JACC: CARDIOVASCULAR INTERVENTIONS
VOL. ■, NO. ■, 2016

ISSN 1936-8798/$36.00
PUBLISHED BY ELSEVIER
http://dx.doi.org/10.1016/j.jcin.2016.08.039

Outcomes Associated With Inferior Vena Cava Filters Among Patients With Thromboembolic Recurrence During Anticoagulant Therapy

Meritxell Mellado, MD,[a] José I. Pijoan, MD,[b] David Jiménez, PhD,[c] Alfonso Muriel, Msc,[d] Drahomir Aujesky, MD,[e] Laurent Bertoletti, MD,[f] Herve Decousus, MD,[f] Deisy Barrios, MD,[c] Albert Clará, PhD,[a] Roger D. Yusen, MD, MPH,[g] Manuel Monreal, PhD,[h] for the RIETE Investigators

ABSTRACT

OBJECTIVES The aim of this study was to assess the effectiveness of inferior vena cava (IVC) filter use among patients who develop recurrent symptomatic venous thromboembolism (VTE) on anticoagulant therapy.

BACKGROUND There is a lack of efficacy evidence of IVC filter therapy in patients with VTE recurrence on anticoagulant therapy.

METHODS In this cohort study of patients with acute VTE identified from the RIETE (Registro Informatizado de la Enfermedad Tromboembólica) registry, the associations between IVC filter placement for VTE recurrence in the first 3 months of anticoagulant therapy and the outcomes of all-cause mortality, pulmonary embolism (PE)–related mortality, second recurrent VTE, and major bleeding rates through 30 days after diagnosis of recurrence were assessed.

RESULTS Among 17 patients treated with filters and 49 matched patients treated without filters for VTE recurrence that presented as deep vein thrombosis, propensity score–matched groups showed no significant differences in death for filter insertion compared with no insertion (17.7% vs. 12.2%; $p = 0.56$). Among 48 patients treated with filters and 91 matched patients treated without filters for VTE recurrence that presented as PE, propensity score–matched groups showed a significant decrease in all-cause death for filter insertion compared with no insertion (2.1% vs. 25.3%; $p = 0.02$). The PE-related mortality rate was not significantly lower for filter insertion than no insertion (2.1% vs. 17.6%; $p = 0.08$), though the point estimates markedly differed.

CONCLUSIONS Among patients with VTE recurrence during the first 3 months of anticoagulant therapy, IVC filter insertion was not associated with a survival benefit in patients who recurred with deep vein thrombosis, although it was associated with a lower risk for all-cause death in patients who recurred with PE. (J Am Coll Cardiol Intv 2016;■:■–■)

From the [a]Angiology and Vascular Department, Hospital del Mar, Barcelona, Spain; [b]Clinical Epidemiology Unit, BioCruces Health Research Institute, Hospital Universitario Cruces, Bizkaia, CIBER Epidemiología y Salud Pública, Madrid, Spain; [c]Respiratory Department, Hospital Ramón y Cajal, Universidad de Alcalá (IRYCIS), Madrid, Spain; [d]Biostatistics Unit, Ramón y Cajal Hospital and Instituto Ramón y Cajal de Investigación Sanitaria, CIBER Epidemiología y Salud Pública, Madrid, Spain; [e]Department of General Internal Medicine, Bern University Hospital, University of Bern, Bern, Switzerland; [f]Thrombosis Research Group, EA3065, Université de Saint-Etienne, Jean Monnet, Inserm, CIE3, Service de Médecine Interne et Thérapeutique, Hôpital Nord, CHU de Saint-Etienne, Saint-Etienne, France; [g]Divisions of Pulmonary and Critical Care Medicine and General Medical Sciences, Washington University School of Medicine, St. Louis, Missouri; and the [h]Department of Internal Medicine, Hospital Universitari Germans Trias i Pujol, Badalona, Universidad Católica de Murcia, Murcia, Spain. The authors have reported that they have no relationships relevant to the contents of this paper to disclose. Drs. Mellado and Pijoan contributed equally to this work.

Manuscript received June 27, 2016; revised manuscript received August 21, 2016, accepted August 25, 2016.

ABBREVIATIONS AND ACRONYMS

CI = confidence interval

DVT = deep vein thrombosis

IVC = inferior vena cava

LMWH = low-molecular weight heparin

PE = pulmonary embolism

VKA = vitamin K antagonist

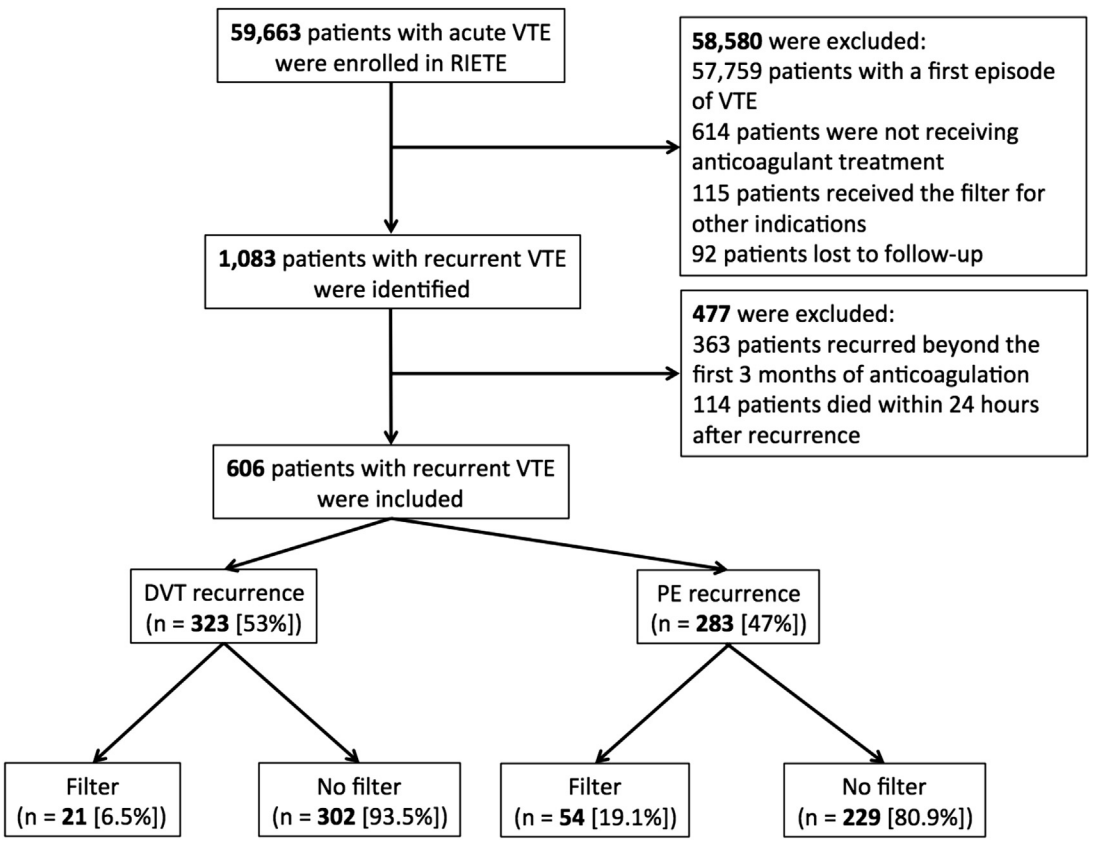
VTE = venous thromboembolism

For the past few decades, conventional treatment for venous thromboembolism (VTE) consisted of initial anticoagulation with parenteral agents (e.g., unfractionated heparin, low-molecular weight heparin [LMWH], fondaparinux) that provided a "bridge" to long-term vitamin K antagonist (VKA) oral anticoagulant therapy (1,2). Recently, the direct oral anticoagulant agents that inhibit factor Xa or IIa have begun replacing conventional therapy (3). Patients who receive VKAs have a 90-day VTE recurrence risk of approximately 6%, with active cancer and failure to rapidly achieve therapeutic levels of anticoagulation as the primary independent clinical predictors of early VTE recurrence (4). Patients enrolled in randomized controlled trials who received direct oral anticoagulant agents for treatment of acute symptomatic VTE had a 2% risk for recurrence during the first 3 to 12 months of treatment (5).

There are no randomized trials or prospective cohort studies that have evaluated the management of patients with recurrent VTE on anticoagulant therapy. On the basis of moderate-quality evidence that LMWH is more effective than VKA therapy in patients with VTE associated with cancer (6,7), the American College of Chest Physicians guideline on antithrombotic therapy suggested switching VTE treatment from VKAs to LMWH (at least temporarily) for patients who have recurrent VTE on VKA anticoagulant therapy (grade 2C) (8). Because the only clinical trial that evaluated the efficacy of inferior vena cava (IVC) filters (in combination with standard anticoagulant therapy) did not determine which patients with VTE recurrence on anticoagulation would benefit from IVC filter therapy (9), it is not known if insertion of a filter in these circumstances is worthwhile.

Given the lack of efficacy and effectiveness evidence of IVC filter therapy in patients with VTE

FIGURE 1 Patient Flow Diagram



DVT = deep vein thrombosis; PE = pulmonary embolism; RIETE = Registro Informatizado de la Enfermedad Tromboembólica; VTE = venous thromboembolism.

recurrence on anticoagulant therapy, we used data collected for an international multicenter registry (10) to assess the association between the insertion of an IVC filter and mortality and other outcomes during the first 30 days after treatment for a symptomatic VTE recurrence in patients who were receiving anticoagulant treatment.

METHODS

STUDY DESIGN. This propensity-matched retrospective cohort study used prospectively collected data from patients enrolled in the multicenter international RIETE (Registro Informatizado de la Enfermedad Tromboembólica) registry (1,10). All patients provided written or oral consent for participation in the registry in accordance with local ethics committee requirements.

STUDY COHORT. At each participating site, RIETE investigators (listed in the Online Appendix) aimed to enroll consecutive patients who had acute symptomatic or asymptomatic VTE confirmed by objective testing (11-13).

ELIGIBILITY. This study screened symptomatic patients who enrolled in RIETE from January 1, 2001, through September 31, 2015, with symptomatic VTE recurrence diagnosed during the first 3 months after VTE diagnosis. This study included only those patients who did not have pre-existing IVC filters, did not undergo filter therapy for the index VTE event, and were receiving anticoagulation for the first VTE event. To avoid immortal time bias, the study excluded those patients who died within 24 hours after VTE recurrence. The RIETE investigators defined deep vein thrombosis (DVT) recurrence as a new noncompressible vein segment or an increase of the vein diameter by at least 4 mm compared with the last available measurement on venous ultrasonography (14) and pulmonary embolism (PE) recurrence as a new ventilation-perfusion mismatch on a lung scan or a new intraluminal filling defect on spiral computed tomography of the chest (12).

STUDY OUTCOMES. This study used all-cause mortality through 30 days after VTE recurrence as the primary endpoint and 30-day PE-related mortality, major bleeding, and second recurrent VTE as secondary endpoints. The RIETE investigators used medical record review to assess vital status. For patients who died, further medical record review, and proxy interviews when necessary, assisted with determining date and cause of death. For deaths confirmed by autopsy or those following a clinically

TABLE 1 Clinical Characteristics of Patients With Deep Vein Thrombosis Recurrence Within 90 Days of the Index Thromboembolic Event Who Did or Did Not Receive Filters

	Received Filter (n = 21)	Did Not Receive Filter (n = 302)	p Value
Clinical characteristics			
Age, yrs	60.9 ± 14.6	60.2 ± 17.5	0.85
Age >80 yrs	2 (9.5)	32 (10.6)	1.00
Male	8 (38.1)	178 (58.4)	0.06
Weight, kg	73.6 ± 13.4	74.0 ± 15.0	0.89
Risk factors for VTE			
History of VTE	3 (14.3)	59 (19.5)	0.56
Cancer*	8 (38.1)	123 (40.7)	0.81
Recent surgery†	3 (14.3)	30 (9.9)	0.52
Immobilization for >4 days‡	4 (19.1)	61 (20.2)	0.90
Comorbid diseases			
Recent major bleeding	2 (9.5)	6 (2.0)	0.09
Clinical symptoms and signs at presentation			
Heart rate >110 beats/min§	4 (21.1)	23 (7.9)	0.09
Laboratory findings			
Abnormal creatinine level‖ (>2 mg/dl)	2 (10.5)	42 (14.1)	1.00
Hemoglobin, g/dl	12.7 ± 2.1	12.8 ± 2.2	0.95

Values are mean ± SD or n (%). *Active or under treatment in the past year. †In the previous month. ‡Immobilized patients are defined as nonsurgical patients who had been immobilized (i.e., total bed rest with bathroom privileges) for ≥4 days in the month before pulmonary embolism diagnosis. §Fourteen missing values. ‖Five missing values.

VTE = venous thromboembolism.

TABLE 2 Clinical Characteristics of Patients With Pulmonary Embolism Recurrence Within 90 Days of the Index Thromboembolic Event Who Did or Did Not Receive Filters

	Received Filter (n = 54)	Did Not Receive Filter (n = 229)	p Value
Clinical characteristics			
Age, yrs	59.1 ± 16.1	64.3 ± 17.0	0.04
Age >80 yrs	6 (11.1)	40 (17.5)	0.31
Male	25 (46.3)	113 (49.3)	0.69
Weight, kg	75.3 ± 13.5	72.6 ± 14.3	0.22
Risk factors for VTE			
History of VTE	9 (16.7)	36 (15.7)	0.86
Cancer*	21 (38.9)	102 (44.5)	0.45
Recent surgery†	10 (18.5)	24 (10.5)	0.10
Immobilization for >4 days‡	8 (14.8)	67 (29.3)	0.03
Comorbid diseases			
Recent major bleeding	2 (3.7)	6 (2.6)	0.65
Clinical symptoms and signs at presentation			
Heart rate >110 beats/min§	12 (24.0)	36 (16.3)	0.22
Laboratory findings			
Abnormal creatinine level‖ (>2 mg/dl)	14 (26.4)	35 (15.8)	0.08
Hemoglobin, g/dl	12.2 ± 2.1	12.5 ± 2.3	0.34

Values are mean ± SD or n (%). *Active or under treatment in the past year. †In the previous month. ‡Immobilized patients are defined as nonsurgical patients who had been immobilized (i.e., total bed rest with bathroom privileges) for ≥4 days in the month before pulmonary embolism diagnosis. §Twelve missing values. ‖Eight missing values.

VTE = venous thromboembolism.

TABLE 3 Patient Characteristics According to Initial Presentation, Before and After Matching

	Before Matching			After Matching		
	No Filter	Filter	Standardized Difference (%)	No Filter	Filter	Standardized Difference (%)
Deep vein thrombosis recurrence	(n = 302)	(n = 21)		(n = 49)	(n = 17)	
Demographic						
Age (yrs)	60.2 ± 17.5	60.9 ± 14.6	-4.5	60.1 ± 12.5	61.6 ± 14.2	-9.8
Duration of anticoagulation (days)	36.4 ± 23.8	26.7 ± 19.9	34.8	35.6 ± 21.4	26.9 ± 18.2	39.8
Comorbidities						
Cancer	123 (40.7)	8 (38.1)	5.3	22 (44.9)	7 (41.2)	7.5
Immobilization	61 (20.2)	4 (19.1)	2.9	13 (26.5)	2 (11.8)	36.7
Recent or active bleeding	6 (2.0)	2 (9.5)	32.1	2 (4.1)	1 (5.9)	7.8
Physical examination						
Heart rate (beats/min)	88.1 ± 16.1	96.9 ± 23.7	-43.4	91.4 ± 19.2	92.4 ± 20.0	-5.1
Laboratory measures						
Abnormal creatinine level (>2 mg/dl)	42 (14.1)	2 (10.5)	13.5	7 (14.3)	2 (11.8)	7.8
Hb level (g/dl)	12.8 ± 2.2	12.7 ± 2.1	8.7	12.1 ± 2.4	12.5 ± 2.3	-15.4
Pulmonary embolism recurrence	(n = 229)	(n = 54)		(n = 91)	(n = 48)	
Demographic						
Age (yrs)	64.3 ± 17.0	59.1 ± 16.1	31.1	61.8 ± 18.9	59.8 ± 16.0	11.6
Duration of anticoagulation (days)	30.0 ± 24.2	18.5 ± 18.5	53.6	19.6 ± 17.7	17.0 ± 17.0	15.3
Comorbidities						
Cancer	102 (44.5)	21 (38.9)	11.4	36 (39.6)	18 (37.5)	4.2
Immobilization	67 (29.3)	8 (14.8)	35.2	19 (20.9)	8 (16.7)	10.7
Recent or active bleeding	6 (2.6)	2 (3.7)	-6.0	1 (1.1)	1 (2.1)	-7.8
Physical examination						
Heart rate (beats/min)	91.3 ± 19.5	97.1 ± 19.7	-29.6	95.0 ± 18.9	96.2 ± 19.4	-6.2
Laboratory measures						
Abnormal creatinine level (>2 mg/dl)	35 (15.8)	14 (26.4)	-26.4	14 (15.4)	13 (27.1)	28.7
Hb level (g/dl)	12.5 ± 2.3	12.2 ± 2.1	14.8	12.1 ± 2.3	12.2 ± 2.1	-2.0

Values are mean ± SD or n (%).
Hb = hemoglobin.

severe PE, either initially or shortly after an objectively confirmed recurrent event, in the absence of any alternative diagnosis, the investigators were instructed to judge death as due to fatal PE.

STATISTICAL ANALYSIS. Because patients who present with PE are more likely to die of recurrent VTE than patients who present with DVT (15), we hypothesized a priori that the type of recurrence (i.e., DVT without symptomatic PE vs. PE with or without concomitant DVT) might confound the relationship between filter therapy and mortality. We therefore performed analyses stratified by type of recurrence.

We used chi-square and Fisher exact tests to compare categorical data between groups. We used the Kolmogorov-Smirnov test to assess continuous data for a normal distribution. We used 2-tailed unpaired Student *t* tests to compare normally distributed continuous data between 2 groups, and we used the Mann-Whitney *U* test for comparisons of continuous data not normally distributed.

Univariate analyses were performed to determine differences between the filter and no-filter groups in baseline demographics, risk factors, and laboratory results. We used a propensity score adjustment to compare treatment effects for patients with similar predicted probabilities of receiving a filter (16). We used logistic regression to estimate propensity scores. We modeled the log odds of the probability that a patient received a filter by using baseline demographic and clinical variables that were previously shown to be associated with mortality and/or treatment selection.

After generation of the propensity scores, we sought to estimate the reduction in 30-day overall mortality attributable to the insertion of a filter by using a greedy matched-paired analysis that has a 3:1 matching algorithm and does allow for replacements. We randomly selected a patient in the filter group and then matched that patient with the nearest patient in the no-filter group within a fixed caliper width of 0.2 times the SD of the logit of the propensity score (17).

To assess the success of the matching procedure, we measured standardized differences (measured in percentage points) in observed confounders between the matched groups (18). We estimated the filter effect using generalized estimating equation methods to incorporate the matched-pairs design, and adjusted for those covariates that remained unbalanced after matching (19). To assess the robustness of the findings, we performed inverse probability of treatment weighting.

We used psmatch2 for the propensity score analyses, and we used Stata version 13.1 (StataCorp, College Station, Texas) for Windows for all other analyses.

RESULTS

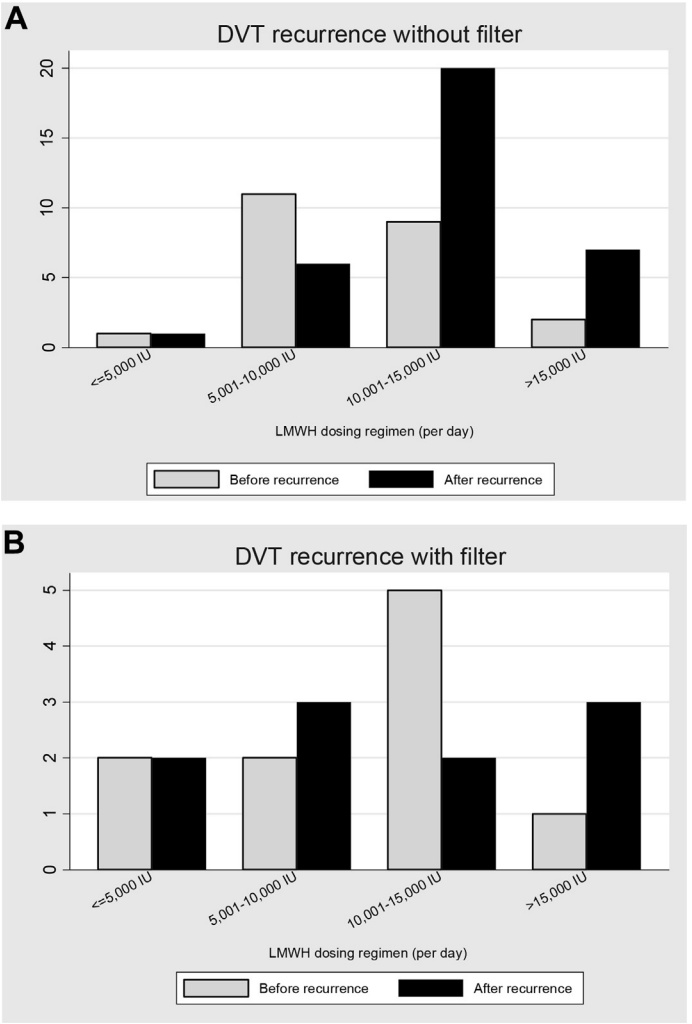
During the 15-year study period, a total of 606 patients with symptomatic, objectively confirmed DVT (53%) or PE (47%) recurrence were enrolled (**Figure 1**).

BASELINE CHARACTERISTICS AND OUTCOMES: UNMATCHED COHORT. The clinical characteristics of the patients in each subgroup are shown in **Tables 1** and **2**. Among the patients who had PE recurrence, those who received filters were younger (mean age 59.1 ± 16.1 years vs. 64.3 ± 17.0 years; p = 0.04) and had less comorbid diseases (immobilization) (14.8% vs. 29.3%; p = 0.03) compared with those who did not receive filters.

Overall, 94 of 606 patients (15.5%; 95% confidence interval [CI]: 12.7% to 18.6%) died (all-cause mortality) through 30 days after the diagnosis of recurrent VTE (10% of the patients with DVT recurrence vs. 21.9% of the patients with PE recurrence). The entire cohort had a 30-day PE-related mortality rate of 7.3% (44 of 606 patients). There were no PE-related deaths among patients with DVT recurrence, compared with 15.5% (44 of 283 patients; 95% CI: 11.6% to 20.3%) of those who had PE recurrence. Of those who had DVT recurrence, 2.2% experienced episodes of fatal or nonfatal major bleeding, compared with 1.8% of those who had PE recurrence during follow-up. Of the patients with DVT recurrence, 4.9% had a second nonfatal recurrence during the 30-day study follow-up period, whereas 3.2% of those with PE recurrence had a second non-fatal recurrence during follow-up.

BASELINE CHARACTERISTICS AND OUTCOMES: MATCHED COHORT. The matching of patients presenting with DVT recurrence yielded 17 patients treated with filters and 49 patients treated without filters. The matching process eliminated some differences that existed between groups regarding preexisting medical conditions or relevant clinical, physiological, and laboratory parameters (**Table 3**).

FIGURE 2 **Low-Molecular Weight Heparin Dosing Regimens Before and After Recurrent Deep Vein Thrombosis Among Patients Who Were Treated Without or With Inferior Vena Cava Filters**

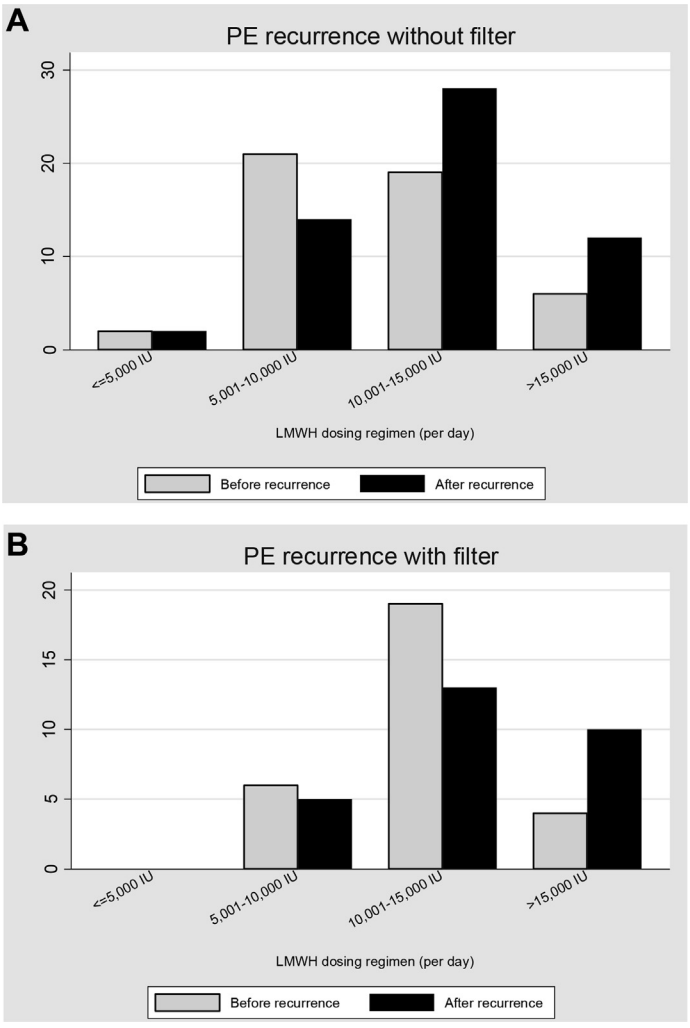


DVT = deep vein thrombosis; LMWH = low-molecular weight heparin.

Propensity analyses of the subgroup of patients with PE recurrence used 48 patients treated with filters and 91 patients treated without filters. The matched sample showed good balance for those variables that were previously shown to be associated with mortality and/or treatment selection (**Table 3**).

Among those patients who had DVT recurrence and did not receive filters, 34 patients (70.8%) received LMWH after the recurrence, compared with 23 patients (46.9%) at the time of the recurrence. **Figure 2A** shows LMWH dosing regimens among patients who did not have filters before and after the DVT recurrence. Among those patients with DVT recurrence who had filters inserted, 10 patients (58.9%) received

FIGURE 3 Low-Molecular-Weight Heparin Dosing Regimens Before and After Recurrent Pulmonary Embolism Among Patients Who Were Treated Without or With Inferior Vena Cava Filters



LMWH = low-molecular weight heparin; PE = pulmonary embolism.

LMWH after the recurrence, compared with 10 patients (58.9%) at the time of the recurrence. Figure 2B shows LMWH dosing regimens among patients who were treated with filters before and after the DVT recurrence.

Among those patients who had PE recurrence and did not have filters, 57 patients (64.0%) received LMWH after the recurrence, compared with 49 patients (53.8%) at the time of the recurrence. Figure 3A shows LMWH dosing regimens among patients who did not have filters before and after the PE recurrence. Among those patients with PE recurrence who had filters inserted, 28 patients (59.6%) received LMWH after the recurrence, compared with 29 patients (63.0%) at the time of the recurrence. Figure 3B shows LMWH dosing regimens among patients who were treated with filters before and after the PE recurrence.

PRIMARY OUTCOME. Overall cohort. Among the 323 patients who had DVT recurrence, 14.3% (3 of 21 patients; 95% CI: 3.1% to 36.3%) of the patients who received IVC filters died and 9.6% (29 of 302 patients; 95% CI: 6.5% to 13.5%) of those who did not receive filters died ($p = 0.44$) during follow-up. In the adjusted analysis, the 2 groups had similar rates of the primary outcome.

Among the 283 patients who had PE recurrence, 1.8% (1 of 54 patients; 95% CI: 0.1% to 9.9%) of the patients who received IVC filters died and 26.6% (61 of 229 patients; 95% CI: 21.0% to 32.9%) of those who did not receive filters died ($p < 0.001$) during follow-up. There was a significant decrease in the primary outcome for filter insertion compared with no insertion in the adjusted analysis ($p < 0.001$).

Matched cohorts. For patients with DVT recurrence, propensity score-matched pairs showed no significant differences in mortality for filter insertion compared with no filter insertion (17.7% vs. 12.2%; $p = 0.56$). For patients with PE recurrence, propensity score-matched pairs showed a significant decrease in all-cause death for filter insertion compared with no insertion (2.1% vs. 25.3%; $p = 0.02$) (Table 4).

SECONDARY OUTCOMES. Matched cohorts. In the matched cohort of patients with DVT recurrence, adjusted major bleeding (0% vs. 4.1%; $p = 1.00$) and second nonfatal recurrent VTE (11.8% vs. 4.1%, $p = 0.29$) rates did not significantly differ between filter insertion and the no filter insertion (Table 4).

Among patients with PE recurrence, analysis of propensity score-matched pairs showed a statistically nonsignificant trend toward a decreased risk for PE-related mortality for filter insertion compared with no insertion (2.1% vs. 17.6%; $p = 0.08$) (Table 4). In the matched cohort of patients with PE recurrence, adjusted major bleeding (4.2% vs. 3.3%; $p = 0.91$) and nonfatal recurrent VTE (4.2% vs. 2.2%; $p = 0.55$) rates did not significantly differ between filter insertion and no filter insertion (Table 4). We found consistent results when we used inverse probability of treatment weighting (data not shown).

DISCUSSION

In this study of patients who developed VTE recurrence during the first 3 months of anticoagulant

therapy for the primary event, IVC filter insertion was associated with a significantly lower risk for all-cause death in patients who recurred with PE, whereas we did not detect such an association in patients who recurred with DVT. However, the study design did not allow us to confirm a causal relationship between filter insertion and outcome.

Many studies have demonstrated the relative efficacy and safety of standard anticoagulant therapy for patients who have DVT or hemodynamically stable PE. Specifically, such patients have a low risk for early VTE recurrence (20). However, patients who have recurrent VTE experience a higher case-fatality rate than those with first events, and patients who develop recurrent PE appear to have a higher case-fatality rate than those with recurrent DVT (21). In fact, PE-associated mortality was the most common cause of death during the first 30 days after diagnosis of recurrence in our study, and the case-fatality rate of 15.5% for recurrent PE was significantly higher than the case-fatality rate that has been reported for the index PE event (1). Therefore, identification of treatment strategies for patients with early recurrent VTE, especially those with PE, has great importance.

Approximately 40% of our study population had active cancer. A previous study demonstrated that patients with cancer have a 3-fold risk for recurrent VTE and a 3-fold to 6-fold risk for major bleeding while receiving anticoagulant treatment with VKAs, compared with patients without cancer (7).

For patients who developed PE recurrence during the first 3 months of anticoagulant therapy, we found an association between IVC filter therapy and a lower death rate in comparison with continuation of anticoagulation without filter therapy. The PREPIC (Prévention du Risque d'Embolie Pulmonaire par Interruption Cave) II study enrolled patients with acute symptomatic PE who had concomitant DVT and at least 1 independent risk factor for fatal PE. Patients were randomized to treatment with a retrievable IVC filter plus anticoagulation versus anticoagulation alone. The study had a primary endpoint of symptomatic recurrent PE at 3 months, and it did not detect a difference in the primary endpoint between the randomized treatment groups (22). Although this trial sought to include patients in a high-risk category for PE recurrence, the 3-month rate (1.0%; 95% CI: 0.1% to 3.6%) of fatal recurrent PE observed in the control group was far lower than the 1-month 17.6% rate in our study. Differences in trial design and patient characteristics might explain some of the discrepant findings between the 2 studies.

TABLE 4 Adjusted Clinical Outcomes

Initial Presentation	30-Day Outcome	Filter	No Filter	OR (95% CI)	p Value
DVT recurrence*	Death	3/17 (17.7%)	6/49 (12.2%)	1.49 (0.39–5.67)	0.56
	PE-related death	0/17 (0.0%)	0/49 (0.0%)	–	–
	Major bleeding	0/17 (0.0%)	2/49 (4.1%)	–	–
	Nonfatal recurrent VTE	2/17 (11.8%)	2/49 (4.1%)	3.30 (0.36–29.41)	0.29
PE recurrence*	Death	1/48 (2.1%)	23/91 (25.3%)	0.06 (0.01–0.69)	0.02
	PE-related death	1/48 (2.1%)	16/91 (17.6%)	0.12 (0.01–1.29)	0.08
	Major bleeding	2/48 (4.2%)	3/91 (3.3%)	1.11 (0.19–6.63)	0.91
	Nonfatal recurrent VTE	2/48 (4.2%)	2/91 (2.2%)	2.13 (0.18–25.81)	0.55

*Adjusted (generalized estimating equation modeling) for variables not achieving 10% standardized difference after matching. The final model included the following covariates: age, sex, body weight, cancer, immobilization, recent major bleeding, previous VTE, heart rate, creatinine level, and hemoglobin level.

CI = confidence interval; DVT = deep vein thrombosis; OR = odds ratio; PE = pulmonary embolism; VTE = venous thromboembolism.

This study did not demonstrate a lower mortality associated with filter insertion in patients who recurred with DVT. In fact, the death rate was numerically higher with filter insertion than with anticoagulant therapy, though the difference was not statistically significant. Patients with DVT recurrence who did not have filters were treated with either dose escalation of LMWH (in patients already anticoagulated with LMWH) or initiation of therapeutic-dose LMWH (in patients who were taking VKAs) more frequently than patients who had filters. The absence of a detectable benefit of the filter may reflect an undersized study population and the limited power of the study to detect a difference in outcomes between the groups. However, given that the no-filter group had better outcomes, this study surprisingly suggests that a larger study population would have a very small chance of showing a benefit associated with filters in those who present with recurrent DVT.

We found a significantly lower mortality rate associated with IVC filter therapy in patients who recurred with PE. Because patients with PE recurrence who did not have filters were also treated with either dose escalation of LMWH or initiation of therapeutic-dose LMWH more frequently than patients who had filters, we hypothesize that filter insertion may have prevented some fatal PE recurrences.

STUDY LIMITATIONS. Potential limitations of our study include those inherent in the registry's observational nature and our retrospective study design. We tried to minimize concerns about treatment bias by using propensity score matching and additional regression-based adjustment to make the patient

groups comparable according to the measured confounders. Studies have found good agreement between the treatment effects in the propensity score studies compared with those in the randomized trials (23). However, residual confounding may still have occurred. In addition to using the propensity scores, we used inverse probability of treatment weighting to further address concerns of bias and to assess the robustness of the study findings. The fact that this method yielded similar conclusions further strengthened the soundness of the results. Despite the large number of patients assessed for this study from the RIETE registry, the relatively small sample size of the propensity-matched cohorts provided low statistical power and therefore raised the chance that the study would not detect a statistically significant difference in outcomes between the treatment groups (i.e., type II error).

CONCLUSIONS

IVC filter therapy might reduce the risk for death compared with anticoagulant therapy in patients who experience PE recurrence during the first 3 months of anticoagulant therapy. However, we did not detect a survival advantage associated with the use of IVC filter therapy in patients who have DVT recurrence while on anticoagulation.

ACKNOWLEDGMENTS The authors thank Sanofi Spain for supporting this registry with an unrestricted educational grant. The authors also thank Bayer Pharma AG for supporting this registry. Bayer Pharma AG's support was limited to the part of RIETE outside Spain, which accounts for 22.88% of the total patients included in the RIETE registry. The authors also thank the RIETE Registry Coordinating Center, S&H Medical Science Service, for their quality control data, logistic, and administrative support.

REPRINT REQUEST AND CORRESPONDENCE: Dr. David Jiménez, Respiratory Department, Hospital Ramón y Cajal, Universidad de Alcalá (IRYCIS), 28034 Madrid, Spain. E-mail: djimenez.hrc@gmail.com.

PERSPECTIVES

WHAT IS KNOWN? The benefits of IVC filter therapy for patients who develop recurrent VTE while on anticoagulant therapy lack clarity.

WHAT IS NEW? For patients who develop recurrent PE on anticoagulant therapy, IVC filter treatment in combination with anticoagulant therapy is associated with a lower risk for all-cause death than continued anticoagulation without filter therapy.

WHAT IS NEXT? A randomized clinical trial is planned that will assess the survival effects of IVC filter insertion in patients who have recurrent PE despite anticoagulant therapy.

REFERENCES

1. Jimenez D, De Miguel-Diez J, Guijarro R, et al. Trends in the management and outcomes of acute pulmonary embolism: analysis from the RIETE registry. J Am Coll Cardiol 2016;67:162–70.

2. Konstantinides SV, Torbicki A, Agnelli G, et al., for the Task Force for the Diagnosis and Management of Acute Pulmonary Embolism of the European Society of Cardiology (ESC). 2014 ESC guidelines on the diagnosis and management of acute pulmonary embolism. Eur Heart J 2014;35:3033–73.

3. Gómez-Outes A, Terleira-Fernández AI, Lecumberri R, Suárez-Gea ML, Vargas-Castrillón E. Direct oral anticoagulants in the treatment of acute venous thromboembolism: a systematic review and meta-analysis. Thromb Res 2014;134:774–82.

4. Heit J, Lahr B, Petterson T, Bailey K, Ashrani A, Melton LR. Heparin and warfarin anticoagulation intensity as predictors of recurrence after deep vein thrombosis or pulmonary embolism: a population-based cohort study. Blood 2011;118:4992–9.

5. van Es N, Coppens M, Schulman S, Middeldorp S, Büller HR. Direct oral anticoagulants compared with vitamin K antagonists for acute venous thromboembolism: evidence from phase 3 trials. Blood 2014;124:1968–75.

6. Carrier M, Le Gal G, Cho R, Tierney S, Rodger M, Lee AY. Dose escalation of low molecular weight heparin to manage recurrent venous thromboembolic events despite systemic anticoagulation in cancer patients. J Thromb Haemost 2009;7:760–5.

7. Schulman S, Zondag M, Linkins L, et al. Recurrent venous thromboembolism in anticoagulated patients with cancer: management and short-term prognosis. J Thromb Haemost 2015;13:1010–8.

8. Kearon C, Akl E, Ornelas J, et al. Antithrombotic therapy for VTE disease: Chest guideline and expert panel report. Chest 2016;149:315–52.

9. Decousus H, Leizorovicz A, Parent F, et al., for the Prévention du Risque d'Embolie Pulmonaire par Interruption Cave Study Group. A clinical trial of vena caval filters in the prevention of pulmonary embolism in patients with proximal deep-vein thrombosis. N Engl J Med 1998;353:1386–9.

10. Laporte S, Mismetti P, Décousus H, et al., for the RIETE Investigators. Clinical predictors for fatal pulmonary embolism in 15,520 patients with venous thromboembolism: findings from the RIETE registry. Circulation 2008;117:1711–6.

11. PIOPED Investigators. Value of ventilation/perfusion scan in acute pulmonary embolism: results of the Prospective Investigation of the Pulmonary Embolism Diagnosis (PIOPED). JAMA 1990;263:2753–9.

12. Remy-Jardin M, Remy J, Wattinne L, Giraud F. Central pulmonary thromboembolism: diagnosis with spiral volumetric CT with the single-breath-hold-technique-comparison with pulmonary angiography. Radiology 1992;185:381–7.

13. Kearon C, Ginsberg JS, Hirsh J. The role of venous ultrasonography in the diagnosis of suspected deep venous thrombosis and pulmonary embolism. Ann Intern Med 1998;129:1044–9.

14. Prandoni P, Cogo A, Bernardi E, et al. A simple approach for detection of recurrent proximal vein thrombosis. Circulation 1993;88:1730–5.

15. Douketis J, Kearon C, Bates S, Duku EK, Ginsberg JS. Risk of fatal pulmonary embolism in patients with treated venous thromboembolism. JAMA 1998;279:458–62.

16. D'Agostino RB Jr. Propensity score methods for bias reduction in the comparison of a treatment to a non-randomized control group. Stat Med 1998;17:2265–81.

17. Austin PC. Some methods of propensity-score matching had superior performance to others: results of an empirical investigation and Monte Carlo simulations. Biometr J 2009;1:171–84.

18. Austin PC. Propensity-score matching in the cardiovascular surgery literature from 2004 to 2006: a systematic review and suggestions for improvement. J Thorac Cardiovasc Surg 2007;134:1128–35.

19. Austin PC, Mamdani MM. A comparison of propensity score methods: a case-study estimating the effectiveness of post-AMI statin use. Statist Med 2006;25:2084–106.

20. Heit JA. Predicting the risk of venous thromboembolism recurrence. Am J Hematol 2012;87:S63–7.

21. Carrier M, Le Gal G, Wells PS, Rodger MA. Systematic review: case-fatality rates of recurrent venous thromboembolism and major bleeding events among patients treated for venous thromboembolism. Ann Intern Med 2010;152:578–89.

22. Mismetti P, Laporte S, Pellerin O, et al., for the PREPIC2 Study Group. Effect of retrievable inferior vena cava filter plus anticoagulation vs anticoagulation alone on risk of recurrent pulmonary embolism. JAMA 2015;313:1627–35.

23. Dahabreh IJ, Sheldrick RC, Paulus JK, et al. Do observational studies using propensity score methods agree with randomized trials? A systematic comparison of studies on acute coronary syndromes. Eur Heart J 2012;33:1893–901.

KEY WORDS deep vein thrombosis, pulmonary embolism, recurrence, survival, vena cava filter, venous thromboembolism

APPENDIX For a list of RIETE investigators, please see the online version of this article.