Randomized clinical trial evaluating the efficacy of a retrievable vena cava filter in the prevention of pulmonary embolism recurrence.

The PREPIC 2 trial: Prévention des récidives emboliques par interruption cave

(Prospective, multicentre, randomized, open study)

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## History of amendments

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| 1   | - Modification of inclusion and exclusion criteria  
     - Opening of new centers: Lille, Besancon, Bichat (Paris), Rennes, Firminy, Angers, Clermont-Ferrand  
     - Clarification regarding the insertion and retrieval of the filter  
     - Prolongation of the interval from inclusion to filter insertion from 48 h to 72 h  
     - HIT events deleted from the list of expected SAE | May 15th 2006 |
| 2   | - Opening of a new center: Amiens  
     - Notification of new associated investigators in open centers: Lille, Saint-Etienne, Clamart, Amiens | June 19th 2006 |
| 3   | - Notification of new co-investigators in an open center: Lille  
     - Addition of a new exclusion criterion  
     - Revision of the bleeding criteria in accordance with international literature and clarification of filter complications  
     - Inclusion of a new member in the Steering Committee: Prof B Tardy | July 17th 2006 |
| 4   | Notification of a new associated investigator in an open center: Brest | November 13th 2006 |
| 5   | Notification of new associated investigators in open centers: Firminy, Nancy, Tours, Angers, Clermont, Montpellier | February 12th 2007 |
| 6   | - Opening of a new center: Lyon  
     - Notification of new associated investigators in open centers: Clermont-Ferrand, Nice | March 12th 2007 |
| 7   | Notification of new associated investigators in open centers: Grenoble, Nice, Lyon | June 11th 2007 |
| 8   | - Opening of a new center: Toulon  
     - Notification of new associated investigators in open centers: Angers  
     - Modification of the composition of the central adjudication committee  
     - Inclusion of a new member in the Steering Committee: Dr S Laporte | November 12th 2007 |
| 9   | - Notification of new associated investigators in open centers: Nancy, Lyon, HEGP (Paris), Toulon, Montpellier  
     - Closure of inactive centers: Bichat (Paris), Rennes  
     - Prolongation of patient inclusion until December 21st, 2010 | March 10th 2008 |
| 10  | Notification of new associated investigators in open centers: Nancy, Angers, Lille, Saint-Etienne | April 14th 2008 |
| 11  | - Opening of a new center: Bordeaux  
     - Notification of new associated investigators in an open center: Angers | May 13th 2008 |
| 12  | - Opening of a new center: Dijon  
| 13  | - Modification of the composition of the DSMB due to retirement of one member  
     - Change in the definition of SAE  
     - Notification of new associated investigators in open centers: Grenoble, Angers, Bordeaux, Dijon  
     - Closure of inactive centers: Tours, Nice, Clamart | November 17th 2008 |
| 14  | - Closure of an inactive center: Nancy  
     - Deletion of the exclusion criterion relating to implantable devices for chemotherapy | April 6th 2009 |
| 15  | Notification of new associated investigators in an open center: Montpellier  
     - Revision of the patient information sheet and consent form to facilitate comprehension | June 8th 2009 |
| 16  | Addition of a futility criterion for premature discontinuation of the study | March 8th 2010 |
| 17  | - Revision of the PE recurrence criteria in accordance with the international literature  
     - Prolongation of patient inclusion until December 21st, 2011 | May 10th 2010 |
| 18  | Opening of a new center: Nice (Lacassagne) | August 23rd 2010 |
| 19  | Closing of inactive centers: Firminy, Tours, Lyon, Grenoble, Amiens | August 1st 2011 |
| 20  | Notification of a new associated investigator in an open center: Lille | October 10th 2011 |
| 21  | Prolongation of patient inclusion until June 30th, 2012 and follow-up until December 31st, 2012 | December 12th 2011 |
I. INTRODUCTION

Pulmonary embolism (PE) remains a frequent and sometimes fatal disease. In France about 10,000 deaths per year are considered to be due to venous thromboembolism, and the estimated incidence of new cases ranges from 35,000 to 66,000 per year [1-3]. In addition, more than 90% of PE are estimated to be triggered by deep-vein thrombosis (DVT) of the lower limbs [3]. Treatment of DVT and PE with anticoagulants is effective in reducing the recurrence rate to less than 5% at 6 months [4].

Besides anticoagulant treatment, partial interruption of inferior vena cava (IVC) by a vena cava filter is sometimes proposed. Consensual recommendations for placement of a vena cava filter are limited and have not been formally validated. They comprise a contraindication to anticoagulation, thromboembolic recurrence despite well-conducted anticoagulant treatment, post-embolic chronic pulmonary hypertension, endarterectomy or surgical pulmonary embolectomy [4,5]. Apart from these indications, despite the extensive literature on this topic, only one randomized clinical trial has been conducted in patients with DVT, namely the PREPIC trial [6-7].

1.1. RESULTS OF THE PREPIC TRIAL

The PREPIC trial (Prévention du Risque d’Embolie Pulmonaire par Interruption Cave) was implemented several years ago to assess the efficacy of a permanent vena cava filter (i.e. left in place indefinitely) in patients treated for a proximal DVT with or without PE, not corresponding to the indications for filter placement cited above. This study was supported by a PHRC grant from the French Ministry of Health in 1994 and the results at two years of follow-up were published in 1998 [6]. However, the permanent nature of this treatment warranted a longer term follow-up. A second PHRC grant from the French Ministry of Health was obtained in 1997, allowing an 8-year follow-up of the 400 patients included in the trial. The results were published in 2005 [7].

The results of this trial showed that:

- the insertion of a permanent vena cava filter decreased by 50% the risk of PE at 2 years compared to no filter insertion (PE in the filter group: 3.4 % versus 6.3% in the no filter group, p = 0.16) [6];
- this effect was maintained in the long term, since the risk reduction was 43% at 8 years (PE in the filter group: 6.2% versus 15.1% in the no filter group, p = 0.008) [7];
- these favorable results in the prevention of pulmonary embolism risk were counterbalanced by a significant (50%) increase in the risk of DVT recurrence at 8 years (filter group: 35.7 % versus 27.5% in the no-filter group, OR = 1.52, p = 0.042), mainly due impairment of venous return [6,7].

Despite the favorable result as regards PE risk, the lack of a difference in terms of overall mortality and the negative impact on recurrence of DVT explain in part why the most recent international consensus advises against the systematic use of vena cava filter for the treatment of DVT/PE [4].

Overall, the insertion of a vena cava filter might be beneficial for patients at high risk of PE, especially those at risk of fatal PE. It therefore seemed important to identify patients at high risk of PE under anticoagulation, for whom the benefit- to-risk ratio of filter placement is likely to be positive, with a beneficial effect on PE risk exceeding the harmful effect on the risk of DVT recurrence.

1.2. IDENTIFICATION OF PATIENTS AT RISK OF PE

Several multivariate analyses have allowed the identification of risk factors for PE recurrence in patients presenting with an acute DVT/PE, namely age (over 75 years), history of DVT/PE, cancer, cardiac and respiratory insufficiency, and stroke [7-11]. In contrast, the presence of an evident triggering factor explaining the DVT/PE, such as recent surgery (less than 3 months previously), appears to be a protective factor associated with a lower risk of PE recurrence.

Even more importantly, the presence of an initial PE as the index venous thrombo-embolic (VTE) event appears to the predominant risk factor for both fatal [6,9] and non-fatal [7, 10-13] PE recurrence. These data were recently confirmed by the MATISSE-PE and MATISSE-DVT randomized clinical trials, where the risk of fatal PE at 3 months was 1.5% in patients with an initial PE versus 0.5% in patients with a proximal DVT without an initial symptomatic PE [12,13]. Moreover, we performed a multivariate analysis on a large prospective cohort of patients experiencing an acute VTE event (RIETE registry, 9902 patients) showing that the risk of PE was even higher in patients presenting a serious PE at inclusion [9].

In view of the impact of the presence of an initial PE on the risk of PE recurrence, it seemed of interest to check whether the previously identified risk factors still remain significant in the specific population of patients with an initial PE. An
insufficiency and hemodynamic impairment were associated with a higher risk of mortality within 3 months following the index PE\textsuperscript{[14]}. Hemodynamic repercussions of EP evaluated by the extent of pulmonary artery obstruction, the degree of right ventricular dysfunction or the presence of biological markers such as troponin I or Brain Natriuretic Peptide have also been identified as risk factors for PE-related mortality\textsuperscript{[15]}. 

The population included in the PREPIC study was a high-risk population in terms of VTE recurrence, but not specifically with regard to PE recurrence: only 39% of patients presented with a symptomatic PE at inclusion, 35% had a history of VTE, 21% presented cardio-respiratory insufficiency and 14% had cancer. In addition, 11% of patients presented a protective factor with regard to recurrence (in particular, recent surgery)\textsuperscript{[6]}. The PREPIC study therefore does not provide a direct clinical answer to the question of the potential value of filter insertion in patients with PE. A subgroup analysis focusing on these patients showed a relative reduction in the risk of PE recurrence of 82% with a filter compared to no filter.

The lack of validated data on the benefit of filter placement in patients presenting an initial PE probably explains why the current recommendations did not support the use of a vena cava filter as first-line treatment\textsuperscript{[4]}. Nevertheless, filters are increasingly used, especially in the US, where an estimated 10% of PE patients received a filter in 1999 versus 5% in 1990\textsuperscript{[16]}.

A further study could therefore be conducted to assess the benefit of vena cava filter insertion in patients at higher risk of PE than those included in the PREPIC trial. Such patients could be identified simply by the presence of an acute symptomatic PE associated with at least one other identified risk factor for PE recurrence or PE-related mortality without taking into account the factor of recent surgery.

### 1.3. TIME TO PE AND DVT RECURRENCE FOLLOWING THE INDEX VTE WITH AND WITHOUT A VENA CAVA FILTER

According to published data, the risk of PE or fatal PE seems to be maximal within the first days or weeks of treatment following the index event\textsuperscript{[6,7,14]}.

In the PREPIC trial, the difference between the filter and no filter groups with regard to PE was greatest within the first 6 months, whereas the difference in terms of DVT recurrence was most pronounced after the first year [6]. Similarly, in the ICOPER registry, the majority of deaths in patients with an initial PE occurred within the first 3 months of anticoagulant treatment\textsuperscript{[14]}. Finally, in the RIETE registry, the median time to fatal PE was 6 days, 5% of the fatal PE occurring within the first 2 weeks of treatment\textsuperscript{[8]}.

The possibility of temporarily implanting a device to achieve partial vena cava interruption during the period corresponding to the highest risk of PE recurrence (during the first 3 months of treatment) and then removing this to avoid exposure to the longer term risk of DVT would therefore be of interest in patients with PE at high risk of recurrence under anticoagulant treatment.

### 1.4. TREATMENT OF PE

#### 1.4.1. Filters designed for optional retrieval

Temporary filters designed to be inserted for 15 to 21 days were initially developed but were rapidly abandoned in view of the major risk of infection associated with the need to maintain vascular access for their retrieval. Subsequently, temporary filters intended to remain in place for a longer duration (6 weeks to 3 months) were developed with a subcutaneous system for retrieval (e.g. Tempofilter II\textsuperscript{®}).

Of even greater interest, permanent vena cava filters designed for optional retrieval, called “optional filters” were developed (Gunhertulip\textsuperscript{®}, Recovery (RNF))\textsuperscript{®}, Op tease\textsuperscript{®}, ALN\textsuperscript{®})\textsuperscript{[17]}. These filters can be left in the vena cava indefinitely or removed after a few days or weeks, even up to 12 months in some cases, the retrieval system being specific to each filter. These filters are nevertheless subject to the same known complications as permanent filters, including tilting, migration, filter thrombosis, and infection or hematoma at the site of insertion point, favoring restriction of their use to high-risk patients.

Several observational studies were performed, the majority retrospective, often with less than 100 patients\textsuperscript{[18-20]}. We constituted a prospective cohort including 135 patients having received an aALN\textsuperscript{®} filter to assess the feasibility of insertion and removal of this device\textsuperscript{[21]}. The main indications were temporary contra-indication to anticoagulation (53%), surgical indication in patients at high risk of VTE (such as recent history of VTE, 33%) and VTE recurrence despite a well-conducted anticoagulant treatment (14%). In this cohort, 36 retrieval attempts were successful, after a median time of insertion of 36 days (from 6 days to 12 months).

It would be interesting to evaluate the efficacy of these optional vena cava filters for 3 months compared to no filter in patients treated for a symptomatic PE and with at least one risk factor for PE recurrence. A 3-month period of filter placement would allow:
2.2. The rate of complications associated with filter insertion and retrieval will also be evaluated.

1.5. Expected effect

The expected effect of a retrievable vena cava filter is a reduction in the risk of fatal or non-fatal PE recurrence. In the literature, non-fatal PE correspond to symptomatic PE objectively confirmed by lung scan or spiral CT scan, fatal PE corresponding to PE documented on autopsy, death preceded by symptoms suggestive of PE or sudden death for which there is no other obvious cause and for which PE cannot be ruled out [12].

We therefore propose to perform a randomized, comparative clinical trial assessing at 3 and 6 months the effect of a retrievable (optionally removable) vena cava filter compared to no filter in patients treated with an anticoagulant for an initial symptomatic PE, having at least one risk factor for PE recurrence and not having undergone recent surgery. Retrieval of the vena cava filter will be attempted systematically at 3 months, i.e. after the period corresponding to the greatest risk of PE recurrence, to avoid exposing the patients to an increased risk of DVT recurrence later on. The beneficial effect of the vena cava filter will be assessed by the incidence of symptomatic PE recurrence and fatal PE within the first 3 months of the study. The rate of complications associated with filter insertion and retrieval will also be evaluated.

II. Objectives

2.1. Primary objective

The primary objective of this study is to assess at 3 months the efficacy of 3-month implantation of a retrievable vena cava filter in preventing recurrent PE in patients presenting with acute pulmonary embolism associated with thrombotic risk factors treated with an anticoagulant.

2.2. Secondary objectives

- To assess at 3 and 6 months the benefit-to-risk ratio of a retrievable vena cava filter implanted for 3 months in the prevention of recurrent pulmonary embolism in patients presenting with acute pulmonary embolism associated with thrombotic risk factors and treated with an anticoagulant, in terms of PE recurrence, DVT, and filter complications.
- To assess the feasibility of systematic removal of a retrievable vena cava filter at 3 months in patients presenting with acute pulmonary embolism associated with thrombotic risk factors, with or without DVT, treated with an anticoagulant.
III. STUDY DESIGN

Prospective, controlled, randomized open clinical trial assessing at 3 and 6 months the effect of retrievable vena cava filter insertion in patients presenting with an acute symptomatic PE, based on the comparison of two groups:

- **Filter group**: anticoagulant treatment + ALN® filter for 3 months with systematic removal of the filter at 3 months and continuation of anticoagulation up to 6 months.
- **No filter group**: anticoagulant treatment alone for 6 months.

IV. STUDY POPULATION

4.1. INCLUSION CRITERIA

Consecutive patients aged 18 years or over, hospitalized for acute, symptomatic pulmonary embolism confirmed by high-probability ventilation/perfusion (V/Q) lung scan, associated with acute lower-limb deep- or superficial-vein thrombosis, confirmed by means of standard objective tests, are eligible for randomization, provided they present at least one additional criterion of severity:

- age over 75 years,
- active cancer (excluding skin cancers with localized development, such as basocellular cancer)
- chronic cardiac or respiratory insufficiency,
- iliocaval DVT,
- bilateral DVT,
- ischemic stroke with leg paralysis for more than 3 days but less than 6 months before randomization, with motor deficit of at least one lower limb resulting in immobility,
- signs of right ventricular dysfunction or myocardial injury resulting from PE, including evidence of right ventricular dilatation or pulmonary hypertension on echocardiography, or abnormal levels of at least one of the following biomarkers: brain natriuretic peptide, N-terminal pro-brain natriuretic peptide, or cardiac troponin T or I.

Written informed consent must be obtained from all patients before randomization.

4.2. EXCLUSION CRITERIA

Patients cannot be included:

- if insertion of a vena cava filter is indicated because of a transient or permanent contraindication to anticoagulation therapy or because recurrent thromboembolism had occurred despite adequate anticoagulant therapy,
- if a vena cava filter had already been inserted,
- if a thrombosis in the vena cava does not allow filter insertion,
- if full-dose anticoagulant treatment had been administered during more than 72 hours before randomization,
- if they had undergone non-cancer surgery within the past three months or cancer surgery within the past ten days,
- in case of known allergy to iodinated contrast media, serum creatinine greater than 180 µmol per liter,
- if life expectancy is estimated to be less than six months,
- in case of pregnancy.

V. MATERIALS EVALUATED – CONCOMITANT TREATMENTS

5.1. DEVICE ASSESSED

The treatment evaluated in the filter group comprises a surgical implant in the form of an ALN® filter inserted in the inferior vena cava. In each participating center, the filters provided for the study will bear a specific label in accordance with the regulations in force.
The ALN® filter is conical in form and is composed of non-magnetic stainless steel struts joined at the apex of the filter by their proximal extremities (see illustration portraying the filter in its final spatial form). The struts are of unequal length, avoiding any possibility of intertwining inside the sheath used for insertion of the filter. The upper level, permitting active anchorage, is formed by the six shorter struts which end in curved hooks. The lower level, ensuring centering, comprises the three longer struts, which together form a concave curvilinear shape reducing the risk of trauma. When the filter is inserted, the longest struts emerge from the sheath first, perfectly centering the filter.

Three routes of insertion are possible: femoral, jugular and brachial, all using the no. 7 French sheath.

The filter is retrieved by the jugular route, by means of a specially designed pincer system, using a no. 9 French sheath. This can also be used for repositioning if necessary.

Retrieval is systematically programmed 3 months after filter insertion. If retrieval proves impossible, either for technical reasons or because of filter thrombosis, the filter may be left in place permanently. The technical data are detailed in Appendix 1 and at the website http://www.aln2b.com. In accordance with the recommendations of the French Society of Radiology, an iodinated contrast agent will not be injected for vena cava angiography during filter insertion and/or retrieval in patients with severe renal insufficiency (Cockroft creatinine clearance < 30 mL/min and/or creatininemia >200 micromoles/L). Instead, filter insertion and retrieval will be performed under echography. In patients fitted with an implantable infusion port, filter retrieval will be performed by an experienced operator.

The “no filter” group will not undergo any partial interruption of the vena cava.

5.2. ANTICOAGULANT TREATMENTS

Patients in both study groups will receive full-dose anticoagulant therapy according to international guidelines for the management of patients presenting PE [4]. For the initial phase of PE treatment, the following injectable anticoagulants may be used:

- intravenous or subcutaneous UFH (mandatory in patients with a creatinine clearance of 30 mL/min or less) at curative doses in order to obtain, according to practice in each center, either an anti-Xa activity of 0.3 - 0.7 IU/mL or a prolongation of aPTT within the target zone defined by each center,
- LMWH: tinzaparin (Innohep®: MA 1999) 175 IU aXa/kg/24 h or enoxaparin (Lovenox®: MA 2005) 100 IU aXa/kg/12 h, fondaparinux (Arixtra®: MA 2005) 7.5 mg/24 h for patients weighing from 50 to 100 kg, 5 mg/24 h for patients weighing <50 kg, 10 mg/24 h for patients weighing >100 kg.

For UFH and LMWH, laboratory monitoring, notably platelet count, will be conducted according to the Summary of Product Characteristics of each product.

If a patient presents a serious symptomatic PE and thrombolytic treatment is indicated, inclusion in the PREPIC II study is possible on condition that filter insertion is delayed beyond 36 h following fibrinolysis. The thrombolytic treatment will be selected and administered according to the usual practice of each center. Short administration protocols will be given preference in accordance with international guidelines [4].

The injectable anticoagulant treatment may be switched to oral VKA therapy prescribed to achieve an International Normalized Ratio (INR) between 2 and 3. This switch may be implemented from the first day of PE treatment, but should be overlapped with coprescription of one of the injectable anticoagulants listed above for at least five days. Treatment with the injectable anticoagulant can be discontinued as soon as the two consecutive INR readings are above 2. Vitamin K antagonist therapy is then to be continued systematically in both groups until the end of the study, i.e. for 6 months. All the VKA with an MA in France (warfarine [Coumadine®], fluindione [Previscan®], acenocoumarol [Sintron®]) are authorized for use during the study. All INR readings will be collected during the 6-month period from the patient’s anticoagulation booklet.

In patients with active cancer (without severe renal insufficiency), it is strongly recommended to maintain treatment with an LMWH for 6 months rather than switching to VKA therapy [4].

Beyond 6 months, the continuation of anticoagulant treatment is left to the investigator’s discretion.
5.3. OTHER TREATMENTS

The use of aspirin at high dose, miconazole, butazolidine and St. John’s wort is contraindicated concomitantly with VKA treatment. For all other drug associations, reference it to be made to the Vidal® drug compendium. Close monitoring of the INR is necessary in the event of initiation or discontinuation of any drug administered concomitantly with a VKA.

VI. EVALUATION CRITERIA

6.1. PRIMARY ENDPOINT

The composite primary endpoint is the incidence of PE recurrence at 3 months defined as:
- symptomatic PE recurrence confirmed by lung scan and/or spiral CT scan and/or pulmonary angiography,
- fatal PE confirmed at autopsy
- unexplained death for which a causative role of PE cannot be ruled out\textsuperscript{12}.

A central adjudication committee (CAC) unaware of the treatment assignment will review all symptomatic events.

6.2. SECONDARY ENDPOINTS

The primary endpoint defined above will also be assessed at 6 months.

In addition, the following criteria will be assessed at 3 and 6 months for estimation of the benefit-risk ratio:
- Recurrences or symptomatic manifestations of DVT confirmed by duplex ultrasonography and or venography,
- Mechanical filter complications defined as:
  - Migration: change in position of the filter by more than 20 mm compared with its initial position at the time of insertion
  - Tilting: deviation $\geq 15^\circ$ from the axis of the vena cava
  - Local or systemic infection: infection related to the filter or to the procedure used for its insertion or retrieval and necessitating systemic antibiotic therapy.
  - Venous penetration: extension of one or more of the filter struts more than 3 mm beyond the wall of the vein detected by imaging.
  - Access site hematoma:
    - leading to prolongation of more than 24 h in application of a compression bandage
    - and/or necessitating bed rest or an increase in bed rest time
    - and/or necessitating a change in anticoagulant treatment
    - and/or necessitating transfusion of one unit or more of packed red blood cells
    - a hematoma measuring 100 cm$^2$ or more
  - Filter thrombosis found in the context of clinical suspicion of DVT or PE
  - Filter removal failure
  - Major bleeding defined as:
    - symptomatic bleeding associated with a fall in hemoglobin concentration of 2 g/dL or more,
    - symptomatic bleeding necessitating transfusion of two or more units of packed red blood cells or whole blood,
    - bleeding in a critical organ (including intracranial, retroperitoneal, intraocular, adrenal, intraspinal, or pericardial bleeding)
    - bleeding resulting in death
- All-cause death.

A central adjudication committee (CAC) unaware of the treatment assignment will review all these events.

VII. RANDOMISATION PROCEDURES

Randomization will be centralized and assured by a professional (ClinInfo) 7 days a week and 24 h a day. Randomization will be stratified by center and on the presence of renal insufficiency at inclusion (creatinine clearance $\leq 30$ mL/min versus $>30$ mL/min).
VIII. COURSE OF THE STUDY

The course of the study is summarized below.

The course of the study for an individual patient is described in more detail below. All items not forming part of the usual management of PE patients are indicated in italics.

Day 0: Before inclusion

- Confirmation of the diagnosis of PE in the context of clinical signs suggestive of PE, according to the usual practice of each center, by:
  - high-probability V/Q lung scan (according to PIOPED criteria) and/or
  - intermediate probability lung scan associated with clinical signs suggestive of PE and a proximal DVT confirmed by Doppler-ultrasonography or venography and/or
  - a positive spiral CT scan and/or
  - an abnormal pulmonary angiography.
- Doppler-ultrasonography or venography confirming the existence of a DVT or a superficial vein thrombosis (SVT)
- Assay of creatinine clearance, troponin, etc.
- Check of inclusion and exclusion criteria
- Provision of the patient information sheet and consent form
- Parenteral anticoagulant treatment (UFH, LMWH or fondaparinux) ± fibrinolytic treatment in the case of severe PE
- Laboratory monitoring (platelet count, anti-Xa activity and/or aPTT)
Day 1: Inclusion and randomization

- Collection of signed consent form (a lead time of 24 h is to be expected for scheduling of filter insertion)
- Phone call to the randomization center to determine the patient’s treatment allocation
- Scheduling of filter insertion for patients allocated to the filter group

Day 1 to Day 3: Filter insertion

- Filter insertion (according to the procedures described in Appendix 1) and plain abdominal X-ray for patients randomized to the Filter group within 72 h after the start of anticoagulant treatment. In the event of thrombolytic treatment, filter insertion will not take place until a minimum of 36 h have elapsed following administration of the thrombolytic. Hydration, analgesia and sedation will be provided for filter insertion in accordance with the practices of each center.
- Scheduling of hospitalization at 3 months ± 15 days for filter removal for patients randomized to the filter group. In patients with an implantable port, filter removal will be performed by an experienced operator.
- Continuation of anticoagulant treatment for all patients in accordance with standard practice
- VKA relay if VKA treatment is envisaged
- Scheduling of a follow-up visit at 3 months ± 15 days

3 months (± 15 days): Follow-up visit and filter removal for patients randomized to the filter group

- Hospitalization for filter removal for patients randomized to the filter group: the duration of any temporary treatment discontinuation envisaged must be less than 48 h. The procedure is described in Appendix 1. Before filter removal, venography or duplex ultrasonography according to the investigator’s choice will be performed to detect any filter thrombosis. Hydration, analgesia and sedation will be provided for filter removal in accordance with the practices of each center.
- Follow-up visit: recording of INR data and any events
- Continuation of treatment according to standard practice
- Scheduling of follow-up visit at 6 months ± 15 days

6 months (± 15 days): End of study

- Follow-up visit: recording of INR data and any events
- Continuation of treatment at the investigator’s discretion

IX. ADVERSE EVENTS

9.1. DEFINITION

This study will consider:
- An adverse effect (AE) related to the device to be any harmful and undesirable reaction to medical device or any incident that could have led to this reaction if an appropriate action had not been taken, in a person participating in the research, or any effect related to malfunctioning or degradation of the medical device causing harm to a person participating research.
- An AE to be any harmful event occurring in a person participating in biomedical research whether or not this event is related to the research or product forming the object of the study.

In this protocol, a serious adverse effect or event (SAE) is defined as any undesirable effect or event that:
- results in death,
- is life-threatening for the person participating in the research,
• necessitates hospitalization or prolongation of hospitalization,
• results in major or persistent disability or handicap.

Any serious adverse effect or event (SAE) mentioned in the package insert of the medical device is considered as an expected SAE (ESAE). Conversely, any SAE not mentioned in the Investigator’s Brochure or the package insert of the medical device is considered as an unexpected SAE (USAE).

However, in view of the characteristics of the population concerned by this study (advanced age, numerous comorbidities...) and the anticoagulant treatment routinely prescribed following PE, we will not consider as serious adverse events any event corresponding to the definition of an EIG but is related to:
- The anticoagulant treatment (e.g. VKA overdose, treatment adjustment, bleeding)
- Investigation of the etiology of the thromboembolic disease
- Etiological investigation or treatment of a disease present before inclusion or discovered after inclusion but not related to the vena cava filter.

Moreover, as DVT and PE comprise the evaluation criteria of this study, hospitalizations, life-threatening situations and death related to either of these events will not be considered SAEs. These events already form the object of a specific declaration in the case report form and are reviewed by the Central Adjudication Committee (CAC). Furthermore, monitoring the incidence of these events in each group is monitored by the independent Data Safety Monitoring Board (DSMB) that is to meet every 6 months and report its conclusions to the Steering Committee which will then decide whether or not to continue the study.

9.2. DECLARATION BY THE INVESTIGATOR TO THE SPONSOR

The investigator must report to the sponsor:
- Any unexpected SAE related to the medical device or any SAE potentially related to the procedure used for its insertion, within 24 h of its occurrence,
- Any expected SAE related to the medical device, within 8 days of its occurrence.

In both cases, the investigator will complete and fax to the sponsor (at +33 (0)4 77 12 78 20) the specific SAE declaration form included in the case report forms. Upon receipt of the SAE declaration form, a clinical research associate (ARC) of the Delegation Regionale à la Recherche Clinique (DRCI) will communicate this event to the members of the SAE validation committee of the University Hospital of Saint-Etienne (the study sponsor), comprising a physician and a pharmacist of the Clinical Research Unit and an ARC of the DRCI. This committee will judge the expected or unexpected nature of this SAE and its imputability to the medical device. All unexpected SAEs for which the validation committee cannot unequivocally exclude any relationship with the medical device or the procedure used for its insertion will be notified to the Agence Française de Sécurité Sanitaire des Produits de Santé (AFSSAPS; French Medicines Agency) by the sponsor.

9.3. DECLARATION BY THE SPONSOR TO THE ETHICS COMMITTEE AND THE HEALTH AUTHORITIES

The University Hospital of Saint-Etienne (study sponsor) will declare to the AFSSAPS and the Ethics Committee (Committee for the Protection of Persons; CPP) any unexpected SAE potentially related to the medical device and any SAE related to the device insertion procedure as soon as it is aware of these events. These declarations will be made using the appropriate form issued by the AFSSAPS and will be sent by post within:
- 7 days for unexpected SAEs potentially related to the medical device and SAEs related to the procedure used for its insertion which result in death of the patient or are life-threatening,
- 15 days for unexpected SAEs potentially related to the medical device and SAEs related to the procedure used for its insertion which necessitate hospitalization or prolongation of hospitalization, or cause major or lasting disability or handicap.

In the case of an incomplete initial declaration of an unexpected SAE potentially related to the medical device or an SAE related to the procedure used for its insertion, the sponsor will address to the AFSSAPS and the CPP, by post, a report of referenced and numbered follow-up report of this unexpected SAE or SAE, within a maximum of:
- 8 days (starting from the end of the initial 7-day period) for any unexpected SAE potentially related to the medical device and SAE related to the procedure used for its insertion which result in death of the patient or are life-threatening,
- 15 days (starting from the end of the initial 15-day period) for any unexpected SAE potentially related to the medical device and any SAE related to the procedure used for its insertion which necessitate hospitalization or prolongation of hospitalization, lead to major or lasting disability or handicap, or result in acongenital anomaly or malformation.

From the time of application of the new regulation (law of August 9, 2004) to studies authorized prior to August 2006, the sponsor must address:
- Every six months, by post, to the CPP and the AFSSAPS, a listing (accompanied by a written summary) of the unexpected SAEs potentially related to the medical device and the SAEs related to the procedure used for its insertion that have occurred during this study
- An annual safety report describing the expected and unexpected SAEs, within 60 days of the anniversary of the authorization of the research by the AFSSAPS.

The occurrence and declaration of expected and unexpected SAEs will be systematically checked during the monitoring visits.

If any new fact (for example, new safety information) comes to light during this study, the sponsor will immediately, on becoming aware of the fact, declare this new fact and any measures taken to the CPP and the AFSSAPS, by post. Any relevant complementary information concerning this new fact will be sent by post to the AFSSAPS and the CPP, within 8 days of dispatch of the initial declaration, in the form of a referenced and numbered follow-up report.

9.4. MODE AND DURATION OF FOLLOW-UP OF PERSONS EXPERIENCING ADVERSE EVENTS

Any person experiencing an adverse effect or event will receive the appropriate care for his or her condition and will be followed up until resolution of the event or until the end of the study. If necessary, use of the medical device may be discontinued.

9.5. SAFETY MEASURES TO BE TAKEN IN THE EVENT OF MALFUNCTIONING OF THE MEDICAL DEVICE, INCLUDING ISOLATED MALFUNCTION WITH NO CLINICAL REPERCUSSIONS AND INAPPROPRIATE USE

In the event of batch recall or malfunction of a vena cava filter in the context of its routine use, the manufacturer undertakes to immediately inform the coordinating investigator and the project manager. In the event of dysfunction of the device in the context of the study, the investigator responsible for the patient concerned will take all the necessary medical measures. The filter manufacturer will be informed of this malfunction by the project manager.

9.6. DESCRIPTION OF THE POSSIBLE RISKS AND EXPECTED ADVERSE EVENTS ACCORDING TO THE AVAILABLE DATA BASE

Potential filter-related complications are described in Appendix 1

X. STATISTICAL METHODS

10.1. DETERMINATION OF SAMPLE SIZE

In patients presenting an initial symptomatic PE, the risk of symptomatic PE recurrent ranged from 3.1 to 5.3% in published randomized studies and registries.\(^{[6,10,12,14,24]}\) The risk of fatal PE, in diagnostic studies and various registries ranged from 1.2 to 8%.\(^{[8,14,25,26]}\) On the basis of these observations, the rate of fatal or non-fatal PE recurrence in an unselected population of patients with PE may be estimated as about 6%. It is therefore reasonable to estimate a higher rate of PE recurrence at 3 months, around 8%, in the population participating in this study, presenting a high risk of PE recurrence. At present, clinical experience with optionally retrievable filters is very limited. In the two largest series, comprising 96 patients\(^{[20]}\) and 135 patients,\(^{[21]}\) respectively, no PE was observed in the ALN filter group, but the patients included in these cohorts did not all present an initial PE. In the PREPIC study, the incidence of PE recurrence at 3 months in patients presenting an initial symptomatic PE was less than 2% in the filter group. Assuming a PE recurrence rate of 8% in the absence of a filter and 2% with a filter, corresponding to a relative reduction of 75% in the risk of recurrence (the relative risk reduction being 82% in the PREPIC study in patients with an initial PE) for a statistical power of 80% and an alpha risk of 5% (two-sided), 200 patients need to be included per group, giving a total sample size of 400 patients.

10.2. REASSESSMENT OF THE SAMPLE SIZE DURING THE STUDY

Taking into account the uncertainty regarding the risk of recurrence in a population of patients presenting PE as well as risk factors, a reassessment of the sample size is planned after the inclusion of 200 patients. Only a potential increase in sample size is envisaged as a result of this reassessment and any change will be based not on the comparative effectiveness of treatment in the two groups but solely on the incidence of PE occurrence observed in the control group with no filter. In the absence of comparison of the two groups, no adjustment of the alpha risk will be necessary.\(^{[27-28]}\)
The Data Safety Monitoring Board (DSMB) will be implicated in this reassessment of the number of subjects. The decision rules are as follows:
- If the 95% confidence interval for the event rate (primary endpoint) in the non-filter group includes the value of 8%, the study will be continued as planned;
- If the 95% confidence interval for the event rate does not include the value of 8%, because the observed incidence in the study is higher, the study will be continued without downward adjustment of the sample size;
- If the 95% confidence interval for the event rate does not include the value of 8% because the observed incidence is lower, the sample size will be reassessed on the same basis as in the initial sample size calculation based on a relative reduction of 75% in the risk of events. If the risk of events is very low, making the study impracticable, the Steering Committee will decide whether or not to stop the study.
These rules will be submitted to the DSMB for approval.

10.3. Statistical analysis

10.3.1. Interim efficacy analysis and stopping rule

A futility analysis will be performed after the inclusion of 200 patients to determine the incidence below which it will not be possible to demonstrate any statistical difference even with 400 patients. This does not constitute an interim analysis because any recommendation to stop the study will be made on the basis of the overall incidence of events in the two treatment groups, without any distinction between groups, and therefore will not be based on any observed treatment effect. This analysis will be performed without any knowledge of the results in the two treatment groups. On the basis of the original hypothesis of the PREPIC 2 study, in other words, a relative risk reduction of about 75% in filter group, as long as the overall incidence is at least 2.5%, it will still be possible to show a significant difference with 400 patients (p <0.05). In contrast, if the overall incidence is less than 2.5%, it will be impossible to demonstrate any treatment effect with 400 patients. Thus, if the analysis based on 200 patients gives a confidence interval of the overall incidence not including 4.0%, the study will not be conclusive with 400 patients and will therefore be stopped.

Moreover, if the DSMB does not recommend discontinuation of the study due to futility, an interim analysis based on the primary endpoint is also planned after the inclusion of 200 patients. This analysis will compare the two groups of patients, the filter group and the no filter group. The decision threshold of this interim analysis will be defined according to the method described by Peto et al., based on the use of a very low statistical threshold during the interim analysis in order to keep a threshold close to the overall risk for the final analysis[29-30]. Discontinuation of the study on the grounds of efficacy will be discussed on the basis of a significant difference between the 2 groups at the threshold \( \alpha = 0.001 \).

10.3.2. Final analysis

The analysis will be performed on the intention-to-treat (ITT) population. The variables will be described for the population as a whole and by treatment group as follows:
- Quantitative data: number of observations, mean, standard deviation of the mean, minimum, maximum.
- Quantitative data for time: number of observations, median, minimum, maximum.
- Qualitative data: number of observations and percentage.

Comparability between groups at baseline will be verified on data recorded at inclusion. Qualitative variables will be compared using the Chi-square test or Fisher’s exact test when the expected frequencies are too low. Quantitative variables will be compared by the Student's t test for normally distributed variables, and by a median comparison test for the time variables.

The incidence of the primary endpoint will be compared between the filter and no filter groups using the Chi-square test or Fisher’s exact test when the expected frequencies are too low. If the rates of death and loss to follow-up are high, the risk of events will be estimated using the Kaplan-Meier procedure in each group and compared by the Log-Rank test. The data concerning subjects who have died or have been lost to follow-up will therefore be censored. In the event of imbalance between the groups at inclusion, adjustments may be made (using logistic regression and the Cox model).

The same procedure will be used for the analysis of secondary endpoints.

10.3.3. Statistical software

The statistical analysis will be performed using SAS-Windows® version 8.
XI. ORGANIZATION OF THE STUDY

11.1. STEERING COMMITTEE

The composition of the Steering Committee is given in Appendix 2. This committee decides on and takes responsibility for the conception, implementation, and discontinuation of the study, and the final study report. It guarantees communication of the study results in agreement with the publication rules. The meetings of the Steering Committee will take place by conference call.

11.2. INDEPENDENT DATA SAFETY MONITORING BOARD (DSMB)

The DSMB comprises three experts not involved in the study and having thorough knowledge of the disease forming the object of the study (Appendix 2). The DSMB guarantees the ethical nature and quality of the study. It monitors the progress of the study and makes decisions based on the results of safety analyses communicated by the coordinating center. According to these results, the DSMB may propose to the Steering Committee that the trial should be discontinued or that the number of subjects should be re-evaluated, the Steering Committee being responsible for the final decision on these issues. The statistician responsible for the study will participate in the meetings of the DSMB.

11.3. CENTRAL ADJUDICATION COMMITTEE (CAC)

The CAC is an independent committee composed of clinicians specialized in venous thromboembolic disease (Appendix 2). It will blindly adjudicate all clinical events occurring in the various study centers. It will confirm or reject the diagnoses made by the individual investigators. In the event of disagreement between the investigator and the CAC, the diagnosis of the CAC will be retained.

11.4. COORDINATING CENTER AND DATA ANALYSIS CENTER

The coordinating center and data analysis center will be the Thrombosis Research Group (EA3065) at the University Hospital of Saint-Etienne (Prof P Mismetti, Dr S Laporte). The physician responsible for project management is Dr K Rivron-Guillot. The statistical analysis will be performed under the responsibility of Dr S. Laporte.

11.5. IMPLICATION OF THREE INSERM CLINICAL INVESTIGATION CENTERS (CIC) BELONGING TO THE THROMBOSIS NETWORK

Three INSERM (Institut National de la Santé et de la Recherche Médicale; French National Institute of Health and Medical Research) clinical investigation centers (CICs) conducting research on venous thromboembolic disease will participate in this project: Saint-Etienne, Brest and Grenoble.

<table>
<thead>
<tr>
<th>CIC Saint-Etienne</th>
<th>CIC Brest</th>
<th>CIC Grenoble</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prof H Décousus, Dr B Tardy</td>
<td>Prof E Oger, Dr K Lacut</td>
<td>Prof M Hommel, Prof JL Bosson Dr JL Cracowski</td>
</tr>
<tr>
<td>Tel +33 (0)4 77 12 08 26 Fax +33 (0)4 77 12 78 20 <a href="mailto:cic@chu-st-etienne.fr">cic@chu-st-etienne.fr</a></td>
<td>Tel +33 (0)2 98 34 73 49 Fax +33 (0)2 98 34 79 44 <a href="mailto:emmanuel.oger@chu-brest.fr">emmanuel.oger@chu-brest.fr</a></td>
<td>Tel +33 (0)4 76 76 92 60 Fax +33 (0)4 76 76 92 62 <a href="mailto:cic@chu-grenoble.fr">cic@chu-grenoble.fr</a></td>
</tr>
</tbody>
</table>

This study forms part of the inter-CIC research project on venous thromboembolic disease submitted to INSERM. The three CICs involved have already jointly participated in several national and international studies, sponsored by public institutions or the pharmaceutical industry.

A part-time Clinical Research Assistant (ARC) will be delegated to each of the three CIC for accomplishment of its mission, according to the following geographic distribution:
The CIC will assure:
- on-site monitoring of the centers and phone calls to prepare the monitoring visits
- notification of intercurrent SAEs to the AFSSAPS (French Medicines Agency)
- documentation of expected events and centralization of documentation for the CAC
- transfer of all information to the coordinating center
- municipal surveys, if necessary
- filter dispensing
- centralization of case report forms

The three CICs are responsible for the quality control and computerized processing of all study data. The monitoring procedures will conform to European Good Clinical Practices.

11.6. INVESTIGATION CENTERS

The principal investigator is Prof Patrick Mismetti, Saint-Etienne. He will assure the medical coordination of the study and the recruitment of investigators; he may also be called upon to intervene with investigators with the aim of improving patient recruitment and the quality of the study.

Approximately 10 investigation centers are planned in total. The following centers have already agreed to participate:

<table>
<thead>
<tr>
<th>Participating centers</th>
<th>Reference CIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHU d’Angers (Dr P M Roy, Dr A. Furber, Dr H. Mottier, Dr A-S Bordot, Dr K. Pattier, Dr R. Monteiro, Dr B. Guillaum-Mazet, Dr J.M. De Boisjolly-Bonnefoi, Dr A. Mercier, Dr F. Prunier, Dr S. Delepine, Dr S. Dambrine, Dr J.P. Alanmy, Dr A.C. Quenouille-Dessaincure)</td>
<td>CIC Brest</td>
</tr>
<tr>
<td>CHU de Brest (Pr D Mottier, Dr K. Lacut, Dr F. Couturaud, Dr C. Leroyer, Dr G. Le Gal)</td>
<td>CIC Brest</td>
</tr>
<tr>
<td>CHU de Lille (Pr P Assemse, Dr J.M Aubert, Dr M Lesenne, Dr JL Auffray, Dr JI Bauchart, Dr J Darchis, Dr P Ennezat, Dr D Montaigne, Dr P. Delsart)</td>
<td>CIC Brest</td>
</tr>
<tr>
<td>AP-HP, Hôpital Européen Georges Pompidou, Paris (Pr G Meyer, Dr O Sanchez, Dr B. Planquette)</td>
<td>CIC Brest</td>
</tr>
<tr>
<td>CHU de Besançon (Pr P Bassand, Dr Nicolas Meneveau) Clinique du Parc, Castelnaud le lez (Dr D. Brisol)</td>
<td>CIC Grenoble</td>
</tr>
<tr>
<td>CHU de Clermont-Ferrand (Pr J Schmidt, Dr N. Breuil, Dr T. Mathevon, Dr S. Heuser, Dr J. Liotier, Dr C. Billaut)</td>
<td>CIC Grenoble</td>
</tr>
<tr>
<td>CHU de Montpellier (Pr I Quéré, Dr J.P. Gallanaud, Dr A. Khau Van Kien, Dr G. Boge, Dr D. Siau)</td>
<td>CIC Grenoble</td>
</tr>
<tr>
<td>CHU de Saint-Etienne, Urgences et Réanimation Médicale (Dr B Tardy, Dr A Viallon, Dr E Diconne, Dr S Guyomar’ch, Dr D Page)</td>
<td>CIC Grenoble</td>
</tr>
<tr>
<td>CHU de Saint-Etienne (Pr H Décousus, Pr P Mismetti, Dr A Buchmuller, Dr L Bertoletti, Dr D Delsart, Dr M Epinat, Dr N Moulin, Dr P. Torris, Dr S. Accassat)</td>
<td>CIC Grenoble</td>
</tr>
<tr>
<td>CHU de Toulon (Dr A. Elias, Dr M. Elias, Dr F. Giauffret, Dr J.N. Poggi, Dr R. Gulino, Dr J.M. Poinsboeuf, Dr M. Simonnet)</td>
<td>CIC Saint-Etienne</td>
</tr>
<tr>
<td>CHU de Bordeaux (Dr C. Jais, Pr J. Constans, L. Leroux, Dr F. Casassus, Dr P. Costes, Dr E. Gerbaud)</td>
<td>CIC Saint-Etienne</td>
</tr>
<tr>
<td>CHU de Dijon (Dr N. Falvo, Dr E. Steinmetz, Dr E. Denaistre, Dr J.L. Lorenzini, Dr R. Brenot, Dr B. Lorcerie, Dr C. Favier, Dr A. Camin, Dr B. Terriet, Dr A.S. Lesne-Padie) Centre Antoine LACASSAGNE, Nice (Dr J. Otto, Dr M. Poudex)</td>
<td>CIC Saint-Etienne</td>
</tr>
</tbody>
</table>

This number of centers may appear low, but the success of the study is based on a small number of highly active centers, provided with support for their clinical investigation work.

An optimal recruitment will be possible with a small number of active centers provided that these “recruiting” centers are provided with Clinical Study Technicians (CSTs) capable of helping them with study management.
External funding has been requested in order to allocate a part-time (on average) CST to each center and/or city. The CSTs will also be responsible for data entry, since the case report form will be electronic and data entry will be accomplished at each center. This case report form will be professionally designed (by Clin-Info) and will incorporate on-line checks of consistency and likelihood.

XII. ETHICAL AND LEGAL CONSIDERATIONS

12.1. GENERAL CONSIDERATIONS

This protocol conforms to the ethical principles established by the 18th World Medical Assembly (Helsinki 1964) and the amendments made during the 29th (Tokyo 1975), 35th (Venice 1983), 41st (Hong Kong 1989), 48th (Somerset West 1996) and 52nd World Medical Assemblies and revised in the 52nd World Medical Assembly (Edinburgh 2000).

This is a study within the scope of the French Huriet law of August 9, 2004 in view of the randomization procedure, constituting a modification of routine clinical practice. The vena cava filter used in this study bears a CE mark (no. 0459).

This protocol will be submitted to the Committee for the Protection of Persons Participating in Biomedical Research (CCPPRB; subsequently known as Committee for the Protection of Persons; CPP) of the Rhône-Alpes Loire region. The investigator will explain the study to each patient and will give him or her an information sheet (Appendix 3) and consent form (Appendix 4). The informed consent form signed and dated by the patient will be obtained before the start of the study.

The sponsor of the study, the University Hospital of Saint-Etienne, has taken out an insurance policy covering this study. As certain data will be processed by computer, the authorizations of the CCTIRS (Comité consultatif sur le traitement de l’information en matière de recherche dans le domaine de la santé) and the CNIL (Commission National de l’Informatique et des Libertés) will be requested.

12.2. BENEFIT-TO-RISK RATIO

In this study, the patients included in the no filter group will receive care in accordance with current medical practice. They will not derive any benefit from their participation in this study but neither will they incur any risk. As for the patients in the filter group, the risks related to filter insertion or removal (filter migration, perforation of the vein, hematoma or infection at the site of venous access) are extremely rare and are generally not serious. Moreover, the filter has a potentially beneficial effect on the risk of PE (a).

There is a chance that removal of the vena cava filter will not be possible at 3 months because of technical difficulties or in the event of filter thrombosis of the filter. In these cases, the partial interruption of the vena cava will be maintained. This is fully acceptable since most of the currently used filters are permanent filters. In addition, as the patients will be hospitalized for filter insertion and removal, the presence of any complication can be checked and immediate treatment provided if necessary.

XIII. CALENDAR

The planned duration of the study was initially 3 years. In view of the delays in patient inclusion, the date for completion of the period of inclusion has been extended to July 31st, 2012. Patient follow-up of the patients will therefore terminate on January 31st, 2013.

XIV. FEASIBILITY

The Thrombosis Research Group (EA3065) at the University Hospital of Saint-Etienne previously completed the first randomized clinical trial (the PREPIC trial) comparing filter placement to no filter in patients presenting deep-vein thrombosis (DVT). This study on 400 patients was funded by the Ministry of Health (PHRC grant) in 1994. The study results were published in the New England Journal of Medicine in 1998(1). A study amendment of the study permitted prolongation of the follow-up to 8 years, this long-term follow-up being supported by another PHRC grant in 1997. The results of the long-term follow-up study were accepted for publication in Circulation in 2005(2). The group has thus already managed this kind of randomized trial.

The inclusion of 400 patients in the PREPIC trial extended over 4 years, during a period when France was poorly structured to carry out this kind of study. Since then, various local, regional and national networks have been created. France is today the most active country in terms of inclusion in international multicenter clinical trials, including patients with DVT with venous...
than 300 patients enrolled per year in this kind of trial.\textsuperscript{11} Lastly, the centers that have consented to participate in this study include the largest investigation centers involved in the previous PREPIC trial.\textsuperscript{6}

The CIC implicated in this project are the three French CIC focused on thromboembolic disease: Saint-Etienne, Brest and Grenoble. They are associated with various centers highly active in clinical investigation related to therapeutic clinical trials conducted in this field. To illustrate this point, during the last study conducted in PE at a worldwide level (2003-2004), the centers of Saint-Etienne (Prof H Décousus, Prof P Mismetti) and Brest (Prof D Mottier) were the two leading French centers in terms of recruitment with respectively 40 patients and 38 patients included during the course of a single year.

Besides these investigating centers associated with a CIC, the other potential investigation centers contacted or envisaged are also very active in terms of inclusions. For example, the centers of Tours, Clamart, Nice and the Georges Pompidou European Hospital (HEGP) in Paris, each included more than 30 patients during a single year in the two most recent randomized trials in PE patients. Together with the CICs of St-Etienne and Brest, this would give a potential recruitment of 200 patients a year with only six centers. The other centers envisaged have similar track records in terms of recruitment.

Even with the participation of 10-12 centers, an optimal recruitment could therefore be assured since the recruiting centers will each have a Clinical Study Technician (CST) to assist them with study management. It is worth noting that even in multicenter trials with numerous investigating centers, Indeed, in the multicenter clinical trial, even if the investigating centers are numerous, a few centers often contribute 75 to 80\% of all patients enrolled.
XV. REFERENCES


APPENDIX 1: SPECIFICATION SHEET OF THE ALN FILTER

This specification sheet concerns the femoral insertion of the filter. The same sheets are available for the jugular and brachial accesses. It also includes the specification sheet of the removal by jugular access (the only way for removal).

AVAILABLE ON REQUEST in a SEPARATE FILE (14 pages).

APPENDIX 2: COMMITTEES OF THE PREPIC2 STUDY

Steering Committee
Pr P Mismetti (Service de Médecine Interne et Thérapeutique, Unité de Pharmacologie Clinique, CHU Bellevue Saint-Étienne)
Dr JL Bosson (Informatique médicale, CIC, Grenoble)
Pr H Décousus (Service de Médecine Interne et Thérapeutique, CIC-EC, Saint-Étienne) Pr D Mottier (Service de Thérapeutique, CIC, Brest)
Pr FG Barral (Service de Radiologie, CHU Nord Saint-Étienne)
Pr JP Beregi (Service de radiologie et d’Imagerie cardiovasculaire, CHU Lille)
Pr P Carpentier (Médecine Vasculaire, CHU Grenoble)
Pr B Charbonnier (Service de Cardiologie, CHRU Tours)
Dr Ph Girard (Service de Pneumologie, Institut Mutualiste Montsouris Paris)
Pr G Meyer (Réanimation Médicale, HEGP Paris)
Pr I Quéré (Médecine vasculaire, CHU Montpellier)
Pr G Simonneau (Pneumologie, AP-HP Clamart)
Dr B Tardy (Service d’Urgence et de Réanimation Médicale, CHU Saint-Étienne)
Mme Silvy Laporte (Bistatisticienne, Unité de Pharmacologie Clinique, CHU Bellevue Saint-Étienne)

Data Safety Monitoring Board
Dr A Leizorovicz (Service de Pharmacologie Clinique, RTH Laennec Lyon)
Pr JM Vergnon (Service de Pneumologie, CHU Nord Saint-Étienne)
Dr F Parent (Médecine Vasculaire, CH Clamart)

Central Adjudication Committee
Dr Isabelle MAHE, CH de Colombes
Dr Marc RIGHINI, CHU de Genève
Dr Philippe LACROIX, CHU Limoges
PATIENT INFORMATION SHEET

Randomized clinical trial evaluating the efficacy of a retrievable vena cava filter in the prevention of pulmonary embolism recurrence.

The PREPIC 2 trial: Prévention des récidives emboliques par interruption cave

(Prospective, multicentre, randomized, open study)

Principal investigator and coordinator:
Prof. Patrick Mismetti
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GLOSSARY

CHU: University Hospital Center

OBJECTIVES

Pulmonary embolism: formation of a clot that obstructs the artery bringing blood to the lungs, preventing it from correctly loading oxygen.

METHODOLOGY

Filter: a sort of tiny umbrella.

COURSE OF THE STUDY

Phlebitis: presence of a clot that obstructs a vein.

RIGHTS

Sponsor: physical or moral person or body responsible for initiating the research, assuring its management and verifying its financing.

PROTECTION OF PERSONS

Vena cava: abdominal vein ascending to the heart.

Femoral vein: one of the large veins of the leg.

Dear Sir or Madam,

You are currently hospitalized with a diagnosed pulmonary embolism. This condition may be fatal. In 90% of cases, pulmonary embolism arises from phlebitis in a leg.

This condition is currently treated with anticoagulant medications. These treatments make the blood more fluid and have shown their efficacy in this disease. However, the risk of recurrence of pulmonary embolism, fatal or not, remains high during the first three months of treatment. This is why a complementary treatment has been developed. This is a non-medicinal treatment, comprising a filter that is inserted into the vena cava. It prevents a clot formed in a leg from ascending into the pulmonary artery. The filter is sometimes associated with
anticoagulant treatments. The first vena cava filters were left in place throughout the patient's life. These are called permanent caval filters. They are inserted to prevent the development of pulmonary embolism. However, the long-term presence of this type of filter increased the risk of delayed phlebitis. For this reason, a new type of filter was invented. This filter has the advantage that it can be removed. The risk of pulmonary embolism is greatest during the first three months, whereas the risk of recurrence of phlebitis reaches a peak at a later stage. The removable filter would ideally be:
- inserted as soon as pulmonary embolism is diagnosed
- removed at the end of three months.

**OBJECTIVES**

We therefore wish to conduct a study with the objective of evaluating whether the placement of a filter during the first three months following the detection of a pulmonary embolism leads to a lower incidence of its recurrence and reduces mortality due to early pulmonary embolism, without increasing the incidence of delayed phlebitis. We will also evaluate the possibility of removing the filter.

**METHODOLOGY**

This study will be conducted in at least nine French CHU. It is planned to enroll at least 400 patients. You have a reflection period of 24 h to decide whether or not you would like to participate in this research.

If you decide to participate in this study, you will be included in one of the following groups:
- In the first group, a filter will be inserted into your vena cava. This will be an ALN filter. You will keep this filter for 3 months. In addition, you will receive an anticoagulant treatment. This will be prescribed, according to usual practice, for 3 to 6 months.
- In the second group, no filter will be inserted, but you will receive an anticoagulant treatment. This will be prescribed, according to usual practice, for 3 to 6 months.

Your allocation to one of these two groups will be determined randomly.

**COURSE OF THE STUDY**

If you are included in the “filter” group, the filter will be inserted in accordance with usual practice:
- under local anesthesia,
- by a radiologist

The femoral vein of one leg (more rarely a vein in the neck or an arm) is pierced to allow introduction of a tiny “tube” containing the filter. This tube is known as a guide. The guide is pushed along until it reaches the vena cava. The filter is then placed in position and the guide is removed. This intervention is conducted under radiological control, allowing verification of the position of the filter. After 3 months, the filter will be removed by means of a similar procedure. The difference is that the guide will be inserted in a vein of the neck and will be
pushed down until it reaches the filter. The filter will then be drawn into the guide and removed at the same time as this. Like its insertion, removal of this implant is painless. However, it may sometimes lead to very rare complications such as:
- filter migration;
- perforation of a vein, resulting in bleeding.

A hematoma may also develop at the site of access to the vein. Infectious complications may occur, but are extremely rare. They may be local or systemic. There is also a chance that it will be impossible to remove the filter:
- either because your state of health does not permit this,
- or because it is technically impossible.

The filter will then become permanent and will have the same properties as other known permanent filters.

If you are included in the “filter” group, you will be hospitalized for 24 h, at the end of 3 months for:
- removal of the filter,
- a check that there are no complications,
- and possibly adjustment of your anticoagulant treatment.

You will then attend a follow-up study visit, according to usual practice, at the end of 3 months, in other words, 6 months after placement of the filter.

If you are included in the “no filter” group, you will attend a follow-up study visit:
- at the end of 3 months,
- and then, in accordance with usual practice, at the end of 6 months.

This will enable the physician to check that there are no complications and if necessary adjust your anticoagulant treatment.
RIGHTS

You will be informed of the overall results of this study after its completion. You may be accompanied by a person in whom you have confidence:
- during your hospitalization,
- at all study visits.

You are free to cease your participation in this study at any time. This will not affect the quality of care provided and will not modify your relationship with the medical and nursing team as a whole.

PROTECTION OF PERSONS

This study was approved by the Rhône-Alpes Loire Consultative Committee for the Protection of Persons in Biomedical Research on November 21st 2005. It is covered by an insurance policy (SHAM no. 106288) taken out by the CHU of Saint-Etienne, the sponsor of this study.

Thank you for your cooperation.
CONSENT TO PARTICIPATE

Randomized clinical trial evaluating the efficacy of a retrievable vena cava filter in the prevention of pulmonary embolism recurrence.

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Mr, Ms. .................................................................[Surname, first name(s)]

Date of birth ....../........../19......

Address.................................................................

Dr............................................ has proposed that I participate in a study organized by the University Hospital (CHU) of Saint-Etienne. He/she has told me that I am free to accept or refuse and that this will not modify our relationship with respect to my treatment.

I received the following information, which I have clearly understood:

- The aim of this study is to evaluate whether the placement of an optionally retrievable vena cava filter can reduce pulmonary embolism recurrences and mortality related to pulmonary embolism during the first three months without increasing the risk of phlebitis,

- According to the result of a draw, I will or will not undergo insertion of a vena cava filter,

- Irrespective of the group to which I am allocated, I will receive medical care in accordance with usual practice for 6 months. If I am included in the “filter” group, I will be hospitalized for 24 h, after 3 months, for removal of the filter.

I accept to participate in this study under the conditions specified in the patient information sheet. My consent to participate does not relieve the study organizers of their responsibilities. I maintain all my legal
rights. If I so wish, I will be free to cease my participation at any time. I will inform Dr ………………… accordingly.

In accordance with the law on “computer processing and liberties”, I have taken note of the fact that the data recorded in the context of this study will form the object of computer processing. My anonymity will be strictly preserved. My personal data will remain strictly confidential. I authorize their consultation solely by persons involved in the conduct of this study and, if necessary, by a representative of the health authorities. I may exercise my right to access and rectify these data at any time by contacting Dr………………

I may at any moment request any complementary information I require from Dr………………by calling…………………………………………………

Signed in……………… on ………/……/200…….in two copies, one of which is given to the participant.

Surname of the physician                            Surname and first name(s) of the patient

………………………………
………………………………

Signature of the physician                            Signature of the patient preceded by the statement “Read and approved”