# Statin therapy associated with improved thrombus resolution in patients with deep vein thrombosis



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## ABSTRACT

**Objective:** Statin therapy has been associated with a decreased incidence of venous thromboembolism (VTE) in clinical trials and enhanced thrombus resolution in animal models. The effect of statins on thrombus resolution has not been reported clinically. This study investigates the association of statins with thrombus resolution or improvement in patients with deep venous thrombosis (DVT).

**Methods:** A retrospective study of the electronic medical records of consecutive adult patients presenting with lower extremity DVT was performed. Patients were divided into two groups based on statin therapy (statin group) or lack thereof (nonstatin group). The two groups were compared with respect to demographics, comorbidities, and risk factors for VTE. Initial as well as all subsequent ultrasound reports were reviewed for each patient to determine extent of DVT and subsequent change in thrombus characteristics. Long-term outcomes examined were mortality, VTE recurrence, and thrombus improvement or resolution on follow-up ultrasound examination. Multivariable analysis was used to determine independent predictors of thrombus resolution or improvement, VTE recurrence, and mortality.

**Results:** A total of 818 patients with DVT were identified (statin group, n = 279 [34%]; nonstatin group, n = 539 [66%]). The patients in the statin group were significantly older ($P < .001$). Patients on statins were more likely to have risk factors for and manifestations of atherosclerosis and to be on antiplatelet therapy ($P < .001$), whereas those in the nonstatin group were more likely to have a hypercoagulable disorder ($P = .009$) or prior DVT ($P = .033$). There was no significant difference in provoked DVT, extent of DVT, or association with pulmonary embolism (PE), but patients on statins were more likely to have high-risk PE ($P = .046$). There was no difference in patients receiving anticoagulation, type and duration of anticoagulation, inferior vena cava filter placement, or treatment with lytic therapy. There was no difference in thrombus resolution, mortality, or recurrence of DVT, PE, or VTE between the groups. On multivariable analysis, age, proximal DVT, CAD, and cancer were associated with higher mortality, whereas anticoagulation with coumadin and direct oral anticoagulants and antiplatelet therapy were associated with lower mortality. Statin therapy, antiplatelet therapy, and younger age were associated with thrombus resolution or improvement.

**Conclusions:** Statin therapy is associated with greater thrombus resolution or improvement in patients with DVT. However, statin therapy in this study was not associated with different clinical outcomes of VTE recurrence or mortality. (J Vasc Surg: Venous and Lym Dis 2019;7:169-75.)

**Keywords:** Thrombus resolution; Statin; Deep vein thrombosis; Venous thromboembolism; Antiplatelet

Anticoagulation agents are the medications of choice for the prevention and treatment of venous thromboembolism (VTE), but numerous studies suggest that statins may also play a role in reducing the risk of initial or recurrent deep venous thrombosis (DVT).[1,2] In population studies of VTE patients on statins, a longer duration of

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Research reported in this publication was supported by National Heart, Lung and Blood Institute of the National Institutes of Health. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Heart, Lung, and Blood Institute or the National Institutes of Health under Award Number T35HL007649. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Author conflict of interest: none.

Presented at the Thirtieth Annual Meeting of the American Venous Forum, Tucson, Ariz, February 22, 2018.

Additional material for this article may be found online at www.jvsvenous.org.

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The editors and reviewers of this article have no relevant financial relationships to disclose per the Journal policy that requires reviewers to decline review of any manuscript for which they may have a conflict of interest.

2213-333X



https://doi.org/10.1016/j.jvsv.2018.10.020

statin use is associated with greater decrease of recurrent VTE.[3] Animal experiments have demonstrated that atorvastatin and rosuvastatin reduce venous thrombus burden and DVT-induced vein wall scarring, whereas simvastatin has been found to promote thrombus resolution in a leporine posterior vena cava thrombus model.[4,5] Clinically, residual vein thrombosis has been shown to be a risk factor for VTE recurrence.[6] Thus, it is plausible that the effects of statins on VTE recurrence are potentially mediated by enhancing thrombus resolution. However, the effect of statins on thrombus remodeling has not been studied clinically. The goal of this study was to investigate the association of statin therapy with thrombus resolution or improvement in patients with DVT.

## ARTICLE HIGHLIGHTS

- **Type of Research:** Single-center, retrospective cohort study
- **Key Findings:** In 818 patients with lower extremity deep venous thrombosis, statin therapy (odds ratio [OR], 3.23), age (OR, 0.97), and antiplatelet therapy (OR, 2.25) were associated with thrombus resolution or improvement ($P < .05$).
- **Take Home Message:** Statin therapy was associated with enhanced thrombus resolution or improvement in patients with lower extremity deep venous thrombosis but protection against venous thromboembolism recurrence or mortality needs further evaluation.

## METHODS

**Study design.** This retrospective study examined consecutive adult patients (age ≥18 years) presenting with newly diagnosed acute lower extremity DVT at a tertiary care center from January 2013 through April 2014. The study protocol and waiver of informed consent was approved by the human investigation committee. Patients were divided into two groups based on statin therapy or lack thereof, and all patient records and ultrasound reports were reviewed. Patients initiating statins after developing the DVT were considered to not have a standing history of statin use and were included in the nonstatin group for initial presentation, but were analyzed with the statin group for long-term outcomes. Patients who had continuous statin use before DVT incidence but discontinued after were included in the statin group for initial presentation, but were analyzed with the nonstatin group for outcomes.

**Variables.** Patient demographics and comorbidities as well as ultrasound characteristics were extracted from the electronic medical records. Patient age, sex, history of hypercoagulable disorders, hypertension, congestive heart failure (CHF), diabetes, hyperlipidemia, coronary artery disease (CAD), peripheral arterial disease (PAD), cerebral vascular disease (CVD), cancer, prior DVT, prior pulmonary embolism (PE), and smoking were recorded. The prescription of antiplatelets (aspirin, clopidogrel, prasugrel, dipyridamole, ticagrelor, ticlopidine) and statins at the time of diagnosis was noted. In addition to these variables, other risk factors for VTE required to calculate the Caprini score were also extracted.[7]

The DVT characteristics were noted as occlusive vs nonocclusive, proximal vs distal, and provoked vs unprovoked. Proximal DVT included thrombi in the popliteal vein or above, and distal DVT included thrombi found exclusively in the tibial veins. Cases that had thrombi in the popliteal vein or above and in the tibial veins were considered proximal. Provoked DVT was defined according to the methodology of Brownson et al and included DVTs associated with trauma, recent surgery, sedentary travel for more than 4 hours, or confinement to bed for more than 72 hours within 30 days of the event, or initiation of oral contraceptives, or a central venous femoral line (if ipsilateral DVT).[8] Associated PE confirmed by imaging was classified by severity. High-risk PE was defined as more than 15 minutes of hypotension (<90 mm Hg); intermediate risk PE was defined by a blood pressure greater than 90 mm Hg with accompanying right ventricular dysfunction (dilation or elevated N-terminal pro brain natriuretic peptide >500 pg/mL or brain natriuretic peptide >90 pg/mL) or myocardial necrosis (troponin I >0.4 ng/mL or troponin T >0.1 ng/mL). Low-risk PE was defined by the lack of these characteristics.[9] Cases without definitive imaging but where PE was highly suspected by the treating physician were also noted.

The treatment of DVT was reviewed for the type of anticoagulation therapy (coumadin, low-molecular-weight heparin [LMWH], or direct oral anticoagulants [DOAC]) and its duration. Only full-dose anticoagulation therapies with an international normalized ratio goal of 2 to 3 or more were noted. The placement of inferior vena cava filters and administration of systemic or catheter-directed thrombolytics were also noted.

**Outcomes and statistical analysis.** The long-term outcomes of mortality, DVT recurrence, PE recurrence, and VTE recurrence were compared between the two groups. Patients who underwent repeat lower extremity venous ultrasound examination after 1 month of diagnosis were noted. The repeat ultrasound report was reviewed, and the radiologist assessment of thrombus burden compared with the initial ultrasound examination was noted as progressed (worsened), stable, improved, or completely resolved. The number of repeat ultrasound examinations varied by patient and thrombus burden may have changed or resolved before the final repeat ultrasound examination, so we noted the date and results of the earliest repeat ultrasound examination after 1 month of diagnosis where no further change in thrombus status was observed in subsequent

examinations. Patients who died during follow-up were excluded from analysis of VTE recurrence. A multivariable analysis was then used to determine the independent factors associated with thrombus improvement or resolution, VTE recurrence, and mortality. Factors that were included in the model consisted of age, sex, provoked vs unprovoked DVT, distal vs proximal DVT, history of DVT, history of PE, smoking, anticoagulation therapy (coumadin, LMWH, or DOAC), antiplatelet therapy, hypertension, CHF, diabetes, hyperlipidemia, CAD, PAD, CVD, and cancer.

Characteristics of the sample were summarized using descriptive statistics and expressed as percentages (number) in the case of categorical variables and mean and standard deviation for continuous variables. Bivariate analyses were conducted using independent samples *t*-tests to compare means and $\chi^2$ tests to compare proportions. Multivariable logistic regression was performed to compare study groups on a dependent bivariate outcome while adjusting for sample characteristics. Statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC).

## RESULTS

**Study population.** A total of 818 patients with DVT were identified during the study period; 279 (34%) were on statin therapy at time of presentation and 539 (66%) were not. Five patients were initiated on statin therapy and another five discontinued a statin shortly after the diagnosis of DVT; these changes were accounted for in the analysis. The three most common statin agents were atorvastatin (10-80 mg/d), simvastatin (20-80 mg/d), and pravastatin (10-80 mg/d), which collectively accounted for about 90% of all statins used. Patients in the statin group were significantly older (72 ± 13 years vs 63 ± 17 years) and were more likely to have risk factors and manifestations of atherosclerosis, including hypertension, CHF, diabetes, hyperlipidemia, CAD, PAD, and CVD. There was no difference in gender between the two groups (Table I).

More patients in the statin group were on antiplatelet therapy (55% vs 20%). In the statin group, 130 patients were on single agent antiplatelet therapy (122 aspirin, 8 clopidogrel) and 24 were on dual agent antiplatelet therapy (21 aspirin and clopidogrel, 3 aspirin and prasugrel or dipyridamole). In the nonstatin group, 97 patients were on single agent antiplatelet therapy (88 aspirin, 9 clopidogrel), and 10 were on both aspirin and clopidogrel. One or more hypercoagulable disorders were found in 44 patients across both groups, the most common including factor V Leiden (n = 12), antiphospholipid syndrome (n = 9), antithrombin III deficiency (n = 5), and protein C deficiency (n = 5). Patients in the nonstatin group had a higher proportion of hypercoagulable disorder or a history of prior DVT, whereas the patients in the statin group had significantly higher mean Caprini scores (Table I).

**Table I.** Patient characteristics

| | Statin group (n = 279) | Nonstatin group (n = 539) | *P* value |
|---|---|---|---|
| Age, years | 72 ± 13 | 63 ± 17 | <.001[a] |
| Female | 51 (140) | 52 (278) | .70 |
| Hypertension | 82 (229) | 50 (268) | <.001[a] |
| Diabetes | 38 (105) | 17 (92) | <.001[a] |
| Hyperlipidemia | 73 (205) | 14 (76) | <.001[a] |
| CHF | 17 (48) | 10 (55) | .007[a] |
| CAD | 35 (98) | 9 (51) | <.001[a] |
| PAD | 9 (25) | 2 (11) | <.001[a] |
| CVD | 20 (57) | 7 (38) | <.001[a] |
| Hypercoagulable disorder | 3 (7) | 7 (37) | .009[a] |
| History of prior DVT | 14 (40) | 20 (110) | .03[a] |
| History of prior PE | 8 (21) | 11 (60) | .10 |
| History of cancer | 41 (113) | 44 (235) | .40 |
| History of smoking | 56 (156) | 56 (301) | .98 |
| Antiplatelet therapy | 55 (154) | 20 (107) | <.001[a] |
| Caprini score | 6.7 ± 2.9 | 6.3 ± 2.8 | .022[a] |

*CAD,* Coronary artery disease; *CHF,* congestive heart failure; *CVD,* cerebral vascular disease; *DVT,* deep venous thrombosis; *PAD,* peripheral arterial disease; *PE,* pulmonary embolism.
Values are presented as percentages (number) or mean ± standard deviation.
[a] $P < .05$.

**DVT characteristics and treatment.** There was a higher proportion of high-risk PE (24% vs 11%; $P = .046$) in the statin group. The two groups showed no significant difference in provoked DVT, proportion of proximal DVTs, or association with PE. The groups also showed no significant difference in the type of anticoagulation received, duration of anticoagulation therapy, inferior vena cava filter placement, and proportion treated by thrombolysis (Table II).

**Long-term outcomes.** There was no difference in the overall duration of follow-up between the two groups (741 ± 569 days vs 710 ± 565 days; $P = .46$). The frequency of repeat ultrasound examination after 1 month (39% vs 45%; $P = .13$) and the intervals at which ultrasound examinations were performed after the initial presentation were not significantly different (496 ± 408 days vs 530 ± 409 days; $P = .46$). There was no significant difference in mortality (41% vs 37%; $P = .32$) or resolution or improvement of thrombus on repeat ultrasound examination between the groups (85% vs 77%; $P = .12$). There was no statistically significant difference in recurrence of DVT (15% vs 17%; $P = .52$), PE (2% vs 4%; $P = .41$), or VTE (16% vs 19%; $P = .43$; Table III). A subgroup analysis of the characteristics of patients who underwent repeat ultrasound examination after 1 month was performed (Supplementary Tables I and II, online only). In this subgroup, there was no significant difference between the statin and nonstatin patients in recurrence of DVT, PE, VTE or mortality (Supplementary Table III, online only).

**Table II.** Deep venous thrombosis (*DVT*) characteristics and treatment

| | Statin group (n = 279), % (No.) | Nonstatin group (n = 539), % (No.) | *P* value |
|---|---|---|---|
| Provoked DVT | 54 (151) | 48 (260) | .10 |
| DVT location | | | .56 |
| Distal | 25 (69) | 27 (144) | |
| Proximal | 75 (209) | 73 (395) | |
| DVT associated with PE | 29 (80) | 25 (135) | .26 |
| Severity of PE | | | .046[a] |
| Low risk | 36 (29) | 39 (52) | |
| Intermediate risk | 40 (32) | 50 (67) | |
| High risk | 24 (19) | 11 (15) | |
| Anticoagulation | | | .23 |
| None | 24 (67) | 20 (108) | |
| Coumadin | 50 (139) | 47 (254) | |
| LMWH | 15 (41) | 18 (97) | |
| DOAC | 11 (32) | 15 (80) | |
| Duration of anticoagulation, months | | | .32 |
| <3 | 22 (41) | 23 (87) | |
| 3-6 | 22 (42) | 28 (106) | |
| 6-12 | 33 (63) | 27 (102) | |
| >12 | 23 (44) | 23 (86) | |
| Placement of IVC filter | 30 (84) | 27 (143) | .28 |
| Catheter-directed thrombolysis of DVT | 2 (6) | 1 (8) | .57 |
| Catheter-directed thrombolysis of PE | 1 (3) | 2 (9) | .76 |
| Systemic administration of thrombolytic agent | 2 (6) | 1 (8) | .57 |

*DOAC*, Direct-acting oral anticoagulant; *IVC*, inferior vena cava; *LMWH*, low-molecular-weight heparin; *PE*, pulmonary embolism.
[a] $P < .05$.

In contrast, a comparison of the patients who did not receive repeat ultrasound examination after 1 month with the patients who underwent repeat ultrasound examination showed significant differences and selection bias. Patients who did not receive a repeat ultrasound examination were older, suffered from more comorbidities, and were less likely to receive anticoagulation or catheter-directed thrombolysis as treatment for DVT. They had significantly higher mortality, shorter follow-up, and less likelihood of having recurrent VTE (Supplementary Tables IV-VI, online only).

**Multivariable analysis of thrombus resolution or improvement.** On multivariable analysis, statin therapy (OR, 3.23; 95% confidence interval [CI], 1.32-7.87) was found to be independently associated with thrombus resolution or improvement on ultrasound after adjusting for potential confounders including those variables in Tables I and II. Distal DVT compared with proximal DVT (OR, 0.53; 95% CI, 0.35-0.8), anticoagulation with coumadin (OR, 0.19; 95% CI, 0.12-0.3) or DOACs (OR, 0.16; 95% CI, 0.09-0.3]) compared with no anticoagulation, and antiplatelet therapy (OR, 0.57; 95% CI, 0.37-0.87) were all independently associated with lower mortality. Age (OR, 1.04; 95% CI, 1.03-1.06), CAD (OR, 3.12; 95% CI, 1.80-5.41), and history of cancer (OR, 4.26; 95% CI, 2.91-6.25) were found to be independently associated with mortality. Finally, there was no significant association of any variable with recurrent VTE (Table IV).

## DISCUSSION

This study suggests an association between statin therapy and thrombus resolution or improvement after DVT, consistent with literature on statin therapy's effects beyond the known lipid-lowering action. However, the retrospective, observational nature of the current study prevents any inference on causation. The statin group was found on univariate analysis to have no significant difference in thrombus characteristics on repeat ultrasound examination, but patients on statins had more cardiovascular comorbidities and were older. The lack of an overt difference in thrombus resolution or improvement between the two groups could be attributed to the counterbalancing influence of older age and possibly greater overall comorbidity that could prevent thrombus remodeling. Even though this effect of statins has been described in animal models, to our knowledge the clinical correlation in humans has not been reported.[4,5] Statins have significant anti-inflammatory properties on the vascular endothelium, which may explain the enhanced thrombus resolution seen in this study.[10] A similar impact was reported in the arterial circulation in a case report describing a patient having an aortic mobile atheroma that was treated with high-dose statin and dual antiplatelets, resulting in complete resolution of the atheroma on serial echocardiography.[11]

However, the impact on thrombus resolution did not translate into a clinical effect of decreased VTE. Although this finding is consistent with the results reported by Brækkan et al,[12] who found a modest but insignificant decrease in recurrent DVTs in patients on statins, other studies showed a clearly protective pattern.[3,12-14] Smith et al[14] found a statistically significant lower risk (26%) of recurrent VTE with statin use. Key differences in the cohorts may account for the differing results. Smith et al[14] studied a larger patient population (N = 4350) and had a longer mean follow-up of 3.4 years. Even though the incidence of recurrent VTE observed in their study (16%) was similar to that of our study, the larger sample and longer duration of follow-up likely allowed Smith et al to demonstrate clinical differences in VTE recurrence that our study did not have enough power to show. Additionally, our current study had a high proportion of patients with cancer (40% vs 23% in the

**Table III.** Long-term outcomes

| | Statin group (n = 279), % (No.) | Nonstatin group (n = 539), % (No.) | *P* value |
|---|---|---|---|
| Days to last follow-up, mean ± SD | 741 ± 569 | 710 ± 565 | .46 |
| Median (IQR) | 891 (91-1283) | 714 (67-1250) | .39 |
| Surviving patients at last follow-up | 59 (166) | 63 (340) | |
| New or recurrent DVT | 15 (25) | 17 (59) | .52 |
| New or recurrent PE | 2 (3) | 4 (12) | .41 |
| Recurrent VTE | 16 (27) | 19 (65) | .43 |
| Mortality | 41 (113) | 37 (199) | .32 |
| Patients with repeat ultrasound >1 month | 39 (110) | 45 (242) | .13 |
| Days to repeat ultrasound ± SD | 496 ± 408 | 530 ± 409 | .46 |
| Thrombus characteristics | | | **.12** |
| Resolution/improvement | **85 (93)** | **77 (187)** | |
| Stable/progression | **15 (17)** | **23 (55)** | |

*DVT,* Deep venous thrombosis; *IQR,* interquartile range; *PE,* pulmonary embolism; *SD,* standard deviation; *VTE,* venous thromboembolism.
Boldface values emphasize key results.

Smith et al study) and a high mortality on follow-up (40%), decreasing further the likelihood of the cohort to demonstrate significant differences in VTE recurrence.[14] Although the JUPITER randomized trial demonstrated the effect of rosuvastatin on prevention of VTE in 17,802 patients followed for 1.9 years, the trial excluded patients with cancer and cardiovascular disease and focused on a population of relatively healthy adults with no history of VTE.[1] In a retrospective study of 170,459 patients with cancer followed for up to 1 year, El-Refai et al[15] found that statins had no statistically significant protective effects against cancer-associated VTEs in most cancer types with the exception of DVT in leukemia and PE in colorectal cancer. Given the high proportion of patients with cancer in the current study, this finding could further explain the lack of association between statins and VTE recurrence.

Antiplatelet therapy, namely aspirin, has been shown to decrease the risk of recurrence of VTEs. The WARFASA study showed that in patients without cancer, aspirin therapy started after 6 to 18 months of oral anticoagulation reduced VTE recurrence by 40%.[16,17] The present study, in which 40% of patients had cancer, did not find a significant association between antiplatelet therapy and VTE recurrence, possibly explained by the previously discussed loss-of-cohort from a high mortality rate. Given the involvement of platelets in venous thrombus formation, it is plausible that antiplatelet agents may promote thrombus resolution in a related manner, as was found to be the case in the current study. However, further investigation is required to confirm this clinical finding. Finally, antiplatelet therapy was found to be independently associated with lower mortality, which is consistent with the Antiplatelet Trialists' Collaboration report of decreased overall mortality and rates of myocardial infarction and stroke in patients using antiplatelet therapy for longer than 1 month.[18]

**Table IV.** Multivariable analysis

| Variable | Thrombus resolution or improvement, OR (95% CI) | Recurrent VTE, OR (95% CI) | Mortality, OR (95% CI) |
|---|---|---|---|
| Statin therapy | **3.23 (1.32-7.87)**[a] | 1.12 (0.55-2.29) | 0.79 (0.49-1.27) |
| Age | 0.97 (0.95-0.99)[a] | 1 (0.98-1.01) | 1.04 (1.03-1.06)[a] |
| Female sex | 1.6 (0.9-2.84) | 1.18 (0.73-1.92) | 1.03 (0.71-1.47) |
| Provoked vs unprovoked DVT | 1.31 (0.68-2.53) | 0.87 (0.5-1.52) | 0.69 (0.47-1.03) |
| Distal vs proximal DVT | 1.77 (0.88-3.57) | 1.13 (0.67-1.91) | 0.53 (0.35-0.8)[a] |
| Coumadin vs no anticoagulation | 1.71 (0.64-4.58) | 1.52 (0.63-3.67) | 0.19 (0.12-0.3)[a] |
| LMWH vs no anticoagulation | 1.2 (0.4-3.66) | 1.76 (0.59-5.29) | 0.61 (0.34-1.07) |
| DOAC vs no anticoagulation | 2.24 (0.73-6.86) | 1.48 (0.54-4.03) | 0.16 (0.09-0.3)[a] |
| Antiplatelet therapy | 2.25 (1.05-4.81)[a] | 0.83 (0.46-1.49) | 0.57 (0.37-0.87)[a] |
| CAD | 0.9 (0.33-2.45) | 0.65 (0.26-1.61) | 3.12 (1.80-5.41)[a] |
| History of cancer | 0.84 (0.42-1.67) | 0.58 (0.32-1.08) | 4.26 (2.91-6.25)[a] |

*CAD,* Coronary artery disease; *CI,* confidence interval; *DOAC,* direct-acting oral anticoagulant; *DVT,* deep venous thrombosis; *LMWH,* low-molecular-weight heparin; *OR,* odds ratio; *PE,* pulmonary embolism.
Boldfaced values emphasize key results.
[a] $P < .05$.

Considering other factors affecting mortality, coumadin and DOACs were associated with lower mortality in the setting of DVT, corroborating clinical evidence to date.[19-21] In contrast, LMWH was not found to be protective, possibly owing to its preferential use as the anticoagulant of choice for DVT in patients with cancer per current treatment guidelines.[22]

Distal DVTs were associated with decreased mortality when compared with proximal DVTs consistent with a prior finding by the Computerized Registry of Patients with Venous Thromboembolism (RIETE) investigators, who attributed the difference to better clinical status of patients with isolated distal DVT whose mortality was mainly due to non–VTE-related deaths.[23] In a study by Martin et al,[24] proximal DVT was associated with a significantly higher incidence of associated PE, which may be another factor contributing to the higher mortality associated with proximal DVTs.

Last, multivariable analysis found that older age, a history of CAD, and a history of cancer were independently associated with higher mortality. These associations are well-known and provide validation of the analytic approach and model used in this study and greater credibility to its primary findings.[25-27]

The variables in multivariable analysis that yielded high odds ratios with large confidence intervals may have done so because of limited exposure across groups and we suggest that these variables be considered in any future retrospective or prospective studies.

This study is limited by its retrospective nature. The lack of continuous and consistent monitoring precluded any meaningful analysis of time to thrombus change. Some clinical information may have been incomplete or unavailable in the medical records. Specifically, dosages of statins were not available consistently and could not be considered in analysis. The maintenance of international normalized ratio goals of patients on anticoagulation therapy were not tracked and compliance with administration of anticoagulation could not be confirmed. Changes in medications beyond the initial encounter were not reviewed and patient adherence to prescribed medication regimen could not be verified. Those patients who developed subsequent VTE or died from PE outside the system could not be captured. Thrombus resolution may enhance venous return and play a role in mitigating the development of post-thrombotic syndrome. The patients in this study were treated and followed by a variety of providers and assessment of post thrombotic syndrome by standard venous disability scoring system was not available. Analysis of patients with repeat ultrasound examination more than 1 month after diagnosis provides an effective time period for anticoagulation therapy to take effect and for us to observe the long-term effects of thrombus remodeling.[28] Finally, decisions to perform ultrasound follow-up were not based on a predefined protocol, but rather clinical presentation and different provider practices. With only approximately one-half of the patients undergoing repeat ultrasound examination, there was a selection bias from the providers caring for the patients (Supplementary Tables IV-VI, online only). Even though additional analysis of patients undergoing repeat ultrasound examination in the statin and nonstatin groups of patients showed no significant difference in time to repeat ultrasound (Supplementary Table VII, online only) and showed similar differences as the entire cohort (Supplementary Table I, online only), it is possible that selection bias unaccounted for between the two groups might have affected the results.

## CONCLUSIONS

In this study, statin therapy seems to be associated with enhanced thrombus resolution or improvement in patients with DVT who underwent repeat ultrasound examination. The role of statin in the overall treatment of VTE needs to be further investigated.

## AUTHOR CONTRIBUTIONS

Conception and design: CH, AL, WF, CC
Analysis and interpretation: CH, JR, CC
Data collection: CH, AB, KB, NH
Writing the article: CH, JR, CC
Critical revision of the article: CH, AB, KB, NH, JR, AL, WF, CC
Final approval of the article: CH, AB, KB, NH, JR, AL, WF, CC
Statistical analysis: JR
Obtained funding: CH, CC
Overall responsibility: CC

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Submitted Mar 31, 2018; accepted Oct 24, 2018.

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**Supplementary Table I (online only).** Patient characteristics of those who received repeat ultrasound examination after 1 month from deep venous thrombosis (*DVT*) diagnosis

| | Statin group (n = 110), % (No.) | Nonstatin group (n = 242), % (No.) | *P* value |
|---|---|---|---|
| Age, years (mean ± SD) | 69 ± 13 | 58 ± 17 | <.001[a] |
| Female | 50 (55) | 54 (131) | .47 |
| Hypertension | 75 (82) | 49 (118) | <.001[a] |
| Diabetes | 45 (50) | 13 (32) | <.001[a] |
| Hyperlipidemia | 75 (82) | 11 (27) | <.001[a] |
| CHF | 17 (19) | 8 (20) | .013[a] |
| CAD | 26 (29) | 7 (18) | <.001[a] |
| PAD | 9 (10) | 2 (5) | .007[a] |
| CVD | 23 (25) | 5 (11) | <.001[a] |
| Hypercoagulable disorder | 4 (4) | 8 (19) | .14 |
| History of prior DVT | 22 (24) | 22 (53) | .99 |
| History of prior PE | 8 (9) | 11 (26) | .46 |
| History of cancer | 29 (32) | 36 (87) | .21 |
| History of smoking | 51 (56) | 54 (130) | .62 |
| Antiplatelet therapy | 48 (53) | 21 (50) | <.001[a] |
| Caprini score, mean ± SD | 6.3 ± 3.1 | 6.0 ± 2.8 | .36 |

*CAD,* Coronary artery disease; *CHF,* congestive heart failure; *CVD,* cerebral vascular disease; *PAD,* peripheral arterial disease; *PE,* pulmonary embolism; *SD,* standard deviation.
[a] $P < .05$.

**Supplementary Table II (online only).** Deep venous thrombosis (*DVT*) characteristics and treatment of patients who received repeat ultrasound after 1 month from DVT incident

| | Statin group (n = 110), % (No.) | Nonstatin group (n = 242), % (No.) | *P* value |
|---|---|---|---|
| Provoked DVT | 51 (56) | 49 (118) | .71 |
| DVT location | | | .17 |
| Distal | 23 (25) | 30 (72) | |
| Proximal | 77 (85) | 70 (170) | |
| DVT associated with PE | 22 (24) | 22 (54) | .92 |
| Severity of PE | | | .33 |
| Low risk | 46 (11) | 44 (24) | |
| Intermediate risk | 29 (7) | 43 (23) | |
| High risk | 25 (6) | 13 (7) | |
| Anticoagulation | | | .48 |
| None | 11 (12) | 10 (24) | |
| Coumadin | 60 (66) | 52 (127) | |
| LMWH | 13 (14) | 17 (42) | |
| DOAC | 16 (18) | 20 (49) | |
| Duration of anticoagulation, months | | | .69 |
| <3 | 15 (15) | 14 (30) | |
| 3-6 | 22 (22) | 28 (62) | |
| 6-12 | 33 (32) | 27 (58) | |
| >12 | 24 (24) | 24 (53) | |
| Not available | 5 (5) | 7 (15) | |
| Placement of IVC filter | 32 (35) | 29 (70) | .58 |
| Catheter-directed thrombolysis of DVT | 5 (5) | 2 (6) | .33 |
| Catheter-directed thrombolysis of PE | 0 (0) | 3 (7) | .1 |
| Systemic administration of thrombolytic agent | 2 (2) | 2 (4) | .99 |

*DOAC,* Direct-acting oral anticoagulant; *DVT,* deep venous thrombosis; *IVC,* inferior vena cava; *LMWH,* low-molecular-weight heparin; *PE,* pulmonary embolism.

**Supplementary Table III (online only).** Long-term outcomes of patients who received repeat ultrasound examination after 1 month from a deep venous thrombosis (*DVT*) incident

| | Statin group (n = 110), % (No.) | Nonstatin group (n = 242), % (No.) | *P* value |
|---|---|---|---|
| Days to last follow-up, mean ± SD | 1042 ± 433 | 1029 ± 432 | .78 |
| Median (IQR) | 1235 (723-1347) | 1200 (697-1337) | .51 |
| Surviving patients at last follow-up | 80 (88) | 80 (194) | |
| New or recurrent DVT | 28 (31) | 32 (77) | .49 |
| New or recurrent PE | 2 (2) | 5 (13) | .16 |
| Recurrent VTE | 29 (32) | 33 (81) | .41 |
| Mortality | 20 (22) | 20 (48) | .97 |

*IQR,* Interquartile range; *PE,* pulmonary embolism; *VTE,* venous thromboembolism; *SD,* standard deviation.

**Supplementary Table IV (online only).** Patient characteristics of those who received repeat ultrasound examination after 1 month from a deep venous thrombosis (*DVT*) diagnosis vs those who did not

| | Repeat ultrasound examination after 1 month (n = 352), % (No.) | No repeat ultrasound examination after 1 month (n = 466), % (No.) | *P* value |
|---|---|---|---|
| Age, years (mean ± SD) | 61 ± 16 | 69 ± 16 | <.001[a] |
| Female sex | 53 (186) | 50 (232) | .39 |
| Hypertension | 57 (200) | 64 (297) | .04[a] |
| Diabetes | 23 (82) | 25 (115) | .63 |
| Hyperlipidemia | 31 (109) | 37 (172) | .07 |
| CHF | 11 (39) | 14 (64) | .25 |
| CAD | 13 (47) | 22 (102) | .002[a] |
| PAD | 4 (15) | 5 (21) | .87 |
| CVD | 10 (36) | 13 (59) | .28 |
| Hypercoagulable disorder | 7 (23) | 5 (21) | .2 |
| History of prior DVT | 22 (77) | 16 (73) | .02 |
| History of prior PE | 10 (35) | 10 (46) | .97 |
| History of cancer | 34 (119) | 49 (229) | <.001[a] |
| History of smoking | 53 (186) | 58 (271) | .13 |
| Antiplatelet therapy | 29 (103) | 34 (158) | .16 |
| Caprini score, mean ± SD | 6.1 ± 2.9 | 6.7 ± 2.9 | .004[a] |

*CAD,* Coronary artery disease; *CHF,* congestive heart failure; *CVD,* cerebral vascular disease; *PAD,* peripheral arterial disease; *PE,* pulmonary embolism; *SD,* standard deviation.
[a] $P < .05$.

**Supplementary Table V (online only).** Deep venous thrombosis (*DVT*) characteristics and treatment of patients who received repeat ultrasound examination after 1 month from DVT incident

| | Repeat ultrasound examination after 1 month (n = 352), % (No.) | No repeat ultrasound examination after 1 month (n = 466), % (No.) | *P* value |
|---|---|---|---|
| Provoked DVT | 49 (174) | 51 (237) | .66 |
| DVT location | | | .4 |
| Distal | 28 (97) | 25 (116) | |
| Proximal | 72 (255) | 75 (349) | |
| DVT associated with PE | 22 (78) | 29 (137) | .02[a] |
| Severity of PE | | | .2 |
| Low risk | 45 (35) | 34 (46) | |
| Intermediate risk | 38 (30) | 51 (69) | |
| High risk | 17 (13) | 15 (21) | |
| Anticoagulation | | | <.001[a] |
| None | 10 (36) | 30 (139) | |
| Coumadin | 55 (193) | 43 (200) | |
| LMWH | 16 (56) | 18 (82) | |
| DOAC | 19 (67) | 10 (45) | |
| Placement of IVC filter | 30 (105) | 26 (122) | .25 |
| Catheter-directed thrombolysis of DVT | 3 (11) | 1 (3) | .007[a] |
| Catheter-directed thrombolysis of PE | 2 (7) | 1 (5) | .28 |
| Systemic administration of thrombolytic agent | 2 (6) | 2 (8) | .99 |

*DOAC,* Direct-acting oral anticoagulant; *IVC,* inferior vena cava; *LMWH,* low-molecular-weight heparin; *PE,* pulmonary embolism.
[a] $P < .05$.

**Supplementary Table VI (online only).** Long-term outcomes of patients who received repeat ultrasound examination after 1 month from a deep venous thrombosis (*DVT*) incident vs those who did not

| | Repeat ultrasound examination after 1 month (n = 352), % (No.) | No repeat ultrasound examination after 1 month (n = 466), % (No.) | *P* value |
|---|---|---|---|
| Days to last follow-up ± SD | 1033 ± 432 | 485 ± 541 | <.001[a] |
| New or recurrent DVT | 31 (108) | 2 (10) | <.001[a] |
| New or recurrent PE | 4 (15) | 2 (9) | .05 |
| Recurrent VTE | 32 (113) | 4 (17) | <.001[a] |
| Mortality | 20 (70) | 52 (242) | <.001[a] |

*PE,* Pulmonary embolism; *SD,* standard deviation; *VTE,* venous thromboembolism.
[a] $P < .05$.

**Supplementary Table VII (online only).** Thrombus resolution or improvement by time to repeat ultrasound examination

| Time to repeat ultrasound examination, years | Statin group (n = 110), % (No.) | Nonstatin group (n = 242), % (No.) | *P* value |
|---|---|---|---|
| <1 | 59 (10) | 65 (20) | .69 |
| 1-2 | 91 (10) | 58 (18) | .07 |
| 2-3 | 85 (11) | 83 (25) | .99 |
| 3-4 | 87 (48) | 83 (104) | .51 |
| >4 | 100 (14) | 83 (20) | .28 |