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Clinical outcomes during anticoagulant therapy in fragile patients with venous thromboembolism

Farès Moustafa MD[1] | Matteo Giorgi Pierfranceschi MD[2] | Pierpaolo Di Micco MD, PhD[3] | Eugenio Bucherini MD[4] | Alicia Lorenzo MD, PhD[5] | Aurora Villalobos MD, PhD[6] | José A. Nieto MD, PhD[7] | Beatriz Valero MD[8] | Ángel L. Sampériz MD, PhD[9] | Manuel Monreal MD, PhD[10] | the RIETE Investigators*

[1]Department of Emergency Medicine, CHU Clermont-Ferrand, Clermont-Ferrand, France

[2]Emergency Department, Val d'Arda Hospital, Piacenza, Italy

[3]Department of Internal Medicine, Ospedale Buon Consiglio Fatebenefratelli, Naples, Italy

[4]Department of Vascular Medicine, Azienda U.S.L. Di Ravenna–O.C. Di Faenza, Ravenna, Italy

[5]Department of Internal Medicine, Hospital Universitario La Paz, Madrid, Spain

[6]Department of Internal Medicine, Hospital Regional Universitario de Málaga, Málaga, Spain

[7]Department of Internal Medicine, Hospital General Virgen de la Luz, Cuenca, Spain

[8]Department of Internal Medicine, Hospital General Universitario de Alicante, Alicante, Spain

[9]Department of Internal Medicine, Hospital Reina Sofía, Tudela, Spain

[10]Department of Internal Medicine, Hospital de Badalona Germans Trias i Pujol, Universidad Católica de Murcia, Badalona, Spain

Correspondence
Farès Moustafa, Service des Urgences Adultes, CHU Clermont-Ferrand, Clermont-Ferrand, France.
Email: fmoustafa@chu-clermontferrand.fr

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Abstract

Background: Subgroup analyses from randomized trials suggested favorable results for the direct oral anticoagulants in fragile patients with venous thromboembolism (VTE). The frequency and natural history of fragile patients with VTE have not been studied yet.

Objectives: To compare the clinical characteristics, treatment and outcomes during the first 3 months of anticoagulation in fragile vs non-fragile patients with VTE.

Methods: Retrospective study using consecutive patients enrolled in the RIETE (Registro Informatizado Enfermedad TromboEmbolica) registry. Fragile patients were defined as those having age ≥75 years, creatinine clearance (CrCl) levels ≤50 mL/min, and/or body weight ≤50 kg.

Results: From January 2013 to October 2016, 15 079 patients were recruited. Of these, 6260 (42%) were fragile: 37% were aged ≥75 years, 20% had CrCl levels ≤50 mL/min, and 3.6% weighed ≤50 kg. During the first 3 months of anticoagulant therapy, fragile patients had a lower risk of VTE recurrences (0.78% vs 1.4%; adjusted odds ratio [OR]: 0.52; 95% confidence intervals [CI]: 0.37-0.74) and a higher risk of major bleeding (2.6% vs 1.4%; adjusted OR: 1.41; 95% CI: 1.10-1.80), gastrointestinal

*A full list of RIETE investigators is given in the Appendix.

bleeding (0.86% vs 0.35%; adjusted OR: 1.84; 95% CI: 1.16-2.92), haematoma (0.51% vs 0.07%; adjusted OR: 5.05; 95% CI: 2.05-12.4), all-cause death (9.2% vs 3.5%; adjusted OR: 2.02; 95% CI: 1.75-2.33), or fatal PE (0.85% vs 0.35%; adjusted OR: 1.77; 95% CI: 1.10-2.85) than the non-fragile.

Conclusions: In real life, 42% of VTE patients were fragile. During anticoagulation, they had fewer VTE recurrences and more major bleeding events than the non-fragile.

KEYWORDS

anticoagulants, hemorrhage, mortality, recurrences, venous thromboembolism

Essentials

- Recent randomized trials suggested fewer bleeding events in fragile patients with VTE receiving DOACs.
- The frequency, clinical characteristics and outcome of these patients have not been reported in real life.
- Fragile patients with VTE had a higher risk for major bleeding or death and a lower risk for recurrences than non-fragile.

1 | INTRODUCTION

In recent years, a number of direct oral anticoagulants (DOACs) have been developed for the treatment of venous thromboembolism (VTE). Their use has been associated with a lower rate of major bleeding compared with standard therapy.[1–5] Hence, apixaban, rivaroxaban, dabigatran, and edoxaban have been approved for the treatment of patients with deep vein thrombosis (DVT) or pulmonary embolism (PE).[6] Subgroup analyses from these randomized clinical trials have delivered further promising results, particularly for the so-called fragile patients, defined as those having creatinine clearance (CrCl) levels ≤50 mL/min, age ≥75 years, or body weight ≤50 kg.[3–5,7] Hence, there are reasons to suggest that fragile patients with VTE could be considered ideal candidates for long-term therapy with DOACs.[4,5,7,8] However, the proportion of fragile patients in real life, and their outcome during the course of anticoagulant therapy have not been thoroughly studied yet.

RIETE (Registro Informatizado Enfermedad TromboEmbólica) is a multicenter, ongoing, international (Spain, Belgium, Brazil, Canada, Czech Republic, Ecuador, France, Israel, Italy, Latvia, Republic of Macedonia, Switzerland, and the United States enroll patients) registry of consecutive patients with symptomatic, objectively confirmed, acute VTE (ClinicalTrials.gov identifier: NCT02832245).[9–13] Since its inception in 2001, the aim of RIETE is to record data including the clinical characteristics, treatment patterns, and outcomes in patients diagnosed with VTE. Using the RIETE database, the current study compared the clinical characteristics, treatment, and outcomes during the first 3 months of anticoagulation in fragile vs non-fragile patients with acute VTE.

2 | PATIENTS AND METHODS

2.1 | Inclusion criteria

Consecutive patients presenting with symptomatic, acute DVT or PE confirmed by objective tests (compression ultrasonography or contrast venography for DVT; helical CT-scan, ventilation-perfusion lung scintigraphy or angiography for PE) were enrolled in RIETE. Patients were excluded if they were currently participating in a therapeutic clinical trial with a blinded therapy. All patients (or their legal power of attorney) provided written or oral consent for participation in the registry, in accordance with local ethics committee requirements.

Physicians participating in the RIETE registry made all efforts to enroll consecutive patients. Data were recorded onto a computer-based case-report form at each participating hospital and submitted to a centralized coordinating center through a secure website. To ensure the validity of the information entered into the database, one of the specially trained monitors visited each participating hospital and compared information in 25-50 randomly chosen patient records with the information entered into the RIETE database. For data quality assessment, monitors assessed 4100 random records from all participating hospitals, which included 1 230 000 measurements. These data showed a 95% overall agreement between the registered information and patient records. RIETE also used electronic data monitoring to detect inconsistencies or errors and attempted to resolve discrepancies by contacting the local coordinators.

2.2 | Study design

We conducted a cohort study that used consecutive patients enrolled in the RIETE registry. For this study, only patients recruited from January 2013 (the year when the first DOAC was approved for use in patients with VTE) were considered. Our aim was to compare the clinical characteristics, treatment, and outcomes in fragile vs non-fragile patients. The major outcome was the rate of VTE recurrences or major bleeding occurring during the first 3 months of anticoagulant therapy.

2.3 | Definitions

Fragile patients were defined as those having CrCl levels ≤50 mL/min, age ≥75 years, or body weight ≤50 kg.[3] Immobilized patients were

TABLE 1 Clinical characteristics in 15 079 fragile and non-fragile patients with acute venous thromboembolism

	Non-fragile	Fragile	Age ≥ 75 y	Weight ≤ 50 kg	CrCl ≤ 50 mL/min
Patients, *N*	8819	6260	5514	537	3059
Clinical characteristics					
Age (y ± SD)	55 ± 14	80 ± 10‡	82 ± 5.0	71 ± 2.0	81 ± 10
Gender (male)	5058 (57%)	2407 (38%)‡	2104 (38%)	73 (14%)	1030 (34%)
Body weight (kg ± SD)	81 ± 17	71 ± 14‡	72 ± 14	47 ± 4.	67 ± 13
Risk factors for VTE					
Immobilization ≥4 d	1342 (15%)	1648 (26%)‡	1488 (27%)	165 (31%)	894 (29%)
Surgery	1097 (12%)	502 (8.0%)‡	406 (7.4%)	48 (8.9%)	228 (7.5%)
Cancer	1894 (21%)	1495 (24%)‡	1235 (22%)	164 (31%)	723 (24%)
Estrogen use	813 (9.2%)	222 (3.5%)‡	160 (2.9%)	53 (9.9%)	92 (3.0%)
Pregnancy/puerperium	172 (2.0%)	7 (0.11%)‡	0	4 (0.74%)	3 (0.10%)
None of the above	4353 (49%)	3004 (48%)	2731 (50%)	175 (33%)	1425 (47%)
Prior VTE	1352 (15%)	906 (14%)	821 (15%)	58 (11%)	419 (14%)
Underlying diseases					
Chronic heart failure	254 (2.9%)	775 (12%)‡	720 (13%)	56 (10%)	469 (15%)
Chronic lung disease	801 (9.1%)	1015 (16%)‡	904 (16%)	62 (12%)	495 (16%)
Recent major bleeding	170 (1.9%)	168 (2.7%)†	132 (2.4%)	15 (2.8%)	82 (2.7%)
Blood tests					
Anemia	2492 (28%)	2514 (40%)‡	2116 (38%)	275 (51%)	1430 (47%)
Platelet count <150 000/μL	1083 (12%)	1036 (17%)‡	884 (16%)	70 (13%)	537 (18%)
Platelet count >450 000/μL	249 (2.8%)	185 (3.0%)	151 (2.7%)	35 (6.5%)	95 (3.1%)
CrCl levels (mL/min ± SD)	108 ± 50	54 ± 24‡	55 ± 23	54 ± 38	36 ± 10
Initial VTE presentation					
Pulmonary embolism	4698 (53%)	3751 (60%)‡	3364 (61%)	280 (52%)	1853 (61%)

CrCl, creatinine clearance; SD, standard deviation; VTE, venous thromboembolism.
Comparisons between fragile and non-fragile patients: *P < .05; †P < .01; ‡P < .001. Anemia was considered in men with haemoglobin levels <13 g/dL or women with levels <12 g/dL.

defined as non-surgical patients who had been immobilized (ie, total bed rest with bathroom privileges) for ≥4 days in the 2-month period prior to VTE.[12] Surgical patients were defined as those who underwent a surgical intervention in the 2 months prior to VTE.[11] Active cancer was defined as newly diagnosed cancer, metastatic cancer, or cancer that was being treated (ie, surgery, chemotherapy, radiotherapy, support therapy).[10] Recent bleeding was defined as any major bleeding episode <30 days prior to VTE.[14] Bleeding events were classified as "major" if they were overt and required a transfusion of two units or more of blood, or were retroperitoneal, spinal, or intracranial, or when they were fatal. Fatal bleeding was defined as any death occurring within 10 days of a major bleeding episode, in the absence of an alternative cause of death.[14] Fatal PE, in the absence of autopsy, was defined as any death appearing within 10 days after symptomatic PE diagnosis, in the absence of any alternative cause of death.[12] Initial therapy was defined as any therapy administered during the first week in case of low-molecular-weight heparin (LMWH), unfractionated heparin, fondaparinux, or apixaban, and during the first 3 weeks in case of rivaroxaban. Long-term therapy was defined as any therapy administered after the end of initial therapy.

2.4 | Treatment and follow-up

Patients were managed according to each participating hospital's clinical practice, and there were no standardized or recommended duration of therapy or follow-up. All patients had to be followed-up for at least 3 months in the outpatient clinic or physician's office. During each visit, any signs or symptoms suggesting VTE recurrences or bleeding complications were noted. Each episode of clinically suspected recurrent VTE was investigated by repeat compression ultrasonography, lung scanning, helical-CT scan, or pulmonary angiography, as appropriate. Most outcomes were classified as reported by the clinical centers. However, if staff at the coordinating center were uncertain how to classify a reported outcome, that event was reviewed by a central adjudicating committee (less than 10% of events).

2.5 | Statistical analysis

Clinical characteristics, risk factors, and initial VTE presentation were analyzed using descriptive statistics for continuous variables and frequency counts and percentages for categorical variables. Categorical

TABLE 2 Treatment strategies in fragile and non-fragile patients with acute venous thromboembolism

	Non-fragile	Fragile	Age ≥75 y	Weight ≤ 50 kg	CrCl ≤ 50 mL/min
Patients, *N*	8819	6260	5514	537	3059
Initial therapy					
LMWH	7288 (83%)	5493 (88%)‡	4879 (88%)	472 (88%)	2660 (87%)
LMWH doses (IU/kg/d)	173 ± 43	172 ± 45	171 ± 44	187 ± 55	169 ± 47
Unfractionated heparin	382 (4.3%)	316 (5.0%)*	244 (4.4%)	26 (4.8%)	215 (7.0%)
Fondaparinux	317 (3.6%)	136 (2.2%)‡	124 (2.2%)	13 (2.4%)	56 (1.8%)
Rivaroxaban	534 (6.1%)	151 (2.4%)‡	134 (2.4%)	14 (2.6%)	44 (1.4%)
Apixaban	27 (0.31%)	17 (0.27%)	16 (0.29%)	1 (0.19%)	11 (0.36%)
Long-term therapy					
LMWH	2551 (29%)	1879 (30%)	1583 (29%)	242 (45%)	965 (32%)
LMWH doses (IU/kg/d)	153 ± 44	146 ± 45‡	145 ± 43	159 ± 48	144 ± 46
Vitamin K antagonists	4415 (50%)	3401 (54%)‡	3069 (56%)	192 (36%)	1643 (54%)
Rivaroxaban	1452 (17%)	505 (8.4%)‡	456 (8.6%)	42 (8.4%)	172 (6.0%)
Apixaban	130 (1.5%)	93 (1.6%)	87 (1.6%)	7 (1.4%)	47 (1.6%)
Dabigatran	28 (0.32%)	21 (0.35%)	21 (0.40%)	2 (0.40%)	6 (0.21%)

CrCl, creatinine clearance; IU, international units; LMWH, low-molecular-weight heparin.
Comparisons between fragile and non-fragile patients: *$P < .05$; †$P < .01$; ‡$P < .001$.

variables were compared using the chi-square test (two-sided) and Fisher's exact test (two-sided). Continuous variables were compared using Student's *t* test. Odds ratios (OR) with 95% confidence intervals (CI), as well as *P*-values (Mann-Whitney test or *t* test for continuous variables and Cochran-Mantel-Haenszel tests for categorical variables) were presented for each variable analyzed. All outcomes were analyzed in the overall follow-up period (0-90 days). Univariate analysis was conducted yielding odds ratios with 95% CI, as well as *P*-values (Cochran-Mantel-Haenszel tests) for each outcome. Kaplan-Meier survival analysis was conducted to investigate the risk of outcomes in both subgroups for the overall period (0-90 days).

Cox proportional hazard models were used to compare the rates of VTE recurrences and major bleeding in the two subgroups during the 90-day follow-up period. Covariates included in the adjusted model were those for which a statistically significant difference (a threshold *P*-value of .1 was set to assess significance of differences) was found between the two subgroups, and a backward selection was used for the covariate selection in the multivariate model. For both Kaplan-Meier survival analyses and Cox regression analyses, if a patient did not have a study outcome of interest before the cut-off time of 90 days or if he died, then the time-to-event was censored. Statistical analyses were conducted with SPSS for Windows Release 20.0 (SPSS, Inc., Chicago, Illinois).

3 | RESULTS

From January 2013 to October 2016, 15 079 patients with acute VTE were recruited in RIETE. Of these, 6260 (42%) were fragile: 5514 (37%) were aged ≥75 years, 537 (3.6%) weighed ≤50 kg, and 3059 (20%) had CrCl levels ≤50 mL/min. Fragile patients were less likely to be men (38% vs 57%) and more likely to have had recent immobility, cancer, chronic heart or lung disease, recent major bleeding, anemia, or abnormal platelet count than the non-fragile, but were less likely to have had recent surgery or estrogen use (Table 1). Fragile patients more likely presented initially with PE (with or without concomitant DVT) as compared with DVT alone (60% vs 53%).

Fragile patients more often received initial therapy with LMWH (88% vs 83%) or UFH (5.0% vs 4.3%), but less often fondaparinux (2.2% vs 3.6%) or rivaroxaban (2.4% vs 6.1%), as shown in Table 2. For long-term therapy, fragile patients more often received VKA (54% vs 50%) and less often rivaroxaban (8.4% vs 17%) than the non-fragile. The proportion of patients receiving apixaban or dabigatran was small and similar in both subgroups. Moreover, fragile patients on long-term LMWH therapy received lower mean daily doses per body weight than the non-fragile. Mean duration of therapy was slightly shorter in fragile than in non-fragile patients (207 ± 190 vs 214 ± 179 days, respectively; $P = .026$).

During the first 3 months of anticoagulant therapy, fragile patients had a lower risk of VTE recurrences (0.78% vs 1.4%; OR: 0.56; 95% CI: 0.40-0.78) and a higher risk of major bleeding (2.6% vs 1.4%; OR: 1.86; 95% CI: 1.47-2.36) than the non-fragile (Table 3). The risk of DVT recurrences was particularly lower (0.37% vs 0.90%; OR: 0.41; 95% CI: 0.26-0.65) while the risk of PE recurrences was non-significantly lower (0.43% vs 0.53%; OR: 0.81; 95% CI: 0.50-1.30). Fragile patients also had a higher risk of all-cause death (9.2% vs 3.5%; OR: 2.82; 95% CI: 2.44-3.25), fatal PE (0.85% vs 0.32%; OR: 2.68; 95% CI: 1.69-4.24), and fatal bleeding (0.35% vs 0.19%; OR: 1.83; 95% CI: 0.97-3.44) compared with non-fragile. In fragile patients, the risk of VTE recurrences was one-third the rate of major bleeding (49 vs 162 events, respectively) from the beginning of therapy (Figure 1). In non-fragile patients, both risks were similar (123 vs 124 events, respectively).

TABLE 3 Clinical outcomes during the first 3 months of anticoagulant therapy in fragile vs non-fragile patients with VTE

	Fragile	Non-fragile	Crude OR (95% CI)	Adjusted OR (95% CI)
Patients, *N*	6260	8819		
Events				
Recurrent VTE	49 (0.78%)	123 (1.4%)	0.56 (0.40-0.78)	0.52 (0.37-0.74)
Recurrent PE	27 (0.43%)	47 (0.53%)	0.81 (0.50-1.30)	—
Recurrent DVT	23 (0.37%)	79 (0.90%)	0.41 (0.26-0.65)	0.41 (0.25-0.67)
Major bleeding	162 (2.6%)	124 (1.4%)	1.86 (1.47-2.36)	1.41 (1.10-1.80)
Sites of major bleeding				
Gastrointestinal	54 (0.86%)	31 (0.35%)	2.47 (1.58-3.84)	1.84 (1.16-2.92)
Cerebral	20 (0.32%)	21 (0.24%)	1.34 (0.73-2.48)	—
Haematoma	32 (0.51%)	6 (0.07%)	7.55 (3.15-18.1)	5.05 (2.05-12.4)
Retroperitoneal	16 (0.26%)	11 (0.12%)	2.05 (0.95-4.42)	—
Death	574 (9.2%)	305 (3.5%)	2.82 (2.44-3.25)	2.02 (1.75-2.33)
Causes of death				
Pulmonary embolism	53 (0.85%)	28 (0.32%)	2.68 (1.69-4.24)	1.77 (1.10-2.85)
Initial PE	49 (0.78%)	23 (0.26%)	3.02 (1.84-4.96)	1.91 (1.14-3.20)
Recurrent PE	4 (0.06%)	5 (0.06%)	1.13 (0.30-4.20)	—
Bleeding	22 (0.35%)	17 (0.19%)	1.83 (0.97-3.44)	—
Cerebral	8 (0.13%)	6 (0.07%)	1.88 (0.65-5.42)	—
Gastrointestinal	4 (0.06%)	3 (0.03%)	1.88 (0.42-8.40)	—
Retroperitoneal	5 (0.08%)	1 (0.01%)	7.05 (0.82-60.3)	—
Respiratory insufficiency	44 (0.70%)	24 (0.27%)	2.59 (1.58-4.27)	—
Sudden, unexpected	16 (0.26%)	12 (0.14%)	1.88 (0.89-3.98)	—

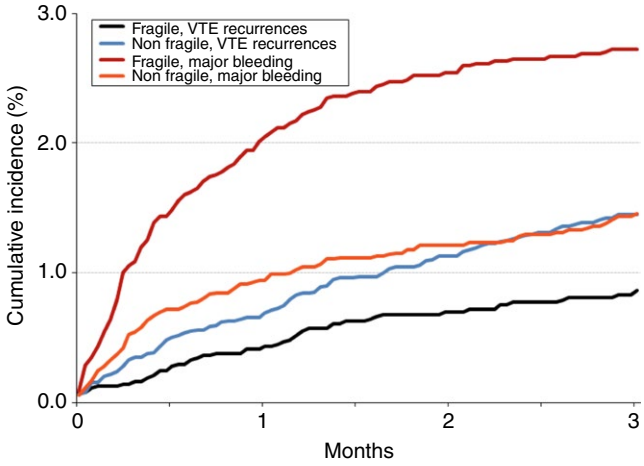
CI, confidence intervals; DVT, deep vein thrombosis; OR, odds ratio; PE, pulmonary embolism; VTE, venous thromboembolism.
Variables included in the multivariable analysis for VTE recurrence: fragile, active cancer, prior VTE, chronic heart failure, abnormal platelet count, and initial VTE presentation (DVT or PE).
Variables included in the multivariable analysis for major bleeding: fragile, gender, active cancer, chronic lung disease, recent major bleeding, anaemia, abnormal platelet count, and initial VTE presentation (DVT or PE).
Variables included in the multivariable analysis for death: fragile, gender, active cancer, recent surgery, recent immobilization, prior VTE, chronic lung disease, chronic heart failure, recent major bleeding, anaemia, abnormal platelet count, and initial VTE presentation (DVT or PE).

When separately analyzing outcomes, the risk of major bleeding in patients weighing <50 kg was similar to the risk in non-fragile, in patients aged ≥75 years it was slightly (but significantly) higher, and in those with CrCl levels <50 mL/min it was over 3-fold higher than in non-fragile (Table 4).

4 | DISCUSSION

The term "fragile" has been recently incorporated into the literature to include VTE patients who are elderly, renally impaired, or with low body weight.[3] This term should not be confused with "frail," which usually refers to elderly people with reduced physiologic reserve associated with increased susceptibility to disability.[15–19] Our findings, obtained from a large series of consecutive patients with VTE, reveal that in real life 42% of patients were fragile, and that during the first 3 months of anticoagulant therapy they had half the risk of VTE recurrences and a higher risk of major bleeding than the non-fragile. Among fragile patients, the risk of VTE recurrences was much lower than the risk of major bleeding (49 vs 162 events). Among non-fragile patients, the risk of VTE recurrences and major bleeding were the same (123 vs 124 events, respectively). Thus, there are reasons to suggest that when choosing an anticoagulant therapy for fragile patients with VTE, safety is an important issue.

Recent randomized trials on patients with VTE provided indirect evidence on a number of advantages in fragile patients receiving DOACs.[5,7,20] In the EINSTEIN-DVT and PE trials, the risk of major bleeding was much lower in fragile patients on rivaroxaban than in those on standard therapy (HR: 0.27; 95% CI: 0.13-0.54).[7] This difference was not seen in non-fragile patients. In the HOKUSAI trial a



	Days	1	10	30	60	90
Fragile	**VTE recurrences**	5 (0.08%)	10 (0.16%)	26 (0.43%)	41 (0.7%)	49 (0.87%)
	Major bleeding	18 (0.29%)	74 (1.2%)	124 (2.05%)	152 (2.54%)	162 (2.72%)
Non-fragile	**VTE recurrences**	7 (0.08%)	31 (0.35%)	60 (0.69%)	97 (1.13%)	123 (1.45%)
	Major bleeding	10 (0.11%)	51 (0.58%)	82 (0.94%)	105 (1.21%)	124 (1.46%)

FIGURE 1 Cumulative incidence of venous thromboembolism (VTE) recurrence and major bleeding during the first 3 months of anticoagulant therapy in fragile vs non-fragile patients

TABLE 4 Rates of VTE recurrences and major bleeding, according to the presence of age ≥75 years, CrCl ≤50 mL/min and/or body weight ≤50 kg

		VTE recurrences		Major bleeding	
	N	*N* (%)	OR (95% CI)	*N* (%)	OR (95% CI)
Non-fragile	8819	123 (1.4%)	Ref.	124 (1.4%)	Ref.
Age ≥75 years only	2967	22 (0.7%)	0.5 (0.3-0.8)	62 (2.1%)	1.5 (1.1-2.0)
CrCl ≤50 mL/min only	521	6 (1.2%)	0.8 (0.3-1.8)	23 (4.4%)	3.2 (2.0-5.0)
Body weight ≤50 kg only	183	3 (1.6%)	1.2 (0.3-3.3)	2 (1.1%)	0.8 (0.1-2.6)
Age ≥75 years and CrCl ≤50 mL/min	2235	16 (0.7%)	0.5 (0.3-0.8)	60 (2.7%)	1.9 (1.4-2.6)
Age ≥75 years and body weight ≤50 kg	51	0	—	1 (2.0%)	1.4 (0.1-7.3)
CrCl ≤50 mL/min and weight ≤50 kg	42	1 (2.4%)	1.7 (0.1-9.0)	2 (4.8%)	3.5 (0.6-12.4)
All 3 conditions	261	1 (0.4%)	0.3 (0.01-1.4)	12 (4.6%)	3.4 (1.8-6.0)

CI, confidence intervals; CrCl, creatinine clearance; OR, odds ratio; Ref., reference; VTE, venous thromboembolism.

higher efficacy (defined as symptomatic recurrent venous thromboembolism) was found using edoxaban than with warfarin in fragile patients (2.5% vs 4.8%; $P = .04$), without any safety concern (11.0% vs 13.7%; $P = .87$).[5] Unexpectedly, however, in our cohort rivaroxaban was less likely to be prescribed in fragile than in non-fragile patients, both initially (2.4% vs 6.1%, respectively) and for long-term therapy (8.4% vs 17%).

Our data confirm that the use of anticoagulant therapy carries a higher risk to bleed than to recur in the elderly and in the renally impaired, as previously reported.[14,21–25] During initial therapy with

LMWH, fragile patients weighing ≤50 kg received slightly higher (non-significantly) mean daily doses per body weight of LMWH compared with non-fragile patients. This might explain, at least in part, the higher risk of major bleeding in fragile patients. Moreover, since fragile patients had more underlying diseases, they probably used more drugs than the non-fragile patients. Thus, the increased risks of major bleeding during anticoagulation in fragile patients could be explained, at least in part, by these other drugs that might have potentiated the effect of the anticoagulant therapy. The similar risk for bleeding than for VTE recurrences in VTE patients weighing ≤50 kg has not been consistently reported.[26–28] These findings suggest the potential benefit of tailored therapy for VTE according to clinical characteristics of the patients and warrant external validation.

The present study has a number of potential limitations. First, since RIETE is an observational registry (and not a randomized trial) our data are hypothesis-generating. They might be a useful basis for future controlled clinical trials comparing different therapeutic strategies, but we should be extremely cautious in suggesting changes in treatment strategies just because of uncontrolled registry data. Second, patients were not treated with a standardized anticoagulant regimen; treatment varied with local practice, and is likely to have been influenced by a physician's assessment of a patient's risk of bleeding. Finally, patients in the RIETE database resided in several different countries. The variability of practices in different countries could potentially affect the study outcomes. Furthermore, a variety of practitioners entered data into the registry, which may lend itself to potential inaccuracies in the data being reported. The main strengths of our observation are the high number of included patients, the strict diagnostic criteria and the reporting of objectively established outcomes (major bleeding and recurrent VTE). Additionally, the population-based sample we used describes the effects of anticoagulant therapy in "real-world" clinical care, as opposed to in a protocol-driven randomized trial, and enhances the generalizability of our findings.

In summary, in real life 42% of VTE patients were fragile, and these patients had fewer VTE recurrences and more major bleeding events during the course of anticoagulant therapy than the non-fragile. Randomized trials are warranted to confirm whether the use of DOACs could be safer than standard anticoagulant therapy in fragile patients with VTE.

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AUTHOR CONTRIBUTIONS

F. Moustafa contributed to the design, analysis, and interpretation of data, collected patients, and wrote the article. M. Giorgi-Pierfranceschi contributed to the interpretation of data, collected patients, and approved the final version of the article. P. Di Micco contributed to the interpretation of data, collected patients, and approved the final version of the article. E. Bucherini contributed to the interpretation of data, collected patients, and approved the final version of the article. A. Lorenzo contributed to the interpretation of data, collected patients, and approved the final version of the article. A. Villalobos contributed to the interpretation of data, collected patients, and approved the final version of the article. JA. Nieto collected patients and approved the final version of the article. B. Valero collected patients and approved the final version of the article. AL. Samperiz collected patients and approved the final version of the article. M. Monreal contributed to the design, analysis, and interpretation of data, collected patients, wrote the article, and obtained funding.

RELATIONSHIP DISCLOSURE

Dr. Moustafa has served as an advisor or consultant for Bayer HealthCare Pharmaceuticals and Sanofi; has served as a speaker for Bayer HealthCare Pharmaceuticals, Boehringer Ingelheim, Daiichi-Sankyo and Sanofi; and has received grants from Sanofi, Bayer HealthCare and LFB. Dr. Monreal has served as an advisor or consultant for Bayer HealthCare Pharmaceuticals, Boehringer Ingelheim, Leo Pharma, Pfizer, and Sanofi; has served as a speaker or a member of a speaker's bureau for Bayer Healthcare Pharmaceuticals, Daiichi-Sankyo, Leo Pharma, and Sanofi; and has received grants for clinical research from Sanofi and Bayer. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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APPENDIX

Coordinator of the RIETE Registry: Manuel Monreal.

RIETE Steering Committee Members: Hervé Decousus, Paolo Prandoni, and Benjamin Brenner.

RIETE National Coordinators: Raquel Barba (Spain), Pierpaolo Di Micco (Italy), Laurent Bertoletti (France), Inna Tzoran (Israel), Abilio Reis (Portugal), Marijan Bosevski (R. Macedonia), Henri Bounameaux (Switzerland), Radovan Malý (Czech Republic), Philip Wells (Canada), and Manolis Papadakis (Greece).

RIETE Registry Coordinating Center: S & H Medical Science Service.

Members of the RIETE Group: SPAIN – Adarraga MD, Agudo P, Aibar MA, Alfonso M, Arcelus JI, Ballaz A, Barba R, Barrón M, Barrón-Andrés B, Bascuñana J, Blanco-Molina A, Cañas I, Casado I, Chic N, del Pozo R, del Toro J, Díaz-Pedroche MC, Díaz-Peromingo JA, Falgá C, Fernández-Aracil C, Fernández-Capitán C, Fidalgo MA, Font C, Font L, Gallego P, García MA, García-Bragado F, Gavín O, Gómez C, Gómez V, González J, Grau E, Grimón A, Guijarro R, Guirado L, Gutiérrez J, Hernández-Comes G, Hernández-Blasco L, Jara-Palomares L, Jaras MJ, Jiménez D, Jiménez J, Joya MD, Llamas P, Lobo JL, López P, López-Jiménez L, López-Reyes R, López-Sáez JB, Lorente MA, Lorenzo A, Lumbierres M, Luque JM, Marchena PJ, Martín-Martos F, Mellado M, Monreal M, Nieto JA, Nieto S, Núñez A, Núñez MJ, Otalora S, Otero R, Pedrajas JM, Pérez G, Pérez-Ductor C, Peris ML, Pons I, Porras JA, Reig O, Riera-Mestre A, Riesco D, Rivas A, Rodríguez M, Rodríguez-Dávila MA, Rosa V, Rosillo-Hernández E, Ruiz-Artacho P, Ruiz-Giménez N, Sahuquillo JC, Sala-Sainz MC, Sampériz A, Sánchez-Martínez R, Sanz O, Soler S, Sopeña B, Suriñach JM, Tolosa C, Torres MI, Troya J, Trujillo-Santos J, Uresandi F, Usandizaga E, Valero B, Valle R, Vela J, Vela L, Vicente MP, Villalobos A, Xifre B, BELGIUM – Vanassche T, Verhamme P, BRAZIL – Yoo HHB, CANADA – Wells P, CZECH REPUBLIC – Hirmerova J, Malý R, Dulíček P, ECUADOR – Salgado E, FRANCE – Bertoletti L, Bura-Riviere A, Farge-Bancel D, Hij A, Mahé I, Merah A, Moustafa F, ISRAEL – Braester A, Brenner B, Tzoran I, ITALY – Antonucci G, Barillari G, Bilora F, Bortoluzzi C, Brandolin B, Bucherini E, Cattabiani C, Ciammaichella M, Dell'Elce N, Dentali F, Di Micco P, Duce R, Giorgi-Pierfranceschi M, Grandone E, Imbalzano E, Lessiani G, Maida R, Mastroiacovo D, Pace F, Parisi R, Pellegrinet M, Pesavento R, Pinelli M, Poggio R, Prandoni P, Quintavalla R, Rocci A, Tiraferri E, Tonello D, Tufano A, Visonà A, LATVIA – Gibietis V, Skride A, Vitola B, REPUBLIC OF MACEDONIA – Bosevski M, Zdraveska M, SWITZERLAND – Bounameaux H, Mazzolai L.