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Original Article

# Statin and all-cause mortality in patients receiving anticoagulant therapy for venous thromboembolism. Data from the RIETE registry

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ABSTRACT

*Background:* The clinical outcomes during the course of anticoagulation in patients with venous thromboembolism (VTE) using statins remain controversial.
*Methods:* We used the RIETE (Registro Informatizado Enfermedad TromboEmbólica) registry to compare the risk for VTE recurrences, major bleeding or death during anticoagulation, according to the use of statins at baseline. We used propensity score-matching (PSM) to adjust for confounding variables.
*Results:* From February 2009 to January 2018, 32,062 VTE patients were included. Of these, 7,085 (22%) were using statins. Statin users were 10 years older (73 ± 11 vs. 63 ± 19 years, respectively) and more likely to have comorbidities or to be using antiplatelets or corticosteroids at baseline than non-users. During the course of anticoagulation (median, 177 days), 694 patients developed VTE recurrences, 848 bled and 3,169 died (fatal pulmonary embolism 176, fatal bleeding 121). Statin users had a similar rate of VTE recurrences (hazard ratio [HR]: 0.98; 95%CI: 0.82–1.17), a higher rate of major bleeding (HR: 1.29; 95%CI: 1.11–1.50) and a similar mortality rate (HR: 1.01; 95%CI: 0.93–1.10) than non-users. On PSM analysis, statin users had a significantly lower risk for death (HR: 0.62; 95%CI: 0.48–0.79) and a similar risk for VTE recurrences (HR: 0.98; 95%CI: 0.61–1.57) or major bleeding (HR: 0.85; 95%CI: 0.59–1.21) than non-users.
*Conclusions:* During anticoagulation for VTE, patients using statins at baseline had a lower risk to die than non-users.

## 1. Introduction

Venous thromboembolism (VTE) is a leading cause of morbidity and mortality [1]. While anticoagulant therapy is effective at preventing VTE recurrences, the substantial bleeding risk associated with anticoagulation may limit its use in patients with a high risk for bleeding. Consequently, alternative options to reduce the mortality rate (ideally without increasing the risk for bleeding) are a matter of current investigation [2–5]. In recent years, there has been a growing interest on the potential role of statins to reduce the risk for VTE (either primarily or as a secondary prevention after VTE) or bleeding [6–17], but there are scarce data on the influence of statins on mortality in patients receiving anticoagulation for VTE [15,18].

The RIETE (Registro Informatizado Enfermedad TromboEmbólica)

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registry is an ongoing, multicenter, observational registry of consecutive patients with objectively confirmed acute VTE (ClinicalTrials.gov identifier: NCT02832245). Data from this registry have been used to evaluate outcomes after acute VTE, such as the frequency of recurrent VTE, major bleeding or mortality, and risk factors for these outcomes [19–23]. The rationale and methodology of RIETE have been published elsewhere [24]. In the current study, we aimed to compare the risk for VTE recurrences, major bleeding or death during the course of anticoagulant therapy, according to the use of statins at baseline.

## 2. Methods

### 2.1. Inclusion criteria

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

### 2.2. Study design

For this study, only patients with a first episode of VTE and available information on the use of statins at baseline were considered. Data related to use of statins was added to RIETE-abstraction forms in February 2009. Therefore, only patients recruited after this date were eligible for the current study. The main study outcomes were VTE recurrences, major bleeding and all-cause death occurring during the course of anticoagulation. Secondary outcomes were fatal PE and fatal bleeding. Bleeding events were classified as 'major' if they were overt and required a transfusion of two units of blood or more, or were retroperitoneal, spinal or intracranial. Fatal PE, in the absence of autopsy, was defined as any death appearing < 10 days after PE diagnosis, in the absence of any alternative cause of death. Fatal bleeding was defined as any death occurring < 10 days after a major bleeding episode, in the absence of any alternative cause of death.

### 2.3. Study variables

The following parameters are recorded in RIETE: patient's baseline characteristics; clinical status including any coexisting or underlying conditions such as chronic heart or lung disease, recent major bleeding, anemia or renal insufficiency; risk factors for VTE; the treatment received upon VTE diagnosis; concomitant drugs and the outcomes during the course of therapy. Immobilized patients were defined as non-surgical patients who had been immobilized (i.e., total bed rest with or without bathroom privileges) for ≥4 days in the 2-month period prior to VTE diagnosis. Surgical patients were defined as those who had undergone an operation in the 2 months prior to VTE. Active cancer was defined as newly diagnosed cancer (< 3 months before) or when receiving anti-neoplastic treatment of any type (i.e., surgery, chemotherapy, radiotherapy, hormonal, support therapy or combined therapies). Recent bleeding was considered in those patients suffering major bleeding < 30 days prior to VTE. Anemia was defined as hemoglobin levels < 13 g/dL for men and < 12 g/dL for women.

### 2.4. Treatment and follow-up

Patients were managed according to the clinical practice of each participating hospital (i.e., there was no standardization of treatment). The type, dose and duration of anticoagulant therapy were recorded. After VTE diagnosis, all patients were followed-up in the outpatient clinic for at least 3 months. 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

Categorical variables were compared using the chi-square test (two-sided) and Fisher´s Exact Test (two-sided). Continuous variables were compared using Student t test. For major bleeding, VTE recurrences and death, hazard ratios (HR) and corresponding 95% confidence intervals (CI) were calculated in multivariable analysis. Incidence rates were calculated as events per 100 patient-years of follow-up and compared between patients receiving and those not receiving statins at baseline, using the hazard ratios. Risks for recurrent VTE, major bleeding or death according to the use of statins were assessed using logistic regression models. Covariates included in the adjusted model were those for which a statistically significant difference (a threshold p-value of 0.1 was set to assess significance of differences) was found, and a backward selection was used for the covariate selection in the multivariable model. A propensity score analysis compared statin users vs. non-users, including in the model the covariates that were associated with the risk for death. They were the following: age, gender, body weight, chronic heart failure, chronic lung disease, recent major bleeding, recent surgery, recent immobility, cancer, initial VTE presentation, anaemia, platelet count < 100.000/μL, creatinine clearance levels < 50 mL/min, total cholesterol levels < 250 mg/dL, LDL-cholesterol levels < 150 mg/dL, diabetes, current smoking, hypertension, prior myocardial infarction, prior ischemic stroke, peripheral artery disease, and concomitant use of antiplatelets or corticosteroids. Propensity score matching (PSM) was done. The nearest neighbor method was used, with a ratio 2:1 and 3:1, and different calipers (corresponding to 0.1 and 0.2 value of standard deviation). Imbalance among covariates was measured with the standardized differences of mean for both continuous and categorical variables. Statistical analyses were conducted with SPSS for Windows Release (version 20, SPSS Inc. Chicago, Illinois).

## 3. Results

From February 2009 to January 2018, 32,062 patients with a first episode of VTE were recruited (Fig. 1). Of these, 7,085 (22%) were using statins at baseline: simvastatin 3,149 patients, atorvastatin 2,678, pravastatin 375, rosuvastatin 507, pitavastatin 143, lovastatin 135, and fluvastatin 99. Overall, 22,764 patients in the cohort (71%) and 4,605 of those using statins (65%) were recruited in Spanish hospitals. Compared with non-users, statin users were 10 years older and more likely to have comorbidities such as chronic heart or lung disease, recent major bleeding, anaemia, renal insufficiency, diabetes, hypertension or prior artery disease (Table 1). Statin users had lower levels of total- and LDL cholesterol at baseline than non-users. They also were more likely to be using antiplatelets or corticosteroids at baseline than non-statin users, but less likely to be currently smoking. Over 50% of patients using antiplatelets at baseline discontinued after being diagnosed with VTE, most likely those not using statins. Finally, statin users were more likely to initially present as PE than as DVT.

Most patients in both subgroups (88% vs. 87%) were initially treated with low-molecular-weight heparin (LMWH), at similar daily doses (Table 2). Among the remaining patients, statin users were more likely to receive unfractionated heparin and less likely to receive direct oral anticoagulants (DOACs) than non-users. For long-term therapy, statin users were more likely to receive vitamin K antagonists (60% vs.

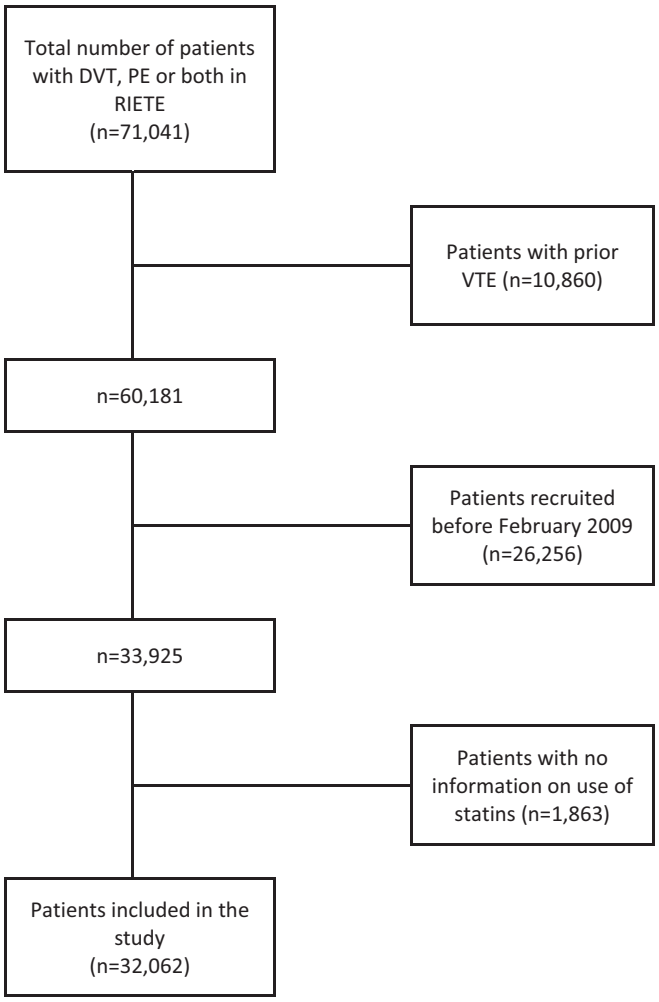


**Fig. 1.** Flow-chart of the patients.

56%) and less likely to receive DOACs than non-users. In all, 57 patients did not receive anticoagulant therapy, and were excluded from the analysis. Median duration of anticoagulant therapy was similar in both subgroups (176 vs. 177 days).

During the course of anticoagulant therapy, 694 patients developed VTE recurrences (333 as PE and 380 as DVT), 848 had major bleeding (gastrointestinal 275, haematoma 165, intracranial 163) and 3,169 died (because of PE 176, bleeding 121, disseminated cancer 1,226, respiratory insufficiency 282, sudden unexpected death 76, infection 248). Statin users had a similar rate of VTE recurrences (hazard ratio [HR]: 0.98; 95%CI: 0.82–1.17), a higher rate of major bleeding (HR: 1.29; 95%CI: 1.11–1.50) and a similar mortality rate (HR: 1.01; 95%CI: 0.93–1.10) than non-users (Table 3). The rates of fatal PE (HR: 0.99; 95%CI: 0.69–1.39) and fatal bleeding (HR: 1.36; 95%CI: 0.91–2.01) were also similar in users and non-users.

On multivariable analysis (after adjusting for patient's age, sex, body weight, chronic lung or heart disease, recent bleeding, diabetes, hypertension, prior artery disease, risk factors for VTE, initial VTE presentation, anaemia, thrombocytopenia, renal insufficiency and use of corticosteroids or antiplatelets), statin users had a similar risk for VTE recurrences (HR: 0.99; 95%CI: 0.73–1.36) or major bleeding (HR: 0.74; 95%CI: 0.52–1.05) and a significantly lower risk for all-cause mortality (HR: 0.62; 95%CI: 0.48–0.79) than non-users (Table 4).

We performed four matching analyses with ratios 2:1 and 3:1, and two caliper widths (0.1 and 0.2 of standard deviation of propensity score). We finally chose the nearest neighbor matching approach with a 2:1 ratio and caliper 0.1 because it did not show imbalance among

**Table 1**
Clinical characteristics in 32,062 patients with VTE, according to use of statins at baseline.

| | Statins users | Non users | Odds ratio (95%CI) |
|---|---|---|---|
| Patients, N | 7,085 | 24,977 | |
| Clinical characteristics, | | | |
| Age (mean years ± SD) | 73 ± 11 | 63 ± 19 | p < 0.0001 |
| Male gender | 3,398 (48%) | 11,998 (48%) | 1.00 (0.95–1.05) |
| Body weight (mean kg ± SD) | 77 ± 15 | 76 ± 17 | p = 0.001 |
| Countries of origin, | | | |
| Spain | 5,031 (71%) | 16,281 (65%) | < 0.001 |
| France | 305 (4.3%) | 1,549 (6.2%) | |
| Israel | 579 (8.2%) | 1,458 (5.8%) | |
| Italy | 487 (6.9%) | 2,650 (11%) | |
| Switzerland | 169 (2.4%) | 666 (2.7%) | |
| Other countries | 514 (7.3%) | 2,373 (9.5%) | |
| Co-morbidities, | | | |
| Chronic lung disease | 1,222 (17%) | 2,681 (11%) | 1.73 (1.61–1.87) |
| Chronic heart failure | 950 (13%) | 1,378 (5.5%) | 2.65 (2.43–2.89) |
| Recent major bleeding | 190 (2.7%) | 565 (2.3%) | 1.19 (1.01–1.41) |
| Risk factors for VTE, | | | |
| Surgery | 848 (12%) | 2,939 (12%) | 1.02 (0.94–1.11) |
| Immobilization ≥4 days | 1,643 (23%) | 5,326 (21%) | 1.11 (1.05–1.19) |
| Estrogen use | 168 (2.4%) | 2,151 (8.6%) | 0.26 (0.22–0.30) |
| Pregnancy or postpartum | 2 (0.03%) | 426 (1.7%) | 0.02 (0.00–0.07) |
| Cancer | 1,729 (24%) | 5,894 (24%) | 1.05 (0.98–1.11) |
| None of the above | 3,257 (46%) | 10,379 (42%) | 1.20 (1.13–1.26) |
| Initial VTE presentation, | | | |
| Pulmonary embolism | 4,241 (60%) | 13,572 (54%) | 1.25 (1.19–1.32) |
| Blood tests, | | | |
| Anaemia | 2,763 (39%) | 8,716 (35%) | 1.19 (1.13–1.26) |
| Platelet count < 100,000/μL | 178 (2.5%) | 685 (2.7%) | 0.91 (0.77–1.08) |
| CrCl levels < 50 mL/min | 2,134 (30%) | 4,917 (20%) | 1.76 (1.66–1.87) |
| Cholesterol levels (mean mg/dL ± SD) | 171 ± 44 | 184 ± 184 | < 0.001 |
| LDL-cholesterol levels (mean mg/dL ± SD) | 104 ± 107 | 123 ± 239 | < 0.001 |
| Arterial risk factors, | | | |
| Diabetes | 2,150 (30%) | 2,754 (11%) | 3.52 (3.30–3.75) |
| Current smoking | 752 (11%) | 3,910 (16%) | 0.64 (0.59–0.70) |
| Hypertension | 5,309 (75%) | 9,890 (40%) | 4.56 (4.30–4.84) |
| Prior myocardial infarction | 1,410 (20%) | 911 (3.7%) | 6.67 (6.11–7.29) |
| Prior ischemic stroke | 952 (14%) | 1,207 (4.8%) | 3.11 (2.84–3.40) |
| Peripheral artery disease | 579 (8.3%) | 562 (2.3%) | 3.94 (3.50–4.44) |
| Additional drugs, | | | |
| Antiplatelets | 2,713 (38%) | 2,669 (11%) | 5.19 (4.87–5.52) |
| Withdrawn at VTE diagnosis *(N = 3,955)* | 1,045 (52%) | 1,222 (64%) | 0.61 (0.54–0.69) |
| Corticosteroids | 817 (12%) | 2,245 (9.0%) | 1.32 (1.21–1.44) |

Abbreviations: SD, standard deviation; VTE, venous thromboembolism; CrCl: creatinine clearance; CI, confidence intervals.

covariates. Results of the PSM involved 4,658 patients (2,801 statin users and 1,663 non users). The matched sample was well balanced in all variables. The matched analysis revealed that statin users had a similar risk for VTE recurrences (HR: 0.98; 95%CI: 0.61–1.57) or major bleeding (HR: 0.85; 95%CI: 0.59–1.21) and a significantly lower risk for all-cause death (HR: 0.62; 95%CI: 0.48–0.79) than non-users (Table 5). Interestingly, statin users had a non-significantly lower risk for fatal PE (HR: 0.58; 95%CI: 0.15–2.17), fatal bleeding (HR: 0.28; 95%CI: 0.06–1.27), fatal arterial ischemic events (HR: 0.21; 95%CI: 0.03–1.74) or even for death for disseminated malignancy (HR: 0.69; 95%CI: 0.44–1.08).

## 4. Discussion

Our data, obtained from a large cohort of consecutive patients with VTE, reveal that one in every 4–5 such patients (22%) were using

**Table 2**
Treatment strategies.

| | Statins users | Non users | OR (95%CI) |
|---|---|---|---|
| Patients, N | 7,085 | 24,977 | |
| Initial therapy, | | | |
| Low-molecular-weight-heparin | 6,205 (88%) | 21,672 (87%) | 1.08 (0.99–1.16) |
| Mean LMWH doses (IU/Kg/day) | 173 ± 43 | 174 ± 43 | 0.007 |
| Unfractionated heparin | 441 (6.2%) | 1,140 (4.6%) | 1.39 (1.24–1.55) |
| Fondaparinux | 118 (1.7%) | 804 (3.2%) | 0.51 (0.42–0.62) |
| Direct oral anticoagulants | 141 (2.0%) | 720 (2.9%) | 0.68 (0.57–0.82) |
| Thrombolytics | 98 (1.4%) | 424 (1.7%) | 0.81 (0.65–1.01) |
| No anticoagulant therapy | 20 (0.28%) | 37 (0.15%) | 1.91 (1.11–3.29) |
| Vena cava filter | 204 (2.9%) | 639 (2.6%) | 1.13 (0.96–1.32) |
| Long-term therapy, | | | |
| Vitamin K antagonists | 4,234 (60%) | 14,003 (56%) | 1.16 (1.10–1.23) |
| Low-molecular-weight-heparin | 2,062 (29%) | 7,498 (30%) | 0.96 (0.90–1.01) |
| Mean LMWH doses (IU/Kg/day) | 148 ± 44 | 150 ± 45 | 0.015 |
| Fondaparinux | 43 (0.61%) | 291 (1.2%) | 0.52 (0.38–0.71) |
| Direct oral anticoagulants | 488 (6.9%) | 2,348 (9.4%) | 0.71 (0.64–0.79) |
| Duration of anticoagulant therapy, | | | |
| Mean days ( ± SD) | 262 ± 298 | 249 ± 276 | 0.001 |
| Median days (IQR) | 176 (99–316) | 177 (100–294) | 0.652 |
| Over 6 months | 3,437 (49%) | 12,168 (49%) | 1.00 (0.94–1.05) |
| Over 12 months | 1,426 (20%) | 4,638 (19%) | 1.11 (1.04–1.18) |

Abbreviations: LMWH, low-molecular-weight-heparin; IU, international units; SD, standard deviation; IQR, interquartile range; CI, confidence intervals.

statins at baseline. Comparing with non-users, statin users were 10 years older and more likely to have comorbidities (such as chronic heart or lung disease, diabetes, hypertension, renal insufficiency or prior artery disease) or to be receiving antiplatelets or corticosteroids concomitantly. Thus, we expected that statin users would have a higher rate of major bleeding and a higher mortality than non-users. We certainly found a (slightly) higher rate of major bleeding during anticoagulation in statin users, but the mortality rate was the same. On multivariable analysis, statin users had a 38% reduction in all-cause mortality compared with non-users, after adjusting for any possible potential confounder. The same reduction was found on propensity score matched analysis. Interestingly, we found a non-significant reduction in the risk of death for most causes of death. However, we failed to find any influence of statin use on the risk for recurrences or major bleeding.

The influence of statins on survival in patients with coronary, cerebrovascular or peripheral artery disease has been largely reported [25–30], but as far as we know only two studies had evaluated their influence on mortality in patients receiving anticoagulation for VTE. One study found that statin users (n = 737) had half the risk to die than non-users (adjusted HR: 0.53; 95%CI: 0.41–0.69), although this study only included patients with PE [13]. Moreover, a case-control study also found that statin users presenting with VTE (n = 3,327) were at a lower risk for death than non-users (HR, 0.77; 95%CI, 0.71–0.84) [17]. However, both studies were based on population registries of records linked with hospital discharge records, where the diagnosis of VTE is based on diagnostic codes (that are less specific) and mortality was a secondary outcome. Our study was based on clinical and instrumental confirmed diagnosis. All-cause death was a major endpoint, but we also found a non-significant reduction in the risk for fatal PE, fatal bleeding and a number of additional causes of death in statin users. This aspect has not been well investigated in the literature. Although we cannot provide a biologically plausible explanation, these findings might not be due to potential confounders (such as the "healthy-user effect") because statin users were older, more likely to have comorbidities and more commonly presented initially as PE for the index event. We hypothesize that, beyond LDL-c reduction, other "pleiotropic" mechanisms (such as platelet inhibition, reduction of inflammation and C-reactive protein, increased production of nitric oxide or down-regulation of the coagulation cascade) could have contributed to the beneficial effects of statins on mortality [30].

Our study has a number of limitations. First, ours is an observational study with no randomization to statins versus no statins, although the number of patients included was high. Thus, some non-measured variables, such as the reason why patients were taken statins, could lead to a possible bias. However, the use of statins would likely imply the presence of cardiovascular disease, and the mortality risk should be higher rather than lower. Second, in RIETE we do not gather information on the use of statins over time: only at baseline. The absence

**Table 3**
Clinical outcomes during the course of anticoagulant therapy.

| | Statins users | | Non users | | Hazard ratio (95%CI) |
|---|---|---|---|---|---|
| | N | Events per 100 patient-years | N | Events per 100 patient-years | |
| Patients, N | 7,085 | | 24,977 | | |
| Recurrent PE | 83 | 1.66 (1.33–2.05) | 250 | 1.48 (1.31–1.67) | 1.12 (0.87–1.43) |
| Recurrent DVT | 78 | 1.55 (1.23–1.92) | 302 | 1.80 (1.61–2.01) | 0.86 (0.67–1.10) |
| Recurrent VTE | 157 | 3.17 (2.70–3.69) | 537 | 3.23 (2.97–3.51) | 0.98 (0.82–1.17) |
| Major bleeding | 235 | 4.70 (4.12–5.33) | 613 | 3.64 (3.36–3.94) | 1.29 (1.11–1.50) |
| Site of major bleeding, | | | | | |
| Gastrointestinal | 68 | 1.35 (1.05–1.70) | 207 | 1.22 (1.06–1.40) | 1.10 (0.83–1.44) |
| Hematoma | 54 | 1.07 (0.81–1.38) | 111 | 0.65 (0.54–0.78) | 1.63 (1.17–2.25) |
| Intracranial | 56 | 1.11 (0.84–1.43) | 107 | 0.63 (0.52–0.76) | 1.76 (1.27–2.42) |
| Myocardial infarction | 25 | 0.49 (0.33–0.72) | 36 | 0.21 (0.15–0.29) | 2.33 (1.38–3.87) |
| Ischemic stroke | 34 | 0.67 (0.47–0.93) | 88 | 0.52 (0.42–0.64) | 1.30 (0.86–1.92) |
| Death | 735 | 14.5 (13.5–15.6) | 2,434 | 14.3 (13.7–14.9) | 1.01 (0.93–1.10) |
| Causes of death, | | | | | |
| Pulmonary embolism | 40 | 0.79 (0.57–1.06) | 136 | 0.80 (0.67–0.94) | 0.99 (0.69–1.39) |
| Bleeding | 35 | 0.69 (0.49–0.95) | 86 | 0.51 (0.41–0.62) | 1.36 (0.91–2.01) |
| Sudden, unexpected | 18 | 0.35 (0.22–0.55) | 58 | 0.34 (0.26–0.44) | 1.04 (0.60–1.74) |
| Respiratory insufficiency | 66 | 1.30 (1.01–1.64) | 216 | 1.27 (1.11–1.45) | 1.02 (0.77–1.34) |
| Myocardial infarction | 7 | 0.14 (0.06–0.27) | 13 | 0.08 (0.04–0.13) | 1.81 (0.68–4.50) |
| Ischemic stroke | 8 | 0.16 (0.07–0.30) | 20 | 0.12 (0.07–0.18) | 1.34 (0.56–2.99) |

Abbreviations: PE, pulmonary embolism; DVT, deep vein thrombosis; CI, confidence intervals.

**Table 4**
Multivariable analyses for VTE recurrences, major bleeding or for all-cause death. Results are expressed as hazard ratio (95% confidence intervals).

| | Recurrent VTE | Major bleeding | Death |
|---|---|---|---|
| Events, N | 694 | 848 | 3,169 |
| Clinical characteristics, | | | |
| Age > 70 years | 0.62 (0.47–0.83) | 2.13 (1.44–3.14) | 1.31 (1.02–1.67) |
| Body weight < 75 kg | - | 1.50 (1.09–2.06) | 1.65 (1.34–2.03) |
| Co-morbidities, | | | |
| Chronic heart failure | - | 1.70 (1.13–2.57) | 2.04 (1.58–2.65) |
| Recent major bleeding | 2.13 (1.08–4.19) | - | - |
| Risk factors for VTE, | | | |
| Surgery | - | 2.04 (1.14–3.62) | 0.41 (0.26–0.65) |
| Immobilization ≥4 days | - | 1.99 (1.15–3.44) | 1.46 (1.09–1.96) |
| Estrogen use | - | 0.29 (0.09–0.92) | 0.37 (0.21–0.65) |
| Active cancer | 2.86 (2.06–3.96) | 2.53 (1.58–4.04) | 4.17 (3.10–5.62) |
| Unprovoked | - | - | 0.62 (0.43–0.91) |
| Blood tests, | | | |
| Anaemia | - | 2.09 (1.54–2.84) | 2.18 (1.79–2.66) |
| Platelet count < 100,000/μL | - | - | 1.84 (1.19–2.84) |
| CrCl levels < 50 mL/min | - | - | 1.83 (1.47–2.28) |
| Concomitant drugs, | | | |
| Statins | 0.99 (0.73–1.36) | 0.74 (0.52–1.05) | 0.62 (0.48–0.79) |
| Corticosteroids | - | - | 1.62 (1.24–2.12) |

Abbreviations: VTE, venous thromboembolism; CrCl, creatinine clearance.

of information on statin use during follow-up is one of the major limitations of the study. Although possible, we think that statin discontinuation is unlikely because most statin users are patients with a long-life prescription for statins. Since anticoagulation is not a contraindication to statin use, we may assume (with limitations) that most patients did continue with this therapy. Furthermore, statin initiation during the anticoagulation period in previously unexposed patients cannot be ruled-out as well. This really lowers the significance and the generalizability of our results. Third, statin users were more likely to have suffered prior myocardial infarction or ischemic stroke than non-users, but they had also survived such events, which means that these events were probably less severe than in the general population. This may have influenced on a better prognosis than in the subgroup of non-users. Finally, uncontrolled healthy-user or healthy-adherer bias cannot be excluded either. But statin users in our cohort were 10 years older and had more comorbidities than non-users. Although we provided adjusted results for several of the outcomes, we cannot exclude the possibility of residual differences in the two groups, and hence residual confounding. Certainly, the propensity score tends to reduce differences in comorbidities, but not the "social effect" where statin users may have a better healthcare.

In conclusion, in patients receiving anticoagulant therapy for VTE, the use of statins was associated with a 38% reduction in all-cause mortality, and no differences in the risk for VTE recurrences or major bleeding. Intervention studies specifically designed to confirm our findings and the potential role of statins in patients receiving anticoagulant therapy for VTE are warranted.

## Addendum

C. Siniscalchi, A. Rocci, R. Quintavalla, A. Riera Mestre, J. Trujillo-Santos, L. Jara-Palomares, B. Bikedeli, F. Moustafa, M. Monreal Designed The Protocol And The Analysis Plan, Conducted The Analyses, And Drafted The Manuscript. M. Monreal, Jm Suriñach, C. Siniscalchi

**Table 5**
Propensity score matched analysis (statin users vs. non-users). Results are expressed as hazerd ratio (95% confidence intervals).

| | Hazard ratio (95%CI) | | | |
|---|---|---|---|---|
| | Ratio 2:1 caliper 0.1 | Ratio 2:1 caliper 0.2 | Ratio 3:1 caliper 0.1 | Ratio 3:1 caliper 0.2 |
| Patients, N | 4,658 | 4,718 | 5,462 | 5,585 |
| Recurrent PE | 0.95 (0.50–1.82) | 0.95 (0.50–1.82) | 1.07 (0.57–2.03) | 1.02 (0.55–1.91) |
| Recurrent DVT | 0.97 (0.49–1.90) | 0.98 (0.49–1.95) | 0.83 (0.44–1.55) | 0.99 (0.52–1.88) |
| Recurrent VTE | 0.98 (0.61–1.57) | 1.00 (0.62–1.60) | 0.93 (0.59–1.45) | 1.01 (0.65–1.59) |
| Major bleeding | 0.85 (0.59–1.21) | 0.78 (0.55–1.10) | 0.78 (0.56–1.10) | 0.76 (0.54–1.06) |
| Site of major bleeding, | | | | |
| Gastrointestinal | 0.68 (0.34–1.38) | 0.55 (0.28–1.09) | 0.68 (0.34–1.34) | 0.60 (0.31–1.18) |
| Hematoma | 0.59 (0.28–1.24) | 0.59 (0.28–1.25) | 0.51 (0.25–1.03) | 0.51 (0.25–1.04) |
| Intracranial | 1.08 (0.52–2.23) | 1.06 (0.52–2.17) | 1.19 (0.58–2.40) | 1.18 (0.59–2.37) |
| Death | 0.62 (0.48–0.79) | 0.60 (0.47–0.76) | 0.61 (0.48–0.78) | 0.61 (0.48–0.78) |
| Causes of death, | | | | |
| Pulmonary embolism | 0.58 (0.15–2.17) | 0.41 (0.12–1.46) | 0.53 (0.15–1.93) | 0.42 (0.12–1.47) |
| Bleeding | 0.28 (0.06–1.27) | 0.25 (0.06–1.12) | 0.26 (0.06–1.12) | 0.25 (0.06–1.12) |
| Sudden, unexpected | 0.75 (0.24–2.32) | 0.92 (0.30–2.82) | 0.93 (0.30–2.89) | 0.79 (0.27–2.33) |
| Respiratory insufficiency | 0.62 (0.28–1.41) | 0.57 (0.26–1.23) | 0.58 (0.27–1.25) | 0.63 (0.29–1.39) |
| Disseminated cancer | 0.69 (0.44–1.08) | 0.63 (0.41–0.99) | 0.66 (0.43–1.01) | 0.69 (0.45–1.07) |
| Arterial ischemic events | 0.21 (0.03–1.74) | 0.22 (0.03–1.85) | 0.24 (0.03–1.95) | 0.31 (0.04–2.70) |
| Infection | 0.56 (0.25–1.22) | 0.66 (0.29–1.48) | 0.59 (0.27–1.27) | 0.59 (0.27–1.27) |

Abbreviations: PE, pulmonary embolism; DVT, deep vein thrombosis; VTE, venous thromboembolism; CI, confidence intervals.

performed the statistical analysis.

## Declaration of Competing Interest

Dr. C. Siniscalchi received speaker's fee for congress presentation by MediK. The others authors state that they have no conflict of interest.

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## Appendix A. Appendix

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