated patients (N=414). Comparisons were further performed to assess differences in platelet counts in age, sex, cardiovascular risk profile, platelet reactivity, and response to antiplatelet therapy. The effects of aspirin dose (75-150 mg) and treatment duration (up to five years) were also evaluated.

Results. Platelet count showed a significant decline with age and a strong dependence on sex. In men, platelet count progressively decreased across all age groups, whereas in women the decline became more evident after the age of 65. No significant association was observed between platelet count and cardiovascular risk factors, nor with aspirin or clopidogrel therapy. Similarly, platelet count did not differ between responders and non-responders to antiplatelet therapy, except in the clopidogrel group, where non-responders exhibited higher platelet counts. Individuals with hyperreactive platelets had significantly higher platelet counts compared to those with optimal platelet reactivity. Neither aspirin dose nor treatment duration significantly influenced platelet count.

Conclusions. Platelet count is primarily determined by age and sex and appears largely independent of cardiovascular risk factors, antiplatelet therapy, treatment dose and duration. Hyper-reactive platelet phenotypes were consistently associated with higher platelet count.



REAL-WORLD EMERGENCY DEPARTMENT USE OF ANDEXANET ALFA FOR FACTOR XA INHIBITOR REVERSAL: AN ITALIAN COHORT

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Background and Aims. Andexanet alfa (AA) has been used for several years as a targeted reversal agent for factor Xa inhibitors in life-threatening or uncontrolled bleeding. Observational studies had already identified an approximately 10% thrombotic-event risk, subsequently confirmed by ANNEXA-I trial, which also triggered a regulatory debate after withdrawal from the North American market. In Europe, however, AA remains authorised, and Italian emergency department (ED) data are scarce. We aimed to describe real-world ED use, safety and clinical profile of AA in patients requiring urgent reversal of factor Xa inhibitors.

Methods. We performed a retrospective analysis of consecutive DOAC-treated patients managed in the ED of Ospedale di Circolo (Varese) from january 2022 up to december 2025 and receiving a specific antidote as reversal agent. This analysis focuses on patients treated with AA. Demographic characteristics, indication for anticoagulation, bleeding site or procedural indication, timing of administration, dose, follow-up imaging, 30-day outcomes, thrombotic and recurrent bleeding events, anticoagulation resumption and mortality were collected.

Results. Among 68 DOAC reversal cases using an antidote, 47 patients received AA. Median age was 80 years (IQR 76–86) and 26 patients (55.3%) were male. The reversed factor Xa inhibitor was apixaban in 30 cases (63.8%), rivaroxaban in 12 cases (25.5%) and edoxaban in 5 off-label cases (10.6%). Atrial fibrillation was the main indication for anticoagulation (40/47, 85.1%). Among patients with documented bleeding site, intracranial bleeding predominated (29/41, 70.7%), followed by gastrointestinal bleeding and other sites (6 cases each); 20 patients (42.6%) had a traumatic event. According to the primary indication, AA was used for life-threatening bleeding (41/47, 87.2%), whereas in 6 additional cases it was administered before urgent surgery in the absence of a documented active bleeding site, as off-label-use. Low-dose and high-dose regimens were used in 27 (57.4%) and 20 (42.6%) patients, respectively. Antidote administration occurred within 3 hours from ED access in 33/47 patients (70.2%). Red-cell transfusion was required in 11 patients (23.4%) and urgent surgery was indicated in 11 (23.4%). Follow-up imaging, when available, was stable or improved in 32/41 patients (78.0%). One recurrent bleeding event occurred within 30 days. Thrombotic events occurred at a mean of 4 days after AA administration and before anticoagulation resumption, with 4 events recorded among 43 evaluable patients (9.3%), consisting of 2 strokes, 1 myocardial infarction and 1 multiple site ischemia associated with endocarditis (one event occurred in an off-label use case). Overall mortality was 12/47 (25.5%). Anticoagulation was resumed in 23/46 evaluable patients (50.0%).

Conclusions. In this Italian ED cohort, AA was used mainly in elderly, high-risk patients with factor Xa inhibitor–associated intracranial bleeding. The observed thrombotic-event rate was consistent with the known safety profile from observational studies and ANNEXA-I trial, without suggesting an unexpected safety signal. In a setting where European authorisation remains unchanged, these data support the continued, carefully selected ED use of AA as a potentially life-saving reversal strategy, while emphasizing the need for early reassessment of antithrombotic therapy, structured follow-up and larger Italian registries.

ABSTRACT N. PO099

CORRELATION BETWEEN DIRECT ORAL ANTICOAGULANTS PLASMA LEVELS AND BRAIN VASCULAR EVENTS

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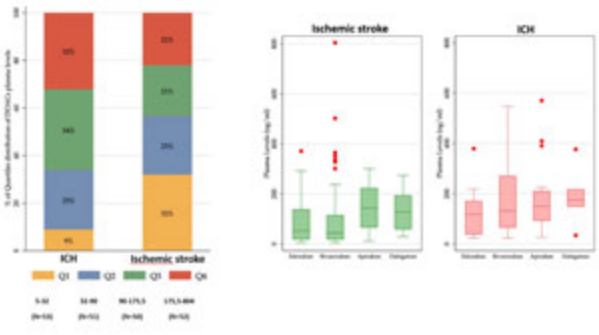
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Background and Aims. The reference ranges of direct oral anticoagulants (DOACs) plasma concentrations demonstrate a high intra- and inter-individual variability. Many studies reported an association between DOACs plasma levels and the risk of thrombotic and bleeding events. The aim of this single-center retrospective observational study was to assess the relationship between DOACs plasma levels measured at the time of acute ischemic stroke or intracerebral hemorrhage (ICH) in patients on DOAC for atrial fibrillation (AF) or venous thromboembolism (VTE).

Methods. The study analyzed 206 patients presented to the emergency department of Maggiore Hospital, Bologna, between November 2022 and July 2025 for acute ischemic stroke (150 patients) or ICH (56 patients) on DOAC at recommended doses for AF-related stroke prevention or VTE prevention, with dose adjustment when indicated, and adherent to treatment. Patients mean age was 80 years (47.1% female) and mean CHA2DS2-VA score was 3.7. 42.2% of patients was on low dose DOAC treatment. Blood samples for DOACs plasma level measurement were collected at the time of emergency room admission. The analysis was performed categorizing DOAC plasma levels into quartiles across the entire population and per single DOAC, calculating the median (IQR) with approximately equal group size.

Results. A significant association was observed between DOAC plasma levels and the type of cerebral event. The proportion of ischemic stroke progressively decreased across increasing quartiles (90.6% in Q1, 72.5% in Q2, 64.0% in Q3 and 63.5% in Q4, p=0.004), whereas ICH showed the opposite trend, increasing from 9.4% in Q1 to 36.5% in Q4 (p=0.004). These trends were observed even calculating the percentages of quartiles distribution of DOACs plasma levels for each single DOAC (figure). In the multivariable logistic regression model the Q1 of DOAC plasma levels, calculated either across the entire population or per single DOAC, was strongly associated with the outcome (OR 3.16, 95% CI 1.26-7.92, p=0.014 and OR 4.83, 95% CI 1.75-13.3, p=0.002 respectively), indicating that patients with the lowest drug concentrations had approximately three/four-fold higher odds of the ischemic event. Conversely, the Q4 was not significantly associated with the hemorrhagic outcome. It was observed that the ICH likelihood increases with DOAC plasma level raising. The relatively limited sample size may have reduced the statistical power to detect modest associations and interaction effects, potentially leading to the lack of statistically significant differences despite observable trends. The numerical difference between brain ischemic and hemorrhagic events in the analyzed cohort may have influenced the reduced predictive power of DOAC plasma levels to accurately predicting ICH.

Conclusions. Low DOAC plasma concentrations consistently emerged as the strongest predictor of brain thromboembolic events. The ICH likelihood increases with DOAC plasma level raising. The results of this study should be interpreted as hypothesis-generating. Larger prospective studies with standardized pharmacokinetic assessment will be required to better define the relationship between DOACs exposure and cerebrovascular outcomes.



ABSTRACT N. PO100

PREVALENCE OF CODING-REGION VARIANTS IN THE *PROC* GENE IN A SINGLE-CENTER COHORT OF PC-DEFICIENT SUBJECTS

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Background. Protein C (PC) deficiency is a rare inherited thrombophilia associated with an increased risk of venous thromboembolism (VTE). This study aimed to investigate the prevalence of *PROC* germline variants in a cohort of patients with PC deficiency.

Methods. Forty patients (M/F 18/22) with persistently low PC levels and no known acquired causes of deficiency were included. Baseline demographics, PC activity, and detailed personal and family histories of thrombosis were collected. The *PROC* gene was analyzed from peripheral blood DNA using next-generation sequencing (NGS) to identify coding region germline variants. Variants were annotated, classified by established criteria, and correlated with biochemical and clinical data.

Results. Thromboembolic events occurred in 15 patients (38%), including 13 venous and 2 arterial cases. Four patients (10%) experienced recurrent episodes. The median age at first event was 28 years (range 17-68). A family history of both PC deficiency and VTE was present in 27.5% of patients, while 20% had a family history of VTE alone and 20% had a family history of PC deficiency without VTE. The median PC activity was 58% (range 38-68%) and did not differ significantly between patients with and without thrombosis (48.5% vs 60%, p=0.0783). NGS identified germline PROC variants in 18 patients (45%), including 8 (20%) with prior VTE and 10 (25%) with a family history of VTE. Missense variants were most common (n=14, 77.8%), including Arg32Cys (n=5, three unrelated families), Gly239Glu (n=3, two families), and Ser382Phe, Val317Phe, Cys160Phe, Leu55Pro, and Asn144Ser (each n=1). One patient had a stop-gained variant (Trp157Ter), and three siblings had a frameshift variant (Val248GlyfsTer2) (Figure). PC activity differed significantly by genotype (Kruskal–Wallis p=0.0003), with higher median values in patients without variants (62.5%, range 49-68%) compared to those with missense (47%, range 38-65%), frameshift (47%, range 41-48%), or stop-gained variants (44%). Five of 22 patients without variants developed VTE. The VTE rate did not differ significantly between patients with and without variants (22.7% vs 20%, p = 0.14).

Conclusions. Approximately 45% of patients carried PROC variants, mainly missense. Patients with variants had lower median PC levels than those without, but mutation type did not affect deficiency severity. Notably, patients without detected variants had a VTE rate similar to those with variants, suggesting the presence of non-coding mutations or copy number variations affecting PROC expression.

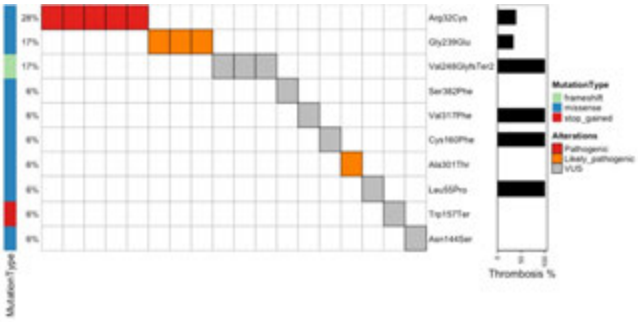


Figure. *Distribution of the identified PROC gene variants in the patient cohort. VUS, variant of uncertain significance.*



COMPREHENSIVE EVALUATION OF COAGULATION PROFILES IN REFRACTORY MODERATE-TO-SEVERE ULCERATIVE COLITIS

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Background and Aims. Patients with inflammatory bowel disease (IBD) are at increased risk of thromboembolic events, though the link between inflammation and hypercoagulability is not fully understood, as standard coagulation tests fail to capture the dynamic changes in hemostasis. Prothrombotic mechanisms are multifactorial, involving elevated procoagulant factors, increased platelet reactivity, and endothelial activation driven by systemic cytokines. This study aimed to characterize the hemostatic profile of patients with moderate-to-severe ulcerative colitis (UC) compared to healthy controls using standard assays, viscoelastic testing, and impedance aggregometry, and to evaluate associations with systemic and mucosal inflammation.

Methods. A prospective, single-center case–control study was conducted. Twenty-three patients with confirmed moderate-to-severe ulcerative colitis (UC), defined by a Mayo endoscopic subscore ≥2, and 23 age- and sex-matched healthy controls were enrolled. All patients had failed at least one prior line of therapy and were awaiting initiation of anti-JAK treatment. Standard coagulation assays were performed alongside rotational thromboelastometry and whole-blood impedance aggregometry. Disease activity in UC patients was assessed using the Mayo endoscopic subscore, as well as total and partial Mayo scores; systemic and mucosal inflammation were evaluated by C-reactive protein (CRP) and fecal calprotectin, respectively. Spearman's correlation analysis was used to assess the relationships between hemostatic parameters and inflammatory markers.

Results. Standard assays demonstrated significantly higher activities of Factor VIII (175 ± 43% vs 143 ± 21%, p=0.003) and Factor X (120 ± 26% vs 98 ± 12%, p<0.001). Rotational thromboelastometry showed a shortened clot formation time (CFT) in the extrinsic pathway (76 ± 22 s vs 101 ± 27 s, p=0.001). In addition, maximum clot firmness (MCF) was significantly increased in the extrinsic (67 ± 5 mm vs 57 ± 4 mm, p<0.001), intrinsic (65 ± 6 mm vs 57 ± 3 mm, p<0.001), and fibrinogen-specific (23 ± 8 mm vs 12 ± 3 mm, p<0.001) assays. Whole-blood impedance aggregometry revealed enhanced platelet aggregation in response to adenosine diphosphate (ADP test) (75 ± 21 vs 55 ± 11 U, p<0.001) and arachidonic acid (ASPI test) (94 ± 30 vs 45 ± 14 U, p<0.001). Regarding disease activity, systemic inflammation, as reflected by CRP levels, showed positive correlations with several procoagulant factors, including Factor VIII (p=0.013) and fibrinogen (p<0.001), as well as fibrinogen-specific MCF (p=0.006). In contrast, markers of localized intestinal inflammation, including fecal calprotectin, and clinical disease severity assessed by Mayo endoscopic subscore, total Mayo score, and partial Mayo score, were not significantly associated with either standard or viscoelastic hemostatic parameters.

Conclusions. Patients with moderate-to-severe ulcerative colitis show a marked hypercoagulable state and increased platelet reactivity versus healthy controls, mainly driven by systemic inflammation rather than local disease activity, underscoring the role of systemic markers in thromboembolic risk assessment; larger prospective studies are needed to confirm mechanisms and guide clinical strategies.



EFFICACY AND SAFETY OF VISCOELASTIC TESTING–GUIDED TRANSFUSION IN CIRRHOSIS UNDERGOING INVASIVE PROCEDURES: A META-ANALYSIS OF RANDOMIZED CONTROLLED TRIALS

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Background and Aims. Bleeding risk in cirrhotic patients undergoing invasive procedures is commonly assessed using conventional coagulation tests, such as the international normalized ratio (INR) and platelet count, often leading to prophylactic transfusion of blood products. However, these tests poorly reflect the rebalanced hemostatic state of cirrhosis. Viscoelastic testing (VET), including thromboelastography (TEG) and rotational thromboelastometry (ROTEM), provides a global assessment of coagulation and may enable a more rational transfusion strategy. We aimed to evaluate the efficacy and safety of VET-guided transfusion strategies in cirrhotic patients undergoing invasive procedures.

Methods. We performed a systematic review and meta-analysis of randomized controlled trials comparing VET-guided transfusion strategies with standard of care. Primary outcomes were procedure-related bleeding and transfusion requirements. Secondary outcomes included platelet transfusion, any fresh frozen plasma (FFP) exposure, and FFP-only transfusion. Risk ratios (RR) with 95% confidence intervals (CI) were pooled using the Mantel–Haenszel method. Subgroup and sensitivity analyses were performed according to VET modality and study population.

Results. Six randomized controlled trials including 296 patients were included in the quantitative synthesis. Procedure-related bleeding was rare and did not differ between groups (RR 0.74, 95% CI 0.24–2.31; I^2=0%). VET-guided strategies significantly reduced transfusion requirements, including any blood product transfusion (RR 0.33, 95% CI 0.26–0.44; I^2=56%), platelet transfusion (RR 0.20, 95% CI 0.13–0.32; I^2=40%), and any FFP exposure (RR 0.40, 95% CI 0.28–0.57; I^2=63%). A marked reduction was observed for FFP-only transfusion (RR 0.22, 95% CI 0.10–0.46; I^2=81%). Results were consistent across subgroup and sensitivity analyses.

Conclusions. VET-guided transfusion strategies significantly reduce blood product utilization without increasing bleeding risk in cirrhotic patients undergoing invasive procedures. These findings challenge the reliance on conventional coagulation tests and support a shift toward a physiology-based, individualized approach to hemostasis, with potential benefits for patient safety and resource optimization



THE EFFECT OF ALBUMIN ON SERUM CONCENTRATION OF DIRECT ORAL ANTICOAGULANTS: A CROSS-SECTIONAL STUDY

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Introduction. One of the main advantages of direct oral anticoagulants (DOACs) in the management of venous thromboembolism (VTE) is the possibility of administering at fixed doses without routine laboratory monitoring. However, concerns emerged regarding their use in obesity, severe chronic kidney disease, and concomitant drug therapy. In these situations, measurement of DOACs plasma concentrations had been proposed as a potential strategy to optimize therapeutic management and improve patient outcomes. DOACs display a relevant degree of binding to plasma proteins, predominantly to serum albumin, which represents the most abundant protein component in plasma. Hypoalbuminemia has been associated with an increased risk of bleeding among patients receiving DOAC therapy. However, few studies evaluated DOACs plasma concentrations. Therefore, the aim of the study was to evaluate the variation in peak and trough DOACs plasma concentrations according to serum albumin levels in a cohort of patients with VTE. Patients attending the study center were eligible if they had age ≥18 years; diagnosis of VTE with DOACs treatment; signed a written informed consent.

Results. The overall population consisted of 88 patients with 56.8% of male patients and a mean age of 67±14 years. 58% of patients presented with hypoalbuminemia. Patients with hypoalbuminemia were significantly older than those with normal albumin levels and showed a higher prevalence of male sex. Regarding risk factors, the prevalence family history of VTE, personal history of VTE, smoking habit, and active malignancy was similar between the two groups. The proportion of patients with a VTE provoked by a persistent or transient risk factor and that of unprovoked VTE were similar between groups. No significant difference was observed in renal function as assessed by eGFR. Correlation analysis did not demonstrate a significant relationship between serum albumin levels and standardized DOACs trough (p =0.78) and peak concentrations (p=0.40). No significant association between serum albumin levels and DOACs trough and peak concentrations has been found.

Discussion. The rationale for investigating the role of serum albumin stems from recent evidence suggesting an association between hypoalbuminemia and adverse outcomes in patients receiving DOACs. We sought to determine whether the increased clinical risk observed in hypoalbuminemic patients could be mediated by alterations in DOAC plasma concentrations. In our cohort, analyses of DOAC plasma concentrations did not demonstrate a significant association with serum albumin levels. Age was the only independent determinant (p = 0.027). One possible explanation for the lack of association between albumin levels and total plasma DOAC concentrations may lie in the mechanisms of fractional drug clearance. In hypoalbuminemia, the reduction in available binding sites leads to an increase in the unbound fraction of drug. Since the free fraction undergoes glomerular filtration, an increase in unbound drug may result in a proportional acceleration of kidney elimination. This mechanism may counterbalance the increase in pharmacologically active drug, leading to stabilization of total plasma concentrations. In conclusion, the present study suggests that serum albumin levels do not represent an independent determinant of total DOAC plasma concentrations.

ABSTRACT N. PO104

BLEEDING AND THROMBOTIC OUTCOMES DURING EXTENDED DIRECT ORAL ANTICOAGULANT THERAPY: AN EIGHT YEAR RETROSPECTIVE ANALYSIS

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Introduction. The optimal duration of anticoagulant therapy after deep vein thrombosis remains a matter of clinical debate. Standard treatment for acute venous thromboembolism (VTE), including deep vein thrombosis and pulmonary embolism, typically ranges from 3 to 6 months, whereas patients with persistent risk factors, recurrent events, thrombophilia, or post-thrombotic syndrome often require extended or indefinite therapy. Whether prolonged anticoagulation effectively reduces the risk of recurrent thromboembolic events while maintaining an acceptable bleeding profile continues to be a relevant clinical question. The introduction of direct oral anticoagulants (DOACs), particularly reduced-dose regimens such as rivaroxaban 10 mg and apixaban 2.5 mg, has provided new options for long-term secondary prevention. The aim of this study was to evaluate the incidence of thromboembolic and hemorrhagic events in a real-world cohort of patients followed at the Hemostasis and Thrombosis Service of Reggio Calabria who continued DOAC therapy beyond six months from diagnosis.

Methods. We retrospectively analyzed clinical data from 201 patients (104 males, 97 females; mean age 63.5 years, range 22–91) managed at our center between November 2017 and September 2025. The mean duration of anticoagulant therapy was 1285.1 days (range 180–3944). All patients were treated for secondary prevention of lower-limb venous thrombosis; 79 had experienced a single VTE episode, while 122 had a history of multiple events. A total of 66 patients had either congenital or acquired thrombophilia, and 4 had comorbidities associated with increased thrombotic risk. Demographic and clinical characteristics are summarized in Table 1.

Results. During follow-up, 9 bleeding events were recorded, including 8 minor episodes (2 epistaxis, 2 rectal bleeding, 2 menorrhagia, 1 gingival bleeding, and 1 microscopic hematuria) and 1 major event (vitreous hemorrhage), which led to discontinuation of anticoagulation. Four cases of superficial thrombophlebitis occurred, prompting escalation from prophylactic to therapeutic DOAC dosing. The cumulative incidence of bleeding events was 4.5% (9/201), while thrombotic events occurred in 2.0% (4/201). When expressed as incidence rates per person-time, bleeding events occurred at 1.27 per 100 patient-years and thrombotic events at 0.57 per 100 patient-years.

Conclusions. In this real-world cohort, extended anticoagulation well beyond the conventional 3–6-month period was associated with a low incidence of both thrombotic and hemorrhagic complications in patients considered at elevated risk of recurrence. Although bleeding events were numerically more frequent than thrombotic events, the absolute rates of both outcomes remained low. Interpretation should consider the limited number of events and the resulting wide confidence intervals. Future comparative analyses involving patients treated with DOACs lacking dedicated prophylactic dosing, as well as those maintained on vitamin K antagonists, may help clarify the relative safety and effectiveness of different long-term anticoagulation strategies.

Table 1. Baseline Characteristics of the Study Population (N = 201)

Characteristic	Value
Sex	n (%)
Male	104 (51.7)
Female	97 (48.3)
Age, mean (range)	63.5 (22–91)
VTE history,	n (%)
Single episode	79 (39.3)
Multiple episodes	122 (60.7)
Duration of therapy, mean (range), d	1285.1 (180–3944)
Thrombophilia, n (%)	66 (32.8)
Factor V Leiden Heterozygous	35
Prothrombin G20210 Heterozygous	26
Others	5
N/A	30
Comorbidities increasing thrombotic risk, n (%)	4 (2.0)
Study period	Nov 2017–Sep 2025

IMPACT OF ECOG PERFORMANCE STATUS ON CANCER-ASSOCIATED THROMBOSIS TREATED WITH DOACS: DATA FROM A MULTICENTER COHORT STUDY

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Background. Data on safety and effectiveness of direct oral anticoagulants (DOACs) in patients with cancer-associated thrombosis (CAT) and impaired functional status is limited. We evaluated the impact of Eastern Cooperative Oncology Group (ECOG) performance status on bleeding and thrombotic events in a real-world cohort.

Methods. Patients with CAT on DOACs were prospectively included in cohorts from six Italian centers and stratified by ECOG status (0–1 vs. 2-4). Primary outcomes were major bleeding (MB) and recurrent venous thromboembolism (VTE); secondary outcome was all-cause mortality. Incidence rates were calculated, and predictors of MB and VTE recurrence were assessed using Cox models within each ECOG subgroup.

Results. Among 817 patients, 702 had ECOG 0–1 and 115 had ECOG 2-4. Patients with ECOG ≥2 were older, had worse renal function, and more comorbidities (Table 1). MB occurred at 10.3% vs. 2.8% patient-years (HR 2.92, 95% CI 1.43–5.94) and recurrent VTE at 7.2% vs. 3.6% patient-years (HR 2.16, 95% CI 0.96–4.86) in ECOG 2–4 compared with 0–1 patients. In ECOG 0–1, bleeding was mainly related to anticoagulant treatment, whereas in ECOG 2-4 it was predominantly associated with chronic kidney disease. All-cause mortality occurred at 78.4% patient-years in ECOG 2–4 and 10.5% patient-years in ECOG 0–1 (HR 6.28, 95% CI 4.69–8.41).

Conclusions. Impaired functional status was associated to higher MB and mortality, while VTE recurrence did not differ across groups. Bleeding mechanisms differed by ECOG status, underscoring the need for individualized anticoagulation. In frail or end-of-life patients, deprescribing and shared decision-making are essential to balance benefit and harm.



ABSTRACT N. PO106

INTERACTIONS BETWEEN DIRECT ORAL ANTICOAGULANTS AND ANTIEPILEPTIC DRUGS (INTER-DOAC): A PROSPECTIVE OBSERVATIONAL STUDY

A. Rafanelli[1], C. Pizzanelli[3], M. Biagini[1], P. Chiarugi[4], M. Casini[4], P. Capozza[5], G. Guarini[5], L. Malloggi[4], G. Siciliano[3], R. De Caterina[5|6], L. Carrozzi[1|2], F. Pistelli[1|2], L. Marconi[2], A. Celi[1|2], R. Pancani[2]

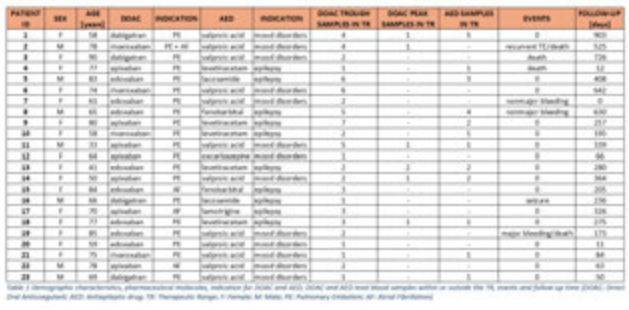
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Background and aims. Potential drug-drug interactions (DDI) limit concomitant use of antiepileptic drugs (AED) and direct oral anticoagulants (DOAC). Indeed, the European Society of Cardiology guidelines on the use of oral anticoagulants in patients with atrial fibrillation (AF) specifically recommend caution for most AED/DOAC combinations. However, knowledge about pharmacokinetic and pharmacodynamic DDI of AED and DOAC is limited and frequently restricted to in vitro findings. Moreover, plasma levels of direct anticoagulants are not routinely monitored with a lack of standardization in laboratory measurements and reference values. The availability of accurate DOAC plasma levels could lead to an improvement in clinical decisions and appropriate management in both emergency and routine situations. Through this study, we want to extend our knowledge about DOAC-AED DDI in vivo.

Methods. In this observational, prospective study, approved by the Italian Ethic Committee (CET03/2023 of 27 July 2023), we enrolled outpatients with non-valvular AF or pulmonary embolism (PE) and an indication for AED attending the Respiratory, Cardiology and Neurology Units in Pisa, Italy. Anthropometric parameters, comorbidities, repeated plasma DOAC and AED levels and clinical events (arterial/venous thrombosis, seizure, major or non-major clinically relevant bleeding, death) were recorded. For each DOAC plasma level we calculated the z-score based on data from 967 patients at the local laboratory, upon verification of their normal distribution. In the absence of universally accepted reference values, we defined the therapeutic range (TR) for DOAC as that corresponding to a z-score between -1.64 and 1.64. For AED, the TR was calculated based on the range provided by the local laboratory.

Results. Baseline characteristics of the study population (n=23), pharmaceutical molecules, DOAC and AED blood level within or outside the TR, events and follow-up time are listed in the table. A total of 136 blood tests were performed from September 2023 to March 2026. Each patient was followed up by the relevant specialist clinically. In 66 out of 68 (97%) trough samples and 7 out of 9 (78%) peak samples, respectively, plasma levels of DOAC were within the TR. In 24 out of 63 (38%) samples in patients with an indication for AED as antiepileptic therapy or mood stabilization, AED levels were within the TR. During follow-up (mean 294 days) we recorded a recurrent thromboembolic event, 2 non-major clinically relevant bleedings, a major bleeding and 2 episodes of seizure (in the same patient). Four patients died during the follow-up period, one of whom as a consequence of intracranial bleeding, one for neoplastic cachexia, one for respiratory failure in severe pulmonary emphysema and one for natural causes associated with advanced age. With the limit of the small sample size, we found no significant correlation between z-scores calculated for each DOAC or AED plasma levels and clinical events.

Conclusions. This study suggests that co-administration of AED and DOAC both in AF and PE patients results in DOAC acceptable blood values in a relevant percentage of cases; recurrences of venous thromboembolism or major bleeding appear to be manageable over a two and a half-year follow-up.





OUTCOME AND RISK OF CANCER IN SUPERFICIAL VENOUS THROMBOSIS WITH AND WITHOUT VARICOSE VEINS

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Introduction. Varicose veins are the main risk factor for superficial vein thrombosis (SVT), whereas SVT occurring in non-varicose veins has been suggested as a sentinel marker for cancer with higher risk of recurrence and venous thromboembolic events (VTE).

Objectives. To investigate if SVT occurring in non-varicose is associated with higher risk of VTE and of cancer development in comparison with varicose vein (VV) associated SVT.

Design. Retrospective cohort conducted in a single tertiary care hospital from 2005 to 2020.

Participants. Consecutive patients diagnosed with symptomatic SVT and without overt cancer underwent routine clinical evaluation, laboratory tests and received antithrombotic treatment.

Primary outcome measures. The cumulative 2-year incidence of objectively confirmed symptomatic PE and/or DVT and/or SVT.

Secondary outcome measures. Cancer development during 2-year follow-up.

Results. 519 patients (327 women-63%, median age 69.9 years IQR 21,5) were included of which 108 (20.8%) occurred in the absence of VV. The primary efficacy outcome occurred in 141 patients with VV (40.8%) and in 35 patients without VV (39.9%), OR 1.06 (95% CI: 0.66–1.71). During follow-up, 26 patients with VV developed new cancers (7.5%) vs. 7 patients without VV (7.8%), OR 0.97 (95% CI: 0.41–2.30). Multivariate regression showed that only recurrent VTE was independently associated with subsequent cancer development (OR: 2.44; 95% CI: 1.18-5.05; p=0.004).

Conclusions. Outcome of SVT occurring in non-varicose veins is similar to that occurring in VV. Patients with recurrent VTE after SVT may deserve extensive screening for occult cancer, regardless of the presence or absence of VV.



DIRECT ORAL ANTICOAGULANTS IN PATIENTS WITH VENOUS THROMBOEMBOLISM RECEIVING LONG-TERM IMMUNOSUPPRESSIVE THERAPY AFTER LIVER AND KIDNEY TRANSPLANTATION: A SINGLE-CENTER EXPERIENCE

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Background and aims. Managing oral anticoagulation in solid organ transplant (SOT) recipients is challenging due to complex thrombo-hemorrhagic risks and pharmacokinetic drug-drug interactions (DDIs). Most immunosuppressants (calcineurin and mTOR inhibitors) and direct oral anticoagulants (DOACs) share the CYP3A4 and P-gp pathways, risking sub-or-supratherapeutic drug levels. These case reports evaluate the safety and efficacy of DOACs in liver and kidney transplant patients.

Case reports. Case 1. A 62-year-old female, kidney transplant recipient due to IgA nephropathy, was managed with apixaban 2.5 mg BID for previous recurrent femoral deep vein thrombosis (DVT). At the 3-month follow-up, neither thrombotic recurrence nor hemorrhagic events were observed. Both tacrolimus levels and apixaban plasma concentrations remained consistently within the therapeutic range. Case 2. A 70-year-old male, kidney transplant recipient with paroxysmal atrial fibrillation treated with dronedarone, developed an idiopathic popliteal DVT. Due to potential multiple DDIs, a reduced dose of apixaban 2.5 mg BID was started after a short course of low-molecular-weight heparin (LMWH). During a 9-month follow-up, the patient presented with significant anemia without clear blood loss. Endoscopy revealed an ampulloma, necessitating temporary discontinuation of anticoagulant therapy, which was resumed 2-weeks later without further complications. Case 3. A 55-year-old male, renal transplant recipient with a history of recurrent superficial vein thrombosis (SVT) of the lower limbs, treated with rivaroxaban 10 mg. At the three-month follow-up, neither hemorrhagic nor thrombotic events were reported, serum levels of rivaroxaban, tacrolimus, and everolimus remained within the therapeutic range. Case 4. A 63-year-old male liver transplant recipient, originally transplanted for HCV-related cirrhosis, with idiopathic left common iliac vein thrombosis, treated with therapeutic dose of LMWH for two weeks, followed by apixaban 5 mg BID for six months, then apixaban 2.5 mg BID. Over a follow-up period exceeding one year, neither thrombotic recurrence nor hemorrhagic complications have been observed, with plasma levels of apixaban, tacrolimus, and everolimus consistently remaining within the therapeutic range. Case 5. A 56-year-old male kidney transplant recipient, for IgA nephropathy, is currently receiving apixaban 2.5 mg BID for previous right iliofemoral venous thrombosis. Throughout the six-month observation period, serum levels of tacrolimus, everolimus, and apixaban have consistently remained within the therapeutic range.

Conclusions. Our real-world data, although based on a small patient cohort, suggest that DOACs represent an effective and viable therapeutic strategy for managing DVT in transplant recipients. In our population, no thrombotic recurrences were observed, and the safety profile remained favorable with an acceptable risk of bleeding. Monthly monitoring of plasma levels for both immunosuppressants and DOACs proved essential in managing drug-drug interactions in these clinically challenging patients. Close multidisciplinary collaboration with nephrologists and hepatologists allowed for a tailored approach, confirming that an integrated model of care is fundamental to optimizing outcomes in such a fragile clinical setting.

ABSTRACT N. PO109

A RARE CASE OF ANEMIA AND THROMBOCYTOPENIA

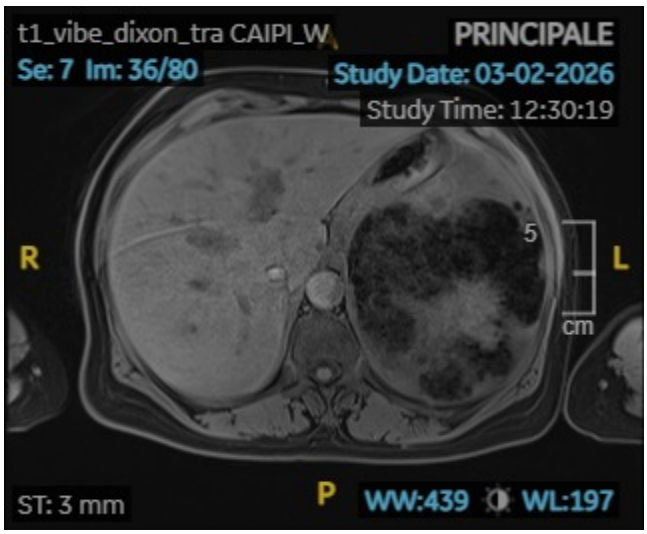
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Background. Fibroblastic reticular cell tumor (FRCT) is an extremly rare neoplasm arising from stromal cells of lymphoid tissues, characterized by aggressive biological behavior and significant diagnostic challenges. Due to its rarity, the current literature is limited to a small number of case reports, underscoring the heterogeneity of its clinical and pathological presentation and the absence of standardized diagnostic and therapeutic approaches.

Case Presentation. We describe the case of a 59-year-old woman followed at our hematology Department for heterozygous sickle cell trait, with a past medical history notable only for hysterectomy. Since 2021, she had developed iron-deficiency anemia associated with mild thrombocytopenia and splenomegaly, requiring repeated blood transfusions and parenteral iron supplementation. In 2023, both EGDS and Colonoscopy were unremarkable. In January 2026, the patient was hospitalized due to worsening anemia. She reported a weight loss of 10kg in the last two years and persistent pain in the left abdominal quadrants, without fever or overt bleeding. Laboratory exams revealed normocytic anemia (Hb 61 g/L) with moderate thrombocytopenia (Pts count 61×10^9/L), normal hemolysis parameters, mild prolongation of coagulation times (PT ratio 1.50, aPTT 1.39), elevated D-dimer levels (1670 µg/L), and increased inflammatory markers (CRP 159 mg/L). A slight increase in AFP was noted, while other tumor markers were negative. Imaging studies demonstrated marked heterogeneous splenomegaly (>18 cm) with a polylobulated lesion of approximately 12 cm, along with suspicious hepatic lesions. PET-CT revealed intense, heterogeneous splenic hypermetabolism with a central hypoactive area and focal hepatic uptake. Bone marrow examination showed hypercellularity with dyserythropoiesis and dysmegakaryocytopoiesis, without evidence of neoplastic infiltration. Liver biopsy identified a high-grade malignant neoplasm positive for cytokeratin MNF116, initially suggestive of undifferentiated sarcomatoid carcinoma. However, the differential diagnosis included accessory cell tumors such as FRCT, particularly given the radiological suspicion of a primary splenic lesion. As these entities differ significantly in prognosis and treatment, and splenic biopsy was contraindicated due to bleeding risk, the patient underwent splenectomy with concurrent thermal ablation of a hepatic lesion. Histological analysis of the spleen revealed a proliferation of spindle and pleomorphic cells with extensive necrosis, immunophenotypically positive for cytokeratin MNF116, consistent with high-grade FRCT. Postoperatively, marked thrombocytosis was observed, followed by stabilization of hematological parameters. One month later, contrast-enhanced CT showed no evidence of disease recurrence. The patient is currently awaiting oncological evaluation for adjuvant chemotherapy.

Conclusions. This case highlights the diagnostic challenges of FRCT, which may mimic undifferentiated carcinoma or sarcoma, particularly in the presence of cytokeratin expression. Accurate diagnosis requires a multidisciplinary approach integrating imaging, histopathology, and immunophenotyping. FRCT should be considered in the differential diagnosis of high-grade splenic tumors, especially when atypical epithelial markers are detected. Splenectomy remains crucial for definitive diagnosis. Further studies are needed to establish optimal management strategies given the rarity of this entity.



ABSTRACT N. PO110

CLINICAL OUTCOMES AND SURVIVAL OF UNUSUAL SITE VENOUS THROMBOSIS IN PATIENTS WITH AND WITHOUT MYELOPROLIFERATIVE NEOPLASMS: A RETROSPECTIVE SINGLE-CENTER STUDY

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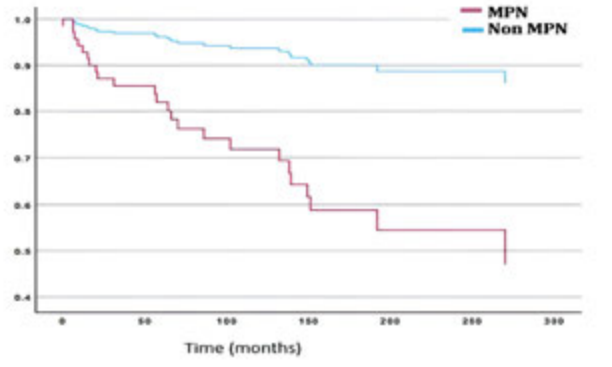
Background and Aims. Unusual site venous thromboses (USVT) are rare conditions involving the cerebral (CVT), splanchnic (SVT), renal, retinal, and gonadal veins. Available evidence regarding specific risk factors, prognosis, recurrence risk and survival is poorer than that for classical manifestations of venous thromboembolism (VTE). Myeloproliferative neoplasms (MPNs) are clonal disorders characterized by growth factor-independent proliferation of hematopoietic stem cells and bone marrow hypercellularity. MPNs are established prothrombotic conditions predisposing to USVT, particularly SVT, and are associated with an increased risk of bleeding complications and thrombotic recurrences. Here we analyze characteristics and long-term outcomes of a large single center cohort of CVT and SVT, associated or not with MPN.

Methods. We conducted a single-center retrospective study including 33 patients with CVT (12 MPN and 21 non-MPN) and 68 patients with SVT (49 MPN and 19 non-MPN) diagnosed and followed at our Department in the last five decades (36 M, 65 F, median age at USVT 42 y, median follow-up 143 m). Patients with malignancies other than MPN or liver cirrhosis at the time of USVT were excluded. Demographic characteristics, VTE risk factors, antithrombotic therapy, thrombosis recurrences in typical or atypical sites, major bleedings, and all-cause mortality were recorded. MPN diagnosis was performed according to current criteria at first observation and, when available, revised to the most recent ICC criteria. Survival analysis was performed with Cox regression model.

Results. Among the 33 CVT patients (12 M, 21 F) 36,4% (n=12) were MPN related, while SVT (24 M, 44 F) was associated with MPN in 72% (n=49) of cases. No gender or median age at USVT differences were observed comparing MPN to non-MPN patients. At least one VTE risk factor was present in 75% of non-MPN patients compared with 39.3% of MPN patients. Cumulative incidence of thrombotic recurrence was similar in the two groups, namely 2.43/100 patients/year in non-MPN (95% CI 1.1-4.2) and 2.96/100 patients/year (95% CI 1.8-4.3) in MPN patients. However, within the CVT subgroup, thrombotic recurrences were more frequent in MPN patients (n = 6) than in non-MPN patients (n=2, p=0.015). Cumulative incidence of major bleeding after USVT was significantly higher in patients with MPN (3.28/100 patients/year, 95% CI 1.94-4.62) compared with those without MPN (0.76/100 patients/year, 95% CI 0.15-1.8). In age-and-sex-adjusted Cox regression analysis, MPN was confirmed as an independent risk factor for major bleeding (HR 5.1, 95% CI 1.5–17.3; p=0.01; Figure 1) in USVT patients. All-cause mortality did not differ between MPN and non-MPN patients.

Conclusions. Among our patients with USVT, MPN patients showed an approximately fivefold higher risk of major bleeding than non-MPN patients, along with a higher rate of thrombotic recurrences in the CVT subgroup. Despite a lower prevalence of additional transient or acquired VTE risk factors, USVT-MPN patients experienced comparable overall recurrence rates, supporting the role of the underlying clonal disorder as a persistent prothrombotic driver. Altogether, our data emphasize the need for prospective studies to better define optimal management strategies and to refine risk-adapted therapeutic approaches in patients with MPN-associated USVT that take into account the delicate balance between thrombotic and hemorrhagic risk in these patients.

Figure 1. Age-and-sex-adjusted Cox regression analysis of major bleedings in patients with and without MPN.





A RARE CASE OF ACUTE PROMYELOCYTIC LEUKAEMIA PRESENTING WITH A PURELY THROMBOTIC DISSEMINATED INTRAVASCULAR COAGULATION PHENOTYPE

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Background. Disseminated intravascular coagulation (DIC) in patients with acute promyelocytic leukaemia (APL) typically manifests with severe haemorrhagic complications. While the coagulopathy of APL is notorious for its life-threatening bleeding risk, a purely thrombotic phenotype is rarely reported. We describe the case of a patient whose APL onset was characterized by widespread, multi-district arterial and venous thrombosis.

Case report. A 52-year-old woman, with a history of arterial hypertension and prior hysterectomy due to fibroids, presented to the Emergency Department with acute left-hand hyposthenia and hypoesthesia. Brain CT (non-contrast, angiography, and perfusion) and MRI confirmed a distal arterial occlusion of a branch of the right middle cerebral artery, associated with venous thrombosis of the right transverse sinus. Laboratory results showed pancytopenia, a mild increase in PT and reduced fibrinogen levels, confirming the diagnosis of DIC. A peripheral blood smear revealed 3% blasts, raising immediate suspicion of acute leukaemia. Treatment with ATRA was started promptly as soon as APL was suspected. Due to the extreme haemorrhagic risk of DIC associated with suspected APL, systemic thrombolysis was ruled out. After neurologic consultation, anticoagulation was initiated with unfractionated heparin (UFH) under rigorous aPTT monitoring. Subsequent total-body CT and Doppler ultrasound revealed a staggering thrombotic burden: thrombosis of the right hepatic vein and the portal branch for segment VIII and deep vein thrombosis (DVT) of the left popliteal vein. Sudden onset of left eye amaurosis, later confirmed by MRI as ischemia of the left retinal artery, resulting in permanent unilateral blindness. During hospitalization, a mild decline in platelet count prompted a switch from UFH to fondaparinux. Heparin-Induced Thrombocytopenia (HIT) was excluded via negative anti-heparin antibody testing. The diagnosis of APL was confirmed through both peripheral smear and bone marrow aspiration revealing the presence of promyelocytes and through FISH and PCR, showing detection of the t(15;17) translocation and the PML-RARα fusion transcript. As the patient was classified as non-high risk (WBC ≤ $10x10^9$/L), ATO was promptly added to the treatment regimen, with prednisone prophylaxis for differentiation syndrome. A good response to therapy was achieved in the absence of thrombotic or haemorrhagic complications, as well as serious adverse effects related to the treatment. At discharge, the patient was in morphological remission; therefore, anticoagulation was transitioned to apixaban, planned for a six-month full-dose course followed by a prophylactic dose (2.5 mg BID) until molecular remission is achieved.

Conclusions. DIC associated with hematologic malignancies is a pathologic condition characterized by increased fibrinolytic conditions and coagulation activation, rendering patients particularly prone to bleeding. This case represents a rare example of an exclusively thrombotic phenotype, which required a tailored therapeutic approach as the need for anticoagulation had to be carefully balanced against the high haemorrhagic risk. Given the lack of strong evidence regarding the optimal type of anticoagulant, the patient required close clinical and laboratory monitoring. Only after the acute phase was managed and the promyelocytic leukaemia treated, a DOAC was selected, a strategy supported by some case reports in the literature.

ABSTRACT N. PO112

REFRAMING THE ENIGMA: ACQUIRED HEMOPHILIA A AS A HARBINGER OF HHV-8–ASSOCIATED MULTICENTRIC CASTLEMAN DISEASE

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Background. Acquired hemophilia A (AHA) is a rare, potentially fatal autoimmune coagulopathy caused by inhibitory autoantibodies targeting factor VIII (FVIII). Its incidence is approximately 1 case per million annually, predominantly affecting older adults, with a smaller peak in postpartum women. Clinically, AHA presents with spontaneous bleeding—typically involving soft tissues, mucosae, or internal organs—in patients without a personal or familial bleeding history. A defining laboratory feature is isolated prolongation of activated partial thromboplastin time (aPTT), uncorrected by mixing studies. In nearly 50% of cases, AHA is associated with underlying conditions, including malignancies, autoimmune disorders, infections, dermatologic diseases, and pregnancy; the remainder are idiopathic. Mortality ranges from 10% to 30%, primarily due to hemorrhagic complications. Castleman disease (CD) is a heterogeneous group of non-clonal lymphoproliferative disorders characterized by lymphadenopathy and systemic inflammation. Multicentric Castleman disease (MCD) represents a systemic and aggressive form, frequently associated with human herpesvirus-8 (HHV-8), particularly in immunocompromised individuals. HHV-8–driven MCD is mediated by dysregulated cytokine production, notably interleukin-6, and may coexist with Kaposi's sarcoma. The association between AHA and MCD is exceedingly rare and diagnostically challenging.

Case Report. A 69-year-old man presented with right lower limb pain and spontaneous hematomas. Deep vein thrombosis was excluded. Laboratory findings revealed normocytic anemia and prolonged aPTT (69.5 s). Coagulation studies showed markedly reduced FVIII activity (3.5%) and FVIII inhibitors (3.5 BU), confirming AHA. Treatment with corticosteroids and activated prothrombin complex concentrate (FEIBA, 4000 IU twice daily) led to clinical improvement, with gradual FVIII recovery and declining inhibitor titer (Figure 1). Imaging revealed multiple hemorrhagic sites (bilateral subdural, adrenal, and thigh hematomas), splenomegaly (16 cm), and diffuse lymphadenopathy. Further evaluation demonstrated elevated chromogranin A and biclonal gammopathy (IgG-kappa and IgG-lambda). Bone marrow biopsy was inconclusive. Virological testing identified active cytomegalovirus and HHV-8 infection, prompting antiviral therapy. Owing to worsening cytopenias and splenomegaly, lymph node excision was performed, establishing HHV-8–positive MCD with microscopic Kaposi's sarcoma. Rituximab was initiated to address both the lymphoproliferative disorder and secondary autoimmune coagulopathy, resulting in progressive clinical stabilization.

Conclusions. This case underscores a rare association between AHA and HHV-8–associated MCD with Kaposi's sarcoma. AHA should be suspected in patients with unexplained bleeding and isolated aPTT prolongation. Thorough evaluation for underlying conditions is essential, particularly in the presence of systemic features such as lymphadenopathy or splenomegaly. A multidisciplinary approach is critical for accurate diagnosis and optimal management. Prompt hemostatic treatment combined with immunosuppression and targeted therapy of the underlying disorder is essential to improve outcomes. This report highlights the importance of recognizing secondary causes of AHA and contributes to the limited literature on its association with HHV-8–related lymphoproliferative disease.

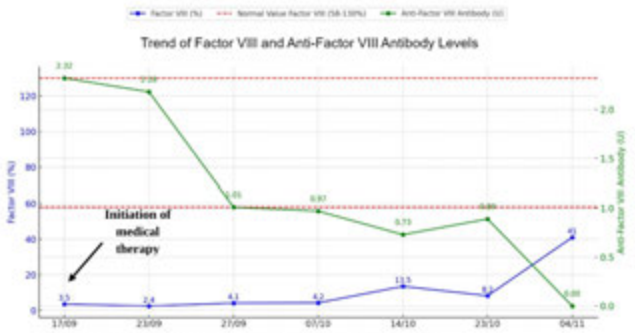


Figure 1. Trend of FVIII and anti-FVIII antibody levels after initiation of medical therapy.

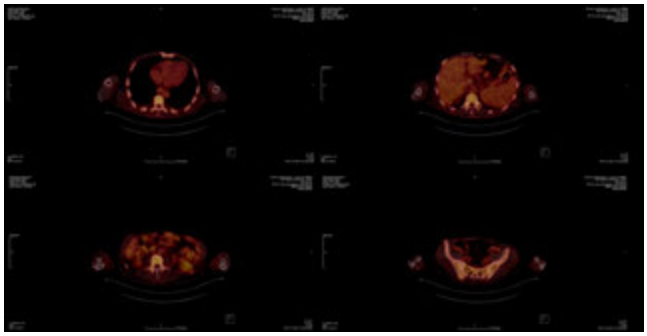
ABSTRACT N. PO113

A STRANGE CASE OF RECURRENT ISOLATED DIGITAL ARTERIAL THROMBOSIS

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Background. Arterial thrombosis is a leading cause of morbidity and mortality, sometimes occurring in uncommon sites without a readily apparent etiology. Polycythemia vera (PV) is a chronic myeloproliferative neoplasm due to a JAK2 gene variant and frequently characterized by arterial and venous thrombosis, even in atypical sites. Diagnosis requires specific Hb and HCT cutoffs along with low EPO level, but BM biopsy is highly recommended. Low dose ASA is suggested for all patients with PV. Cytoreductive therapies can be used in addition to aspirin and phlebotomy for patients with prior thrombosis to reduce thrombotic risk.
Case Report. We present the case of a 65 years old male patient with relapsing isolated digital arterial thrombosis. Patient was admitted in November 2025 to our hospital for an acute digital ischemia of the 4th finger of the left hand while on therapy with Rivaroxaban 10 mg OD for the extended prophylaxis of an idiopathic VTE episode. A CT angiography of the aorta excluded embolism, dissection and neoplastic lesions, so the patient was discharged with coumadin with an appointment to our ambulatory service for further diagnostic testing. However, after a few days he was re-admitted to ED for a recurrent thrombosis in the same site, so he was referred to our internal medicine department. The patient's medical history included multiple unprovoked VTE episodes treated with various antithrombotic regimens. There was no history of smoking or drug use, nor hypertension. The patient had a gastric NET treated with total gastrectomy, with persistently negative follow-up. Color doppler US confirmed obstruction of the 4th interdigital artery. Lab test showed negativity of APLAs (LA, aCL IgM-IgG, aβ2GPI IgM-IgG) and the whole autoimmune panel (ANA, ENA, ANCA, crioglobulins, C3/C4, HLA-B51). Both APCR and the G2021A prothrombin gene polymorphism were negative. Homocysteine was only modestly increased (23 μmol/L), while glycemic and lipidic profile were in range according to ADA and ESC targets, respectively. Gastroscopy, colonoscopy and PSA were all negative, while serum protein electrophoresis demonstrated hypergammaglobulinemia with no evidence of a monoclonal component. Contrast-enhanced whole-body CT scan showed only a moderate splenomegaly but excluded cancer, vasculitis, dissection or aTOS. 18F-FDG-PET showed a moderate BM uptake without a morphological lesion on CT. TTE showed no vegetations or thrombi, and ambulatory ECG monitoring revealed no AF or flutter. VKA was stopped in favor of therapeutic UFH, with rapid remission of symptoms. After 7 days, we switched back to coumadin and added aspirin 100 mg without further relapse. Since lab tests led to inconclusive diagnosis, considering the findings described above, we investigated the JAK2 V617F mutation which was positive. Subsequent BM examination confirmed the diagnosis of PV. A treatment based on hydroxyurea was started along with DAT (coumadin + aspirin). TTR at 1 year was very good (> 90%), and patient didn’t have thrombotic recurrence nor evidence of major bleeding or CRNMBs.
Conclusions. Unexplained recurrent arterial thromboses in unusual sites are rare, yet they offer an interesting diagnostic challenge requiring a systematic approach. Once most common causes have been ruled out, rarer causes must be addressed. Among these, PV is condition at high thrombotic risk. However, once correctly diagnosed, treatment can prevent relapse in the majority of patients.





A CASE OF ACQUIRED HEMOPHILIA AFTER TAVI AND CORONARY ANGIOPLASTY IN PATIENT WITH ATRIAL FIBRILLATION AND MULTIPLES CARDIOVASCULAR RISK FACTORS – THE ART AND SCIENCE OF THERAPEUTIC CONFLICT

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Background. Acquired hemophilia A (AHA) is a rare autoimmune disorder characterized by inhibitory autoantibodies against FVIII. Half of cases are associated with autoimmune diseases, cancer, infections, drugs, or pregnancy. Symptoms usually include subcutaneous and intramuscular bleeds, unlike congenital hemophilia which affects mainly the joints. Diagnosis is made by prolonged aPTT not correcting on a mixing test, along with reduced FVIII activity and the presence of inhibitors. Treatment aims to control bleeding and eradicate the inhibitor. Hemostatic therapy includes bypassing agents (rFVIIa or aPCC) or rpFVIII. In recent years, Emicizumab, a bispecific monoclonal antibody that mimics FVIII's action bridging FIXa and FXa, has emerged as a novel off-label therapeutic option. Steroids, Rituximab, or Cyclophosphamide, are used to suppress autoantibody production.
Case report. We present the case of a 83 years old female patient with acquired A haemophilia diagnosed after TAVI and coronary angioplasty. Clinical history included multiple cardiovascular risk factors, including CAD and LEAD previously treated with revascularization. In December 2025, the patient presented to ED with an episode of HF secondary to newly diagnosed AF with echocardiographic evidence of severe aortic stenosis. A coronary angiography showed significant CAD progression on the circumflex and the right coronary arteries, so the patient was transferred to the Cardiology Department where she underwent TAVI and revascularization on the culprit arteries. A triple antithrombotic therapy (TAT) with aspirin, clopidogrel, and DOAC (rivaroxaban) was started. Pre-procedural coagulation test showed a spontaneous aPTT prolungation (72 ms). After the procedure, the patient began to present spontaneous hematomas in the upper limbs. Coagulation factor assays revealed a FVIII deficiency (4%) along with positivity of FVIII inhibitor at high titer (52.90 U/mL), confirming the diagnosis of AHA. TAT was withheld and treatment with prednisone 1 mg/Kg, cyclophosphamide 1 mg/Kg, and emicizumab (LD 6 mg/Kg on the 1st day and 3 mg/Kg on the 2nd day, MD 1.5 mg/Kg weekly) was started. After normalization of the aPTT and FVIII activity, aspirin was resumed and, after 1 week, DAPT with clopidogrel was restarted. Screening for infectious (HBV, HCV, HIV, Parvovirus B19, EBV, CMV) and autoimmune (ANA, ENA, RF, CCP, LA, aβ2GPI, aCL) causes was negative. Contrast-enhanced whole-body CT scan, 18F-FDG-PET and thyroid US excluded lesions suspicious for cancer. For progressive thrombocytopenia (nadir: 66,000/mm3) likely secondary to cytotoxic therapy, and good laboratory response with FVIII activity persistently in range, it was decided to maintain Clopidogrel exclusively, and the patient was discharged with an appointment at our Bleeding Disorders Center for further follow-up. Unfortunately, 3 weeks later, the patient died of unknown causes.
Conclusions. AHA is a rare but potentially life-threatening disorder, especially if under-recognized and treated late. Since it's more common in older adults who currently have multiple cardiovascular diseases requiring antithrombotic medications, treatment decisions are extremely challenging, bordering between art and science. A personalized approach is essential to modulate the intensity of antithrombotic therapy and bleeding prophylaxis in this patient population, even though outcomes can often be unfavorable.



AL AMYLOIDOSIS IN A PATIENT WITH SEVERE HEMOPHILIA A AND INHIBITORS WHO HAD A MONOZYGOTIC TWIN: SAME GENES, DIFFERENT OUTCOMES

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Background. Severe hemophilia A with inhibitors has been associated, in the “pre-emicizumab era”, with high bleeding risk and complex management. AL amyloidosis is a rare plasma cell dyscrasia characterized by monoclonal light chain deposition with systemic involvement. We report a case of AL amyloidosis in a patient with severe hemophilia A and high-titer inhibitors, who had a monozygotic twin.
Case report. The patient and his monozygotic twin were referred to our center in 1973 at the age of 10 for severe hemophilia A; the proband had also a high-titer inhibitor, developed after repeated treatment with pdFVIII and blood components. He was subsequently managed with bypassing agents. Molecular analysis later identified a F8 splice-site mutation (c.1537+1G>A). In 1991, the patient tested positive for HCV with spontaneous viral clearance. In 1995, a first immune tolerance induction (ITI) attempt using the Malmö protocol failed. Thereafter the clinical course was complicated by multiple major bleeding events; nevertheless the patient repeatedly refused a new ITI course. After two iliopsoas hematomas, the first in 2010 and the second in 2014, he agreed to a second ITI course, initiated in July 2014 using pdFVIII/vWF concentrate (100 IU/kg/day). A transient inhibitor rise was observed, reaching a peak of 1715 BU after two weeks from ITI start. In August 2014 a severe episode of diffuse abdominal bleeding occurred, treated with large amount of rFVIIa in the emergency department. Thereafter, no further hemorrhagic events were reported, and the inhibitor titer progressively declined, reaching <1 BU in October 2016. Then, pdFVIII/vWF concentrate was tapered until reaching a dose of 40 IU/Kg/day in March 2017. In August 2014, during the hospitalization, laboratory investigations revealed an IgD-lambda monoclonal gammopathy, with a kappa/lambda free light chain ratio of 0.04 and urinary lambda Bence-Jones protein excretion of 195 mg/24 h. The patient was a physician and at that time declined further evaluation of the monoclonal gammopathy. Two years later, in August 2016, the patient was diagnosed with heart failure with reduced ejection fraction and concentric left ventricular hypertrophy. Cardiac magnetic resonance imaging was suggestive of transthyretin amyloidosis, although AL amyloidosis could not be excluded. A periumbilical fat biopsy confirmed AL amyloidosis diagnosis, and treatment with VCD (bortezomib, cyclophosphamide, and dexamethasone) was initiated. A few days after starting therapy, in April 2017, the patient died from sudden cardiac death. We report that the twin brother never developed an inhibitor and has a lambda monoclonal gammopathy without evidence of organ involvement. Finally, the last year he developed a cholangiocarcinoma.
Conclusions. This case shows the rare coexistence of severe hemophilia A with inhibitors and AL amyloidosis in a monozygotic twin, whose brother did never develop an inhibitor. This suggests that genetic background alone is not sufficient to determine the inhibitor event. Moreover, as regards the AL amyloidosis, we could speculate if previous treatment with cyclophosphamide, but also the immune stimulation during ITI may have contributed to clonal progression; otherwise his twin brother without inhibitor present a stable monoclonal gammopathy and developed a cholangiocarcinoma. Environmental factors could have had an impact on these divergent clinical histories: same genes, different outcomes.



MONOCENTRIC EXPERIENCE OF DOACS REVERSAL MANAGEMENT AT L SACCO HOSPITAL, MILAN: A REAL-WORLD RETROSPECTIVE STUDY

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Background and Aims. The increasing use of direct oral anticoagulants (DOACs) has made the management of major bleeding and non-deferrable urgent surgery a relevant clinical challenge. Specific reversal agents are available for selected DOACs, such as andexanet alfa (AA) for factor Xa inhibitors, whereas four-factor prothrombin complex concentrate (4F-PCC) remains the most widely used non-specific option. At L. Sacco Hospital (Milan, Italy), a multidisciplinary institutional protocol based on ISTH recommendations is applied. This study aims to evaluate whether our institutional DOACs reversal strategy—based on 4F-PCC or AA—is consistent with current evidence and published case series in terms of safety and clinical outcomes.

Methods. We conducted a retrospective, single-center observational study including all consecutive DOACs reversal requests managed by the Transfusion Medicine Service (January 1, 2023 – December 31, 2025). Patients undergoing non-deferrable invasive procedures received 4F-PCC (25–50 IU/kg). Patients with intracranial hemorrhage (ICH) on apixaban or rivaroxaban received AA, while those on edoxaban or with major bleeding at other sites received 4F-PCC (25–50 IU/kg). Safety outcomes included in-hospital mortality and thrombotic events. Hemostatic effectiveness was assessed using published criteria (effective/ineffective for bleeding; ineffective/partially effective/effective for surgery), as in Khorsand et al, 2021, and Piran et al, 2018.

Results. A total of 41 reversal episodes were managed: 36 with 4F-PCC and 5 with AA. In the 4F-PCC group, hemostatic effectiveness was 82.35% in urgent surgery and 68.42% in major bleeding ($p<0.0001$). In-hospital mortality in the 4F-PCC group was 19%, with a trend toward higher mortality in bleeding vs surgical cases (31.58% vs 5.88%, $p=0.055$). The majority of 4F-PCC use was observed in patients undergoing abdominal and urogenital surgery. Bleeding site and age were not associated with mortality. Thrombotic events occurred in 4/36 patients. Mortality increased with worsening hemostatic effectiveness (21.4% effective, 50% partially effective, 100% ineffective), although data were limited by low number. In the AA group, the small sample size and diverse clinical indications precluded meaningful comparisons between reversal strategies. However, follow-up brain CT scans showed hematoma stability or reduction in 80% with 20% in-hospital mortality.

Conclusions. In this real-world monocentric cohort, outcomes after DOACs reversal appeared more related to baseline patient risk and clinical presentation than to the reversal strategy. Higher mortality was observed in bleeding vs post-surgical patients, while post-sugical mortality was lower tahn previously reported. Hemostatic effectiveness in bleeding was consistent with the pooled estimates reported from Piran et al. (Blood Advances), while in-hospital mortality was comparable to that reported in the literature and prior case series. Any differences in outcome may reflect population heterogeneity and the reason for admission (major bleeding and its site vs urgent surgery). Overall, findings support the applicability of our institutional protocol in real-world practice. A key limitation is the lack of rapid DOAC level assessment, limiting confirmation of anticoaugulant activity. Prospective or larger studies are needed to identify the optimal reversal strategy across different patient subgroups.

ABSTRACT N. PO117

LONGITUDINAL THROMBIN GENERATION PROFILING IN A PATIENT WITH SEVERE HEMOPHILIA A DURING ANTITHROMBIN-LOWERING THERAPY, CANCER, AND MAJOR SURGERY

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Background and aims. Thrombin generation (TG) represents one of the few functional assays available to assess the hemostatic balance in patients with hemophilia receiving non-replacement therapies. However, longitudinal data over extended periods and during major biological stressors such as cancer and surgery are limited. We aim to describe five-year longitudinal changes in plasma TG in a patient with severe hemophilia A receiving an siRNA-based antithrombin-lowering non-replacement therapy, including the impact of cancer diagnosis and major surgery.

Methods. Serial TG measurements were performed in platelet-poor plasma from 2020 to 2025 using the calibrated automated thrombogram (CAT). TG was assessed at low (1 pM) and intermediate (5 pM) tissue factor (TF) concentrations at predefined clinical timepoints: pre-treatment, stable therapy, peri-cancer diagnosis, and post-surgical resection. Lag time, endogenous thrombin potential (ETP), peak thrombin, velocity index, and tail formation were analyzed. Antithrombin levels were measured in parallel. Pooled normal plasma was included as a reference. Written informed consent was obtained according to local ethical standards.

Results. At 1 pM TF, a trend toward shorter lag time and higher peak thrombin was observed during the pre-tumor phase compared with stable therapy, while ETP remained non-measurable due to persistent thrombin activity. No relevant changes were observed around colorectal cancer diagnosis. Following colorectal cancer resection in March 2024, thrombin generation at 1 pM TF became fully measurable at the first post-surgical assessment, with ETP increasing from unmeasurable to 895 nM·min and late-phase tail formation (StartTail 55 min), despite only moderate peak thrombin (45 nM) (Figure 1). Antithrombin levels ranged between approximately 15–30% during stable follow-up before surgery and decreased to about 10-26% after surgery. At 5 pM TF, TG remained consistently high throughout the entire observation period, confirming preserved thrombin-generating capacity.

Conclusions. In this long-term longitudinal case, colorectal cancer diagnosis was not associated with major changes in low-trigger TG, consistent with a localized disease stage. In contrast, surgical resection induced a distinct qualitative shift in TG dynamics, with the emergence of sustained thrombin activity despite moderate peak values. These findings suggest that, in pharmacologically rebalanced hemophilia, major biological stressors may primarily affect thrombin persistence rather than overall thrombin generation.

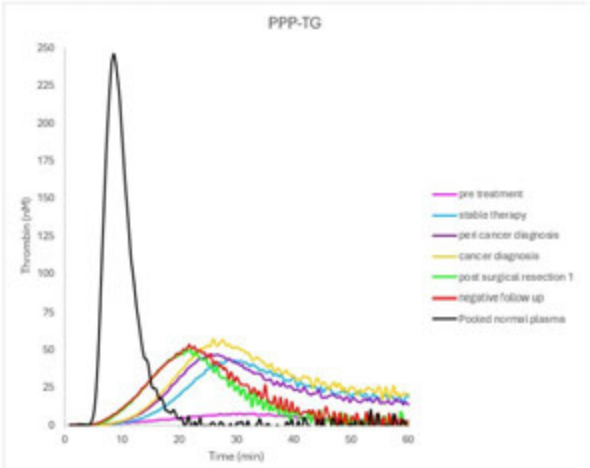


Figure 1. Platelet-poor plasma thrombin generation (PPP-TG) assessed at low tissue factor concentration (1 pM TF) at different longitudinal time points in a patient with severe hemophilia A under antithrombin-lowering non-replacement therapy. Curves represent pre-treatment, stable antithrombin-lowering therapy, peri-cancer diagnosis, cancer diagnosis, post-surgical resection, and negative follow-up phases. Pooled normal plasma is shown for reference. Low-TF conditions allow visualization of qualitative differences in thrombin generation dynamics, particularly in the decay phase and curve closure over time.

ABSTRACT N. PO118

VARIATION OF EGFR IN PATIENT IN DOACS THERAPY

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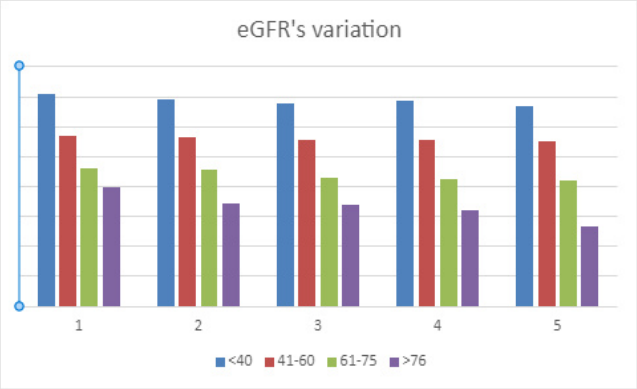
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Background and Aims. The introduction of direct oral anticoagulant drugs (DOACs) into clinical practice has represented a revolution in the prevention and treatment of thrombotic events in different clinical settings. Their use is now well established in the prevention of systemic thromboembolism in patients with non-valvular atrial fibrillation (AF) and in the prophylaxis and treatment of venous thromboembolism (VTE). Their application is also expanding in other clinical settings. The factors that have led to such a large diffusion of DOACs lie essentially in their pharmacological characteristics. The more predictable dose-response relationship, the lower interaction with other drugs and with food, and the overcoming of the need to monitor anticoagulant activity represent undoubted advantages over vitamin K antagonists (VKAs). However, the use of DOACs should be evaluated during therapy based on several data, including liver and kidney function. This study focused on the change in renal function during therapy and as age increased.

Methods. We conducted a retrospective observational study on patients enrolled in the Hemostasis Center of the AORN S. Moscati (AV) and receiving therapy with DOACs (dabigatran, rivaroxaban, apixaban and edoxaban). The study court consists of 105 patients aged 21-90 years. The study cohort was divided into four groups: patients aged < 40 years; patients aged 41-60; patients aged 61-75; patients aged >76 years. Patients were periodically evaluated for glomerular filtration rate (eGFR) according to the following schedule: First assessment after six months of treatment. Second assessment after 12 months of treatment. Third assessment after 18 months of treatment. Fourth assessment after 24 months of treatment.

Results. From November 2013 to February 2026, 105 patients (43 males) with DOACs therapy were included in the study. At entry, the mean patient age was 65 +/- 4 years. 38% in edoxaban (4% in low dose), 17% in apixaban (4% in low dose), 2% in dabigatran (150mg), 43% in rivaroxaban (25% in low dose and 8% in medium dose). The eGFR was calculated using the Cockcroft-Gault formula. The reduction in eGFR capacity is indirectly proportional to advancing age. The group with the greatest change in eGFR was patients aged >76 years. Conversely, the group with a miron variation in eGFR was the one aged 41-60 years (Image).

Conclusions. DOACs, due to their pharmacological characteristics and safety profile, have represented an important step forward in anticoagulant therapy. The potential loss of some of their most advantageous properties, such as the predictability of the dose-response relationship, implies that their use must be carefully evaluated especially in patients with an advanced age as these are more critical: they represented the group with the greatest variation in eGFR.



ABSTRACT N. PO119

BARTONELLA HENSELAE INFECTION ASSOCIATED WITH A MULTISYSTEMIC THROMBO-INFLAMMATORY SYNDROME IN AN IMMUNOCOMPETENT ADULT

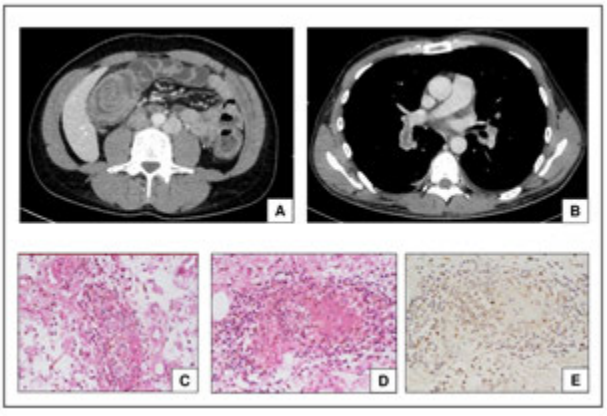
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Background. Bartonella henselae is a Gram-negative intracellular bacterium classically associated with cat-scratch disease, a usually self-limited condition characterized by regional lymphadenitis. However, occasionally may lead to severe systemic manifestations, particularly in immunocompromised hosts.

Case reports. Here we report, a previously healthy 43-year-old man presented in Emergency Department on April 2023 with abdominal pain, rectal bleeding, low-grade fever, and severe thrombocytopenia (19×10^9/L). Abdominal CT revealed ileocolic intussusception, splenic ischemic lesions, hepatomegaly, and retroperitoneal lymphadenopathy (Fig. 1A), leading to urgent right hemicolectomy. Six days later, a CT scan performed as diagnostic workup showed pulmonary embolism with deep vein thrombosis (Fig. 1B). Treatment with intravenous immunoglobulin and corticosteroids resulted in partial platelet recovery. A vena cava filter was placed, and anticoagulation with apixaban was initiated. In May 2023, the patient experienced recurrent fever and migratory arthritis and was treated with a two-week course of prednisone and antibiotics, with improvement. Four weeks later, arthritis recurred and blood tests showed acute kidney injury with nephrotic-range proteinuria and recurrent thrombocytopenia. Physical examination showed mild bilateral exophthalmos and ocular motility impairment. A brain MRI demonstrated multiple microembolic ischemic lesions. Fluorescein angiography and Optical coherence tomography showed abnormalities, suggestive of secondary serous retinal detachment. Laboratory testing revealed elevated inflammatory markers and lupus anticoagulant positivity, while autoimmune screening, ADAMTS-13 activity, and extensive infectious work-up were initially negative. Complement levels were within the normal range. The patient received prednisone and was then transferred to a tertiary center. There, he recalled a recent exposure to purulent material from an infected pet dog. Expanded microbiological testing detected Bartonella henselae DNA by whole-blood PCR. Retrospective histopathological review of the surgical showed small-vessel endothelial inflammation and thrombosis compatible with infection-associated microangiopathy (Fig. 1C-E). Cardiac MRI demonstrated inflammatory cardiomyopathy, and renal MRI showed inflammatory renal injury. Targeted antimicrobial therapy with doxycycline was initiated and extended to five weeks due to persistent PCR positivity. Corticosteroids were gradually tapered and anticoagulation was maintained. Clinical improvement followed antimicrobial therapy, with normalization of platelet counts, stabilization of renal function, regression of thrombotic manifestations, and, eventually, PCR negativity. Lupus anticoagulant testing at 12 weeks was negative. The patient remained asymptomatic at the latest follow-up visit on March 2026.

Conclusions. This case describes a severe multisystem thrombo-inflammatory syndrome associated with B. henselae infection in an immunocompetent adult. The clinical picture initially suggested CAPS or other primary TMAs. However, available laboratory findings did not support a diagnosis of overt microangiopathic hemolysis. Bartonella species exhibit endothelial tropism and may promote vascular inflammation and prothrombotic phenomena. Bartonella infection should be considered in patients with unexplained TMA-like presentations, particularly when routine investigations remain inconclusive.





UNEXPLAINED BLEEDING IN A YOUNG WOMAN: A CASE REPORT OF SUPERWARFARIN TOXICITY

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Background. Superwarfarins are long-acting anticoagulant rodenticides, that share the same mechanisms of action as warfarin. They inhibit the vitamin K epoxide reductase complex, preventing the γ-carboxylation of vitamin K–dependent coagulation factors (II, VII, IX, and X) as well as proteins C and S. This results in severe coagulopathy and potentially life-threatening hemorrhage, which may persist for months and often requires prolonged high-dose vitamin K1 therapy.
Case Report. A 49 years old woman came to our attention due to the onset of epistaxis originating from a varix in the right nasal cavity and painful spontaneous bruising associated with functional joint impairment, which had developed over several months in the absence of trauma. She had no personal or family history of bleeding disorders. Initially, laboratory findings showed a haemoglobin (Hb) level of 13 g/dL and a platelet (PLT) count of 220000/mm3. Coagulation tests revealed a markedly prolonged prothrombin time (PT) beyond measurable limits (INR 20), and activated partial thromboplastin time (aPTT) of 60 seconds. Than the patient was admitted to our ward and coagulation factor assays showed reduced levels of FVll 7.7%, FX 13.8%, FIX 23%. Mixing studies corrected, C Protein 38%, S Protein 8,7%. High-dose intravenous vitamin K was promptly initiated. After one week of treatment, partial improvement of coagulation parameters was observed, PT 10s, INR 7,1, aPTT 63s, ratio 2,11. The patient was referred to a tertiary care center for further evaluation because of an inadequate response to high-dose vitamin K therapy. Laboratory findings remained consistent with vitamin K deficiency: PT 69.9 s, INR 6.55, aPTT 69.5 s, ratio 2.79, AT 133%, FVll 155%, S protein 21%, C protein 28%. Vitamin K supplementation was confirmed and on suspicion of poisoning with an anti–vitamin K substance, a sample is sent for toxicological analysis. The anticoagulant poisoning panel ultimately revealed high levels of Brodifacoum, Difenacoum, and Bromadiolone. Vitamin K therapy was therefore confirmed at high dose (10 mg/die per os). After five months despite the absence of major bleeding, a mild cutaneous bruising persisted. Coagulation parameters normalized (PT 10.1 s, INR 0.92, aPTT 24.8 s) and vitamin K was discontinued.
Conclusions. This case highlights the importance of through social and toxicological investigation in patients presenting with unexplained coagulopathy suggestive of severe vitamin K defciency, particularly to identify possible exposure to long-acting anticoagulant rodenticides.



IMMUNOTHROMBOSIS AND MULTIPLE-SITE VENOUS THROMBOEMBOLISM IN ACUTE TOXOPLASMOSIS: A CASE REPORT

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Introduction. Immunothrombosis can limits pathogen dissemination and enhances antimicrobial activity at the microvascular level but this process can progress to pathological thrombosis (thromboinflammation). Infections can trigger venous thromboembolism (VTE) through crosstalk between inflammatory and coagulation pathways, a mechanism described mainly in viral illnesses but also reported in bacterial and parasitic infections. Multisite VTE work-up focuses on malignancy, inflammation, autoimmune issues, thrombophilia, and infections. Toxoplasmosis is a global parasitic disease, in healthy individuals, infection is usually asymptomatic or causes mild illness; organ involvement is rare. Immunocompromised patients may experience severe organ involvement (central nervous system CNS, lungs, liver, or other organs), especially if Toxoplasma reactivates from dormant cysts. VTE during acute Toxoplasma infection is extremely rare and documented only in isolated case reports.
Case Report. A 63-year-old male with psoriatic arthritis, receiving adalimumab and MTX therapy, presented with fever, pneumonia, and generalized seizures. Head CT demonstrated a right parietal hemorrhagic infarction, while brain MRI identified cerebral venous sinus thrombosis involving both transverse and sigmoid sinuses with extension to the internal jugular veins. Contrast-enhanced CT revealed severe consolidation in the right lung, multisite splanchnic thrombosis— with involvement of the splenic and superior mesenteric veins—and microinfarcts suggestive of embolic phenomena across multiple organs. DVT, endocarditis, and sinusitis were excluded; autoimmune panel and thrombophilia screening was negative, complement was normal. The patient was initiated on UFH, subsequently switched to warfarin. Whole-body PET/CT detected multiple hypermetabolic lymphadenopathies at thoracic and external iliac stations. Serological testing for Toxoplasma gondii indicated recent primary infection and PCR confirmed its presence in blood. Due to CNS and visceral organ involvement, oral trimethoprim–sulfamethoxazole was administered for six weeks, resulting in clinical improvement.
Conclusions. VTE at unusual sites represents a diagnostic challenge. In the present case, an extensive etiological workup for multisite/unusual-site VTE was unremarkable, with no alternative provoking factors identified; subsequent investigations were therefore guided by immune status and organ involvement. Experimental evidence indicates that the parasite can induce endothelial injury and promote coagulation at the neurovascular interface. The mechanisms underlying thrombosis associated with toxoplasmosis remain incompletely defined. T. gondii tachyzoites invade endothelial cells, leading to endothelial activation and disruption of barrier integrity within the microvasculature. This process results in upregulation of procoagulant pathways and adhesion molecules, thereby favoring local platelet–fibrin clot formation, consistent with infection-driven immunothrombosis. Concomitant cytokine release, further enhances endothelial permeability and promotes complement activation. Local reductions in blood flow may decrease the threshold for thrombosis. Collectively, these mechanisms provide a biologically plausible explanation for thrombotic events observed in primary toxoplasmosis. Our report identifies acute toxoplasmosis as a rare cause of thrombosis and supports targeted T. gondii testing in febrile patients with multisite VTE

ABSTRACT N. PO122

SUCCESSFUL MANAGEMENT OF THERAPEUTIC ANTICOAGULATION FOR PROVOKED VENOUS THROMBOEMBOLISM IN A PATIENT WITH FACTOR VII DEFICIENCY AND SEPTIC SHOCK

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Background. Venous and arterial thrombotic events have occasionally been reported in patients with inherited factor VII (FVII) deficiency. Here, we describe the management of provoked venous thromboembolism (VTE) in a patient with severe FVII deficiency.

Case Report. An 82-year-old woman presented to the Emergency Department because of worsening right lower limb pain and edema following a fall. Her medical history was notable for inherited FVII deficiency (basal FVII activity of 6%), managed with on-demand replacement therapy only. On admission, she was stable but tachypneic on low-flow oxygen. Initial laboratory tests showed increased inflammatory markers, acute kidney injury and a prolonged prothrombin time ratio of 2.18. Shortly after admission, she developed septic shock, for which norepinephrine and empiric antibiotics were started. A chest-abdomen contrast-enhanced computed tomography (CT) ruled out pneumonia and other uncontrolled infectious sources, but revealed multiple thromboembolic filling defects in the main, segmental, and subsegmental pulmonary arteries. CT angiography of the right lower limb showed a filling defect in the popliteal vein with surrounding soft tissue edema. Troponin and NT-proBNP were increased, whereas transthoracic echocardiography showed no signs of acute right ventricular dysfunction. To allow for the start of therapeutic anticoagulation with unfractionated heparin, plasma-derived FVII concentrate was started (Provertinum 20 IU/kg every 12 hours). FVII activity increased from 27% pre-infusion to 84% post-infusion. Following improvement of the kidney function, the patient was switched to intermediate-dose enoxaparin (6000 IU twice daily). An attempt to reduce Provertinum to once daily while maintaining enoxaparin was followed by hemoptysis and epistaxis, prompting the restoration of the twice-daily regimen. After one month of full-dose anticoagulation, compression ultrasonography and repeat chest CT angiography showed complete resolution of both the deep vein thrombosis and pulmonary embolism. Provertinum was then discontinued and apixaban was reduced to 2.5 mg twice daily. No further bleeding or thrombotic events occurred during the following 30 days. Thrombin generation assay (TGA) results are summarized in Table 1. During the acute phase, TGA showed prolonged lag time (min) and time to peak (min), consistent with severe FVII deficiency, but markedly increased peak-thrombin (nM/L) and endogenous thrombin potential (ETP, nM x min). The ETP ratio with/without thrombomodulin was high, suggesting reduced sensitivity to thrombomodulin-mediated anticoagulant activity. Of note, this assessment was performed close to the episode of mucosal bleeding occurred during anticoagulation, although the assay did not clearly capture this bleeding tendency. At follow-up, lag time and time to peak remained prolonged, whereas ETP and peak-thrombin normalized or decreased. However, the ETP ratio with/without thrombomodulin remained high. Overall, these findings point towards a hypercoagulable state despite severe FVII deficiency, particularly pronounced during the acute phase of disease.

Conclusions. We described a case of successful anticoagulation obtained with careful dosing of replacement therapy in a FVII deficiency patient with provoked VTE. TGA may provide useful information beyond standard clotting tests in this context, although its clinical interpretation should remain closely integrated with clinical data.

Table 1. Thrombin generation assay parameters of a control subject and of the patient during the acute phase and during follow-up

Parameter	Control 28/11 R1P1	Control 28/11 R1P1+TM	Patient acute phase 28/11 R1P1	Patient acute phase 28/11 R1P1+TM	Control 16/01 R1P1	Control 16/01 R1P1+TM	Patient follow-up 16/01 R1P1	Patient follow-up 16/01 R1P1+TM
Lag time, min	6.56	7.67	12.17	15.17	6	7	12	18
Time to peak, min	10.3	10.7	14.5	17.2	10	10	14	20
Peak thrombin, nM	273	187	512	509	244	139	218	244
ETP, nM×min	1832	1050	3400	2987	1788	839	1335	1113
ETP ratio with/without TM	—	0.57	—	0.88	—	0.47	—	0.83

Legend: TM, thrombomodulin; ETP, endogenous thrombin potential. R1P1 indicates TGA performed with a mixture of tissue factor (1pM), a blend of synthetic phospholipids (1μM). . The ETP ratio is expressed as ETP with TM / ETP without TM; higher values indicate reduced sensitivity to thrombomodulin-mediated anticoagulant activity. The acute-phase assay was performed during LMWH therapy .

ABSTRACT N. PO123

PERIOPERATIVE MANAGEMENT OF FEMORAL FRACTURE SURGERY IN AN ELDERLY PATIENT WITH ACQUIRED HEMOPHILIA A RECEIVING EMICIZUMAB

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Background. Acquired hemophilia A (AHA) is a rare autoimmune bleeding disorder predominantly affecting elderly patients, in whom major surgery represents a particularly high-risk clinical scenario. Although emicizumab was originally developed for congenital hemophilia A, its use has progressively extended to patients with AHA, particularly in cases characterized by recurrent bleeding or difficult disease control. However, evidence guiding perioperative management in this setting remains extremely limited, and specific recommendations for patients with AHA receiving emicizumab prophylaxis are lacking.

Case report. We report the case of an 80 years old woman with AHA complicated by a high-titer factor VIII inhibitor and marked clinical frailty. The disease course was characterized by recurrent bleeding episodes and fluctuating factor VIII levels despite immunosuppressive therapy with corticosteroids and cyclophosphamide. Following a severe relapse, emicizumab prophylaxis was initiated, leading to clinical stabilization. In September 2025, the patient sustained a femoral fracture requiring urgent orthopedic surgery. Perioperative hemostatic management was based on continuation of emicizumab prophylaxis combined with recombinant activated factor VII (rFVIIa, eptacog alfa), administered at tapering doses over a total of seven days, together with adjunctive tranexamic acid. Surgery was successfully performed. A postoperative hemoglobin decrease required transfusion support, but the patient remained hemodynamically stable, with no major bleeding or thrombotic complications. In the postoperative period, a partial remission of acquired hemophilia A was observed, with factor VIII activity rising above 30%, allowing discontinuation of emicizumab prophylaxis (Figure 1).

Conclusions. To our knowledge, this is the first reported case of femoral fracture surgery in an elderly patient with AHA receiving emicizumab prophylaxis. This case demonstrates that major orthopedic surgery can be successfully managed in selected AHA patients under emicizumab using a structured perioperative approach with rFVIIa. The absence of specific recommendations for this setting highlights the importance of shared clinical experience and structured reporting to support decision-making in this high-risk population.

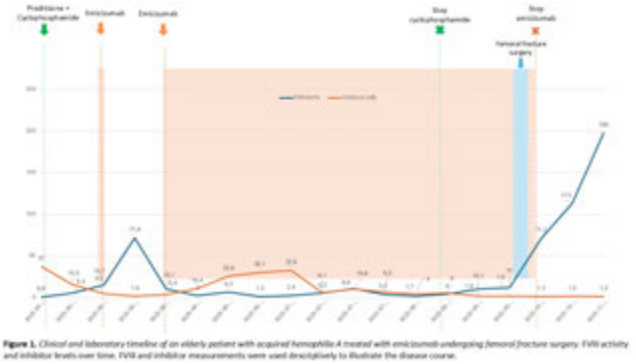


Figure 1. *Clinical and laboratory timeline of an elderly patient with acquired hemophilia A treated with emicizumab undergoing femoral fracture surgery. FVIII activity and inhibitor levels over time. FVIII and inhibitor measurements were used descriptively to illustrate the disease course.*

ABSTRACT N. PO124

BLEEDING COMPLICATIONS DURING ANTICOAGULATION WITH DOACS FOR NVAF AND THEIR MOST COMMON RISK FACTORS

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Background and Aims. CHADS[2]VASc is a score used in the last 15 years to evaluate thrombotic risk in patients with non-valvular atrial fibrillation (NVAF) to address them to anticoagulation with direct oral anticoagulants (DOACs). Yet after years of clinical experience CHADS[2]VASc has been discovered to have also some skill in the identification of bleeding risk. Yet a fine evaluation of its potential role in patients that experienced bleedings during anticoagulation with DOACs is still matter of discussion. Therefore, we analyzed risk factors for bleedings present in two different risk score (i.e. CHADS[2]VASc and RIETE) in 50 inpatients in internal medicine with recent bleeding. The aim of the study is to identify a possible single item that may help to predict possible bleeding during anticoagulation.

Methods. We retrospectively analyzed bleeding risk factors in patients hospitalized in internal medicine ongoing DOACs for any reason. We included in our analysis items presents in two different score as RIETE score for anticoagulated patients after a venous thromboembolism and as CHADS2VASC. Furthermore, we included the chronic use of NSAIDs for any reasons. Items evaluated as bleeding risk factors are summarized in table 1.

Results. Type of bleeding, previous bleeding, ongoing heart failure, kidney failure, ongoing cancer, female sex, age 40-74 years, age ≥75 years, chronic use (not abuse) of NSAIDs, chronic anaemia, previous venous thrombosis, diabetes, hypertension, other thrombosis in secondary prevention were the items retrospectively analyzed; all of them extracted by two different scores as CHADS[2]VASc and RIETE. Sex distribution and age ≥75 years were equally distributed in the population. Gastrointestinal bleeding was the most common bleeding complication. Hypertension and diabetes were greatly represented in the cohort as far as in the general population. Chronic anaemia, previous bleeding, kidney failure, other thrombotic disease in secondary prevention and heart failure are frequently present in patients with bleedings during anticoagulation with DOACs for NVAF.

Conclusions. Phase III clinical trial gave us the chance to understand that cardioembolic stroke prophylaxis with DOACs were not associated to bleedings in particular intracranial hemorrhage. However, in our daily clinical management we noted an increased rate of gastrointestinal bleeding. This difference with phase III clinical trial was probably due to the long-term administration of DOACs in real life compared to the clinical observation of trials (i.e. shorter than 24 months). For these reasons we tried to identify items present in hemorrhagic risk score used in clinical practice hoping to identify a possible major bleeding risk factor. Therefore our cross analysis with items present in RIETE score (a score validated for bleeding risk during anticoagulation) and CHADS[2]VASc (a score used to start anticoagulation for thrombotic risk in NVAF but also associated to bleeding prediction) we find that chronic anaemia, previous bleeding, kidney failure, other thrombotic disease in secondary prevention and heart failure are the most common risk factors in patients hospitalized in internal medicine with bleedings during anticoagulation with DOACs. Further studies on larger cohorts are warranted to confirm our findings, but seems that the complexity of patients is more frequent of a single common risk factor in the bleeding complication during long term anticoagulation for DOACs.

Table 1. Baseline clinical features of the 50 cases studied

Clinical characteristics		
Total	Number	50
Age 40 to 74, number (%)		50
Age over 75, number (%)		50
Female gender, number (%)		50
Gastrointestinal bleeding, number (%)		65
NSAIDs use, number (%)		6
Comorbidities, number (%)		
Chronic Heart Failure		26
Hypertension		72
Chronic Anaemia		46
Chronic kidney disease		33
Diabetes mellitus		20
Active malignant neoplasia		6
Previous venous thrombosis		6
Previous bleeding		26
Other thrombotic disorder in treatment		33



ROMIPLOSTIM FOR CHEMOTHERAPY-INDUCED THROMBOCYTOPENIA IN ADVANCED SOLID TUMORS: A SINGLE-CENTER EXPERIENCE

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Background and Aims. Chemotherapy-induced thrombocytopenia (CIT) is a common hematologic toxicity in cancer patients treated with cytotoxic agents. Platinum derivatives, taxanes, and antimetabolites are the most frequently involved drugs. CIT negatively impacts oncologic treatments by causing dose reductions and delays, potentially compromising efficacy and overall survival. TPO mimetics, such as Romiplostim, have been explored to stimulate platelet production and, although approved for immune thrombocytopenia (ITP), they may have a role in off-label management of CIT. This study conducted in our centre aimed to assess the appropriateness and effectiveness of romiplostim in patients with advanced solid tumors.

Methods. We conducted a retrospective analysis of 7 patients (4 females, 3 males) with CIT referred for hematologic evaluation between 2024 and 2026. All patients at referral had advanced-stage tumors (stage IV) and median age at cancer diagnosis was 57 years (range 37-77). They were heavily pretreated with 5 patients (72%) having received 3 or more lines of chemotherapy. Median platelet count at CIT onset was 78×10^9/L (range 23-113), without bleeding manifestations. All patients underwent bone marrow evaluation to assess infiltration. Romiplostim was finally administered just to 3 patients based on clinical judgement, initially with a median dose of 1 µg/kg (range 0.5-2), and platelet response was assessed at 7, 14, and 21 days. Adverse events were recorded.

Results. Bone marrow findings varied: 2 patients had preserved hematopoiesis, 1 patient partially preserved hematopoiesis, the others showed diffuse tumor infiltration. About the population who started Romiplostim 2 out of 3 patients (67%) responded with a significant increase in platelet counts, enabling continuation of oncologic treatment. The non-responder was a patient with extensive marrow involvement and during follow-up had a rapid progression of the disease. Median platelet count increased from 73 $\times10^9$/L (range 31-101) at baseline to 102 $\times10^9$/L at day 14 (range 14-127) and during follow-up. Treatment schedules varied (one/weekly to once every 3 weeks). About complications 1 patient experienced pulmonary embolism after trauma. Median follow-up was 2 months overall (range 1-12) and 5 months (range 1-12) among patients treated with TPO mimetics. In the latter group, 2 patients died due to disease progression, both with marrow infiltration, while 1 patient remains on treatment for both CIT and the underlying malignancy.

Conclusions. In our experience, Romiplostim appears to be an effective option for managing CIT in selected patients with advanced solid tumors, particularly in the presence of preserved bone marrow reserve; indeed its efficacy seems limited in cases of extensive marrow infiltration. Complications need to be monitored, and careful assessment of thrombotic risk is essential.



HIGH-DOSE INTRAVENOUS IMMUNOGLOBULINS FOR LONG-TERM PREVENTION OF RECURRENT GASTROINTESTINAL BLEEDING IN A PATIENT WITH ACQUIRED VON WILLEBRAND SYNDROME ASSOCIATED WITH MGUS

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Background. Acquired von Willebrand syndrome (AVWS) is a rare bleeding disorder associated with various underlying conditions and diverse pathogenic mechanisms, resulting in functional interference or increased clearance/degradation of von Willebrand Factor (VWF). Recurrent gastrointestinal (GI) bleeding is a common and challenging symptom, particularly in elderly patients. While treating the underlying disorder remains the only potentially curative approach, hemostatic therapies -including desmopressin, VWF/Factor VIII (FVIII) concentrates, and antifibrinolytic agents- show variable efficacy in controlling acute bleeding. Other reported interventions include plasmapheresis, recombinant activated factor VII, and high-dose intravenous immunoglobulins (HDIVIg). The latter have proven effective in patients with AVWS associated with IgG monoclonal gammopathy of undetermined significance (MGUS). Here, we report the long-term management using HDIVIg in a woman with recurrent GI bleeding secondary to AVWS and MGUS.

Case Report. A 76-yr-old woman presenting with recurrent GI bleeding and severe anemia underwent multiple endoscopic examinations, including video capsule endoscopy, which revealed active bleeding in the duodenum and proximal jejunum. Repeated clip placements and adrenaline infiltrations were unsuccessful. Consequently, surgery to resect the fourth portion of the duodenum and proximal jejunum was needed. However, life-threatening postoperative bleeding occurred, requiring multiple red blood cell transfusions. Previous documentation of Lupus Anticoagulant led to overlook a persistently prolonged aPTT (ratio 1.7). Following the postoperative complications, further testing revealed FVIII (17%) and VWF deficiencies (antigen 16%, ristocetin cofactor activity 19%). A low-concentration IgG-MGUS, known since 2003, was also noted. Suspecting AVWS, the patient was treated with VWF/FVIII concentrates, which provided only partial and transient bleeding control. High doses (40–50 IU/kg) every 12–24 hours failed to maintain VWF activity levels above 20%, despite adequate FVIII levels. Treatment with HDIVIg (1 g/kg for 2 days) was then initiated, resulting in the prompt normalization of FVIII and VWF levels (>200% after 3 days). No recurrence of bleeding or anemia was observed and HDIVIg administration was repeated after 4 weeks. Hematological consultations repeatedly ruled out the indication for direct MGUS treatment. To maintain clinical stability, HDIVIg cycles were administered every 5 weeks for 8 months, then extended to 6 and later 7 weeks. The patient has now been followed for 26 months. Although normal VWF and FVIII levels are only maintained for approximately 3 weeks post-infusion, she has remained free of clinically evident GI bleeding with stable hemoglobin levels. The IgG-MGUS concentration was substantially unchanged. Recently, long-acting octreotide was introduced as an alternative approach for prevention of GI bleeding recurrence.

Conclusions. HDIVIg was confirmed to be effective in this patient with severe GI bleeding due to AVWS associated with MGUS. Data regarding long-term management in this setting remain scarce. Our experience suggests that HDIVIg administration intervals can be successfully extended. The clinical benefit may persist beyond the hemostatic effects related to the actual VWF levels, potentially due to favorable anti-angiogenic modulation resulting from partially restored VWF concentrations.



ANAPHYLACTIC REACTION TO RECOMBINANT ACTIVATED FVII IN A MILD HEMOPHILIA A PATIENT WITH INHIBITOR: A CASE REPORT

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Background. A small proportion of patients with mild haemophilia A develop factor VIII inhibitors, which can convert a mild disorder into a severe spontaneous bleeding. Intensive perioperative use of factor VIII and some specific mutations induce a particularly high risk for inhibitor development, but risk factors are incompletely understood. Management aims to control the bleeding mainly with by-passing agents and to eradicate the inhibitor when the spontaneous clereance doesn't occur. Emicizumab provides effective prophylaxis in difficult-to-treat mild haemophilia A patients with inhibitor. However, bypassing agents, preferably recombinant activated factor FVII, are required for effective bleed management. No serious adverse events have been described so far with the use of recombinant activated factor VII.

Case Report. A 54-years old man affected with mild haemophilia (FVIII level 7%) was referred to our hospital from another center for a prothesic knee surgery due to advance haemohilic artropaty on October 2025. On demand therapy with plasmatic FVIII was maintained until the surgery with very few infusion over the years and no history of inhibitor. The surgery was managed with blous of FVIII immediately before, then with continuous infusion for the first four days and again boulus of plasmatic FVIII for three weeks included rehabilitation period. No inhibitor was detected at discharge from the hospital. After one month, spontaneous muscle haematoma of left thigh happened and the coagulation check showed severe decrease of FVIII (<1%) with high title inhibitor (20 UB) and mild anemia (Hb level of 9 g/l). Recombinant activated FVII (approximately ten infusions) was used to control the bleeding with improvement of it and after one week the patient start prophylaxis with Emicizumab. At the beginning of Genuary 2026 the patient reported a leg trauma with tibial haematoma so two infusions of recombinant FVII was repeted. At the second infusion severe hypotension, desaturation, vomit and transient loss of consciousness occurred and the diagnois of anaphylactic reaction was made. Treatment with intravenously steroid, anthistamin, hydratation and adrenaline was administrated with slow improvement of general condition. Actually patient is maintaing emicizumab treatment, inhibitor is still at high tile (49 UB) and no other bleeding has been developed until now. Activated prothrombic complex concentrate is available in case of bleeding, for a low-dose using. Survellance of inhibitor title is actively maintained and discussion about future management of the case, included immunotholerance is still ongoing.

Conclusions. To our knowledge this is the first report of anaphylactic reaction to recombinant FVII. This adverse event rapresents a challenge in the management of a mild hamophilia case with inhibitor due to the limited approach in case of bleeding.

ABSTRACT N. PO128

FROM SEVERE THROMBOSIS TO SUCCESSFUL PREGNANCIES: ORTHOTOPIC LIVER TRANSPLANTATION IN INHERITED AFIBRINOGENEMIA WITH BUDD–CHIARI SYNDROME

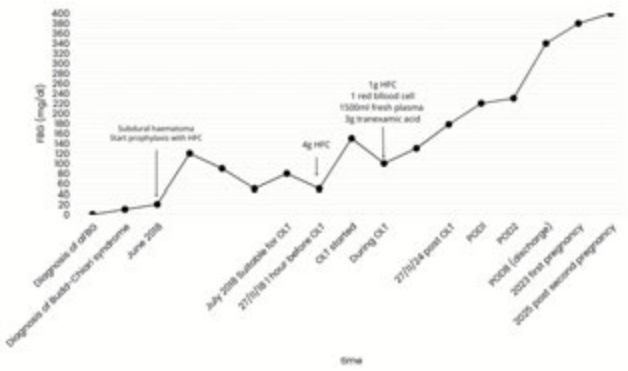
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Background. Fibrinogen (FBG) is involved in the final steps of coagulation as a precursor of fibrin monomers. Inherited FBG disorders are generally classified as quantitative or qualitative. Quantitative disorders include afibrinogenemia (aFBG), which is characterized by the complete absence of FBG. aFBG is the result of homozygosity or combined heterozygosity for the causative mutations. The diagnosis is based on the measurement of FBG activity and antigen levels which define the severity of the disorder. Clinical manifestations vary from being asymptomatic to developing catastrophic life-threatening bleeds. Although the clinical phenotype is predominantly hemorrhagic, paradoxical thrombotic events have been increasingly reported, reflecting the complex pathophysiology of this condition. The main treatment for quantitative FBG disorders is FBG supplementation.

Case report. We report the case of a 30-year-old woman diagnosed with inherited aFBG during infancy following severe gingival bleeding that required treatment with fresh frozen plasma (FFP) and red blood cell (RBC) transfusions. Throughout childhood and adolescence, she experienced recurrent mucocutaneous bleeding episodes managed with on-demand replacement therapy. In adulthood, her clinical course was complicated by recurrent hemoperitoneum secondary to hemorrhagic corpus luteum rupture, requiring surgical intervention and transfusion support. Combined oral contraceptives were subsequently introduced to prevent recurrence. In January 2018, following a spontaneous haematoma of the abdominal wall treated with FFP, a CT scan revealed splenomegaly, an enlarged and distorted liver, caudate lobe hypertrophy, no visualization of the right suprahepatic vein, leading to a diagnosis of partial Budd–Chiari syndrome. In the absence of identifiable thrombophilic conditions, the event was attributed to a multifactorial prothrombotic state associated with aFBG, estrogen exposure, and repeated FFP administration. The progression to advanced chronic liver disease, with a Model for End-Stage Liver Disease (MELD) score of 30, prompted the indication for orthotopic liver transplantation (OLT). In June 2018, a chronic right subdural haematoma was incidentally discovered during a brain CT scan performed as part of pre-OLT screening. Taking into account the complex nature of the case, there was no indications for evacuation, and it was treated conservatively. Prophylaxis with HFC (4 grams, every 72 hours) was initiated with the aim of achieving a peak > 1.5 g/L. On 27 November 2018, OLT transplant was performed after infusion of 4 g 1 hour before surgery with the aim of achieving a peak > 1.5 g/L. Intraoperative management required intensive hemostatic support, including FFP, RBC transfusions, and tranexamic acid. The postoperative course was uneventful, with rapid normalization of FBG levels the same day of OLT. Thromboprophylaxis with low-molecular-weight heparin was initiated on the first postoperative day. During long-term follow-up, the patient remained free from both bleeding and thrombotic events. Notably, she successfully completed two pregnancies with favorable outcomes under appropriate antithrombotic prophylaxis, highlighting the restoration of effective hemostatic function following transplantation.

Conclusions. We report one of the few cases of inherited aFBG, complicated with Budd-Chiari syndrome successfully treated with OLT.



ABSTRACT N. PO129

CLINICAL BENEFIT OF RECOMBINANT ADAMTS13 IN CTTP ASSOCIATED WITH HOMOZYGOUS PD173G MUTATION AND UNDETECTABLE ACTIVITY

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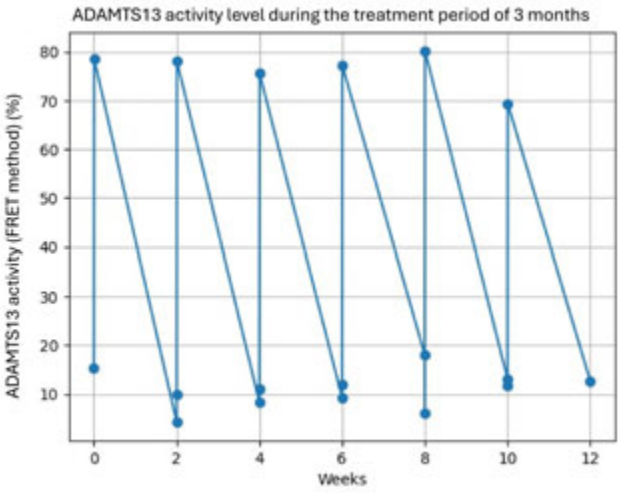
Background. Congenital thrombotic thrombocytopenic purpura (cTTP) is a rare hereditary disorder caused by severe deficiency of the ADAMTS13 enzyme, leading to recurrent thrombotic microangiopathy. We report the case of a 34-year-old male with homozygous missense mutation p.D173G, associated with 0% ADAMTS13 activity, diagnosed after presenting with thrombocytopenia, hemolytic anemia, and neurological risk features. Family history revealed consanguinity and a sibling death from similar manifestations, supporting a genetic etiology.

Methods. Clinical history, laboratory findings, genetic analysis, and therapeutic interventions were reviewed. The patient previously received on-demand Fresh Frozen Plasma (FFP) infusions for acute episodes, with increasing frequency (4–5/year) and declining tolerability. Over the past 3 months, a prophylactic regimen with recombinant ADAMTS13 (rADAMTS13, provided by Takeda) was initiated at 40 U/kg intravenously every 2 weeks. Clinical response, adverse events, and episode recurrence were monitored.

Results. Before prophylaxis, episodes were frequently triggered by respiratory infections and required hospitalization, with delayed platelet recovery and adverse reactions to FFP, including respiratory distress and cutaneous reactions. Following initiation of rADAMTS13, the patient experienced no cTTP relapses over 3 months, always showing ADAMTS13 levels at trough>5% (Fig. 1). Notably, even during bronchitis episodes, historically associated with disease flares, platelet counts remained stable, and no symptoms of microangiopathy occurred. Intravenous administration was well tolerated, with no infusion-related or systemic adverse events observed.

Discussion. This case highlights the clinical burden of recurrent cTTP and limitations of FFP therapy, including adverse reactions and suboptimal efficacy over time. Prophylactic rADAMTS13 appears to provide sustained enzymatic replacement of ADAMTS13, never observed at a level <5% (Fig. 1), preventing trigger-induced relapses. The favorable safety profile and effectiveness observed in this patient align with emerging evidence supporting recombinant therapy as a disease-modifying strategy.

Conclusions. Prophylactic recombinant ADAMTS13 demonstrated excellent short-term efficacy and safety in a patient with cTTP due to homozygous p.D173G mutation associated with absent enzymatic activity. This approach may represent a superior alternative to plasma-based therapy, particularly in patients with frequent relapses or intolerance to FFP. Longer follow-up is warranted to confirm durability of response.



ABSTRACT N. PO130

HEMORRHAGIC AND THROMBOTIC COMPLICATIONS DURING DOACS TREATMENT: THE IMPORTANCE OF A REGULAR AND PROLONGED FOLLOW-UP

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Background and Aims. Direct Oral Anticoagulants (DOAC) are the recommended drugs to be employed in the primary and secondary prophylaxis of the cardioembolic risk in patients with Atrial Fibrillation (AF). Nevertheless, ischemic stroke and major bleeding are still important outcomes to be considered. In particular, adherence to therapy has generally been found unsatisfactory. The aim of this prospective observational study is to record the percentages of ischemic and hemorrhagic events in a relatively large cohort of patients regularly followed in our Hemostasis and Thrombosis Unit over a long follow-up period.

Methods. A total of 570 patients (256 women and 314 men, median age 78, range 65-95 years) with AF have been regularly followed for a median follow-up of 5 years (range 0.5-12 years, 2741 patient/years). The DOACs employed were: apixaban (n=357, 62.6%), Rivaroxaban (n=67, 11.7%), Edoxaban (n=79, 13.8%), and dabigatran (n=67, 11.7%). The DOAC regimen was given at either the recommended full or reduced dose. All bleeding episodes and thrombotic events have been documented by objective evidence. Each follow-up visit has been made on clinical grounds, with laboratory tests including Hb, platelet count, estimated glomerular filtration rate, and liver function tests. Non-parametric ANOVA was utilized to compare the clinical events across all DOACs.

Results. Major bleeding events was 33 (1.2x100/patients/year), spontaneous intracerebral hemorrhages were 4 (0.15 x 100 patients-years), while post-traumatic cerebral hemorrhages were 3 (2 subdural and 1 subarachnoid) (0.11 x 100 patients-years). Clinically relevant non-major bleeding episodes were 28 (0.2 x 100 patients-years). Thrombotic events were as follows: ischemic strokes (n=9), upper right embolic event (n=1), atrial thrombosis (n=1), transient ischemic attacks (n=4) (0.55 x 100 patients-years). No differences were found when all these clinical adverse events were compared among all four DOACs (Table).

Conclusions. This prospective study demonstrates that all DOACs perform well when patients with AF are regularly followed and monitored in a Hemostasis and Thrombosis Unit over an extended follow-up period. The results are significantly better than those achieved in the registrative trials, underscoring the importance of periodic follow-up for these patients. The role of the Hemostasis and Thrombosis Unit is crucial in managing therapy, which often faces adherence issues when patients are left to manage their treatment independently after the initial prescription.

Table. Haemorrhagic and thrombotic events, expressed as 100 patients-years, referred to each DOAC

	Apixaban	Dabigatran	Edoxaban	Rivaroxaban
Major Bleeding	0.97	1.4	2.4	1.0
Clinical Rilevant Non Major Bleeding	1.3	0.82	0.91	0
Intracerebral haemorrhages	0.18	0	0	0.26
Post-traumatic cerebral haemorrhages	0.18	0	0	0
Thrombotic events	0.36	0.82	0.91	0.51

ANOVA (Kruskal Wallis) not significant for all the parameters considered



BEYOND THE INHIBITOR TITER: THE IMPORTANCE OF EARLY COMBINED IMMUNOSUPPRESSIVE THERAPY IN THE MANAGEMENT OF ACQUIRED HEMOPHILIA A

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Background. Acquired hemophilia A (AHA) is a rare autoimmune bleeding disorder caused by factor VIII (FVIII) inhibitors, typically characterized by an isolated prolongation of activated partial thromboplastin time (aPTT). Current evidence suggests that bleeding severity does not strictly correlate with inhibitor titers, which may lead to an underestimation of clinical severity.

Case Report. We report the case of an 80-year-old woman with a history of hypertension, dyslipidemia, and a biological prosthetic valve on antiplatelet therapy, who was admitted to the Emergency Department with diffuse spontaneous ecchymoses. Laboratory evaluation showed a prolonged aPTT (89.1 s), a normal prothrombin time (PT), a hemoglobin level of 10.3 g/dL, a non-corrective mixing test, FVIII activity of 0.8%, and the presence of a low-titer anti-FVIII inhibitor (2.39 BU). Despite the low inhibitor titer and the absence of major bleeding, the patient exhibited extensive mucocutaneous hemorrhagic manifestations and very low residual FVIII levels (<1%). After secondary causes were excluded, a diagnosis of idiopathic AHA was made. In accordance with current clinical guidelines, combined therapy with recombinant activated factor VII (rFVIIa), corticosteroids, cyclophosphamide, and tranexamic acid was promptly initiated. The patient showed rapid clinical and laboratory improvement, with normalization of FVIII levels (83%), eradication of the inhibitor, and stabilization of hemoglobin levels. A biochemical relapse (FVIII 24%, inhibitor 2.2 BU) during follow-up was effectively treated with the same immunosuppressive regimen, achieving a new remission.

Conclusions. This case report highlights that inhibitor titers can be misleading in AHA. Consistent with current recommendations, therapeutic decisions should be guided primarily by the clinical presentation. An early combined immunosuppressive approach, in the absence of contraindications, can lead to rapid and sustained remission even in frail patients, although careful follow-up is required due to the risk of relapse and treatment-related complications. Clinical suspicion, based on isolated prolongation of aPTT, remains crucial for timely diagnosis and management.



POST KIDNEY TRANSPLANT PRESENTATION OF ACQUIRED THROMBOTIC THROMBOCYTOPENIC PURPURA: A CASE OF PRE-EXISTING ADAMTS13 INHIBITORS

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Background and aims. Acquired thrombotic thrombocytopenic purpura (aTTP), otherwise known as Moschcowitz syndrome, is a subtype of thrombotic microangiopathy characterized by the simultaneous presence of microangiopathic hemolytic anemia, thrombocytopenia and multiorgan ischemic damage. The pathogenetic mechanism underlying the above-mentioned triad lies in the unsuccessful degradation of the high molecular weight multimers of von Willebrand factor (vWF), secreted by the endothelial cells, because of a deficiency in ADAMTS13, a metalloproteasis aiming to prevent an excessive linkage and consumption of platelets when adherent to subendothelium through the vWF. The pathogenetic mechanism of the acquired ADAMTS13 deficiency is predominantly autoimmune, because of the presence of circulating antibodies of the IgG family directed against the cysteine-rich spacer cathalytic domain of the metalloproteasis. Acquired thrombotic thrombocytopenic purpura (aTTP) is a rare but critical complication after kidney transplantation. Its diagnosis is often masked by post-operative complications or drug-induced microangiopathic hemolytic anemia (TMA), requiring high clinical suspicion for timely intervention. The aim of this abstract is to report a rare case of early-onset post-transplant aTTP in a patient with no prior hematological history, highlighting the diagnostic process and the effectiveness of a multimodal therapeutic strategy including Caplacizumab.

Case report. A 56-year-old Caucasian woman with end-stage renal disease of unknown etiology underwent deceased-donor kidney transplantation in August 2025. The patient's medical history was unremarkable for any known autoimmune or hematological disorders. Standard immunosuppression was initiated with steroids, mycophenolate mofetil, tacrolimus, and anti-thymocyte globulin (ATG). Despite an initially stable nephrological course, the patient developed severe thrombocytopenia (18,000/mmc) and a drop in hemoglobin (10.1 g/dL) on post-operative day (POD). Laboratory findings on POD 6 revealed TMA picture: hemoglobin 7.5g/dL, Platelets 18.000/mmc, schistocytes 1.6%, elevated LDH (709 U/L), indirect bilirubin 2.3 mg/dL and undetectable haptoglobin (<0.3 g/L), with a negative direct Coombs test. Coagulation profiles and graft function (creatinine 0.99 mg/dL) remained stable. With a PLASMIC score of 5 (intermediate risk), ADAMTS13 testing was performed. Results confirmed aTTP, showing ADAMTS13 activity <0.01 U/mL and an inhibitor titer of 19.34 BU. Treatment commenced with daily plasma exchange (PEX) and Rituximab (RTX, 375 mg/sqm), alongside adjusted baseline immunosuppression to mitigate infectious risk. Due to post-operative haemorrhagic risk, Caplacizumab was started after 24 hours. Retrospective analysis of pre-transplant serum revealed positive ADAMTS13 inhibitors (20 BU). Clinical remission was achieved within 5 days, leading to PEX discontinuation. Following rapid ADAMTS13 recovery (0.71 UI/m) and inhibitor clearance, the final RTX dose was omitted. Caplacizumab was ceased after 30 days. The patient was discharged in full clinical and serological remission on POD 30 with stable graft function.

Conclusions. This case highlights the diagnostic challenge of post-transplant aTTP and the critical importance of early ADAMTS13 assessment. The retrospective finding of pre-existing inhibitors suggests that the surgical stress or induction therapy may have triggered the clinical manifestation of a previously silent autoimmune state.



RECURRENT SUPERFICIAL VENOUS THROMBOSIS AS AN ATYPICAL MANIFESTATION OF WHIPPLE'S DISEASE: A CASE REPORT

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Background. Whipple's disease is a rare chronic multisystem infection caused by the Gram positive bacterium Tropheryma whipplei. It is classically characterized by both gastrointestinal and joint symptoms. Migratory arthralgias of the large joints often occur years before other symptoms appear, thus leading to frequent misdiagnosis of seronegative inflammatory arthritis. Thrombotic manifestations have generally not been recognized as clinical features of Whipple's disease. Nonetheless, recent case reports have highlighted a potential link between Whipple's disease and venous thrombosis.

Case Report. A 58-year-old man presented with a two-year history of seronegative oligoarthritis affecting his right wrist, which was refractory to both conventional and biologic disease-modifying antirheumatic drugs. He experienced three recurrent episodes of superficial venous thrombosis (SVT), each of them involving the great saphenous vein. There was no evidence of major or moderate risk factors for venous thromboembolism, as the patient had no family history of VTE and denied smoking. The only potential mild risk factor was an increased BMI (Body weight 95 kg, BMI 30 kg/m2). The first episode was treated with fondaparinux 2.5 mg daily for 45 days. The second episode was managed with fondaparinux followed by sulodexide, while the third was treated with fondaparinux 2.5 mg followed by rivaroxaban 10 mg daily. In light of the recurrent thrombotic events, a thrombophilia work-up was undertaken and ruled out both hereditary and acquired thrombophilic disorders. Three months later, the onset of chronic, non-bloody diarrhoea prompted diagnostic reassessment. Upper gastrointestinal endoscopy with duodenal biopsies showed mild chronic inflammation, and polymerase chain reaction testing was positive for Tropheryma whipplei, confirming Whipple's disease. Due to the microbiological response, an antibiotic therapy was started: he was treated with ceftriaxone 2g iv for 5 days, followed by doxyciclin 100 mg bid and hydroxychloroquine 200 mg bid. After one week of antibiotic treatment, he reported a significant improvement of arthralgias. No further episodes of venous thromboembolism were reported.

Conclusions. This case directs clinical attention toward the potential association between Whipple's disease and venous thromboembolism (VTE), aligning with recent case reports that propose venous thrombosis as an atypical manifestation of the disease. From a pathophysiological perspective, Tropheryma whipplei infection may heighten thrombotic risk through immunothrombotic mechanisms. However, further studies are warranted to explore this hypothesis and to determine whether targeted antimicrobial therapy can effectively reduce the risk of recurrent thrombotic events.



FAMILIAL HYPERCHOLESTEROLEMIA 57-GENE PANEL MUTATIONAL ANALYSIS: INSIGHT INTO CARDIOVASCULAR RISK GENETIC PREDISPOSITION

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Methods. We analyzed 191 patients with possible/probable/definite FH according to Dutch Lipid Clinic Network (DLCN) score. A targeted 57 genes (lipid metabolism, dyslipidaemias, polygenic FH) panel was evaluated through Illumina technology, using MiSeq platform. Variants identified were classified according to American College of Medical Genetics (Richards S et al.,2015) criteria. Continuous variables were expressed as median (interquartile range).

Results. We identified 80 rare variants in LDLR gene across 76 subjects. Sixty-eight of them had likely pathogenic (LP)/pathogenic (P) variants and we considered them as LDLR-positive (LDLR+). The remaining 123 patients were LDLR-negative (LDLR-), including 115 with no LDLR variants and 8 carrying LDLR benign (B)/likely benign (LB)/uncertain significance (VUS) variants. When patient clinical characteristics were considered across the two groups, LDLR+ subjects showed significantly higher LDL-C levels and a higher DLCN score [LDL-C: 233.0 (208.3-285.0) vs 220.0 (199.0-247.5) mg/dL, p=0.001; DLCN: 6 (4-7) vs 4 (4-5); p=0.000003], compared with LDLR- subjects. A trend towards higher levels of total cholesterol (TC) and higher CHD incidence was observed in LDLR+ [TC: 312.0 (281.5-360.5) vs 300.0 (267.0-331.0) mg/dL; p=0.07; CHD: 19.1% vs 9.8 %, p=0.08]. Higher Talmud score values in LDLR- with respect to LDLR+ [1.02 (0.90-1.11) vs 0.98 (0.86-1.06), p=0.08] were also found. Among LDLR+ patients, only 5 had variants exclusively in LDLR while 63 patients harboured at least one rare variant in other genes of the panel, of whom 17 had B/LB/VUS variants in APOB and LDLRAP1. Among LDLR- patients, a high proportion carried multiple rare variants: 67.5% had at least two and 36.6% had three or more rare variants across the 56-gene panel. Specifically, 39 rare variants were found in APOB, 3 in PCSK9 and 6 in LDLRAP1, alongside 297 in 45 of the remaining 53 panel genes. Patients with rare variants in both LDLR and other genes exhibited a trend of higher LDL-C levels compared to those with variants solely in LDLR [236.0 (220.0-288.0) vs 206.0 (195.5-254.0) mg/dL; p=0.17]. In particular, focusing on genes mainly associated to monogenic and polygenic FH (APOB, PCSK9, LDLRAP1, APOE, ABCG5, ABCG8, CELSR2, HFE, MYLIP, SLC22A1, NYNRIN, ST3GAL4), LDLR+ patients with at least two other variants in the selected panel exhibited significantly higher levels of TC and LDL-C compared to other LDLR+ [TC: 354.5 (312.0-400.3) vs 300.0 (276.3-336.3) mg/dL, p=0.02; LDL-C: 275.5 (246.3-314.8) vs 227.5 (203.3-265.3) mg/dL, p=0.01] and a trend toward higher DLCN score [6.5 (5.8-9.0) vs 6.0 (4.0-7.0), p=0.07].

Conclusions. These findings highlight the complexity of FH genetics, suggesting the possible contribution of rare or common genetic variants burden in modulation of clinical phenotype not only in polygenic hypercholesterolemia but also in LDLR+ monogenic FH.

ABSTRACT N. PO135

CHRONIC ERYTHROCYTE REMODELING AND IMPAIRED RHEOLOGICAL FUNCTION IN PATIENTS WITH PATENT FORAMEN OVALE

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Background and Aims. Patent foramen ovale (PFO) is associated with migraine with aura, cryptogenic stroke, and a prothrombotic phenotype. While the contribution of platelet activation and endothelial dysfunction is recognized, the impact of chronic abnormal intracardiac flow on erythrocyte biology remains poorly explored. Red blood cells (RBCs) are sensitive to mechanical and oxidative stress, which can alter their morphology, deformability, and aggregability, thus affecting microcirculatory flow and thrombogenicity. We previously observed increased erythrocyte oxidative stress and reduced hematological parameters in PFO patients, suggesting chronic RBC remodeling associated with PFO. We aimed to characterize erythrocyte morphology and rheological properties in patients with PFO before and after percutaneous closure.

Methods. Sixty-seven patients with PFO were evaluated before closure (T0) and at 6-month follow-up after closure (T1), and compared with 28 healthy subjects (HS). Standard hematological parameters, including erythrocyte count and red cell distribution width (RDW-CV), were assessed by automated blood count. Erythrocyte ultrastructure was evaluated by scanning electron microscopy (SEM). Functional erythrocyte properties, including deformability under shear stress and aggregation behavior, were analyzed using LoRRca.

Results. Patients with PFO displayed evidence of erythrocyte structural remodeling. RDW-CV was significantly increased compared with HS (13.43% ± 1.36 vs 12.44% ± 0.53; p = 0.0011), indicating greater heterogeneity in erythrocyte size, and remained elevated at 6-month follow-up after closure (13.82% ± 1.75), suggesting persistence of long-lived structural alterations. SEM revealed morphological heterogeneity in PFO patients. In addition to biconcave RBCs, a “shield-shaped” erythrocyte phenotype was observed in PFO samples but not in HS, identifying a previously undescribed RBC morphological signature associated with PFO (Figure). Functional analysis showed that in PFO patients RBC deformability under prolonged shear stress was significantly reduced at baseline compared with post-closure values, indicating increased membrane rigidity and reduced mechanical resilience (elongation index 0.18 ± 0.03 vs 0.20 ± 0.04; p=0.019). Conversely, erythrocyte aggregability was significantly increased before PFO closure and improved after closure (amplitude 36.45 ± 3.66 vs 34.07 ± 3.36; p=0.0002), suggesting partial restoration of physiological rheological behavior after elimination of abnormal intracardiac flow. These findings are consistent with a model of chronic mechanical conditioning of erythrocytes in PFO, resulting in persistent structural remodeling and altered functional behavior.

Conclusions. PFO is associated with a distinct erythrocyte phenotype characterized by structural heterogeneity, abnormal morphology, impaired deformability, and increased aggregability. These alterations are consistent with chronic erythrocyte remodeling induced by prolonged exposure to abnormal hemodynamic stress. Partial recovery after PFO closure supports a causal relationship between PFO-related flow disturbance and erythrocyte dysfunction. Given the role of RBC rheology in vascular homeostasis and thrombosis, erythrocyte alterations may represent an additional contributor to the thromboinflammatory burden associated with PFO. Funding: M6C2I2.1_PNRR_NEXT_GENERATION_EU, PNRR-MAD-2022-12376277, CUP-B43C22001110008 Clinical trial: NCT06046508

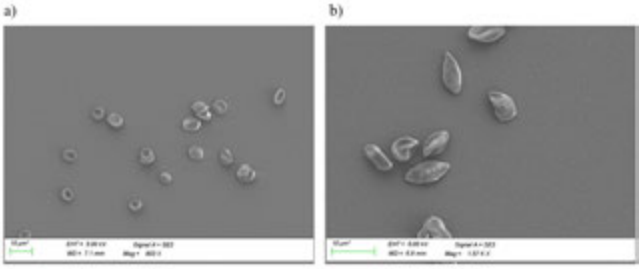


Figure. Ultrastructural analysis of erythrocytes in a) healthy subject and b) patient with patent foramen ovale.

ABSTRACT N. PO136

PHENOTYPE CHARACTERIZATION OF PATIENTS HOSPITALIZED FOR ACUTE SARS-COV2 INFECTION WITH AND WITHOUT ACUTE CEREBRAL ISCHEMIA

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Background and Aims. Severe acute SARS-CoV2 infection is a well known model of systemic inflammatory response syndrome (SIRS), characterized by a strong activation of both inflammatory and coagulation pathways leading to multiorgan vascular and microvascular damage. To date, evidence on cerebrovascular complications occurring during acute SARS-CoV2 infection is still scarce. This study aims to estimate the prevalence of acute cerebral ischemia in a large cohort of patients hospitalized for acute SARS-CoV2 infection and to identify the main patient- and disease-related risk factors.

Methods. All patients included in the frame of the COVID-19 Network with available information on the primary endpoint (cerebral ischemia yes/no) were enrolled. The Registry, started from March 2020, included all consecutive adults (aged ≥18 years) with a positive RT-PCR result for SARS-CoV-2 at the time of hospital admission. All the Register-related details are reported elsewhere (doi: 10.1016/j.cmi.2020.06.028).

Results. Among 1412 patients hospitalized for acute Sars-CoV2 infection, we observed 19 cases with acute cerebral ischemia, including 11 imaging-proven ischemic stroke (IS) and 8 transient ischemic attack (TIA). Patients with acute cerebral ischemia (TIA or IS) were older compared with patients without, with a higher proportion of hypertension, ischemic heart disease/heart failure and history of IS/TIA. As regards laboratory parameters, we observed higher troponin levels and lower platelet and lymphocyte counts in patients with acute cerebral ischemia. Routine hemostatic and inflammatory laboratory parameters were comparable and within normal range in both groups. In-hospital mortality was significantly higher in patients with acute cerebral ischemia during acute SARS-CoV2 infection (Table). Consistently, reservoir mask was used more in these patients (18.8% vs 3.5 %, p=0.001).

Conclusions. In a large cohort of patients hospitalized for acute Sars-CoV2 infection (n=1412), we found an incidence proportion of 1.3% of acute cerebral ischemia, 0.8% of IS. Specific patient-related features (age, hypertension, history of IS/TIA, ischemic heart disease/heart failure) seemed to influence the risk of acute cerebral ischemia during acute SARS-CoV-2 infection. In these patients, the early detection of IS/TIA is very important considering its impact on in-hospital mortality risk. Monitoring specific laboratory parameters of disease severity (platelet count, lymphocytes and tropinin level) could be useful.

	Cerebral ischemia (N=19)	No cerebral ischemia (N=1393)	p
Patient-related features			
age, median (IQR), years	76 (64-83)	63 (52-76)	**0.001**
female sex, n (%)	8 (42)	473 (34)	0.46
history of IS or TIA, n (%)[1]	5 (38.5)	83 (6.1)	**<0.0001**
current/former smoker, n (%)[2]	2 (10.5)	230 (24.7)	0.15
hypertension, n (%)[3]	14 (73.7)	615 (45.4)	**0.014**
hyperlipidemia, n (%)[4]	5 (26.3)	206 (15.3)	0.19
diabetes mellitus, n (%)[5]	3 (15.8)	252 (18.7)	0.75
chronic kidney disease on dialysis, n (%)[6]	1 (5.3)	18 (1.3)	0.15
ischemic heart disease/heart failure, n (%)[6]	5 (35.7)	163 (12.1)	**0.008**
Disease-related features			
dyspnea, n (%)[7]	9 (47.4)	757 (54.8)	0.52
requiring oxygen, n (%)[8]	14 (73.7)	1007 (73.2)	0.97
hemoglobin, median (IQR), g/dL	12.7 (11.8-14.3)	12.8 (11.4-13.9)	0.47
platelet count, median (IQR), $x10^9$/L	195 (149-292)	232 (174-309)	**0.051**
WBC, median (IQR)/μL	8535 (7278-12932)	7010 (5030-9575)	0.26
lymphocytes, median (IQR), $x10^9$/L	0.98 (0.58-1.38)	1.03 (0.72-1.42)	**0.057**
troponin, median (IQR), ng/L	533 (220-747)	11.1 (6.3-23.2)	**0.098**
PT ratio, median (IQR)	1.2 (1.1-1.2)	1.1 (1.0-1.2)	0.52
aPTT ratio, median (IQR)	0.99 (0.9-1.0)	0.95 (0.9-1.0)	**0.045**
LDH, median (IQR), IU/L	260 (220-554)	274 (213-361)	0.42
CRP, median (IQR), mg/dL	6.0 (1.9-9.3)	5.3 (2.2-10.6)	0.43
Fibrinogen, median (IQR), mg/dL	419 (177-633)	536 (435-648)	0.12
D-Dimer, median (IQR), μg/L	2503 (788-13900)	929 (588-1675)	0.23
ferritin, median (IQR), μg/L	725 (456-1082)	780 (399-1307)	0.77
Outcomes			
in-hospital mortality, n (%)[9]	6 (46.2)	222 (16.0)	**0.003**
lenght of hospital stay, median (IQR), days	12 (9-28)	13 (7-23)	0.65
non-home discharged, n (%)[10]	3 (27.3)	303 (26.1)	0.93

[1]available in 13/19 and 1352/1393 patients, [2]19/19 and 930/1393 patients, [3]19/19 and 1356/1393 patients, [4]19/19 and 1346/1393 patients, [5]19/19 and 1349/1393 patients, [6]14/19 and 1349/1393 patients, [7]19/19 and 1381/1393 patients, [8]19/19 and 1375/1393 patients, [9]13/19 and 1391/1393 patients, [10]11/19 and 1160/1393.



SMAD3 VARIANTS IN LOEYS-DIETZ SYNDROME: RELATIONSHIP WITH NON-AORTIC CARDIOVASCULAR FEATURES

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Background. Loeys-Dietz syndrome (LDS) is an autosomal dominant connective tissue disorder typically characterised by vascular, skeletal, craniofacial, cutaneous, and ocular abnormalities. LDS is strictly defined by the triad of hypertelorism, bifid uvula/cleft palate, tortuosity, and aortic/arterial aneurysms. LDS type 3 (LDS3) is associated with mutations in the SMAD3 gene, which codes for mothers against decapentaplegic homolog 3, a component of the transforming growth factor beta (TGF-β) signalling pathway. SMAD3 variants are known to be associated with hereditary thoracic aortic disease (HTAD) and significant osteoarthritis features. While aortic aneurysms and dissections are the primary concern, previous studies have also reported the association of SMAD3 variants with severe non-aortic cardiovascular phenotypes. Due to limited information concerning SMAD3 genotype-phenotype correlation and variability in clinical presentation, cardiovascular manifestations in SMAD3 variant-carriers have been explored.

Methods. A cohort of 224 patients [median age 50 (IQR 37-61) years, 155 males and 69 females] attending the Regional Referral Centre for Marfan Syndrome and Related Disorders in Florence was investigated for differential diagnosis of aortopathy-related conditions and hereditary thoracic aortic disease (HTAD). Subjects underwent multidisciplinary evaluations, including cardiologic and genetic assessment. Targeted Next Generation Sequencing (NGS) of at least 17 genes was performed. All rare variants identified were classified according to the American College of Medical Genetics (ACMG) guidelines for variant interpretation (Richards S et al., 2015).

Results. Rare likely pathogenic(LP)/pathogenic(P) variants in SMAD3 gene (NM_005902) were identified in 7 index cases out of the 223 subjects investigated: five missense (p.Arg80Trp in the MH1 domain; p.Arg287Gln, p.Lys378Arg, p.Phe360Cys and p.Arg373His in the MH2 domain), one nonsense (p.Phe343Ter) and one splicing variant (c.1009+2T>C). Six out of the 7 index patients underwent thoracic aortic surgery. Four out of the 7 patients carrying SMAD3 LP/P variants also exhibited non-aortic cardiovascular phenotypes [P001 showed dilated cardiomyopathy and heart failure, leading him to death; P010 had a hemorragic stroke; P014 experienced a short term cardiac arrest and P016 heart failure]. Segregation analysis in the relatives of 5 index cases identified 11 additional carriers of SMAD3 variants. Among the combined cohort of 18 subjects SMAD3-variant carriers (7 index cases and 11 relatives), mitral valve disorders also represent frequently reported manifestations; really seven subjects had mitral valve prolapse (MVP), and three of these also had mitral annular disjunction (MAD); moreover, one patient underwent surgery for a ruptured mitral chord.

Conclusions. Data from this study confirm that SMAD3 genetic variants contribute to a range of phenotypic manifestations associated with Loeys-Dietz syndrome type III. Beyond aortopathy, further non-aortic cardiovascular phenotypes may be present, so underlying the need of an appropriate clinical and genetic evaluation in the index cases and in their relatives. Further investigation is recommended to deepen the molecular mechanisms underlying these genotype-phenotype correlations.



THE START-SIAPAV-PAD REGISTRY: RATIONALE, STUDY DESIGN AND BASELINE CHARACTERISTICS OF AN ITALIAN MULTICENTRE REGISTRY

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Background. Peripheral artery disease (PAD) is a common and clinically heterogeneous manifestation of systemic atherosclerosis, PAD reflects systemic atherosclerotic burden and confers high cardiovascular morbidity and mortality rates. In Italy, contemporary real-world evidence on diagnostic pathways, adherence to GDMT, use of revascularisation strategies, and on long-term outcomes remains fragmented. Heterogeneous patient pathways, involvement of multiple specialties, and limited number of high-volume centres reduce the feasibility of adequately powered randomised clinical trials across the full clinical disease spectrum. Thus, prospective observational research is essential to generate high-quality, generalisable evidence to guide everyday practice. The START-SIAPAV-PAD registry was designed to describe characteristics, management and clinical history of patients with PAD in Italy. Baseline characteristics and treatment are here reported

Methods. START-SIAPAV-PAD is a prospective, multicentre, observational registry enrolling consecutive adults with objectively documented symptomatic PAD managed at 20 Italian Vascular centres. Standardised electronic case-report forms collect demographics, risk factors, comorbidities, haemodynamic parameters, vascular anatomy, medical therapies. Follow-up is planned for a minimum of 3 years. PAD severity is classified according to the Leriche–Fontaine scale, and risk-factor targets follow the 2024 ESC guidelines

Results. The present analysis includes 517 patients (72.0% male; median age 71 years) with a high prevalence of hypertension (79.2%), dyslipidaemia (85.0%), diabetes (36.9%), smoking (96.1% current or former) and chronic kidney disease (21.2%). Nearly half reported a walking distance <200 m, 77.5% had a resting ankle–brachial index ≤0.80, and 17.2% presented with Leriche–Fontaine stage IV. Femoropopliteal disease was most frequent (69.8%), with multilevel involvement in 43.4%. Previous revascularisation was common, major amputation was rare. LDL-cholesterol targets (<55 mg/dL) were achieved in 27.9% despite lipid-lowering therapy in 82.1%. Dual pathway inhibition, advanced lipid-lowering therapies, supervised exercise and structured smoking-cessation programmes were insufficiently adopted.

Conclusions. In a population with advanced PAD and multiple risk factors we observed a substantial gap between guideline recommendations and real-world practice. Longitudinal follow-up will assess outcomes and opportunities to improve PAD management

ABSTRACT N. PO139

PFO-LIKE INTRACARDIAC FLOW IS SUFFICIENT TO INDUCE A PROTHROMBOTIC PLATELET PHENOTYPE: EVIDENCE FROM A MICROFLUIDIC MODEL OF PATENT FORAMEN OVALE

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Background and Aims. Patent foramen ovale (PFO) is increasingly recognized as a clinically relevant condition associated with migraine with aura and thromboembolic complications. Beyond paradoxical embolism, growing evidence suggests that PFO patients display a prothrombotic phenotype characterized by platelet activation, oxidative stress, and increased exposure of platelet-associated Tissue Factor (TF), a key initiator of thrombin generation. However, the mechanisms underlying this phenotype remain poorly understood. It is unclear whether platelet activation is primarily driven by circulating biochemical mediators or by the abnormal intracardiac flow dynamics generated by blood passage through the PFO tunnel. Computational fluid dynamics simulations indicate that blood cells traversing PFO-like geometries are exposed to abnormal shear gradients and mechanical stress, potentially contributing to platelet activation. We aimed to investigate whether PFO-like hemodynamics is sufficient to induce platelet activation and to reproduce the prothrombotic platelet phenotype observed in patients with PFO.

Methods. Platelet phenotype was first analyzed in PFO patients before percutaneous closure and after a 6-month follow-up, and compared with healthy subjects (HS) by flow cytometry. Platelet activation was assessed by measuring TF exposure and reactive oxygen species (ROS) generation. To investigate the mechanistic contribution of altered flow, a microfluidic platform reproducing the geometry and hemodynamic conditions of a PFO tunnel was developed based on computational fluid dynamics simulations (Figure). Whole blood from HS was perfused through the PFO-mimicking chip or through a linear physiological-flow chip used as control. Platelet TF expression, P-selectin exposure, activated GPIIbIIIa (aGPIIbIIIa) and ROS generation were analyzed by flow cytometry. In selected experiments, blood was pre-incubated with aspirin or a P2Y12 inhibitor (ARMX) before perfusion.

Results. PFO patients showed a significantly enhanced platelet prothrombotic phenotype, characterized by increased TF-positive platelets and ROS production compared with HS, which significantly decreased after PFO closure, supporting a direct link between PFO and systemic platelet activation. Perfusion of whole blood from HS through the PFO-mimicking chip was sufficient to reproduce this phenotype ex vivo. Passage through the PFO chip induced a significant increase in platelet TF expression, ROS production and P-selectin exposure (2-fold vs linear chip), whereas linear flow conditions did not significantly modify these parameters. In contrast, aGPIIbIIIa showed only a non-significant increase. Pre-incubation with the ARMX significantly reduced TF expression and ROS generation induced by PFO-like flow, whereas aspirin mainly reduced ROS.

Conclusions. These findings provide mechanistic evidence that abnormal PFO-associated intracardiac flow is sufficient, per se, to induce a prothrombotic platelet phenotype characterized by TF exposure. The ability of the microfluidic PFO model to recapitulate the platelet phenotype observed in vivo supports a direct causal role of hemodynamic stress in PFO-related thromboinflammation. This model may represent a valuable translational platform to dissect mechanisms of platelet activation in PFO and to test targeted antithrombotic strategies. Funding: M6C2I2.1_PNRR_NEXT_GENERATION_EU, PNRR-MAD-2022-12376277, CUP-B43C22001110008 Clinical trial: NCT06046508

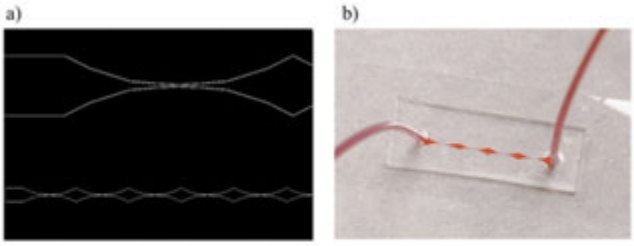


Figure. Microfluidic chip reproducing PFO-like geometries. a) AutoCAD software imagine used for project design (single and multiple feature); b) chip in use where blood flow can be observed.

ABSTRACT N. PO140

HISTORY OF FALLS IN PATIENTS WITH ATRIAL FIBRILLATION: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Background and Aims. In patients with Atrial Fibrillation (AF), falls pose substantial challenges in the management, particularly due to the increased risk of bleeding, and uncertainties on the use of oral anticoagulants (OAC). Nonetheless, epidemiological data on falls in patients with AF and their consequences are still scarce. We aimed to perform a systematic review and meta-analysis to evaluate the prevalence of history of falls in patients with AF, and their association with use of OAC, and with long-term clinical outcomes.

Methods. We performed a systematic review and meta-analysis, according to PRISMA Guidelines. MEDLINE and EMBASE were searched up to May 2025; we included all studies reporting either the prevalence of history of falls or the association of history of falls with long-term outcomes (all-cause death, stroke/thromboembolism [TE], major bleeding, intracranial hemorrhage [ICH], and recurrent falls) in patients with AF. Among the studies included, we also evaluated the use of OAC according to history of falls. Data on the prevalence of history of falls were pooled using a generalized linear mixed model, and results were reported as pooled prevalence and 95% Confidence Intervals (95%CI). Number of patients prescribed with OAC and total number of patients were pooled using random-effect models, and results were reported as pooled Odds Ratios (OR) and 95%CI. For long-term outcomes, we extracted Hazard Ratios (HR) and 95%CI and converted them to log-scale for pooling; where HR and 95%CI were unavailable, number of events and total number of patients were extracted. Results were reported as pooled Hazard Ratios (HR) and 95%CI. Heterogeneity was estimated using the restricted maximum-likelihood estimator, and the inconsistency index (I^2) was also reported. Subgroup analyses and meta-regressions were also performed to explore potential sources of heterogeneity.

Results. 4,357 studies were found through literature search; after duplicates removal, screening of records, and cross-reference search, 37 studies were included, with over 2 million patients with AF. The pooled prevalence of history of falls was 11.4% (95%CI: 8.3-15.4%), with substantial heterogeneity observed across studies (I^2=99.9%; Figure 1, left panel). History of falls was associated with lower odds of receiving OAC (OR: 0.57; 95%CI: 0.39-0.83 across 14 studies; I^2=98.6%); prevalence of male sex, and higher uptake of direct oral anticoagulants were associated with higher odds of receiving OAC at meta-regression analysis. History of falls was associated with a higher risk of long-term outcomes (Figure 1, right panel), including all-cause mortality (HR 1.63, 95%CI: 1.23-2.18, I^2=91.4%), stroke/TE (HR: 1.30, 95%CI: 1.01-1.66, I^2=70.6%), major bleeding (HR: 1.54, 95%CI: 1.14-2.06, I^2=91.8%) and ICH (HR: 1.71, 95%CI: 1.14-2.58, I^2=82.8%). only 2 studies reported data on recurrent falls, both showing an increased risk in patients with previous falls, although without statistical significance at pooled analysis. Results were consistent at subgroup analyses and meta-regressions.

Conclusions. A history of previous falls is frequently found in patients with AF. Previous falls lead to lower use of OAC and are associated with a higher risk of all AF-related long-term outcomes. These patients require further efforts and dedicated approach to improve thromboembolic risk prevention, and to improve their prognosis.



ABSTRACT N. PO141

PLASMA METABOLOMIC PROFILING IDENTIFIES PLATELET-RELATED METABOLIC CHANGES AFTER PFO CLOSURE IN MIGRAINE WITH AURA

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Background and Aims. Patent foramen ovale (PFO) is frequently observed in patients with migraine with aura (MA), although the biological mechanisms linking the two conditions remain incompletely understood. Beyond paradoxical embolism, increasing evidence suggests that PFO may be associated with systemic platelet activation, enhanced thrombin-generating potential and oxidative stress imbalance. These processes are closely interconnected with mitochondrial function and energy metabolism, supporting the concept that a circulating prothrombotic and redox-sensitive milieu may contribute to PFO-associated migraine pathophysiology. Plasma metabolomics offers a systems-level approach to investigate these mechanisms by identifying molecular signatures associated with thrombo-inflammatory activation, oxidative stress and altered metabolic homeostasis. In this context, the longitudinal metabolic profiling before and after percutaneous PFO closure may provide insight into potentially reversible biological pathways involved in the PFO–-MA phenotype. The aim of this study was therefore to characterize the plasma metabolomic profile of patients with MA and PFO before and at 6-month post-PFO closure, with particular focus on pathways related to energy metabolism, lipid utilization and oxidative balance.

Methods. In this prospective study, 120 patients with MA and PFO undergoing percutaneous closure were enrolled. Plasma samples were collected before the procedure and at 6-month follow-up. Untargeted metabolomic analysis was performed using high-resolution proton nuclear magnetic resonance spectroscopy (^{1}H-NMR). Spectral data were processed to identify metabolites and pathway-level changes associated with PFO closure.

Results. NMR-based metabolomic profiling revealed consistent modulation of metabolites involved in glycolysis, lipid β-oxidation, ketone body metabolism, and the tricarboxylic acid cycle following PFO closure. At baseline, the metabolic profile was characterized by increased reliance on lipid-derived substrates, as indicated by elevated ketone bodies and lipid-related metabolites, alongside reduced levels of glycolysis-related metabolites such as lactate and alanine. At 6 months, a metabolic reprogramming was observed, with increased levels of lactate and alanine and reduced ketone bodies, indicating a shift toward glucose-based energy metabolism. Overall, these changes suggest improved metabolic flexibility and a reduction in lipid-driven energy reliance, consistent with a lower systemic metabolic stress burden.

Conclusions. In patients with MA and PFO, plasma metabolomics identified a baseline metabolic signature consistent with a systemic redox-sensitive and prothrombotic environment, in line with previously reported platelet activation and oxidative imbalance. The observed post-closure metabolic shift toward glucose utilization supports the hypothesis that PFO contributes to a metabolically dysregulated state that may be, at least partially, reversible after closure (Figure 1). These findings highlight metabolomics as a valuable tool to investigate the molecular mechanisms underlying the PFO–migraine association and to link metabolic reprogramming with platelet-driven thrombo-inflammatory processes.

Funding: M6C2I2.1_PNRR_NEXT_GENERATION_EU, PNRR-MAD-2022-12376277, CUP-B43C22001110008 Clinical trial: NCT06046508.

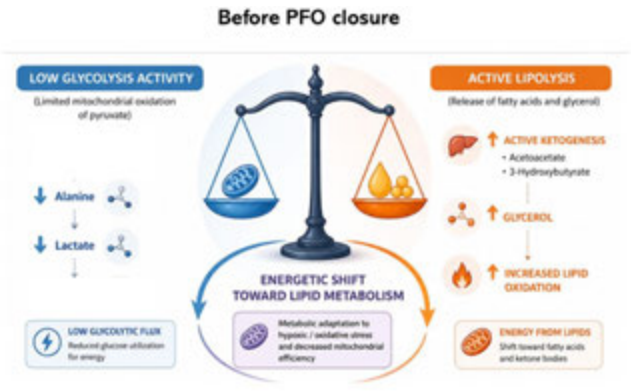


Figure 1. Metabolic shift toward lipid-based energy metabolism in PFO patients.

ABSTRACT N. PO142

CROSS-TALK BETWEEN HEART AND BRAIN IN ATRIAL FIBRILLATION: ASSOCIATIONS BETWEEN CARDIAC REMODELING AND CEREBROVASCULAR LESION BURDEN IN THE STRAT-AF STUDY

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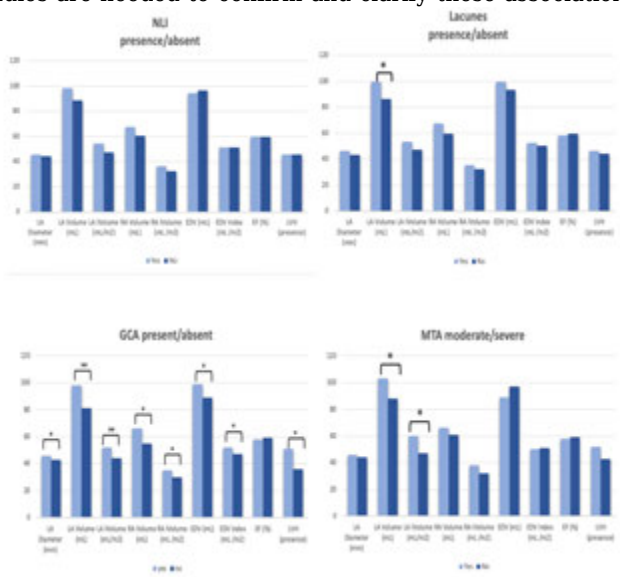
Background. Atrial fibrillation is the most common arrhythmia, associated with increased risk of ischemic stroke and mortality. Neuroimaging has shown a high prevalence of cerebral small vessel disease markers in AF patients, but the underlying mechanisms remain unclear.

Objectives. To investigate the association between microangiopathic and non-microangiopathic neuroimaging markers of cerebrovascular damage and cardiac morphological features in elderly atrial fibrillation patients on oral anticoagulants.

Methods. We performed a cross-sectional analysis within the Strat-AF 2 study. From March 2021 to June 2022, we consecutively enrolled patients >65 years with AF on oral anticoagulants for thromboembolic prevention. All underwent clinical assessment, neuroimaging (magnetic resonance imaging, or computed tomography scan), and echocardiography.

Results. A total of 179 patients were included (mean age 78.6 ± 6.7 years, 58% male): 100 underwent magnetic resonance imaging and 79 computed tomography. Non-lacunar infarcts were present in 26%, while 79.3% showed at least one cerebral small vessel disease marker. Mean indexed left atrial volume was 48.5 ± 19.8 mL/m². In multivariate analysis, non-paroxysmal atrial fibrillation was independently associated with non-lacunar infarcts (OR 2.95; 95% CI 1.07–8.12; p=0.036). Larger left atrial volume was independently associated with both moderate-to-severe medial temporal lobe atrophy (OR 1.025 per mL/m²; 95% CI 1.003–1.047; p=0.024) and lacunes (OR 1.008; 95% CI 1.010–1.017; p=0.05).

Conclusions. In elderly AF patients on OAC, cardiac structural parameters were associated with both microangiopathic and non-microangiopathic brain lesions, even in the absence of prior ischemic stroke. Larger longitudinal studies are needed to confirm and clarify these associations.



ABSTRACT N. PO143

GENDER DIFFERENCES IN COAGULATION PROFILE IN OBSTRUCTIVE CORONARY ARTERY DISEASE: PRELIMINARY RESULTS FROM AN ANGIOGRAPHICALLY CONTROLLED COHORT STUDY

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Background and Aims. Gender differences in ischemic heart disease are widely reported but remain still not fully understood. In the present study we aimed to assess sex-related variations in coagulation profiles among individuals with angiographically confirmed obstructive coronary artery disease (CAD).

Methods. This analysis was conducted within the framework of the Verona Heart Study - Rovereto cohort, which is an observational study enrolling clinically stable subjects scheduled for elective coronary angiography. Obstructive CAD was defined by lumen stenosis >50% in at least one epicardial vessel. Subjects who were using oral anticoagulants, had any acute illness or had experienced a myocardial infarction within the past three months were excluded from the analysis. The coagulation panel included coagulant activity of factors II, V, VII, VIII, IX, X, XI, and XII, as well as global coagulation test, like thrombin generation assay (TGA), and biomarkers of tissue factor (TF) pathway, such as tissue factor pathway inhibitor (TFPI) and activated factor VII-antithrombin (FVIIa-AT) complex.

Results. Complete coagulation profiles were obtained for 64 females and 257 males with obstructive CAD (mean age 68.9 ± 9.4 years). With respect to general clinical and laboratory characteristics, females were older, had lower body mass index (BMI), and higher LDL cholesterol plasma concentration, while no difference was found for prevalence of hypertension, diabetes, dyslipidemia and smoking habit. Compared to males, females had significantly higher levels of coagulant activity of factors V, VII, XI, and XII, as well as higher plasma concentration of FVIIa-AT (Table 1). Female sex remained associated with increased levels of both FVII coagulant activity and FVIIa-AT plasma concentration after adjustment for age, BMI, renal function, plasma lipids and coagulant activity of the other factors by linear regression models. On the other hand, there was no significant difference for TGA parameters (Table 1).

Conclusions. Women with obstructive CAD showed specific differences in their coagulation profiles and biomarkers compared to men, though there was no impact on overall TGA parameters.

Table 1: Differences in coagulation parameters according to gender

	Total (n = 321)	Males (n = 257)	Females (n = 64)	p *
Coagulant activity of coagulation factors				
FII:C (%)	88.9 ± 11.8	88.3 ± 11.7	91.5 ± 12.2	0.077
FV:C (%)	86.6 ± 18.1	85.1 ± 18.2	93.3 ± 16.3	**0.004**
FVII:C (%)	87.4 (84.9-89.9)	85.4 (82.8-88.1)	96.2 (89.7-103.2)	**0.001**
FVIII:C (%)	98.8 (95.2-102.7)	98.4 (94.3-102.7)	100.6 (92.5-109.5)	0.656
FIX:C (%)	116.6 ± 18.9	116.6 ± 18.4	116.6 ± 21.4	0.997
FX:C (%)	93.9 (92.0-96.0)	93.4 (91.2-95.6)	96.4 (91.6-101.4)	0.247
FXI:C (%)	102.1 ± 19.7	100.3 ± 19.0	110.0 ± 20.9	**0.001**
FXII:C (%)	98.0 ± 25.4	95.8 ± 25.1	107.1 ± 24.6	**0.004**
Thrombin generation assay				
Lag time (min)	3.70 (3.59-3.80)	3.73 (3.62-3.85)	3.55 (3.31-3.80)	0.159
Time to peak (min)	7.13 (6.96-7.32)	7.17 (6.98-7.37)	6.99 (6.54-7.46)	0.428
Peak (nM)	166 (158-174)	167 (159-176)	161 (142-174)	0.523
ETP (nM*min)	1001 (967-1036)	998 (962-1036)	1013 (924-1109)	0.746
MRI (nM/min)	49.1 (45.7-52.7)	49.5 (45.8-53.5)	47.4 (39.5-56.9)	0.633
Biomarkers of TF pathway				
FVIIa-AT (pM)	101.1 (95.7-106.8)	96.0 (90.2-102.2)	124.0 (111.9-137.3)	**<0.001**
Total TFPI (ng/mL)	65.5 ± 14.5	64.7 ± 13.7	68.7 ± 16.9	0.060

* by t-test.

ETP: Endogenous Thrombin Potential; MRI: Mean Rate Index; TF: Tissue Factor; TFPI: Tissue Factor Pathway Inhibitor



KIV2 LPA POLYMORPHISM: ROLE IN BAV CLINICAL COMPLICATIONS ACCORDING TO DIFFERENT CLINICAL SETTINGS

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Background and Aims. Bicuspid aortic valve (BAV) is the most common congenital cardiopathy affecting 0.5-2.0% of general population. BAV is associated with different complications such as valvular aortic stenosis, calcification, aortic insufficiency and thoracic aortic aneurysm. Beyond hemodynamic valvular impairment, dyslipidemia and elevated lipoprotein (a) [Lp(a)] levels also favour BAV progression/complications. Lp(a) levels are known to be under strict genetic control and largely influenced by *LPA* Kringle IV type 2 (KIV2) size polymorphism, with the repeat number inversely correlating with Lp(a) levels. Accordingly, we characterized *LPA* KIV2 repeats, using digital droplet PCR (ddPCR), in a cohort of Italian BAV patients.

Methods. One hundred nine subjects of Caucasian origin referred to the Regional Referral Center for Marfan syndrome and related disorders and to the Advanced Molecular Genetics Laboratory (Atherothrombotic Diseases Center, Careggi University Hospital, Florence) were enrolled. Patients were divided into two groups according to the different clinical settings: 1) patients undergoing valve replacement surgery (VRS, n=41) and 2) patients not undergoing valve replacement surgery (NVRS, n=68).

Results. NVRS and VRS patients showed, respectively, significant differences in median age (IQR) [45 (28-52) vs 66 (57–75), p<0.001] and in classical cardiovascular risk factors such as dyslipidaemia [11(16.2%) vs 19 (46.3%), p=0.0009], hypertension [20 (29.4%) vs 26 (63.4%), p=0.0007] and smoking habit [7 (10.3%) vs 23 (56.1%), p=0.0001], as well as a higher prevalence of BAV-associated complications (aortic stenosis, calcification and root/ascending aorta dilatation) in the VRS patient group, as expected. We also observed a significant difference in KIV2 repeats median number between the two groups [13 (8.1 – 22.6) in NVRS vs 33.6 (19.1 – 42.9) in VRS, p<0.001]. As concerns KIV2 repeat evaluation according to BAV clinical complications, NVRS patients with complications showed a trend towards reduction in KIV2 repeats number with respect to NVRS patients without complications [stenosis: 10.9 (7.1 – 19.9) vs 13.2 (9.2 – 24.4), p=0.341; calcification: 12.6 (7.2 – 20.3) vs 15 (9.9 – 24.5), p=0.319; root and/or ascending aorta dilatation: 11.9 (7.0 – 18.4) vs 19.4 (11.4 – 26.0), p=0.032]. In particular, higher prevalence of subjects showing a KIV2 repeat value below the distribution median value (n=18.9) in the aortic dilatation group (75.6%) with respect to those without aortic dilatation (47.8%) was observed (p=0.0310). In VRS patients, instead, no trend towards reduction in KIV2 repeats number, according to the presence or absence of BAV clinical complications, was found.

Conclusions. Our analysis suggests that in NVRS patients, younger and with a lower prevalence of traditional cardiovascular risk factors than VRS ones, higher levels of genetically determined lipoprotein (a) might contribute to the development of BAV complications and in turn to a worse prognosis. This datum, together with the observation obtained from a recent GWAS meta-analysis in which we collaborated (Thériault et al, Circulation 2026), from 17 studies in Europe and North America, of *LPA* among the novel loci associated with BAV, might contribute to underline *LPA* role in BAV predisposition and clinical complications. Data observed in VRS patients might be likely due to the not negligible impact of cardiovascular risk factors burden in influencing the phenotype severity.

ABSTRACT N. PO145

KINETIC ASSESSMENT OF PLATELET REACTIVITY DURING DUAL ANTIPLATELET THERAPY IN ACUTE CORONARY SYNDROMES: PRELIMINARY RESULTS FROM AN ONGOING STUDY

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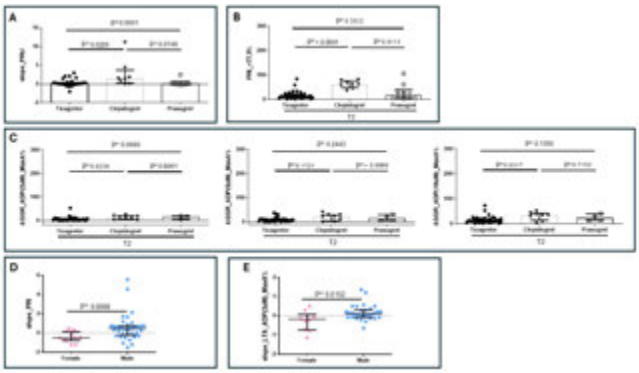
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Background and aims. Dual antiplatelet therapy (DAPT) with aspirin and a $P2Y_{12}$ receptor inhibitor represents the gold standard for patients with acute coronary syndromes (ACS) undergoing percutaneous coronary intervention (PCI). Clopidogrel and prasugrel achieve irreversible $P2Y_{12}$ receptor inhibition, similarly to the irreversible action of aspirin on cyclooxygenase 1 (COX 1), whereas ticagrelor exerts reversible $P2Y_{12}$ blockade. Despite the irreversible nature of aspirin, accelerated recovery of COX 1 activity within 24 hours has been described in a subset of patients, resulting in suboptimal platelet inhibition and residual high on treatment platelet reactivity (HPR), possibly due to higher platelets turnover. The present study aimed to characterize the kinetics of platelet reactivity over the dosing interval during DAPT and to investigate whether a similar recovery of pharmacological target activity occurs for $P2Y_{12}$ inhibitors within 24 h, as observed for aspirin, using multiple platelet function assays.

Methods. Patients with ACS undergoing PCI and treated with guideline-recommended DAPT (aspirin plus clopidogrel, prasugrel or ticagrelor) were prospectively enrolled. Platelet function was assessed at two time points, T1 (10 h after drug intake) and T2 (12 h for ticagrelor and 24 h for prasugrel and clopidogrel), to evaluate platelet inhibition across the dosing interval. $P2Y_{12}$ inhibition was assessed by light transmission aggregometry (LTA), VerifyNow $P2Y_{12}$ and VASP phosphorylation. Changes in target recovery rate were quantified by the T1–T2 slope (T2-T1/14). Recruitment is ongoing and this is an interim analysis.

Results. Platelet reactivity kinetics differed according to the $P2Y_{12}$ inhibitor used. In patients treated with clopidogrel, VerifyNow $P2Y_{12}$ reaction units (PRU) were consistently higher at both T1 and T2 compared with patients receiving ticagrelor or prasugrel ($p < 0.05$), indicating greater residual $P2Y_{12}$ dependent HPR over the dosing interval. In addition, the increase in PRU slope was greater in clopidogrel treated patients compared with those treated with ticagrelor ($p= 0.0226$) (A). Consequently, platelet reactivity index (PRI) values measured by VASP were higher at both time points in clopidogrel treated patients compared with those receiving ticagrelor or prasugrel ($p < 0.05$) (B). Likewise, ADP induced platelet aggregation at all tested concentrations (2, 5 and 10 µM) was greater in clopidogrel treated patients than in ticagrelor treated patients (C). Recovery of $P2Y_{12}$ dependent platelet reactivity was further modulated by biological factors. Regardless of the drugs, the slope of PRI was significantly higher in men ($Rho = 0.466$; $p = 0.001$) (D), and a comparable sex related effect was observed for ADP induced LTA at low agonist concentration (2 µM; $Rho = 0.384$; $p = 0.015$) (E).

Conclusions. In this preliminary analysis, variability in the recovery rate of platelet reactivity over the dosing interval, previously described for aspirin, also occurs for the $P2Y_{12}$ pathway. Despite irreversible receptor inhibition, patients treated with clopidogrel exhibit greater residual and $P2Y_{12}$ dependent platelet reactivity compared with those receiving ticagrelor and prasugrel over the dosing interval. This recovery seems to be sex-influenced and suggests that pharmacodynamic recovery of platelet function represents an additional mechanism, beyond impaired bioactivation, contributing to suboptimal response to clopidogrel.



ABSTRACT N. PO146

COMPARISON OF COAGULATION AND CHROMOGENIC METHODS IN PHARMACOKINETICS WITH EXTENDED HALF-LIFE FACTOR VIII

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Background and Aims. Personalized prophylaxis is still considered the standard of care for severe Hemophilia A. Replacement prophylaxis can now rely on extended half-life factor VIII concentrates (FVIII-EHL), very effective but difficult to monitor. For some of them, differences in Factor VIII levels are found using different dosage methods and it is still unclear which is the optimal assay. For each pharmacokinetic, performed as an essential step in the patient's therapeutic pathway, we investigated: a) whether, for some concentrates, the differences between methods highlighted a more suitable to monitoring recovery in vivo; b) if our data matched the manufacturer's recommendation for monitoring.

Methods. A total of 56 pharmacokinetics were performed. For each timepoint, plasma FVIII levels were assessed on an ACL TOP 750 (Werfen Company - Barcelona, Spain) using the following methods: 1. One-stage clotting assay (OSA) with SynthasIL reagent 2. Chromogenic substrate assays (CSA) with Coamatic FactorVIII

Results. A sufficient number to compare results between methods was reached only for the pharmacokinetics with 3 concentrates: 2 FVIII-EHL (Turoctocog Alfa and Damoctocog Alfa Pegol, both B domain deleted) and a single-chain FVIII (Lonoctocog Alfa). Turoctocog Alfa (16 kinetics) and Lonoctocog Alfa (8 kinetics), in line with literature data, highlighted higher FVIII levels when tested with CSA. However for Lonoctocog Alfa levels found with CSA they are not double compared to those with OSA (as indicated in the technical data sheet) and moreover the differences at 24 hours seem to disappear. Instead, Efmoroctocog Alfa (despite only 4 kinetics have been evaluated) at some timepoints did not show significant differences between OSA and CSA. For all these concentrates the same behavior (differences or equivalences) was observed for all patients. But for the kinetics with Damoctocog Alfa Pegol (11 kinetics), OSA and CSA highlighted differences but with heterogeneous behavior between patients. The numerically significant kinetics are reported in the histograms of the *Figure 1*.

Conclusions. To offer the best personalized replacement prophylaxis, it is essential to know whether in vivo factor levels can be monitored interchangeably with CSA and OSA (and which reagent for aPTT) or necessarily with one of these. The availability of a product-specific laboratory standard could eliminate the differences and becomes crucial when a concentrate presents heterogeneity in behavior among patients and the most appropriate method is unpredictable.



ABSTRACT N. PO147

FEBRILE BILATERAL PULMONARY EMBOLISM IN A YOUNG ADULT WITH PFAPA SYNDROME: A POSSIBLE PROTHROMBO-INFLAMMATORY CONTRIBUTOR IN A MULTIFACTORIAL EVENT

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Background. periodic fever, aphthous stomatitis, pharyngitis and cervical adenitis (PFAPA) is an autoinflammatory syndrome increasingly recognized in adults. Although a direct association with venous thromboembolism has not been established, recurrent systemic inflammation may promote thrombosis through thrombo-inflammatory pathways and amplify the effect of transient provoking factors. Pulmonary embolism (PE) may also present with fever, pleuritic pain and peripheral consolidations, mimicking infection.
Case Report. a 26-year-old physically active former smoker had recurrent febrile pharyngitis since 2018, associated with aphthous stomatitis, cervical lymphadenitis, increased C-reactive protein and serum amyloid A during attacks, and negative throat swabs. Genetic testing for autoinflammatory disease was negative, and rheumatologic evaluation confirmed adult PFAPA syndrome. In November 2024 he was admitted with bilateral pulmonary embolism after two days of fever and fluctuating left pleuritic chest pain. He reported a recent short-haul flight and right tibial trauma about five weeks earlier, followed by persistent leg edema. CT pulmonary angiography showed multiple bilateral distal filling defects, mainly in lower lobe branches, with bilateral peripheral lower lobe consolidations, more evident on the left, and minimal left pleural effusion. Troponin and NT-proBNP were normal, whereas C-reactive protein and D-dimer were elevated. Lower-limb venous Doppler ultrasound was negative for deep vein thrombosis. During hospitalization he had a further febrile episode; antibiotics were withheld because the presentation was considered consistent with his autoinflammatory phenotype, and blood cultures remained negative. Antiphospholipid antibodies and thrombophilia screening were negative. Screening for occult malignancy was unremarkable, including complete abdominal and testicular ultrasound. He was treated with fondaparinux followed by edoxaban, with favorable clinical course. Follow-up rheumatologic evaluation in July 2025 confirmed PFAPA and did not identify alternative diagnoses. Overall, the event was considered multifactorial: trauma and air travel were plausible triggers, but the inflammatory febrile presentation, absence of documented DVT and negative extended work-up support a possible contributory prothrombo-inflammatory role of PFAPA.
Conclusions. this case highlights that pulmonary embolism in a young adult with PFAPA may present with fever and inflammatory radiologic findings, creating a difficult differential diagnosis with infection or inflammatory flare. In a multifactorial setting, PFAPA should not be regarded as a proven direct cause of venous thromboembolism, but it may represent a biologically plausible amplifying cofactor.



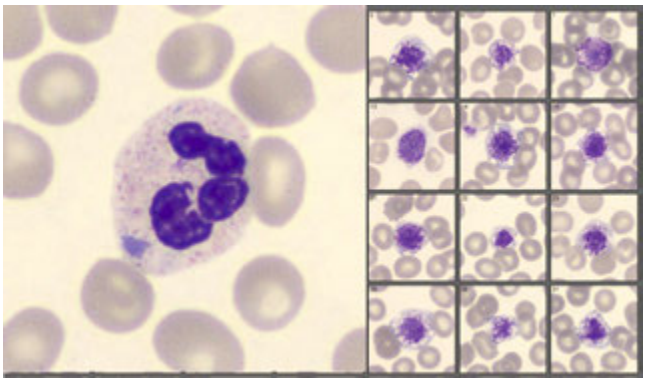
ABSTRACT N. PO148

ANALYTICAL DISCREPANCY IN PLATELET COUNTING REVEALING MYH9-RD: A CASE REPORT

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Background. MYH9-related disease (MYH9-RD) is a rare autosomal dominant disorder caused by pathogenic variants in the MYH9 gene, encoding non-muscle myosin IIA. It is characterized by congenital macrothrombocytopenia, with giant platelets and a variable bleeding tendency, and may be associated with extra-hematological manifestations such as sensorineural hearing loss, nephropathy, cataracts, and liver enzyme abnormalities. Although thrombocytopenia is often stable over time, the condition is frequently underdiagnosed and may be misinterpreted as immune thrombocytopenia, leading to inappropriate management. Morphological hallmarks include giant platelets and Döhlelike inclusions in the neutrophil cytoplasm. Accurate diagnosis relies on integration of clinical, laboratory, and genetic findings, and is essential for appropriate patient management and follow-up.
Case Report. A 31-year-old pregnant woman underwent routine first-trimester blood testing, revealing severe thrombocytopenia (5,000/µL) measured by impedance methodology, with otherwise normal hematological parameters. Platelet histogram and leukocyte scattergrams suggested the presence of giant platelets. Subsequent platelet counting using fluorescence methodology showed a higher value (19,000/µL), highlighting a significant discrepancy between the two methods. Peripheral blood smear examination confirmed true thrombocytopenia, excluded platelet clumping, and demonstrated numerous giant platelets, some comparable in size to erythrocytes. Additionally, basophilic cytoplasmic inclusions were observed in neutrophils. Further clinical history revealed a known diagnosis of MYH9-related disease, and the inclusions were interpreted as Döhle-like bodies, a pathognomonic feature of the condition. Longitudinal data showed persistently low but stable platelet counts (mean ~30,000/µL). No evidence of renal involvement was found, with no proteinuria or hematuria, while mild elevation of liver enzymes suggested possible hepatic involvement. The discrepancy between counting methods was attributed to the presence of macroplatelets, which may be misclassified as red blood cells inmpedance-based systems, whereas fluorescence methods provide more accurate platelet identification.
Conclusions. This case highlights the importance of a comprehensive and integrated approach to thrombocytopenia, particularly during pregnancy, when common benign or gestational causes may obscure rare inherited conditions. Morphological evaluation of peripheral blood smear remains essential for identifying key diagnostic features such as giant platelets and neutrophil inclusions. The observed discrepancy between platelet counting methods underscores the limitations of impedance-based systems in the presence of macrothrombocytes and supports the use of fluorescence-based techniques for accurate quantification. Awareness of MYH9-related disease laboratory features is crucial to avoid misdiagnosis and inappropriate treatment, ensuring proper clinical management and follow-up.





MANAGEMENT OF ANTITHROMBOTIC THERAPY IN A PATIENT WITH HEMOPHILIA C AND ATRIAL FIBRILLATION

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Background. Factor XI (FXI) deficiency, also known as hemophilia C, is a rare, autosomal recessive inherited coagulopathy first described in the 1950s. Prevalence in the general population is estimated at around 1 in 1 million. The most common manifestations include prolonged bleeding after trauma or surgery, frequent nosebleeds, easy bruising, bleeding gums, and, in women, menorrhagia and prolonged postpartum bleeding. The management of patients with FXI deficiency presents several critical clinical challenges; elderly patients, in particular, face challenges related to the management of both bleeding and thrombotic complications.
Case Report. We describe the clinical case of an 85-year-old male patient with new-onset arrhythmia and concomitant diagnosis of congenital FXI deficiency. The patient, with a medical history of Parkinson's disease, was initially admitted to the Emergency Department for dyspnea secondary to pneumonia. During hospitalization, the patient developed new-onset atrial fibrillation with a high ventricular rate, up to 150 bpm. He was initially treated with beta-blockers for rate control, but he soon experienced severe episodes of sinus bradycardia, with his heart rate dropping to 37 bpm. Consequently, beta-blocker therapy was immediately discontinued. Holter monitoring subsequently confirmed a diagnosis of tachycardia-bradycardia syndrome. He was therefore designated a priority candidate for permanent pacemaker implantation (PPM). Laboratory tests revealed an isolated prolongation of the activated partial thromboplastin time (aPTT). Specific hematological analyses ruled out the presence of LAC and factors IX or VIII deficiency, but confirmed a diagnosis of congenital FXI deficiency, with FXI levels measured at 10% and 22% in two separate samples. The clinical management of this patient presents a significant dilemma: balancing cardioembolic and hemorrhagic risks both in anticipation of permanent pacemaker (PPM) implantation and in the long term. In preparation for the planned implantation of a PPM, a multidisciplinary hemostatic plan is established. To manage FXI deficiency, the patient receives perioperative replacement therapy with fresh frozen plasma via continuous infusion. This treatment begins 24 hours before surgery and continues postoperatively to ensure stable hemostasis while the surgical wound heals. For long-term stroke prevention, the strategy focuses on balancing the predominant cardioembolic risk with the patient's general frailty and risk of falls. After a brief period of prophylactic heparin suspension prior to surgery, the patient receives reduced-intensity direct oral anticoagulant (DOAC) therapy. Additionally, percutaneous left atrial appendage closure (LAAC) is considered a strategic alternative in case future complications or frailty make pharmacological anticoagulation unsustainable.
Conclusions. This case highlights the crucial importance of maintaining a high index of clinical suspicion and focusing on the management of rare conditions, such as factor XI deficiency, especially when they coexist with common comorbidities such as atrial fibrillation. Although the current strategy favors a personalized DOAC regimen, the LAAC as a future safety measure allows the treatment plan to remain adaptable to the patient's evolving needs. However, further data from larger patient groups will be useful to better define the long-term outcomes and safety of this integrated approach.

ABSTRACT N. PO150

FACTOR XII DEFICIENCY IN THE SETTING OF RECURRENT THROMBOSIS AND EXTENDED VENOUS OBSTRUCTION: A CASE ANALYSIS

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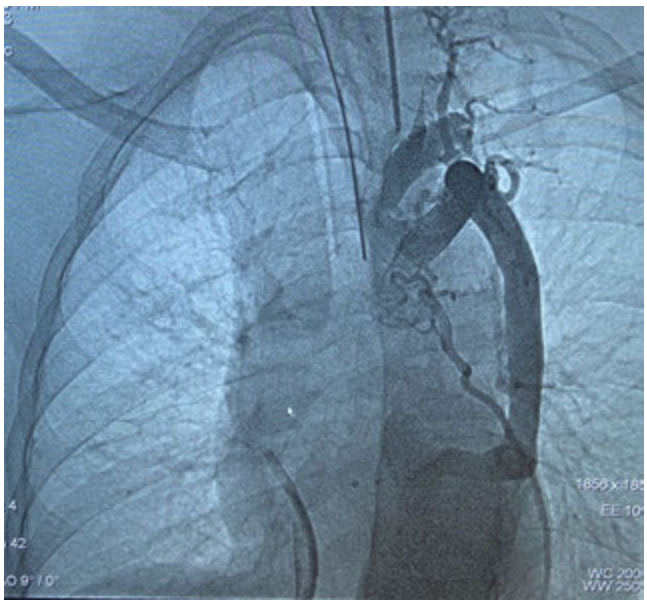
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Background. Factor XII (FXII), also known as Hageman factor, is a plasma serine protease that plays a key role in the initiation of the intrinsic pathway of coagulation and in the kallikrein–kinin system. [1] Congenital FXII deficiency is a rare autosomal recessive disorder characterized by a prolonged activated partial thromboplastin time (aPTT) in the absence of a bleeding tendency. [2] Despite its apparent importance in vitro, FXII deficiency is paradoxically not associated with clinical hemorrhage, and its physiological role in hemostasis remains controversial. Emerging evidence has suggested a potential link between FXII deficiency and thromboembolic risk, although this association remains debated. [3;4]. We report a clinical case in which FXII deficiency emerged during the evaluation of recurrent venous thrombosis.

Case Report. A 46-year-old woman with a history of end-stage chronic kidney disease on hemodialysis due a congenital kidney, and a previous total splenopancreatectomy for pancreatic neuroendocrine tumor complicated by secondary diabetes mellitus, was evaluated. The patient also has a history of multiple thrombotic and hemorrhagic events. Her thrombosis history included recurrent catheter-related thrombosis, chronic superior vena cava (SVC) with extensive collateral circulation, pulmonary embolism, portal vein thrombosis, and inferior vena cava thrombosis (IVC). A history of lupus anticoagulant (LAC) positivity was reported, although the details were unclear. Despite the high thrombotic burden, anticoagulation had previously been avoided due to recurrent severe hemorrhagic events, including gastrointestinal bleeding from angiodysplasias and esophageal varices. The patient was admitted for acute respiratory failure requiring high-flow oxygen therapy. Computed tomography (CT) scan revealed extensive thrombosis involving the azygos vein and the SVC, extending to the right atrium, without evidence of pulmonary embolism. Pulmonary scintigraphy was non-diagnostic due to impaired tracer flow caused by SVC thrombosis. Multidisciplinary evaluation, including hematology and vascular surgery consultation, found no indication for surgical intervention and recommended anticoagulation therapy. Interventional radiology assessment excluded the feasibility of SVC stenting due to the extent of thrombosis. Anticoagulation with unfractionated heparin was initiated. Given the history of recurrent thrombosis with a reported prior positivity for LAC, antiphospholipid antibody testing was performed. LAC, anti-cardiolipin, and anti-β2 glycoprotein I antibodies were negative; however, low-titer positivity for anti-phosphatidylserine/prothrombin IgM antibodies was detected (42.5 U; normal value <30).In light of the prolonged aPTT, a mixing test was performed and showed normal results, suggesting the absence of circulating inhibitors. Coagulation factor assays were requested, revealing mild deficiencies in factors VII, IX, and XI (42%, 61%, and 49%, respectively) and a moderate deficiency of factor XII (25%). Long-term anticoagulation with warfarin was initiated, but the patient continued to have unexplained respiratory failure. Repeat CT showed unchanged thrombotic burden and suggested a systemic-to-pulmonary shunt. Phlebography confirmed occlusion of the intrahepatic IVC and SVC, with patent subclavian and hemiazygos veins; recanalization was unsuccessful.The patient was discharged on high-flow oxygen therapy, maintained on anticoagulation, with continuation of thrice-weekly hemodialysis sessions. Approximately two weeks later, she was referred to the Emergency Department for progressively worsening dyspnea, hypotension, and tachycardia. Diagnostic evaluation demonstrated cardiac tamponade, so she subsequently underwent emergent pericardiocentesis, which yielded a hemorrhagic pericardial effusion.

Conclusions. This case highlights the diagnostic complexity of thrombosis in patients with multiple risk factors, including malignancy, chronic central venous catheters, and vascular abnormalities. Although Factor XII deficiency is classically regarded as non-hemorrhagic, emerging evidence suggests it may paradoxically contributing to inflammatory and prothrombotic processes implicated in a wide range of pathological conditions across multiple medical disciplines. [4]

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ABSTRACT N. PO151

HIGH-RISK SURGERY IN SEVERE HAEMOPHILIA B: PERIOPERATIVE MANAGEMENT WITH ALBUTREPENONACOG ALFA

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Background. Perioperative management in severe haemophilia B remains challenging, particularly in patients undergoing surgery at high bleeding risk. In this setting, extended half-life recombinant factor IX products may offer effective haemostatic coverage while reducing treatment burden and allowing a more flexible dosing schedule. Clinical experience in complex surgical settings, however, is still limited.

Case Report. We report the case of a 72-year-old man with severe haemophilia B receiving prophylaxis with albutrepenonacog alfa 3000 IU weekly since November 2021, after previous treatment with standard half-life factor IX. His medical history included major craniofacial trauma approximately 40 years earlier requiring surgery, osteoarthritis, previous HCV infection. In late June 2024, he presented to the Emergency Department with painful left frontal swelling associated with local erythema, in the absence of fever. Brain computed tomography showed multiple defects involving the inner and outer tables of the left frontal bone, while the frontal sinus and anterior ethmoidal cells were partially occupied by hyperdense material. Initial antibiotic treatment with amoxicillin/clavulanate resulted in only partial improvement. Subsequent otolaryngological and neurosurgical evaluation, together with contrast-enhanced brain magnetic resonance imaging, confirmed inflammatory-infectious involvement of the left frontal region and anterior ethmoidal cells, communicating with an overlying subcutaneous collection, thus leading to the indication for combined surgical treatment. The patient was admitted on July 29, 2024 for a procedure considered at high haemorrhagic risk. Surgery was performed on August 1, 2024 and included uncinectomy, anterior ethmoidectomy with drainage of purulent material and thick grayish secretions suggestive of fungal infection, and frontal sinusotomy with surgical toilette extended to the most lateral and cranial compartment, with drainage of two mucocele cavities. Histological examination showed respiratory mucosa with inflammatory changes and aggregates of fungal hyphae. Perioperative haemostatic management was planned by the Haemostasis and Thrombosis Service. The last scheduled home dose of albutrepenonacog alfa had been administered on July 29. Preoperative laboratory testing showed factor IX activity around 50%. A replacement regimen with albutrepenonacog alfa 4000 IU intravenously approximately 30 minutes before surgery, followed by 3000 IU at 24, 48, and 72 hours, was initially planned and subsequently adjusted according to serial factor IX monitoring. Factor IX activity reached 107% at 24 hours after surgery, was 75.7% at 48 hours, 68% at 96 hours, 91.6% on postoperative day 5, and 60.2% on postoperative day 6, prompting additional 2000 IU doses when required (Fig. 1). No perioperative or postoperative bleeding complications occurred. Postoperative brain CT and MRI showed no evidence of haemorrhage, and the clinical course was uneventful.

Conclusions. This case highlights the practical usefulness of albutrepenonacog alfa in the perioperative management of severe haemophilia B undergoing high-bleeding-risk surgery. A tailored regimen based on serial factor IX assessment, within a multidisciplinary setting, allowed effective haemostatic control and safe completion of a complex surgical procedure without haemorrhagic complications.

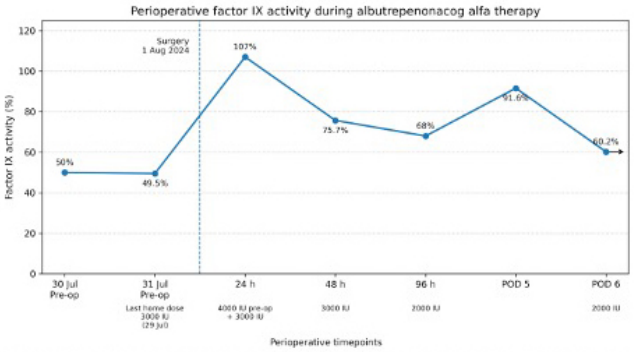


Figure 1. Perioperative trend of factor IX activity during replacement therapy with albutrepenonacog alfa. Following the preoperative dose, factor IX activity increased to 107% at 24 hours and remained within an adequate haemostatic range throughout the postoperative period, with further administrations guided by laboratory monitoring. No bleeding complications occurred.



A CASE REPORT OF HEREDITARY HEMORRHAGIC TELANGIECTASIA WITH PULMONARY ARTERIOVENOUS FISTULA

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Background. Hereditary hemorrhagic telangiectasia (HHT), is an autosomal dominant vascular disorder characterized by heterogeneous clinical expression (recurrent epistaxis, gastrointestinal bleeding, iron deficiency anemia, mucocutaneous telangiectasia and visceral arteriovenous malformations involving the pulmonary, hepatic, and cerebral circulations). Clinical diagnosis is based on established criteria, including epistaxis, characteristic telangiectasias, visceral arteriovenous malformations (AVMs) and a positive family history. Confirmation can be achieved through molecular testing identifying genetic variants (ACVRL1, ENG, SMAD4). Management includes local and systemic approaches to control bleeding, correction of anemia, embolization of AVMs, and the use of antifibrinolytic or anti-angiogenic therapies.
Case Reports. A 57-year-old woman presented to the Emergency Department with dyspnea, severe hypoxemia (arterial pO2 60 mmHg) and anemia. Medical history included recurrent epistaxis and iron deficiency anemia. Contrast enhanced chest CT showed two large vascular lesions in the right lower lobe, consistent with arteriovenous malformations. The underwent successful embolization of the AVMs. Given the suspicion of HHT, otolaryngologic evaluation revealed small capillary ectasias in the right nasal cavity and mild varicose ectasias at the base of the tongue. Abdominal ultrasound demonstrated hepatic AVMs in the right lobe while brain MRI excluded cerebral involvement. Genetic testing (heterozygous variant in the ACVRL1 gene) confirmed the diagnosis of HHT. After one year of follow-up, the patient is asymptomatic for dyspnea with normal arterial pO2.
Conclusions. HHT is a diagnostic challenge due to often underrecognized early symptoms, highly variable clinical expression ranging from mild to severe disease and silent vascular malformations. In our case, embolization of pulmonary AVMs has been completely successful. HHT requires multidisciplinary management, appropriate treatment and has a relevant familial impact due to its autosomal dominant inheritance, making family screening essential.

ABSTRACT N. PO153

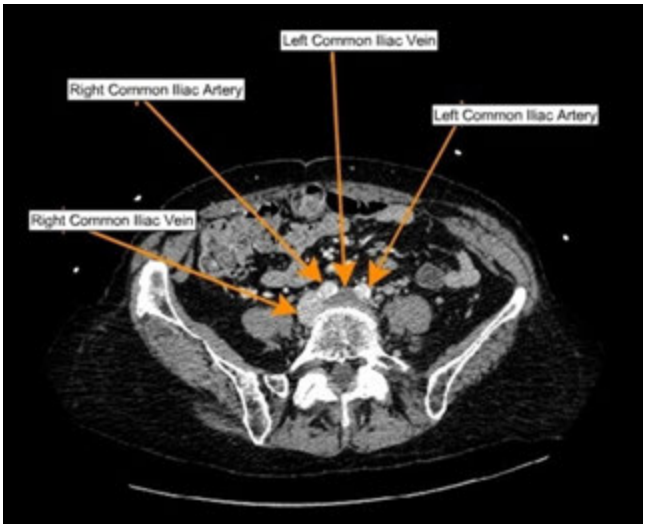
MAY–THURNER SYNDROME MIMICKING INFERIOR VENA CAVA SYNDROME: A CASE REPORT

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May–Thurner syndrome (MTS), also known as iliac vein compression syndrome, is a vascular disorder caused by compression of the left common iliac vein by the right common iliac artery. This condition leads to venous outflow obstruction and predisposes affected individuals to deep vein thrombosis (DVT). Although typically presenting with unilateral lower limb swelling, MTS may rarely mimic inferior vena cava (IVC) syndrome, presenting with bilateral lower extremity edema and extensive venous congestion. We report a case of May–Thurner syndrome initially suspected to be inferior vena cava obstruction due to the presence of bilateral lower limb swelling and dilated abdominal wall veins. Imaging studies ultimately demonstrated severe compression of the left common iliac vein with extensive collateral circulation. Endovascular management resulted in clinical improvement. This case highlights the importance of considering May–Thurner syndrome in the differential diagnosis of venous outflow obstruction and illustrates how extensive collateralization may mimic IVC syndrome.

Case Presentation. Patient Information; a 42-year-old female presented to the emergency department with progressive swelling of both lower extremities for two weeks. The swelling was associated with mild discomfort and heaviness while walking. The patient denied recent trauma, prolonged immobilization, malignancy, previous thromboembolic events. She reported no significant past medical history and was not taking oral contraceptives. Clinical Findings; physical examination revealed: bilateral lower limb edema extending to the thighs, prominent superficial abdominal veins, and mild tenderness of the left calf. Vital signs were stable. No signs of heart failure or liver disease were observed. Because of the bilateral nature of the swelling, initial clinical suspicion was directed toward inferior vena cava obstruction. Diagnostic Assessment; laboratory investigations revealed mildly elevated D-dimer levels, normal coagulation profile, and normal liver and renal function tests. Thrombophilia screening was negative. Discussion; may–Thurner syndrome represents an underdiagnosed cause of venous outflow obstruction. Studies suggest that up to 20–30% of individuals may have some degree of iliac vein compression, although only a minority develop clinically significant symptoms. Pathophysiology; the primary mechanism involves chronic pulsatile compression of the left common iliac vein by the overlying right common iliac artery. This leads to: endothelial injury, intimal hypertrophy, formation of fibrous spurs, venous stasis. Together, these changes fulfill Virchow's triad, promoting thrombosis. Mimicking Inferior Vena Cava Syndrome; in advanced cases, extensive collateral venous networks develop within the pelvis and abdominal wall. These collateral pathways may produce clinical findings similar to inferior vena cava syndrome, including: bilateral leg swelling dilated abdominal wall veins, pelvic venous congestion. Because the inferior vena cava remains patent, diagnosis requires advanced imaging modalities such as CT or MR venography.





CORONARY REVASCULARIZATION IN ACUTE CORONARY SYNDROME IN PATIENT WITH MILD HEMOPHILIA B: A CASE REPORT

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Background. Coronary angiography in patients with Hemophilia requires careful multidisciplinary management to prevent bleeding complications.
Case report. A 84-year-old man with mild hemophilia B (FIX 20%) was admitted to our Hospital for management of bleeding in recent placement of percutaneous endoscopic gastrostomy (PEG). His past medical history was significant for hypertension, hyperlipidemia, permanent atrial fibrillation (AF) on therapy with Vitamin K Antagonist (VKA) at a reduced range of INR (1.5-1.8) and a history of previous acute myocardial infarction (AMI), udergone to percutaneous coronary intervention (PCI) and placement of drug-eluting stent (DES) on left anterior descending (LAD) in 2013. During his hospital stay, the patient experienced recurrent chest tightness lasting less than 30 minutes, unaccompanied by autonomic symptoms and/or radiation always with complete spontaneous resolution. The patient had been reporting these symptoms as frequent in the last 3 months, even at home. Serial electrocardiograms showed bradycardic fibrillo-flutter associated with left anterior hemiblock (unclear whether new onset) in the absence of obvious ST-T segment alterations. However, a myocardial necrosis enzyme curve appeared abnormal and warranting further diagnostic testing. Therefore, considering the patient's cardiovascular history, clinical findings and laboratory abnormalities, despite the absence of dys/akinesia detected by cardiac echocolor doppler, the need for coronary angiography (CAG) was evident. CAG was performed using the left radial artery access and with an adequate peri-interventional factor substitution. It showed a critical left main (LM) ostial stenosis and stent restenosis on the LAD. Given the clinical complexity and the severity of the Coronary Artery Disease (CAD), the patient was evaluated by the local Heart team, along with the Hemophilia experts. Although the operative surgical risk was low (EuroSCORE II = 1.6%), taking into account the relevant comorbidities, the Heart team established PCI to be more appropriate than surgical approach in this case. The serum FIX dosage before the procedure was around 10%, so, as the guidelines suggest, the patient was prepared with rFIX maintaining a minimum level >50% within 24h after PCI and >20% during Dual Antiplatelet Therapy (DAPT)[1]. The final result was satisfactory, in absence of postprocedural complications. The patient was discharged with the recommendation to continue FIX prophylaxis therapy, keeping levels >20% during DAPT. Nevertheless, our patient had an additional factor that made management of antithrombotic therapy more difficult: AF requiring anticoagulation. Given the extremely high bleeding risk of triple antithrombotic therapy, the high thrombotic risk associated with the stenting site (LM) and the not extremely high thromboembolic risk (CHADsVA 4), it was decided to maintain DAPT after the procedure with subsequent reevaluation of anticoagulation after at least 3 months.
Conclusions. This complex clinical case highlights the delicate balance between thrombotic and bleeding risks in the management of hemophilic patients with AMI. The presence of hemophilia B, combined with multiple cardiovascular risk factors, further complicates decision-making regarding revascularization strategies and antithrombotic therapy. A multidisciplinary approach is essential to optimize short- and long-term outcomes.

[1]https://pmc.ncbi.nlm.nih.gov/articles/PMC10256340/



MANAGEMENT OF ANTICOAGULANT THERAPY IN IMMUNOTHROMBOSIS SECONDARY TO TOXOPLASMA INFECTION

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Introduction. Immunothrombosis can limits pathogen dissemination and enhances antimicrobial activity at the microvascular level in physiological way. When dysregulated, its can progress to pathological thrombosis (thromboinflammation). Infections can trigger venous thromboembolism (VTE) through crosstalk between inflammatory and coagulation pathways, a mechanism described mainly in viral illnesses but also reported in bacterial and parasitic infections. VTE during acute Toxoplasma infection is extremely rare and documented only in isolated case report. The management of anticoagulant therapy in this condition can be very challenging because of potential drug interactions

Case Report. A 63-year-old male with psoriatic arthritis, receiving adalimumab and MTX therapy, presented with fever, pneumonia, and generalized seizures. Head CT demonstrated a right parietal hemorrhagic infarction, while brain MRI identified cerebral venous sinus (CVS) thrombosis involving both transverse and sigmoid sinuses with extension to the internal jugular veins. Contrast-enhanced CT revealed severe consolidation in the right lung, multisite splanchnic thrombosis—including splenic and superior mesenteric veins—and microinfarcts suggestive of embolic phenomena across multiple organs. DVT, endocarditis, and sinusitis were excluded; autoimmune panel and thrombophilia screening was negative, complement was normal. The patient was initiated on UFH, subsequently switched to warfarin. Whole-body PET/CT detected multiple hypermetabolic lymphadenopathies at thoracic and external iliac stations. Serological testing for Toxoplasma gondii indicated recent primary infection and PCR confirmed its presence in blood. Due to CNS and visceral organ involvement, oral trimethoprim–sulfamethoxazole was prescribed for six weeks. During treatment, the patient reported nausea and vomiting, so the therapy was modified by prescribing pyrimethamine-sulfadiazine. After approximately 10 days, the patient was admitted to the Nephrology ward because of AKI caused by bilateral nephritis and ureteral lithiasis, both adverse effects of the treatment. During anti-toxoplasma treatment, extreme INR variability was observed, with over-anticoagulation (INR >10); therefore, warfarin was discontinued and calcium heparin was continued. Upon improvement of renal function, calcium heparin was replaced with tinzaparin. Because PCR testing for Toxoplasma on plasma remained positive 4 months after diagnosis, and as immunosuppressive therapy had to be resumed, the infectious disease specialist initiated treatment with azithromycin and clindamycin for 6 weeks. At the end of antimicrobial treatment, anticoagulant therapy was modified by switching from tinzaparin to apixaban 5 mg twice daily. After 8 months of anticoagulant treatment, the patient underwent repeat brain MRI, which showed persistent partial thrombosis of the transverse sinus and sigmoid sinus. During treatment with both tinzaparin and apixaban, no hemorrhagic adverse events or thrombotic recurrences were observed.

Conclusions. Specific anti-Toxoplasma therapy is indicated in cases of CNS involvement or severe visceral disease, particularly in immunocompromised patients. The current recommended treatment for CVS thrombosis is AVK; however, because of the extreme INR variability related to drug interactions, it was preferred to continue LMWH until discontinuation of antimicrobial therapy, followed by a switch to apixaban to improve patient compliance.



DIRECT ORAL ANTICOAGULANTS FOR THE TREATMENT OF VTE IN PATIENTS WITH CANCER: A SURVEY AMONG CAMPANIAN INTERNAL MEDICINE WARDS

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Premises and purpose of the study. Venous thromboembolism (VTE) is an important cause of morbidity and mortality among patients with cancer. According to recent guidelines its initial treatment may involve low-molecular-weight heparin (LMWH) or a direct oral anticoagulant (DOAC), as well as for long-term anticoagulation. Therefore, we conducted this Survey aimed at knowing aspects of the treatment of VTE in patients with cancer in the Campania Region.

Materials and methods. In December 2023, a questionnaire (Q) with 14 questions relating to the treatment of VTE in patients (pts) with cancer was sent to FADOI members in Campania. 55 pratictioners from 40 Internal Medicine Wards of Campania.

Results. The percentage of pts with cancer admitted in Internal Medicine ward presenting VTE: <25% (69%), 25-50%(31%). All pts with cancer and VTE begin anticoagulant treatment during hospidalitation. Its initial treatment is based on LMWH: all pts (29%), a small part 9%, most (62%), while on DOAC: all pts (11%), none (1.8%), a small part (52.7%), most 34.5%. Comorbidities in the 70% of the cases influence the choice of treatment. Mortality of this pts: <20% (42%), 20-40%(22%),41-60%(4%), unknown (32%). In the discharge letter of pts with cancer and VTE, LMWH are prescribed: <25% (45.5%), 25-50% (31%), 51-75% (9%), >75% (14.5%), while DOAC: <25% (11%), 25-50% (31%), 51-75% (16%), 75% (42%).

Conclusions. In Internal Medicine Wards of Campania LMWH is preferred over DOAC in initial treatment of VTE in pts with camcer, while for long-term anticoagulation DOAC is preferred over LMWH.



DIAGNOSTIC CHALLENGES IN PREGNANCY-TRIGGERED IMMUNE-MEDIATED THROMBOTIC THROMBOCYTOPENIC PURPURA: A CASE FOR EARLY AND ACCURATE IDENTIFICATION

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Background. Immune-mediated thrombotic thrombocytopenic purpura (iTTP) is a rare and potentially fatal thrombotic microangiopathy (TMA) characterized by severe ADAMTS13 deficiency due to the presence of inhibitory autoantibodies. iTTP typically presents with the classic pentad of thrombocytopenia, microangiopathic hemolytic anemia, neurological symptoms, renal dysfunction, and fever. However, the clinical presentation can overlap with other pregnancy-related TMAs, such as subset of HELLP syndrome and atypical hemolytic uremic syndrome (aHUS), complicating timely diagnosis. Pregnancy is a known trigger for iTTP, and rapid recognition is crucial to avoid maternal and fetal complications. The PLASMIC score has been validated as an effective tool for early risk stratification, facilitating prompt therapeutic intervention. Early diagnosis and treatment with plasma exchange, immunosuppressive agents, and novel therapies such as caplacizumab are critical for improving outcomes in this life-threatening condition.

Patients and Methods. A 28-year-old woman at 32 weeks of gestation presented with abdominal pain, severe asthenia and acute neurological symptoms. Laboratory evaluation revealed severe microangiopathic hemolytic anemia and thrombocytopenia with hemoglobin 5.1 g/dL (reference range [RR] 12–16), platelet count 40 $\times 10^3/mm^3$ (RR 150–400), markedly elevated lactate dehydrogenase 2279 U/L (RR 135–250), reticulocytosis 330.9 $\times 10^3/\mu L$ (RR 22.0–139.0), indirect hyperbilirubinemia 0.99 mg/dL (RR 0.1–0.9) and undetectable haptoglobin, in the absence of coagulopathy and with mild renal impairment. Due to maternal-fetal deterioration, emergency cesarean section was performed. Peripheral blood smear demonstrated 3% schistocytes. Early clinical probability of severe ADAMTS13 deficiency was assessed using the PLASMIC score. A comprehensive diagnostic work-up excluded secondary TMAs, including autoimmune disorders (ANA, ENA, antiphospholipid antibodies, ANCA, lupus anticoagulant), infections (CMV, EBV, HBV, HCV, HIV, TORCH), malignancy, immune hemolysis (Coombs tests) and active infections (negative microbiological cultures).

Results. The PLASMIC score was 6, indicating high risk of severe ADAMTS13 deficiency. ADAMTS13 activity was undetectable (0%) with detectable inhibitory anti-ADAMTS13 autoantibodies, confirming iTTP. Immediate treatment with therapeutic plasma exchange, high-dose corticosteroids and caplacizumab resulted in rapid neurological recovery and platelet count normalization. Persistently suppressed ADAMTS13 activity prompted early anti-CD20 therapy with rituximab, achieving progressive enzymatic recovery. The patient was discharged in stable condition and scheduled for close hematologic monitoring.

Conclusions. This case underscores the importance of rapid hematologic assessment and early risk stratification in pregnancy-associated TMAs. Integration of PLASMIC score–guided decision-making with prompt initiation of plasma exchange, caplacizumab and immunosuppressive therapy represents the current standard of care for iTTP and is feasible and effective even in the peripartum setting.

ABSTRACT N. PO158

A RARE CASE OF ISCHEMIC STROKE: CAROTID WEBS

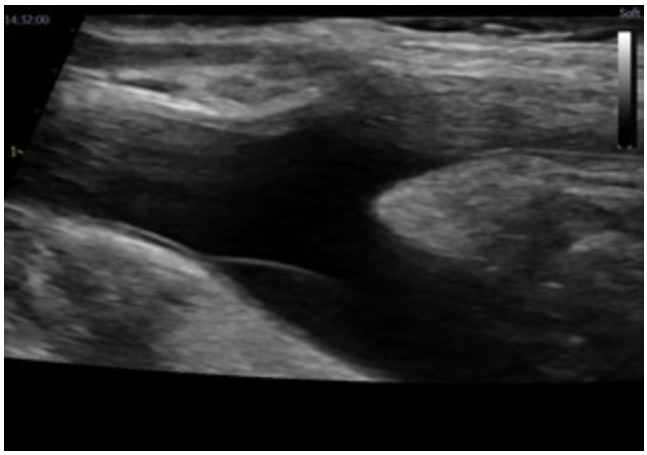
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Background. A carotid web (CaWeb) is a rare, atypical variant of fibromuscular dysplasia, characterized by a fibrous intimal flap of the carotid bulb and projecting into the arterial lumen, which can cause altered blood flow, stasis, and thereby promoting thrombogenesis. Latest studies documented strong associations between CaWebs and recurrent TIA or severe strokes of unknown etiology, with a prevalence between young with few traditional cardiovascular risk factors. The gold standard imaging for CaWeb diagnosis is currently computed tomography angiography (CTA), followed by duplex ultrasound (DUS) and magnetic resonance angiography (MRA). While antiplatelet therapy or anticoagulation used to be the cornerstone of management, medical therapy alone has been found to be insufficient for stroke prevention in symptomatic patients. Definitive intervention includes carotid artery stenting or carotid endarterectomy (CEA); both have demonstrated excellent safety and efficacy.

Case report. A 63-year-old woman with history of hypertension and a previous right atrial myxoma, treated 2-years prior with mass removal surgery, shows up for sudden symptoms of left facial paresthesia, right retrobulbar pain, clumsiness in the upper limbs and confusion. The CT cranial scan showed an ischemic right area cortico-subcortical temporo-parietal; the CT angiography and MRI confirmed an occlusion of the right middle cerebral artery's M2 branch. As a collateral finding on CT angiogram, an opacification defect was reported at right carotid bulbs, suspicious for CaWeb. The ischemic event was classified as minor stroke (NHISS=3) therefore dual antiplatelet therapy was started. In view of the angiographic finding, a DUS of supre-aortic trunks was performed, which confirmed the suspect of carotid web. Meanwhile, other causes of stroke were ruled out by transcranial echocolordoppler which excluded the possibility of a patent foramen ovale (PFO) and an extensive electrocardiographic study excluded arrhythmic events. Lastly a transthoracic echocardiogram and the subsequent transesophageal echocolordoppler were performed, which reported the presence of mobile material at the left atrial appendage, of doubtful interpretation between myxoma recurrence or thrombotic material adhered to the Teflon residues left from the myxoma operation as a complication of the procedure. Given the new findings, and since a cardio-embolic stroke could not be ruled out at that point, warfarin therapy was promptly undertaken, and the patient was transferred to a surgical setting for subsequent removal of the mass and histological examination.

Conclusions. This clinical case confronted us with two possible causes of ischemic stroke, both possible, but which were ultimately given as large-vessel cardio-embolic stroke, considering the higher probability associated. However, the possibility of an event related to CaWeb, even if rare, shouldn't completely be ruled out. The prevalence in patients with ischemic stroke is around 1-1,2%, however in patients with cryptogenic stroke, especially in cases with no other clear risk factors, the prevalence of CaWeb is markedly higher. One case-control study identified CaWeb to be present in 9,4% of patients under age 60 with cryptogenic stroke. Carotid webs should always be excluded in all cases of cryptogenic ischemic events, especially in young patients without relevant risk factors, even if the diagnosis remains one of exclusion.





HOW DOES DRUG ABSORPTION CHANGE IN THE PRESENCE OF NEOPLASTIC GASTROINTESTINAL DISEASE?

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Background. Neoplastic diseases, especially those affecting the gastrointestinal tract, can significantly influence the pharmacokinetics and pharmacodynamics of drugs by altering their absorption, metabolism, and clinical response. For warfarin, an oral anticoagulant with a narrow therapeutic index, such interference can cause unpredictable changes in dosage requirements, complicating the management of oral anticoagulant therapy in cancer patients.

Materials and Methods. We describe the clinical case of a patient who was treated with warfarin (Coumadin®) for approximately 16 years as a recipient of a mechanical aortic valve prosthesis (therapeutic range with INR between 2.00 and 3.00), maintaining a stable drug requirement of about 40 mg per week and a TTR (time in therapeutic range) of 83%. During follow-up, the patient experienced repeated episodes of melena associated with reduced hemoglobin levels, necessitating serial endoscopic examinations by gastroscopy and colonoscopy. On several occasions, erosive gastroduodenopathy was documented, including a gastric ulcer approximately 0.8 cm in diameter, covered with fibrin and surrounded by hypertrophic fibrous tissue, which was treated endoscopically by applying metal clips.

Results. At the end of 2024, the patient was diagnosed with gastric neoplasia and underwent surgery followed by chemotherapy. In preparation for surgery, five days before the procedure and during the postoperative period, oral anticoagulant therapy (OAT) was suspended and replaced with low molecular weight heparin. When oral anticoagulant therapy was resumed, a significant and unexpected reduction in the weekly warfarin requirement was observed, decreasing from 40 mg to approximately 15 mg per week to maintain the therapeutic range.

Conclusions. This case demonstrates that active neoplastic disease, along with anatomical and functional changes in the gastrointestinal tract and oncological treatments, can profoundly alter the pharmacokinetics and pharmacodynamics of warfarin. This underscores the need for close monitoring and continuous re-evaluation of dosage in complex patients.



THE USE OF ANTIDEPRESSANT DRUGS AND BENZODIAZEPINE HYPNOTICS AS AN UNUSUAL RISK FACTOR FOR VTE

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Background. Venous thromboembolism (VTE) involving the inferior vena cava (IVC) is a rare but life-threatening condition. Antidepressant drugs and benzodiazepine hypnotics have sedative effects that cause reduced activity in the patient and may increase the risk of VTE. We report a case of massive IVC thrombosis in a patient with major depressive disorder on long-term pharmacological treatment.

Case Report. A 69-year-old celiac woman with a history of major depression (diagnosed in 2020), arterial hypertension, dyslipidemia and hypothyroidism was admitted in October 2024 for the presence of acute-onset bilateral swelling and pain in the lower limbs. The patient was on chronic treatment with duloxetine, valproic acid, lormetazepam and pregabalin. In a previous hospitalization, a right parathyroid incidentaloma (7 mm) was found, and subsequently in periodic follow-up. Imaging studies (TC scan and ultrasonography of the abdomen and lower limbs) revealed an extensive thrombosis of the IVC, sparing the supra-hepatic segment, with bilateral iliac and femoral vein involvement, extending to the popliteal veins on the right side. Initial dilation of the abdominal aorta (42 mm) was also evidenced. The episode of VTE was apparently unprovoked, because of the absence of known thrombotic provoking factors. Antiphospholipid syndrome or other autoimmune systemic disorders and active cancer were excluded. However, a hereditary protein S deficiency was diagnosed, and confirmed with repeated evaluations (ranging from 40 to 43%). The patient was treated with a low molecular weight heparin (enoxaparin 100 IU /kg of body weight, every 12 hours), and then apixaban, 5 mg twice daily, was started. The patient's psychiatric status improved during the hospitalization, under continued psychiatric support. Follow-up imaging with lower limb ultrasonography after two weeks showed a complete recanalization of the femoral veins.

Conclusions. This case underscores the importance of the evaluation of patient's existing VTE risk factors (e.g. thrombophilic conditions, hypothyroidism, obesity) during the treatments with antidepressant drugs and benzodiazepine hypnotics. The sedative effects of these drugs may be associated to the development of VTE in predisposed patients.



A REGIONAL DIGITAL NETWORK FOR THE MANAGEMENT OF ACQUIRED HEMOPHILIA A: A MODEL FOR INTEGRATED CARE

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Background. Acquired hemophilia A (AHA) is a rare, potentially fatal autoimmune coagulopathy caused by the presence of neutralizing autoantibodies directed against factor VIII. It primarily affects older adults and is frequently underdiagnosed, resulting in diagnostic delays and fragmented care. This is associated with preventable bleeding complications, increased mortality, and rising healthcare costs. Despite the availability of effective hemostatic and immunosuppressive therapies, the long-term management of recurrent or refractory forms remains complex outside of specialized centers.

Objectives. To establish a regional care pathway supported by a digital platform capable of connecting local and hospital services with a Hemophilia Reference Center, in order to accelerate diagnosis, guide initial treatment decisions, and improve the continuity and appropriateness of follow-up care.

Methods. A secure digital platform was developed to connect emergency departments, hematology units, laboratories, local pharmacies, and primary care physicians with the Regional Hemophilia Reference Center in Palermo. The platform was designed based on actual clinical workflows and enables rapid teleconsultations in cases of suspected AHA, centralized interpretation of coagulation tests, and shared decision-making regarding hemostatic and immunosuppressive therapies. During follow-up, clinicians can update clinical data, bleeding events, treatments, and laboratory results in real time, allowing specialists to adjust treatment promptly. A dedicated patient section facilitates communication following discharge. Access to the platform is governed by differentiated authorization profiles and complies with current data protection regulations.

Results. Development of the platform began on December 6, 2023, and regional implementation was completed in February 2025. Four physicians from four peripheral hospitals were involved—two from emergency departments and two from hematology units. Twelve specialist consultations for suspected AHA were conducted through the platform. Two patients with confirmed diagnoses were managed entirely through the shared care pathway—one identified in the emergency department and one in the hematology setting. After discharge, follow-up was ensured through regular clinical and laboratory updates entered by primary care physicians and reviewed by the referral center. In both cases, therapy was adjusted remotely, resulting in complete remission. In one patient, structured monitoring also enabled the diagnosis of a neoplasm during follow-up, highlighting the platform's potential role in cancer surveillance as well, given the well-known association between AHA and neoplasms, which can sometimes be diagnosed after the onset of bleeding symptoms. In its first six months of operation, the platform improved communication between centers, strengthened continuity of care, and reduced unnecessary or inappropriate interventions.

Conclusions. A digitally integrated care network can improve access to specialized expertise in rare diseases even when that expertise is centralized. In the AHA, it helps reduce diagnostic time, harmonize treatment decisions, and ensure structured long-term monitoring. This model can potentially be extended to other rare diseases, helping to improve equity of access, appropriateness of care, and efficiency of the National Health Service, as well as facilitating the collection of real-world data.



A RARE CASE OF PLATELET DISORDER MIMICKING HEMOPHILIA A

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Background. Congenital platelet function disorders can occasionally present with severe bleeding phenotypes resembling hemophilia A, leading to diagnostic confusion. We report a rare case of Glanzmann thrombasthenia (GT) presenting with hemophilia like bleeding and normal coagulation factor VIII levels.

Case Presentation. A 12-year-old boy presented with recurrent hemarthroses and mucocutaneous bleeding since early childhood. Initial workup suggested hemophilia A, but factor VIII levels were normal. Platelet aggregation studies revealed absent aggregation with ADP, collagen, and epinephrine, confirming Glanzmann thrombasthenia. Genetic testing identified a homozygous ITGA2B mutation. Clinical Features; Recurrent hemarthroses of knees and elbows; Frequent epistaxis and gingival bleeding; No history of hematologic malignancy or liver disease. Laboratory Investigations; Complete blood count: Hemoglobin 12.1 g/dL, WBC 6.5 × 10^9/L, platelets 210 × 10^9/L; Coagulation profile: PT 12.5 s (normal), aPTT 32 s (normal); Factor VIII activity: 110% (normal); von Willebrand factor (vWF) antigen: 95% (normal); Platelet function analysis: Absent aggregation with ADP, collagen, and epinephrine; normal ristocetin-induced aggregation. Genetic Testing Targeted sequencing revealed a homozygous pathogenic variant in ITGA2B (c.1774G>A, p.Glu592Lys), confirming Glanzmann thrombasthenia.

Discussion. Glanzmann thrombasthenia is a rare autosomal recessive disorder (~1:1,000,000) characterized by defective platelet aggregation . Most patients present with mucocutaneous bleeding; however, severe GT can mimic hemophilia A or B, particularly when hemarthroses occur. Differential Diagnosis; Hemophilia A/B: Normal factor VIII and IX levels excluded this; Other platelet function disorders: Bernard-Soulier syndrome presents with thrombocytopenia and giant platelets, unlike GT; Acquired platelet disorders: Excluded by history and family screening. Diagnostic Approach; Platelet aggregation testing: Gold standard for GT diagnosis. Absence of aggregation with ADP, collagen, and epinephrine, and normal ristocetin response, is diagnostic [4]; Flow cytometry: Detects αIIbβ3 integrin expression; Genetic testing: Confirms mutation, informs prognosis, and facilitates genetic counseling. Management: Bleeding prophylaxis: Local measures, antifibrinolytics, recombinant factor VIIa; Surgery: Prophylactic recombinant factor VIIa or platelet transfusions; Gene therapy: Under investigation, not yet standard [5]. Early recognition prevents misdiagnosis, avoids unnecessary factor replacement therapy, and allows appropriate family counseling.

Conclusions. Severe platelet function disorders can mimic coagulation factor deficiencies. Early recognition is essential to avoid inappropriate therapy and to guide genetic counseling and management.