Dynamics of case-fatalilty rates of recurrent thromboembolism and major bleeding in patients treated for venous thromboembolism

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Summary

In patients with venous thromboembolism (VTE), assessment of the risk of fatal recurrent VTE and fatal bleeding during anticoagulation may help to guide intensity and duration of therapy. We aimed to provide estimates of the case-fatality rate (CFR) of recurrent VTE and major bleeding during anticoagulation in a 'real life' population, and to assess these outcomes according to the initial presentation of VTE and its etiology. The study included 41,826 patients with confirmed VTE from the RIETE registry who received different durations of anticoagulation (mean 7.8 ± 0.6 months). During 27,110 patient-years, the CFR was 12.1% (95% CI, 10.2–14.2) for recurrent VTE, and 19.7% (95% CI, 17.4–22.1) for major bleeding. During the first three months of anticoagulant therapy, the CFR of recurrent VTE was 16.1% (95% CI, 13.6–18.9), compared to 2.0% (95% CI, 0–4.2) beyond this period. The CFR of bleeding was 20.2% (95% CI, 17.5–23.1) during the first three months, compared to 18.2% (95% CI, 14.0–23.2) beyond this period. The CFR of recurrent VTE was higher in patients initially presenting with PE (18.5%; 95% CI, 15.3–22.1) than in those with DVT (6.3%; 95% CI, 4.5–8.6), and in patients with provoked VTE (16.3%; 95% CI, 13.6–19.4) than in those with unprovoked VTE (5.5%; 95% CI, 3.5–8.0). In conclusion, the CFR of recurrent VTE decreased over time during anticoagulation, while the CFR of major bleeding remained stable. The CFR of recurrent VTE was higher in patients initially presenting with PE and in those with provoked VTE.

Keywords

Deep-vein thrombosis, pulmonary embolism, major bleeding, recurrent thromboembolism, case-fatality rate

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Financial support:
This Registry is supported by unrestricted educational grants from Sanofi Spain and Bayer Pharma AG.

Received: February 15, 2013
Accepted after major revision: May 21, 2013
Prepublished online: July 11, 2013

doi:10.1160/TH13-02-0132
Thromb Haemost 2013; 110: 834–843

Introduction

Acute venous thromboembolism (VTE) is a commonly diagnosed condition with significant morbidity and mortality (1). Current guidelines recommend patients with VTE to be initially treated with unfractionated heparin (UFH), low-molecular-weight heparin (LMWH) or fondaparinux, followed by long-term anticoagulation, which is usually acomplished with vitamin K antagonists (VKA) (2, 3). The need for long-term therapy of VTE and the preferred intensity of anticoagulation have been established by randomised clinical trials (2-10). However, since most clinical trials were underpowered to assess fatal VTE or fatal bleeding events, recommendations are mainly based on the rates of recurrent VTE, major bleeding and all-cause mortality. Furthermore, a number of patients are often excluded from randomised trials of anticoagulant therapy because of comorbid conditions, short life expectancy, pregnancy, or contraindications to therapy, which means that treatment regimens based on the results from randomised clinical trials might not be generalizable to all patients with VTE.

The advantages of anticoagulation must be weighed against the risk of adverse effects — primarily bleeding. Moreover, when weighing the risks and benefits of anticoagulation in an individual patient, in addition to considering the absolute risk of thrombosis and major bleeding, the consequences associated with each of these outcomes need to be considered. In this sense, the case-fatality rate (CFR) of recurrent VTE and major bleeding, defined as the proportion of patients who die as a consequence of these conditions, could provide useful information to balance the risks and benefits of anticoagulant therapy. A recent systematic study of 13 prospective cohort studies and 56 randomised controlled trials found that the CFR of recurrent VTE and major bleeding events were similar during the initial period of VTE treatment (3 or 6

months), but the CFR of recurrent VTE decreased after completion of the initial period of anticoagulation (11). However, estimates came from heterogeneous trial and cohort populations and were not derived from patient-level longitudinal data. Moreover, investigators did not estimate CFRs for different intervals of the anticoagulation period. Thus, they could not compare the benefits and harms associated with different lengths of treatment.

To provide reliable estimates of the risk of fatal recurrent VTE and the risk of fatal bleeding while on anticoagulant therapy, we studied an inception cohort of patients with objectively confirmed VTE who were enrolled in the international, multicentre, prospective Registro Informatizado de la Enfermedad Trombo-Embólica (RIETE) registry (12-16). We also assessed these outcomes according to patients' initial presentation (deep-vein thrombosis [DVT], or pulmonary embolism [PE]) and VTE etiology (secondary to transient risk factor, cancer-related, or unprovoked).

Methods

Study design

This study used a cohort design to assess data from patients prospectively enrolled in the RIETE registry. At each participating site, RIETE investigators enrolled consecutive patients that had acute symptomatic VTE confirmed by objective testing that consisted of high probability ventilation-perfusion (V/Q) scintigraphy or positive contrast-enhanced, PE-protocol, helical chest computerised tomography (CT) [single or multi-detector CT] for PE, and lower limb venous compression ultrasonography positive for proximal DVT. RIETE did not enforce a diagnostic algorithm. RIETE also did not enforce a treatment algorithm, though it excluded those patients who participated in blinded randomised VTE treatment trials. All patients provided written or oral consent for participation in the registry in accordance with local ethics committee requirements. The RIETE coordinating centre used multiple data quality control procedures to optimise data quality (14). Briefly, participating site investigators or designees recorded data on a computer-based case report form and submitted the forms to a centralised coordinating centre through a secure website. The study coordinating centre responsible for all data management assigned patients with a unique identification number to maintain patient confidentiality. The coordinating centre regularly monitored the data to detect inconsistencies or errors, and sent queries to each site, which required resolution by the local coordinators. During periodic visits to participating hospitals that compared medical records with the submitted data, contract research organisations also monitored data quality.

Baseline variables

Patients enrolled in RIETE had the following data from around the time of VTE diagnosis collected: age; gender; body weight; presence of coexisting conditions such as chronic heart or lung disease; recent (<30 days prior to VTE) major bleeding; presence of risk factors for VTE including active cancer (defined as newly diagnosed cancer or cancer undergoing treatment [i.e. surgery, chemotherapy, radiotherapy, hormonal, or support therapy]), recent immobility (defined as non-surgical patients assigned to bed rest with bathroom privileges for ≥4 days in the two months prior to VTE diagnosis), surgery (defined as those who had undergone surgery in the two months prior to VTE); and laboratory results at hospital admission.

Table 1: Clinical characteristics, treatment strategies and outcome in 41,826 patients with acute VTE, according to their initial presentation.

	PE	DVT	P-value
Patients, N	20,543	21,283	
Clinical characteristics			
Gender (males)	9,480 (46%)	11,047 (52%)	<0.001
Age (mean years ± SD)	68 ± 17	64 ± 18	<0.001
Body weight (mean kg ± SD)	75 ± 15	74 ± 15	0.004
Risk factors			
Immobility ≥ 4 days	4,706 (23%)	5,009 (24%)	0.129
Postoperative	2,511 (12%)	2,293 (11%)	<0.001
Cancer	4,498 (22%)	4,614 (22%)	0.592
Pregnancy/puerperium	184 (0.9%)	362 (1.7%)	<0.001
Estrogen use	897 (4.5%)	1,015 (4.9%)	0.041
None of the above (non-provoked)	9,633 (47%)	9,872 (46%)	0.298
Prior VTE	3,058 (15%)	3,497 (16%)	<0.001
Underlying diseases			
Chronic lung disease	2,826 (14%)	1,750 (8.2%)	<0.001
Chronic heart disease	1,796 (8.7%)	906 (4.3%)	<0.001
Abnormal creatinine levels	3,661 (18%)	2,731 (13%)	<0.001
Treatment			
Duration (mean months ± SD)	8.4 ± 10	7.2 ± 8.6	<0.001
Initial therapy, UFH	2,444 (12%)	620 (2.9%)	<0.001
Initial therapy, LMWH	17,503 (85%)	20,174 (95%)	<0.001
Initial therapy, thrombolytics	188 (0.9%)	23 (0.1%)	<0.001
Initial therapy, fondaparinux	272 (1.3%)	334 (1.6%)	0.036
Initial therapy, other	103 (0.5%)	93 (0.4%)	0.335
Long-term, VKA drugs	15,028 (73%)	14,319 (67%)	<0.001
-Mean INR values -INRs in range 2.0–3.0 (%)	2.50 1.12 61%	2.34 0.73 56%	<0.001 0.002
Long-term, LMWH	4,430 (22%)	6,261 (29%)	<0.001
Inferior vena cava filter	590 (2.9%)	408 (1.9%)	<0.001

SD, standard deviation; PE, pulmonary embolism; DVT, deep-vein thrombosis; VTE, venous thromboembolism; UFH, unfractionated heparin; LMWH, low-molecular-weight heparin; IU, international units; VKA, vitamin K antagonists.

Cohort subgroups

We placed patients into subgroups according to initial presentation of VTE (DVT alone, and PE with or without concomitant DVT) and VTE etiology (cancer-related, secondary to a transient risk factor, or unprovoked). We defined unprovoked VTE as occurring in the absence of malignancy, surgery, leg trauma, leg fracture, medical immobilisation, pregnancy, puerperium or hormonal therapy use.

Treatment and follow-up

Clinicians at RIETE-enrolling sites managed patients according to their local practice (i.e. no standardisation of treatment). Most patients received initial anticoagulation with intravenous UFH or LMWH, and then long-term therapy with VKA drugs. RIETE recorded information related to all patient outcomes through a minimum of three months after the diagnosis of the acute VTE.

Table 2:Clinical outcomes during anticoagulation. Events expressed as number of events per 100 patient-years (and 95% CI).

Outcomes	PE (n = 20,543)		DVT (n = 21,283)		P-value
	N	Events per 100 patient-years	N	Events per 100 patient-years	
Recurrent PE	315	1.63 (1.46–1.82)	169	0.90 (0.77–1.04)	<0.001
Recurrent DVT	177	0.92 (0.79–1.06)	372	1.97 (1.78–2.18)	<0.001
Major bleeding	619	3.27 (3.02–3.53)	458	2.41 (2.19–2.64)	<0.001
Gastrointestinal	209	1.10 (0.96–1.26)	167	0.88 (0.75–1.02)	0.027
Cerebral	116	0.61 (0.51–0.73)	76	0.40 (0.32–0.50)	0.003
Haematoma	63	0.33 (0.26–0.42)	42	0.22 (0.16–0.30)	0.039
Muscular	64	0.34 (0.26–0.43)	36	0.19 (0.13–0.26)	0.005
Genitourinary	37	0.20 (0.01–0.27)	44	0.23 (0.17–0.31)	0.453
Retroperitoneal	34	0.18 (0.01–0.25)	35	0.18 (0.13–0.25)	0.921
Menorrhagia	13	0.07 (0.00–0.11)	13	0.07 (0.04–0.11)	0.990
Other	83	0.44 (0.35–0.54)	45	0.24 (0.17–0.31)	0.001
Death	2,067	10.3 (9.89–10.8)	1,321	6.70 (6.34–7.07)	<0.001
Causes of death					
Fatal PE	427	2.21 (2.01–2.42)	34	0.18 (0.13–0.25)	<0.001
Fatal, initial PE	336	1.74 (1.56–1.93)	0	-	-
Fatal, recurrent PE	91	0.47 (0.38–0.57)	34	0.18 (0.13–0.25)	<0.001
Respiratory insufficiency	213	1.07 (0.93–1.22)	79	0.40 (0.32–0.50)	<0.001
Sudden, unexpected	58	0.29 (0.22–0.37)	30	0.15 (0.10–0.21)	0.003
Bleeding	118	0.62 (0.52–0.74)	94	0.49 (0.40–0.60)	0.093
Malignancy	540	2.70 (2.48–2.93)	498	2.53 (2.31–2.75)	0.283
Infection	167	0.83 (0.72–0.97)	146	0.74 (0.63–0.87)	0.290
Heart failure	87	0.43 (0.35–0.53)	33	0.17 (0.12–0.23)	<0.001
Multi-organ failure	46	0.23 (0.17–0.30)	36	0.18 (0.13–0.25)	0.301
Bronchoaspiration	39	0.19 (0.14–0.26)	23	0.12 (0.08–0.17)	0.049
Myocardial infarction	21	0.11 (0.07–0.16)	10	0.05 (0.03–0.09)	0.055
Ischaemic stroke	16	0.08 (0.05–0.13)	21	0.11 (0.07–0.16)	0.393
Renal insufficiency	19	0.09 (0.06–0.15)	14	0.71 (0.40–1.16)	0.414
Bowel occlusion	20	0.10 (0.06–0.15)	9	0.05 (0.02–0.08)	0.047
Other	57	0.28 (0.22–0.37)	40	0.20 (0.15–0.27)	0.099
Unknown	285	1.43 (1.27–1.60)	292	1.48 (1.32–1.66)	0.644

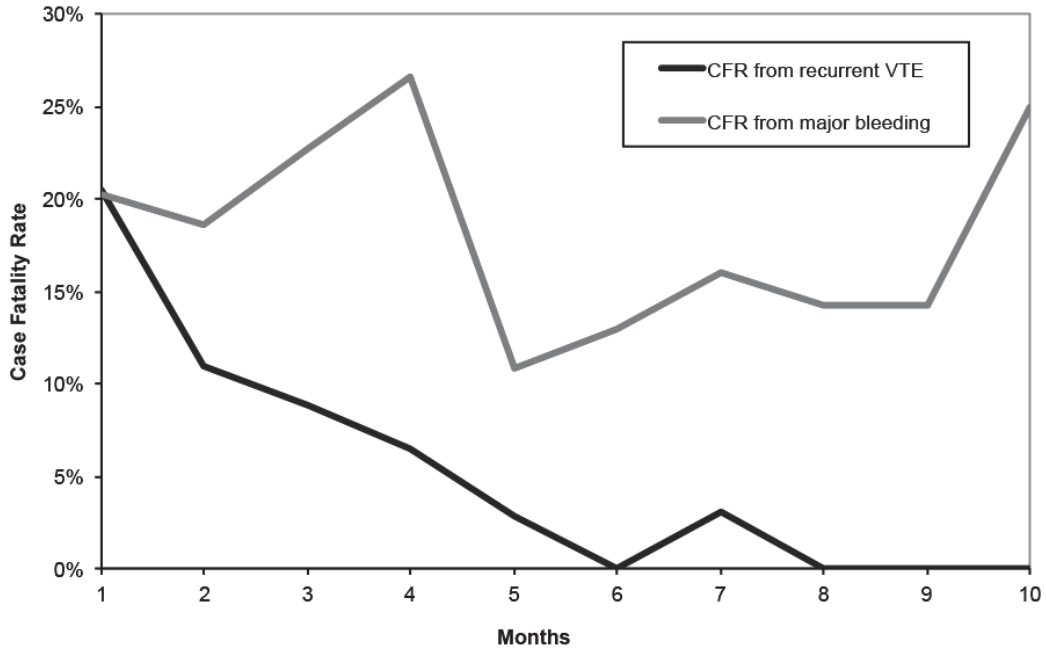
PE, pulmonary embolism; DVT, deep-vein thrombosis.

Clinical outcomes

During follow-up of the cohort, the RIETE investigators assessed the following outcomes: recurrent DVT (defined as a new non-compressible vein segment, or an increase of the vein diameter by at least 4 mm compared with the last available measurement on venous ultrasonography); recurrent PE (defined as a new ventilation–perfusion mismatch on lung scan or a new intraluminal filling defect on spiral CT of the chest); fatal recurrent VTE (defined as any death appearing within the first 10 days after an objectively confirmed VTE recurrence, in the absence of any alternative cause of death); major bleeding (defined as fatal, retroperitoneal, spinal or intracranial, or if it required a transfusion of at least 2 units of blood); and fatal bleeding (defined as any death occurring within the first 10 days after a major bleeding episode, in the absence of an alternative cause of death). The RIETE investigators assessed mortality using medical record review, and proxy interviews when necessary. The CFR of recurrent VTE was defined as the proportion of all recurrent VTE events (non-fatal and fatal) that were fatal. The CFR of major bleeding was defined as the proportion of all major bleeding events (non-fatal and fatal) resulting in fatal bleeding.

Statistical analysis

The rates of fatal recurrent VTE, non-fatal recurrent VTE, fatal bleeding, and non-fatal major bleeding during anticoagulant therapy were expressed as events per 100 patient-years to standardise for different durations of anticoagulant treatment. We characterised anticoagulant therapy as the duration of treatment in months (mean and range) and as the proportion of patients who received therapy for 3 months, or more than 3 months. Student's t-test and



Months		1	2	3	4	5	6	7	8	9	10
Patients at risk		41,826	39,934	38,082	31,186	27,923	24,810	20,596	18,218	16,419	15,012
Recurrent VTE	N	426	200	113	46	35	20	33	16	17	10
	Fatal VTE	87	22	10	3	1	0	1	0	0	0
	CFR	20.4%	11.0%	8.8%	6.5%	2.9%	0	3.0%	0	0	0
Major bleeding	N	599	129	75	49	37	31	25	14	14	8
	Fatal bleeding	121	24	17	13	4	4	4	2	2	2
	CFR	20.2%	18.6%	22.7%	26.5%	10.8%	12.9%	16.0%	14.3%	14.3%	25.0%

VTE, venous thromboembolism; PE, pulmonary embolism; CFR, case-fatality rate.

Figure 1: Case-fatality rate of recurrent VTE and major bleeding during the course of anticoagulation.

Chi-square test were used to compare continuous and categorical variables, respectively. The odds ratios (ORs) and 95% confidence intervals (CIs) were calculated. For the assessment of candidate variables predictors of death after recurrent VTE or major bleeding a multivariate analysis was carried out using stepwise logistic regression with both, forward selection and backward elimination. For this analysis, time from diagnosis to recurrent VTE or major bleeding was dichotimised into before and after 90 days. The SPSS software (version 15, SPSS Inc., Chicago, IL, USA) was used for statistical management of the data. A two-sided p-value of <0.05 was considered to be statistically significant.

Results

Patient characteristics

Of 41,826 patients with objectively confirmed, acute symptomatic VTE enrolled in RIETE from March 2001 to April 2012, the cohort included 20,527 men and 21,299 women. Of these, 20,543 patients (49%) initially presented with PE (with or without concomitant DVT) and 21,283 (51%) presented with DVT alone. Their clinical characteristics at baseline are shown in ►Table 1. In patients with PE, 15% had a history of prior VTE, 22% had cancer at the time of diagnosis, 40% had PE in association with a transient VTE risk factor, and 47% had unprovoked PE. In patients with DVT, 16% had a history of previous VTE, 22% had cancer at the time of diagnosis, 41% had DVT in association with a transient VTE risk factor, and 46% had unprovoked DVT. Most patients (37,677; 90%) received initial therapy with LMWH, 3,064 (7.3%) received UFH, 998 (2.4%) an inferior vena cava filter, 606 (1.5%) fondaparinux, and 211 (0.5%) thrombolytic therapy. For long-term therapy, 29,347 patients (70%) received VKA and 10,691 (26%) received LMWH. Mean duration of anticoagulation was 7.8 ± 0.6 months (median 6.1). Anticoagulant therapy was maintained for at least three months in 40,102 patients (96%), six months in 26,285 (63%), and 12 months in 12,637 (30%) patients.

Outcomes

During the course of anticoagulation, there were 484 recurrent PE events (1.27 per 100 patient-years; 95% CI: 1.16-1.38) and 549 recurrent DVT (1.44 per 100 patient-years; 95% CI: 1.32-1.56) (►Table 2). Half of PE recurrences (246 of 484; 51%) and one third of DVT recurrences (180 of 549; 33%) occurred during the

Table 3: Case-fatality rates of recurrent PE, recurrent DVT and major bleeding, according to risk factors for VTE and initial VTE presentation.

	All patients	Unprovoked	Cancer	Provoked, non cancer
All patients, N	**41,826**	**19,505**	**9,112**	**13,209**
Recurrent VTE	**1,033**	**402**	**402**	**229**
Fatal VTE	125 (0.3%)	22 (0.1%)	66 (0.7%)	37 (0.3%)
CFR (95% CI)	12.1% (10.2–14.2)	5.5% (3.5–8.0)	16.4% (13.0–20.3)	16.2% (11.8–21.4)
Major bleeding	**1,077**	**348**	**384**	**345**
Fatal bleeding	212 (0.5%)	56 (0.3%)	93 (1.0%)	63 (0.5%)
CFR (95% CI)	19.7% (17.4–22.1)	16.1% (12.5–20.2)	24.2% (20.1–28.7)	18.3% (14.5–22.6)
PE patients, N	**20,543**	**9,633**	**4,498**	**6,412**
Recurrent VTE	**492**	**190**	**185**	**117**
Fatal VTE	91 (0.4%)	21 (0.2%)	46 (1.0%)	24 (0.4%)
CFR (95% CI)	18.5% (15.3–22.1)	11.1% (7.2–16.1)	24.9% (19.0–31.5)	20.5% (13.9–28.5)
Major bleeding	**619**	**226**	**186**	**207**
Fatal bleeding	118 (0.6%)	40 (0.4%)	42 (0.9%)	36 (0.6%)
CFR (95% CI)	19.1% (16.1–22.3)	17.7% (13.1–23.1)	22.6% (17.0–29.0)	17.4% (12.7–23.0)
DVT patients, N	**21,283**	**9,872**	**4,614**	**6,797**
Recurrent VTE	**541**	**212**	**217**	**112**
Fatal VTE	34 (0.2%)	1 (0.01%)	20 (0.4%)	13 (0.2%)
CFR (95% CI)	6.3% (4.5–8.6)	0.5% (0.0–2.3)	9.2% (5.9–13.6)	11.6% (6.6–18.6)
Major bleeding	**458**	**122**	**198**	**138**
Fatal bleeding	94 (0.4%)	16 (0.2%)	51 (1.1%)	27 (0.4%)
CFR (95% CI)	20.5% (17.0-24.4)	13.1% (8.0-20.0)	25.8% (20.0-32.2)	19.6% (13.6-26.8)

VTE, venous thromboembolism; PE, pulmonary embolism; DVT, deep vein thrombosis; CFR, case-fatality rate; CI, confidence intervals.

first month of anticoagulation. Beyond that period, the rate of VTE recurrences progressively decreased over time (►Figure 1).

Patients initially presenting with PE were more likely to have PE than DVT as manifestation of recurrent VTE (1.63 [95% CI: 1.46-1.82] vs 0.92 [95% CI: 0.79-1.06] events per 100 patient-years), whereas those initially presenting with DVT were more likely to recur as DVT than PE (1.97 [95% CI: 1.78-2.18] vs 0.90 [95% CI: 0.77-1.04] events per 100 patient-years) (►Table 2).

The risk of VTE recurrence in patients with an initial event that was provoked by a temporary risk factor was lower than in patients with unprovoked VTE (OR: 0.84; 95% CI, 0.71-0.99) with no evidence that this effect was modified by the length of anticoagulant therapy or the location of VTE.

During the course of anticoagulation, there were 1,077 major bleeding events (2.57 per 100 patient-years; 95% CI: 2.43-2.73). The most common sites of major bleeding were the gastrointestinal tract (376 patients), central nervous system (192), haematoma (105), muscular (100), genitourinary (81) and retroperitoneal (69). Approximately 50% of these events (599 of 1,077; 56%) occurred during the first month of anticoagulation. Beyond that period, the rate of major bleeding progressively decreased over time (►Figure 1). The incidence of major bleeding was higher in patients initially presenting with PE than in patients presenting with DVT (3.27 [95% CI: 3.02-3.53] vs 2.41 [95% CI: 2.19-2.64] events per 100 patient-years, respectively) (►Table 2). The risk of major bleeding in patients with an initial event that was provoked by a temporary risk factor was higher than in patients with unprovoked VTE (OR: 1.48; 95% CI, 1.27-1.72) with no evidence that this effect was modified by the location of VTE.

Finally, 3,388 patients died (8.10 per 100 patient-years; 95% CI: 7.83-8.38). Of these, 336 deaths were ascribed to the initial PE event, 125 to recurrent PE, 292 to respiratory insufficiency, 88 had sudden unexpected death, 212 died of bleeding, 1,038 of disseminated malignancy, and 1,297 died of other reasons (►Table 2). The mortality rate was higher in patients initially presenting with PE than in those with DVT (10.3 [95% CI: 9.89-10.8] vs 6.7 [95% CI: 6.34-7.07] deaths per 100 patient-years, respectively).

Case-fatality rates

Overall, the CFR of recurrent VTE during anticoagulant therapy was 12.1% (95% CI, 10.2% - 14.2%), while the CFR of major bleeding was 19.7% (95% CI, 17.4% - 22.1%). Regarding the initial presentation, the CFR of recurrent VTE was higher in patients initially presenting with PE (18.5%; 95% CI: 15.3% - 22.1%) than in those with DVT (6.3%; 95% CI: 4.5% - 8.6%). However, the CFR of major bleeding was similar in both subgroups (19.1%; 95% CI: 16.1% - 22.3% vs 20.5%; 95% CI: 17.0% - 24.4%, respectively).

The CFR of recurrent VTE was lower in patients with unprovoked VTE (5.5%; 95% CI: 3.5% - 8.0%) than in those with VTE in association with cancer (16.4%; 95% CI: 13.0% - 20.3%) or secondary to temporary risk factors (16.2%; 95% CI: 11.8% - 21.4%) (►Table 3). The CFR of major bleeding was slightly higher in patients with cancer (24.4%; 95% CI: 20.1% - 28.7%), compared to patients without malignancy (17.5%; 95% CI: 14.2% - 21.3%).

Interestingly, the CFR of recurrent VTE decreased over time. The CFR of recurrent VTE during the first three months of anticoagulation was 16.1% (95% CI, 13.6-18.9) compared to 2.0% (95% CI, 0-4.2) beyond this period (►Figure 1). On the contrary, the CFR of major bleeding remained more stable. The CFR of major bleeding was 20.2% (95% CI, 17.5-23.1) during the first three months of anticoagulation and 18.2% (95% CI, 14.0-23.2) beyond this period. Multivariate analysis showed that the time elapsed since diagnosis of the initial VTE episode to VTE recurrence or major bleeding is an independent predictor of death (►Table 4). However, the OR if the event occurred before or after 90 days was 11.7 (95% CI, 4.7-29) for recurrent VTE, compared to 1.6 (95% CI, 1.1-2.4) in the case of major bleeding.

Table 4: Multivariate analysis assessing death in the first 10 days following recurrent VTE or major bleeding event.

	Recurrent VTE	Major bleeding
	OR (95% CI)	OR (95% CI)
Clinical characteristics		
Gender (males)	-	-
Age (>75 years)	2.5 (1.7–3.8)‡	-
Body weight (>70 kg)	-	0.7 (0.5–0.9)*
Risk factors		
Non-provoked	1 (ref.)	1 (ref.)
Cancer	3.1 (1.8–5.3) ‡	1.7 (1.1–2.5)*
Provoked-non cancer	2.6 (1.4–4.7) †	1.1 (0.7–1.8)
Prior VTE	-	-
Prior bleeding	-	-
Underlying diseases		
Chronic lung disease	-	
Chronic heart disease	-	
Abnormal creatinine levels	-	1.5 (1.1–2.1)*
Bleeding		
Gastrointestinal		2.1 (1.4–3.2)‡
Cerebral		6.0 (3.8–9.6)‡
Retroperitoneal		2.6 (1.3–5.1)†
Others		1 (ref.)
Event before 90 days	11.7 (4.7–29) ‡	1.6 (1.1–2.4)*
Initial VTE presentation		
Pulmonary embolism	3.4 (2.2–5.3) ‡	-
Treatment		
Initial therapy, LMWH	-	-

*p<0.05; †p<0.01; ‡p<0.001; -non significant. ref., reference.

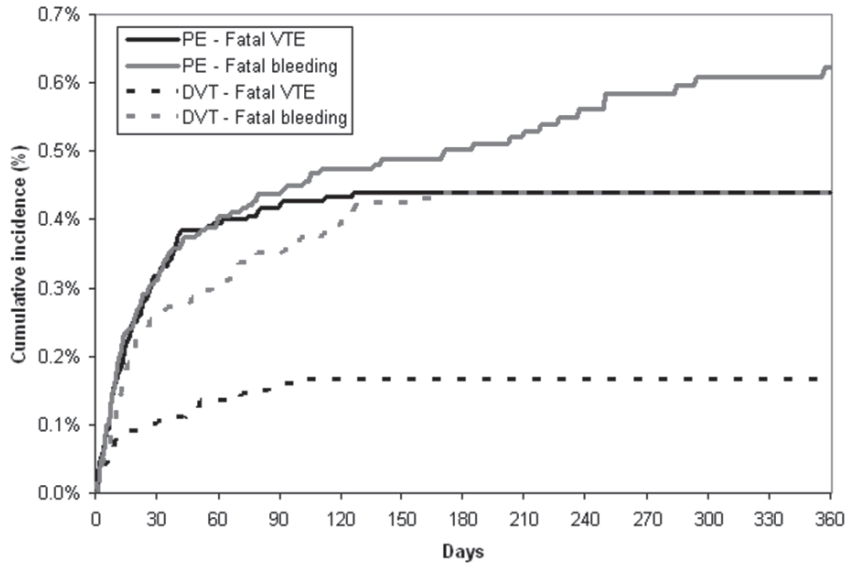
Cumulative mortality

►Figure 2 shows the cumulative incidence of fatal recurrent VTE and fatal bleeding during anticoagulation, according to initial VTE presentation. Of 20,543 patients initially presenting with PE, 91 patients died of recurrent VTE and 118 died of bleeding. During the first 30 days of anticoagulation, the risk of dying of recurrent VTE was similar to the risk of dying of bleeding (63 vs 62 deaths, respectively). After the first month, the risk of dying of recurrent VTE was two times lower than the risk of dying of bleeding (28 vs 56 deaths). Of 21,283 patients initially presenting with DVT, 34 patients died of recurrent VTE and 94 died of bleeding. During the first 10 days of anticoagulation, the risk of dying of recurrent VTE was similar to the risk of dying of bleeding (16 vs 22 deaths, respectively). After the first 10 days, the risk of dying of recurrent VTE was four times lower than the risk of dying of bleeding (18 vs 72 deaths, respectively).

Discussion

Our findings, obtained from a large series of consecutive patients with VTE, reveal that the absolute incidence of recurrent VTE and major bleeding during anticoagulation was similar. Consistently with previous findings, the highest incidence of both complications was observed in the first weeks after the index diagnosis and decreased afterwards (17). In contrast, the CFR of recurrent VTE and major bleeding during anticoagulant therapy, followed different patterns. Although initially similar, the CFR of recurrent VTE progressively decreased during anticoagulation, while the CFR of major bleeding barely varied over time. The CFR of major bleeding exceeded the CFR of recurrent VTE after the first month of therapy, leading to a higher cumulative mortality from this cause. Although some previous reports provided estimates of CFR of bleeding and recurrent VTE during and after anticoagulant therapy, their different behaviour during the course of anticoagulation had not been described so far (11, 17, 18). It seems reasonable to believe that the later a recurrent VTE develops, the higher degree of thrombus regression and patients' adaptation has been achieved, and consequently the impact of VTE recurrence would be less severe (19). In fact, in a recent report, recurrences within the first weeks after an index PE event were associated with significantly higher mortality (20).

Herein, we also confirm that PE patients recur more often as PE, while DVT patients recur more often as DVT, thus implying a lower CFR of recurrent VTE (18). Since the CFR of recurrent VTE



Days		10	30	90	150	240	360
PE	Patients at risk	19,866	19,273	18,079	13,759	9,216	6,554
	Fatal VTE	33 (0.2%)	63 (0.3%)	83 (0.4%)	86 (0.4%)	86 (0.4%)	86 (0.4%)
	Fatal bleeding	34 (0.2%)	62 (0.3%)	86 (0.4%)	94 (0.5%)	102 (0.6%)	107 (0.6%)
DVT	Patients at risk	21,078	20,660	19,525	14,078	9,036	6,083
	Fatal VTE	16 (0.1%)	22 (0.1%)	33 (0.2%)	34 (0.2%)	34 (0.2%)	34 (0.2%)
	Fatal bleeding	22 (0.1%)	55 (0.3%)	73 (0.3%)	85 (0.4%)	87 (0.4%)	87 (0.4%)

PE, pulmonary embolism; DVT, deep-vein thrombosis; VTE, venous thromboembolism.

Figure 2: Cumulative incidence of fatal recurrent PE and fatal bleeding during anticoagulation, according to initial presentation. Only the first 360 days of follow-up are shown.

was higher in patients initially presenting with PE (18.5%; 95% CI: 15.3% - 22.1%) than in those with DVT (6.3%; 95% CI: 4.5% - 8.6%) while the CFR of major bleeding was similar in both subgroups (19.1%; 95% CI: 16.1% - 22.3% vs 20.5%; 95% CI: 17.0% - 24.4%), the difference between CFR of recurrent VTE and bleeding was more pronounced in patients with initial DVT. In patients initially presenting with PE, the rates of fatal recurrent VTE and fatal bleeding in the first month were similar (63 vs 62 deaths). However, since the CFR of recurrent VTE markedly decreased over time, the cumulative incidence of fatal VTE after the first month of anticoagulation was two times lower than that of fatal bleeding (28 vs 56 deaths). In patients initially presenting with DVT, the rate of fatal VTE was three times lower than the rate of fatal bleeding (34 vs 94 deaths) from the beginning.

These data could be important in the design of VTE treatment trials. The much higher risk of dying from bleeding than from VTE in these patients suggests that a less aggressive anticoagulant strategy might likely reduce fatal bleeding more than it would increase fatal VTE. In fact, in some recent clinical trials the intensity of long-term anticoagulant therapy was reduced after an initial phase treatment (21-24). However, well-designed randomised trials are needed before systematically recommending a reduction in the intensity of anticoagulation after the first weeks of therapy.

The influence of risk factors on the CFR of VTE recurrence and major bleeding is another non-previously reported finding. Indeed, cancer patients showed not only the highest incidence of recurrent VTE and bleeding (in accordance with previous observations [25]) but also the highest CFRs of both complications. Surprisingly, patients with unprovoked VTE showed lower CFR of recurrent VTE than those with VTE associated with a temporary risk factor, independent of the location of the initial episode. Although we lack a definite explanation for this result, since CFR of recurrent VTE decreases over time, we hypothesise that the shorter duration of therapy in patients with VTE secondary to transient risk factors compared to idiopathic VTE (data not shown) could justify our results. Indeed, patients' comorbidities could also play a role. However in the multivariate analysis performed, their role as independent predictors of death in the following days after a VTE recurrence or a major bleeding event was limited. Current ACCP (American College of Chest Physicians) guidelines recommend treatment with anticoagulation for at least three months, and then to evaluate for the risk-benefit ratio of extended therapy (1). Our data further support that the intensity and duration of anticoagulation should be tailored to the clinical characteristics of the patients.

The present study has several limitations. First, RIETE is an observational registry, not a randomised trial. Our data are hypothesis-generating and might be a useful basis for future controlled clinical trials investigating modified anticoagulant regimens, but we should be extremely cautious in suggesting changes in treatment strategies just because of registry data. In addition, there is no external control of the data entered, and there is no external adjudication of the events. Second, patients were not treated with a standardised anticoagulant regimen; treatment varied with local practice, and is likely to have been influenced by a physician's assessment of patients' risk of bleeding. The CFR of recurrent VTE of 12.1% observed in our series is similar to the 11.3% reported in a recent systematic review of 13 prospective cohort studies and 56 randomised controlled trials, but the CFR of major bleeding of 19.7% in the current analysis is much higher than their 11.3% (11). We suspect that this higher CFR of major bleeding in our study reflects enrolment of consecutive unselected patients, including more elderly patients and patients with multiple risk factors for bleeding who are often excluded from randomised clinical trials. Of course, the quality of the anticoagulation with VKA could influence our results. Although we lack data on the individual time in therapeutic INR range (TTR), the % of INRs in range in our series reached 60%. This percentage of INR controls in range is similar to the obtained in an observational study including Italian and Spanish patients (the most active countries recruiting patients in RIETE), in which the TTR were 68.9% and 64.4%, respectively (26). Similar estimates were observed in two other studies (27, 28). Thus, at least in our setting, the TTR in daily practice would not significantly differ from those observed in the setting of the clinical trials included in the a aforementioned systematic review (11). In addition, differences in the CFR of recurrent VTE and bleeding depending on the use or VKA o LMWH for long-term anticoagulant therapy cannot be excluded. LMWH are as effective a VKA for the long-term treatment of symptomatic VTE and may result in fewer bleeding episodes (29). However, in RIETE patients, this assessment would be biased because most patients receiving long-term LMWH were cancer patients, whose CFRs are higher than those of patients without malignancies. Third, to comply with the definition of fatal recurrent VTE it is mandatory in RIETE that patients must experience an objectively confirmed recurrent VTE followed by death within the first 10 days. Thus, it is possible that

What is known about this topic?

- Since most clinical trials were underpowered to assess fatal VTE or fatal bleeding events, recommendations on length and intensity of anticoagulant therapy are mainly based on the rates of recurrent VTE, major bleeding and all-cause mortality.
- The estimation of the case-fatality rate (CFR) of recurrent VTE and major bleeding could provide useful information to balance the risks and benefits of anticoagulant therapy.

What does this paper add?

- While the CFR of recurrent VTE decreases over time during anticoagulant therapy, the CFR of recurrent bleeding remains stable. The CFR of major bleeding exceeds the CFR of recurrent VTE after the first month of therapy, leading to a higher cumulative mortality from this cause.
- The CFR of recurrent VTE varies according to the location and etiology of the index VTE event.
- These results can be helpful to tailor the intensity and duration of anticoagulant therapy according to the clinical characteristics of the patients.

some sudden death related to PE were missed especially after hospital discharge. In our series, 53% of sudden unexpected deaths happened in the first month after the initial VTE event, decreasing afterwards. If all sudden unexpected deaths were considered as fatal recurrent VTE, the dynamics of reduction of CFR during the course of anticoagulant therapy would persist. Nevertheless, a study with autopsies of subjects dying suddenly outside of hospital found a rate of PE of only 9% (30), limiting the risk of bias in our study. Finally, some fatal VTE events appeared shortly after a major bleeding, and some fatal bleeding events appeared shortly after recurrent VTE. Most of these deaths would have not appeared in the absence of prior major bleeding or recurrent VTE, and this may have influenced the rate of these events.

In summary, during anticoagulation the CFR of recurrent VTE was high at the beginning of treatment and then progressively dropped to less than 10% after three months, while the CFR of major bleeding was high (around 20%) and only slightly decreased over time. These findings might stimulate further clinical trials on initial phase and long-term anticoagulant therapy.

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 15,54% of the total patients included in the RIETE Registry. We also thank the Registry Coordinating Centre, S & H Medical Science Service, for their quality control, logistic and administrative support, and Prof. Salvador Ortiz, Universidad Autónoma de Madrid and Statistical Advisor S& H Medical Science Service for the statistical analysis of the data presented in this paper.

Conflicts of interest

None declared.

Appendix

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