European Journal of Internal Medicine xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

European Journal of Internal Medicine

journal homepage: www.elsevier.com/locate/ejim

Original Article

Recurrence of venous thromboembolism in patients with recent gestational deep vein thrombosis or pulmonary embolism: Findings from the RIETE Registry☆

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ARTICLE INFO

Article history:
Received 30 July 2015
Received in revised form 21 January 2016
Accepted 11 February 2016
Available online xxxx

ABSTRACT

Introduction: The aim of this study was to investigate the recurrence rate of venous thromboembolism (VTE) and the prevalence of major bleeding or death in patients with previous VTE in pregnancy and puerperium. Risk factors for VTE recurrence were also assessed.
Materials and methods: We evaluated a cohort of patients enrolled in the international, multicenter, prospective Registro Informatizado de la Enfermedad Trombo-Embólica (RIETE) registry with objectively confirmed VTE.

Abbreviations: VTE, venous thromboembolism; DVT, deep vein thrombosis; IVC, inferior vena cava; LMWH, low-molecular-weight heparin; PE, pulmonary embolism; UFH, unfractionated heparin.

☆ **Condensation**: The 2-year recurrence rate was 3.3% in patients developing venous thromboembolism (VTE) during pregnancy or puerperium. Use of thrombolytics or inferior vena cava filter was associated with increased risk of VTE recurrence.

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http://dx.doi.org/10.1016/j.ejim.2016.02.013

Keywords:
Deep-vein thrombosis
Pulmonary embolism
Major bleeding
Recurrent thromboembolism
Pregnancy
Puerperium

Results: In the registry, 607 women were presenting with VTE that occurred during pregnancy or puerperium. The 2-year VTE recurrence rate was 3.3% (CI: 95 1.5–5.0%) and the recurrent VTE incidence rate was 2.28 events/100 patients-year. Among the 16 cases of VTE recurrence 11 cases appeared during drug treatment while only five cases were diagnosed after therapy discontinuation. No significant difference was found in treatment duration among these two subgroups of VTE recurrence cases and women without recurrence. Furthermore, the use of thrombolytics and inferior vena cava filter in initial treatment was associated to an increased risk of VTE recurrence.

Conclusions: The current study provides new insights on VTE recurrence rate in patients with deep vein thrombosis (DVT) or pulmonary embolism (PE) that occurred in pregnancy or postpartum period. These findings can contribute to risk assessment of thrombotic burden, thereby allowing for better decision making regarding antithrombotic management in this clinical setting.

1. Introduction

Among pregnant women, acute venous thromboembolism (VTE) is a leading cause of maternal mortality and morbidity [1–4]. VTE is a reported complication in 1–2 per every 1000 pregnancies [5–7]. Current guideline of antithrombotic therapy recommends treating VTE initially with unfractionated heparin (UFH), low-molecular-weight heparin (LMWH), or fondaparinux, followed by long-term anticoagulation (with LMWH or vitamin K antagonists — VKA) [8]. However, guidelines are based on the results of randomized clinical trials, and pregnancy is a common exclusion criterion to be recruited in these trials [9–13]. Moreover, as sample size of controlled studies is often too small to evaluate fatal outcomes, therapies are evaluated according to their effect on recurrence rate, major bleeding, and death from any cause [8]. Consequently, therapeutic regimens proposed by randomized controlled trials may not be applied to all patients affected with VTE [8]. As a result, management of VTE during pregnancy is not standardized between centers or countries [5].

VTE occurring during pregnancy and/or puerperium is considered a provoked event like VTE secondary to surgery, trauma, prolonged immobilization, oral contraception, or hormonal replacement therapy [14–18]. A recent meta-analysis estimated that the rate of recurrence in patients with symptomatic index VTE provoked by transient non-surgical risk factors (considering also pregnancy) was 4.2% during the first year and 8.4% during the first 2 years [19] but the number of reported cases of VTE during pregnancy is rather low [20].

We studied a cohort of patients enrolled in the international, multicenter, prospective Registro Informatizado de la Enfermedad Trombo-Embólica (RIETE) registry that included only patients with objectively confirmed VTE [8,21]. We also assessed these outcomes according to patients' initial presentation (deep-vein thrombosis [DVT], or pulmonary embolism [PE]) [8]. The aim of this study was to investigate the rate of DVT or PE recurrence, major bleeding or death in patients developing DVT or PE during pregnancy and puerperium, and try to identify predictors for VTE recurrence.

2. Methods

2.1. Inclusion criteria

We considered all consecutive patients in the RIETE Registry enrolled between January 2001 and June 2013 presenting with symptomatic, acute DVT or PE, confirmed by objective tests. We included only women with a diagnosis of VTE or PE developing during pregnancy or puerperium (up to 42 days after delivery). The exclusion criteria were patient involvement in therapeutic trials with a blind medication or a follow-up of less than three months after the diagnosis. All patients gave an oral or written informed consent for participation in the registry, according to local ethics committee requirements.

2.2. Follow-up

All patients included in this prospective observational registry were managed according to the local clinical practice of each participating hospital. All included patients were followed-up for at least 3 months and signs or symptoms of recurrence or bleeding were recorded. Each episode of clinically suspected recurrent disease was documented by appropriate imaging tests and blood examinations.

2.3. Considered outcomes

The primary outcome was the development of recurrent PE (with or without DVT signs), recurrent DVT or major bleeding appearing during the course of anticoagulant therapy. Secondary outcomes were fatal VTE and fatal bleeding. Bleeding complications were classified as "major" if they were overt and required a blood transfusion of two or more units of blood, or were retroperitoneal, spinal, intracranial, or when they were fatal. We considered as fatal recurrent VTE any new diagnosis post-mortem, immediately before death by diagnostic imaging, or by clinical suspicions of a high probability of fatal pulmonary embolism as adjudicated by the study investigators. In addition, we considered fatal bleeding any death occurring within seven days of a major bleeding episode, in the absence of other specific cause of death. Study outcomes are adjudicated by the attending physicians. We also considered the possible risk factors to predict VTE recurrence.

2.4. Study variables and definitions

Data on the following factors are collected in the RIETE Registry: patient's baseline characteristics; clinical status including any coexisting or underlying conditions; additional risk factors for VTE; the treatment received upon VTE diagnosis; and the outcome. Immobilized patients were defined as non-surgical patients who had been immobilized for ≥4 days in the 2-month period prior to VTE diagnosis. Surgical patients were defined as those who underwent an operation (including cesarean section) in the 2 months prior to VTE diagnosis. Recent major bleeding was considered in patients who suffered from major bleeding <30 days prior to VTE. Creatinine clearance level was calculated according to the Cockcroft and Gault formula using the first creatinine level measured after VTE diagnosis [22].

2.5. Statistical analysis

Data were analyzed using R v3.0.1 with $p < 0.05$ considered significant. T-test, Wilcoxon test, Kruskal–Wallis test, chi-square test, Fisher exact tests, and Logrank tests were performed in addition to univariate and multivariate Cox proportional hazards regression analysis. For the Cox proportional hazards regression analysis, VTE recurrence or major bleeding was used as selected outcome and the possible predictive

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factors were considered in the model. In addition, in the final model only those factors found by stepwise selection were included.

3. Results

Among 46'770 patients registered in the RIETE Registry, 607 (1.3%) were women presenting with objectively confirmed, acute symptomatic VTE that occurred during pregnancy or puerperium. Among these 607 women 16 had a VTE recurrence and none had over one recurrence. Among women with PE, the prevalence of recent surgery was higher than among women presenting with DVT alone (Table 1). Moreover, while during pregnancy DVT was more common than PE, PE was more common during puerperium. The most common drug used as initial therapy was LMWH, and then unfractioned heparin (Table 1). Thrombolytics and inferior vena cava (IVC) filter were also used, particularly among patients presenting with PE. These two latter treatments were more commonly applied in patients that developed a recurrence during follow-up and especially in those with PE who relapsed. Furthermore, in women initially presenting with PE the use of IVC filter was associated with a shorter period of treatment (127.0 days; IQR 96.8–184.8) compared to the remaining patients with PE (204.0 days; IQR 135.5–344.5) ($p < 0.05$). However, this difference was not significant when considering the total study population of patients with VTE [157.5 days (IQR 103.0–227.5) vs 188.0 days (IQR 117.0–280.0); $p = 0.180$]. In addition, the use of thrombolytics was not associated with significant differences in treatment duration between women receiving thrombolytics compared to those not receiving thrombolytics [286.5 days (IQR 105.5–411.5) versus 187 days (IQR 116.5–273.5); $p = 0.334$].

Patients presenting with PE had a higher prevalence of respiratory signs or symptoms (i.e. dyspnea, chest pain, or hypoxemia) than those presenting with DVT (Table 2). There were no significant differences in thrombophilia testing among the studied groups. Women presenting with recurrent PE had a non-significantly higher prevalence of antithrombin deficiency ($p = 0.136$). Factor V Leiden was more common in women with DVT (9.8%; 39/396) than in those with PE (5.2%; 11/211) ($p < 0.05$). Prothrombin G 20210 A was also more frequently found in women with DVT (9.1%; 36/396) compared to those with PE (4.7%; 10/211) ($p = 0.054$).

Fig. 1 shows that all death events and major bleeding happened within the first year from diagnosis and treatment initiation. The overall recurrence prevalence, not considering the follow-up time, was 2.6% (16/607). At 6-month follow-up, the cumulative events were 1.8% (CI: 95 0.7–2.9%), at one year 2.7% (CI: 95 1.2–4.2%), and at two years 3.3% (CI: 95 1.5–5.0%) (Fig. 1). Furthermore, the recurrent VTE

Table 1
Clinical characteristics and treatment strategies of pregnant patients with acute VTE, according to initial presentation.

	DVT	DVT with recurrence	PE	PE with recurrence	p
Patients, N	385	11	206	5	
Follow-up time (person-years)	445.8	7.2	265.6	1.5	
Clinical characteristics					
Age (years ± SD)	31.59 (±6.33)	31.73 (±6.45)	32.94 (±7.07)	28.00 (±5.61)	(1)
Body weight (kg ± SD)	69.38 (±13.76)	68.27 (±8.55)	71.22 (±14.24)	75.80 (±15.4)	NS
BMI (kg/m^2 ± SD)	25.48 (±4.57)	26.12 (±3.27)	26.54 (±5.07)	24.50 (±0.71)	NS
Inpatients	31.9% (123)	36.4% (4)	39.3% (81)	40% (2)	NS
Underlying conditions					
Chronic lung disease	0.5% (2)	0% (0)	1.9% (4)	0% (0)	NS
Chronic heart failure	0% (0)	0% (0)	1% (2)	0% (0)	NS
Abnormal creatinine levels	0.8% (3)	0% (0)	0.5% (1)	0% (0)	NS
Hemoglobin level (g/dl)	11.81 (±3.95)	11.35 (±1.32)	11.43 (±1.63)	12.32 (±1.18)	NS
Anemia	12.7% (49)	9.1% (1)	18% (37)	0% (0)	NS
Risk factors for VTE					
Surgery	20.8% (80)	9.1% (1)	37.9% (78)	40.0% (2)	(1)
Immobility ≥4 days	14.5% (56)	18.2% (2)	12.1% (25)	0% (0)	NS
Cancer	1.0% (4)	9.1% (1)	1.0% (2)	0% (0)	NS
Prolonged travel	1.0% (4)	0% (0)	0.5% (1)	0% (0)	NS
None of the above	66.2% (255)	63.6% (7)	52.4% (108)	60.0% (3)	(1)
History of previous VTE (before pregnancy)	10.6% (41)	9.1% (1)	12.6% (26)	0% (0)	NS
Pregnancy characteristics					
First trimester	24.4% (94)	18.2% (2)	18% (37)	0% (0)	(*1)
Second trimester	11.2% (43)	0% (0)	8.7% (18)	20% (1)	NS
Third trimester	26% (100)	45.5% (5)	22.8% (47)	20% (1)	NS
Puerperium	38.4% (148)	36.4% (4)	50.5% (104)	60% (3)	(1)
Initial therapies					
Median lengths (days) (*)	7 (4–11)	7 (6–14)	7 (4–10)	3 (1–5)	(4)
LMWH	95.3% (367)	90.9% (10)	87.9% (181)	100% (5)	(1)
Mean LMWH dose (IU/kg/day)	181.09 (±40.38)	176.29 (±21.85)	182.75 (±50.2)	190.08 (±24.22)	NS
Unfractionated heparin	6.2% (24)	18.2% (2)	15.0% (31)	20.0% (1)	(1)
Fondaparinux	0.8% (3)	0% (0)	1.9% (4)	0% (0)	NS
Thrombolytics	0.5% (2)	0% (0)	2.4% (5)	20.0% (1)	(1,*2,*4)
Inferior vena cava filter	3.9% (15)	9.1% (1)	6.8% (14)	40.0% (2)	(**1,2,4)
Long-term therapies					
Median lengths (days)	109 (74–184)	140 (112–232)	151 (84–225)	114 (34–316)	(1)
Vitamin K antagonists	49.9% (192)	72.7% (8)	64.6% (133)	80.0% (4)	(1)
LMWH	63.1% (243)	63.6% (7)	52.4% (108)	40.0% (2)	(1)
Mean LMWH dose (IU/kg/day)	154.74 (±52.51)	157.93 (±38.07)	168.89 (±75.47)	167 (±20.88)	(***1)
Fondaparinux	1% (4)	0% (0)	0.5% (1)	0% (0)	NS

Abbreviations: PE, pulmonary embolism; DVT, deep vein thrombosis; SD, standard deviation; VTE, venous thromboembolism; LMWH, low-molecular weight heparin; IU, international units. (*) This length is referred only to medical therapies and not to inferior vena cava filter. Significant differences ($p < 0.05$): (1) between DVT and PE; (2) between patients without recurrence and with recurrence; (3) among subset of patients with initial diagnosis of DVT between patients without recurrence and with recurrence; (4) among subset of patients with initial diagnosis of EP between patients without recurrence and with recurrence. Other interesting differences: (*1) $p = 0.057$; (**1) $p = 0.063$; (***1) $p = 0.055$; (*2) $p = 0.193$; (*4) $p = 0.136$.

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Table 2
Initial VTE presentation and diagnostic tests.

	DVT	DVT with recurrence	PE	PE with recurrence	p
Patients, N	385	11	206	5	
Signs or symptoms					
Dyspnea	3.1% (12)	0% (0)	79.1% (163)	80% (4)	(1)
Chest pain	2.3% (9)	0% (0)	69.9% (144)	100% (5)	(1)
Hemoptysis	0.5% (2)	0% (0)	6.3% (13)	0% (0)	(1)
Syncope	0.3% (1)	0% (0)	12.6% (26)	0% (0)	(1)
Pain in affected limb	90.1% (347)	90.9% (10)	26.2% (54)	20% (1)	(1)
Swelling in affected limb	87.3% (336)	100% (11)	23.8% (49)	0% (0)	(1)
Proximal DVT	84.4% (325)	90.9% (10)	24.8% (51)	0% (0)	(1)
Upper-extremity DVT	3.6% (14)	9.1% (1)	2.4% (5)	0% (0)	NS
Blood gases					
PO2 levels (mm Hg)	98.97 (±15.79)	NA	86.75 (±27.72)	106.6 (±24.68)	(1,*4)
PCO2 levels (mm Hg)	31.33 (±5.21)	NA	31.53 (±5.53)	31 (±4.53)	NS
Sat O2 levels (%)	97.27 (±3.35)	NA	94.94 (±4.63)	97.6 (±1.14)	(1)
Electrocardiography					
Atrial fibrillation	0% (0)	0% (0)	0.6% (1)	0% (0)	NS
D-dimer levels					
Tested	67.5% (260)	63.6% (7)	81.6% (168)	100% (5)	(1)
Positive	91.5% (238)	100% (7)	88.1% (148)	80% (4)	NS
Thrombophilia testing					
Known thrombophilia	9.6% (37)	0% (0)	10.7% (22)	20% (1)	NS
Unknown thrombophilia	348	11	184	4	
Not tested	18.4% (64)	9.1% (1)	15.8% (29)	25% (1)	NS
Positive	24.1% (84)	36.4% (4)	20.7% (38)	25% (1)	NS
Type of thrombophilia					
Protein C deficiency	1.6% (6)	0% (0)	2.4% (5)	0% (0)	NS
Protein S deficiency	3.1% (12)	9.1% (1)	5.3% (11)	0% (0)	NS
Antithrombin deficiency	1.8% (7)	0% (0)	2.4% (5)	20% (1)	(**4)
Factor V Leiden	10.1% (39)	0% (0)	5.3% (11)	0% (0)	(1)
Hyperhomocysteinemia	3.4% (13)	0% (0)	3.4% (7)	0% (0)	NS
Antiphospholipid syndrome	2.9% (11)	9.1% (1)	4.9% (10)	0% (0)	NS
Prothrombin G 20210 A	8.8% (34)	18.2% (2)	4.9% (10)	0% (0)	(*1)

Abbreviations: PE, pulmonary embolism; DVT, deep vein thrombosis; VTE, venous thromboembolism; SBP, systolic blood pressure. Significant differences ($p < 0.05$): (1) between DVT and PE; (2) between patients without recurrence and with recurrence; (3) among subset of patients with initial diagnosis of DVT between patients without recurrence and with recurrence; (4) among subset of patients with initial diagnosis of EP between patients without recurrence and with recurrence. Other interesting differences: (*4) $p = 0.058$; (**4) $p = 0.136$; (*1) $p = 0.054$.

incidence rate was 2.28 events/100 patients-year. In addition, we found no patients with more than one VTE recurrence.

Among the 16 cases of VTE recurrence 11 cases appeared during drug treatment while in five cases the recurrence was diagnosed after therapy discontinuation. In one case, of these five, the recurrence occurred four years after the end of treatment while in four cases the recurrence appeared within one year after the end of treatment. None of these had a IVC filter implanted. The median total treatment duration in these five cases was 226 days (198–262) while in the other cases of recurrence was 250 days (139–347) (p = n.s.) and in patients without any recurrence was 186 days (116–275) (p = n.s.).

No significant differences were found in term of selected outcomes according to initial VTE presentation or the cumulative events according to time of follow-up (Table 3) (Fig. 2). A higher prevalence of major

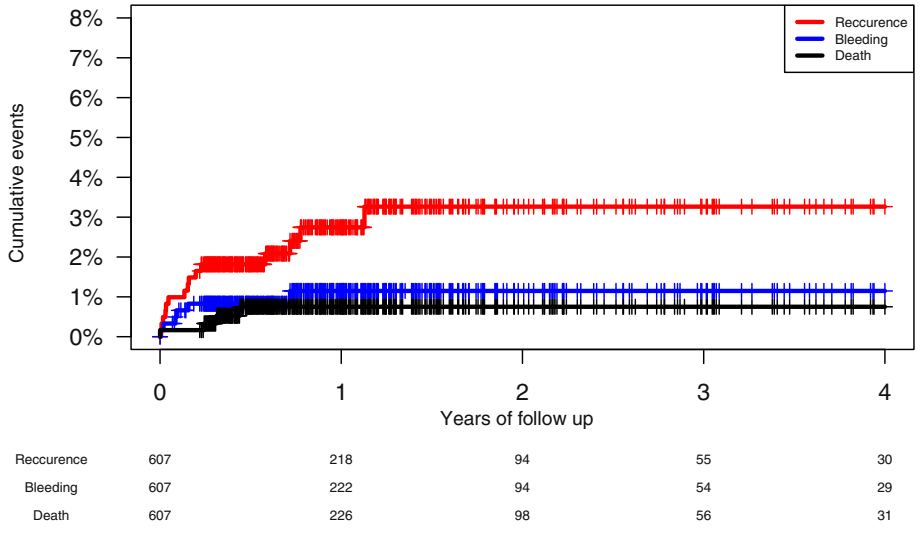

Fig. 1. Plot showing cumulative events of VTE recurrences, of major bleeding, or of death.

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Table 3
Outcome according to initial presentation.

	DVT	PE	p-Value
Patients, N	396	211	
Recurrence	2.8% (11)	2.4% (5)	0.765
Recurrent DVT	2.3% (9)	0.9% (2)	0.244
Recurrent PE	0.5% (2)	1.4% (3)	0.234
Recurrent VTE	0% (0)	0% (0)	1.000
Any bleeding	2.5% (10)	4.7% (10)	0.146
Gastrointestinal	0% (0)	20% (2)	
Cerebral	0% (0)	0% (0)	
Hematoma	10% (1)	20% (2)	
Muscular	0% (0)	0% (0)	
Retroperitoneal	10% (1)	0% (0)	
Urinary	10% (1)	10% (1)	
Menorrhagia	60% (6)	30% (3)	
Other	10% (1)	20% (2)	
Major bleeding	0.8% (3)	1.4% (3)	0.431
Hematoma	33.3% (1)	0% (0)	
Retroperitoneal	0% (0)	33.3% (1)	
Menorrhagia	33.3% (1)	66.7% (2)	
Other	33.3% (1)	0% (0)	
Overall death	0.8% (3)	0.5% (1)	

Table 4
Cox proportional hazards regression models (univariate and multivariate analysis §). In this table are reported the hazard ratio (HR), the relative 95% confidence interval, and the p-value for venous thromboembolism recurrence according to possible prognostic factors.

Recurrences	HR (95% CI)	p	HR (95% CI) (§)	p
Thrombolytics	6.11 (0.80–46.48)	0.080	8.26 (1.02–66.80) (*)	<0.05
Inferior vena cava filter	5.38 (1.51–19.19)	<0.05	5.67 (1.56–20.63) (**)	<0.05
Major bleeding				
UFH	4.80 (0.88–26.22)	0.070		NS
Vitamin K antagonists	3.84 (0.45–32.89)	0.220		NS

Recurrences — (*) Correction for: Mother age, use of inferior vena cava filter, and initial presentation (TVP or EP). (**) Correction for: Mother age, use of thrombolytics, and initial presentation (TVP or EP).

bleeding was found in patients with an initial diagnosis of PE compared to those with an initial diagnosis of DVT.

The study also included an analysis by Cox proportional hazards regression model that considers the follow up time. Among the possible prognostic factors considered (age, body weight, blood oxygenation, thrombophilia, timing of thrombophilia diagnosis, type of thrombophilia, type of initial therapies, type of long-term therapies, and treatment duration) on univariate and multivariate analysis, the use of thrombolytics or IVC filter independently predicted the risk for VTE recurrence (Table 4). No independent predictors of major bleeding were found.

4. Discussion

In the literature, there is paucity of reported studies with a sufficient number of patients to allow drawing conclusions on this specific subject. A recent meta-analysis based on limited numbers published in the literature considered VTE in pregnancy and postpartum as part of VTE provoked by transient non surgical risk factors [14–18,20]. The rate of recurrence in these patients was found to be 4.2% during the first year and 8.4% during the first 2 years [19]. Results of our analysis revealed a lower 2-year VTE recurrence rate of 3.3% (CI: 95 1.5–5.0%) compared to those reported by Iorio et al. in women with the index episode during pregnancy and puerperium.

In accordance with the literature we found an increased prevalence of VTE throughout the pregnancy that reached maximum just after delivery (Table 1) [23].

Cesarean section, co-morbidities, obesity, and hospitalization are recognized risk factors for VTE [6,7]. In our series previous surgery was associated more frequently with PE, while immobility, and chronic diseases were equally distributed among patients with an initial diagnosis of PE and DVT. None of these factors was associated with increased VTE recurrence. We also found no significant association between VTE recurrence and treatment discontinuation. In particular 68.8% had VTE recurrence during therapy.

To the best of our knowledge, this is the first study that found an association between the use of thrombolytics, or of IVC filter and the VTE recurrence rate in post-partum and puerperium. In PE, thrombolytics were used in more severe cases with lower oxygen saturation. In these cases, which we regarded as life-threatening events, alternative treatments could be considered, for example AngioJet rheolytic thrombectomy [24]. The use of IVC filter in patients with PE seems to be associated with a shorter treatment period. Anyway, in multivariate analysis even after correction for treatment duration the use of IVC filter appeared to result in an increased risk of VTE recurrence. A recent analysis including also non-pregnancy associated DVT found a significantly increased risk of recurrence related to IVC filter [25]. The authors concluded that in patients with a acute symptomatic VTE who are at a high bleeding risk IVC filter placement may reduce the risk of PE-related mortality [25]. But as a consequence of this management the lack of anticoagulation or thrombosis associated with IVC filters may increase the risk of recurrent VTE [25]. Further studies are needed to determine the patients that would most benefit from thrombolytics or IVC filter with the aim to reduce their use only to the most appropriate situations.

The main strength of this study is the number of patients with VTE in pregnancy and puerperium included in the analysis. In fact, this is a rare event and only limited data are available in the literature. However, the present study has several limitations. The main limitation is that RIETE is an observational registry which precludes conduction of randomized trials. Therefore, the information obtained has limited value without a confirmation by randomized clinical trials. As a consequence, one should be extremely cautious when suggesting changes in treatment strategies. Other limitations are the lack of an external control of the entered data, the absence of external adjudication of the events, and absence of information about provoking events in cases of VTE recurrence. Finally, standardized anticoagulant regimens were not applied to the patients. As a consequence, treatment varied with local practice, and is likely to have been influenced by physician's experience and assessment of patients' risk of bleeding.

Despite the above limitations, our results may have relevant therapeutic implications.

In summary, our study provides new insights on VTE recurrence rate in patients with deep vein thrombosis or pulmonary embolism occurring in pregnancy and postpartum period and provides valuable information to clinicians for better decision making in this setting.

Conflict of interest

The authors declare that they have no potential conflicts of interest relevant to this article.

Acknowledgements

We express our gratitude to Sanofi Spain for supporting this Registry with an unrestricted educational grant. We also express our gratitude to Bayer Pharma AG for supporting this Registry. Bayer Pharma AG's support was limited to the part of RIETE outside Spain, which accounts for a 22.33% of the total patients included in the RIETE Registry. We also thank the RIETE Registry Coordinating Center, S & H Medical Science Service, for their quality control data, logistic and administrative support.

Please cite this article as: Barillari G, et al, Recurrence of venous thromboembolism in patients with recent gestational deep vein thrombosis or pulmonary embolism: Findings from the RIETE Registry, Eur J Intern Med (2016), http://dx.doi.org/10.1016/j.ejim.2016.02.013

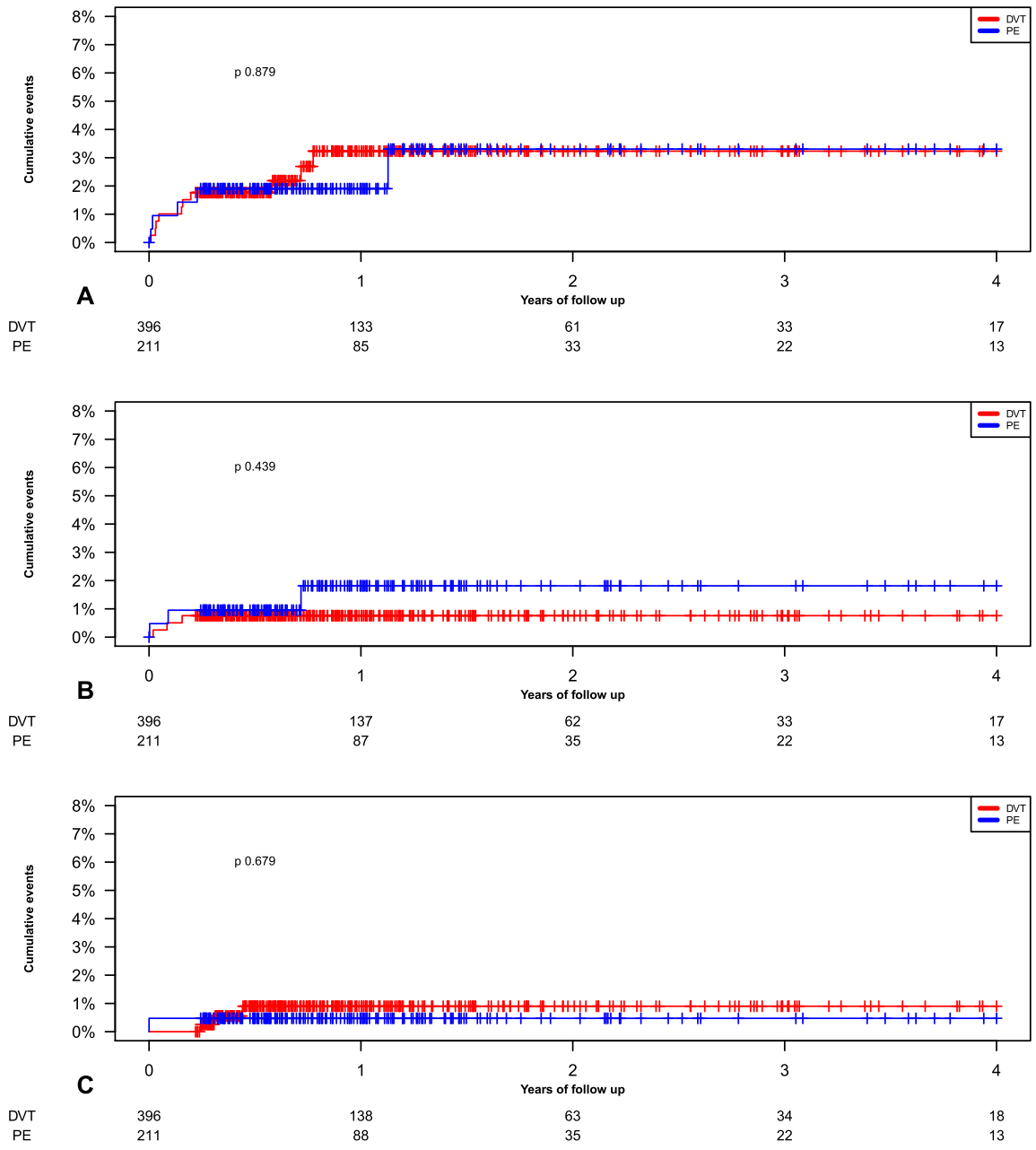

Fig. 2. Plot showing difference in cumulative events of VTE recurrences (A), of major bleeding (B), or of death (C). p-Values refer to Log-rank test.

Appendix A

Members of the RIETE Group

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Please cite this article as: Barillari G, et al, Recurrence of venous thromboembolism in patients with recent gestational deep vein thrombosis or pulmonary embolism: Findings from the RIETE Registry, Eur J Intern Med (2016), http://dx.doi.org/10.1016/j.ejim.2016.02.013

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