Rationale and design of a study on D-dimer use to stratify patients after a first unprovoked venous thromboembolism for their risk of recurrence: extended low-dose Apixaban given only to patients with positive D-dimer results. The Apidulcis study

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ABSTRACT

Optimal duration of anticoagulation in patients with a first venous thromboembolism (VTE) is still uncertain. Extended anticoagulant treatment beyond the first 3 to 6 months is recommended in patients with unprovoked VTE for their high risk of recurrence, provided the risk of bleeding during anticoagulation is not high. Recent meta-analyses indicated that only one-third of these patients have a recurrence 10 years after anticoagulation is stopped, whereas the risk of major bleeding is consistent and persistent during anticoagulation. We designed the prospective, multicenter Apidulcis study to test whether serial D-dimer measurements, using commercial assays with predefined sex-specific cutoffs (350 ng/mL and 500 ng/mL for men and women, respectively, for assays expressing results as fibrinogen equivalent units), may be useful to stratify patients for the risk of recurrence. Those presenting positive D-dimer results, considered at higher risk, will receive low dose Apixaban, 2.5 mg tablets BID for 18 months, whereas those with persistently negative D-dimer results, considered at lower risk, will remain without anticoagulant treatment. Outpatients with a first VTE (unprovoked or associated with weak risk factors), aged 18 to 74 years, who have already received anticoagulation for at least 12 months are eligible for the study.

INTRODUCTION

Venous thromboembolism (VTE), encompassing deep vein thrombosis (DVT) of lower limbs and/or pulmonary embolism (PE), tends to recur. Anticoagulation is the mainstay treatment for acute and long-term VTE events, as well as for secondary prevention. It has been shown, however, that whatever the duration of anticoagulant treatment, its benefit fades after anticoagulation is stopped and the risk of recurrence increases again.[1-4] The duration of anticoagulant therapy can be regulated by the estimated risk of recurrence. This is low when the event is provoked

by a reversible risk factor, such as surgery, thus deserving short treatment,[5] or very high when VTE is associated with a permanent factor such as cancer in which case anticoagulant therapy is usually continued indefinitely.[6] When the initial thrombotic event occurs without any apparent provoking factor ("unprovoked" or "idiopathic" VTE), or when it is associated with weak risk factors (such as minor surgery or short bed resting, etc.), the risk of recurrence can be intermediate and the indication for an indefinite anticoagulation is uncertain, especially if the risk of major bleeding - inevitably associated with anticoagulation – is considered. A recent meta-analysis showed that the rate of recurrence after an unprovoked event is about 10% in the first year after interruption of anticoagulation and decreases in following years, reaching a cumulative incidence of 36% at 10 years.[7] On the other hand, the risk of major bleeding is persistent during extended anticoagulation and was found to be 1.74% pt-y in patients treated with vitamin K antagonists (VKAs) and 1.12% pt-y in those receiving direct oral anticoagulants (DOACs).[8] It would be useful to stratify individual risk of recurrence to avoid extension of anticoagulant treatment in patients at lower risk. It was shown that patients with unprovoked VTE have a higher risk of recurrence if they have elevated D-dimer levels after stopping therapy.[9-11] However, whether negative D-dimer levels can be used to stop anticoagulation after the usual period of treatment is still uncertain and conflicting results have been reported. Kearon *et al*.[12] showed that in patients with negative D-dimer results, using a qualitative D-dimer assay, the rate of recurrent VTE was 6.7% (CI, 4.8%-9.0%), exceeding the limit (5% per patient-year) suggested by the International Society for Thrombosis and Hemostasis to decide which patients with unprovoked VTE can stop anticoagulation after a VTE.[13] In contrast, the Dulcis management study,[14] where D-dimer levels were repeatedly assessed using quantitative assays, showed that recurrent VTE developed in the 3.0% pt-y (CI, 2.0-4.4%) of patients with D-dimer results persistently lower than pre-established cutoffs who stopped anticoagulation. In patients who resumed anticoagulation at the first positive D-dimer result (above the predefined cutoffs values) the rate of recurrence was 0.7% pt-y (CI, 0.2-1.7; P=0.0006). However, after resuming anticoagulation with VKAs (the only anticoagulant drug available at that time), the rate of major bleeds was quite high, standing at 2.3% pt-y (CI, 1.3-3.9) in these patients. In the following years, DOACs became available for use in our country to treat VTE. In particular, the administration of low dose apixaban (2.5 mg × 2 daily) for secondary prophylaxis after a period of standard anticoagulation in patients with a first unprovoked VTE was shown to be effective in reducing the rate of recurrence compared to placebo and associated with a low risk of bleeding events.[15]

We designed the prospective, multicenter Apidulcis study to test whether D-dimer assay, performed during and after standard anticoagulation, can be used to stratify the risk of recurrence in patients with a first unprovoked proximal DVT or PE. Patients with a positive D-dimer result, considered at higher risk, will receive Apixaban 2.5 mg twice a day for 18 months, whereas those with persistently negative D-dimer results, considered at lower risk, will remain without any specific treatment. All patients will be followed-up for 18 months. The final aim of the study is to see whether, in patients with a first VTE that was unprovoked or associated with weak risk factors (WRFs), it is possible to achieve a rate of recurrence comparable to that expected in a population of patients with provoked VTE, using D-dimer assay to give low dose Apixaban for extended treatment to patients with positive D-dimer and avoid extension of anticoagulation in those with negative D-dimer and at lower recurrence risk.

METHOD AND ANALYSIS

Primary and secondary objectives

The primary efficacy objective is the composite of confirmed recurrent proximal DVT and/or PE episodes, and of VTE-related mortality. The primary safety endpoint is the incidence of major bleeding (MB) complications occurring during the follow-up period in all included patients.[16] The secondary endpoint for efficacy is the composite of hospitalization and deaths due to cardiovascular events. Secondary safety endpoint is the cumulative incidence of MB, clinically relevant non major bleeding (CRNMB) complications,[17] and overall mortality. Signs and/symptoms of post-thrombotic syndrome will also be recorded using the Villalta score.[18] All suspected outcome events and deaths will be evaluated by a central adjudication committee whose members will be unaware of patient name, D-dimer testing results, type of management or enrolling center.

Patients, study design

The Apidulcis is an investigator-initiated, multicenter, prospective cohort, no-profit study conducted in many (>40) Italian study sites. Patients of both genders are eligible for the study, aged >18 and up to 74 years at screening, with first episode of lower extremity proximal DVT and /or PE, idiopathic or associated with weak or removed risk factors and who have completed a course of anticoagulant treatment (regardless of the drug used) of at least 12 months. The inclusion and exclusion criteria are listed in Table 1. Prior to enrollment, the investigators obtain informed consent from patients and recommend continuing ongoing anticoagulant therapy until first D-dimer test is performed. As shown in Figure 1, the first D-dimer assay

Table 1. Criteria for inclusion/exclusion in the study.

Inclusion criteria	Prespecified criteria for exclusion
- Age >18 y and not >74 y - First episode of proximal DVT of lower limbs and/or PE that was: idiopathic or associated with one or more of following factors: minor, arthroscopic, or laparoscopic general surgery, pregnancy or puerperium, contraceptive or replacement hormonal therapy, long trip (>6 h), minor trauma (not requiring hospitalization, plaster casting, or immobilization), hospitalization in medical hospital, reduced mobility (not complete immobilization) - Ability to provide informed consent	- Age <18 y or >74 y - Duration of anticoagulation after the event < 12 months - VTE post major surgery, trauma, plasters, or immobilization (within 3 months) - VTE post bed resting (>4 d) - High bleeding risk - Limited life expectation (<1 y) - Increased systolic pulmonary arterial pressure (values >35 mm Hg [or > 40 mm Hg if BMI >30] estimated with echocardiography) - Geographical inaccessibility - Venous thrombosis in different sites - >1 documented VTE episode (proximal DVT and/or PE) - Active cancer or hematologic disease - Known serious thrombophilic alterations - Antiphospholipid antibody syndrome (Sydney criteria) - PE with shock or life-threatening prolonged hypotension - Different indications for anticoagulation - Severe cardiorespiratory insufficiency (NYHA 3 or 4) - Pregnancy or puerperium (first 6 weeks after birth) at the time of screening examination - Severe renal (creatinine level > 2 mg/dL [177 mmol/L]) or liver failure (eg, acute hepatitis, chronic active hepatitis, or cirrhosis; or an alanine aminotransferase level that was 3 times the upper limit of the normal range or higher) - Inability or refusal to give consent

DVT: deep vein thrombosis; PE: pulmonary embolism; VTE: venous thromboembolism; BMI: body mass index; NYHA: New York Heart Association.

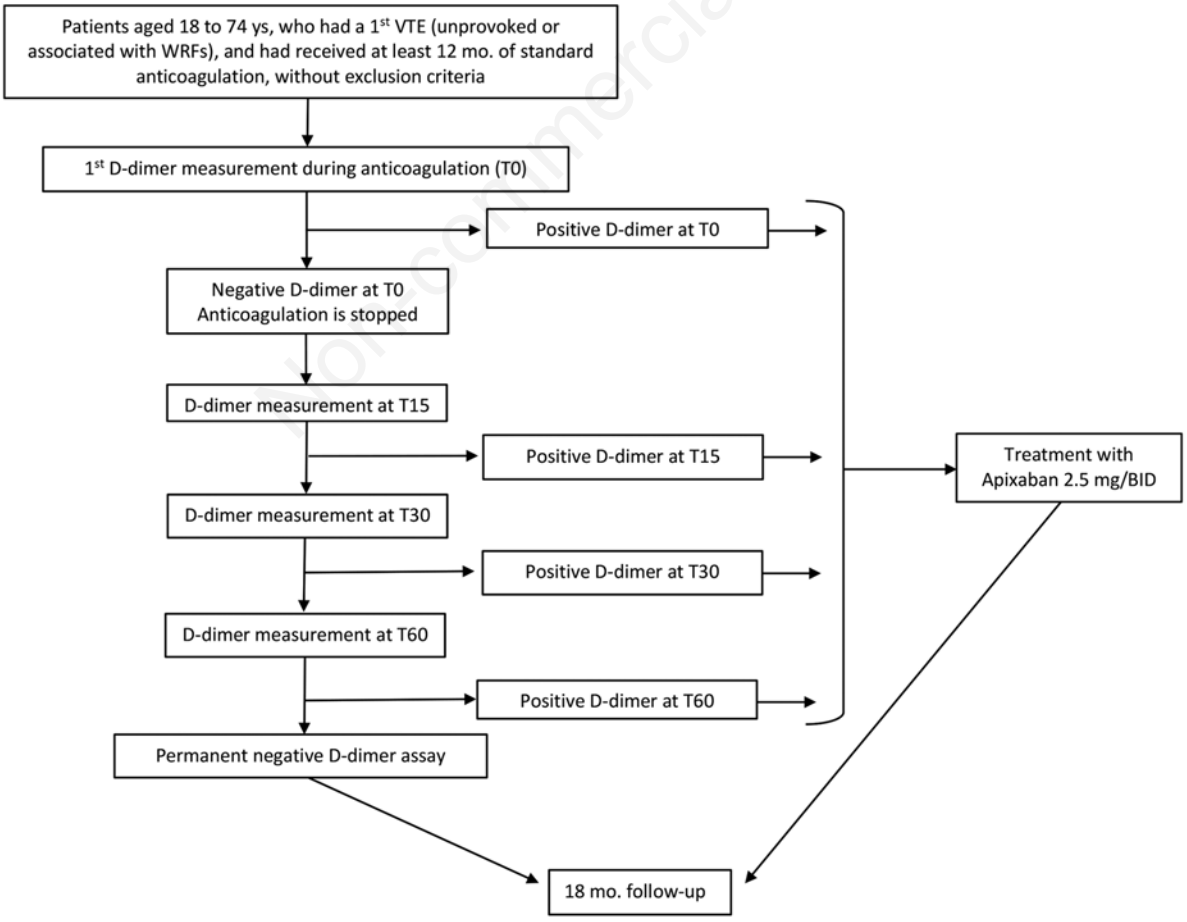

Figure 1. Flow chart of the study.

is carried out, using commercial assays, during anticoagulant treatment; if the result is negative (below predefined cutoff levels) the patient is invited to stop treatment and receives three dates for further D-dimer testing (15, 30 and 60 days after anticoagulation discontinuation). At first positive D-dimer assay patients are invited to continue or resume anticoagulation treatment using Apixaban 2.5 mg tablets (kindly provided by Alliance BMS-Pfizer) for the subsequent 18 months. Patients with persistently negative D-dimer assay are asked to stay off anticoagulation. All patients are followed for 18 months. The study aims to enroll a total of 1150 patients.

In Table 2 are listed the commercial D-dimer assays allowed in the study and the respective cutoff levels for negative/positive results. The cutoffs for men are lower than those for women, to compensate for the higher risk of recurrences in men. In contrast, no different cutoff levels are adopted in relation to patient age, even though it is well known that D-dimer levels physiologically increase with age. In the previous Dulcis study the cutoffs adopted were higher in patients aged 70 years or more;[14] however, the clinical results of the study were not satisfying in that patient population. According to the ACCP guidelines,[19] elderly patients (especially if >75 years) are at high bleeding risk during anticoagulant therapy, and therefore extended treatment beyond the first 3-6 month from acute event should not be recommended. For the above reasons, patients aged 75 years, or more are excluded from this study.

Data management

Demographic data (collected anonymously), information about index VTE event, baseline general clinical conditions, possible complications, new events or diseases, and adverse events (AEs) are all recorded by investigators in the electronic case-report-form (eCRF) and collected in the central database. All patient information will be stored securely and kept confidential. Study sites are supervised by a dedicated remote monitor throughout the entire study. Before starting patient enrolment, investigators receive visual electronic training sessions with the study monitor to clarify study design, protocol requirements and correct eCRF use. The study monitor will make sure study procedures are stuck to and check completeness and correctness entries into the eCRF

Patients are instructed to contact the clinical center immediately if symptoms develop suggestive of VTE or in case of bleeding. In case of suspected recurrent DVT, compression ultrasonography (CUS) is compared with the last available previous CUS. A recurrent DVT is diagnosed if a previously fully compressible segment (contralateral or ipsilateral) is no longer compressible or if an increase of at least 4 mm in the diameter of the residual thrombus during compression is detected.[20] In case of suspected PE, recurrence will be diagnosed based on objective algorithms,[21,22] including clinical probability, helical CT (or ventilation-perfusion lung scanning), CUS, and D-dimer testing as appropriate. Suspected outcome events and deaths are evaluated by a central adjudication committee (appendix A) whose members are unaware of the patient's name, the enrolling center, the results of D-dimer performed at inclusion, and whether the patient was receiving or not Apixaban therapy at the moment of the event.

Patients are censored in case of primary outcomes, serious adverse events, occurrence of a pathology requiring full anticoagulant treatment, onset of cancer or other serious pathology, withdrawal of informed consent, or a decision by the attending physician. Temporary discontinuation is permitted in case of surgery, invasive procedure, or whenever prophylactic treatment with LMWH is recommended by the attending physician. Pharmacovigilance for the patients receiving apixaban will be carried out by Dr. Elisabetta Bigagli, from the "Dipartimento di Neuroscienze, Psicologia, Area del Farmaco e Salute del Bambino, NEUROFARBA", University of Florence, Italy (farmacovigilanza-noprofit@neurofarba.unifi.it).

Table 2. Predefined D-dimer cut-off levels (ng/ml) for negative/positive results in men or women (aged 18-74 years).

	Men	Women
Methods that espress results in FEU - VIDAS D-dimer, - Innovance D-dimer, - Stago Liatest D-dimer, - HemosIL D-dimer HS 500)	350	500
Methods that espress results in D-dimer units - HemosIL D-dimer HS, - Sclavo Auto D-dimer	175	250

D-dimer should be measured at the following time points.
T0 = during anticoagulation
T1 = 15±2 days after anticoagulation is stopped
T2 = 30±4 days after anticoagulation is stopped
T3 = 60±5 days after anticoagulation is stopped

Statistical considerations and sample size

The aim of this management study is to show that, in patients with a first unprovoked VTE, combining the use of a prediction rule based on D-dimer assay with low-dose Apixaban in subjects at higher risk of recurrence can determine a recurrence risk similar to that in patients with provoked VTE. Our calculations are based on the following assumptions: i) Based on the results of the Dulcis study,[14] approximately 52% of all eligible patients are expected to discontinue anticoagulation after permanently negative D-dimer assay, with an annual rate of recurrent VTE events around 3% (95% 2.0 to 4.4%); ii) In the remaining 48% of patients who will be encouraged to use low-dose apixaban, the expected rate of recurrent VTE

based on the results of the Amplify Extension study is around 1.7% after the first year of treatment;[15] iii) Based on the metanalysis by Iorio *et al*.[5] the annual recurrence risk in patients with provoked VTE is 3.7% (CI, 0.9-15.5). Based on these assumptions, we expect the recurrence rate at 12 months to be: 0.52*0.03+0.48*0.017=2.4%. With an expected annual recurrence rate of 2.4% in the study population, we calculate the sample size to demonstrate, with an 80% power, that the upper limit of 95% CI is below 3.5% according to Shen.[23] The required sample size is about 1150 patients to be recruited for the purpose of the Apidulcis study.

Safety endpoint and interim analysis

Based on a 2.2% annual event rate, a total sample size of around 1150 patients and 18 months of follow-up, we expect around 38 recurrences and 2 major bleedings in our study. Since low-dose Apixaban may be considered the gold-standard treatment, we plan an interim analysis where 20 primary endpoints are registered. A Data Monitoring and Safety Board (DMSB) will perform the interim analysis and apportion the primary endpoints to the two groups of patients. The study will be interrupted if the relative risk of primary endpoints (HR) in the observational non-treatment group is >3 HR, with a P value <0.0001, compared to the group receiving Apixaban.

Statistical plan

All included subjects will be examined for efficacy and safety. Collected data for continuous variables will be described as mean with standard deviation and 95% confidence interval if normally distributed, or as median with range interquartile and 95% CI in case of deviation from a normal distribution. Nominal variables will be described as absolute and relative frequency tables. Statistical analysis of the baseline variables [analysis of variance (ANOVA) complemented with the Tukey and Dunnet tests, or Kruskal–Wallis test, as appropriate, and chi-square test for nominal variables] is planned for those variables that at the descriptive analysis throw up potential differences in terms of clinical relevance. Kaplan–Meier survival curves will be plotted to estimate the cumulative incidence of symptomatic recurrent VTE; hazard ratios (HR) and their 95% confidence intervals (CI) will be calculated for subgroup analysis. The Villalta score,[18] will be analyzed as a continuous variable and as a nominal variable, using the cut-off >5 points to identify the post-thrombotic syndrome and the cut-off >14 to classify the syndrome as severe.

Ethics and dissemination

The Apidulcis is an investigator-initiated study promoted by the "Arianna Anticoagulazione" Foundation (Bologna, Italy). The study is supported by Alliance BMS-Pfizer, which also will provide the drug Apixaban 2.5 mg × BID. The study is registered at https://www.clinicaltrials.gov (NCT03678506, registration date 19/09/2018) and at EudraCT (2017-002340-32). The study protocol (V1.1 date 16/01/2018), was designed in compliance with the current version of the Declaration of Helsinki and the GCP, and was authorized by AIFA ("Agenzia Italiana del Farmaco" ref. number AIFA/SC/P/16556, date 15/02/2018); it was approved by the independent Ethics Committee of the Azienda Ospedaliera Careggi, Florence, Italy (reference number: CE 12152_spe, dated 17/04/2018) as lead ethics committee and will be approved by ethics committees at all participating sites before enrolment starts. The study will be conducted in accordance with the Declaration of Helsinki. Written informed consent will be collected before starting. Protocol amendments will be communicated to study sites by the sponsor. The steering committee (appendix A) has responsibility for the design, carrying out and analysis of the study as well as decisions on publication of results and has full access to the data set. All safety and efficacy endpoints will be evaluated by an independent Data Monitoring Safety Board (DMSB, appendix A) blind to the treatment of patients, eCRF, e-trial system, data capture and monitoring. A DMSB (appendix A), blind to patient D-dimer results and treatment, will supervise the study and will perform interim analysis. The trial supporter (Alliance BMS-Pfizer) has no role in collection, analysis and interpretation of data, or submission of results. Study findings will be disseminated to Alliance BMS-Pfizer, to the participating centers, at research conferences, and in peer-reviewed journals.

DISCUSSION

The optimal duration of anticoagulant treatment to avoid recurrence after a first VTE is still an open issue. While some authors do not agree with the idea of distinguishing VTE events between unprovoked and provoked to decide the duration of anticoagulation,[24,25] international guidelines still recommend indefinite anticoagulant treatment (extended beyond the first 3-6 months) only in subjects with an unprovoked first VTE event, provided the risk of bleeding is not high. A recent systematic review and meta-analysis reported a cumulative incidence of recurrence in patients with a first unprovoked VTE of 16.0% (13.3% to 18.8%) at 2 years, 25.2% (21.3% to 29.3%) at 5 years, and 36.1% (27.8% to 45.0%) at 10 years after stopping anticoagulation.[7] This means that about two-third of all patients with unprovoked events are expected to remain free from recurrence over 10 years. On the other hand, a recent meta-analysis has calculated an incidence of MB events during extended anticoagula-

tion of 1.74 (1.34 to 2.20 events) per 100 patient-years with VKAs and 1.12 events (0.72 to 1.62) with DOACs, with a 5-year cumulative incidence of 6.3% (3.6% to 10.0%) with VKAs (no data are available for treatment with DOACs beyond one year).[8] Furthermore, while the rate of recurrence decreases over time, bleeding is stable during anticoagulant treatment. Additionally, the case-fatality rate of MB is much higher compared to that of recurrent events (more than double according to data in the above-mentioned meta-analysis studies: MB: 8.3% and 9.7% during VKA or DOAC treatments, respectively, versus 4% of recurrences).

The above-mentioned meta-analyses indicate that only one-third of subjects with a first unprovoked VTE event will have a recurrence in 10 years and that the risk of MB and of associated complications is not-negligible during anticoagulation. It seems justified, therefore, to look for management strategies aimed at stratifying subjects at risk of recurrence after a first unprovoked event. To this end, and in line with what was done in the Dulcis study,[14] serial D-dimer assay in the Apidulcis study will be used to stratify higher or lower risks of recurrence in patients with positive or negative D-dimer results. The former will receive extended anticoagulation, whereas the latter will go without anticoagulation or other specific treatment. A crucial difference versus Dulcis is that in the present study low-dose Apixaban (2.5 mg BID) will be used for extended anticoagulant treatment, in line with what was done in the Amplify Extension study,[15] instead of VKAs (at usual INR 2.0-3.0 range) as used in the Dulcis. We expect in this way to have less MB and a similar protection against recurrence in treated patients as that of the Dulcis study. Another important difference versus the Dulcis and Amplify Extension studies is that in the present study patients are eligible only after completion of at least 12 months of standard anticoagulant treatment, compared to at least three months in Dulcis and 6-12 months in Amplify-Extension. We recognize that this is not an inclusion criterion decided by the Steering Committee of the Apidulcis but rather the sole criterion Alliance BMS-Pfizer required for providing the drug for the study. We believe that the main scope for this long anticoagulant treatment course before inclusion is to assure that the included patients will really deserve an extended treatment. In fact, it will be a factor in favor of inclusion of patients at high risk of recurrence, since the treating physicians tend to give lengthier anticoagulation to subjects considered at high risk. While we have accepted this criterion, we believe it may be a factor for delayed inclusion of patients and, potentially, for a final patient population in the Apidulcis study which will present important differences from that included in the Amplify Extension and in the Dulcis studies.

In contrast with Dulcis, but in line with another recent study,[12] patients aged 75 years or more will be excluded from the present study. This exclusion is justified by the high risk of bleeding during anticoagulation for these patients,[19] as well as the fact that the predictive value of D-dimer testing is expected to be lower in elderly patients since D-dimer levels increase with age.[26]

An interim analysis of the study results is pre-defined when 20 primary outcomes (both for efficacy and safety) occur during the study. We have opted for the interim analysis because we want to be sure that new patients will not be enrolled in case the incidence of outcomes would result unacceptably higher in patients with negative D-dimer assay, who remain without anticoagulation, compared to those who will receive low dose Apixaban. In principle, all patients included in the study can technically be considered at high risk of recurrence and therefore would deserve extended anticoagulation.

The study has some limitations. First, it is an investigator-initiated study, with limited financial resources. For this reason, periodic on-site monitoring will not be possible. However, a dedicated remote monitor will assure adequate training of all participant investigators for the study procedures before enrolling the first patient. Moreover, the dedicated monitor will regularly check site compliance to protocol and complete and correct entry into eCRF. Second, though sites are asked to enroll all consecutive patients eligible to the study, we cannot be sure this will happen since some sites are often overwhelmed by routine work, especially in this pandemic period.

CONCLUSIONS

The aim of the prospective, multicenter Apidulcis study is to find out whether it is possible to stratify, for risk of recurrence, patients who have had a single VTE event (proximal DVT of the lower limb and/or PE) unprovoked or associated with WRF, and who have already received at least one year of standard anticoagulant treatment after the event. Stratification is done by performing serial D-dimer assay using local routinely used, quantitative methods and adopting pre-specified cutoff levels different for men and women. Patients with persistently negative D-dimer results (considered at low risk) will go without anticoagulant therapy, whereas patients at first positive result will receive Apixaban 2.5 mg BID. All patients will be followed-up for 18 months.

REFERENCES

1. Pinede L, Ninet J, Duhaut P, et al. Comparison of 3 and 6 months of oral anticoagulant therapy after a first episode of proximal deep vein thrombosis or pulmonary embolism and comparison of 6 and 12 weeks of therapy after isolated calf deep vein thrombosis. Circulation 2001;103:2453-60.

2. Agnelli G, Prandoni P, Santamaria MG, et al. Three months versus one year of oral anticoagulant therapy for idiopathic deep venous thrombosis. N Engl J Med 2001;345:165-9.
3. Couturaud F, Sanchez O, Pernod G, et al. Six Months vs Extended Oral Anticoagulation After a First Episode of Pulmonary Embolism: The PADIS-PE Randomized Clinical Trial. JAMA 2015;314: 31-40.
4. Couturaud F, Pernod G, Presles E, et al. Six months versus two years of oral anticoagulation after a first episode of unprovoked deep-vein thrombosis. The PADIS-DVT randomized clinical trial. Haematologica 2019;104:1493-501.
5. Iorio A, Kearon C, Filippucci E, et al. Risk of recurrence after a first episode of symptomatic venous thromboembolism provoked by a transient risk factor: a systematic review. Arch Intern Med 2010;170:1710-6.
6. Prandoni P, Lensing AWA, Piccioli A, et al. Recurrent venous thromboembolism and bleeding complications during anticoagulant treatment in patients with cancer and venous thrombosis. Blood 2002;100:3484-8.
7. Khan F, Rahman A, Carrier M, et al. Long term risk of symptomatic recurrent venous thromboembolism after discontinuation of anticoagulant treatment for first unprovoked venous thromboembolism event: systematic review and meta-analysis. BMJ 2019;366: l4363.
8. Khan F, Tritschler T, Kimpton M, et al. Long-Term Risk for Major Bleeding During Extended Oral Anticoagulant Therapy for First Unprovoked Venous Thromboembolism: A Systematic Review and Meta-analysis. Ann Intern Med 2021;174:1420-9.
9. Palareti G, Cosmi B, Legnani C, et al. D-dimer testing to determine the duration of anticoagulation therapy. N Engl J Med 2006;355:1780-9.
10. Douketis J, Tosetto A, Marcucci M, et al. Patient-level meta-analysis: effect of measurement timing, threshold, and patient age on ability of D-dimer testing to assess recurrence risk after unprovoked venous thromboembolism. Ann Intern Med 2010;153:523-31.
11. Cosmi B, Legnani C, Tosetto A, et al. Usefulness of repeated D-dimer testing after stopping anticoagulation for a first episode of unprovoked venous thromboembolism: the PROLONG II prospective study. Blood 2010;115: 481-8.
12. Kearon C, Spencer FA, O'Keeffe D, et al. D-dimer testing to select patients with a first unprovoked venous thromboembolism who can stop anticoagulant therapy: a cohort study. Ann Intern Med 2015;162:27-34.
13. Kearon C, Iorio A, Palareti G. Risk of recurrent venous thromboembolism after stopping treatment in cohort studies: recommendation for acceptable rates and standardized reporting. J Thromb Haemost 2010;8:2313-5.
14. Palareti G, Cosmi B, Legnani C, et al. D-dimer to guide the duration of anticoagulation in patients with venous thromboembolism: a management study. Blood 2014;124:196-203.
15. Agnelli G, Buller HR, Cohen A, et al. Apixaban for extended treatment of venous thromboembolism. N Engl J Med 2013;368:699-708.
16. Schulman S, Kearon C. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. J Thromb Haemost 2005;3:692-4.
17. Kaatz S, Ahmad D, Spyropoulos AC, et al. Definition of clinically relevant non-major bleeding in studies of anticoagulants in atrial fibrillation and venous thromboembolic disease in non-surgical patients: communication from the SSC of the ISTH. J Thromb Haemost 2015;13:2119-26.
18. Villalta S BP, Piccioli A, Lensing AWA, et al. Assessment of validity and reproducibility of a clinical scale for the post-thrombotic syndrome. Haemostasis 1994;24:158a.
19. Kearon C, Akl EA, Ornelas J, et al. Antithrombotic Therapy for VTE Disease: CHEST Guideline and Expert Panel Report. Chest 2016;149:315-52.
20. Prandoni P, Cogo A, Bernardi E, et al. A simple ultrasound approach for detection of recurrent proximal-vein thrombosis. Circulation 1993;88:1730-5.
21. Fedullo PF, Tapson VF. The evaluation of suspected pulmonary embolism. N Engl J Med 2003;349:1247-56.
22. Kearon C. Diagnosis of pulmonary embolism. Can Med Assoc J 2003;168:183-94.
23. Shen LZ. Sample size determination for controlling the upper confidence limit of incidence rate of a binomial endpoint. J Biopharm Stat 1998;8:489-96.
24. Albertsen IE, Piazza G, Goldhaber SZ. Let's Stop Dichotomizing Venous Thromboembolism as Provoked or Unprovoked. Circulation 2018;138:2591-3.
25. Prins MH, Lensing AWA, Prandoni P, et al. Risk of recurrent venous thromboembolism according to baseline risk factor profiles. Blood Adv 2018;2:788-96.
26. Tosetto A, Testa S, Martinelli I, et al. External validation of the DASH prediction rule: a retrospective cohort study. J Thromb Haemost 2017;15:1963-70.