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Assessment of bleeding events in patients receiving DOACs with or without statins to treat venous thromboembolism: insights from the RIETE registry

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ABSTRACT

Objective To evaluate the impact of coadministering statins with direct oral anticoagulants (DOACs) on the risk of major bleeding events in patients with venous thromboembolism (VTE).

Design Observational cohort analysis based on a multicentre international registry.

Setting Data were extracted from the Registro Informatizado de Enfermedad TromboEmbolica Registry, which involves 205 centres across 27 countries.

Participants A total of 73 659 patients diagnosed with VTE were classified based on their anticoagulant therapy (DOACs) versus low-molecular-weight heparin (LMWH) or vitamin K antagonists (VKAs) and concurrent use of statins.

Methods Multivariable Cox proportional hazards models adjusted for confounding variables to assess the risk of major bleeding events stratified by the type of anticoagulant use and statin use.

Results From October 2013 to February 2023, 73 659 patients were recruited: 2573 were statin users on DOACs, 14 090 were statin users on LMWH or VKA therapy, 10 088 were non-statin users on DOACs and 46 908 were non-statin users on LMWH or VKA therapy. Statin users were 10 years older and more likely to have hypertension, diabetes, renal failure or prior artery disease. During anticoagulation (median, 187 days), 1917 patients (2.6%) suffered major bleeding. Rates of major bleeding per 100 patient-years were 2.33 (95% CI 1.72 to 3.09), 3.75 (95% CI 3.43 to 4.10), 1.39 (95% CI 1.13 to 1.69) and 3.10 (95% CI 2.93 to 3.27), respectively. On multivariable analysis, patients treated with DOACs had a significantly lower risk of major bleeding compared with those on LMWH or VKA therapy (adjusted HR 0.59; 95% CI 0.48 to 0.74). The adjusted HR in statin users versus non-users was 1.03 (95% CI 0.92 to 1.14), while in statin users on DOACs versus the rest of patients, it was 1.18 (95% CI 0.79 to 1.76).

Conclusions In patients with VTE receiving statins, long-term anticoagulation with DOACs was associated with a reduced risk of major bleeding, regardless of the statin use. These findings support the safety profile of DOACs over VKAs or LMWH in the management of VTE in patients requiring statins.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This study leveraged real-world data from more than 73 000 patients with venous thromboembolism.
⇒ We applied multivariable analyses to detect associations with outcomes.
⇒ Potential for unmeasured confounding in the observational study design.
⇒ Generalisability is limited to the Registro Informatizado de Enfermedad TromboEmbolica registry population.

INTRODUCTION

Venous thromboembolism (VTE) is a common and potentially life-threatening condition, necessitating prompt anticoagulant therapy to prevent clot progression and recurrent events.[1 2] In clinical practice, patients with VTE often present with a complex clinical profile, including various comorbidities that require concurrent medication for their management, such as the use of statins for dyslipidaemia control.[3–5]

The coexistence of VTE and dyslipidaemia in patients poses a clinical challenge, as the optimal management of these conditions, particularly regarding the combined use of statins and anticoagulants, remains a topic of ongoing investigation. While previous research has shed light on the interactions between statins and traditional anticoagulants, such as vitamin K antagonists (VKAs),[6 7] the specific implications of combining statins with direct oral anticoagulants (DOACs) in VTE patients are less well defined. Recent studies have suggested potential benefits of coadministering statins and DOACs in patients with non-valvular atrial fibrillation, showing reductions in major bleeding risk, all-cause mortality and ischaemic events.[8] However, the dedicated investigation into

Table 1 Baseline characteristics of patients, according to long-term therapy with DOACs versus standard anticoagulation and the use of statins

	Statin users		Non-statin users	
	DOACs	**LMWH or VKA therapy**	**DOACs**	**LMWH or VKA therapy**
Patients, N	2573	14 090	10 088	46 908
Demographics				
Female sex	1274 (50%)	7141 (51%)	4838 (48%)	23 795 (51%)
Age, mean years±SD	72±11*	72±11*	60±18†	63±18†
BMI, mean kg/m^2±SD	29±5*	29±5*	28±5‡	28±6*
Comorbidities				
Chronic lung disease	337 (13%)	2243 (16%)	779 (7.7%)*	5122 (11%)
Hypertension	1850 (72%)	10 429 (74%)	3567 (35%)†	18 547 (40%)†
Diabetes	682 (27%)	4355 (31%)	932 (9.2%)‡	5413 (12%)‡
Prior MI or stroke	672 (26%)	3972 (28%)	560 (5.6%)†	3592 (7.7%)†
Recent major bleeding	46 (1.8%)	398 (2.8%)	162 (1.6%)	1124 (2.4%)
Risk factors for bleeding				
Active cancer	165 (6.4%)	2612 (19%)‡	635 (6.3%)	9615 (20%)‡
With metastases	68 (2.6%)	1373 (9.7%)‡	282 (2.8%)	5506 (12%)‡
Liver cirrhosis	4 (0.2%)	52 (0.4%)	22 (0.2%)	324 (0.7%)
Gastroduodenal ulcer	33 (1.3%)	215 (1.5%)	62 (0.6%)	560 (1.2%)
Anaemia	717 (28%)	5357 (38%)‡	2346 (23%)*	16 623 (35%)*
Platelet count <100×10^9/L	27 (1.1%)	389 (2.8%)*	120 (1.2%)	1383 (3.0%)*
Abnormal prothrombin time	151 (5.9%)	996 (7.1%)	619 (6.1%)	3455 (7.4%)
CrCl levels <60 mL/min	842 (33%)	5882 (42%)*	1865 (18%)‡	13 423 (29%)
Concomitant drugs				
Antiplatelets	905 (38%)	5136 (39%)	921 (9.9%)†	4962 (11%)†
Corticosteroids	268 (12%)	1516 (12%)	667 (7.2%)*	4324 (9.9%)
NSAIDs	174 (7.5%)	995 (7.7%)	489 (5.3%)	3012 (6.9%)
Type of statins				
Simvastatin	671 (26%)	3922 (28%)	0	0
Atorvastatin	996 (39%)	3514 (25%)‡	0	0
Rosuvastatin	199 (7.7%)	534 (3.8%)*	0	0
Pravastatin	124 (4.8%)	537 (3.8%)	0	0
Lovastatin	19 (0.7%)	106 (0.7%)	0	0
Fluvastatin	11 (0.4%)	102 (0.7%)	0	0
Pitavastatin	17 (0.7%)	88 (0.6%)	0	0
Not provided	536 (21%)	5287 (38%)‡	0	0

Differences between patients receiving DOACs and statins versus the other subgroups
*Standardised difference ≥0.1.
†Standardised difference ≥0.5.
‡Standardised difference ≥0.2.
BMI, body mass index; CrCl, creatinine clearance; DOACs, direct oral anticoagulants; LMWH, low-molecular-weight heparin; MI, myocardial infarction; NSAIDs, non-steroidal anti-inflammatory drugs; VKA, vitamin K antagonists.

the safety and efficacy of this combination therapy in the context of VTE management remains limited.[9–11] Understanding the safety profile and potential outcomes associated with the concurrent use of statins and DOACs is crucial for guiding treatment decisions and optimising patient care in this vulnerable population.

To address this knowledge gap, we used data from the RIETE (Registro Informatizado de Enfermedad TromboEmbolica) registry[12] to compare the incidence rates of major bleeding events during anticoagulation therapy in VTE patients using statins, stratified by long-term therapy with DOACs versus other anticoagulants. The

Table 2 Baseline characteristics of patients, according to long-term therapy with DOACs versus other anticoagulants

	Statin users		Non-statin users	
	DOACs	**LMWH or VKA therapy**	**DOACs**	**LMWH or VKA therapy**
Patients, N	2573	14090	10088	46908
Time elapsed from baseline,				
Median days (IQR)	10 (7–22)	6 (2–10)‡	11 (7–22)‡	6 (2–10)‡
Duration of therapy,				
Median days (IQR)	168 (100–343)	192 (103–378)‡	144 (98–273)‡	188 (103–361)‡
Mean days (SD)	276±313	340±451*	251±308	334±503*
Type of DOACs,				
Rivaroxaban	1160 (45%)	0	5567 (55%)†	0
20 mg daily	1075 (42%)	0	5291 (52%)†	0
<20 mg daily	85 (3.3%)	0	275 (2.7%)	0
Apixaban	984 (38%)	0	3071 (30%)*	0
10 mg daily	881 (34%)	0	2802 (28%)*	0
<10 mg daily	103 (4.0%)	0	269 (2.7%)	0
Edoxaban	332 (13%)	0	1156 (11%)	0
60 mg daily	268 (81%)	0	989 (86%)*	0
30 mg daily	64 (19%)	0	165 (14%)*	0
Dabigatran	97 (3.8%)	0	294 (2.9%)	0
220 mg daily	87 (3.4%)	0	277 (2.7%)	0
<220 mg daily	10 (0.4%)	0	17 (0.2%)	0
Standard therapy				
VKA	0	8259 (59%)	0	26769 (57%)
LMWH	0	4975 (35%)	0	17343 (37%)
Fondaparinux	0	85 (0.6%)	0	511 (1.1%)

Differences in median days of therapy between patients receiving DOACs and statins versus the other subgroups: *p <0.1; †p <0.01; ‡p <0.001 (Mann-Whitney U test).
Differences in proportions between patients receiving DOACs and statins vs the other subgroups: *standardized difference ≥0.1; †standardized difference ≥0.2; ‡standardized difference ≥0.5.
DOACs, direct oral anticoagulants; LMWH, low-molecular-weight heparin; VKA, vitamin K antagonist.

comprehensive and diverse patient cohort included in this registry provided a robust foundation for analysing the interplay between statin use, choice of anticoagulant therapy (DOACs vs other agents) and the associated risk of major bleeding events. By investigating potential differences in bleeding risk between these patient subgroups while controlling for confounding factors, our study aimed to generate valuable insights and evidence that could inform clinical practice and enhance treatment strategies for patients with VTE. Ultimately, our research endeavours to contribute to the existing literature and empower clinicians with the knowledge needed to make informed and personalised decisions in the management of VTE.

METHODS
Data source and study cohort
The present study used the RIETE registry, a comprehensive, multicentre, prospective registry collecting data from consecutive patients diagnosed with VTE, including deep vein thrombosis (DVT) and pulmonary embolism (PE), across 205 centres in 27 countries (ClinicalTrials.gov identifier, NCT02832245).[13] Patients who were participating in a blind/double-blind clinical therapeutic trial were excluded. Clinicians participating in this RIETE registry have made every reasonable attempt for enrolling consecutive patients. This manuscript is in conformity with the statement of the Strengthening the Reporting of Observational studies in Epidemiology (STROBE).[14 15]

Study design and population
We conducted a registry-based, observational cohort study to evaluate the risk of major bleeding events associated with the use of DOACs and statins, compared with traditional anticoagulants such as low-molecular-weight heparin (LMWH) and VKAs. Patients were stratified into four groups based on their exposure to anticoagulant therapy and use of statins at the time of their VTE event from October 2013 to February 2023.

Table 3 Bleeding rates according to the use of statins in patients receiving anticoagulation with DOACs or LMWH and VKA therapy

	Statins		No statins	
	N	N per 100 patients-years (95% CI)	N	N per 100 patients-years (95% CI)
DOACs users				
Patients, N	2573		10 088	
Length of therapy				
Median days (IQR)	168 (100 to 343)***		144 (98 to 273)	
Major bleeding, any	45	2.33 (1.72 to 3.09)**	96	1.39 (1.13 to 1.69)
Gastrointestinal	21	1.08 (0.69 to 1.62)*	36	0.52 (0.37 to 0.71)
Haematoma	10	0.51 (0.26 to 0.92)	16	0.23 (0.14 to 0.37)
Intracranial	8	0.41 (0.19 to 0.78)	17	0.25 (0.15 to 0.39)
Retroperitoneal	0	to	1	0.01 (0.00 to 0.07)
Urinary	1	0.05 (0.00 to 0.25)	4	0.06 (0.02 to 0.14)
Uterine	1	0.05 (0.00 to 0.25)	14	0.20 (0.12 to 0.33)
Other sites	6	0.31 (0.13 to 0.64)	11	0.16 (0.08 to 0.28)
Non-major bleeding	359	5.74 (4.73 to 6.90)	359	5.34 (4.81 to 5.91)
Fatal bleeding	5	0.26 (0.09 to 0.57)	5	0.07 (0.03 to 0.16)
Gastrointestinal	1	0.10 (0.02 to 0.34)	1	0.01 (0.00 to 0.07)
Intracranial	3	0.05 (0.00 to 0.25)	3	0.04 (0.01 to 0.12)
LMWH or VKA therapy users				
Patients, N	14 090		46 908	
Length of therapy				
Median days (IQR)	192 (103 to 378)**		188 (103 to 361)	
Major bleeding, any	477	3.75 (3.43 to 4.10)***	1299	3.10 (2.93 to 3.27)
Gastrointestinal	152	1.18 (1.00 to 1.38)	455	1.07 (0.98 to 1.18)
Haematoma	110	0.85 (0.71 to 1.03)	256	0.60 (0.53 to 0.68)
Intracranial	94	0.73 (0.59 to 0.89)**	253	0.60 (0.53 to 0.67)
Retroperitoneal	39	0.30 (0.22 to 0.41)	93	0.22 (0.18 to 0.27)
Urinary	40	0.31 (0.22 to 0.42)	66	0.16 (0.12 to 0.20)
Uterine	6	0.05 (0.02 to 0.10)**	55	0.13 (0.10 to 0.17)
Other sites	48	0.37 (0.28 to 0.49)	142	0.33 (0.28 to 0.39)
Non-major bleeding	657	5.26 (4.87 to 5.67)***	1811	4.39 (4.19 to 4.60)
Fatal bleeding	75	0.58 (0.46 to 0.72)	218	0.51 (0.45 to 0.58)
Gastrointestinal	15	0.12 (0.07 to 0.19)	59	0.14 (0.11 to 0.18)
Intracranial	44	0.34 (0.25 to 0.45)*	89	0.21 (0.17 to 0.26)

Differences between patients not using statins and those using statins: *p< 0.05, **p< 0.01; ***p <0.001.
Results are expressed as number of events per 100 patient-years and 95% CIs (in brackets).
DOACs, direct oral anticoagulants; LMWH, low-molecular-weight heparin; VKA, vitamin K antagonist.

The main study outcome was the development of major bleeding during anticoagulant therapy. Bleeding was considered major if it was overt and required a transfusion of 2 or more units of blood, involved a critical site (retroperitoneal, spinal or intracranial) or was fatal. The definition of major bleeding here used is based on the original definition used in RIETE registry since its creation in 2001 and is in accordance with the International Society on Thrombosis and Hemostasis.[16–18] Clinically relevant non-major bleeding (CRNMB) was defined as any overt bleeding requesting medical assistance but not fulfilling criteria for major bleeding. Fatal bleeding was defined as any death that occurred within 10 days after a major bleeding episode if there was no other cause of death.

Anticoagulation management was in accordance with the clinical practice of each participating institution (ie, there was no standardisation of therapy). Type, dose and the duration of anticoagulation treatment were registered. After VTE diagnosis, all patients were followed in the outpatient setting for a minimum of 3 months, and then as long as possible. Most outcomes were classified and reported from each participant's sites.

Table 4 Major bleeding rates according to the use of different statins

		DOACs		LMWH or VKAs	
	N	**N**	**N per 100 patients-years (95% CI)**	**N**	**N per 100 patients-years (95% CI)**
Patients, N		2573		14 090	
Any statins	16 663	45	2.33 (1.72 to 3.09)	477	3.75 (3.43 to 4.10)**
Atorvastatin	4510	23	3.07 (1.99 to 4.53)	152	4.88 (4.15 to 5.71)*
Simvastatin	4593	9	1.80 (0.88 to 3.30)	123	3.48 (2.91 to 4.14)*
Rosuvastatin	733	3	2.19 (0.56 to 5.95)	18	3.99 (2.44 to 6.18)
Pravastatin	661	2	1.95 (0.33 to 6.45)	12	2.46 (1.33 to 4.18)
Lovastatin	125	0	–	1	0.79 (0.04 to 3.91)
Fluvastatin	113	0	–	3	2.66 (0.68 to 7.25)
Pitavastatin	105	0	–	4	4.54 (1.44 to 11.0)
Not provided	5823	8	2.00 (0.93 to 3.80)	164	3.41 (2.92 to 3.96)

Differences between patients on standard anticoagulation versus those on DOACs: *p< 0.05, **p<0.01; ***p<0.001.
Comparison between patients receiving DOACs versus those on LMWH or VKA therapy. Results are expressed as number of events per 100 patient-years and 95% CIs (in brackets).
DOACs, direct oral anticoagulants; LMWH, low-molecular-weight heparin; VKAs, vitamin K antagonists.

Data collection

The following parameters were recorded: patient demographics, comorbidities and relevant medications. Comorbidities included previous cardiovascular diseases, lung diseases and cardiovascular risk factors. Risk factors for bleeding such as recent (<2 months before) major bleeding, anaemia or renal insufficiency were registered and defined, respectively, as newly diagnosed cancer or receiving antineoplastic treatment of any type; haemoglobin levels <130 g/L for men and <12 g/dL for women; creatinine clearance levels according to the Cockcroft and Gault formula <60 mL/min.[19] We also included medications of non-steroidal anti-inflammatory drugs, glucocorticoids and antiplatelet drugs.

Statistical analysis

We performed descriptive analyses to summarise patient demographics, treatment modalities and clinical outcomes. Given the large sample size, it was crucial to determine not just statistical significance but also clinical relevance. Therefore, standardised differences (STDs) greater than 0.1 were used to denote clinically meaningful disparities between groups (statin users vs non-users and those on different anticoagulation regimens). Major bleeding rates were calculated per 100 patient-years, along with 95% CIs, to facilitate a standardised comparison between treatment groups. ORs were calculated to measure the strength and direction of the association between anticoagulant type (DOACs vs LMWH/VKAs) and major bleeding events, stratified by statin use. P values were calculated to compare the median duration of treatment in each group using the Mann-Whitney U test.

Crude and adjusted models were also computed. Multivariable analysis was performed using the Cox proportional hazards model to assess the adjusted risk of major bleeding, accounting for potential confounders such as age, sex, initial VTE presentation (isolated DVT vs PE), active cancer, recent surgery, recent immobility, recent major bleeding, liver cirrhosis, gastroduodenal ulcer, anaemia, thrombocytopaenia, abnormal prothrombin time, renal failure, concomitant use of antiplatelets or corticosteroids and study sites. We incorporated interaction terms between DOACs and statin use to provide a clearer understanding of the combined effects on bleeding risk (online supplemental figure 1). Any missing values were imputed. Statistical analyses were conducted with SPSS for Windows (V.20, SPSS).

This manuscript is in conformity with the statement of the STROBE.[11]

Patient and public involvement

Not applicable.

RESULTS

Patient demographics and treatment groups

During the study period from October 2013 to February 2023, a total of 73 659 patients with VTE were included in the RIETE registry. Of these, 2573 (3.5%) were statin users receiving DOACs, 14 090 (19.1%) were statin users on LMWH or VKAs, 10 088 (13.7%) were non-statin users receiving DOACs and 46 908 (63.7%) were non-statin users on LMWH or VKAs. The most commonly used statins were as follows: simvastatin (4593), atorvastatin (4510), rosuvastatin (733), pravastatin (661), lovastatin (125), fluvastatin (113), pitavastatin (105), not provided (5823). The most commonly used DOACs were as follows: rivaroxaban (1160) and apixaban (984). As for other therapies, the most commonly used drugs were as follows: VKAs (35 028), LMWH (22 318) and fondaparinux (596). Five variables in the analyses had some missing values: hypertension 0.4%, diabetes 0.6%, anaemia 0.3%, creatinine clearance 4.5% and prothrombin time 14.6%.

Table 5 Univariable and multivariable analysis for major bleeding

Variables	Non-adjusted model	Adjusted model
DOACs (vs LMWH/VKAs)	0.38 (0.31 to 0.47)	0.59 (0.48 to 0.74)
Statins (vs no statins)	1.22 (1.10 to 1.36)	1.03 (0.92 to 1.14)
DOACs+statins (vs rest)	1.45 (1.00 to 2.10)	1.18 (0.79 to 1.76)

Covariables included in the adjusted model: age, gender, initial VTE presentation (pulmonary embolism versus isolated deep vein thrombosis), active cancer, recent surgery, gastroduodenal ulcer, liver cirrhosis, recent (<30 days) major bleeding, anaemia, platelet count <100 000/µL, abnormal prothrombin time, creatinine clearance levels <60 mL/min, concomitant use of antiplatelets, concomitant use of corticosteroids and centre. Results are expressed as HR and 95% CIs.
DOACs, direct oral anticoagulants; LMWH, low-molecular-weight heparin; VKAs, vitamin K antagonists; VTE, venous thromboembolism.

Statin users were an average of 10 years older than non-statin users, with a mean age of 72 years compared with 62 years (table 1). Statin users also exhibited a higher prevalence of comorbidities such as hypertension (74% vs 39%), diabetes (30% vs 11%), renal failure (40% vs 27%), prior myocardial infarction or ischaemic stroke (28% vs 7.3%) or to be using antiplatelet drugs concomitantly (36% vs 10%) compared with non-statin users (STD>0.1 for all comparisons). Moreover, patients receiving DOACs were less likely to have active cancer (6.3% vs 20%; STD>0.1) or metastatic cancer (2.8% vs 11%; STD>0.1) than those on long-term therapy with LMWH/VKAs. The median time elapsed from VTE diagnosis to start of long-term anticoagulation was longer in patients receiving DOACs than in those on SA (11 vs 6 days, respectively), as shown in table 2.

Major bleeding events
During long-term anticoagulation (median duration, 187 days), a total of 1917 patients experienced major bleeding events, resulting in an overall major bleeding rate of 2.6% among all patients included in the study. The major bleeding rates per 100 patient-years for each group were as follows: statin users on DOACs, 2.33 (95% CI 1.72 to 3.09); statin users on LMWH or VKA therapy, 3.75 (95% CI 3.43 to 4.10); non-statin users on DOACs, 1.39 (95% CI 1.13 to 1.69) and non-statin users on LMWH or VKA therapy, 3.10 (95% CI 2.93 to 3.27), as shown in table 3. Gastrointestinal bleeding (n=664), haematoma (n=392) and intracranial (n=372) were the most common sites of major bleeding. We found no significant differences in the rates of major bleeding between patients using atorvastatin (3.07 per 100 patient-years: 95% CI 1.99 to 4.53), simvastatin (1.80; 95% CI 0.88 to 3.30) or rosuvastatin (2.19; 95% CI 0.56 to 5.95) (table 4). There were 303 fatal bleeding events, which accounted for 15.8% of all major bleeding incidents. Among the patients who developed major bleeding while on VKAs, INR distribution at the time of bleeding was as follows: 25% had an INR below 2.0, 29% had an INR within the therapeutic range (2.0–3.0) and 34% had an INR above 3.0 (online supplemental table 1).

Supplementary analysis of anticoagulant types
Patients receiving LMWH showed a higher rate of major bleeding compared with those on VKAs (online supplemental table 2). The incidence of major bleeding was significantly higher among LMWH users than in those on VKAs, which can be attributed to the higher proportion of patients with active cancer in this group (41% in LMWH users vs 5.7% in VKA users). Moreover, we found a consistently lower risk for major bleeding among patients treated with DOACs compared with those on VKAs or LMWH, regardless of statin use. Finally, we did not find differences in bleeding rates between statin users versus non-users with active cancer (online supplemental table 3).

Influence of statins on bleeding risk
Multivariable analysis, adjusted for age, sex, comorbidities and other potential confounders, revealed significant differences in major bleeding risk between the treatment groups. Specifically, patients treated with DOACs, including both statin users and non-users, had a significantly lower risk of major bleeding compared with those on LMWH or VKA therapy (adjusted HR 0.59; 95% CI 0.48 to 0.74), as shown in table 5. The adjusted HR for major bleeding in statin users versus non-users was 1.03 (95% CI 0.92 to 1.14), while in statin users on DOACs versus the remaining patients, it was 1.18 (95% CI 0.79 to 1.76) (table 5).

CRNMB events
The rates of CRNMB events were also evaluated, revealing no significant differences influenced by statin use among the different anticoagulant drugs (online supplemental tables 2,3).

DISCUSSION
Our findings, obtained from a large cohort of consecutive patients with VTE, indicate that the coadministration of DOACs and statins in VTE patients is associated with a lower risk of major bleeding compared with patients treated with LMWH or VKAs, similar to that observed in non-statin users. This observation is significant given the increasing use of both DOACs and statins in clinical practice. These results may offer a practical and safe alternative for managing VTE in patients requiring statin therapy, potentially minimising the concern of bleeding complications. The lower risk of major bleeding seen with DOACs compared with LMWH or VKA therapy in both statin

users and non-users raises intriguing questions. DOACs have gained popularity due to their predictable pharmacokinetics and reduced need for monitoring compared with traditional anticoagulants such as VKAs.[20] However, in peculiar situations (eg, major trauma, traumatic brain injury, acute surgery) evaluation of DOAC plasma concentrations might be recommended by local institutions, practices or guidelines.[21] This study adds to the growing body of evidence supporting the safety profile of DOACs in VTE management.[22 23] Notably, the reduced bleeding risk associated with DOACs is held even in the presence of statins, which are commonly prescribed in this patient population due to their cardiovascular benefits. However, it is important to note that the risk of bleeding is not entirely eliminated, and individual patient factors should continue to guide treatment decisions.

The similarities in major bleeding risk between statin users on LMWH or VKA therapy and non-statin users on LMWH or VKAs suggest that statin therapy alone may not significantly influence bleeding risk in VTE patients. However, the precise mechanisms behind these findings warrant further investigation. Additionally, our subgroup analysis highlighted notable differences in bleeding risks between patients on VKAs and those on LMWH. The higher bleeding rates in LMWH users, particularly among those with active cancer, underscore the complex management needs of this subgroup. Moreover, the potential interaction between statins, DOACs and bleeding risk requires deeper exploration. Further research should aim to elucidate these factors to refine treatment guidelines and optimise outcomes for VTE patients with concomitant statin therapy.

Certainly, discussing the limitations of this study is a crucial aspect. We acknowledge the significant demographic differences between our study groups and their potential impact on our findings. While our multivariable analysis attempts to adjust for these differences, we recognise that residual confounding may still exist. Future studies, ideally with matched cohorts or randomised designs, are necessary to fully elucidate the impact of statins on bleeding risks in patients on anticoagulants. Second, the choice of anticoagulant therapy, including the decision to prescribe statins, was likely influenced by patient-specific factors and physician discretion. This introduces the potential for selection bias, as patients receiving DOACs or LMWH and VKA therapy may have inherently different bleeding risks that were not fully accounted for in the analysis. Third, the study population consisted of patients registered in the RIETE registry, which may not fully represent the broader population of VTE patients. The registry includes data from multiple centres, but the results may not be generalisable to regions or populations not included in the database. Fourth, despite efforts to adjust for potential confounders, it is challenging to eliminate the influence of unmeasured variables that could affect bleeding. Factors such as genetic predisposition and adherence to medication regimens were not consistently captured and may impact outcomes. However,

the study leveraged data from the RIETE registry, which captures real-world clinical practice and outcomes with over 73 000 patients, thus providing statistical power to detect meaningful associations and outcomes, enhancing the reliability of our findings. Finally, another consideration in interpreting our findings is the potential of prevalent user bias. This bias occurs when patients already on a treatment regimen (like statins) are included in the study, possibly obscuring the onset of adverse effects of the drug's full impact due to pre-existing conditions or adaptations.

In conclusion, our findings indicate that among patients with VTE receiving statin therapy, long-term anticoagulation with DOACs is associated with a reduced risk of major bleeding compared with LMWH or VKA therapy, aligning with the risk observed in non-statin users.

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Ethics approval The study was conducted in accordance with the ethical standards outlined in the Declaration of Helsinki. The use of deidentified patient data from the RIETE registry was approved by the relevant ethics committees at participating centres. The study was approved by the Ethics Committee on Research from the Hospital Universitari Germans Trias i Pujol (Badalona, Spain) on 7 April 2017 (code IRB00002131). The protocol for patient enrolment has been approved by all ethics committees of the participating sites. All patients and/or their healthcare delegates provided informed consent to participate in the registry, according to local ethical committee requirements in each centre. Patients who were participating in a blind/double-blind clinical therapeutic trial were excluded. Clinicians participating in this RIETE registry have made every reasonable attempt for enrolling consecutive patients.

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Data availability statement Data are available on reasonable request. Data may be obtained from a third party and are not publicly available. Supplementary and raw data can be placed online alongside the article although we prefer raw data to be made publicly available and linked to in a suitable repository (eg, Dryad, FigShare). We may request that you separate out some material into supplementary data files to make the main manuscript clearer for readers.

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