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A CLINICAL TRIAL OF VENA CAVAL FILTERS IN THE PREVENTION OF PULMONARY EMBOLISM IN PATIENTS WITH PROXIMAL DEEP-VEIN THROMBOSIS

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ABSTRACT

Background The efficacy and safety of vena caval filters in the prevention of pulmonary embolism in patients with proximal deep-vein thrombosis are still a matter of debate.

Methods Using a two-by-two factorial design, we randomly assigned 400 patients with proximal deep-vein thrombosis who were at risk for pulmonary embolism to receive a vena caval filter (200 patients) or no filter (200 patients), and to receive low-molecular-weight heparin (enoxaparin, 195 patients) or unfractionated heparin (205 patients). The rates of recurrent venous thromboembolism, death, and major bleeding were analyzed at day 12 and at two years.

Results At day 12, two patients assigned to receive filters (1.1 percent), as compared with nine patients assigned to receive no filters (4.8 percent), had had symptomatic or asymptomatic pulmonary embolism (odds ratio, 0.22; 95 percent confidence interval, 0.05 to 0.90). At two years, 37 patients assigned to the filter group (20.8 percent), as compared with 21 patients assigned to the no-filter group (11.6 percent), had had recurrent deep-vein thrombosis (odds ratio, 1.87; 95 percent confidence interval, 1.10 to 3.20). There were no significant differences in mortality or the other outcomes. At day 12, three patients assigned to low-molecular-weight heparin (1.6 percent), as compared with eight patients assigned to unfractionated heparin (4.2 percent), had had symptomatic or asymptomatic pulmonary embolism (odds ratio, 0.38; 95 percent confidence interval, 0.10 to 1.38).

Conclusions In high-risk patients with proximal deep-vein thrombosis, the initial beneficial effect of vena caval filters for the prevention of pulmonary embolism was counterbalanced by an excess of recurrent deep-vein thrombosis, without any difference in mortality. Our data also confirmed that low-molecular-weight heparin was as effective and safe as unfractionated heparin for the prevention of pulmonary embolism. (N Engl J Med 1998;338:409-15.)

PLACING a barrier in the inferior vena cava to prevent pulmonary embolism arising from venous thrombi was first suggested by Trousseau in 1868.[1] The procedure became common after intracaval filters became available in the late 1960s.[2] However, unfractionated heparin followed by oral anticoagulants for three months prevents pulmonary embolism in 95 percent of patients with proximal deep-vein thrombosis.[3,4] In these patients, the generally accepted indications for filter placement are therefore restricted to contraindications to or failures of anticoagulant therapy.[5-7]

The ease of insertion of the new filters by the percutaneous route and the reportedly low complication rates have increased their use and probably widened the indications for their use.[8-10] According to industry sources, 30,000 to 40,000 filters are inserted each year in the United States.[10] Among patients who have received filters and anticoagulants,[5] between 10 and 50 percent have presented with acute deep-vein thrombosis and concomitant pulmonary embolism,[11] chronic cardiac or pulmonary insufficiency,[12,13] advanced age,[14] cancer,[15] or large proximal[16] or free-floating[16,17] thrombi. Evidence support-

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ing the effectiveness of filters is lacking because there have been no randomized trials.[5,18,19] We undertook a randomized trial to evaluate the benefits and risks of prophylactic filter placement in addition to anticoagulant therapy in patients with proximal deep-vein thrombosis who were considered to be at high risk for pulmonary embolism.

Low-molecular-weight heparins have been shown to be at least as effective and safe as unfractionated heparin in the treatment of deep-vein thrombosis.[4] There was a need to evaluate these compounds in patients presumed to be at high risk who might receive a vena caval filter for prophylactic purposes. A two-by-two factorial design allowed us to compare both the use of a filter with no filter and low-molecular-weight heparin with unfractionated heparin.

METHODS

Study Design

In a multicenter, randomized, open trial at 44 centers in France, we compared the installation of a permanent vena caval filter with no filter and fixed-dose subcutaneous low-molecular-weight heparin with adjusted-dose intravenous unfractionated heparin. The protocol was approved by the institutional review boards of all participating institutions.

Patients

Consecutive hospitalized patients over 18 years of age were eligible if they had acute proximal deep-vein thrombosis confirmed by venography, with or without concomitant symptomatic pulmonary embolism, and if their physicians considered them to be at high risk for pulmonary embolism. Patients were excluded if they had any of the following: placement of a previous filter, contraindication to or failure of anticoagulant therapy, curative anticoagulant therapy lasting more than 48 hours, an indication for thrombolysis, short life expectancy, allergy to iodine, hereditary thrombophilia, severe renal or hepatic failure, pregnancy, or likelihood of noncompliance. After the patients gave written informed consent, randomization (stratified according to center) was performed by means of a central 24-hour computer telephone system.

Treatments

Four types of permanent vena caval filters were used: Vena Tech LGM (B. Braun, Boulogne, France), titanium Greenfield (Boston Scientific, Watertown, Mass.), Cardial (Bard, Saint-Etienne, France), and Bird's Nest (Cook Group, Bloomington, Ind.). These percutaneous filters were inserted under fluoroscopic control through a femoral or jugular vein immediately after the patient was randomized and cavography was performed.

Patients assigned to unfractionated heparin (Fournier, Paris) received an intravenous bolus dose of 5000 IU, then a continuous intravenous infusion of 500 IU per kilogram of body weight per day for 8 to 12 days, adjusted according to the activated partial-thromboplastin time so that the ratio of the patient's value to the control value remained between 1.5 and 2.5, according to the reagent used. Tests were performed four to six hours after the beginning of treatment or after a subtherapeutic activated partial-thromboplastin time had been recorded, and then at least daily. Patients assigned to low-molecular-weight heparin were given a weight-adjusted dose (1 mg, or 100 International Factor Xa Inhibitory Units, per kilogram) of subcutaneous enoxaparin (Bellon Rhône–Poulenc Rorer, Montrouge, France) every 12 hours for 8 to 12 days.

Warfarin or acenocoumarol therapy was started on day 4 and continued for at least three months. The dose was adjusted to achieve an international normalized ratio of 2 to 3. Treatment with either unfractionated heparin or low-molecular-weight heparin was continued until the international normalized ratio was 2 or more for two consecutive days. If the use of an oral anticoagulant was not possible, subcutaneous unfractionated heparin was used (ratio of activated partial-thromboplastin time to control value, 1.5 to 2) for at least three months. Graded-compression stockings were prescribed for the same period.

Base-Line Evaluation of Pulmonary Perfusion

All patients underwent base-line ventilation–perfusion scanning within 48 hours of enrollment. Pulmonary angiography was performed if the ventilation–perfusion scan was not available and was strongly recommended if the ventilation–perfusion scan was abnormal. A diagnosis of initial pulmonary embolism was made if there were positive findings on pulmonary angiography (intraluminal filling defect or sudden arterial cutoff) or, when pulmonary angiography was unavailable, if a ventilation–perfusion scan showed a high probability of pulmonary embolism.[20]

Follow-up and Surveillance

When clinically suspected pulmonary embolism occurred during the first 12 days, a ventilation–perfusion scan was obtained. Pulmonary angiography was performed if the ventilation–perfusion scan showed that the patient's condition was becoming worse (at least one new segmental perfusion defect) or if a scan could not be obtained. The same procedure was systematically performed between days 8 and 12 in all patients in whom pulmonary embolism was not confirmed before that date, in order to detect asymptomatic embolism. During initial treatment, full blood counts were obtained at base line, then twice weekly and when there was any bleeding.

At discharge, all patients and their general practitioners were asked to report any new symptoms of recurrent venous thromboembolism or any bleeding to the investigating center immediately. Follow-up visits were scheduled at three months and one year. At two years, the patient received a telephone call from a physician from the coordinating center who was unaware of the treatment assignments. During each visit or telephone call, the patient was asked about new symptoms of thromboembolic or hemorrhagic events and was asked to come to the investigating center again if such symptoms developed. For all events, radiologic, biologic, and clinical data, obtained at the time of occurrence, were recorded centrally by the coordinating center.

Assessment of Outcome Events

The primary outcome event was the occurrence of pulmonary embolism, either symptomatic or asymptomatic, within the first 12 days after randomization. Diagnosis of pulmonary embolism was based on a comparison between the base-line findings and those obtained when pulmonary embolism was suspected or between days 8 and 12. The angiographic diagnosis required the visualization of a new intraluminal filling defect or a sudden new arterial cutoff. When pulmonary angiography was unavailable, the diagnosis based on the ventilation–perfusion scan required the visualization of at least two new segmental mismatched perfusion defects, with no current improvement in other areas in cases of initial extensive perfusion defects.[21,22] Symptomatic pulmonary embolism included fatal pulmonary embolism diagnosed on the basis of strong clinical evidence or at autopsy.

Secondary outcome events were all symptomatic and included pulmonary embolism, recurrent deep-vein thrombosis, death, major filter complications, and major bleeding during the two-year follow-up period. Diagnosis of recurrent venous thromboembolism was based on a comparison between the previous findings and those obtained when thromboembolism was suspected. The diagnostic procedures for pulmonary embolism were identical to those for the primary outcome event. Recurrence of deep-vein thrombosis was diagnosed if there was a new intralumi-

nal filling defect on venography or if there was a lack of compressibility at a new site or an extension to a new venous segment of the thrombus on duplex ultrasonography.[23,24] In suspected venous thromboembolism, patency of the filter had to be assessed by duplex ultrasonography, cavography, or abdominal computed tomography. Major filter complications included thrombosis at the filter site, erosion into the wall of the vena cava, infection, and migration of the filter. Major bleeding was defined as overt hemorrhage that was fatal or that required transfusion of at least two units of red cells, surgical intervention, or cessation of treatment.

All pulmonary investigations performed within the first 12 days and all documented symptomatic events, including deaths, were validated by an independent adjudication committee whose members were unaware of the treatment assignments.

Statistical Analysis

The incidence of symptomatic pulmonary embolism in patients with proximal deep-vein thrombosis who were treated with intravenous unfractionated heparin alone was estimated to be about 1 to 2 percent during the first 12 days of treatment.[25,26] Since we decided to study a population presumably at high risk and also to consider both symptomatic and asymptomatic pulmonary embolism, we estimated that this incidence would be about 5 percent in the no-filter group and 1 percent in the filter group.[5] A reduction in the incidence of pulmonary embolism from 5 to 1 percent, with a two-tailed test at an alpha level of 5 percent and a beta risk of 10 percent, would require a sample size of 400 patients per group, or a total of 800 patients. However, the study was interrupted when, after the enrollment of 400 patients over four years, the steering committee, unaware of the results, decided that the slow recruitment rate was not compatible with continuation of the study.

All analyses were performed on an intention-to-treat basis. The chi-square test, Fisher's exact test, and Student's t-test were used. For long-term end points, Kaplan–Meier analysis of the cumulative rate of events was performed. Data on patients who died or were lost to follow-up were censored. Statistical significance was assessed with the Mantel–Haenszel method. Because of the factorial design, tests for interaction were performed.[27]

RESULTS

Study Population

Between September 1991 and February 1995, 400 patients were recruited. The log books, which were available from 13 centers (from which 272 patients were enrolled), recorded 735 patients who met the inclusion criteria. Of these, 370 (50 percent) were excluded, for the following reasons: placement of a previous filter (30 patients), contraindication to or failure of anticoagulant therapy (40 patients), anticoagulant therapy lasting more than 48 hours (88 patients), indication for thrombolysis (52 patients), short life expectancy (58 patients), follow-up impracticable (43 patients), and other reasons (59 patients). Of the 365 eligible patients, 93 did not consent to participate.

Of the 400 patients, 200 were randomly assigned to receive filters and 200 to receive no filters; 195 patients were randomly assigned to receive low-molecular-weight heparin and 205 to receive unfractionated heparin. The base-line characteristics of the treatment groups were similar (Table 1). A total of 197 patients presented with initial pulmonary embolism (145 symptomatic and 52 asymptomatic patients), which was confirmed by angiography in 84 percent of patients and by ventilation–perfusion scanning in 16 percent of patients. Ninety percent of patients presented with at least one, and 61 percent with at least two, of the following features: initial symptomatic pulmonary embolism, chronic cardiac or respiratory insufficiency, age of more than 70 years, cancer, or iliocaval thrombosis.

TABLE 1. BASE-LINE CHARACTERISTICS OF THE STUDY PATIENTS.

CHARACTERISTIC	FILTER (N=200)	NO FILTER (N=200)	LOW-MOLECULAR-WEIGHT HEPARIN (N=195)	UNFRACTIONATED HEPARIN (N=205)
Mean (±SD) age — yr	73±11	72±11.5	73±10.5	72±12
			number (percent)	
Male sex	92 (46)	98 (49)	93 (48)	97 (47)
History of venous thromboembolism	70 (35)	71 (36)	70 (36)	71 (35)
Chronic cardiac or respiratory insufficiency	47 (24)	39 (20)	50 (26)	36 (18)
Surgery in past 60 days	17 (8)	26 (13)	18 (9)	25 (12)
Cancer	32 (16)	24 (12)	24 (12)	32 (16)
Upper limit of deep-vein thrombosis				
Popliteal	13 (6)	10 (5)	15 (8)	8 (4)
Femoral	113 (56)	105 (52)	102 (52)	116 (57)
Iliac	70 (35)	77 (38)	74 (38)	73 (36)
Caval	4 (2)	8 (4)	4 (2)	8 (4)
Symptomatic initial pulmonary embolism	77 (38)	68 (34)	68 (35)	77 (38)
Asymptomatic initial pulmonary embolism	25 (12)	27 (14)	24 (12)	28 (14)

Treatments and Follow-up

Among the 200 patients assigned to receive a filter, 4 either refused the filter or had their filter removed because it failed. Among the 200 patients assigned to receive no filter, 8 received a filter within the first 12 days (4 in each heparin group), because of major bleeding or pulmonary embolism.

All patients received initial low-molecular-weight heparin or unfractionated heparin. Four patients assigned to receive unfractionated heparin received low-molecular-weight heparin. Ninety-four percent of the patients received the assigned heparin treatment for at least eight days. Premature discontinuation of heparin was not medically justified in two patients. At discharge, 91 percent of the patients were receiving oral anticoagulants, and 8 percent were receiving subcutaneous unfractionated heparin; 1 percent received no anticoagulants because of major bleeding. Ninety-four percent of the patients were still receiving anticoagulants at three months, and 38 percent at two years, with no significant differences between groups.

A systematic detection of asymptomatic pulmonary embolism between days 8 and 12 could not be undertaken for 28 patients: 4 who died of causes not related to pulmonary embolism before systematic investigation was undertaken, and 24 whose investigations were not performed or were not interpretable. Information about the primary outcomes for these patients was missing. At two years, the vital status of one patient was unknown, and whether nonfatal events had occurred was unknown for three patients.

Filter Compared with No Filter

Of the patients assigned to receive a filter, 56 percent received a Vena Tech LGM filter, 26.5 percent received a titanium Greenfield filter, and 15.5 percent received a Cardial or Bird's Nest filter. Two percent received no filter.

Thromboembolism

By day 12, two patients (1.1 percent) in the filter group and nine patients (4.8 percent) in the no-filter group had had symptomatic or asymptomatic pulmonary embolism ($P=0.03$) (Table 2). The difference was still significant when the analysis was adjusted for heparin therapy. When only patients with pulmonary embolism at enrollment were considered, similar results were obtained (1.1 percent and 8.6 percent, respectively).

After two years, symptomatic pulmonary embolism had occurred in 6 patients (with one death) in the filter group and in 12 patients (with five deaths) in the no-filter group ($P=0.16$) (Table 3). By multivariate analysis, an initial pulmonary embolism (whether symptomatic or not) was not a significant prognostic indicator of subsequent pulmonary embolism. Recurrent deep-vein thrombosis occurred in

TABLE 2. PRINCIPAL END POINTS WITHIN THE FIRST 12 DAYS AFTER RANDOMIZATION TO THE FILTER OR NO-FILTER GROUP.

END POINT	FILTER	NO FILTER	ODDS RATIO (95% CI)*	P VALUE
	number (percent)			
Pulmonary embolism				
Symptomatic†	2	5		
Asymptomatic	0	4		
All‡	2 (1.1)	9 (4.8)	0.22 (0.05–0.90)	0.03
Major bleeding	9 (4.5)	6 (3.0)	1.49 (0.53–4.20)	0.44
Death	5 (2.5)	5 (2.5)	0.99 (0.29–3.42)	0.99

*CI denotes confidence interval.

†The category includes certain or highly probable fatal pulmonary embolism.

‡Information about the primary end point was missing for 28 patients. Percentages were based on the 372 patients who were evaluated.

TABLE 3. PRINCIPAL END POINTS DURING THE TWO-YEAR FOLLOW-UP PERIOD IN THE FILTER AND NO-FILTER GROUPS.*

EVENT AND TIME OF OCCURRENCE	FILTER	NO FILTER	ODDS RATIO (95% CI)	P VALUE
	number (percent)			
Symptomatic pulmonary embolism†				
Enrollment–3 mo	2	6		
>3 mo–1 yr	0	4		
>1–2 yr	4	2		
All	6 (3.4)	12 (6.3)	0.50 (0.19–1.33)	0.16
Recurrent deep-vein thrombosis				
Enrollment–3 mo	9	6		
>3 mo–1 yr	8	7		
>1–2 yr	20	8		
All	37 (20.8)	21 (11.6)	1.87 (1.10–3.20)	0.02
Major bleeding				
Enrollment–3 mo	11	10		
>3 mo–1 yr	5	8		
>1–2 yr	1	4		
All	17 (8.8)	22 (11.8)	0.77 (0.41–1.45)	0.41
Death				
Enrollment–3 mo	15	10		
>3 mo–1 yr	12	12		
>1–2 yr	16	18		
All	43 (21.6)	40 (20.1)	1.10 (0.72–1.70)	0.65

*Estimates of incidence were derived from Kaplan–Meier survival analysis. CI denotes confidence interval.

†The category includes certain or highly probable fatal pulmonary embolism.

37 patients (20.8 percent) assigned to receive a filter and in 21 patients (11.6 percent) assigned to receive no filter (odds ratio, 1.87; 95 percent confidence interval, 1.10 to 3.20; P = 0.02) (Table 3). Recurrent venous thromboembolism occurred in 37 patients (20.8 percent) assigned to receive a filter and 29 patients (15.5 percent) assigned to receive no filter.

Mortality

In the first 12 days, five patients in the filter group died (two from bleeding on days 10 and 12, one from myocardial infarction on day 1, one from respiratory failure on day 10, and one from acute renal insufficiency on day 9), and five patients in the no-filter group died (four from pulmonary embolism on days 3, 4, 6, and 7, and one from infectious disease on day 4) (Table 2). After two years, 43 patients (21.6 percent) in the filter group had died, as compared with 40 patients (20.1 percent) in the no-filter group (Table 3). The causes of death were cancer (18 patients), cardiac or respiratory failure (13 patients), infectious disease (9 patients), bleeding (9 patients), pulmonary embolism (6 patients), and other causes (28 patients). According to multivariate analysis, chronic cardiac or respiratory insufficiency, age, and cancer were significant prognostic indicators of mortality. Adjustment for these factors did not change the results of the analysis.

Major Bleeding

With respect to the occurrence of major bleeding, no significant difference between groups was observed at day 12 (Table 2) or during long-term follow-up (Table 3).

Major Symptomatic Complications in the Filter Group

Examination for filter patency was performed in the 37 patients who had symptomatic recurrent venous thromboembolism within the two-year follow-up period. The examination found a thrombosis at the filter site in 16 patients (12 with recurrent deep-vein thrombosis and 4 with concomitant pulmonary embolism and recurrent deep-vein thrombosis). No other major complications were observed.

Low-Molecular-Weight Heparin Compared with Unfractionated Heparin

Thromboembolism

By day 12, three patients in the low-molecular-weight–heparin group (1.6 percent) and eight patients in the unfractionated-heparin group (4.2 percent) had had symptomatic or asymptomatic pulmonary embolism (P = 0.14) (Table 4). Analysis adjusted for filter assignment gave similar results. When only patients with pulmonary embolism at enrollment were considered, similar results were obtained (2.2 percent and 7.2 percent, respectively).

At three months, recurrent venous thromboembolism had been confirmed in 10 patients (5.3 percent) assigned to low-molecular-weight heparin (3 with pulmonary embolism and 7 with recurrent deep-vein thrombosis) and in 12 patients (6.0 percent) assigned to unfractionated heparin (4 with pulmonary embolism, 1 with pulmonary embolism and recurrent deep-vein thrombosis, and 7 with recurrent deep-vein thrombosis). At two years no difference was observed between the two groups (Table 5).

TABLE 4. PRINCIPAL END POINTS WITHIN THE FIRST 12 DAYS AFTER RANDOMIZATION TO THE LOW-MOLECULAR-WEIGHT–HEPARIN OR UNFRACTIONATED-HEPARIN GROUP.

END POINT	LOW-MOLECULAR-WEIGHT HEPARIN	UNFRACTIONATED HEPARIN	ODDS RATIO (95% CI)*	P VALUE
	number (percent)			
Pulmonary embolism				
Symptomatic†	2	5		
Asymptomatic	1	3		
All‡	3 (1.6)	8 (4.2)	0.38 (0.10–1.38)	0.14
Major bleeding	7 (3.6)	8 (3.9)	0.90 (0.33–2.49)	0.84
Death	4 (2.05)	6 (2.9)	0.69 (0.20–2.46)	0.57

*CI denotes confidence interval.

†The category includes certain or highly probable fatal pulmonary embolism.

‡Information about the primary end point was missing for 28 patients. Percentages were based on the 372 patients who were evaluated.

Mortality

In the first 12 days, four patients in the low-molecular-weight–heparin group died (one from pulmonary embolism on day 6, one from bleeding on day 12, one from infectious disease on day 4, and one from respiratory failure on day 10), and six patients in the unfractionated-heparin group died (three from pulmonary embolism on days 3, 4, and 7, one from bleeding on day 10, one from myocardial infarction on day 1, and one from renal insufficiency on day 9) (Table 4). After two years, 20.6 percent of the patients in the low-molecular-weight–heparin group and 21.1 percent of the patients in the unfractionated-heparin group had died (Table 5).

Major Bleeding

By day 12, seven patients in the low-molecular-weight–heparin group (3.6 percent) and eight patients in the unfractionated-heparin group (3.9 percent) had had major bleeding (Table 4). After three months, major bleeding had occurred in 10 patients

TABLE 5. PRINCIPAL END POINTS DURING THE TWO-YEAR FOLLOW-UP PERIOD IN THE LOW-MOLECULAR-WEIGHT–HEPARIN AND UNFRACTIONATED-HEPARIN GROUPS.*

EVENT AND TIME OF OCCURRENCE	LOW-MOLECULAR-WEIGHT HEPARIN	UNFRACTIONATED HEPARIN	ODDS RATIO (95% CI)	P VALUE
	number (percent)			
Symptomatic pulmonary embolism†				
Enrollment–3 mo	3	5		
>3 mo–1 yr	1	3		
>1–2 yr	3	3		
All	7 (3.9)	11 (5.7)	0.66 (0.26–1.70)	0.38
Recurrent deep-vein thrombosis				
Enrollment–3 mo	7	8		
>3 mo–1 yr	7	8		
>1–2 yr	15	13		
All	29 (16.6)	29 (15.8)	1.05 (0.62–1.75)	0.86
Major bleeding				
Enrollment–3 mo	10	11		
>3 mo–1 yr	5	8		
>1–2 yr	1	4		
All	16 (8.5)	23 (12.0)	0.72 (0.38–1.36)	0.30
Death				
Enrollment–3 mo	10	15		
>3 mo–1 yr	12	12		
>1–2 yr	18	16		
All	40 (20.6)	43 (21.1)	0.96 (0.62–1.48)	0.85

*Estimates of incidence were derived from Kaplan–Meier survival analysis. CI denotes confidence interval.

†The category includes certain or highly probable fatal pulmonary embolism.

(with two deaths) in the low-molecular-weight–heparin group and in 11 patients (with two deaths) in the unfractionated-heparin group (Table 5).

Thrombocytopenia

Within the first 12 days, heparin-induced thrombocytopenia was observed in two patients in the low-molecular-weight–heparin group and four patients in the unfractionated-heparin group. All cases were reversible without complications after the discontinuation of heparin treatment.

Interaction between Filter and Heparin Comparisons

Of the 11 patients who had a pulmonary embolism by day 12, 1 patient among the 2 in the filter group and 2 patients among the 9 in the no-filter group had received low-molecular-weight heparin. The interaction between the filter and heparin regimens was not statistically significant for the primary or secondary outcome events.

DISCUSSION

This study was undertaken to assess the efficacy and safety of vena caval filters in the prevention of pulmonary embolism in patients with proximal deep-vein thrombosis. We found that, in addition to heparin therapy, the use of a permanent filter initially reduced the occurrence of symptomatic or asymptomatic pulmonary embolism without major complications. However, no effect was observed on either immediate or long-term mortality. In addition, after two years, the initial beneficial effect of filters was counterbalanced by a significant increase in recurrent deep-vein thrombosis, which could be related to thrombosis at the filter site. Whatever its cause, this excess recurrence of deep-vein thrombosis should increase the incidence of the post-thrombotic syndrome and raises the question of whether long-term anticoagulant therapy should be administered after placement of a permanent filter.[5,28]

As compared with unfractionated heparin, low-molecular-weight heparin produced a better outcome in terms of the incidence of symptomatic or asymptomatic pulmonary embolism at day 12 and of recurrent venous thromboembolic events and mortality at three months, but the differences were not statistically significant. These results, observed in patients presumed to be at high risk, were consistent with those of a meta-analysis[4] of trials comparing low-molecular-weight heparin and unfractionated heparin in the treatment of isolated deep-vein thrombosis and with those of a recent study[29] comparing low-molecular-weight heparin with unfractionated heparin in the treatment of deep-vein thrombosis with or without concomitant pulmonary embolism. Although a significant reduction in major bleeding has been reported with the use of low-molecular-weight heparin,[4] we observed a similar incidence of major bleeding with low-molecular-weight and unfractionated heparin. A possible explanation for this difference may be the inclusion in our study of an older population more prone to bleeding,[30] whatever the treatment.

Although no significant interaction was found between the use or nonuse of a filter and the use of low-molecular-weight or unfractionated heparin, the initial beneficial effect of filters with concomitant low-molecular-weight heparin remains to be assessed.

This study demonstrated the initial efficacy of filters for the prevention of pulmonary embolism in patients presumed to be at high risk who had proximal deep-vein thrombosis and were receiving anticoagulants. However, because of the observed excess rate of recurrent deep-vein thrombosis and the absence of any effect on mortality among patients receiving filters, their systematic use cannot be recommended in this population. In addition, this study

showed that low-molecular-weight heparin was as effective and safe as unfractionated heparin for the initial treatment of proximal deep-vein thrombosis in patients presumed to be at high risk.

APPENDIX

The members of the Prévention du Risque d'Embolie Pulmonaire par Interruption Cave Study Group were as follows (all in France): **Participating Centers** *(in order of the number of patients enrolled): Bellevue Hospital, Saint-Etienne:* Y. Page, B. Tardy, P. Mismetti, I. Cusey, C. Comtet, and J.C. Bertrand; *Antoine Béclère Hospital, Clamart:* F. Parent, G. Simonneau, and D. Musset; *Clinique St. Vincent, Besançon:* R. Faivre and P.Y. Petiteau; *Trousseau Hospital, Tours:* G. Pacouret and B. Charbonnier; *General Hospital, Firminy:* P. Sagnol and P. Mathern; *Laënnec Hospital, Paris:* G. Meyer and H. Sors; *Cavale Blanche Hospital, Brest:* L. Bressolette and D. Mottier; *General Hospital, Roanne:* P. Mottet and G. Tempelhoff; *Hôtel Dieu Hospital, Angers:* A. Furber and P. Geslin; *Lariboisière Hospital, Paris:* G. Simoneau, P. Molho-Sabatier, and J.F. Bergmann; *General Hospital Lucien Hussel, Vienne:* C. Poulain and B. Veyre; *Belle-Isle Hospital, Metz:* J. Hermann and H. Joffreau; *Nord Hospital, Marseilles:* C. Juhan and Y. Alimi; *Clinique St. Hilaire, Agen:* R. Constans and J.L. Leymarie; *Fleyriat Hospital, Bourg en Bresse:* G. Demingeon and L. Holzapfel; *Côte de Nacre Hospital, Caen:* O. Coffin; *Clinique du Mail, La Rochelle:* J.P. Marcadé and J.P. Chantereau; *Pasteur Hospital, Nice:* F. Lemoigne; *St. Joseph Hospital, Paris:* P. Priollet, I. Lazareth, and G. Farkas; *Germon et Gauthier Hospital, Béthune:* B. D'Hautefeuille, C. Mycinski, and A. Senoussi; *Lyon Sud Hospital, Lyons:* C. Guerin; *Hôtel Dieu Hospital, Rennes:* B. Schleich and A. Le Helloco; *General Hospital, Albi:* M. Ammor and D. Galley; *General Hospital, Allauch:* M. Escande and B. Diadema; *General Hospital, Annecy:* J.B. Driancourt and P. Achard; *General Hospital, Bourgoin-Jailleux:* A. Pinel; *General Hospital Louis Pasteur, Dole:* F. Apffel and D. Magnin; *La Tronche Hospital, Grenoble:* P. Carpentier; *General Hospital, Le Mans:* D. Fagart; *Dupuytren Hospital, Limoges:* P. Lacroix; *Broussais Hospital, Paris:* J. Emmerich and J.N. Fiessinger; *R. Beauchant Hospital, Poitiers:* J. Allal; *Clinique de la Jomayère, Saint-Etienne:* J.M. Gallot-Lavallée; *Avicenne Hospital, Bobigny:* L. Guillevin; *Pellegrin Hospital, Bordeaux:* G. Sassous; *Intercommunal Hospital, Fréjus:* R. Mossaz; *Emile Roux Hospital, Le Puy:* J.P. Saboye and M. Viallet; *Croix Rousse Hospital, Lyons:* J.C. Guerin; *Salvator Hospital, Marseilles:* J.M. Sainty; *La Beauchée Hospital, St. Brieuc:* F. Zimbacca; *General Hospital, St. Chamond:* J.H. Payre; *Purpan Hospital, Toulouse:* A. Barret; **Steering Committee:** H. Decousus, Y. Page, X. Barral, L. Barritault, H. Boccalon, J.P. Boissel, P. Carpentier, B. Charbonnier, J.N. Fiessinger, Y. Huet, A. Leizorovicz, J. Marzelle, G. Meyer, E. Neuhart, H. Rousseau, and G. Simonneau; **Adjudication Committee:** P. Girard, M. Defour-Decousus, P. Hervé, and C. Lamer; **Independent Supervision Committee:** M.M. Samama, C. Caulin, and C. Chastang; Permanent Guest: A. Leizorovicz; **Coordinating Center:** *Clinical Pharmacology Unit, Bellevue Hospital, Saint-Etienne:* H. Decousus, A. Buchmuller, A. Devillard, D. Ollagnon, and B. Chastel; **Central Data Management Offices:** *Clinical Pharmacology Unit, Bellevue Hospital, Saint-Etienne:* S. Laporte and E. Venet; *Clinical Pharmacology Unit, Cardiological Hospital, Lyons:* A. Leizorovicz, S. Delair, and C. Fernandez; **Sponsor:** *Bellon Rhône–Poulenc Rorer Laboratories, Montrouge:* Y. Huet, E. Neuhart, P. Ill, and J.Y. Darmon; **Cosponsors:** Ministère Français de la Santé, Caisse Nationale d'Assurance Maladie, Structure Régionale d'Evaluation Interhospitalière Rhône-Alpes, Fondation de l'Avenir, Laboratoire B. Braun France, Laboratoires Diagnostica Stago France.

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