Original Investigation

Effect of a Retrievable Inferior Vena Cava Filter Plus Anticoagulation vs Anticoagulation Alone on Risk of Recurrent Pulmonary Embolism
A Randomized Clinical Trial

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IMPORTANCE Although retrievable inferior vena cava filters are frequently used in addition to anticoagulation in patients with acute venous thromboembolism, their benefit-risk ratio is unclear.

OBJECTIVE To evaluate the efficacy and safety of retrievable vena cava filters plus anticoagulation vs anticoagulation alone for preventing pulmonary embolism recurrence in patients presenting with acute pulmonary embolism and a high risk of recurrence.

DESIGN, SETTING, AND PARTICIPANTS Randomized, open-label, blinded end point trial (PREPIC2) with 6-month follow-up conducted from August 2006 to January 2013. Hospitalized patients with acute, symptomatic pulmonary embolism associated with lower-limb vein thrombosis and at least 1 criterion for severity were assigned to retrievable inferior vena cava filter implantation plus anticoagulation (filter group; n = 200) or anticoagulation alone with no filter implantation (control group; n = 199). Initial hospitalization with ambulatory follow-up occurred in 17 French centers.

INTERVENTIONS Full-dose anticoagulation for at least 6 months in all patients. Insertion of a retrievable inferior vena cava filter in patients randomized to the filter group. Filter retrieval was planned at 3 months from placement.

MAIN OUTCOMES AND MEASURES Primary efficacy outcome was symptomatic recurrent pulmonary embolism at 3 months. Secondary outcomes were recurrent pulmonary embolism at 6 months, symptomatic deep vein thrombosis, major bleeding, death at 3 and 6 months, and filter complications.

RESULTS In the filter group, the filter was successfully inserted in 193 patients and was retrieved as planned in 153 of the 164 patients in whom retrieval was attempted. By 3 months, recurrent pulmonary embolism had occurred in 6 patients (3.0%; all fatal) in the filter group and in 3 patients (1.5%; 2 fatal) in the control group (relative risk with filter, 2.00 [95% CI, 0.51-7.89]; $P = .50$). Results were similar at 6 months. No difference was observed between the 2 groups regarding the other outcomes. Filter thrombosis occurred in 3 patients.

CONCLUSIONS AND RELEVANCE Among hospitalized patients with severe acute pulmonary embolism, the use of a retrievable inferior vena cava filter plus anticoagulation compared with anticoagulation alone did not reduce the risk of symptomatic recurrent pulmonary embolism at 3 months. These findings do not support the use of this type of filter in patients who can be treated with anticoagulation.

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Observational studies show a sharp increase in the placement of inferior vena cava filters over the past 3 decades, including their use as add-on therapy to anticoagulant therapy in unselected patients presenting with acute venous thromboembolism.[1-5] However, due to the paucity of reliable data on the long-term benefit-risk ratio of these devices, guidelines vary significantly.[6-10]

A previous randomized study among patients with proximal deep vein thrombosis, with or without pulmonary embolism, showed that placement of a permanent inferior vena cava filter in addition to anticoagulation significantly reduced the risk of recurrent pulmonary embolism compared with anticoagulation alone.[11,12] However, this benefit was offset by a greater delayed risk of recurrent deep vein thrombosis (associated with filter thrombosis in 46% of cases) and a lack of effect on all-cause mortality. Temporary filter placement, now feasible, combined with anticoagulation and followed by anticoagulation alone after filter removal, may prevent early pulmonary embolism recurrence and avoid delayed deep vein thrombosis.[11-13] Moreover, filter benefit may be greater in patients at higher risk of early pulmonary embolism recurrence, ie, those whose initial event was pulmonary embolism, particularly if associated with additional risk factors.[6,7,12]

We conducted a randomized, open-label, blinded end point trial to assess the efficacy and safety of retrievable vena cava filter placement in association with anticoagulation compared with anticoagulation alone for prevention of pulmonary embolism recurrence in patients with pulmonary embolism who have a high risk of recurrence. Filter retrieval was mandatory at 3 months from placement and anticoagulation was continued for at least 6 months in all patients.

Methods

The Prévention du Risque d'Embolie Pulmonaire par Interruption Cave 2 (Prevention of Recurrent Pulmonary Embolism by Vena Cava Interruption 2; PREPIC2) study was conducted in accordance with the ethical principles stated in the Declaration of Helsinki, Good Clinical Practice, and relevant French regulations regarding ethics and data protection. The protocol and amendments were approved by the central independent ethics committee Comités de Protection des Personnes Sud-Est1 (Supplement 1). Written informed consent was obtained from all patients before randomization.

Patients

Consecutive patients aged 18 years or older, hospitalized for acute, symptomatic pulmonary embolism associated with acute lower-limb deep vein or superficial vein thrombosis, confirmed by means of standard objective tests, were eligible for randomization. Objective tests included spiral computed tomography, ventilation-perfusion lung scan, or pulmonary angiography to confirm pulmonary embolism, and bilateral compression ultrasonography and/or venography to confirm lower-limb vein thrombosis. Patients had to present at least 1 additional criterion for severity: older than 75 years, active cancer, chronic cardiac or respiratory insufficiency, ischemic stroke with leg paralysis within the last 6 months (but more than 3 days before randomization), deep vein thrombosis that involved the iliocaval segment or was bilateral, or at least 1 sign of right ventricular dysfunction or myocardial injury.[12,14-18] Signs of right ventricular dysfunction or myocardial injury included evidence of right ventricular dilatation or pulmonary hypertension on echocardiography, or abnormal levels of at least 1 of the following biomarkers: brain natriuretic peptide, N-terminal pro-brain natriuretic peptide, or cardiac troponin T or I.

Patients were excluded (1) if insertion of a vena cava filter was indicated because of a transient or permanent contraindication to anticoagulation therapy or because recurrent thromboembolism had occurred despite adequate anticoagulant therapy, (2) if a vena cava filter had already been inserted, (3) if a thrombosis in the vena cava did not allow filter insertion, or (4) if full-dose anticoagulant treatment had been administered during more than 72 hours before randomization. Patients were also excluded if they had undergone noncancer surgery within the past 3 months or cancer surgery within the past 10 days.[16] Other exclusion criteria were known allergy to iodinated contrast media, serum creatinine greater than 2.04 mg/dL per liter (to convert to micromoles, multiply by 88.4), life expectancy less than 6 months, and pregnancy.

Randomization, Treatments, and Follow-up

Patients were randomized to the filter group or control group by a central, 24-hour, interactive voice response system, which ensured concealed allocation. Randomization was performed in randomly permuted blocks of 4 or 6 with stratification according to center and patient creatinine clearance (estimated using the Cockcroft and Gault formulas; 30 mL/L or less vs more than 30 mL/L).

Patients in both study groups received full-dose anticoagulant therapy according to guidelines for at least 6 months (eMethods in Supplement 2). Continuation of anticoagulation thereafter was at the investigator's discretion. Although the choice of anticoagulant therapy was left to the investigators' discretion (ie, any injectable anticoagulant agent followed by vitamin K antagonist as soon as possible), investigators were strongly encouraged to use unfractionated heparin as the injectable agent in patients with a creatinine clearance of less than 30 mL/min, and, whenever possible, a low-molecular-weight heparin for 6 months rather than a vitamin K antagonist in patients with cancer.

Patients assigned to the filter group had a retrievable vena cava filter (ALN filter, ALN Implants Chirurgicaux)[19-22] inserted within 72 hours from randomization. In patients who had received thrombolytic therapy for the index event, insertion of the filter was to be postponed to more than 36 hours after thrombolysis. Filters were to be retrieved at 3 months. In all participating centers, filters were placed and retrieved by experienced vascular and interventional radiologists according to a standardized procedure, based on the technical documentation provided by the manufacturer. All patients underwent cavography before and after filter placement and conventional abdominal x-ray 24 hours to 48 hours after implan-

tation. Before filter retrieval, ultrasonography or venography was performed to detect filter thrombosis. Cavography was performed after retrieval in all patients.

Patients attended follow-up visits at 3 and 6 months from randomization, and were instructed to report to the study center immediately if any symptoms or signs suggestive of venous thromboembolism or bleeding occurred between visits.

Outcome Measures

The primary efficacy outcome was fatal or symptomatic nonfatal pulmonary embolism recurrence at 3 months. Secondary efficacy outcomes were fatal or nonfatal symptomatic pulmonary embolism recurrence at 6 months and new or recurrent symptomatic deep vein thrombosis at 3 and 6 months. Safety outcomes were major bleeding and death from any cause at 3 and 6 months. Filter complications, including thrombosis, migration, tilting, penetration of the vena cava wall, access site hematomas, and infections, were assessed from insertion to retrieval. Assessment of outcomes was based on accepted criteria (eMethods in Supplement 2).

All efficacy and safety outcomes were reviewed by the central adjudication committee, the members of which were blinded to treatment assignments.

Statistical Analysis

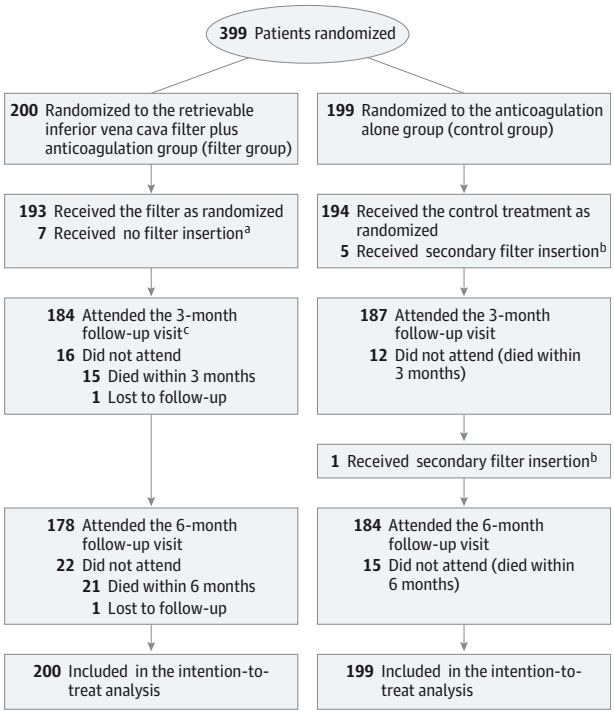
We assumed an 8.0% incidence of the primary efficacy outcome in the control group based on rates of recurrent fatal pulmonary embolism and case fatality rates of venous thromboembolism recurrence observed in previous studies[16,23,24] and considering that our study population would be in the highest risk category for recurrent pulmonary embolism. An unpublished subgroup analysis of a previous study[11] showed an 82% reduction in this risk in patients with pulmonary embolism receiving a permanent vena cava filter as well as anticoagulation compared with those treated with anticoagulation alone. We, therefore, postulated a 75% reduction in risk of the primary outcome in the filter group. Based on these assumptions, a sample size of 200 patients per group had an 80% power to detect a difference between the 2 groups. Statistical tests were 2-sided and statistical significance was indicated by a *P* value of less than .05.

All analyses were performed on the intention-to-treat population, defined as all randomized patients. Patients for whom no information was available concerning efficacy outcome were considered as missing for this end point. A 2-sided Fisher exact test at the 5% significance level was performed for all outcomes, and resulting *P* values were reported. Absolute differences and relative risks with 95% CIs (normal approximation) were also reported. An additional primary efficacy analysis was performed, considering for the comparison only patients assigned to filter placement who actually received a filter. To take into account patients with censored information on outcomes, a time-to-event analysis was performed using the Kaplan-Meier method, and between-group comparisons were performed using the log-rank test. The hazard ratio and corresponding 95% CI were calculated. Time within the therapeutic international normalized ratio (INR) range was calculated using standard methods,[25] excluding the initial parenteral anticoagulant therapy lead-in period and with a correction for planned interruptions.

An interim analysis after inclusion and follow-up of the first 200 patients was planned to assess whether the study should be stopped due to futility or early efficacy (eMethods in Supplement 2). Early efficacy was defined as a significant difference between the 2 groups at the 2-sided threshold of $\alpha = .001$. Based on the results of this interim analysis, the study was continued as planned.

Statistical analyses were performed using SAS software (SAS Institute), version 9.3.

Figure 1. Patient Flow Diagram for the Prevention of Recurrent Pulmonary Embolism by Vena Cava Interruption 2 (PREPIC2) Trial



The number of patients screened for eligibility is not available.

[a] Detailed information on patients who could not receive the intervention in the filter group is provided in Figure 2.

[b] Of the 199 patients assigned to the control group, all received the control treatment as randomized; 6 subsequently underwent filter insertion during the study (4 because anticoagulation was to be stopped prior to a planned invasive procedure or surgery at days 10, 19, 39, and 116, and 2 due to a bleeding complication at days 8 and 17).

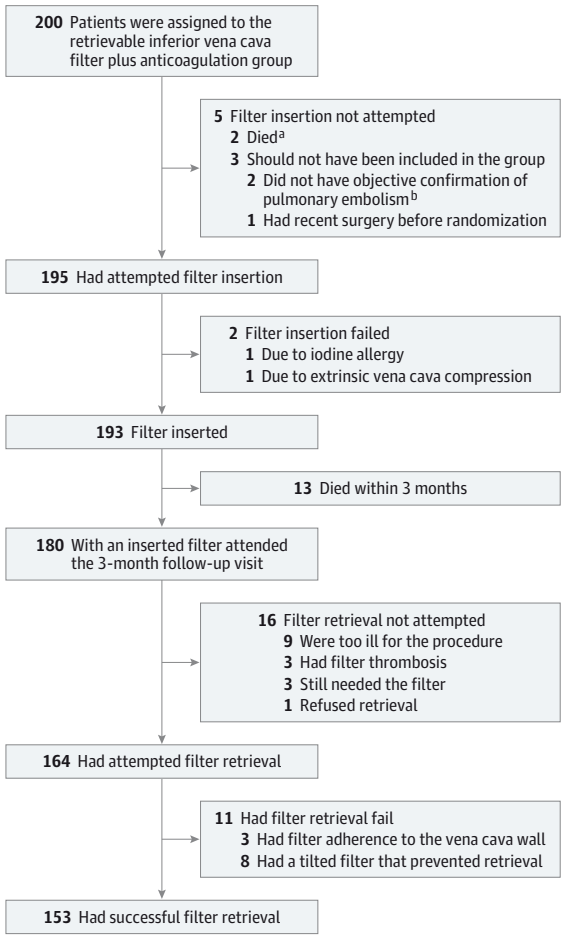
[c] Four of these patients had no filter implanted (Figure 2).

Results

Study Population and Treatments

Between August 2006 and July 2012, 399 patients were randomized in 17 French centers, 200 to the filter group and 199 to the control group (**Figure 1**). In the filter group, the diagnosis of pulmonary embolism could not be objectively documented in 2 patients (eTable 1 in Supplement 2). Of these 2 participants, 1 was lost to follow-up and is not included in the

Figure 2. Flow Diagram for Filter Insertion and Retrieval in the Filter Group for the Prevention of Recurrent Pulmonary Embolism by Vena Cava Interruption (PREPIC2) Trial



[a] One patient with active cancer was included in the study on February 27, 2009. Full-dose unfractionated heparin had been started on February 26, 2009. The patient experienced a cardiac arrest during the filter insertion procedure on February 28, 2009. The other patient was included in the study on January 8, 2010. Full-dose unfractionated heparin had been started on January 5, 2010. Filter insertion was planned on January 8, 2010, but could not be performed as the patient was unable to sustain the supine position during the procedure. Cardiac arrest occurred during the night between January 9, 2010, and January 10, 2010. Autopsy revealed bilateral pulmonary carcinoma with multiple pulmonary emboli.

[b] One of these 2 patients was lost to follow-up and was considered as missing in the analysis. The other patient was included in the intention-to-treat population.

outcome measures. The other participant continued in the study protocol and was included in the intention-to-treat analyses (**Figure 2**). Most baseline characteristics and features of the index event (**Table 1**), as well as antithrombotic treatments received during the study (**Table 2**), were well balanced between the 2 groups, except that more filter-treated patients had chronic respiratory failure.

Filter insertion was attempted in 195 of the 200 patients (97.5%) assigned to the filter group, and was successful in 193 of those 195 patients (99.0%) (Figure 2). The mean time between randomization and the attempt was 1.5 days (SD, 0.6). Filter retrieval was attempted in 164 of the 180 patients (91.1%) who had a filter inserted and attended the 3-month follow-up visit, being successful in 153 of those 164 patients (93.3%) (Figure 2). Of the 199 patients assigned to the control group, 6 subsequently underwent filter insertion during the study, 4 because anticoagulation was to be stopped prior to a planned invasive procedure or surgery (at days 10, 19, 39, and 116), and 2 due to a bleeding complication (at days 8 and 17).

Clinical Outcomes

By 3 months, pulmonary embolism had recurred in 6 patients (3.0% [95% CI, 1.1% to 6.5%]) in the filter group and 3 patients (1.5% [95% CI, 0.3% to 4.3%]) in the control group (relative risk with filter, 2.00 [95% CI, 0.51 to 7.89]; $P = .50$) (**Table 3**). The absolute difference in risk was +1.50 percentage points (95% CI, −1.4 to 4.4). All episodes in the filter group and 2 of 3 in the control group were fatal. Similar results were observed when considering only patients in the filter group who had actually received a filter (Table 3). One additional pulmonary embolism recurrence was observed in each group between 3 and 6 months. The time-to-event analysis confirmed these results (eTable 2 and eFigures 1-3 in Supplement 2).

No difference was observed between the 2 treatment groups with respect to deep vein thrombosis, major bleeding, or death from any cause at 3 and 6 months (Table 3 and eTables 3-4 in the Supplement 2). The main cause of death in both treatment groups was cancer. Among the 193 patients receiving a filter, access site hematoma occurred in 5 patients (2.6%), filter thrombosis in 3 patients (1.6%) and retrieval failure due to mechanical reasons in 11 patients (5.7%) (Figure 2). One participant experienced a cardiac arrest during filter insertion.

Discussion

The availability of retrievable inferior vena cava filters has probably contributed to the increasing use of filters for managing acute venous thromboembolism, including their use in addition to full-dose anticoagulant therapy in patients with pulmonary embolism, a large clot burden, a poor cardiopulmonary reserve, or a suspected increased risk for recurrence,[1-5] as advocated by several guidelines.[8-10] The results of the present study do not support such a strategy, showing that, compared with anticoagulation alone, placement of a retrievable inferior vena cava filter for 3 months in addition to anticoagulation provided no benefit in terms of pulmonary embolism recurrence or mortality in patients presenting acute symptomatic pulmonary embolism.

A previous randomized study investigating permanent filter deployment in addition to anticoagulation compared with anticoagulation alone in patients with proximal deep vein thrombosis suggested that filters were effective in preventing long-term risk of symptomatic pulmonary embolism recurrence.[11,12] In this study, however, the rate of recurrent symptomatic pulmonary embolism was not significantly lower in the filter group during the first 90 days of follow-up, when all patients were receiving anticoagulant treatment.[11] The risk of pulmonary embolism recurrence was lower in the filter

group at 8-year follow-up, but the cessation of anticoagulant treatment in about half of the study population by then may have contributed to this apparent benefit, the majority of recurrent events in the control group occurring after anticoagulation had been stopped.[12] Another recent (although smaller) randomized study showed that permanent filters in addition to fondaparinux did not reduce the rate of recurrent pulmonary embolism at 3 months compared with fondaparinux alone in cancer patients with acute venous thromboembolism.[26] As previously reported,[11,12] we found that filters did not reduce overall mortality. In addition, we observed low rates of deep vein thrombosis recurrence. This finding was consistent with our study design requirement that filters be systematically retrieved at 3 months and with the known propensity of patients with pulmonary embolism to experience recurrence in the form of pulmonary embolism rather than as deep vein thrombosis.[6,7]

Although we sought to include patients in a high-risk category for pulmonary embolism recurrence, as reflected by our inclusion criteria, the 3-month 1.5% rate (95% CI, 0.31% to 4.34%) of pulmonary embolism recurrence observed in the control group was far below the expected 8.0% rate. This rate, however, was mainly based on the results of older cohort studies in which anticoagulation was likely to be suboptimal compared with current practice and the present study, especially in cancer patients. In recent clinical trials evaluating new oral anticoagulant agents, the rates of pulmonary embolism recurrence in patients receiving standard anticoagulation therapy were much lower (1.0% to 2.0% at up to 12 months), and close to ours.[27-29] Moreover, the rates of venous thromboembolism recurrence (including deep vein thrombosis recurrence) observed in these recent studies remain low (1.8% to 2.6%) even when considering patients with pulmonary embolism only,[27-29] including subgroups of patients older than 75 years, or presenting intermediate-risk pulmonary embolism or active cancer.[27,30] Therefore, we believe that the low rate of events observed in the control group of our study is consistent with contemporary care, indicating that modern management with full-dose anticoagulation therapy is likely very effective even in patients usually considered to be at high risk for recurrence, rendering unnecessary additional therapy such as inferior vena cava filters. By targeting patients at high risk of recurrence, we also recruited patients at high risk of major bleeding (5% within 3 months) because risk factors for venous thromboembolism are often risk factors for bleeding as well (eg, advanced age and cancer).

We used a single filter model to ensure study homogeneity, selecting the ALN filter because of its widespread use in France and the substantial experience with its placement for more than 1 month.[22,31] Our rates of successful filter implantation (99.0%) and retrieval (92.2%) compare well with those previously reported with this[19-22,31,32] or other filters.[33] We believe that our negative findings likely reflect the low event rate with effective anticoagulation alone rather than lack of filter efficacy, and as there is no evidence showing efficacy differences between retrievable filter models, our results are probably applicable to other retrievable filters. In addition, the filter

Table 1. Baseline Characteristics of the Patients in the PREPIC2 Trial[a]

	Group, No. (%)	
	Filter (n = 200)	Control (n = 199)
Age, mean (SD), y	74.2 (10.8)	72.7 (12.4)
Women	102 (51.0)	105 (52.8)
BMI ≥30	52 (27.7)	48 (25.0)
Creatinine clearance category, mL/min		
<30	1 (0.5)	5 (2.5)
30-<50	41 (20.5)	34 (17.1)
≥50	158 (79.0)	160 (80.4)
Risk factors for venous thromboembolism		
Personal history of venous thromboembolism	70 (35.0)	71 (35.7)
History of cancer (excluding active cancer)[b]	15 (7.5)	23 (11.6)
Hormone therapy[c]	18 (9.0)	13 (6.5)
Known thrombophilia	2 (1.0)	2 (1.0)
Main characteristics of the index pulmonary embolism		
Unprovoked[d]	148 (74.0)	158 (79.4)
Objectively confirmed	198 (99.0)	199 (100.0)
With a systolic blood pressure <100 mm Hg at least once	35 (17.9)	20 (10.9)
Concurrent Symptomatic Venous Thrombosis		
Vein thrombosis		
Proximal deep	137 (68.8)	138 (69.7)
Isolated distal deep	57 (28.6)	54 (27.3)
Isolated superficial	5 (2.5)	6 (3.0)
Severity criteria for eligibility		
Aged >75 y	110 (55.0)	99 (49.7)
Active cancer[b]	33 (16.6)	29 (14.6)
Chronic respiratory failure[e]	35 (17.5)	19 (9.5)
Chronic heart failure[e]	18 (9.0)	17 (8.5)
Ischemic stroke with leg paralysis within the past 6 mo	4 (2.0)	4 (2.0)
Deep vein thrombosis involving the iliocaval segment	18 (9.0)	17 (8.5)
Bilateral deep vein thrombosis	26 (13.0)	27 (13.6)
At least 1 sign of right ventricular dysfunction or myocardial injury[f]	126 (66.7)	120 (65.2)

Abbreviation: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared).

[a] Denominators may be lower than 200 and 199 due to missing data for some variables.

[b] Active cancer defined as treatment ongoing or stopped within the past year.

[c] Estrogen-containing hormonal replacement therapy, oral contraception, or cancer treatment.

[d] Pulmonary embolism was considered to be unprovoked if not occurring in a context of surgery within the previous 3 months, active cancer, bed rest for 3 consecutive days or more due to an acute medical disease within the previous 3 months, or any neurological disorder within the previous 3 months.

[e] Documented and receiving continuous treatment.

[f] Signs of right ventricular dysfunction included ratio of right ventricular and left ventricular diameters of more than 0.9 and systolic pulmonary artery pressure higher than 40 mm Hg; signs of myocardial injury included elevated levels of brain natriuretic peptide, N-terminal pro-brain natriuretic peptide, cardiac troponin T or cardiac troponin I; cutoff levels for defining elevated levels of biological markers reflecting myocardial injury were defined by the department of clinical chemistry at each participating site.

Table 2. Characteristics of Antithrombotic Treatment Received During the PREPIC2 Trial

	Group, No. (%)	
	Filter (n = 200)	Control (n = 199)
Thrombolytic therapy	4 (2.0)	2 (1.0)
Main initial parenteral anticoagulation[a]	200 (100.0)	199 (100.0)
Low-molecular-weight heparin	120 (60.0)	113 (56.8)
Unfractionated heparin	46 (23.0)	44 (22.1)
Fondaparinux	34 (17.0)	42 (21.1)
Duration in patients receiving subsequent vitamin K antagonist therapy, median (IQR), d[b,c]	12 (8-24)	11 (7-22)
Long-term parenteral therapy	34 (17.0)	22 (11.1)
Duration in patients not receiving subsequent vitamin K antagonist therapy, median (IQR), d[b]	184 (171-196)	183 (171-187)
Vitamin K antagonist[d]	166 (83.0)	177 (88.9)
INR at the time initial parenteral therapy was stopped, median (IQR)[e]	2.3 (2.0-2.7)	2.3 (2.1-2.7)
Duration, median (IQR), d[b,c]	182 (170-187)	181 (171-187)
Median percentage of time spent with INR in a given range, %		
<2.0	19.7	15.9
2.0-3.0	58.3	61.5
>3.0	11.8	13.7

Abbreviations: INR, international normalized ratio; IQR, interquartile range.

[a] In patients still alive at the end of their treatment period.

[b] Received for more than 1 day; patients could receive more than 1 parenteral anticoagulant treatment.

[c] The median (IQR) duration of treatment was comparable between the 2 groups for each category of parenteral treatment.

[d] A total of 56 patients did not receive vitamin K antagonist therapy, 52 because they had proven or highly suspected cancer and 4 because they died before the switch from parenteral therapy to vitamin K antagonist therapy could be accomplished. Among the 62 patients who had proven active cancer at inclusion, 38 patients (61.3%) received solely low-molecular-weight heparin, and 24 patients (38.7%) switched from parenteral therapy to a vitamin K antagonist (median duration of parenteral treatment, 13 d [IQR, 7-115]). The percentage of time spent in each INR category was calculated for each patient using linear interpolation.

[e] Data were missing for 29 patients in the filter group and 35 in the control group.

Table 3. Clinical Outcomes For Patients With at Least 1 Event in the PREPIC2 Trial

	Group, No. With Events (%)			
Clinical Outcomes	Filter (n = 200)[a]	Control (n = 199)	Relative Risk, % (95% CI)	*P* Value[b]
At 3 Months				
Recurrent pulmonary embolism (primary efficacy outcome)[c]	6 (3.0)	3 (1.5)	2.00 (0.51-7.89)	.50
Fatal	6 (3.0)	2 (1.0)		
Nonfatal	0 (0.0)	1 (0.5)		
Recurrent deep vein thrombosis	1 (0.5)	1 (0.5)	1.00 (0.06-15.9)	>.99
Recurrent venous thromboembolism	7 (3.5)	4 (2.0)	1.75 (0.52-5.88)	.36
Major bleeding	8 (4.0)	10 (5.0)	0.80 (0.32-1.98)	.63
Death	15 (7.5)	12 (6.0)	1.25 (0.60-2.60)	.55
At 6 Months				
Recurrent pulmonary embolism[c]	7 (3.5)	4 (2.0)	1.75 (0.52-5.88)	.54
Fatal	6 (3.0)	3 (1.5)		
Nonfatal	1 (0.5)	1 (0.5)		
Recurrent deep vein thrombosis	1 (0.5)	2 (1.0)	0.50 (0.05-5.47)	>.99
Recurrent venous thromboembolism	8 (4.0)	6 (3.0)	1.33 (0.47-3.77)	.59
Major bleeding	13 (6.5)	15 (7.5)	0.87 (0.42-1.77)	.69
Death	21 (10.6)	15 (7.5)	1.40 (0.74-2.64)	.29

[a] One patient in the filter group was lost to follow-up and was considered as missing in the analysis.

[b] Fisher exact test. Patients who died, with no event recorded before death, were considered as having experienced no event.

[c] The cumulative rates of events at 3 months were 3.0% in the filter group and 1.5% in the control groups when estimated using the Kaplan-Meier method, censoring data on patients who died or were lost to follow-up; hazard ratio (HR), 2.02 (95% CI, 0.51-8.09). Corresponding figures at 6 months were 3.5% in the filter group and 2.0% in the control group; HR, 1.78 (95% CI, 0.52-6.09). Similar efficacy results were observed when considering in the filter group only patients who had actually received a filter: pulmonary embolism recurrence was observed in 4 of 193 patients (2.1%) in the filter group and 3 of 199 patients (1.5%) in the control group (relative risk with filter, 1.37 [95% CI, 0.31-6.06]; *P* = .72).

complication rates observed in the present study are within the range of those previously reported for ALN and other filters.[9,22,34]

Potential limitations of our study include those inherent in its open-label nature, which we tried to minimize by using a concealed randomization system and a central adjudication committee blind to treatment assignments. It could be argued that the absence of a detectable benefit of the filter may reflect an undersized study population. Indeed, the wide 95% CI of the relative risk between the 2 groups with respect to the primary outcome (0.51 to 7.89) is consistent with low statistical power. However, given that the point estimate favored the control group, it seems reasonable to conclude that even assuming that filters might have conferred a benefit in a larger study population, this would have been extremely small. In addition, the observed lower limit of the 95% CI in absolute risk difference (−1.4%) in favor of filter placement suggests that such a benefit would not be clinically meaningful. Indeed, this small difference is smaller than the value of the noninferiority margin currently used in randomized clinical trials in this field and so may be considered as clinically irrelevant.[23,27,28]

We excluded patients with a contraindication to anticoagulation therapy and those experiencing recurrence despite adequate anticoagulant therapy. However, as in these patients filter placement represents practically the sole therapeutic option, their inclusion in a randomized trial raises ethical issues. Finally, our results do not exclude a possible benefit of filters in addition to anticoagulation in other subgroups of patients with venous thromboembolism, such as those with pulmonary embolism and hemodynamic instability, as recently suggested.[35-37]

Conclusions

Among hospitalized patients with severe acute pulmonary embolism, the use of a retrievable inferior vena cava filter plus anticoagulation compared with anticoagulation alone did not reduce the risk of symptomatic recurrent pulmonary embolism at 3 months. These findings do not support the use of this type of filter in patients who can be treated with anticoagulation.

ARTICLE INFORMATION

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