Extended duration of vitamin K antagonist during 18 months versus placebo after 6 months of anticoagulation for a first episode of idiopathic pulmonary embolism: a multicenter double-blind randomized trial. « PADIS PE » study.

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**SUMMARY**

**Rational:** after a first episode of idiopathic venous thromboembolism (VTE) treated during 3 to 6 months, the risk of recurrent VTE is elevated (10% to 15% per year) compared to the risk of recurrent VTE if VTE was provoked by a major transient risk factor, such as surgery (3% per year), whether or not the patients had an initial pulmonary embolism (PE) or an initial proximal deep vein thrombosis (DVT). If initial anticoagulation should not be inferior to three months, however, the benefit risk ratio of anticoagulation extended to 6 or 12 months is uncertain as the risk of bleeding also increases under treatment. Scientific society therefore recommends at least 6 months of oral anticoagulant after a first episode of idiopathic VTE. However, these recommendations appears inadequate for the following reasons: (1) no study compared longer duration of anticoagulation (e.g.; 2 years) with 6 months of anticoagulation in order to validate 6 months; and (2), if the frequency of recurrent VTE appears similar after initial PE or initial proximal DVT, however, the case-fatality rate of recurrent VTE after initial PE is about 12% whereas case-fatality rate of recurrent VTE after initial proximal DVT is 5%.

**Objectives:** the main objective is to demonstrate that, after a first episode of symptomatic idiopathic PE treated during 6 months, extended duration of vitamin K antagonist (VKA) during 18 months is associated with a higher benefit risk ratio (recurrent venous thromboembolism and major bleeding) than that observed with placebo. Secondary objectives were: (1) to determine the association between the risk of recurrent VTE after 6 months of VKA therapy and the presence or the absence of lung V/Q scan residual PE and the persistence or not of elevated D-dimer concentrations; and (2), to determine, after the study treatment period of 18 months, the impact of extended duration on the risk of recurrent VTE over an additional period of median follow-up of 2 years.

**Methods:** french multicenter, prospective, double-blind, parallel-arm, placebo-controlled study. Inclusion and exclusion criteria and PE diagnosis criteria are predefined. Patients will be eligible if they had had a first episode of symptomatic idiopathic PE initially treated during 6 months with VKA. At 6 months of initial anticoagulation, patients will have a V/Q lung scan and D-dimer testing; investigators will be unaware of the results. Then patients will be randomized (stratified randomization per center) and allocated to continue VKA therapy during 18 months with a target INR between 2 and 3 or to receive a placebo of VKA monitored with generated “false” INR. Investigators, radiologists and patients will be unaware of the study treatment allocation. The research proposal is presented to the ethic board committee. A written informed consent will be obtained for each patients.

**Expected results and sample size:** the expected cumulative frequency of recurrent VTE or major bleeding at 18 months is 6% in the active group compared to 15% in the placebo group. For a $\alpha$ risk of 5% (risk to falsely conclude to a true difference) and a $\beta$ risk of 20% (risk to falsely conclude to an absence of
difference), and given that about 5% of patients will be lost of follow-up, therefore, a total of 374 patients is required.

**Feasibility:** on average 50 patients with idiopathic PE are hospitalized each year in the department of internal medicine and chest diseases of Brest University Hospital. Four additional Hospital Centre, with a similar recruitment will participate: HEGP (Pr Meyer, Dr Sanchez), Antoine Béclère (Dr Parent), Saint Etienne (Pr Mismetti) and Grenoble (Pr Pison). The Hospital Centre of Tours (Pr Gruel), Rennes (Dr Gueret) and Nantes (Dr Pottier) will include about patients. Thus, the inclusion period of at least 18 months is required in order to include the 374 patients. The study coordination will be performed by the CIC of Brest and a coordination of other CIC will be organized. INR monitoring will be performed by the Clinique des anticoagulants d’Ille-de-France (Dr Cambus).

**Clinical implications:** the first implication is to demonstrate that the benefit risk ratio of extended duration of anticoagulation during 18 months is superior to that observed with placebo in patients who had a first episode of idiopathic PE initially treated during 6 months during but also after the period of randomized study treatment. In addition, this study has the potential to validate or to infirm the role of V/Q lung scan and of D-dimers as predictors of an increased risk of VTE. The impact will be also medico-economic.
1- RATIONAL

Pulmonary embolism (PE) and deep vein thrombosis (DVT) are two clinical manifestations of the same disease: venous thromboembolism (VTE). After a first episode of VTE, the main complications are the risk of recurrent VTE in the absence of anticoagulation and the risk of anticoagulant-related bleeding. (1). Based on the results of large randomized trial comparing different durations of anticoagulation after VTE and two large prospective cohorts, the following observations are of interest:

(1) After stopping anticoagulation that was conducted during 3 to 6 months for a first episode of VTE, the risk of recurrent VTE is low (i.e.; about 3% per year) in patients who had VTE provoked by a major reversible risk factor (i.e.; surgery) whereas this risk is comparatively high (7% to 14% per year) in patients with idiopathic VTE (no apparent clinical risk factor) or in patients with VTE associated with a persistent risk factor (i.e.; cancer) (table 1) (2-9). ;

(2) If the risk of recurrent VTE appears similar after PE or proximal DVT, however, the case-fatality rate of recurrent VTE is 3 to 4 fold higher after PE than after DVT. (10-22).

Based on the first observation, several randomized trials comparing extended duration of anticoagulation (1 to 2 years) versus conventional duration of anticoagulation (i.e.; 3 months) have been performed in patients with a first episode of idiopathic VTE (23-26). If all of these studies shown that 3 months of anticoagulation was inappropriate (high risk of recurrent VTE), conversely, these studies failed to demonstrate an improved benefit risk ratio with longer duration of anticoagulation: in two studies, one year of anticoagulation did not improved the long term risk of recurrent VTE; in one study, patients who have been allocated to receive 2 years of anticoagulation were not followed after stopping study treatment and the risk of major bleeding over an average 10 months of anticoagulation (the study stopped prematurely) was high. Thus, at least 6 months of therapy have
been recommended, mainly based on the DURAC trial conducted by Schulman and coworkers comparing 6 months to 6 weeks of VKA for a first episode VTE and subgroup of patients with idiopathic VTE. (1,4).

However, these guidelines are not satisfying for the following reasons: (1) no study have compared 6 months of anticoagulation with a longer duration (i.e.; 1 or 2 years) of anticoagulation in order to evaluate the benefit risk ratio of these regimens on long-term risk of recurrent VTE and anticoagulant-related bleeding; (2) no study have specifically evaluated extended duration of anticoagulation in patients with a first episode of idiopathic PE although case-fatality rate of recurrent VTE after idiopathic PE is much higher than that after a first episode of proximal DVT; and (3), in all of the available studies, primary outcome was defined by the rate of recurrent VTE, however, given the risk of anticoagulant-related bleeding, a combined criteria encompassing the rate of recurrent VTE and the rate of major bleeding appears more accurate in order to evaluate the strategy (extended duration of anticoagulation or not) that will be most beneficial for the patients and from an individual decision analysis.

**JUSTIFICATION OF ANTICOAGULATION FOR MORE THAN 6 MONTHS**

**Effect of extended duration of anticoagulation with VKA**

The benefit and the risk of extended duration of anticoagulation after a first episode of idiopathic VTE have been evaluated in four studies.

In the double-blind randomized study of Kearon and coworkers, patients initially received 3 months of warfarin for a first episode of idiopathic proximal DVT with or without PE and were then allocated to receive 2 additional years of warfarin (target INR ranged from 2 to 3) or a placebo (23). This study was prematurely discontinued at 10 months of follow-up based on the results of an intermediate analysis that found an unexpected high risk of recurrent VTE (27% per year in the placebo group). If, in this study, a 95% risk reduction of recurrent VTE has been observed on warfarin, in contrast, a high risk of major anticoagulant-related
bleeding (3.8% per year) was also reported. Thus, this study mainly demonstrated that 3 months of anticoagulation for a first episode of idiopathic VTE is too short. However, given this premature discontinuation of this study, it has not been determined if the reported benefit of extended duration of anticoagulation on the risk of recurrent VTE could have been observed for a longer (e.g.; 2 years) or a lower (e.g.; 6 months) duration of anticoagulation than 10 months.

In the open-label randomized trial of Agnelli et collaborators (WODIT-DVT), patients with a first idiopathic DVT idiopathic received also 3 months of warfarin and were then randomized to prolong warfarin therapy during 9 months (target INR from 2 to 3) or to stop warfarin (24). During the study treatment period of 9 months, the risk of recurrent VTE was reduced in the warfarin group compared to the no treatment group (3% versus 8.3%). However, during the period of follow-up (2 years on average) after the study treatment period, the benefit of extended anticoagulation on the risk of recurrent VTE did not persist (16% of recurrent VTE in the two groups). Thus, if 3 months of anticoagulation was too short, a moderate extension of anticoagulation for 9 additional months was not found to influence long-term risk of recurrent VTE. The main limitation was that this randomized study was open and the risk of recurrent VTE in the group with no treatment might have been underestimated.

The same team, has also conducted a study (WODIT-PE) in 326 patients with a first episode of PE, comparing 3 months to 6 months of warfarin therapy when PE was provoked by a provoking risk factor (145 patients) and 3 months to 12 months of warfarin therapy when PE was idiopathic (181 patients) (25). During the 36 months of follow-up after the first 3 months of anticoagulation in patients with idiopathic PE, the risk of recurrent VTE was 4.2% per year in the one year anticoagulation versus 4.6% per year in the 3 months anticoagulation group. The main limitations were the open design and the small sample size of the study.

Similarly to the three studies described above, the study of Ridker and coworkers also focused extending duration of anticoagulation in patients with idiopathic VTE but with a different approach (26). After a first course of warfarin therapy of 6.5 months (target INR 2 to 3) for a first (in one-third of cases) or a
second (in two-third of cases) episode of idiopathic VTE, patients were randomized to prolong indefinitely warfarin therapy with a low intensity (target INR ranged from 1.5 to 2.0) versus placebo. During the 4.3 years of follow-up, the risk reduction of recurrent VTE was 64% in the active treatment group, independently of the presence or the absence of common inherited thrombophilia. In subgroup analysis, the benefit of extended low intensity anticoagulation was mainly observed after a first rather than a second episode of idiopathic VTE. Bleeding complications et deaths were similar in the two arms of the study.

**Justification to continue VKA treatment at conventional dose (INR between 2 and 3)**

In the double-blind randomized placebo-controlled ELATE study, Kearon and coworkers compared long-term warfarin treatment at conventional dose (target INR ranged from 2 to 3) to a long-term warfarin at low dose (target INR ranged from 1.5 to 1.9) in 738 patients with a first (one third) or a second (two-third) episode of idiopathic VTE which has been initially treated by 3 or 6 months of warfarin at conventional dose (27). During a mean duration of study treatment of 2.4 years, the risk of recurrent VTE was higher (OR 2.8 95%CI, 1.1-7.0) and the risk of major bleeding similar in the VKA “INR 2 to 3” group compared to the VKA “INR 1.5 to 1.9” group. These results lower the impact of the study by Ridker and coworkers (69) as its shows that if anticoagulation is prolonged indefinitely because the patient is considered to have a high risk of recurrence, therefore, the optimal target INR is ranged between 2 and 3 rather than an INR ranged from 1.5 to 1.9. However, this study, including a majority of patients who had 2 episodes of previous idiopathic VTE, does not indicate what should be the optimal duration of anticoagulation after a first episode of idiopathic VTE.

Lastly, the benefit and the risk of a high intensity of anticoagulation have been evaluated in a randomized controlled trial including patients who had at least one episode of VTE or an arterial thrombosis in association with a proven antiphospholipid antibody syndrome (28). Over 2.7 years of mean duration of
anticoagulation, the risk of recurrent venous or arterial thrombosis was not statistically different between patients treated with a target INR ranged from 3.1 to 4.0 and patients treated with a target INR ranged from 2.0 to 3.0. Bleeding complications were also similar in both groups. Finally, this study reinforces the observation that a target INR ranged from 2 to 3 is optimal in patients considered at high risk of recurrence and eligible for indefinite anticoagulation. (1).

Synthesis

Based on the results of randomized trials, 3 months of anticoagulation for a first episode of VTE appears too short in order to prevent recurrent VTE whereas the benefit risk ratio of anticoagulation of one year or more remains uncertain. If the treatment should be continued indefinitely, the optimal INR is ranged from 2 to 3. Finally, guidelines are mainly based on the largest randomized trial (DURAC trial study (4)) having shown that 6 months of warfarin therapy was superior to 6 weeks after a first episode of VTE. Thus, a minimum of 6 months are recommended for the treatment of a first episode of idiopathic VTE, although 6 months have not been compared to longer duration of anticoagulation (i.e.; 2 years). In addition, there is no recommendation about factors that might be considered in order to prefer either 6 months or 12 months a first episode of idiopathic PE (1).

JUSTIFICATION OF A STUDY ON PULMONARY EMBOLISM

- Case-fatality rate of recurrent VTE after PE or DVT

If, after PE or proximal DVT, the risk of recurrent VTE is similar, however, the case-fatality rate of the recurrent VTE is highly more severe than that after proximal DVT (4,10,11-13). Indeed, after an episode of PE, the risk of recurrent VTE with the clinical presentation of PE is four-fold increased compared to that after an episode of proximal DVT (12-14): the clinical presentation of recurrent VTE is therefore similar to the first episode in 80% of cases. The case-fatality rate of PE is about 15% (10% of patients died before hospital admission (15-17) and 5% of
patients with diagnosed and treated PE will decease from PE (13,14,18-21) and the case-fatality rate of DVT is 2% or less (38,12,14,18,22). When combining the proportion of recurrent VTE presenting as PE or DVT and the case-fatality rate of each of these complications, the case-fatality rate of recurrent VTE after PE is about 12% whereas after proximal DVT the case-fatality rate of recurrent VTE should not exceed 5%. For this last estimate, a case-fatality rate of recurrent VTE of 5.1% after proximal DVT treated 3 months has been reported in a recent meta-analysis (12). Thus, if extended duration of anticoagulation should and can be demonstrated, it is in first instance in patients with idiopathic PE.

- Risk of bleeding related to VKA

Long term oral anticoagulant, adjusted in order to obtain an INR ranged from 2 to 3, is associated with a very low risk of recurrent VTE (risk closed from 0% in under-treatment analysis) whereas the risk of major bleeding is on average of 3% per year (23,29,30,31); major bleedings are fatal in about 20% of case (annual incidence rate of fatal major bleeding of 0.6% per year) (31). However, the risk of major bleeding differs according to a number of risk factors, such as: age (> 65 years), previous digestive hemorrhage, stroke, alcohol, diabetes, concomitant antiplatelet agents (30-35). The risk of anticoagulant-related bleeding is also higher during the first days of the initiation of anticoagulation and when INR while on oral anticoagulants are unstable (31,32). In addition, the case-fatality rate of major bleeding while on VKA appears to be different according to the design of the studies: if a case-fatality rate of 20% has been reported in most of the prospective cohorts with patients on long term VKA therapy who have a high risk of recurrent VTE or who have atrial fibrillation, however, a meta-analysis combining the results of randomized trials comparing different durations of anticoagulation in VTE patients found a case-fatality rate of 10% (36).

- Estimation of the benefit risk balance of extended duration of anticoagulation after PE or proximal DVT
When comparing the case-fatality rate of recurrent VTE and the case-fatality rate of major bleeding, the frequency of death due to anticoagulation-related to major bleeding is about two-fold higher than the frequency of death related to recurrent VTE after an initial episode of PE and 4-fold higher than the frequency of death related to recurrent VTE after an initial episode of proximal DVT. Therefore, in order to justify extended duration of anticoagulation with VKA in patients with a risk of anticoagulant-related major bleeding of 3% per year, the risk of recurrent VTE per year needs to be at least of 6% per year after an initial PE and of 12% per year after an initial proximal DVT. (23,29-31,37). This analysis supports the hypothesis of a benefit of extended oral anticoagulation after an episode of idiopathic PE. In addition, given the frequency and the case-fatality rate of recurrent VTE and that of major hemorrhage, a composite clinical outcome of these two complications should be used as primary outcome and not only the risk of recurrent VTE.

IMPACT OF OTHER RISK FACTORS OF RECURRENT VTE

In the randomized trials comparing different durations of oral anticoagulant, idiopathic PE was associated with an increased and independent risk of recurrent VTE: excepted cancer (38-41) and major thrombophilia, such as antiphospholipid syndrome (42), the risk of recurrent is elevated whether or not patients have a minor thrombophilia (heterozygous factor V Leiden or heterozygous prothrombin gene mutation), thrombotic sequelae or initial PE or proximal DVT (2,3,4,23).

However, the association between residual vein thrombosis and an increased risk of recurrent VTE remains uncertain. In a prospective cohort including a heterogeneous population of patients with proximal DVT (some patients had cancer or asymptomatic DVT), the persistence of residual DVT after 3 months of oral anticoagulant was associated with an increased risk of recurrent VTE (75% were ipsilateral) (43). In this study, the presence of residual DVT was associated with extensive initial symptomatic DVT and cancer. In another prospective cohort,
the relative risk of recurrent VTE was 2.9 in the presence of residual DVT; however, more than 80% of patients with recurrent VTE had an initial idiopathic DVT or in association with thrombophilia (44). Lastly, the impact of residual PE (either on V/Q scan or on spiral CT scan) has not been evaluated.

D-dimers are the product of the fibrin degradation and might contribute to identify patients with a low risk of recurrent VTE. In two prospective cohorts, low D-dimer concentration, after stopping anticoagulation, was associated with a decreased risk of recurrent VTE (8,45). However, the impact of the duration of anticoagulation (highly variable in these studies) was not evaluated.

**SCIENTIFIC HYPOTHESIS**

In this *superiority* study, we test the hypothesis that extended duration of VKA therapy during 18 months (target INR ranged from 2 to 3) after 6 months of VKA treatment will be associated with a lower risk of cumulative risk of recurrent VTE or major bleeding than 18 months of placebo. This benefit will be directly observed on the rate of recurrent VTE and major bleeding and indirectly on the case-fatality rate of these medical events. This last hypothesis is also plausible as the case-fatality rate of recurrent VTE after a first episode of PE is 3 to 4 fold higher than that after a first episode of proximal DVT.

**2- OBJECTIVES**

**Primary objective**

The primary objective is to demonstrate, after 6 months of vitamin K antagonist (VKA) therapy for a first episode of acute symptomatic idiopathic Pulmonary Embolism (PE), that extended duration of VKA during 18 additional months (target INR ranged from 2 to 3) is associated with a lower cumulative risk of symptomatic recurrent VTE or major bleeding (clinical composite outcome) compared to that with 18 additional months of placebo.
Secondary objectives

- To determine (in the placebo group at 18 months and in the all cohort on the entire study period of a median duration of 42 months) the association between the risk of recurrent VTE and the followings:
  - the presence of residual DVT in the lower limb on leg ultrasound or residual PE in the lung on V/Q scan at the inclusion of patients
  - the persistence of elevated D-dimers performed at the inclusion
  - the presence of acquired or inherited thrombophilia,
  - the presence of a right ventricular dilatation at the time of the diagnostic of PE.

- To determine the impact of extended duration of anticoagulation during 18 months versus 18 months of placebo on the long-term risk of recurrent VTE; this risk will be evaluated during median follow-up of 2 years after stopping the study treatment.

- To determine additional diagnosis criteria of residual thrombosis on ultrasound and residual PE on lung scan.

- To evaluate the risk of recurrent VTE in patients who refused to participate in the PADIS PE study or who did not satisfy eligibility criteria of the study (non-inclusion register).

- To evaluate the medical impact in terms of cost efficacy of the non-invasive testing performed at 6 months of the treatment of a first episode of idiopathic PE.

3- DESIGN

French multicenter, prospective, double-blind, parallel-arm, placebo-controlled trial comparing 18 months of VKA (Warfarin) with a target INR of 2 to 3 versus placebo.
4- POPULATION

Inclusion criteria

- Patients with a first episode of symptomatic idiopathic PE initially treated during 6 months (5.5 to 6.5 months) with VKA with a target INR ranged from 2 to 3.

Exclusion criteria

- Age < 18 years,
- Allergy to warfarin,
- Refusal or incapacity to give a written informed consent to participate to the study,
- Isolated proximal or distal DVT,
- PE provoked by a major reversible risk factor (see definitions)
- Occurrence of a documented recurrent VTE while on VKA in the therapeutic range or an anticoagulant-related bleeding during the first 6 months of anticoagulation,
- Presence of known major thrombophilia (protein C, S or antithrombin deficiency, antiphospholipid antibodies, homozygous factor V Leiden),
- Previous documented PE or proximal DVT,
- Indication of VKA treatment for another reason than VTE (atrial fibrillation, mechanic valves…),
- Patients in whom antiplatelet agents were stopped at the initial phase of PE treatment and for whom antiplatelet agents should be restarted after stopping VKA,
- Present pregnancy or expected pregnancy in the 18 months of the study treatment,
- Childbearing without proper contraceptive measures,
- Major surgery planned the 18 months of the study treatment,
- Active cancer or cancer resolved for less than two years,
• High risk of bleeding (e.g.; active gastric ulcer, recent hemorrhagic cerebral attack) and other contra-indication to VKA,
• Platelets < 100 x 10^9/L
• Life expectancy of less than 18 months (e.g.; patients with an end-stage chronic disease).

Non-inclusion register
All patients who refused or did not satisfy eligibility criteria to participate in the study will be registered in a non-inclusion register; these patients will be followed without any predefined therapeutic intervention (the extension or the discontinuation of the duration of VKA will be decided from an individual basis by the investigators).

5- DEFINITIONS

• Thromboembolic events: PE and/or DVT.

• Idiopathic PE: PE occurring in the absence of major reversible risk factor.

• Major reversible risk factors:
  ➢ Surgery with loco-regional or general anesthesia higher than 30 minutes in the past three months,
  ➢ Trauma or plaster cast of lower limbs in the past three months,
  ➢ Bed-rest for more than 72 hours in the past three months.

• Pretest probability of PE: modified Geneva score (APPENDIX I).

• Proximal DVT: venous thrombus located above the popliteal trifurcation.

• Diagnostic of proximal DVT:
A proximal DVT is diagnosed on the basis of the followings:

- Leg B-mode ultrasound: non-compressibility of a popliteal or a more proximal vein, or
- Phlebography: presence of a constant intraluminal filling defect in a popliteal or more proximal vein.

**Diagnostic of symptomatic PE:**

PE is diagnosed on the basis of a clinical suspicion of acute PE and the followings:

- Ventilation perfusion lung scan (V/Q scan): high probability scan according to PIOPED criteria (at least 2 segmental perfusion defects with a normal ventilation) associated with a high pretest probability, or
- A proximal DVT associated with low or intermediate PIOPED probability on V/Q scan, or
- Spiral CT scan: a constant intraluminal defect of a segmental or more proximal pulmonary artery, or
- Pulmonary angiography: a constant intraluminal filling defect or sudden cut-off of a pulmonary artery > 2.5 mm in diameter.

**6- STUDY FLOW**

- Day 0: admission of patient for inclusion in the study:
  - Admission of patients for a consultation in the clinical research centres of each participating investigator,
  - Verification of inclusion and exclusion criteria,
  - Randomization and study treatment allocation if the patient is included,
  - D-dimers testing,
  - Blood sample in order to store it in a frozen biobank (serum, plasma, DNA),
  - Leg ultrasound
  - Lung V/Q scan,
Echocardiography,

If the patient refuses to participate in the randomized trial or is not eligible, the patient will be proposed for a non-inclusion register. The patient’s care and follow-up are under the physician’s responsibility and is free of any planned intervention.

- Follow-up from Day 0 to 18 months:
  - One visit every three months during the first 6 months and every 6 months during study treatment.
  - INR monitoring and adaptation (see chapter 8)
  - Application of the predefined procedure described in the chapter 10 and 11 in cases of recurrent VTE or major bleeding.
  - In the 2 arms of the study treatment, objectively confirm recurrent VTE and major bleeding complications,
  - Visits every 6 months during 18 months.

- Follow-up from 18 months to 42 months:
  - 2 medical visit (one at 1 year and the other at 2 year after the study treatment period and 2 phone calls between (at an interval of 6 months).

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Follow-up phone call

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§ INR will be performed at least one time per month and after every change in the daily warfarin dose and after every additional concomitant medication.

7- TREATMENTS AND RANDOMIZATION PROCEDURE

- Active treatment Arm 1: continuing an anticoagulant treatment via tablets containing Warfarin at 1 mg, 2 mg and 5 mg (monitoring for an INR 2-3 for an 18-month period).

- Placebo treatment Arm 2: Warfarin placebo treatment via tablets similar to Active arm Warfarin.

  The placebo is manufactured and packaged (similar packaging and labelling as Active treatment) by the Pharmacy Brest University Hospital (Brest CHU). Three doses will be available: 1 mg, 2 mg and 5 mg

  The packaging and labelling of both Active and Placebo tablets are done by Brest CHU pharmacy.

  Patients must note in their diary the precise hour of the night dose, and the precise hour of the morning dose, the night before and the day of the visits, respectively.

Treatment Description

Both Warfarin and Placebo tablets are smashed and put into boluses. Three doses will be available: 1 mg, 2 mg and 5 mg. The boluses will be packaged in jars (jars of 1 mg, jars of 2 mg and jars of 5 mg boluses) for sufficient number of boluses
for 3 months. Given that the average daily dose per patient is 5 mg, each patient will receive a treatment jar of 100 x 1 mg, 200 x 2 mg, and 100 x 5 mg boluses.

Each jar will be labelled with the followings: « PADISEP study », dosage, administration route, number of boluses, study code, patient number and initials, center number, order number, dosage guide, study treatment name (warfarin), principal investigator (Francis Couturaud), expiration date, storing and handling guide, as well as « only for clinical trial use » and « keep out of children’s reach ». Additional information may be added to this label according to local center’s needs.

The packaging and labelling of both Active and Placebo treatments are done by Brest CHU pharmacy. The treatments will be dispatched by CHU Brest to all the study centers’ pharmacies.

All the study treatments will be stored in a safe area and at optimal conditions and will be put at patient’s disposal under the responsibility of the investigator.

Randomization procedure

- Each patient is assigned to an ID number: after inclusion and obtaining patient consent, a patient ID number will be assigned by the investigator in charge who will forward patient’s initials and randomisation number to the collaborating Clinical Investigation Center (CIC).

- Department in charge of Randomization: Brest CIC biostatistician will generate a computerized list of randomization numbers per center. This list will be forwarded to the INR monitor named “Paris Region (île de France) Anticoagulation Clinic” (PRAC) not involved in the patient’s care. Each CIC will receive a list of numbers derived from the randomization list allowing the assignment of an inclusion number
for each patient. The CIC in charge will forward this list to all study centers’ pharmacies.

- **INR performing place**: the INR monitoring will be done at each Center’s (CHU) haemostasis laboratory as well as private city-based laboratories (close by patient’s homes) that will consent to participate in the study. The INR results, as well as the patient ID and name will only be forwarded to PRAC (the patient and the investigator will be blinded to this data). All the INRs performed for balancing the anticoagulation treatment (in the absence of an emergency, severe bleeding, and recurrent thromboembolic events) will be done as many times as needed between Monday and Friday. Whenever there is a need for an INR to be done on a Saturday or Sunday, in order to balance the anticoagulants treatment, the PRAC staff on-call duty will be available to ‘adjust’ the INR according to patient’s randomization number.

**INR adjustment according to randomization number:**

For the placebo arm, a computerized generated random fake list of numbers will be assigned. This software program has been developed by Dr Cambus of the anticoagulants clinic.

PRAC, after the reception of the true INR values, will be in charge of emitting ‘adjusted’ INR according to the patient ID and the patient’s treatment arm. When the patient is assigned to receive the Placebo, the PRAC staff will forward the fake INR number to the investigators. When the patient is assigned to active ‘conventionally dosed’ treatment arm (INR range 2-3), the PRAC staff will forward the ‘true’ INR values to the investigators. In this manner, PRAC staff and the hemostasis laboratory technicians will know the ‘true’ INR values whereas the patient and the investigator in charge will be blinded to this value.

The investigator in charge of the patient will adjust the INR according to the corrected INR value and will schedule the next INR monitoring date.
Active treatment dosage adjustment

The INR will be performed at least once a month, and this along with or in addition to the follow-up visits. Coumadine dosage will be adjusted to maintain an INR of 2-3, i.e. within an optimal risk / benefit therapeutic range. After each change of dosage or initiation or withdrawal of a concomitant treatment, the novel INR dosage needs to be applied and even maintained in the following days until optimal therapeutic range is reached. All the INR values and study treatment dosage changes will be collected and recorded in a specific file (see Appendix VI).

Patients will be informed and educated on the signs of recurrent VTE and hemorrhage by the physician investigator during the Randomization visit. This would be a recall - these patients have been on anticoagulants already since 6 months (Cf appendix 7: the principals of therapeutic education for patients on vitamin K antagonist (VKA). The physician investigator will ensure patient’s treatment knowledge. In other words, all the nutritional and well-being advises will be recalled and patients will be warned about intake of all concomitant treatments without informing their general family physician (GP) or the study investigator. In case of any invasive intervention (dental care, biopsy…), the patients must inform their health care giver of patient’s participation in the study (clinical trial). In this manner, if an intervention is required, the health care giver can contact the study investigator to temporarily cease the VKA.

Unblinding

Unblinding will be done after occurrence of an undesirable event and only if study Active treatment continuation or Placebo continuation is contraindicated for such event, e.g. severe bleeding or occurrence of recurrent VTE according to the ‘study endpoints’, respectively. In other words, the investigator can at any time initiate ‘unblinding’ if he / she believe that is required. Unblinding can be done potentially hen the investigator performs an unchanged INR (i.e. the INR results will not be sent to PRAC to be changed). Final unblinding is done when the study investigator,
according to the anticoagulants clinical outcomes, finds out which treatment arm has been assigned to the patient (‘Active’ vs ‘Placebo’). In such cases, the investigator and the PRAC clinical research associate (CRA) must inform Brest CIC to unblind and thus withdraw the patient from the study.

Emergency Procedures

If the clinical circumstances require the knowledge of ‘true’ INR via physician investigator in charge (e.g. confirmed recurrent VTE or severe bleeding), the latter can at any time obtain this information from PRAC CRA without any explanation nor prior authorization from coordinating center, Brest CHU (i.e. calling PRAC hotline 24h/7). Brest CHU will be informed shortly after.

If additional (unplanned due to a medical emergency) INR are performed, the results will be directly sent by the hemostasis laboratory to the study investigator without going through the PRAC CRA.

A daily permanence will be held in each participating CHU, at the study investigator’s unit:

- Investigators call on duty
- Nursing care phone of investigator’s unit will appear in each participating center as 24hrs/24hrs hotline. The unit nurses will be in charge of contacting the on call investigator physician.

Patients will be given the unit physician investigator’s phone number to reach in case of recurrent thromboembolic event or bleeding.

Finally, all patients leaving on vacation, will be provided with a prescription including the followings:

- Patient is participating in a double-blind randomized trial comparing a long duration oral anticoagulant therapy, i.e. normal intensity (INR range of 2-3), with placebo.
- Phone numbers to Investigator’s unit nursing care,
- Phone number of PRAC

Treatment Contraindications
- Anti-platelet drugs: are not contraindicated. If there is a temporary need to replace them with VKA, then the patients must be withdrawn from the study.
- Non-steroidal anti-inflammatory drugs

8- OUTCOMES

Primary outcome
Cumulative frequency of recurrent symptomatic and objectively proven VTE (fatal and non-fatal) or major bleeding (fatal and non-fatal) during the 18 months of the study treatment. Unexplained sudden death will be considered as fatal PE if death could not be explained by another cause.

Secondary outcomes
Mortality: to determine the frequency and other causes of death in the two arms of the study.

Outcome measurements (46,47)

Diagnostic of recurrent VTE (46)

- Symptomatic recurrent PE: association between a suspicion of PE and:
  - New segmental or larger perfusion defect with normal ventilation on V/Q scan, or
  - New intraluminal filling defect in a segmental or more proximal pulmonary artery or an intraluminal filling defect in a segmental or more proximal pulmonary artery in an area where perfusion was normal in V/Q scan performed at the initial diagnostic of PE
  - A constant intraluminal filling defect or sudden cut-off of a pulmonary artery > 2.5 mm in diameter on pulmonary angiography, or
In cases of non conclusive V/Q scan, CT scan or pulmonary angiography: a new non compressibility of a proximal veins, or PE on autopsy.

- Symptomatic recurrent DVT (47): association of a clinical suspicion of DVT and a non compressibility of a proximal segment of proximal vein that was fully compressible at the diagnostic of PE.

**Definition of recurrent VTE**
- Fatal recurrent VTE: death caused by recurrent VTE assessed on the above criteria or sudden death that was unexplained by another cause.
- Non-fatal recurrent VTE: see above criteria of recurrent PE or recurrent DVT.

**Definition of major bleeding**
- Fatal bleeding,
- Clinical overt bleeding associated with a fall of hemoglobin level of 2 g/dl or more,
- Clinically overt bleeding requiring transfusion of at least 2 units of red cells,
- Bleeding involved in a critical organ: intra-cerebral, medullar, retroperitoneal, pericardic, non-traumatic intra-articular.

9- PREDEFINED INTERACTION AND CONFOUNDING VARIABLES

**Major variable on the primary objective:**
- Randomized study treatment (active warfarin versus placebo).

**Minor variables on the primary and secondary objectives:**
- Demographic data: age, sex, weight,
- Extension and severity of initial PE,
- Association with DVT,
- Presence of right ventricular dilatation (RV/LV > 0.6),
- Presence or not of inherited or acquired thrombophilia,
- Presence or not of residual DVT or residual PE,
- Plasmatic D-dimer concentration,
- Time to therapeutic range (TTR) of INR,
- Concomitant treatments such as antipsychotics.

**Diagnostic criteria of residual DVT (43,44)**

- Persistence of a non fully compressibility of a deep proximal vein that was initially non-compressible in one or the two lower limbs,
- Or (and) presence of a popliteal reflux.

**Diagnostic criteria of residual PE (48)**

- Persistence of perfusion defects on V/Q scan in the segments that were initially involved, or
- Persistence of intraluminal filling defect in segmental or more proximal pulmonary arteries that were initially involved on lung spiral CT scan or pulmonary angiography.

**10- LABORATORY AND IMAGING PROCEDURES**

**Vascular ultrasound exploration of lower limbs**

Via a bi-dimensional ultrasound, using electrodes at 3.5 and 7.5 MHz, exploration of deep vein system can be done bilaterally from inferior vena cava to tibial and fibular veins in longitudinal then transversal segments. This exploration will show the presence or absence of complete vein compression. Thrombosis diagnosis will be done in the absence of complete compression of venous segment with or without endovenous echogenic imaging. The ultrasound results will give an accurate position of the clot, in particular, the superior end of the thrombus: the thrombosis is called ‘distal’ (i.e. under the popliteal trifurcation) or ‘proximal’.
**Ventilation perfusion lung scintigraphy**

A perfusion scintigraphy is done by intravenous injection (IV) of macro-antiplatelets of albumin marked with Technetium $^{99}$. Whereas a ventilation scintigraphy uses an aerosol made with either Technetium or Krypton. Six lung scintigraphies are realised in dorsal decubitus. Results interpretation is done according to PIOPED criteria.

**Spiral CT scan**

A helicoidal tomodensimetry allows obtaining at least a slice per second. Draining the brachial vein by a 18 or 20 G needle catheter, followed by injection of 100 to 140 mL of an iodine contrast agent (> [200mg/mL]) and a flow of 4 to 5 mL/s and a helical acquisition with a maximum 3mm collimation, a 2mm reconstruction interval, a 1.5 to 2 pitch value, allows imaging acquisition of the entire pulmonary arterial tree (system) through a single apnea after deep breath intake.

**D-Dimers**

VIDAS and STAGO D-Dimers, measured at inclusion, will be measured again using frosted blood sample tubes at the end of the study in order to evaluate the role of D-Dimer dose variation in recurrence of thromboembolic risk.

**Sampling**

Biological exams will be conducted in accordance with 26 November 1999 legal framework related to Good Practice of Medical Biology Analyses. All of the samples will be taken between 8 and 10 am, fasting, in a seating position, from the concave interior part of the elbow after applying pressure via a Vacutainer brand pompe. The time of sampling will be recorded. The tubes will be labelled with the inclusion number.

In practice, all of the samples assigned to the Biologic Bank will be performed or sent to (right after the sampling is done in a clinical unit) the Brest
CIC which will ensure the labelling check, packaging and storage under the responsibility of Pr. Emmanuel Oger.

The sampling will include:

- 2 EDTA tubes of 7 mL for DNA extraction. From one of the tubes, the search for genetic mutations of: Factor V (mutation G to A at 1691 nucleotide segment of factor V gene), prothrombin (transition G to A at 20210 nucleotide segment in the 3’ un-transcribed region of the prothrombin), and the thermolabile mutant of the methylene tetrahydrofolate reductase.

The second tube will be forwarded to Brest CIC. After two consecutive centrifuges (at 2500 g during 15 minutes at 15°C room temperature), the separated plasma will will partitioned into ten 500 µl aliquots and stored at – 80°C. Other searches for polymorphisms or mutations will be done according to up to date knowledge progress.

- 3 silicone tubes containing tri-sodium citrate (one to nine blood volume, 5 mL CTAD Vacutainer, total of 15 mL) will be forwarded to Brest CIC. Plasma poor in platelets will be obtained via two consecutive centrifuges (at 2500 g during 15 minutes at 15°C room temperature). The plasma will be partitioned into ten 250 µl aliquots and stored at – 80°C.

- 1 dry tube of 10 mL, kept away from the light, will be forwarded rapidly to Brest CIC. After two consecutive centrifuges (at 2500 g during 15 minutes at 15°C room temperature), the separated plasma will will partitioned into ten 500 µl aliquots and stored at – 80°C.

Overall, 39 mL of blood will be sampled.

All of these samples, assigned for genetic studies, will be preserved in accordance with in vigor law and legislation. The laboratories will guaranty an internal Quality Control (QC). In addition to the standard calibration procedures, two samples ‘controls’ derived from a plasma pool will be placed inside of each dosage series to evaluate intra- and inter series variations. Moreover, a plasma pool will be used for iterative (repeated) dosing every 6 months to assure the
absence of biological bank denaturation under the storing conditions. From this biological bank, the investigators will have the right to use the doses later on. All of the required dosages will be done at the end of the study.

11- MEASURES TO BE TAKEN IN CASE OF RECURRENT VENOUS THROMBOEMBOLIC EVENT

The blinding should be kept for as long as the recurrent thromboembolic event is not confirmed:

- Do not perform an INR until the event suspicion is confirmed,
- The evaluations must be performed urgently,
- A low molecular weight heparin (LMWH) curative dose injection (Tinzaparine if a suspicion of PE, or any other LMWH if a suspicion of DVT) is authorized while awaiting additional explorations results.

All recurrent VTE, whether lethal or not is taken into account as an expected adverse event and should be declared to the study promoter.

A confirmed non-lethal recurrent VTE is characterized as a critical event and consequently, the affected patient should be withdrawn from the study. If the event is lethal, in any case, it will be declared as a severe adverse event. Given the therapeutic consequences, the unblinding should be done in case of confirmed recurrent VTE. The follow-up of the therapeutic care is left at the investigator’s discretion. The following guidelines are indicated for information purposes:

- **Recurrence in the absence of anticoagulant treatment**
  Restart of a LMWH treatment or un-fractioned heparin associated with a VKA.

- **Recurrence under VKA while INR < 2**
  Immediate restart of a LMWH treatment or un-fractioned heparin for at least 5 days and until obtaining an INR = 2 (2 > INR < 3 within 24 hrs)
Recurrence under well-managed VKA therapy
Indication for placement of a Vena Cava filter

12- MEASURES TO BE TAKEN IN CASE OF HAEMORRHAGE VKA

Only severe haemorrhages are characterized as critical events and severe adverse events leading to the patient’s withdrawal from the study as well as unblinding. In case of non-severe haemorrhage, blinding is maintained and the treatment must be carried on.

- Care for non-severe haemorrhage:
  1. Treating the cause of bleeding and continuing trial treatment,
  2. Absence of unblinding,
  3. This guideline is adopted in the standard of care of patients treated with VKA.

- Care for a severe haemorrhage:
  1. Discontinuation of trial anticoagulant treatment,
  2. Blood sampling for INR dose measurements as well as other parameters: coagulation and haemostasis,
  3. Administration of Vit K and / or powder prothrombin sub-cutaneous (PPSB) solvent detergent according to the investigator’s or the physician’s in charge of patient care,
  4. Administration of all therapeutic means necessary for the management of haemorrhage,

All severe or non-severe haemorrhage is regarded as an expected adverse event and should be declared to the study sponsor.

13- CONDITIONS FOR WITHDRAWAL FROM THE STUDY OR CESSATION OF THE TREATMENT
Withdrawal from the study (patients will not be monitored according to study’s visits schedule):
  - Death
  - Patient choice

Treatment cessation without withdrawal from the study (patient’s monitoring will continue according to the study’s visits schedule):
  - Fatal recurrent VTE or unconfirmed recurrent VTE by para-clinical investigations,
  - Fatal or non-fatal severe haemorrhage
  - Pregnancy,
  - Non-elective major surgery:
In case of major surgery, unblinding becomes mandatory, INR doses are needed for the intervention, and the patient is withdrawn from the study. On the other hand, in case of an elective surgery, it will be scheduled after the trial treatment. However, if the intervention is done during the trial treatment, then the trial treatment is ceased four days before the surgery, and a post-operative prophylaxis is given by the surgeon, and according to the surgeon and investigator consensus the trial treatment will be restarted along with LMWH at curative dose for maintaining a 2-3 INR range.

14- SAMPLE SIZE CALCULATION

The sample size was calculated on the following assumptions:

Frequency of recurrent VTE and major bleeding after idiopathic PE
In the presence of VKA:
  - Annual rate of recurrent VTE = 1%
  - Annual rate of major bleeding = 3%
  - > Cumulative risk [recurrent VTE + bleeding] at 18 months = 6%
In the absence of VKA (i.e.; on placebo in the study):
- Annual rate of recurrent VTE = 9%
- Annual rate of major bleeding = 1%
- > Cumulative risk [recurrent VTE + bleeding] at 18 months = 15%

**Case fatality rate of recurrent VTE and major bleeding after idiopathic PE**
- The case-fatality rate of recurrent VTE after PE is 12%; if the frequency of recurrent VTE is 13.5% over 18 months of placebo, therefore, the case-fatality rate of recurrent VTE will be 1.62% over 18 months of placebo.
- The case-fatality rate of major bleeding is 20%; if the frequency of major bleeding is 3% over 18 months of anticoagulation, therefore, the case-fatality rate of major bleeding will be 0.60% over 18 months of anticoagulation.

**Benefit risk over 18 months**
- In the presence of VKA: for a cumulative frequency of 6% of recurrent VTE (2%) and major bleeding (4%), therefore, the cumulative case-fatality rate over 18 months of these events will be 1.04% (0.24% + 0.8%).
- In the absence of VKA: for a cumulative frequency of 15% of recurrent VTE (13.5%) and major bleeding (1.5%), therefore, the cumulative case-fatality rate over 18 months of these events will be 1.92% (1.62% + 0.3%).

→ The cumulative frequency recurrent VTE or major bleeding (defined as a composite criteria) is the primary outcome; it is a surrogate of the case-fatality rate of these events that is known for recurrent VTE and major bleeding. Thus, for an α risk of 5% to falsely conclude to a true difference and for a β risk of 20% to falsely conclude to an absence of difference between the two arms of the study, 178 patients per group are required; as about 5% of patients will be lost of follow-up, thus, a total of 374 patients should be included during a period of 18 months.

**15- STATISTICAL ANALYSIS**
**Descriptive statistics:** calculation of the frequencies and 95% confidence intervals (95%CI) for categorical variables; calculation of means and standard deviations after verification of a normal distribution for continuous variables.

**Analytic statistics:**
- The primary analysis will be performed in “intention to treat”; a secondary analysis in “per protocol” will be then performed.
- Univariate analysis: comparison of the frequencies using a Chi-Square orde Fisher test as appropriate on the primary endpoint; estimation of the Odds Ratio and 95%CI. Determination of confusion and interaction between each predefined variable and the primary outcome. Comparison of means using a T Student Test.
- Multivariate analysis: determination of confusion and interactions of variables of the result of the study.
- Although the sample size has been estimated from a Chi-Square Test, a univariate analysis using a Log Rank test and a multivariate analysis using a proportional Cox Model will be performed.

**Logiciel**: SPSS version 12.0

**Datamanagement**: utilisation statistical team of the Clinical Investigation Center CIC INSERM 0502 of Brest.

**16- AVOIDING BIAS**

The experimental design in a randomized and double-blind fashion will allow to limit diagnostic and intervention biases. Thus, the study treatment (active treatment or placebo) is administered blinded: nor the patient or the investigator is aware of the treatment allocation. The radiologists, physicians who perform ultrasound, and biologists will also not be aware of the study treatment allocation. Diagnostic biases are also limited by the use of predefined diagnostic criteria of PE
at the inclusion and of recurrent VTE that are based on objective, standardized and validated criteria.

17- FEASIBILITY

Approximately 150 to 200 patients per year are referred for PE to the internal medicine and pneumology unit of Brest CHU. Half of these PE are idiopathic, i.e. an average of 75 events per year. The other participating centers (A. Beclère, HEGP, St Etienne, Grenoble) have a similar yearly capacity of 50 to 75 idiopathic PE. Other centers (Tours, Rennes et Nantes) have a yearly inclusion capacity of 30 patients per center. In this manner, an 18 – month inclusion period will be sufficient to include the expected number of patients.

18- ETHICAL ASPECTS

This is a trial with potential direct individual benefit. The group assigned to receive a VKA treatment for an extended duration of 18 months will be at a lower accumulated risk of recurrent VTE and severe bleeding compared with the Placebo group. The latter group has already been treated in accordance with the latest French guidelines. All participating patients will be willing and informed clearly through written documents describing the study objectives, the methodology, the research duration, the expected benefits, the involved constraints and risks. Before any patient participation, an informed written patient consent will be obtained by the investigator. In particular, the patient will be informed that neither the patient, nor the physician IP, nor the refereeing GP will be aware of INR doses. The patient will be free to withdraw from the study whenever he or she desires (appendices II and III).

Ethics Committee and guardianship authorities:
The protocol, the subject information and consent form (Informed Consent) will be put in for “Ouest 5” Ethics Committee (EC) approval (in line with the law of n°2004-806 of 09 August 2004. The announcement of EC approval will be forwarded to the study’s sponsor and appropriate authority.

The sponsor’s approval is required, in case of any substantial modification applied to the protocol by the investigator. Prior to the trial implementation, the sponsor will be in charge of obtaining the EC approval (January 2006 session) and the AFSSAPS (French National Health Agency) authorization within their respective relevant framework. If required, a new subject’s informed consent will be obtained.

The trial will be performed in accordance with the recommendations guiding physicians in biomedical research involving human subjects adopted by the 18th World Medical Assembly (Helsinki, Finland, 1964 and later revisions), the Tri-Council Policy Statement and the ICH Guidelines.

An authorisation request will be sent by the sponsor to the AFSSAPS before the study initiation.

Insurance:

The sponsor will sign up for an insurance policy for the duration of the study to guarantee sponsor’s civil responsibility as well as that of all the physicians involved in the study implementation. This assurance policy will cover also the whole compensation of all the human damages of the subjects or their legal beneficiaries, who underwent the trial, due to the conduct of the study. The policy will not cover other proved causes of damage not attributable to the study conduct or its actors as well as any event after the withdrawal of a subject who had given consent at study’s initiation.

Declaration to CNIL: Official website of French data protection authority
Patient’s anonymity will be kept, patients will have the right to access their personal (e.g. Name, Surname, BOD,…) data and in case of discrepancy to correct these data. This study is within the framework of “Méthodologie de Référence” (MR-001) in accordance to the French regulatory provisions (“article 54 alinéa 5 de la loi n°78-17 du janvier 1978”) modified in regard to computer science, to data security and privacy. This amendment was harmonized through the January 5, 2006 decision. Brest CHRU, the study sponsor, signed a compliance agreement to this “Méthodologie de Référence”.

**Adverse events (AE)**

An AE is any untoward medical occurrence in a patient administered a pharmaceutical product, which may or may not have a causal relationship with the treatment. An AE can be any unfavourable and unintended sign (e.g., including an abnormal laboratory finding), symptom, or disease temporally associated with the use of the study drug, whether or not it is considered to be study drug-related. This includes any newly occurring event or previous condition that has increased in severity or frequency since the first administration of study drug.

**Serious adverse events (SAE)**

An SAE is any AE, occurring at any dose and regardless of causality that:

- Results in death
- Is life-threatening. Life-threatening means that, in the opinion of the Investigator or sponsor, the patient/subject was at immediate risk of death from the reaction as it occurred; i.e., it does not include a reaction which hypothetically might have caused death had it occurred in a more severe form.

- Requires inpatient hospitalization or prolongation of existing hospitalization. Hospitalization admissions and/or surgical operations scheduled to occur during the study period, but planned prior to study entry are not considered AEs if the illness or disease existed before the patient was enrolled in the
trial, provided that it did not deteriorate in an unexpected manner during the trial (e.g., surgery performed earlier than planned). Other study specific exceptions noted below.

- Results in persistent or significant disability/incapacity. Disability is defined as a substantial disruption of a person's ability to conduct normal life functions.
- Is a congenital anomaly/birth defect.

Is an important medical event. An important medical event is an event that may not result in death, be life-threatening, or require hospitalization but may be considered an SAE when, based upon appropriate medical judgment, it may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in the definitions for SAEs.

In the present study, recurrent venous thromboembolism, major bleeding, deaths, pregnancy during the study period and non-planned surgeries will be classified as SAE.

**Unexpected adverse events (UAE)**

An unexpected adverse event is any adverse drug event, the specificity or severity of which is not consistent with the current Investigator Brochure (or Package Insert for marketed products). Also, reports which add significant information on specificity or severity of a known, already documented adverse event constitute unexpected adverse events. For example, an event more specific or more severe than described in the Investigator Brochure would be considered “unexpected”.

**Non-serious adverse events (NSAE)**

The following hospitalizations are not considered SAEs in this clinical trial:

- Admissions per protocol for a planned medical/surgical procedure.
- Routine health assessment requiring admission for baseline/trending of health status (e.g., routine colonoscopy).
- Medical/surgical admission for purpose other than remedying ill health state and was planned prior to entry into the study. Appropriate documentation is required in these cases.
- Admission encountered for another life circumstance that causes no bearing on health status and requires no medical/surgical intervention (e.g., lack of housing, financial inadequacy, care-giver respite, family circumstances, administrative).

Declaration of serious adverse events (SAE)

Adverse event will be recorded during all study duration. In case of unexpected withdrawal from the study, adverse event will be recorded at least 48h after the last treatment administration.

All SAE must imperatively be reporting to the study sponsor as soon as possible and the latest 24 hrs after their occurrence (or as soon as the physician investigator is informed).

The initial reporting can be followed by forwarding other relevant additional information: within 7 days in case of a fatal or life threatening event and within 15 days in all other cases.

All AE, regardless of the cause and effect relationship between them and the trial drug, must be declared by e-CRF.

There is a specific e-CRF page reserved for SAE. As soon as this page is open and filled in, an automatic email will be sent to the Sponsor’s DRCI. The investigator can contact the pharmacovigilance when needed.

Reporting of SAE by the investigator to the sponsor

The investigator is in charge of noting and reporting all AE occurring during the study. Furthermore, regardless of the event occurrence deadline after the end of the study, all SAE that may be due to the research must be declared to the sponsor when there is no other cause and effect accounted for.
The sponsor is subject to regulation (L.209-12 de la Loi n° 88-1138 du 20 décembre 1988) obligations declaring the trial. Sponsor is subject to other obligations such as forwarding of all unexpected SA (effects) of the experimental drug (Coumadin) to the regulatory authorities (AFSSAPS and CPP).

The sponsor must send the DSURS and the summary of the final report at the end of the trial, within the regulatory deadline (within 7 days from initial reporting date and within 15 days for other cases), to the appropriate authorities (AFSSAPS).

**Processing of data and saving (archiving) of data and documents**

*Case Report Form (CRF)*

The CRF should not include other data but those required for publishing. All other data related to the patient and required for his / her follow up will be brought together in his / her medical file. All the protocol required information should be notified in the CRFs. The data should be collected step by step, and be recorded into the CRF accurately. Each missing data should be codified.

This e-CRF will be set up in each of the centers thanks to the web support system for data collection. An instruction manual for using of this device will be provided to the investigators.

*Data recording and processing*

Data recording will be done into a secured electronic system via a web navigator. Filling in the CRF via web support by the investigator allows a rapid remote visualization of the data by the CRA. The investigator is in charge of accuracy, the quality and the relevancy of all collected data. In addition, during data recording, data will be immediately checked for consistency thanks to a consistency control system.
In this manner, the investigator must approve all modifications applied to the e-CRF data. These modifications are subject to a trail audit. An explanation can eventually be added to the commentary.

Data archiving

Documents archiving will be in accordance with the GCP guidelines and the applied in force regulations.

Publishing rules

All actors who have contributed substantially in study design, data collection, data analysis and interpretation, manuscript preparation and critical revising, and in final manuscript version approval, will be affiliated as authors. The sponsor and the PHRC will be acknowledged in the published manuscript.

A summary of the final report made in accordance with the reference plan of the appropriate authority will be send to this authority as well as to the EC within a year after the end of the clinical research, i.e. the last visit means the last followed up subject. The final report of the research will be written in collaboration with the coordinator, the sponsor and the biostatistician of the research trial. A final version should be endorsed by the signature of each of the investigators and be addressed to the sponsor within a brief deadline after the actual end of the research trial.

19- ROLE OF DIFFERRENT COMMITTEES AND CIC

Scientific Committee (Steering Committee)

Role:
• Writing and validation of protocol and the CRFs. Proposal and / or evaluation of additional studies.
• Set up of different committees,
• Scientific decisions in regard to the study progress (discontinuation or extention of the study, sample size increase),
• Validation of statistical analysis, coordination of documenting and reporting of study results,
• Set up of all needed means for sustainable motivation of the centers,
• Set up of collaboration with the responsible parties of other topic -related trials,
• Building professional press relations

Organisation:
The steering committee will be held as often as needed and at least twice per year.

Critical Events Committee (CEC)

The CEC is an independent central adjudication committee (ICAC). The responsibility of the CEC is to review, to adjudicate and to classify the following suspected critical events notified during the study: all fatal and non-fatal recurrent VTE and all fatal and non-fatal haemorrhages for a follow-up of 18-month and 42-month for main objective and secondary objectives respectively. Before statistical analysis, all critical events should have been validated by the CEC. When a critical event occurs, the investigator informs the sponsor and send all necessary documents for the validation of the event by the CEC.

The results validated by CEC will be sent to Brest CIC data management and the Data Safety Monitoring Board (DSMB).
CEC will provide a centralized re-reading of all scintigrapies, (spiral thoracic angioscanners) spiral CT-scan and angiographies by independent physicians of the study. This centralized re-reading is achieved through accessing the CD-recordings of all additional exams data by each center.
CEC will be held for as many times as needed as well as per the Steering Committee.

Data Safety Monitoring Board (DSMB):

Role:
- An independent DSMB will be appointed to monitor the progress of the trial and to ensure that the safety of patients enrolled in the trial is not compromised in any way.
- During the study, the DSMB will receive all DSUR reports. DSMB will advise on the continuation or discontinuation of the study (unexpected study ending, patient inclusion ending, request for intermediate analysis) in accordance with the data provided by the Brest CIC biostatician.

Organisation:
The DSMB will consist of a chairperson with experience in clinical trials (Pr Bergmann), several independent physicians experienced in clinical trials and a statistician.

The first DSMB meeting will take place before the start of the study in order to write and approve DSMB SOP. Then, DSMB will define meeting schedule and needed data.

DSMB will be held after the first 5 validated events, after the first 100 patients included as well as per the study requirements. It can also be held as per the sponsor’s request. Then DSMB will report all written conclusions to the sponsor and the Steering Committee.

CIC
- Providing a nursing service for sampling,
- Providing the CRA for filling in the CRFs, follow-up of the visits schedule, documentation (all required recordings for SAE, non-SAE and critical events declaration)
- Storage and preservation of blood samples (thrombophilia and D-dimers),
- Archiving of the CRFs,
- Providing the consultation and sampling rooms for planned and unplanned visits,
- Retrieving INR doses values from PRAC.

**Brest CIC :**
- Same functions as for other CICs,
- Building of study data management center (thanks to the biostaticians and data managers involved). Brest CIC being the sponsoring CIC, none of the CIC responsible actors (Pr. Oger and Dr. Lacut) can not take part in data base constitution and analysis. The latter function will be under the responsibility of Brest CIC biostatistician who will send the data and all useful results to the DSMB as well as reporting the number of inclusions per center and per month to the Steering Committee.
- Centralizing and storage of all centers' frosted blood samples (D-dimers and thrombophilia),
- Brest CIC will take part in study methodology validation.

**20- CLINICAL IMPLICATION OF THE STUDY**

The first significance of the trial is to show that a 6-month anticoagulant treatment for a first idiopathic PE event is not sufficient in terms of cumulative recurrent thromboembolic risk and severe haemorrhage. Furthermore, to show that in such events, an 18-months VKA therapy leads to more benefits than risks. In other words, the study highlights that total treatment duration of 2 years compared
to a 6-month therapy allows to reduce the risk of recurrent thromboembolic events after stopping anticoagulation.

This study is powerful enough to show that there is a higher risk of recurrent VTE in presence of an event at 6 months, a higher D-dimer and / or in presence or absence of hereditary thrombophilia. The clinical significance is doubled by allowing to identify one or several subgroups of patients at high risk of recurrence and to justify or not to the cost-benefit analysis of performing lower limbs ultrasound, V/Q lung scan as well as thrombophilia screening at month 6 of anticoagulant therapy. In France, there are 400 000 cases of PE diagnosed every year and half of these are idiopathic, i.e. 150 000 to 200 000 patients every year can benefit from the study results.
Table 1:

Annual risk of VTE after stopping anticoagulant therapy according to the presence or the absence of major reversible risk factor:

<table>
<thead>
<tr>
<th>Studies</th>
<th>Size (n)</th>
<th>Recurrent VTE</th>
<th>Relative Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Presence of reversible risk factor</td>
<td>Absence of reversible risk factors</td>
</tr>
<tr>
<td>B.T.S. (2)</td>
<td>712</td>
<td>0,9%</td>
<td>6,9%</td>
</tr>
<tr>
<td>Levine (3)</td>
<td>398</td>
<td>1,9%</td>
<td>14,2%</td>
</tr>
<tr>
<td>Schulman (4)</td>
<td>898</td>
<td>3,4%</td>
<td>9,0%</td>
</tr>
<tr>
<td>Prandoni* (5)</td>
<td>250</td>
<td>2,4%</td>
<td>12,1%</td>
</tr>
<tr>
<td>Pini (6)</td>
<td>187</td>
<td>1,5%</td>
<td>11,1%</td>
</tr>
<tr>
<td>Pinède (7)</td>
<td>720</td>
<td>5,2%</td>
<td>8,9%</td>
</tr>
<tr>
<td>Baglin* (8)</td>
<td>570</td>
<td>2,9%</td>
<td>7,8%</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td><strong>2,9%</strong></td>
<td><strong>9,3%</strong></td>
</tr>
</tbody>
</table>

* Prospective cohort; other studies are randomized trials

** Percentages are weighted on study size
APPENDIX I: Pre-test probability of pulmonary embolism (modified score of Geneva).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Risk factors</strong></td>
<td></td>
</tr>
<tr>
<td>Age &gt; 65 years</td>
<td>+1</td>
</tr>
<tr>
<td>Previous DVT or PE</td>
<td>+3</td>
</tr>
<tr>
<td>Surgery or fracture within one month</td>
<td>+2</td>
</tr>
<tr>
<td>Active malignancy</td>
<td>+2</td>
</tr>
<tr>
<td><strong>Symptoms</strong></td>
<td></td>
</tr>
<tr>
<td>Unilateral lower limb pain</td>
<td>+3</td>
</tr>
<tr>
<td>Hemoptysis</td>
<td>+2</td>
</tr>
<tr>
<td><strong>Clinical signs</strong></td>
<td></td>
</tr>
<tr>
<td>Heart rate</td>
<td></td>
</tr>
<tr>
<td>75 to 94 beats per minute</td>
<td>+3</td>
</tr>
<tr>
<td>≥ 95 beats per minute</td>
<td>+5</td>
</tr>
<tr>
<td>Pain on lower limb deep vein palpation and unilateral edema</td>
<td>+4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Clinical probability</th>
<th>Total No. of points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>0-3</td>
</tr>
<tr>
<td>Intermediate</td>
<td>4-10</td>
</tr>
<tr>
<td>High</td>
<td>≥ 11</td>
</tr>
</tbody>
</table>


APPENDIX II: Information et consentement des patients.

NOTE D’INFORMATION DU PATIENT

TITRE DE L’ÉTUDE:
**BUT DE L’ÉTUDE**

Madame, Monsieur,

Depuis six mois, un traitement anticoagulant en comprimés (traitement qui fluidifie le sang) vous a été prescrit au décours d’un épisode aigu d’embolie pulmonaire (présence d’un caillot dans une artère pulmonaire). Ce caillot est survenu en l’absence de facteur évident (absence d’intervention chirurgicale récente, d’immobilisation stricte pendant plus de trois jours, de traumatisme des membres inférieurs telle une fracture, de cancer).

Des études scientifiques récentes ont démontré que les patients qui présentent une embolie pulmonaire spontanée ont un risque très élevé de récidive d’un caillot dans les veines des jambes ou dans les artères pulmonaires après arrêt d’un traitement anticoagulant d’une durée de trois mois. En revanche, le risque de récidive est extrêmement bien prévenu lorsque la durée de traitement est de plus de trois mois (un an ou plus).

Cependant, lorsque le traitement est prolongé, on observe des saignements graves au niveau du tube digestif, des muscles ou du cerveau, pouvant entraîner une hospitalisation chez environ 3 % des patients par année de traitement. Pour cette raison, les sociétés savantes recommandent de traiter pendant au moins 6 mois un premier épisode de phlébite spontanée. Toutefois, il y a de bonnes raisons de croire que le risque total de récidive d’embolie pulmonaire et de saignement est inférieur lorsque le traitement est poursuivi pour une durée de 18 mois comparé au risque total observé après arrêt du traitement (notamment par la fréquence très élevée des récidives d’embolie pulmonaire). L’étude à laquelle nous vous proposons de participer vise à comparer deux durées de traitement pour déterminer celle qui est la plus avantageuse, c'est-à-dire celle qui vous expose à un risque moindre de survenue d’une complication de votre maladie ou de son traitement.

**DÉROULEMENT DE L’ÉTUDE**

374 patients présentant une embolie pulmonaire sans raison apparente (idiopathique) seront recrutés dans cette étude nationale coordonnée par le groupe de recherche en thrombose de Brest (Groupe d’Etude de la Thrombose de Bretagne Occidentale).
Si vous acceptez de participer, votre prise en charge débutera par un examen clinique complété par un écho doppler veineux des membres inférieurs, une scintigraphie pulmonaire et une échographie cardiaque. Un prélèvement sanguin sera effectué en vue du dosage des D-dimères et en vue de constitution d’une sérothèque, plasmathèque et DNAthèque (ces prélèvements seront congelés à – 80 °C en vue de dosages ultérieurs) qui serviront à approfondir les connaissances de la maladie veineuse thrombo-embolique ultérieurement. Le traitement qui vous sera alloué sera tiré au sort et vous recevrez soit un traitement anticoagulant actif (la warfarine, traitement classiquement donné dans ce type de pathologie) soit un placebo. Le traitement par placebo aura strictement la même couleur, odeur et goût que le traitement actif. Ni vous, ni votre médecin, ne saurez à quel groupe vous appartenez. Une information détaillée vous sera fournie concernant le traitement par Warfarin (règles hygiéno-diététiques, auto-médication autorisée, contraception…). Pendant votre participation à l’étude, vous continuerez d’avoir des prélèvements de sang réguliers (tous les mois), à l’hôpital ou en ville, pour ajuster le dosage de votre traitement anticoagulant et vous rencontrerez l’investigateur (c’est-à-dire le médecin responsable) pour une visite de suivi tous les six mois. Puis ce traitement interrompu, vous serez suivi sur une période de 2 ans à raison d’une consultation ou un contact téléphonique tous les 6 mois pour surveiller qu’il n’y a pas de récidive.

En cas de suspicion de récidive, vous contacterez votre angiologue référent afin qu’il réalise une nouvelle échographie doppler des jambes. En cas de survenue d’hématome ou tout autre saignement, vous devrez contacter votre médecin traitant.

<table>
<thead>
<tr>
<th>Période d’essai</th>
<th>J0</th>
<th>M3</th>
<th>M6</th>
<th>M12</th>
<th>M18</th>
<th>M24</th>
<th>M30</th>
<th>M36</th>
<th>M42</th>
</tr>
</thead>
<tbody>
<tr>
<td>Traitement de l’étude</td>
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<td>*</td>
<td>*</td>
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<tr>
<td>Consentement écrit</td>
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<tr>
<td>Critères inclusion/exclusion</td>
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<tr>
<td>Examen clinique</td>
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<tr>
<td>Doppler MI / scintigraphie V/P</td>
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<tr>
<td>Echographie cardiaque</td>
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<td>INR$</td>
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<td>*</td>
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<tr>
<td>Thrombophilie / D-dimères</td>
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<tr>
<td>Evènements indésirables</td>
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<tr>
<td>Visites de suivi (ex clinique)</td>
<td>*</td>
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<tr>
<td>Contact téléphonique de suivi</td>
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<td>*</td>
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</tbody>
</table>

§ Les INR seront réalisés au minimum une fois par mois et après chaque changement de dose ou introduction ou arrêt d’un traitement concomitant.
RISQUES ET INCONVÉNIENTS

Bien que ce soit peu probable, il est possible que le traitement anticoagulant prolongé de 18 mois soit associé à un risque hémorragique trop important; les responsables de l’étude vérifieront régulièrement l’innocuité du traitement. Si des effets secondaires survenaient (hémorragie, allergie, arthralgies, diarrhée, alopécie…), vous devrez informer votre médecin traitant qui contactera l’investigateur (médecin responsable au Centre d’Investigation Clinique de Brest) si nécessaire.

BÉNÉFICES POTENTIELS

Il est fort probable que le traitement prolongé de 18 mois soit plus avantageux en terme de risque total de récidive d’embolie pulmonaire et de saignements comparé au placebo. Il existe un bénéfice direct pour les patients assignés à ce traitement.

Sur votre demande auprès du coordonnateur de l’étude, vous serez informé en fin d’étude des résultats globaux de cette recherche.

PARTICIPATION À L’ÉTUDE

Votre participation à cette étude est strictement volontaire. Si, au cours de l’étude, des nouvelles informations pouvant affecter la poursuite de votre participation à ce projet de recherche nous parvenaient, vous en seriez immédiatement avisé.

Le refus de participer à cette étude n’impliquera pas de pénalité, de perte de bénéfices ou de réduction de la qualité des soins médicaux que vous recevez. Vous bénéficierez alors de la prise en charge classique de votre maladie et tous les traitements habituels demeureront accessibles et disponibles pour vous.

RETRAIT DE L’ÉTUDE

Vous acceptez librement de participer à cette étude et êtes libre de vous retirer en tout temps. Un tel retrait ne portera aucun préjudice à la qualité des soins que vous recevrez.

FRAIS et COMPENSATION

Les frais induits par cette recherche sont pris en charge par l’étude et aucune indemnisation n’est prévue pour votre participation.
CONFIDENTIALITÉ ET LÉGISLATION

Cette étude a reçu un avis favorable du Comité pour la Protection des Personnes de Brest du 7 mars 2006. Le promoteur de l’étude, le CHU de Brest a souscrit à une assurance spécifique (SHAM n°111650), conformément à la loi du 20 Décembre 1988 relative à la protection des personnes qui se prêtent à la recherche biomédicale.

Dans le cadre de la recherche biomédicale à laquelle le CHU de Brest vous propose de participer, un traitement de vos données personnelles va être mis en œuvre pour permettre d’analyser les résultats de la recherche.

A cette fin, les données médicales vous concernant seront transmises au Promoteur de la recherche. Ces données seront identifiées par un numéro de code et vos initiales. Ces données pourront également, dans des conditions assurant leur confidentialité, être transmises aux Autorités de Santé Françaises. Conformément aux dispositions de la loi relative à l’informatique, aux fichiers et aux libertés, vous disposez d’un droit d’accès et de rectification. Vous disposez également d’un droit d’opposition à la transmission des données couvertes par le secret professionnel susceptibles d’être utilisées dans le cadre de cette recherche et d’être traitées.

Vous pouvez également accéder directement ou par l’intermédiaire d’un médecin de votre choix à l’ensemble de vos données médicales en application des dispositions de l’article L1111-7 du Code de la Santé Publique. Ces droits s’exercent auprès du médecin qui vous suit dans le cadre de la recherche et qui connaît votre identité.

Votre anonymat sera respecté et les résultats de l’étude ne seront utilisés qu’à des fins scientifiques.

INFORMATIONS

Votre médecin ou son représentant seront disponibles pour répondre à toutes les questions qui pourraient survenir en rapport avec le traitement décrit ou le déroulement de l’étude. Si vous avez de telles questions, vous pouvez contacter le Docteur Francis Couturaud au 02 98 34 73 48, Département de médecine interne et pneumologie, ou l’un des investigateurs de l’étude (même numéro de téléphone).

COORDONNEES

Coordinateur de l’étude : Dr Francis Couturaud,
Maître de conférence des universités et praticien hospitalier, EA 3878
Département de Médecine Interne et Pneumologie
CHU La Cavale Blanche, 29609 BREST cedex
Tél : 02 98 34 73 48 ou 02 98 34 78 26 ou 02 98 34 73 53
Fax : 02 98 34 79 44

Promoteur de l’étude : CHU de Brest
Délégation à la Recherche Clinique
CHU Morvan
5, avenue Foch
29200 BREST
Tél : 02 98 22 39 43

Clinique des Anticoagulants d’Ile de France :
Pr Ludovic Drouet
Mme Bal dit Sollier
Hôpital Lariboisière (AP-HP)
Hématologie biologique
2, rue Ambroise Paré
Tél : 01 49 95 85 78
Fax : 01 49 81 90 49
Prolongation d'un traitement par Antivitamine K (AVK) pendant dix-huit mois versus placebo au décours d'un premier épisode d'embolie pulmonaire idiopathique traité six mois: un essai randomisé multicentrique en double aveugle

Essai « PADIS-EP »

FORMULAIRE DE CONSENTEMENT DU PATIENT

De M………………………………………………………………………………..(nom, prénom)
Adresse…………………………………………………………………………………………………………
…………………………………………………………………………………………………………
Le Docteur…………………………………….m'a proposé de participer à une coordonnée par le CHU de Brest, promoteur de l'étude, sur le traitement des embolies pulmonaires.
L'objectif de cette étude est de démontrer, après 6 mois de traitement anticoagulant, que le risque total de récidive d'embolie pulmonaire et de saignement est inférieur lorsque ce traitement est prolongé pendant 18 mois comparé au risque total observé après arrêt du traitement anticoagulant.
On m'a informé adéquatement au sujet des objectifs, du déroulement et des risques impliqués par cette étude. J'ai eu la possibilité d'obtenir toutes les informations, ainsi que la possibilité de poser toutes les questions nécessaires à ma compréhension. J'ai eu un délai de réflexion suffisant.
J'accepte de participer à cette étude dans les conditions précisées ci-dessus. Mon consentement ne décharge pas les organisateurs de la recherche de leurs responsabilités.
Je conserve tous mes droits garantis par la loi.
Si je le désire, je serai libre à tout moment d'arrêter ma participation. J'en informerai alors le Docteur………………………………..
J'accepte que les données enregistrées à l'occasion de cette recherche comportant des données notamment génétiques puissent faire l'objet d'un traitement informatisé par le promoteur ou pour son compte. J'ai bien noté que le droit d'accès prévu par la loi du 6 janvier 1978 relative à l'informatique, aux fichiers et aux libertés (article 39) s'exerce à tout moment auprès du médecin qui me suit dans le cadre de la recherche et qui connaît mon identité. Je pourrai exercer mon droit de rectification et d'opposition auprès de ce même médecin qui contactera le promoteur de la recherche.
Je pourrai à tout moment demander toute information complémentaire au
Docteur…………………………………..
Département de Médecine Interne et Pneumologie
Hôpital Cavale Blanche
Bd Tanguy
29609 Brest Cedex
Tél : 02 98 34 73 48

Fait à Brest, le ……………………
Signature de l'investigateur    Signature du patient

Un exemplaire cosigné pour le patient, un exemplaire cosigné pour l'investigateur.
APPENDIX III : Information aux médecins traitants et laboratoires de ville.

Prolongation d’un traitement par Antivitamine K (AVK) pendant dix-huit mois versus placebo au décours d’un premier épisode d’embolie pulmonaire idiopathique traité six mois: un essai randomisé multicentrique en double aveugle

Essai « PADIS-EP »

OBJET : lettre d’information adressée aux médecins traitants des patients ayant consenti, par écrit, à participer à l’étude « PADIS-EP ».

Madame, Monsieur,


BRÈVE DESCRIPTION DE LA PROBLÉMATIQUE

Les complications majeures de la maladie thrombo-embolique veineuse sont le risque de récidive thrombo-embolique en l’absence de traitement anticoagulant et le risque de saignement induit par le traitement anticoagulant.

Chez les patients ayant eu un épisode d’embolie pulmonaire idiopathique (c’est à dire survenant en l’absence de facteur de risque apparent tel une intervention chirurgicale récente, une immobilisation prolongée, un traumatisme ou un cancer), le risque de récidive thrombo-embolique est élevé (environ 10 à 20% par an) après arrêt d’un traitement anticoagulant oral d’une durée de trois mois. L’allongement de la durée (1 an ou plus) du traitement anticoagulant administré par voie orale (antivitamine K) chez ces patients réduit ce risque à 0% par an tant que les patients poursuivent leur traitement par antivitamine K. En revanche, le risque de saignement massif est approximativement de 3% par an sous traitement anticoagulant. Pour cette raison, les sociétés savantes recommandent 6 mois minimum de traitement anticoagulant. Toutefois, aucun essai n’a comparé 6 mois à un traitement allongé (1 an ou plus). Compte-tenu de la fréquence mais aussi de la létalité d’une récidive thrombo-embolique au décours d’une embolie pulmonaire (létalité de 12% après une embolie pulmonaire comparée à 5% après une phlébite), il est fort probable que la balance bénéfice risque d’un traitement anticoagulant prolongé de 18 mois après 6 mois initiaux soit supérieure à celle observée sous placebo de 18 mois (après 6 mois initiaux de traitement actif).

MODALITÉS DE L’ÉTUDE

Il s’agit d’une étude randomisée contrôlée dans laquelle les patients ayant été traités pendant 6 mois pour un premier épisode d’embolie pulmonaire idiopathique, recevront soit un traitement anticoagulant (warfarine) avec un INR entre 2 et 3, soit un placebo de warfarine.
(qui sera adapté sur des INR « factices » générés par ordinateur). Les patients seront traités pendant 18 mois. Une visite au CHU aura lieu les 1, 3, 6, 12, 18, 24, 30, 36 et 42ème mois. Les patients recevront un antivitamine K appelé Warfarine. Ce produit sera délivré par la pharmacie centrale du CHU de Brest.

Les INR seront réalisés au laboratoire d’hémostase du CHU où le patient a été inclus ou dans le laboratoire libéral de son choix. Le résultat sera transmis à la Clinique des anticoagulants d’Ile de France où l’INR sera « modifié » en fonction du résultat de la randomisation : si les patients reçoivent un traitement anticoagulant d’intensité conventionnelle (INR 2,0 – 3,0), alors l’INR sera transmis au médecin investigateur sans être modifié (il s’agit du « vrai » INR) ; si les patients reçoivent un placebo, alors un INR « factice » sera envoyé à l’investigateur responsable. Ni le patient, ni le médecin investigateur et ni vous ne seront au courant du vrai INR. Seul la Clinique des anticoagulants d’Ile de France sera au courant du vrai INR.

Bien sûr, en cas de suspicion de récidive thrombo-embolique ou de saignement grave, il sera possible de connaître le véritable INR auprès de la Clinique des anticoagulants et des laboratoires ; un dosage de l’INR pourra même être effectué afin de connaître le « vrai » INR dans un laboratoire en ville ou aux urgences; le principe de double-aveugle sera alors levé. Dès lors, il est aussi possible de connaître la valeur des INR antérieurs. Dans tous ces cas de figure, il serait souhaitable d’alérer un médecin investigateur responsable ; en conséquence, une liste d’astreinte sera composée de telle manière qu’un des investigateurs puisse être contacté 24 heures sur 24 dans le cadre du protocole. Les patients seront munis d’une ordonnance qui mentionne qu’ils participent à ce protocole ; les numéros de téléphone nécessaires y seront inscrits.

La participation définitive de votre patient dans cette étude comprend, outre les critères d’éligibilité requis, le consentement écrit du patient ainsi que votre consentement oral. Pour le bon déroulement de l’étude et dans l’intérêt de votre patient, je suis à votre entière disposition pour toute information complémentaire.

Bien confraternellement,

Pour l’ensemble des investigateurs, Dr Francis Couturaud, coordinateur de l’étude PADIS-PE à Brest.

Nom et Prénom du patient inclus : __________________________________________

Nom et Prénom du médecin investigateur : __________________________________________

Tél :

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Hématoargie biologique
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Tél : 01 49 95 85 70
Fax : 01 49 81 90 49

APPENDIX IV: circuit de l’adaptation de l’INR
If INR > 5:

- The laboratory which did INR measure should contact by phone the PRAC INR monitor;
- then PRAC INR monitor by phone the research nurse or the investigator of the center once INR has been received by the laboratory.
APPENDIX : emergency procedure
Patient

INR testing

Emerge

CIC

Laboratory of haemostasis in CHU
Sending true result

Laboratory of haemostasis in town
Sending true result

The investigator:
Makes appropriate treatment of patient

PRAC INR monitor
To give previous true
Blinding broken if required

Blinding not systematically broken

Promotor

CIC, URC or investigator
To inform of critical event or serious adverse event

Safety Committee

Critical Event Committee

Steering Committee

Pharmacology-safety Unit
BREST

CIC INSERM 0502
BREST

59
## Protocol : PADIS PE

Nº Study: |2|
Nº Centre: |__|__|
INITIALS PATIENTS |___|___|
NUMERO PATIENT |___|___|

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What you should know

1- What is a VKA drug?

A VKA is an anticoagulant medication, i.e. a drug that slows down blood coagulation. It works by inhibiting the vit K activity which promotes blood coagulation, i.e. “vitamin K antagonist”.

Administration route is oral, normally for a long period of time (several weeks, several months, even lifelong for some patients).

It becomes effective gradually in 2 to 4 days and disappears gradually in a few days after treatment discontinuation.

2- When does one prescribe Vitamin K antagonist?

VKA is prescribed to prevent the formation or evolution or recurrence of a “thrombosis” or a “PE”. A thrombosis is the reaction of blood network in the veins or the heart to the formation of a blood clot or ‘thrombus’. An embolism is due to the splitting off of a clot away from its initial position through the blood network to a remote vein, especially at the lungs.

The indications for VKA prescriptions are:
- phlebitis (clot inside of a vein) or phlebitis risk,
- pulmonary embolism (PE) or PE risk,
- certain cardiovascular disorders (atrial fibrillation),
- abnormal or artificial cardiac valves,
- certain myocardial infarctions

It can also be prescribed in prevention of clot formation inside of a catheter.

3- What are the risks of a VKA treatment?

VKA intake by a patient consist of two major risks: hemorrhage due to overdose, thrombosis due to underdose.
It is therefore essential to closely monitor your treatment (i.e. be in strict compliance) for the right dose intake.

4- Why should you monitor your treatment?

Right at VKA onset, the appropriate dose for each patient needs to be found, i.e. VKA doesn’t promote the same anticoagulation effect (i.e. slowing down clot formation) in all patients.

Then, a routine monitoring during treatment period is mandatory to prevent an overdose leading to hemorrhage risk and underdose leading to thrombosis risk.

This monitoring goes through an INR check.

5- What does an INR stand for?

INR denotes International Normalized Ratio, a lab test done on a blood sample.

INR allows assessment of VKA treatment activity. It measures coagulation time of a patient and compares it to that of a control not being treated with VKA. In the latter, INR dose is equal to 1. In a VKA treated patient, the more liquid or fluid the blood, the longer the coagulation time is and the higher INR value is (> 2). It is advised (according to the guidelines) to always measure the INR in the same laboratory. Target INR is defined as the assessment of INR dose for an optimal and balanced treatment (absence of hemorrhage and thrombosis risk).

What should be monitored?

6- What doses of INR are searched for: “target” INR?

In a patient treated with VKA, INR is adapted for each individual case. "Target" INR depends on the treated pathology.

In most cases, INR should be between 2 and 3 (i.e. consistent with a coagulation time 2-3 times longer compared to that of a VKA non-treated control).

- INR < 2 means not a sufficient dose,
- INR > 3 means a too high of a dose, with a potential hemorrhage risk.

In the above case, you should contact your referring physician.

In some specific cases to achieve an efficient treatment, a high INR dose of 3 to 4.5 may be required.

In all cases, an INR > 5 is associated with an increased risk of hemorrhage.

A well balanced / dosed INR is defined as a consistent INR retrieved after several consecutive monitoring of the same dose.

7- When should you monitor your INR?

At the onset of the treatment, INR should be monitored as frequently as possible to find the right dose of VKA allowing to obtain « target » INR after several consecutive tries.

As soon as the right and appropriate dose has been achieved, INR monitoring can be reduced gradually, yet is to be done at least once a month.

Under certain circumstances, treatment imbalance may be provoked either by an increase or decrease in treatment efficiency. These circumstances, most likely provoked by other concomitant medication intake require additional INR monitoring and dose adjustment.
8- Under what circumstances should you suspect a hemorrhage?

A hemorrhage (even if the suspicion is of a minor bleeding) should be suspected under the following circumstances:

- bleeding gums,
- bleeding nose,
- Red eyes syndrome, i.e. conjunctival hemorrhage of the eye,
- Blood presence in the urine,
- Abnormally heavy menstrual flow,
- Appearance of hematomas (“bruises”),
- Presence of redish blood in the stools, or dark-colored stools, i.e. presence of digested blood,
- Vomiting or bloody sputum,
- Wound non-stop bleeding,
- Signs of a suspicion of internal bleeding,
- Unusual fatigue,
- Abnormal breathlessness,
- Unusual pale skin,
- Head-ache not relieved by usual treatment,
- Unexplained faintness,

In case of a suspicion of hemorrhage, you should immediately contact your refereeing physician.

What to do and not to do?

9- Could you take other medication concomitant with VKA?

It’s dangerous to take other medications than what has been prescribed by your physician, several class of medications can alter VKA activity either by increasing or decreasing VKA effect (i.e. overdose, leads to hemorrhage risk; underdose, leads to thrombosis risk).

The rule of thumb is to never take other un-prescribed medications. You should not self-medicate yourself even with the over the counter (OTC) drugs such as ASA.

This rule should be applied in all circumstances even under most ordinary ones such as in case of pain, rheumatism or infection requiring medical consultation of your referral physician.

10- Should you inform and tell your health care provider that you take VKA?

Yes, in order to prevent all risk of hemorrhage, you should tell your health care provider that you take VKA:

Physician, surgeon, anesthesiast, dentist, midwife, physiotherapist, nurse, biologist…

Wear or carry information that you take VKA.

11- What to do if you miss taking your VKA dose?
Take the missed dose as soon as possible within 8 hours from the regular daily intake time on the same day (i.e. after this delay, just skip this dose). Do not take a double dose the next day to make up for the missed one (Hemorrhage risk). Only take your daily dose the next day.

Examples: if you are used to taking your dose at 8 pm, in case of missing it, you will have until your bedtime to take the dose. Do not take your 8 pm missed dose later than 8 hours past 8 pm.

If you are used to take your VKA dose at 4 pm, in case of missing it, (4 pm + 8 = 12 midnight), you can take the dose until midnight. Otherwise, please skip this dose and wait until the next day to only take your daily dose once.

In order to avoid missing daily doses, please try using a weekly pill box. Please do inform your physician in case of missed dose. Record any missed doses in your VKA intake diary and tell your physician.

12- What should you do in case of an infection?

Call or tell your health care provider if you are sick caused by an infection (fever, flu, pharyngitis, ...) and inform them that you are on VKA to avoid all risk of treatment imbalance.

13- What to do if you are pregnant or planning to become pregnant?

VKA intake is contraindicated while pregnant. It can have harmful effect on pregnancy progress. It is very important to inform your health care provider if you plan or are pregnant.

14- Which precaution in hemorrhage prevention?

To avoid a hemorrhage, you should tell your health care provider that you are on VKA, avoid doing sports or violent behaviours that may cause trauma leading to bleeding, avoid Intra-muscular injections causing hematomas, handle sharp objects with care.

15- Should you change your food intake while on VKA?

No, however, you should know that certain foods are high in vitamin K: tomato, broccoli, lettuce, spinach, cabbage, cauliflower, Brussels sprouts. In practice, these foods, which can reduce the VKA effect, are not contraindicated. Nevertheless, caution must be taken to balance their intake while on VKA.

Fasting can increase the anticoagulant effect. Being under an acute or chronic alcohol poisoning, anticoagulant effect is increased or decreased respectively.

What you should know

16- Take home message

For an optimal efficacy and a minimum risk, it is important to remember the followings:

- VKA treatment should be taken every day at the same hour (preferably night time),
- VKA should be dosed accurately: overdosing leads to bleeding risk, underdosing leads to thrombosis risk,
- VKA dose should be monitored through regular (at least once monthly) INR measurements preferably done in the same laboratory,
- Target INR dose should be 2-3,
- If bleeding, call / contact your health care provider immediately,

Do not take non-prescribed medication.
All the above take home messages will be recorded into your follow-up diary given to you by your physician, your biologist, or pharmacist.

REFERENCES


