Bleeding complications of oral anticoagulant therapy: from ISCOAT to the START Register. A memory of Gualtiero Palareti

Francesco Marongiu

Internal Medicine, University of Cagliari; Hemostasis and Thrombosis Departmental Unit, University Hospital, Cagliari; Fondazione Arianna Anticoagulazione.it, Bologna, Italy

ABSTRACT

On December 12, 2025, I had the honor of delivering a special lecture titled *Bleeding Complications of Oral Anticoagulant Therapy: From ISCOAT to the START Register* at the 20th Meeting on Bleeding and Thrombosis Care in Castellammare di Stabia, Naples (Italy). This lecture was dedicated to Gualtiero Palareti from Bologna, who sadly passed away on August 8 of the same year. Speaking at this event was a privilege, as Gualtiero was a remarkable figure in hemostasis and thrombosis, both in Italy and internationally. He was also an invaluable teacher to many of us. I took this opportunity to honor his legacy and reflect on his contributions over the past 36 years. In my lecture, I provided a brief history of anticoagulants that underpinned Gualtiero's work, along with a general overview of the field. Additionally, I shared my personal observations on the Italian Federation of Anticoagulation Clinic and discussed studies conducted by ISCOAT (Italian Study on the Complications of Oral Anticoagulant Therapy) and the START Register, in which Gualtiero Palareti played a pivotal role.

Key words: anticoagulation clinics, FCSA, START Register, Fondazione Arianna, direct oral anticoagulants.

Introduction

On December 12, 2025, I was invited by Antonio Coppola and Domenico Prisco, two prominent Italian scientists, to deliver a special lecture titled *Bleeding Complications of Oral Anticoagulant Therapy: From ISCOAT to the START Register* at the 20th Meeting on Bleeding and Thrombosis Care in Castellammare di Stabia, Naples (Italy). This lecture was held in honor of Gualtiero Palareti from Bologna, who passed away on August 8 of the same year. It was a privilege for me, as Gualtiero has been a leading figure in the field of hemostasis and thrombosis in Italy and worldwide. I met Gualtiero for the first time in 1978, when I attended a course at the *Sant'Orsola* Hospital in Bologna. He was the teacher, and I was the student. When, several years later, I began to work with him, I felt like a *ball boy,* who reached to play with the champion he had admired for so long. In this article, I wish to remember Gualtiero Palareti and his contributions over the past 36 years. I had to select the papers to describe from among the many he published over the years. I also wished to write a brief history of anticoagulants, preliminary to the work of Gualtiero, and to provide readers with a general overview, along with my final personal observations on the activities of Italian Anticoagulation Clinics (joined in Italian Federation of Anticoagulation Clinic, FCSA) and the types of studies conducted starting from the ISCOAT (Italian Study on the Complications of Oral Anticoagulant Therapy) up to those related to the START Registry.

Corresponding author: Francesco Marongiu, Internal Medicine, University of Cagliari; Hemostasis and Thrombosis Departmental Unit, University Hospital, Cagliari; Fondazione Arianna Anticoagulazione.it, Bologna, Italy.
E-mail: francesco.marongiu@unica.it

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Oral anticoagulants and bleeding: a brief history

The history of oral anticoagulants began in the 1920s, when veterinarians Schofield and Roderick observed that cows developed a hemorrhagic disease associated with spoiled sweet clover hay used as feed.[1,2] These two American veterinarians discovered that eliminating this spoiled hay eliminated the disease. They noted that the affected animals exhibited prolonged clotting times. The problem arises when spoiled sweet clover is ingested, as it contains a compound called coumarin that is oxidized by moldy clover, a process catalyzed by *Aspergillus* hay mold. This reaction produces dicumarol (4-hydroxycoumarin), whose structure was first reported by Campbell and colleagues in 1940.[3] Patent rights were offered to the *Wisconsin Alumni Research Foundation*. The compound was called *Warfarin* (the first letters of the foundation, with the suffix *arin*), whose use in humans was reported by Bing-

ham *et al.* in 1941 and was adopted as a rat poison.[4] In 1974, Joahn Stenflo discovered the mechanism of action, which consists of inhibiting the enzyme epoxide reductase that restores the vitamin K epoxide (coming from having driven carboxylation) to its reduced form, capable of inducing carboxylation of the Gla-protein residues of 4 vitamin K-dependent coagulative factors (II, VII, IX, and X).[5] Several years previously, Zweifler *et al*. reported that various studies on oral anticoagulation in hospitalized patients found that bleeding occurs in about 10% of cases.[6] Those researchers observed that bleeding is even more prevalent among outpatients, affecting one in every three individuals treated in the United States and England. They also raised the question of whether warfarin-associated bleeding might result from an additive effect of platelet or vascular abnormalities. This hypothesis is supported by the findings of Jacques *et al.*,[7] who demonstrated that in rats treated with dicumarol, hemorrhage does not occur unless at least one additional hemostatic mechanism is compromised. They also noted petechiae and muco-cutaneous bleeding in some patients receiving oral anticoagulants, suggesting that platelet and vasculature-related factors may contribute to bleeding during treatment.[8,9] Twenty years later, Reyers *et al*. confirmed that the bleeding time was prolonged in rats treated with warfarin.[10] These latter results, after a discussion with Giovanni de Gaetano and Maria Benedetta Donati, two eminent Italian researchers, in 1986, prompted us to perform the bleeding time in a group of patients treated with acenocoumarol in a steady state, during overdose, and after recovery.[11] The results showed that patients on stable anticoagulation had longer bleeding times (BT) compared to normal controls. Those in the overdose phase exhibited even longer BT values than both the controls and the patients who were in a stable state. After recovery, the BT values of the overdose patients returned to levels similar to those of patients on stable anticoagulation. Additionally, we found a significant linear correlation between BT and the Thrombotest, which was the prothrombin time (PT) monitoring test used during that period. The impairment in primary hemostasis may be due to either inadequate fibrin deposition in the hemostatic plug or a deficiency of a potential vitamin K-dependent vascular *bleeding factor*.[12] In fact, it was demonstrated that the vascular arterial wall could produce a Gla-containing protein. It was therefore thought that oral anticoagulants may play a vital role in limiting fibrin involvement in primary hemostasis. This hypothesis was supported by the observation that patients, even when in a stable state of anticoagulation, may still experience bleeding episodes, such as epistaxis or hematuria. These episodes resemble those observed in patients with thrombocytopenia or thrombocytopathies.[13] Nevertheless, while interesting, the possible role of platelets in the course of vitamin K antagonist (VKA) has not been further studied.

The laboratory monitoring of oral anticoagulants

Laboratory monitoring of VKAs was initially characterized by the use of several thromboplastins, which differed in sensitivity and in the preparation of calibration curves.[14] Rodman *et al.* recommended using only one thromboplastin preparation to reduce discrepancies among laboratories.[15] It is worth noting that these authors also recommended reporting results in seconds rather than percent activity: the first step toward a better PT standardization. However, several years were to pass before Leon Poller introduced, in 1970, a new method for standardizing PT results: the British comparative thromboplastin as a reference, which provides a means to express results as the patient's PT relative to the British comparative thromboplastin normal value, thus of expressing results as the patient's PT relative to the British comparative thromboplastin normal value, thereby obtaining the British ratio.[16] Nevertheless, this method was not followed, so Poller in 1982 reminded that this approach would be important to improve the results of studies that afforded oral anticoagulation. However, this method was not followed, leading Poller in 1982 to emphasize that this approach is crucial for improving the results of studies involving oral anticoagulation.[17] The next year, a revolutionary methodological approach was introduced by Tom Kirkwood, who developed a calibration model establishing that working thromboplastins should be calibrated against an international standard, distributed by the World Health Organization. That was the birth of the International Normalized Ratio (INR).[18] Again, Poller in 1985 reinforced the importance of INR, stating that all manufacturers should have been obliged to calibrate their reagents, thus expressing PT in INR and facilitating the process of creating more precise therapeutic equivalents with specific reagents.[19]

Bleeding and the initial clinical reports

While these efforts to optimize thromboplastin calibration using INR values were underway, several retrospective clinical studies were published between 1986 and 1993 (Table 1).[20-26] Those studies, primarily from US, showed high bleeding rates,

Table 1. Main findings of some studies between 1986 and 1993.

Study (ref)	Patients number	Major bleeding (%), 1, 2, 4 years	Prothrombin time measurement
Peititti 1986 (20)	2029	18, 26, 41	Not reported
Gurwitz 1988 (21)	321	5, 12, 12	Not reported
Petty 1988 (22)	310	2, 7, 7 (3 years)	Seconds
Landefeld 1988 (24)	565	3, 11, 22	PT ratio
Bussey 1989 (23)	82	0, 2, 15.5 (100 pat/years)	Seconds
Laumbjerg 1991 (25)	560	2.7 (100 pat/years)	Percentage
Fihn 1993 (26)	920	1, 2, 5	PT ratio and INR

PT, prothrombin time; INR, International Normalized Ratio.

likely in part due to poor PT monitoring, since American thromboplastins (rabbit brain) were characterized by low sensitivity to reduced activity of vitamin K-dependent factors (II, VII, IX, and X), so leading to the use of higher dosages.[19]

The foundation of the *Italian Federation of Anticoagulation Clinics* and the *Italian Study on the Complications of Oral Anticoagulant Therapy* study

In 1989, nine researchers in the field of oral anticoagulation founded the Italian Federation of Anticoagulation Clinics (FCSA) in Parma (Figure 1). FCSA had several aims: i) the creation of anticoagulation clinics throughout Italy, to improve the management of VKAs in the country, ii) more precise criteria to establish the indication of oral anticoagulation, iii) the organization of educational courses and congresses, iv) the periodical laboratory control of INR, and v) the planning and publishing of clinical studies in the field. Gualtiero Palareti served as FCSA President for six consecutive years, enabling, after a couple of years, the publication in The Lancet of the first prospective, multi-center cohort observational study dedicated to VKA hemorrhagic complications using INR for anticoagulation monitoring: the ISCOAT study.[27] A total of 34 Italian anticoagulation clinics enrolled 2745 consecutive patients from the start of their oral anticoagulation (warfarin in 64%, acenocoumarol in the rest). The main indications were as follows: venous thromboembolism (32.5%), non-ischemic heart disease (24.1%), ischemic heart disease (14.7%), atrial vascular disease (10.2%), heart-valve prosthesis (10.8), and heart-valve disease (6.7%). During the follow-up, 153 bleeding complications occurred (7.6 per 100 patient-years). Five were fatal (all brain hemorrhages, 0.25 per 100 patient-years), while 23 were severe (1.1), and 125 were mild (6.2). The event rate was similar across gender, coumarin type, enrollment center size, and target INR. The rate was higher in older patients: 10.5 per 100 patient-years in those aged 70 or over, 6.0 in those aged under 70 (RR 1.75, 95% CI 1.29-2.39). The results of this study showed significantly lower bleeding rates than those reported in the studies cited above. The strength points of ISCOAT were: i) the optimal activity of the anticoagulation clinics as a result of the educational approach of FCSA in the previous years, ii) the use of a computerized system for results and prescriptions by twenty-five centers[28] and iii) the implementation of INR as a methodological approach for monitoring the anticoagulant therapy. On the other hand, the INR system had already been studied for several years before by the Palareti group in Bologna aimed to spread the capacity of this system to improve the inter-laboratory comparability everywhere.[29]

Italian Federation of Anticoagulation Clinics and the elderly

Some years later, Palareti *et al.* examined oral anticoagulant treatment in the elderly through a nested, prospective, multicenter case-control study.[30] Bleeding events were recorded during VKA

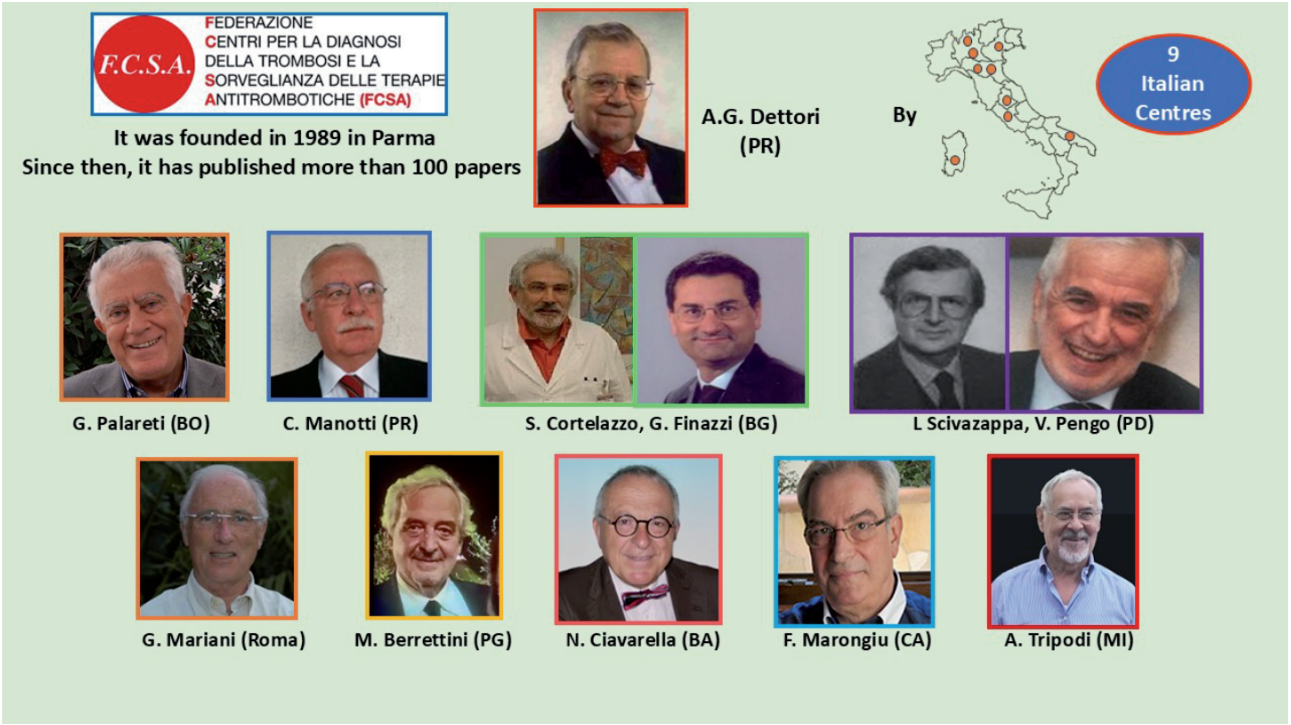

Figure 1. The foundation of FCSA in 1989.

therapy in 461 patients aged 75 years or older at VKA initiation and in 461 patients younger than 70 years. Patients were matched for sex, VKA indication, and treating center. Bleeding rate was in general higher in elderly patients (9.9%) in comparison with the younger patients (6.6%) without reaching a significant difference (p=0.07). A similar result was obtained for major bleeding: 2.1% and 1.1% (p=0.19). However, 6 and 1 events, respectively, were intracranial and fatal (relative risk, 6.4; p=0.05). An important finding was to demonstrate that bleeding in the elderly was almost half (4.5%) when the INR was between 2.0 and 2.9 thus indicating the importance to maintain elderly people within this range which is therefore to be considered safe for this category of patients. The following year, another study was conducted, focused on very elderly patients.[31] Again, this study, a multicenter prospective observational study, involved 27 FCSA Centers. Daniela Poli, the principal investigator, and the Gualtiero Palareti group included 4093 patients [median age 84 years (80-102)] who were naïve to VKAs and were treated for atrial fibrillation (73.7%) or venous thromboembolism (26.3%). Follow-up was 9,603 patient-years. The number of major bleedings was surprisingly low: 179 (rate 1.87 per 100 patient-years), of which 26 were fatal (rate 0.27 per 100 patient-years). The intracranial hemorrhages (ICH) were 53 for a rate of 0.55 per 100 patient-years**.** The authors concluded that, in this large study of very elderly patients receiving VKA, age alone should not be considered a contraindication to treatment, as the incidence of bleeding complications was low. With proper management of VKA therapy, including careful monitoring in specialized centers, very old and frail patients can successfully benefit from VKA thromboprophylaxis. In an accompanying editorial to this study, Jack Ansell underlined the importance of the findings of Poli *et al.*, stating that the message is to help ease doctors' fears about treating the elderly, thereby reducing barriers to VKAs use in this population.[32] This was an important viewpoint against defensive medicine, which does not align with good medical practice and can lead to poor outcomes.[33]. Another important study, published in 2014 by Poli *et al.*, focused on the recurrence of ICH after resumption of VKAs, enrolled 267 patients (163 male, median age 73.9 years).[34] During the follow-up (778 patient-years), ICH recurred in 20 patients (7.5%; rate 2.56 per 100 patient-years) and was fatal in 5 (25%; rate 0.4 per 100 patient-years). Male sex, hypertension, prosthetic heart valves, previous ischemic stroke, renal failure, cancer, and spontaneous events were associated with the risk of recurrence. Moreover, one-third of spontaneous recurrences occurred in patients with a posttraumatic index event. The results of this study had the merit of disclosing the main risks of ICH recurrence, which should be carefully considered before restarting anticoagulant therapy.

FCSA-START register and warfarin challenged *versus* direct oral anticoagulants

In 2005, the Italian Anticoagulation Clinics were already planning to change their approach to the new anticoagulants, which opened a revolutionary road and did not require PT monitoring.[35] As a matter of fact, ximelagatran, a thrombin inhibitor,[36] had already been tested in a randomized clinical trial (RCT),[37] although later withdrawn.[38] Some years later, between 2009 and 2013, four new anticoagulants, dabigatran, rivaroxaban, apixaban, and edoxaban, were evaluated against warfarin in non-inferiority trials. The FCSA steering committee published an overview of this new therapy in 2012,[39] and the following year, two meta-analyses highlighted the advantages of DOACs over warfarin, except for an increased risk of gastrointestinal bleeding.[40,41] However, it is crucial to emphasize that the bleeding rates of the treatment with the four DOACs, either major (from 3.04 to 3.43 per 100 patient-years) or ICH (0.70 to 0.85 per 100 patient-years), were much higher than those reported in the previous study ISCOAT (1.1 per 100 patient-years and 0.25 per 100 patient-years). In 2017, Palareti *et al.*[42] reinforced this observation by publishing a new ISCOAT study, *i.e.,* an observational cohort study that reported the rates of major bleeding and ICH among 5707 patients treated with VKAs. This study followed these patients over an 8906 patient-year follow-up period, and was conducted by the Italian Anticoagulation Clinics included in the START2 register. The average age of the patients was 73.0 years, with 28.1% being over 80 years. Additionally, 61.6% of the patients received treatment for atrial fibrillation. The annual rates of major bleeding and ICH in the atrial fibrillation group were 1.4% and 0.43%, respectively. As a matter of fact, these figures are significantly lower than those reported in the four RCTs. The differences were even more pronounced in patients over 75, as shown in the four RCTs comparing warfarin, according to Schafer *et al.*[43] The substantial decrease observed in Italian Anticoagulation Clinics may be attributed to improved monitoring compared to the global centers involved in the four RCTs, as noted by Wallentin *et al.*, particularly concerning dabigatran.[44] However, this may likely have also occurred in the other three trials.

The *Fondazione Arianna Anticoagulazione* and the START2 register

Founded in 2014 by Associazione Italiana Pazienti Anticoagulati (AIPA) Bologna and Gualtiero Palareti, the Arianna Anticoagulation Foundation aims to serve as *a compass for anticoagulant and antithrombotic treatments*. The foundation encourages and supports independent clinical studies on anticoagulant and antithrombotic medications. Its focus encompasses all aspects of these drugs, including their pharmacological characteristics, clinical trial results, and the evaluation and improvement of their effectiveness and safety in real-life therapeutic use. In 2014, Emilia Antonucci, a key figure at the Fondazione Arianna, introduced the START-Register − Survey on Anticoagulated Patients Registry. This independent, inception-cohort, observational, and collaborative database was designed to prospectively track the clinical history of adult patients who are beginning anticoagulant treatment for various reasons and using any medication.[45] A total of 5,252 patients were enrolled in the study, with 97.6% receiving VKAs, as direct oral anticoagulants (DOACs) were only recently available in Italy. The median age of the participants was 74 years (range: 64-80), and 53.7% of the patients were male. This analysis specifically focuses on the 3,209 patients with non-valvular atrial fibrillation, who represent 61.1% of the total cohort. The mean CHADS2 score among these patients was 2.1±1.1, while the CHA_2DS_2-VASc score averaged 3.1±1.3. The median age of the non-valvular atrial fibrillation patients was 76 years (interquartile range: 70-81). Additionally, 168 patients (5.3%) were found to have severe renal failure (creatinine

clearance <30 ml/min), while moderate renal failure (creatinine clearance 30-59 ml/min) was observed in 1265 patients (39.5%).

In 2018, Sophie Testa published a report on bleeding events among patients treated with DOACs.[46] This was a prospective, international, multicenter study that documented the hemorrhagic complication of these drugs. One hundred seventeen patients with major bleeding on DOACs were enrolled from several Countries. The study was conducted across 15 centers in 7 countries (Belgium, Brazil, Germany, Italy, Switzerland, USA, and Thailand): 32 patients were on apixaban (63% and 37% taking 5 or 2.5 mg twice daily, respectively), 32 on dabigatran (75% and 25% taking 150 or 110 mg twice daily, respectively), and 51 on rivaroxaban (61% and 39% taking 20 or 15 mg once daily). Non-valvular atrial fibrillation was the reason for treatment in 84% of the cases, with 62% of those being males. Among the patients, 53 experienced intracranial bleedings, 13 of which were fatal. Therapeutic interventions to manage bleeding were performed in 71% of patients. The treatment strategies used, which included both surgical and non-surgical approaches, were fluid replacement, red blood cell transfusions, prothrombin complex concentrates (3- or 4-factor), antifibrinolytic drugs, and idarucizumab. In this study, specific DOAC blood levels were measured in 23% of the patients. The mortality rate during hospitalization was 11.9%, and at the 6-month follow-up, it increased to 15.5%. This experience revealed significant variability in the management of bleeding complications among patients treated with DOACs. The authors rightly concluded that several improvements are needed: i) the development of standardized and more structured guidelines; ii) the availability of reversal agents; iii) the need for DOAC-specific measurements that are quickly accessible in emergencies; iv) specialized training on anticoagulation reversal for emergency department physicians; and v) the presence of expert consultants in thrombosis and hemostasis to ensure upgraded, consistent, and likely more effective management of acute major bleeding complications in patients on anticoagulation therapy. A 2019 study by Daniela Poli *et al*. again focused on elderly patients with atrial fibrillation. The authors analyzed a cohort of 1.124 patients aged 85 years or older who initiated anticoagulation therapy. Among these patients, 58.7% were treated with VKAs and 41.3% with DOACs. This prospective cohort study included patients with atrial fibrillation and was part of the Survey on Anticoagulated Patients Registry (START2-Register).[47] The study aimed to evaluate mortality rates and the occurrence of bleeding and thrombotic events during long-term follow-up. In the Cox proportional-hazards model, hazard ratio (HR) and 95% Confidence Intervals (95% CI) for major bleeding showed no difference between drug classes (HR: 0.99, CI 95%: 0.50-1.97). This study demonstrated that anticoagulation in the elderly is safe. Once again, a result against defensive medicine, which often avoids prescribing anticoagulation to very old patients.[48] In 2020, Gualtiero Palareti presented via the British Medical Journal a prospective cohort of 2,728 patients with Venous Thromboembolism included in the Survey on anticoagulaTed pAtients RegisTer (START2-Register) from January 2014 to June 2018.[49] This study involved 60 FCSA centers across Italy. Patients were treated with either DOACs (80%) or VKAs. Bleeding events, major and clinically relevant non-major bleeding, were not different between the two treatment groups (2.7 *vs* 3.1; 95% CI: 0.81, 0.48-1.37). However, VTE rates were higher in the DOAC group (2.73%) than in the VKA group (0.49%) during late follow-up. Palareti and coworkers explained this result as being a consequence of poor adherence to DOACs therapy due to irregular patient follow-up after 180 days. Therefore, regular patient visits, even during long-term therapy with DOACs, are emphasized to underscore the need for complete treatment adherence and to prevent future complications. Another topic addressed by Palareti *et al.* was the difference in major bleeding between men and women.[50] In that study, 1,298 women were compared with 1,290 men. Women were older and more often had renal diseases. In both women (2.9 per 100 patient-years) and men (2.1 per 100 patient-years), the bleeding rate was similar. When uterine bleeding was included in the analysis, the rate increased to 3.5 per 100 patient-years (p=0.0141). This finding has been confirmed by Grandone *et al*.[51] who reported that women of childbearing age taking oral anticoagulants often experience fluctuations in hemoglobin values and uterine bleeding during treatment, with uterine fibroids significantly contributing to these changes. However, the primary message of this study was directed at those who believe that, in general, bleeding occurs more frequently in women than in men and who hold a mistaken belief regarding a hypothetical higher frailty.[52,53] Finally, I wish to report here the *MAS study* (Measure and See) conducted by Gualtiero Palareti and Sophie Testa, along with many coworkers.[54] In this study, venous blood was collected 15 to 30 days after initiation of DOACs in patients with atrial fibrillation, who were then followed for 1 year to document major and clinically relevant non-major bleeding. During a follow-up period of 1606 years, 50 bleeding events were recorded, yielding an incidence rate of 3.11 per 100 patient-years. Of these, 15 bleeding events (4.97 per 100 patient-years) occurred in patients with C-trough standardized values in the highest activity class. In contrast, 35 events (2.69 per patient-years) were observed in patients with values in the two lower activity classes. This difference was statistically significant (p=0.0401). Interestingly, increasing DOAC levels and low-dose DOAC use were associated with increased bleeding risk in the first 3 months of treatment**.** More bleeding occurred in patients on the low (4.3 per 100 patient-years) *vs* standard (2.2 per 100 patient-years; p=0.016) DOAC dose. The authors concluded that low-dose DOACs do not always prevent high levels of drug activity, which can increase the bleeding risk for patients. Therefore, they suggested measuring anticoagulant levels at the start of DOAC treatment, particularly in patients with atrial fibrillation receiving low doses, to help prevent persistently high or low DOAC activity. This approach may potentially reduce the occurrence of bleeding or thrombotic events. I remember a debate that took place many years ago at a meeting in Parma, when Cesare Manotti was the president of FCSA. Armando D'Angelo, a prominent and internationally recognized Italian scientist in the field of hemostasis and thrombosis, and I proposed that measuring DOAC levels at the onset of anticoagulation therapy could lead to adjustments or, if levels were found to be either too high or too low, replacement of the drug with another. However, all the colleagues present were against this idea! While this approach could be beneficial, it remains outside current international guidelines and is challenging to implement because measuring DOAC levels at a national scale remains difficult.[55]

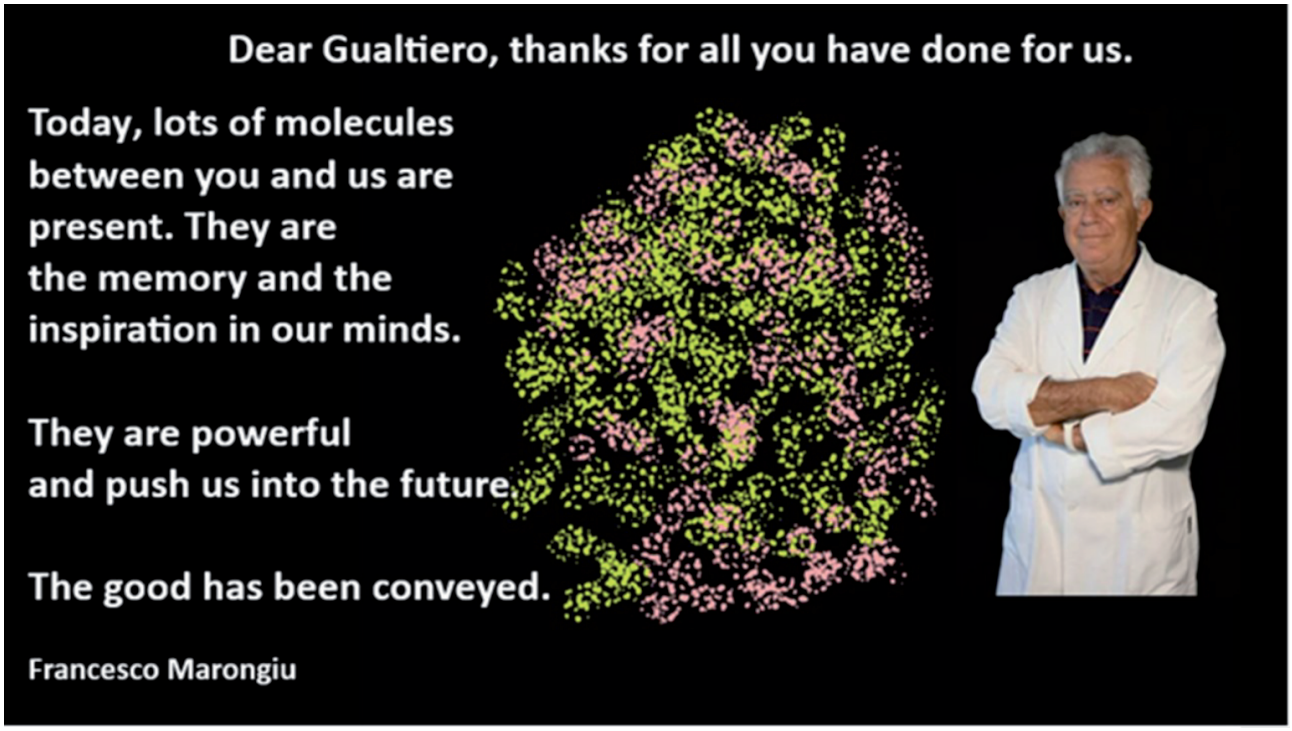

Figure 2. My greeting to Gualtiero.

What kind of research for Fondazione Arianna?

The Arianna Anticoagulation Foundation mainly publishes independent cohort observational studies. They assure independence from the pharmaceutical industry, which, although necessary, often prioritizes commercial interests. All these procedures, despite their limitations, can yield essential and practical results, especially when a RCT is not feasible, for ethical reasons.[56,57] These types of studies, if well conducted, may produce results not so different from RCTs, the cornerstone of evidence-based medicine, as demonstrated by Concato *et al.* and Benson and Hartz.[58-60] They suggested that findings from other scientific disciplines support the view that research design should not be overly rigidly constrained by a strict hierarchy. The Arianna Foundation has confirmed its primary research focus: encouraging and supporting independent clinical studies. Finally, three special women have played pivotal roles in the Foundation: Emilia Antonucci, Stefania Cavazza, and Cristina Legnani. The first has built the START2 registers, strictly monitoring the several registries proposed by the Foundation; the second is a physician who has been able to sustain Fondazione Arianna and lead the journal Anticoagulazione.it for many years, while the third exerted an essential role in Laboratory science from FCSA, Fondazione Arianna, and the whole international scientific community to the present days. She is consistently featured among the authors of the numerous papers published by Fondazione Arianna. She will continue to give her invaluable effort on this topic.

Conclusions

FCSA and Fondazione Arianna have emphasized the paramount role of the Thrombosis Centers, as they have demonstrated the safety of anticoagulants and the sound management of both VKAs and DOACs over time. They should always be encouraged to provide ongoing support to anticoagulated patients through regular follow-up and research. They should also be prepared to incorporate all new research findings, including new drugs for implementation in routine clinical practice. I think that Gualtiero has played a paramount role in all of this. To greet him, I would like to share what I wrote in the final figure of this article (Figure 2).

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