Protocol APIDULCIS
Final Version 1.1 in date 16.1.2018

Title of Study:	APIDULCIS: Extended anticoagulation with low-dose apixaban after a standard course anticoagulation in patients with a first venous thromboembolism who have positive D-dimer
Code of Study:	FAA Int1. 7-2017 (APIDULCIS)
Numero EudraCT:	2017-002340-32
Version of Protocol:	Final Version 1.1
Date:	January 16, 2018
Supporter	The study was supported by a grant from Bristol-Myers Squibb (BMS); Alliance BMS-Pfizer kindly provided the drug. All data and results and all intellectual property rights to the data and results derived from the study will be the property of Arianna Anticoagulazione Foundation
Sponsor	Arianna Anticoagulazione Foundation Via Paolo Fabbri 1/3 40138 Bologna (BO) Tel 051 341471 Fax 051 343604 e-mail: segreteria@fondazionearianna.org
Coordinator site	SOD Malattie Aterotrombotiche dell'Azienda Ospedaliero - Universitaria Careggi di Firenze
Principal Investigator:	Dott.ssa Daniela Poli SOD Malattie Aterotrombotiche dell'Azienda Ospedaliero - Universitaria Careggi di Firenze, Largo G. Alessandro Brambilla, 3, 50134 Firenze Tel 0039 055 7945453 Fax 00 39055 7946218 e-mail: daniela.poli.mail@gmail.com e-mail polida@aou-careggi.toscana.it

Title of the study : **APIDULCIS: Extended anticoagulation with low-dose apixaban after a standard course anticoagulation in patients with a first venous thromboembolism who have positive D-dimer**

Sponsor

Prof. Gualtiero Palareti

Presidente Fondazione Arianna

Anticoagulazione

Author of study:
Prof. Gualtiero Palareti
Presidente Fondazione Arianna Anticoagulazione
Tel +39 3282279868
Fax +39 051343604
gualtiero.palareti@unibo.it

Prof. Paolo Prandoni
Dipartimento di Scienze Cardiologiche, Toraciche e Vascolari
UOSD Coagulopatie - Università di Padova
paoloprandoni@tin.it

Contact information

Sponsor	Gualtiero Palareti Fondazione Arianna Anticoagulazione Via Paolo Fabbri 1/3 40138 Bologna (BO) Tel 051 341471 Fax 051343604 gualtiero.palareti@unibo.it segreteria@fondazionearianna.org
Pharmacovigilance	Emilia Antonucci Fondazione Arianna Anticoagulazione Via Paolo Fabbri 1/3 40138 Bologna (BO) Tel 051 341471 Fax 051343604 e.antonucci@fondazionearianna.org

List of abbreviations

ACCP	American College of Chest Physician
AE	Adverse Event
AVK	Antagonisti della Vitamina K
BMI	Body Mass Index
CI	Confidence Interval
CTscan	Computerized Tomography scan
CUS	Compression Ultrasonography
CV	CardioVascolar
DDU	D-Dimer Unit
DOAC	Direct oral anticoagulant
DVT	Deep Vein Thrombosis
DVT ± PE	Deep Vein Thrombosis with or without Polmunary Embolism
eCRF	Elettronic Case Report Form
FEU	Fibrinogen Equivalent Units
GCP	Good Clinical Practice
HR	Hazard Ratio
ICH	International Council for Harmonisation
MI	Miocardial Infarction
NAE	Not Serius Adverse Event
PE	Polmunary Embolism
VTE	Venous ThromboEmbolism
SAE	Serius Adverse Event
sPAP	Systolic Pulmonary Artery pressure
VQ scan	(Pulmonary) Ventilation/ Perfusion scan

Indice

INTRODUCTION

The APIDULCIS is a prospective cohort study which aims at optimizing the long-term and extended management of patients with venous thromboembolism (VTE), including patients at a first episode of proximal deep vein thrombosis (DVT) and/or pulmonary embolism (PE), whose pathogenesis is either unknown (unprovoked VTE) or associated with weak risk factors for thrombosis, with the help of a predefined algorithm.

BACKGROUND

The cumulative incidence of recurrent symptomatic VTE events at 10 years after stopping anticoagulation is approximately 50% after a first unprovoked VTE, and about 20% after a provoked event [1]. These figures are not related to the duration of anticoagulant treatment, the long-term rate of recurrent events after discontinuing anticoagulation being virtually unmodified after 3,6,12 and 24 months of treatment [2].

The latest ACCP international guidelines suggest an indefinite duration of anticoagulation in all patients after an unprovoked event, provided they are at low or moderate risk of bleeding [3]. However, the rate of fatal bleeding while on indefinite treatment is comparable to that of fatal PE in patients in whom anticoagulation is discontinued [4], and the case-fatality rate of major bleeding is higher than that of symptomatic recurrent events [5]. It should also be pointed-out that the ACCP guidelines propose a score to assess the individual bleeding risk which evaluates as at high bleeding risk subjects aged > 75 years. All these evaluations stem from studies in whom vitamin K antagonists (VKA) had been used for the secondary prevention of VTE disorders. Accordingly, most physicians do not accomplish these recommendations [6]. In clinical practice, prolonging indefinitely anticoagulation beyond the first months appears a reasonable choice only in some categories of patients, including those with a personal or familiar history of VTE, those with known major thrombophilic disorders (such as deficiencies in the natural anticoagulants or the antiphospholipid syndrome), those with severe presentations (such as life-threatening PE) and those with a cava filter.

New scenarios have recently been offered by the use of the novel direct oral anticoagulants (DOACs), both for initial and standard anticoagulation course and for extended treatment. In particular for the last clinical scope, low-dose apixaban (2.5 mg BID) [7], aspirin (100 mg OD) [8], and sulodexide (500 mg BID) [9], proved effective (though with different extent) and with better safety results than expected by using VKAs. Indeed, randomized placebo-controlled clinical trials conducted in patients with unprovoked VTE who had received 3-12 months of conventional anticoagulation showed a reduction of the incidence of recurrent events of approximately 80% with low-dose apixaban [7], 35% with aspirin [8] and 50% with sulodexide [9], respectively.

Finally, in the DULCIS management study [10] it was shown that in patients with an unprovoked (or associated with a weak risk factor) symptomatic episode of proximal DVT and/or PE who had received a standard course of anticoagulation with VKA, serial D-dimer measurement in combination with the assessment of residual thrombosis in the deep leg veins is suitable in clinical practice to

distinguish VTE patients who have low recurrence risk (annual rate, 3.0%) and can discontinue anticoagulation from those who have, in contrast, a high risk of recurrence and deserve extended anticoagulation. It was also found that after 12 months of anticoagulation the rate of recurrent events was not different in subjects with or without residual vein thrombosis. In the DULCIS study, however, the rate of major bleeding complications in those who resumed VKA anticoagulation was substantially high (3.7%; 2.3% annually). In addition, the number of patients older than 70 and that of patients with isolated PE was not high enough to yield robust conclusions.
The use of D-dimer assessment after anticoagulation is stopped has also been suggested by the latest ACCP guidelines [3] as a tool to guide deciding on extended anticoagulation or not.

AIM OF THE STUDY

The main aim of this prospective cohort study is to assess the efficacy and safety of a management procedure to decide on giving or not an extended anticoagulation (administering apixaban 2.5 mg BID) to outpatients with a single episode of proximal DVT of the lower limbs and/or PE who had received 12-18 months anticoagulation (whatever the anticoagulant drug used). The study seeks to assess whether a management procedure involving D-dimer testing assessment can identify a subset of subjects at low risk of recurrence in whom an extended anticoagulation can be safely avoided.

STUDY DESIGN

Phase IV, multicenter, national, prospective cohort study

STUDY POPULATION

The study includes outpatients with a single episode of venous thromboembolism (VTE), at a first episode of proximal deep vein thrombosis (DVT) and/or pulmonary embolism (PE), whose pathogenesis is either unknown (unprovoked VTE) or associated with weak risk factors for thrombosis, who had received 12-18 months anticoagulation (whatever the anticoagulant drug used).

SCREENING OF PATIENTS AND INCLUSION/EXCLUSION CRITERIA

Screening and inclusion of patients

All consecutive patients who have experienced a single episode of proximal DVT of the lower limb and/or PE that was unprovoked or associated with a risk factor that was removed (see Table 1), and have completed 12-18 months of anticoagulation (whatever the drug used) will be screened by the participant centers when they are still being treated with anticoagulants and the screening form completed.
Those who do not have any of the exclusion criteria listed in Table 2 will be invited to participate in the APIDULCIS study (DVT- or PE-subgroup study).

INCLUSION CRITERIA

Table 1

Nature of the index VTE events that may be included in the study

- Event that was unprovoked or associated with a risk factor that was removed
- Events that occurred in association with one or more risk factors that are no longer present
- Female and male patients of all ethnicity
- Signature of informed consent
- Age older than 18 or younger than 75 years
- Patients who completed 12-18 months of anticoagulation (whatever the drug used)

EXCLUSION CRITERIA

Table 2

Exclusion criteria regarding the index event

A1) Events usually associated with low risk of recurrence

- DVT/PE occurred within 3 months from major surgery or major trauma
- Isolated Distal DVT (thrombosis of calf veins)

A2) Events associated with a very high risk of recurrence or occurrence of life-threatening recurrent events

- PE episode with shock or life-threatening
- Isolated PE with a systolic pulmonary artery pressure > 60 mmHg at presentation
- DVT/PE associated with active cancer, antiphospholipid syndrome or long-standing medical illnesses
- More than one idiopathic event

- For the patients listed in A2 the risks of recurrence or of seriousness of recurrent events are too high to accept an interruption of anticoagulation, even if temporary. According to the present management protocol these patients should be invited to continue the anticoagulant treatment. Participants in the APIDULCIS study are however recommended to follow-up these patients, taking note of the decision about anticoagulation and of their clinical history during follow-up.

A3) Index VTE events not included in the study

- All VTE events that occurred in different sites than deep veins of the lower limbs or pulmonary arteries

Exclusion criteria present at the moment of patients' screening:

- More documented unprovoked VTE episodes
- Pregnancy or puerperium or planning to become pregnant during the following 18 months
- Severe post-thrombotic syndrome (=> 15 points at the Villalta score)
- Solid neoplasia or blood disease in active phase or requiring chemotherapy/radiotherapy
- All the clinical conditions requiring prolonged treatment with LMWH
- Presence of overt, active chronic diseases (i.e. inflammatory bowel disease)
- Known serious thrombophilic alterations
- Any absolute contraindication to anticoagulant therapy
- Any contraindication to apixaban (as per local SmPC)
- Presence of antiphospolipid syndrome
- Presence of cava filter
- Concomitant conditions (such as atrial fibrillation) requiring indefinite anticoagulation
- Severe cardio-respiratory insufficiency (NYHA 3 or 4)
- Life expectancy shorter than 1 year
- Refuse interruption of anticoagulation to perform serial D-dimer assessment
- Duration of anticoagulant treatment over 18 months
- Geographically inaccessible location
- Inability or refusal to give consent
- Patients already enrolled to other non observational clinical trials

Premature Discontinuation

Study treatment will be permanently stopped if any of the following events occur:

- pregnancy. Women of childbearing potential must perform a pregnancy test in case of delayed menstruation and stop treatment immediately in case of positive result.
- a serious adverse event (SAE) warranting premature termination.
- Withdraw of given informed consent
- Occurence of a condition requiring indefinite anticoagulant treatment
- Occurence of cancer or other conditions requiring Apixaban stopping

Temporary Discontinuation

Study treatment can be temporarily stopped in case of surgery, invasive procedures or non-major but clinically relevant bleeding

STUDY PROCEDURE FOR THE APIDULCIS STUDY

Eligible patients

The APIDULCIS study includes two pre-specified types of patients:
The DVT patients, with proximal DVT, alone or associated with PE)
The PE patients, with isolated PE without any DVT)

Patients are screened for inclusion in the study during anticoagulation and only when they have completed 12-18 months of anticoagulant treatment·

1) CLINICAL INVESTIGATIONS AT SCREENING AND INCLUSION

A. COMPRESSION ULTRASONOGRAPHY (CUS) AND VILLALTA SCORE

DVT-patients

Patients with proximal DVT, alone or associated with PE, who have the inclusion and no one of the exclusion criteria are invited to proceed to the bilateral ultrasound examination of the common femoral vein, superficial femoral vein (at the mid-thigh) and popliteal vein (involving the trifurcation). The diameter of RVT at compression (or no RVT) should be measured and reported in the forms. Patients should also be examined according the Villalta score and excluded from further participation in the study if the score is => 15 points. Whatever the result of CUS, and if the Villalta score is < 15 points, the patients are invited to participate in the APIDULCIS DVT-subgroup study and to sign informed consent. These patients are invited to undergo to the serial D-dimer testing.

Isolated PE-patients

Patients who as index event presented with an isolated PE (not associated to any deep vein leg thrombosis), who have completed 12-18 months anticoagulation, whatever the anticoagulant drug used, and who do not have any of the above listed exclusion criteria, are eligible for inclusion in the PE-subgroup study.

Patients should receive a bilateral proximal CUS at screening; if CUS gives completely negative results (no signs of previous DVT) they are asked to participate in the PE-subgroup study and to sign the informed consent. Those with ultrasound signs of a previous leg DVT cannot be included in the Isolated PE-Subgroup, but can be included in the DVT-Subgroup study.

B. Echocardiography Examination

Patients who had suffered of PE (either isolated or associated with DVT) should receive an echocardiography investigation before deciding the suspension of anticoagulation in order to identify the possible presence of a pulmonary hypertension. Patients with a systolic pulmonary artery pressure (sPAP) above the following cut-off limits (> 35mmHg, or > 40mmHg in elderly or obese patients) are recommended to continue anticoagulation and to undergo to cardiological examination; they are excluded from further progression in the study.

C. **Perfusional Pulmonary Scintigraphy** (not mandatory)

This assessment, if available, will be used to record the possible persistence of residual thrombotic occlusion in pulmonary arteries and verify its relationship with recurrence during follow-up. All patients, however, will undergo to serial D-dimer assay to decide on interruption or extension of anticoagulation independently on presence/absence of residual arterial thrombi.

2) D-DIMER ASSESSMENT

Patients included in both Subgroups of the study are invited to undergo D-dimer measurements. They are informed that:
a) the cut-off value used in the study can be different than the limit values shown in the laboratory reports of the tests;
b) in case D-dimer assay would give a positive result (above the study cut-off value established for the used assay) they would be advised to continue anticoagulation or, if anticoagulation has already been stopped, to resume anticoagulant treatment by assuming in both cases the novel direct oral anticoagulant drug apixaban (Eliquis) 2.5 mg BID, provided by the study, that is associated with a low risk of bleeding, according to the currently available scientific literature. The patients will then receive a serial determination of D-dimer assay (a maximum of four determinations in case of negative results) by using the routinely locally adopted method assay (provided it is one of those listed in Appendix 1).

The D-dimer measurement should be performed at the moment of patient screening, when patients still assume their anticoagulant treatment (T0), and at 15±2 days (T1), 30±4 days (T2), and 60±5 (T3) days after their anticoagulant treatment has been stopped.

Patients with a positive D-dimer assay who may refuse to continue anticoagulation will be followed for the next 18 months.

Patients with positive D-dimer results at T0 (see Appendix 1 for D-dimer cut-off levels according sex) are offered to continue anticoagulant treatment by shifting to receive apixaban (Eliquis) 2.5 mg BID. If they accept to be treated with apixaban they are included in the study and followed-up for 18 months; if they decide to continue their current anticoagulant treatment (different than apixaban 2.5 mg BID) they are excluded from further participation in the study. Patients with negative D-dimer result at T0 are invited to stop assuming their anticoagulant therapy and continue on serial D-dimer measurements. At the first positive D-dimer result in serial testing, they are invited to resume anticoagulation by assuming apixaban (Eliquis) 2.5 mg BID.

Patients with persistently negative results of the four serial D-dimer measurements, are invited to stay definitively without anticoagulation and discouraged from resuming any antithrombotic drug for secondary VTE prevention.

3) RESUMING ANTICOAGULATION: APIXABAN

At the first positive D-dimer results (during anticoagulation or after its temporary withdrawal) the patients are invited to assume Eliquis (apixaban) 2.5 mg twice daily (kindly provided by Alliance BMS-Pfizer), and continue this therapy for the following 18 months. Patients who were treated with

VKA (warfarin) will be invited to stop warfarin for 3 days and then start with apixaban 2,5 mg BID (according to apixaban SmPC). Those patients who are treated with another direct oral anticoagulant will start apixaban treatment at the next scheduled dose.
The choice of giving apixaban at the dose reported above is based on the results of the AMPLIFY-Extension study [7] that enrolled symptomatic DVT or PE patients who had completed 6 to 12 months of anticoagulation therapy and for whom there was clinical equipoise regarding the continuation or cessation of anticoagulation therapy. In that study the included patients were randomized to receive apixaban 5 mg BID or 2.5 mg BID doses, or placebo for the following 12 months. Treatment with apixaban 5 mg BID and that with 2.5 mg BID doses were superior to placebo in prevention of symptomatic, recurrent VTE or death from any cause ($p< 0.001$ for both comparisons). The rate of major bleeding was similar in the three treatment groups at 0.5% (n = 4) with placebo, 0.2% (n = 2) with apixaban 5 mg and 0.1% (n = 1) with apixaban 2.5 mg. In addition, the rate of major or clinically relevant non-major bleeding was 2.7% in the placebo group, 4.3% in the apixaban 5 mg group and 3.2% in the apixaban 2.5 mg group.
Other new direct oral anticoagulants have been investigated for extended treatment in patients with VTE after an initial period of standard anticoagulation. However, dabigatran and rivaroxaban were found to be associated with a higher rate of major and non-major clinically relevant bleeding than placebo.
Based on these data, in the APIDULCIS study it was decided to give apixaban (Eliquis) 2.5 mg BID to patients who deserve resuming anticoagulation according to the management procedure adopted in the study.

Contraindications to use of apixaban (Table 3)

- Hypersensitivity to the active substance or to any of the excipients listed in the RCP of apixaban (section 6.1.)
- Active clinically significant bleeding.
- Hepatic disease associated with coagulopathy and clinically relevant bleeding risk.
- Lesion or condition if considered a significant risk factor for major bleeding. This may include:

✓ current or recent gastrointestinal ulceration, presence of malignant neoplasms at high risk of bleeding, recent brain or spinal injury, recent brain, spinal or ophthalmic surgery, recent intracranial hemorrhage, known or suspected esophageal varices, arteriovenous malformations, vascular aneurysms or major intra-spinal or intracerebral vascular abnormalities;

✓ concomitant treatment with any other anticoagulant agent e.g., unfractionated heparin (UFH), low molecular weight heparins, heparin derivatives (fondaparinux, etc.), oral anticoagulants (warfarin, rivaroxaban, dabigatran, etc.) except under specific circumstances of switching anticoagulant therapy or when UFH is given at doses necessary to maintain an open central venous or arterial catheter.

The patients with one of the absolute contraindications to Eliquis are invited to resume anticoagulation using a different anticoagulant drug.

FOLLOW-UP AND STUDY END-POINTS

All patients included in the study, a) those with persistently negative D-dimer who stopped anticoagulation, b) those with positive D-dimer who continued or resumed anticoagulant treatment by assuming apixaban 2.5 mg BID, and c) those with positive D-dimer who may refuse to assume apixaban as well as any other anticoagulant or antithrombotic agent for secondary VTE prevention, will be followed up for at least 18 months after recruitment in the study. They will be examined or interviewed telephonically every 3-6 months in order to assess their health conditions and to check the occurrence of events. All primary events occurring during the follow-up, including objectively proven recurrent VTE, major or clinically relevant non-major bleedings and deaths from any cause will be objectively documented according to widely accepted guidelines and recorded. All the events will be adjudicated by a central adjudication committee. All the patients are invited to immediately refer to the enrolling center at the appearance of signs or symptoms compatible with venous thromboembolism or other complications (such as bleeding episodes).

Primary efficacy end-point: the composite of confirmed recurrent VTE and VTE-related death occurring during follow-up in all included patients

Primary safety end-point: major bleeding [11] complications occurring during the follow-up period in all included patients

Secondary efficacy end-points: other thromboembolic events, (severe) post-thrombotic syndrome (at the end of follow-up period patients with DVT as index event should receive a final evaluation of the Villalta score),

Secondary safety end-points: clinically relevant non major bleeding complications, overall mortality

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.

STUDY ASSESSMENTS AND PROCEDURES

This study is divided into 2 main periods:

1. Screening: After obtaining written informed consent, all potential patients will complete the screening visit. If fulfilling the eligibility assessments, they will be enrolled. Evaluation of results of D-dimer laboratory results, if the value is positive the patients are invited to continue anticoagulant treatment by assuming Apixban 2,5 mg BID for 18 months. Patients with negative value stop the must anticoagulation and will repeat the D-dimer test 15±2 days later.
   Pregnancy is highly discouraged in these patients and if programmed patients are excluded from the study. If sexually active, be practicing an effective method of birth

control (e.g., intrauterine device, double---barrier method) before entry and throughout the study. A pregnancy test is mandatory before enrollment.

2. Course of the study: Every three-six months, a physical examination or a phone call will be made to assess compliance to treatment, health status and the occurrence of events.

The follow up will be performed until the completion of the study for these kinds of patients:

- those with persistently negative D-dimer who stopped anticoagulation,
- those with positive D-dimer who continued or resumed anticoagulant treatment by assuming apixaban 2.5 mg BID, and
- those with positive D-dimer who may refuse to assume apixaban as well as any other anticoagulant or antithrombotic agent for secondary VTE prevention, will be followed up for at least 18 months after recruitment in the study.
- those who had premature discontinuation.

Procedure	**Screening Visit (T0)**	**D-Dimer test T1, T2, T3**			**Last Visit**	**Notes**
		Patient with negative D-Dimer	**Patient with positive D-Dimer**	**Patient with positive D-Dimer who refuse Apixaban**		
Eligibility Assessments						
Informed Consent	X					
Inclusion/Exclusion Criteria	X					
Medical History	X					
Safety Assessments						
Physical Examination	X				X	
Targeted Physical Examination	X				X	
Vital Signs	X					
Assessment of Signs and Symptoms	X				X	
Compression Ultrasound Doppler (CUS) evaluation	X					
Echocardiography evaluation	X					
Pregnancy test	X					
D-Dimer Test	X	X				
Follow up every 3-6 Months until 18 months		X	X	X		
Clinical Drug Supplies						
Dispense Study Treatment			X			From the first

Procedure	Screening Visit (T0)	D-Dimer test T1, T2, T3			Last Visit	Notes
		Patient with negative D-Dimer	Patient with positive D-Dimer	Patient with positive D-Dimer who refuse Apixaban		
						positive D-Dimer test Apixaban will be dispensed every 6 months
Efficacy End Points						
Primary		X	X	X	X	
Secondary		X	X	X	X	
Safety End Points						
Primary		X	X	X	X	
Secondary		X	X	X	X	

STATISTICAL CONSIDERATIONS

The aim of this management study is to demonstrate that in patients with a first unprovoked VTE a combination of a prediction rule based on D-dimer and low-dose DOAC in those at higher recurrence risk result in a recurrence risk comparable to the population of patients with provoked VTE.

Assumptions
based on the results of the DULCIS study[10], approximately 45% of all eligible patients are expected to discontinue anticoagulation, with an annual rate of recurrent VTE events around 3% (95% 2.0 to 4.4%).
In the remaining 55% of patients who will be encouraged to use apixaban, based on the results of the Amplify Extension study the expected rate of recurrent VTE is around 1.7% after the first year of treatment.
Based on the metanalysis[12] the annual recurrence risk in patients with provoked VTE is 3.3%

Based on these assumptions, we expect the recurrence rate at 12 months to be:

$$0.45*0.03+0.55*0.017=2.2\%$$

Sample size: With an expected annual recurrence rate of 2.2% in the APIDULCIS population, we calculated the sample size to demonstrate, with an 80% power, that the 95% CI is below 3.5% according to Shen [12]. The required sample size is 1148 patients to be recruited for the purpose of the APIDULCIS study.

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 analyses.

Safety end-points and interim analysis

Based on a 2.2% annual event rate, a total sample size around 1150 patients and 18 months of follow-up, we expect around 38 recurrences and 2 major bleeding in our study. Since low-dose apixaban may be considered as the treatment gold-standard at the time of release of the study protocol, we plan an interim analysis when 20 primary endpoints are registered. The study will be interrupted if the relative risk of primary endpoints (HR) in the observational non-treatment arm will be >3 HR, with a p value <0.0001.

PROTOCOL SYNOPSIS

Title:	APIDULCIS: Extended anticoagulation with low-dose apixaban after a standard course anticoagulation in patients with a first venous thromboembolism who have positive D-dimer
Country:	Italy
Number of Sites:	53 centers
Research Hypothesis:	The cumulative incidence of VTE recurrence 10 years after stopping anticoagulation is about 50% and 20% after a first unprovoked and provoked event respectively. It is not related to the duration of anticoagulant treatment. In addition, the rate of fatal bleeding on indefinite treatment is comparable to that of fatal PE in patients with anticoagulation discontinuation, and the case-fatality rate of major bleeding is higher than that of symptomatic recurrent events The latest ACCP international guidelines suggest an indefinite duration of anticoagulation in all patients after an unprovoked event, at low or moderate risk of bleeding. All the available evaluations derive from studies on vitamin K antagonists (VKA) treatment. The use of the novel direct oral anticoagulants (DOACs) offers a valid alternative to vitamin k antagonist and in particular, for the extended treatment, low-dose apixaban (2.5 mg BID) proved effective with better safety results than VKA. The DULCIS management study showed that in VKA patients with an unprovoked (or associated with a weak risk factor) symptomatic episode of proximal DVT, serial D-dimer measurement with the assessment of residual thrombosis allows to detect those VTE patients at low recurrence risk (annual rate, 3.0%) who can discontinue anticoagulation. The latest ACCP guidelines suggest the use of D-dimer assessment after stop anticoagulation to decide the extended treatment.
Study Schema: Drugs / Doses / Length of Treatment)	Apixaban 2.5mg Treatment: 18 months

Study Objectives: Primary: Secondary:	Primary Efficacy end-point: VTE recurrent and VTE-related death Safety end-point: major bleeding Secondary: other thromboembolic events (severe) post-thrombotic syndrome (Villalta score) clinically relevant non major bleeding overall mortality
Study Design:	Phase IV, multicenter, national, prospective cohort study
Accrual Goal: (Total number of subjects)	1,200
Accrual Rate: (Number of subjects expected per month)	Recruitment time: 14-18 months
Inclusion Criteria:	Event that was unprovoked or associated with a risk factor that was removed Events that occurred in association with one or more risk factors that are no longer present Female and male patients of all ethnicity Signature of informed consent Age older than 18 or younger than 75 years Patients who completed 12-18 months of anticoagulation (whatever the drug used)

Exclusion Criteria:	A)Exclusion criteria regarding the index event 1)Events usually associated with low risk of recurrence DVT/PE occurred within 3 months from major surgery or major trauma Isolated Distal DVT (thrombosis of calf veins) 2) Events associated with a very high risk of recurrence or occurrence of life-threatening recurrent events PE episode with shock or life-threatening Isolated PE with a systolic pulmonary artery pressure > 60 mmHg at presentation DVT/PE associated with active cancer, antiphospholipid syndrome or long-standing medical illnesses More than one idiopathic event 3) Index VTE events in different sites than deep veins of the lower limbs or pulmonary arteries B) Exclusion criteria present at the moment of patients' screening: More documented unprovoked VTE episodes Pregnancy or puerperium or planning to become pregnant during the following 18 months Severe post-thrombotic syndrome (=> 15 points at the Villalta score) Solid neoplasia or blood disease in active phase or requiring chemotherapy/radiotherapy All the clinical conditions requiring prolonged treatment with LMWH Presence of overt, active chronic diseases (i.e. inflammatory bowel disease) Known serious thrombophilic alterations Any absolute contraindication to anticoagulant therapy Any contraindication to apixaban (as per local SmPC) Presence of antiphospolipid syndrome Presence of cava filter Concomitant conditions (such as atrial fibrillation) requiring indefinite anticoagulation Severe cardio-respiratory insufficiency (NYHA 3 or 4) Life expectancy shorter than 1 year Refuse interruption of anticoagulation to perform serial D-dimer assessment Duration of anticoagulant treatment over 18 months Geographically inaccessible location Inability or refusal to give consent Patients already enrolled to other non observational clinical trials

Criteria for Evaluation: (Efficacy, safety, stopping rules, etc.)	Criteria for definitions of efficacy and safety endpoints are detailed in Appendix 2; criteria for stopping rules are detailed in the interim analysis.
Statistics:	The aim of this management study is to demonstrate that in patients with a first VTE a combination of a prediction rule based on D-dimer and low-dose DOAC in those at higher recurrence risk result in a recurrence risk comparable to the population of patients with provoked VTE. Based on assumption, we expect the recurrence rate at 12 months to be: 0.45*0.03+0.55*0.017=2.2% Based on the aim of the study, that the rate of recurrence should be comparable, a rate estimate with sufficient precision is only necessary and there is no need to conduct hypothesis testing. The upper limit of the 95% CI can be below 0.035 for around 800 subjects given observed p=0.022. 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 analyses. Safety end-points and interim analysis Based on a 2.2% annual event rate, a total sample size around 1150 patients and 18 months of follow-up, we expect around 38 recurrences and 2 major bleeding in our study. Since low-dose apixaban may be considered as the treatment gold-standard at the time of release of the study protocol, we plan an interim analysis when 20 primary endpoints are registered. The study will be interrupted if the relative risk of primary endpoints (HR) in the observational non-treatment arm will be >3 HR, with a p value <0.0001.

Study Drug/Treatment: Apixaban

Study drugs: Apixaban 2.5 mg

The drugs will be provided by BMS.
The investigated drug is Apixaban 2.5 mg, a film coated tablet. It should be administered orally, every day BID.
The treatment should be performed for all the treatment period. Drug product is to be stored according to labeled storage conditions.

Patients who continue or resume anticoagulation will receive Apixaban 2.5 mg BID for 18 months

SAFETY AND REPORTING

1. *DEFINITIONS*

SERIOUS ADVERSE EVENTS

- A ***Serious Adverse Event (SAE)*** is any untoward medical occurrence that at any dose:
- results in death
- is life-threatening (defined as an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- requires inpatient hospitalization or causes prolongation of existing hospitalization (see **NOTE** below)
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention [eg, medical, surgical] to prevent one of the other serious outcomes listed in the definition above.) Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.)
- Suspected transmission of an infectious agent (eg, pathogenic or nonpathogenic) via the study drug is an SAE.
- Although pregnancy, overdose, potential drug-induced liver injury (DILI), and cancer are not always serious by regulatory definition, these events must be handled as SAEs.
- Any component of a study endpoint that is considered related to study therapy should be reported as an SAE (eg, death is an endpoint, if death occurred due to anaphylaxis, anaphylaxis must be reported).

NOTE: (PI determines if this information regarding hospitalizations are considered SAEs and should be included in the protocol. This is supplemental information that is included in BMS-sponsored trials)

- The following hospitalizations are not considered SAEs in BMS clinical studies:
    - a visit to the emergency room or other hospital department < 24 hours, that does not result in admission (unless considered an important medical or life-threatening event)
    - elective surgery, planned prior to signing consent
    - admissions as per protocol for a planned medical/surgical procedure
    - routine health assessment requiring admission for baseline/trending of health status (eg, routine colonoscopy)
    - Medical/surgical admission other than to remedy ill health and planned prior to entry into the study. Appropriate documentation is required in these cases.

- Admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (eg, lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason).
- Admission for administration of anticancer therapy in the absence of any other SAEs (applies to oncology protocols)

ADVERSE EVENTS

An Adverse Event (AE) is defined as any new untoward medical occurrence or worsening of a preexisting medical condition in a clinical investigation participant administered study drug and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (such as an abnormal laboratory finding), symptom, or disease temporally associated with the use of investigational product, whether or not considered related to the investigational product.
The causal relationship to study drug is determined by a physician and should be used to assess all adverse events (AE). The casual relationship can be one of the following:
Related: There is a reasonable causal relationship between study drug administration and the AE.
Not related: There is not a reasonable causal relationship between study drug administration and the AE.
The term "reasonable causal relationship" means there is evidence to suggest a causal relationship.
Adverse events can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a subject. (In order to prevent reporting bias, subjects should not be questioned regarding the specific occurrence of one or more AEs.)

NONSERIOUS ADVERSE EVENT

- Non-serious Adverse Events (AE) are to be provided to BMS in aggregate via interim or final study reports as specified in the agreement or, if a regulatory requirement [eg, IND US trial] as part of an annual reporting requirement.
- Non-serious AE information should also be collected from the start of a placebo lead-in period or other observational period intended to establish a baseline status for the subjects.

A ***non-serious adverse event*** is an AE not classified as serious.

Laboratory Test Abnormalities

All laboratory test results captured as part of the study should be recorded following institutional procedures. Test results that constitute SAEs should be documented and reported to BMS as such.
The following laboratory abnormalities should be documented and reported appropriately:

- any laboratory test result that is clinically significant or meets the definition of an SAE
- any laboratory abnormality that required the participant to have study drug discontinued or interrupted
- any laboratory abnormality that required the subject to receive specific corrective therapy.

  It is expected that wherever possible, the clinical rather than laboratory term would be used by the reporting investigator (eg, anemia versus low hemoglobin value).

Adverse Events of Special Interest

In this study, the following adverse events are to be reported to BMS, regardless of whether these reports are classified as serious or unexpected.

Potential or suspected cases of liver injury including but not limited to liver test abnormalities, jaundice, hepatitis or cholestasis.

Pregnancy

If, following initiation of the investigational product, it is subsequently discovered that a study participant is pregnant or may have been pregnant at the time of investigational product exposure, including during at least 5 half-lives after product administration, the investigational product will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for participant). The investigator must immediately notify Worldwide.Safety@bms.com of this event via the Pregnancy Surveillance Form in accordance with SAE reporting procedures.
Protocol-required procedures for study discontinuation and follow-up must be performed on the participant.
Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable, offspring information must be reported on the Pregnancy Surveillance Form [provided upon request from BMS]
Any pregnancy that occurs in a female partner of a male study participant should be reported to BMS. Information on this pregnancy will be collected on the Pregnancy Surveillance Form. In order for Sponsor or designee to collect any pregnancy surveillance information from the female partner, the female partner must sign an informed consent form for disclosure of this information.

Overdose

An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. All occurrences of overdose must be reported as an SAE.

Other Safety Considerations

Any significant worsening noted during interim or final physical examinations, electrocardiograms, X-rays, and any other potential safety assessments, whether or not these procedures are required by the protocol, should also be recorded as a non-serious or serious AE, as appropriate, and reported accordingly.

2. *ADVERSE EVENTS REPORTING*

Serious Adverse Events (SAEs) Collecting and Reporting

Following the subject's written consent to participate in the study, all SAEs, whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specified procedures. All SAEs must be collected that occur during the screening period and within

30 days of discontinuing dosing. If applicable, SAEs must be collected that relate to any later protocol-specific procedure (such as follow-up skin biopsy).
The investigator should report any SAE occurring after these time periods that is believed to be related to study drug or protocol-specified procedure.
An SAE report should be completed for any event where doubt exists regarding its status of seriousness.
If the investigator believes that an SAE is not related to study drug, but is potentially related to the conditions of the study (such as withdrawal of previous therapy, or a complication of a study procedure), the relationship should be specified in the narrative section of the SAE Report Form.
SAEs, whether related or unrelated to the study drug, and pregnancies must be reported to BMS within 24 hours. SAEs must be recorded on the CIOMS Form I Pregnancies on a Pregnancy Surveillance Form.

SAE Email Address: Worldwide.Safety@BMS.com
SAE Fax Number: 609-818-3804

If only limited information is initially available, follow-up reports are required. (Note: Follow-up SAE reports should include the same investigator term(s) initially reported.)
If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, a follow-up SAE report should be sent within 24 hours to the BMS (or designee) using the same procedure used for transmitting the initial SAE report.
All SAEs should be followed to resolution or stabilization.

Non-Serious Adverse Events (NSAEs) Collecting and Reporting

The collection of non-serious adverse event (NSAE) information should begin at initiation of study drug. Nonserious adverse event information should also be collected from the start of a placebo lead-in period or other observational period intended to establish a baseline status for the subjects.
Nonserious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious. Follow-up is also required for nonserious AEs that cause interruption or discontinuation of study drug, or those that are present at the end of study treatment as appropriate.
Nonserious Adverse Events are provided to BMS via annual safety reports (if applicable), and interim or final study reports.

SAE Reconciliation

The investigator will reconcile the clinical database SAE cases transmitted to BMS Global Pharmacovigilance (GPV&E). Reconciliation will occur every three months and once just prior to database lock/Final Study Report (FSR). The investigator will request a safety data reconciliation report to **AEPBUSINESSPROCESS@BMS.COM**. BMS GPV&E will e-mail upon request from the investigator, the GPV&E reconciliation report. The data elements listed on the GPV&E safety data reconciliation report will be used for case identification purposes. If the investigator determines a case was not transmitted to BMS GPV&E, the case will be sent immediately.

Note: Although not always adverse events by regulatory definition, the following events associated with a BMS product must be reported:

- Exposure to infant during lactation
- Lack of efficacy

- Abuse
- Misuse
- Off-label use
- Occupational exposure
- Medication error and potential medication error
- Suspected transmission of an infectious agent e.g., any organism, virus or infectious particle pathogenic or nonpathogenic, via the medicinal product

DATA COLLECTION DIRECTLY IN ELECTRONIC CASE REPORT FORM

All sites participating in this study will use e-CRF for all data.
The investigator is warned of any errors detected and can take action immediately. In addition, monitors and data manager(s) can follow the quality of
the data input in real time and perform check of forms on line. Each modification is made by clicking on the item, which generates a change that the investigator validates electronically.

CERTIFICATION OF THE DATA

The data signature can follow immediately after the data input, or after an email request for validation is sent to the center investigator. A formatted version of the data can be submitted to the center investigator for control and validation at any time.

SECURITY

Each individual with access to the eCRF will have a user name and a password associated with a profile that defines user access level (access denied, read-only access, read-write capability) on each function of the application. For example, center investigators have full access to their patients data, not those of the other centers but they can consult them.

STUDY TIMELINES

- Estimated study period for recruitment: 14-18 months
- Study period per patient: maximum duration 18 months
- Estimated total duration of the study: 36 months
- Scheduled first inclusion: September 2017
- Report: 2021

STUDY FEASIBILITY

We expect that at each participating site at least 15 patients/18 months, in average 30/18 months will be enrolled. Thus, with the participation of 35-40 Italian centers we plan to complete enrolment in 18 months. With the last patient in completing the study follow-up in 18 months, study completion is expected in 3 years.

DATA QUALITY CONTROL

The trial will be monitored by the promoter according to the current Standard Operating Procedure for the monitoring of clinical trials. Shortly before the trial starts, the Trial Center Manager will meet with the investigator and all staff involved to review the procedures regarding trial conduct and recording the data into the eCRF system. During the trial, the investigator shall permit the Trial Center Manager to verify the progress of the trial at the center as frequently as necessary. The investigator shall make the electronic data screens available, provide missing or corrected data, and will correct the data in the eCRF system. Personal information will be treated as strictly confidential and will not be made publicly available. The promoter will ensure that appropriate Quality Control (QC) steps are included into the different clinical processes to guarantee adequate protection of the trial subjects and quality of the data. For any data transfer, measures will be undertaken to protect subject data handed over against disclosure to unauthorized third parties and subject confidentiality will be maintained at all times.

ETHICAL CONDUCT OF THE STUDY

The study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and in compliance with national legislation. The study will be conducted in compliance with the protocol and ICH-GCP. The protocol and any amendments and the informed consent form (or information/non-opposition letter, as allowed by local regulations) will have to obtain Institutional Review Board or Ethics committee (IRB/EC) approval prior to initiation of the study. Study personnel involved in this study will be qualified by education, training, and experience to perform their respective task(s).

DIRECT ACCESS TO SOURCE DATA/DOCUMENT

The subjects will be informed in writing that representatives of Fondazione Arianna Anticoagulazione, EC/IRB, or regulatory authorities may inspect their records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws. If the results of the study are published, the subject's identity will remain confidential. The investigator will retain a secure list to enable the patients' records to be identified.

CONFIDENTIALITY

All records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available.
The promoter of the study will provide the measures to safeguard the subject's privacy and the protection of personal data according to the legislative decree 30th June 2003, n. 196.

INFORMED CONSENT FORM

Informed consent will be obtained in accordance with the Declaration of Helsinki, ICH GCP and local regulations. A properly executed, written, informed consent will be obtained from each subject prior to entering the subject into the trial. Information should be given in both oral and written form and

subjects (or their legal representatives) must be given ample opportunity to inquire about details of the study. If appropriate and required by the local IRB/IEC, assent from the subject will also be obtained. If a subject is unable to sign the informed consent form (ICF) a legal representative may sign for the subject. A copy of the signed consent form will be given to the subject or legal representative of the subject and the original will be maintained with the subject's records
Once a patient has been enrolled in the study he/she may withdraw his/her consent to participate in the study at any time without prejudice. Participation in this study is entirely voluntary.

INSTITUTIONAL REVIEW BOARD / INDEPENDENT ETHICS COMMITTEE

Before study initiation, the investigator must have obtained written and dated approval from the Institutional Review Board/ Independent Ethics Committee (IRB/EC) for the protocol, the patient informed consent form (or information/non-opposition document, as allowed by local regulations), subject recruitment materials/process (e.g. advertisements), and any other written information to be provided to subjects. The investigator or promoter should provide the IRB/EC with reports, updates and other information (e.g. amendments) according to regulatory requirements or institution procedures of each country. Protocol amendments, except where necessary to eliminate an immediate hazard to subjects, will be issued by Fondazione Arianna Anticoagulazione. Agreement from the investigator must be obtained for all protocol amendments and amendments to the patient informed consent form (or information/non-opposition document, as allowed by local regulations). The IRB/EC must be informed of all amendments and give written approval, which must be provided to Fondazione Arianna Anticoagulazione.

DATA HANDLING AND RECORD KEEPING

All data and results and all intellectual property rights to the data and results derived from the study will be the property of Fondazione Arianna Anticoagulazione according to D.M. 17 Dicembre 2004. This study is a No Profit Study (D.M. 17 Dicembre 2004, Art. 1, comma 2, lettera c)

ARCHIVING OF DATA

The investigator should arrange for the archiving of the study documentation file and the raw data from the hospital for the longest of the following period of time. At least 7 years after completion/discontinuation of the study. Patient hospital files and other source data should be kept for not less than 7 years.

FINAL REPORT AND PUBLICATION

Upon completion of the trial and in accordance with ICH-GCP, the promoter provides the IRB/IEC with a summary of the trial's outcome, and the regulatory authority(ies) with any reports required. This study will be registered on the site www.clinicaltrials.gov (_____). All data and results and all intellectual property rights to the data and results derived from the study will be the property of Fondazione Arianna Anticoagulazione, who may utilize the data in various ways, such as for submission to government regulatory authorities or disclosure to other investigators. All publication or communication (oral or written) will respect the international requirements: "Uniforms requirements for Manuscripts Submitted to Biomedical Journals".

NO PROFIT STUDY

This study has all the necessary requirements according to the Ministerial Decree of 17 December 2004 (Art.1, subparagraph 1 and 2) for the definition of "clinical trials designed to improve clinical practice as an integral part of health care and not for industrial purposes".

Study Promoter

Name: Fondazione Arianna Anticoagulazione
Address: Via Paolo Fabbri 1⁄3 Bologna (BO)
Phone 051 341471
Fax 051 343604
e-mail: fondazionearianna@anticoagulazione.it

Coordinator Site

SOD Malattie Aterotrombotiche AOU Careggi Firenze

Principal Investigator

Name : Daniela Poli
Address: Viale Morgagni 85 Firenze
Phone: 055-794545
Fax 055-7946218
e-mail polida@aou-careggi.toscana.it

INSURANCE

All subjects participating in the study will be covered by an insurance policy taken out by Fondazione Arianna Anticoagulazione, which is in accordance with applicable laws and/or regulations (D.M. 14 Luglio 2009).

REFERENCES

1. Prandoni P, Noventa F, Ghirarduzzi A, et al. The risk of recurrent venous thromboembolism after discontinuing anticoagulation in patients with acute proximal deep vein thrombosis or pulmonary embolism. A prospective cohort study in 1,626 patients. Haematologica the Hematology Journal 2007; 92: 199-205.
2. Boutitie F, Pinede L, Schulman S, et al. Influence of preceding length of anticoagulant treatment and initial presentation of venous thromboembolism on risk of recurrence after stopping treatment: analysis of individual participants' data from seven trials. BMJ 2011; 342: d3036.
3. Kearon C, Akl EA, Ornelas J, et al. Antithrombotic Therapy for VTE Disease: CHEST Guideline and Expert Panel Report. Chest 2016; 149: 315-52.
4. Douketis JD, Gu CS, Schulman S, et al. The risk for fatal pulmonary embolism after discontinuing anticoagulant therapy for venous thromboembolism. Ann Intern Med 2007; 147: 766-U36.
5. Castellucci LA, Cameron C, Le Gal G, et al. Clinical and safety outcomes associated with treatment of acute venous thromboembolism: a systematic review and meta-analysis. JAMA 2014; 312: 1122-35.
6. Ageno W, Samperiz A, Caballero R, et al. Duration of anticoagulation after venous thromboembolism in real world clinical practice. Thromb Res 2015; 135: 666-72.
7. Agnelli G, Buller HR, Cohen A, et al. Apixaban for extended treatment of venous thromboembolism. N Engl J Med 2013; 368: 699-708.
8. Simes J, Becattini C, Agnelli G, et al. Aspirin for the prevention of recurrent venous thromboembolism: the INSPIRE collaboration. Circulation 2014; 130: 1062-71.
9. Andreozzi GM, Bignamini AA, Davi G, et al. Sulodexide for the Prevention of Recurrent Venous Thromboembolism: The Sulodexide in Secondary Prevention of Recurrent Deep Vein Thrombosis (SURVET) Study: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial. Circulation 2015; 132: 1891-7.
10. 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.
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. 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.
13. 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.
14. 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.
15. 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.

APIDULCIS STUDY

APPENDIX 1

TIMING OF D-DIMER MEASUREMENTS

D-dimer should be measured at the following time points after anticoagulation is stopped.

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

PREDEFINED CUT-OFF LEVELS FOR NEGATIVE/POSITIVE

D-dimer cut-off levels (ng/ml) for males and females (aged 18-75 years)

	Males	Females
Methods with results in FEU		
- VIDAS D-Dimer (bioMerieux)	350 ng/mL	500 ng/mL
- Innovance D-dimer (Siemens)	0.35 mg/L	0.50 mg/L
- Sta Liatest D-Di (Diagnostica Stago)	0.35 µg/mL	0.50 µg/mL
- HemosIL D-Ddimer HS 500 (Werfen)	350 ng/mL	500 ng/mL
- HemosIL D-Dimer HS (Werfen)	350 ng/mL	500 ng/mL
- AcuStar D-Dimer (Werfen)	350 ng/mL	500 ng/mL
Methods with values in DDU		
- HemosIL D-Dimer HS (Werfen)	175 ng/mL	250 ng/mL
- HemosIL D-Dimer (Werfen)	175 ng/mL	250 ng/mL
- Sclavo Auto D-dimer (Dasit)	175 ng/mL	250 ng/mL

APPENDIX 2

OUTCOME DEFINITIONS

VENOUS THROMBOEMBOLISM (VTE)

Pulmonary embolism (PE)

Symptoms of PE with one of the following findings.

- A new intraluminal filling defect in (sub) segmental or more-proximal branches on spiral computed tomography (CT) of the chest.
- A new intraluminal filling defect, or an extension of an existing defect, or a new sudden cutoff of vessels more than 2.5 mm in diameter on the pulmonary angiogram.
- A new perfusion defect of at least 75% of a segment, with a local normal ventilation result (high probability) on ventilation/perfusion lung scintigraphy (VQ scan).
- Inconclusive spiral CT, pulmonary angiography, or VQ scan evidence of a new or recurrent PE, with demonstration of a new or recurrent deep vein thrombosis (DVT) in the lower extremities by compression ultrasound (CUS) or venography.

Proximal deep vein thrombosis (DVT)

Symptoms of DVT with one of the following findings.

(a) For a NEW DVT: abnormal CUS, or an intraluminal filling defect on venography.

(b) For a RECURRENT DVT:

- abnormal CUS where compression had been normal or, if non-compressible during screening, a substantial increase (4 mm or more) in diameter of the thrombus during full compression, or
- an extension of an intraluminal filling defect, or a new intraluminal filling defect, or an extension of non-visualization of veins in the presence of a sudden cut-off on venography.

DEATH

For all patients who died during the study, the cause of death was adjudicated to one of the following categories.

- VTE-related death
  - ✓ PE (based on objective diagnostic testing, autopsy)
  - ✓ Unexplained death (and VTE cannot be ruled out)
  - ✓ Sudden death (and VTE cannot be ruled out).

- Cardiovascular (CV)-related death
  - ✓ Myocardial infarction (MI)
  - ✓ Stroke
  - ✓ Other CV event (to be specified).

- Other
  - ✓ Cancer
  - ✓ Bleeding
  - ✓ Infectious disease
  - ✓ Other known cause (to be specified).

BLEEDING EVENTS

Major bleeding event

A major bleeding event was defined as a bleeding event (as per International Society on Thrombosis and Haemostasis guidelines [11]), as follows.

- Acute clinically overt bleeding accompanied by one or more of the following.
  - ✓ a decrease in hemoglobin of 2 g/dl or more
  - ✓ a transfusion of 2 or more units of packed red blood cells
  - ✓ bleeding that occurs in at least one of the following critical sites: intracranial, intraspinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome, retroperitoneal
  - ✓ fatal bleeding.

Clinically relevant non-major bleeding event

The definition of clinically relevant non-major bleeding (from Kaatz 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: 2119-2126)

Any sign or symptom of hemorrhage (e.g., more bleeding than would be expected for a clinical circumstance,including bleeding found by imaging alone) that does not fit the criteria for the ISTH definition of major bleeding but does meet at least one of the following criteria:
i requiring medical intervention by a healthcare professional
ii leading to hospitalization or increased level of care
iii prompting a face to face (i.e., not just a telephone or electronic communication) evaluation

Minor bleeding events

All acute clinically overt bleeding events not meeting the criteria for either major bleeding or clinically relevant non-major bleeding were classified as minor bleeding.

Fatal bleeding event

A fatal bleeding event was defined as a bleeding event that the adjudication committee determined was the primary cause of death or contributed directly to death.

Flow-chart of the study