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Statin Therapy Associated with Improved Thrombus Resolution in Patients with Deep Vein Thrombosis

A Thesis Submitted to the

Yale University School of Medicine

in Partial Fulfillment of the Requirements

for the Degree of Doctor in Medicine

By

Charles Hsu

2020

Abstract

Objectives: 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 vein 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 (non-statin 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 thrombus improvement or resolution on follow up ultrasound, VTE recurrence, mortality. 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%), non-statin group: n = 539 (66%)]. The patients in the statin group were significantly older ($P < .001$). Patients on statin were more likely to have risk factors for and manifestations of atherosclerosis and to be on antiplatelet therapy ($P < .001$) while those in the non-statin 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 PE (pulmonary embolus), but patients on statin 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 while anticoagulation with warfarin and DOACs 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.

Acknowledgements:

This work was performed under the guidance of Cassius Iyad Ochoa Chaar, MD, MS, Associate Professor of Surgery, the Division of Vascular Surgery, Department of Surgery, Yale University School of Medicine. Other contributors to this work include Anand Brahmandam, MD, Kirstyn E Brownson, MD, Nancy Huynh, MD, Jesse Reynolds, MS, Alfred I Lee, MD, PhD, and Wassim H Fares, MD, MSc. Contributions are described in detail in the Methods section.

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Introduction:

Venous thromboembolism (VTE) is a common condition affecting hundreds of thousands of patients every year, including those with deep vein thrombosis (DVT) and pulmonary embolism (PE), a potentially life-threatening condition.[1] Patients with VTE are often managed using anticoagulation agents, the medications of choice for the prevention and treatment of VTE, however there remains an unmet need for those who cannot tolerate their side effects or may be inadequately treated. Studies suggest that statins, also known as 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors and most commonly known for their cholesterol-lowering effects, may also play a role in reducing the risk of initial or recurrent DVT.[2,3] In addition, population studies of VTE patients on statins have shown that longer duration of statin use is also associated with greater reduction of recurrent VTE.[4] The precise mechanisms of this observed antithrombotic effect have been explored in a variety of preclinical experiments. In animals, atorvastatin and rosuvastatin have been shown to reduce venous thrombus burden and DVT-induced vein wall scarring, while simvastatin has been found to promote thrombus resolution in a leporine posterior vena cava thrombus model.[5,6] Clinically, residual vein thrombosis has been shown to be a risk factor for VTE recurrence.[7] 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 following sections review both the nonclinical and clinical literature supporting the above concepts to establish the context and rationale for the work performed in this thesis.

Anti-thrombotic effects of statins on the coagulation cascade

Statins are most commonly known for their efficacy in the management of hyperlipidemia and its associated sequelae (i.e. coronary artery disease), and have also shown to significantly reduce the risk of major cardiovascular events.[8] However, statins have also been shown to provide cardiovascular benefit via a number of "pleiotropic" effects independent from cholesterol lowering, notably including anti-thrombotic properties at multiple levels of the coagulation cascade.[9] The lipophilic statins simvastatin and fluvastatin (but not the hydrophilic pravastatin) decrease tissue factor (TF) expression in macrophages via nuclear factor κB (NF-κB) inhibition *in vitro*, an effect which was not reversed by the addition of cholesterol, suggesting that statin's effect on TF occurs independently of intracellular cholesterol lowering. Instead, a different downstream product, geranylgeranyl pyrophosphate (GGPP) is thought to play a crucial role in the regulation of TF expression.[10] As TF expression has been shown to be upregulated in lipid-laden macrophages at the core of atherosclerotic plaques and is thought to promote intravascular thrombosis, the down-regulating effect of statins on TF would explain another cholesterol-independent aspect of statins' cardioprotective properties.[11] Indeed, a study in humans found that carotid artery plaques removed from patients treated with atorvastatin for 4-6 months had significantly lower TF antigen levels and activity as compared with those on placebo.[12]

Further downstream in the coagulation cascade is thrombin, the key to activating thrombus formation and the common target of several marketed anticoagulant therapies. Statins, particularly atorvastatin, simvastatin, and pravastatin, have been shown in both

experimental and clinical studies to decrease thrombin formation, however measurements of thrombin markers such as prothrombin fragments 1.2 (F1.2) and thrombin-antithrombin complex (TAT) have yielded less consistent findings, ranging between mild to neutral effects. This effect is particularly notable in patients with hypercholesterolemia, where even 3-days of simvastatin (40mg/d) treatment in fourteen men with LDL cholesterol levels >130 mg/dL on low-dose aspirin (75mg/d) resulted in a significantly reduced level of prothrombin activation at sites of microvascular injury, accompanied by delayed Factor Va generation and accelerated activated Protein C-mediated Factor Va inactivation, on top of the anticoagulant effects of aspirin alone.[13-15]

To a lesser degree of scientific concordance, statins have also been found to exert anti-thrombotic effects on the coagulation cascade via decreased fibrinogen cleavage, decreased Factor XIII activation, increased thrombomodulin expression, and increased Factor Va inactivation.[16-18] Other pleiotropic effects of statins include improved endothelial function via increased nitric oxide bioavailability, inflammation suppression, atherosclerotic plaque stabilization, immune-modulation, inhibition of cardiac hypertrophy, and reduced smooth muscle cell proliferation.[16] These mechanisms, in concert with each other, are likely to underpin the anti-thrombotic and vascular protective effects observed in animal and clinical studies.

Statins and the risk of venous thromboembolism

The clinical relevance of the antithrombotic effects of statins has been investigated by many studies. In 2000, the Heart and Estrogen/Progesterone Replacement Study (HERS)

found in a secondary analysis of the impact of hormonal therapy on the risk of VTE that use of statins (but not any other lipid-lowering drug) in a postmenopausal population was associated with a decreased risk of VTE (relative hazard 0.5 [0.2 – 0.9]).[19] In 2001, Ray et al. showed through a large Canadian retrospective cohort study that any dose of statin use in individuals greater than 65 years old was associated with a 22% lowered incidence of venous thromboembolisms.[20] This association has been supported by a number of case-control, cohort, or observational studies, including studies finding statin-associated VTE risk reduction in patients with underlying hypercoagulable states such as cancer and nephrotic syndrome.[21-23] One study by Ramcharan et al. found that different statin types and treatment durations were all associated with a decreased risk of VTE (OR 0.45 [0.36 – 0.56]).[23] However, not all studies have found a positive association between statins and reduced VTE risk, including a population-based retrospective follow-up nested case-control analysis of the United Kingdom's General Practice Research Database and a prospective open cohort study in England and Wales.[24,25] Considering the divergent findings in these various retrospective studies, perhaps the single most important trial is then the randomized, double-blinded, placebo-controlled Justification for the Use of statins in Prevention: an Interventional Trial Evaluating Rosuvastatin (JUPITER) study published in 2009. In the JUPITER study, the trialists found that 20 mg/d of rosuvastatin reduced the risk of VTE in asymptomatic patients (men over 50 years old and women over 60 years old) with no evidence of cardiovascular disease, LDL-cholesterol <130 mg/dL, and CRP >2 mg/L (at first visit) over the course of 1.9-years of follow-up. The study found significant reductions in DVT or PE (34 events in the treatment arm vs 60 events in the placebo arm, HR 0.57 [0.37–0.86]), with the largest reduction in isolated

DVT (55%), however failed to reduce the occurrence of PE (OR: 0.77 [0.41–1.46]) or VTE death (OR: 0.50 [0.20–1.24]).[2] A meta-analysis of 4 cohort and 4 case-control studies published in 2011 by Pai et al. sought to expand investigation beyond the healthy older adults studied in JUPITER to include a more heterogeneous (younger or comorbid) populations. Pai et al. found that while statin use was significantly associated with a lower rate of VTE (OR 0.67; 95% CI 0.53 – 0.84), its association with lower rate of DVT (OR 0.53; 95% CI 0.22 – 1.29) did not meet significance and was likely attributable to a small sample size. The body of evidence taken together suggest that while statins' effect on reducing VTE may be variably observed based on population and underlying medical comorbidities, the possibility of a clinically meaningful association deserves further study.

Residual thrombus in DVT and the post-thrombotic syndrome

There is a myriad of risk factors associated with the recurrence of VTE, and one of interest is residual venous thrombus. Many studies have attempted to understand the individual risk of VTE recurrence to better align treatment duration with patient-specific benefit-risk profiles. In a 2011 systematic review, Tan et al. found that residual thrombosis was positively associated with VTE recurrence, suggesting that assessing residual venous obstruction may be useful in individual risk assessment.[26] However, this finding did not seem to translate to clinical management, as the contemporaneously conducted REVERSE cohort study by L. E. Gal et al. did not find a significantly higher risk of recurrent VTE in patients who were found to have residual thrombus at the time of completing 5-7 months of anticoagulant therapy.[27] While this finding does not support

the assessment for residual thrombus in the clinical determination of individual treatment duration, the presence of a residual thrombus remains pathologically significant given the chronic sequelae of venous hypertension and vein wall scarring which characterizes post-thrombotic syndrome (PTS).[28,29] In PTS, typical symptoms include pain, swelling, and cramping of the leg, generally worsened when standing, and in severe cases can lead to venous ulceration. Despite optimal anticoagulation by conventional therapies, many patients with iliofemoral venous thrombosis continue to develop PTS, highlighting an unmet medical need, particularly around thrombus resolution. While the prevention of PTS is rooted in DVT prevention and the active management of incident DVT's, cases of extensive DVT can be treated with open or endovascular thrombus removal (e.g. catheter-directed thrombolysis).[28,30] In the 2016 CaVenT trial, Haig et al. showed that patients randomized to catheter-directed thrombolysis by alteplase within 21 days from symptom onset plus standard therapy (anticoagulation therapy and compression stockings) were less likely to develop PTS compared to those on standard therapy alone at 5 years follow-up.[31] This supports the notion that thrombus resolution may be associated with improved outcomes and suggests that in the absence of intervention (which may not be universally accessible) there may be a role for medications that promote thrombus resolution beyond currently available anticoagulants.

Statins and thrombus resolution

In addition to its lipid-lowering and antithrombotic effects, statins have also been found to improve the resolution of venous thrombi. In a murine study published in 2015, Kessinger et al. demonstrated a 25% thrombus burden reduction in mice with stasis-

induced (IVC ligation) venous thrombi treated with atorvastatin or rosuvastatin, which was accompanied by a significant reduction in platelet aggregation and clot stability, as well as anti-inflammatory effects most notable early after thrombus formation, and a 50% reduction in thrombus-induced vein wall scarring.[5] A similar model in rabbits was later studied by Feng et al., finding that simvastatin increased thrombus resolution, likely through anti-inflammatory effects independent of its lipid-lowering properties.[6] The authors also noticed that simvastatin affected thrombus size sooner than low molecular weight heparin (3-day vs 14-day), with effects equalizing in the 14-day arm, likely explained by their different mechanisms of action. These preclinical models suggest that statins may be an effective treatment in patients with VTE who cannot otherwise tolerate currently available options for anticoagulation. While there is evidence from a single case report of aggressive combination statin and antiplatelet therapy leading to rapid regression of an unstable mobile thrombus aortic atheroma, no other clinical studies have been reported exploring the effect of statins on thrombus resolution in humans.[32]

Aim

Based on a comprehensive review of the literature above, statins appear to have a strong mechanistic rationale supporting clinical findings of its anti-thrombotic effects in preventing VTE, however when it comes to resolution of an incident VTE, only animal trials have been conducted. This study hypothesizes that statins are associated with greater thrombus resolution or improvement in humans. The aim of this study is to investigate thrombus resolution and improvement in a group of patients treated for DVT while on statin compared to patients not receiving statin. Thrombus resolution and clinically significant recurrence of VTE will be correlated with statin use.

Methods:

Study design

This is a retrospective study examining consecutive adult patients (age ≥ 18) presenting with newly diagnosed acute lower extremity DVT at an academic 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 2 groups based on their use of statin therapy or lack thereof, and all patient records and ultrasound reports were reviewed. Patients initiating statins after developing DVT were considered to not have a standing history of statin use and were included in the non-statin group for initial presentation but were analyzed with the statin group for long-term outcomes. Patients who had continuous statin use prior to DVT incidence but discontinued after were included in the statin group for initial presentation but were analyzed with the non-statin group for outcomes.

Variables

Patient demographics and comorbidities as well as ultrasound characteristics were extracted from the electronic medical records. Patients' 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 (including metastatic disease where present), prior DVT, prior pulmonary embolism (PE), and smoking were recorded. In addition to the aforementioned variables, other risk factors for VTE required to calculate the Caprini score were also extracted.[33] These included concurrent presentation of varicose veins or

swollen legs, concurrent central venous access, history of inflammatory bowel disease, sepsis within the past month, pneumonia, chronic obstructive pulmonary disease, long distance travel, immobilizing plastic cast, multiple trauma, paralysis, major surgery, elective major lower extremity arthroplasty, and hip, pelvis, or leg fracture. The prescription of antiplatelets (aspirin, clopidogrel, prasugrel, dipyridamole, ticagrelor, ticlopidine) and statins at the time of diagnosis was noted.

The DVT characteristics were noted as occlusive vs non-occlusive, proximal vs distal, and provoked vs unprovoked. Proximal DVT included thrombi in the popliteal vein or above, while distal DVT included thrombi found exclusively in the tibial veins. Cases that had thrombi in both 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 >4 hours, or confinement to bed >72 hours within 30 days of the event, or initiation of oral contraceptives, or a central venous femoral line (if ipsilateral DVT).[34] Associated PE confirmed by imaging was classified by severity. High-risk PE was defined as >15 min of hypotension (<90 mmHg); intermediate-risk PE was defined by blood pressure >90 mmHg 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), and finally low-risk PE was defined by the lack of these characteristics.[35] 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 [warfarin, low molecular weight heparin (LMWH), or direct oral anticoagulant (DOAC)] and its duration. Only full-dose anticoagulation therapies with INR goal of 2-3 or more were noted. The placement of inferior vena cava (IVC) 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 2 groups in follow-up through summer of 2017. The patients who underwent repeat lower extremity venous ultrasound after one month of diagnosis were noted. The repeat ultrasound report was reviewed, and the radiologist assessment of thrombus burden compared to the initial ultrasound was noted as: progressed (worsened), stable, improved, or completely resolved. The number of repeat ultrasound exams varied by patient and thrombus burden may have changed or resolved prior to the final repeat ultrasound, so we noted the date and results of the earliest repeat ultrasound after one month of diagnosis where no further change in thrombus status was observed in subsequent exams. 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 (warfarin, LMWH, or DOAC), antiplatelet therapy, hypertension, CHF, diabetes, hyperlipidemia, CAD, PAD, CVD, and cancer.

Statistical analysis

Characteristics of the sample were summarized using descriptive statistics and expressed as percentages (n) 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-square 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.

Attribution of work performed

Identification of consecutive adult patients presenting with DVT in the study period was performed by Nancy Huynh MD, Anand Brahmandam MD, and Kirstyn Brownson MD, including basic demographic information and characteristics of DVT such as location, associated PE, anti-thrombotic treatment, and history of underlying hypercoagulable risk factors (e.g. cancer, oral contraceptives, immobilization, long travel, surgery, et cetera). This data was double-checked by the author Charles Hsu, who then additionally collected information including comorbidities and past medical history, medication use (including statin and antiplatelet use), timing of statin initiation relative to presenting DVT, radiographic reports upon presentation and on subsequent follow-up, and long-term follow-up of outcomes through summer of 2017 (mortality, VTE recurrence). The author

performed a comparison of radiographic reports between initial and follow-up encounters to determine change in the status of thrombus burden of DVT. All statistical analysis was done by Jesse Reynolds in collaboration with Cassius Iyad Ochoa Chaar MD MS and the author. The author drafted the manuscript for submission to the Journal of Vascular Surgery: Venous and Lymphatic Disorders and the manuscript was reviewed by Cassius Iyad Ochoa Chaar MD MS, Alfred Lee MD PhD, Wassim Fares MD MSc, and Jesse Reynolds MS.

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. There were 5 patients who were initiated on statin therapy and another 5 who discontinued statin therapy shortly after the diagnosis of DVT; these were accounted for in the analysis. The three most common statin agents were atorvastatin (10 to 80 mg daily), simvastatin (20 to 80 mg daily), and pravastatin (10 to 80 mg daily), which collectively accounted for ~90% of all statins used. Patients in the statin group were significantly older (72 ± 13 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 significant difference in sex, history of cancer, or history of smoking between the 2 groups (Table 1).

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 non-statin 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 non-statin group had a higher proportion of hypercoagulable disorder or a

history of prior DVT while the patients in the statin group had significantly higher mean Caprini scores. Additionally, there was no significant difference in the history of prior PE (Table 1).

DVT characteristics and treatment

There was a higher proportion of high-risk PE (24% vs 11%, P = .046) in the statin group. The 2 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, IVC filter placement, and proportion treated by thrombolysis (Table 2).

Long-term outcomes

There was no difference in the overall duration of follow-up between the 2 groups (741 ± 569 days vs 710 ± 565 days, P = .46). The frequency of repeat ultrasound after one month (39% vs 45%, P = .13) and the intervals at which ultrasounds were performed following 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 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 3). A subgroup analysis of the characteristics of patients who underwent repeat ultrasound after one month was performed (Supplement Tables 1 and 2). In this subgroup, there was no significant difference between the statin and non-statin patients in

recurrence of DVT, PE, VTE or mortality (Supplement Table 3). On the other hand, a comparison of the patients who did not receive repeat ultrasound after one month to the patients that underwent repeat ultrasonography showed significant differences and selection bias. Patients who did not receive a repeat ultrasound 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 (Supplement Tables 4, 5, and 6). Furthermore, there was no significant difference in time to repeat US between the statin and non-statin groups when stratified into groups based on thrombus resolution status and time to repeat US < 1 year, 1 – 2 years, 2 – 3 years, 3 – 4 years, and > 4 years (Supplement Table 7).

Multivariable analysis

On multivariable analysis, which adjusted for potential confounders including those variables in Tables 1 and 2, statin therapy (OR 3.23, 95% CI [1.32 – 7.87]) and antiplatelet therapy (OR 2.25 [1.05 – 4.81]) were found to be independently associated with thrombus resolution or improvement on ultrasound. Older age (OR 0.97 [0.95 – 0.99]) was found to be associated with lower thrombus resolution or improvement. No significant association was found between thrombus resolution or improvement and the following factors: sex, provoked vs unprovoked DVT, distal vs proximal DVT, CAD, history of cancer, or anticoagulation by warfarin, LMWH, or DOAC as compared with no anticoagulation (Table 4).

Distal DVT compared to proximal DVT (OR 0.53 [0.35 – 0.8]), anticoagulation with warfarin (OR 0.19 [0.12 – 0.3]) or DOACs (OR 0.16 [0.09 – 0.3]) as compared to no anticoagulation, and antiplatelet therapy (OR 0.57 [0.37 – 0.87]) were all independently associated with lower mortality. Age (OR 1.04 [1.03 – 1.06]), CAD (OR 3.12 [1.80 – 5.41]), and history of cancer (OR 4.26 [2.91 – 6.25]) were found to be independently associated with mortality. Mortality outcomes were not associated with statin therapy, sex, provoked vs unprovoked DVT, or anticoagulation by LMWH as compared to no anticoagulation (Table 4).

Finally, there was no significant association of any variable with recurrent VTE (Table 4).

Discussion:

This study found that statin therapy is associated with thrombus resolution or improvement after DVT, consistent with the literature on statin's pleiotropic cardiovascular effects beyond its known lipid-lowering action. However, the retrospective nature of this study places significant limitations on our ability to draw inference on causation. On univariate analysis, the statin group was found to have no significant difference in thrombus characteristics on repeat ultrasound from the non-statin group, but patients on statins had significantly 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 impairing or otherwise adversely affecting the ability of thrombus remodeling. Even though this effect of statins has been described in animal models, the clinical correlation in humans has not been reported, to our knowledge.[5,6] As established in the introduction, statins have both significant anti-thrombotic effects and anti-inflammatory properties on the vascular endothelium, which may explain the enhanced thrombus resolution seen in this study.[36] 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 anti-platelets resulting in complete resolution of the atheroma on serial echocardiography.[32]

This study found that the impact on thrombus resolution did not translate into a clinical effect of decreased recurrent VTE. While this is consistent with the findings of Brækkan et al., who found a modest but insignificant decrease in recurrent DVTs in patients on

statins, other studies showed a clearly protective pattern.[4,37-39] Smith et al. 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. studied a larger patient population (n = 4,350) 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 resolve. Additionally, our current study had a high proportion of cancer patients (40% vs 23% in Smith et al.) and a high mortality on follow up (40%) decreasing further the likelihood of the cohort to demonstrate significant differences in VTE recurrence.[39] While 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 "apparently healthy adults" with no history of VTE.[2] In a retrospective study of 170,459 patients with cancer followed for up to 1 year, El-Refai et al. 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.[40] Therefore it is plausible that the high proportion of cancer in the current study could explain the lack of association between statins and VTE recurrence.

Since the submission of the original manuscript for publication, additional studies have been published in the literature exploring topics covered in this thesis. In a 2019 Japanese study (n = 3027) from the COMMAND VTE Registry, Yoshikawa et al. found that

patients who were on statins at baseline had a significantly lower cumulative 3-year incidence of recurrent VTE both before adjusting for potential confounders and after (HR 0.49 [0.29 – 0.78], P = .002), and was insensitive to subgroup analysis with and without active cancer. Similar to this study, Yoshikawa et al. also found that patients in their statin group, when compared to the non-statin group had greater age (71 ± 12 vs 67 ± 16, P < .001), and more cardiovascular risk factors such as CHF, HTN, diabetes, CAD. Additionally, significantly more patients in their statin group were women (67% vs 60%, P = .009), and had chronic kidney disease (24% vs 18%, P = .003) and connective tissue disease (11% vs 7.6%, P = .02). Departing from the results in the present study, a much lower proportion of patients in both groups had cancer, with far fewer in the statin group with history of cancer (20% vs 33%, P < .001) as well as active cancer (12% vs 25%, P < .001). Additionally, they found a greater history of major bleeding in the non-statin group (4.3% vs 8.2%, P = .005).[41] The longer follow-up compared to the present study (3 years vs ~2 years) may explain in part the difference in finding of protection against VTE recurrence. One plausible hypothesis to explain this difference may be extended from a concept derived from El-Rafai et al., that a higher cancer proportion in the statin study group may disfavor finding an association against VTE recurrence, as they generally found no protective effects of statins against recurrent VTE in multiple cancer populations. However, the sensitivity analysis conducted by Yoshikawa et al. does not support this hypothesis, leaving us to believe that more likely the present study was not adequately powered in sample size or follow-up duration to detect a difference in VTE recurrence.

In a 2019 study of data from the RIETE registry of 32,062 VTE patients, Siniscalchi et al. found that on univariate analysis statin users had a similar risk of VTE recurrence (HR 0.98 [0.82 – 1.17]) and a similar mortality rate (HR 1.01 [0.93 – 1.10]). However, on propensity score matching, they found that statin users had a significantly lower risk for death (HR 0.62 [0.48 – 0.79]) while the risk of VTE recurrence remained similar (HR 0.98 [0.61 – 1.57]). The baseline characteristics of the statin and non-statin groups between Siniscalchi et al. and the present study were also similar, with statin group patients being older (73 ± 11 vs 63 ± 19, P < .0001), a larger proportion on antiplatelet therapy (38% vs 11%, OR 5.19 [4.87 – 5.52]), and with significantly more cardiovascular comorbidities: CHF (13% vs 5.5%, OR 2.65 [2.43 – 2.89]), HTN (75% vs 40%, OR 4.56 [4.30 – 4.84]), CAD (20% vs 3.7%, OR 6.67 [6.11 – 7.29]), CVD (14% vs 4.8%, OR 3.11 [2.84 – 3.40]), and diabetes (30% vs 11%, OR 3.52 [3.30 – 3.75]). Notably, the proportion of patients with history of cancer in both groups were identical (24%) and significantly lower than the proportions in the present study (41% vs 44%).[42] The finding of no association of statins with VTE recurrence is consistent with the results of the present study, however directly conflicts with the findings of Yoshikawa et al. and other studies. Given that Siniscalchi et al. studied patient populations with proportions of cancer within the range found in the Yoshikawa et al. study, we would expect that both studies would show similar findings, and the fact that no association was found by Siniscalchi et al. only further preserves the controversy of the topic. They hypothesize that their observed mortality benefit likely stems from statin's pleiotropic cardiovascular effects. On the other hand, the impact of statin therapy on thrombus remodeling was not specifically studied in any of the recent publications.

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 6-18 months of oral anticoagulation reduced VTE recurrence by 40%.[43,44] The present study, which had 40% cancer patients, 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 in this study, 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 longer than 1 month.[45]

Considering other factors affecting mortality, the anticoagulant agents warfarin and DOACs were associated with lower mortality in the setting of DVT, corroborating clinical evidence to date.[46-48] On the other hand, LMWH was not found to be protective, possibly due to its preferential use as the anticoagulant of choice for DVT in cancer patients per current treatment guidelines.[49]

Provoked vs unprovoked DVT did not appear to be independently associated with recurrent VTE in this study. This is inconsistent with the results of the landmark 2003

publication by Baglin et al. in which 570 consecutive patients were prospectively followed for 2 years, and found that patients with unprovoked VTE were at a 2.2-fold higher risk of recurrence than those with non-surgically provoked events, while none of the patients with surgically provoked events experienced recurrence.[50] In Baglin et al., however, key exclusion criteria were malignancy and antiphospholipid syndrome, which clouds direct comparison with the high cancer proportion in the present study, which may have been a pathologic confounder if not at least contributing to higher loss-of-cohort due to mortality.

Distal DVTs were associated with decreased mortality when compared to 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.[51] In a study by Martin et al., 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.[52]

Lastly, multivariable analysis found that older age, history of CAD, and 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.[53-55]

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. Additionally, as proportion of cancer patients appears to be relatively inconsistent across various trials investigating the effects of statins on recurrence of VTE, future study should focus on isolating this variable to better elucidate an association or lack thereof.

This study is limited by its retrospective nature. The lack of continuous and consistent monitoring precluded the opportunity for any meaningful analysis of time to thrombus change. Such analysis would have helped quantify the differential impact of statin therapy on the rate of thrombus resolution, potentially offering new insight on the timescale and/or mechanisms of its effects. Some clinical information may have been incomplete, or unavailable in the medical records. Specifically, dosages of statins were not consistently available and could not be considered in analysis. Maintenance of INR 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 PTS. The patients in this study were treated and followed by a variety of providers and assessment of PTS by standard venous disability scoring system was not available. Analysis of patients with repeat ultrasound greater than one 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.[56] Finally, decisions to perform ultrasound follow-up were not based on a pre-defined protocol but rather clinical presentation and different provider practices. With only approximately half of the patients undergoing repeat ultrasound, there was a selection bias from the providers caring for the patients (Supplement Tables 4-6). However, selection bias in repeat US would only affect the findings of our study if they were a different bias in the statin group versus the non-statin group, which in our supplemental analysis we did not find to be significant. Even though additional analysis of patients undergoing repeat ultrasound in the statin and non-stating groups of patients showed similar differences as the entire cohort (Supplement Table 1), it is possible that selection bias unaccounted for between the 2 groups might have affected the results.

Additionally, patients may have different responses in the anti-thrombotic effects of statin therapy due to unmeasured differences in their genetic profile. For example, the +5466G allelic variant of the TF gene, occurring in 16% of individuals of European descent, has been shown in patients with ischemic heart disease to result in a greater decrease in rate of thrombin formation after 3-month administration of simvastatin, as compared with those with the +5466AA genotype.[57] Other yet-to-be-discovered pharmacogenetic factors may influence statin's cholesterol-lowering, anti-thrombotic, or anti-inflammatory effects in different patients, potentially leading to differences in the long-term outcomes measured in this study.

The totality of evidence from preclinical studies of statins' mechanistic influence on hemostasis suggest that the effect occurs independently of its lipid-lowering effects. However, the present study and all other retrospective clinical studies to date have been conducted in patient populations with dyslipidemia, as statin use is clinically warranted only in the presence of elevated lipid levels (notable exception being the JUPITER trial involving healthy adults). As a result, the association of thrombus resolution or improvement with the use of statins in this study cannot be definitively attributed independent of statins' lipid-lowering properties.

This work was presented as an oral presentation at the 30th American Venous Forum, Tucson, AZ, on February 22, 2018, and subsequently published in the Journal of Vascular Surgery: Venous and Lymphatic Disorders in March 2019.

Conclusion:

Statin therapy appears to be associated with enhanced thrombus resolution or improvement in patients with DVT who underwent repeat ultrasound, however, there was no association with recurrence of VTE or mortality. The role of statin therapy in the resolution of venous thrombi and overall treatment of VTE needs to be further investigated.

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Table 1: Patient characteristics

	Statin group (n = 279) % (n)	**Non-statin group (n = 539) % (n)**	***P* value**
Age (years ± SD)	72 ± 13	63 ± 17	<0.001*
Female	51 (140)	52 (278)	0.70
Hypertension	82 (229)	50 (268)	<0.001*
Diabetes	38 (105)	17 (92)	<0.001*
Hyperlipidemia	73 (205)	14 (76)	<0.001*
CHF	17 (48)	10 (55)	0.007*
CAD	35 (98)	9 (51)	<0.001*
PAD	9 (25)	2 (11)	<0.001*
CVD	20 (57)	7 (38)	<0.001*
Hypercoagulable disorder	3 (7)	7 (37)	0.009*
History of prior DVT	14 (40)	20 (110)	0.03*
History of prior PE	8 (21)	11 (60)	0.10
History of cancer	41 (113)	44 (235)	0.40
History of smoking	56 (156)	56 (301)	0.98
Antiplatelet therapy	55 (154)	20 (107)	<0.001*
Caprini score ± SD	6.7 ± 2.9	6.3 ± 2.8	0.022*

*Statistically significant P < .05; SD: standard deviation, DVT: deep vein thrombosis, PE: pulmonary embolism, CHF: congestive heart failure, CAD: coronary artery disease, PAD: peripheral arterial disease, CVD: cerebral vascular disease

Table 2: DVT characteristics and treatment

	Statin group (n = 279) % (n)	**Non-statin group (n = 539) % (n)**	***P* value**
Provoked DVT	54 (151)	48 (260)	0.10
DVT location			0.56
Distal	25 (69)	27 (144)	
Proximal	75 (209)	73 (395)	
DVT associated with PE	29 (80)	25 (135)	0.26
Severity of PE			0.046*
Low risk	36 (29)	39 (52)	
Intermediate risk	40 (32)	50 (67)	
High risk	24 (19)	11 (15)	
Anticoagulation			0.23
None	24 (67)	20 (108)	
Warfarin	50 (139)	47 (254)	
LMWH	15 (41)	18 (97)	
DOAC	11 (32)	15 (80)	
Duration of anticoagulation			0.32
< 3 months	22 (41)	23 (87)	
3-6 months	22 (42)	28 (106)	
6-12 months	33 (63)	27 (102)	
> 12 months	23 (44)	23 (86)	
Placement of IVC filter	30 (84)	27 (143)	0.28
Catheter-directed thrombolysis of DVT	2 (6)	1 (8)	0.57
Catheter-directed thrombolysis of PE	1 (3)	2 (9)	0.76
Systemic administration of thrombolytic agent	2 (6)	1 (8)	0.57

*Statistically significant P < .05; LMWH: low molecular weight heparin, DOAC: direct-acting oral anticoagulant, IVC: inferior vena cava, DVT: deep vein thrombosis, PE: pulmonary embolism

Table 3: Long-term outcomes

	Statin group (n = 279) % (n)	**Non-statin group (n = 539) % (n)**	***P* value**
Days to last follow-up Mean ± SD Median (IQR)	741 ± 569 891 (91 – 1283)	710 ± 565 714 (67 – 1250)	0.46 0.39
Surviving patients at last follow up	59 (166)	63 (340)	
New or recurrent DVT	15 (25)	17 (59)	0.52
New or recurrent PE	2 (3)	4 (12)	0.41
Recurrent VTE	16 (27)	19 (65)	0.43
Mortality	41 (113)	37 (199)	0.32
Patients with repeat US > 1 month	39 (110)	45 (242)	0.13
Days to repeat ultrasound ± SD	496 ± 408	530 ± 409	0.46
Thrombus characteristics Resolution / Improvement Stable / Progression	 85 (93) 15 (17)	 77 (187) 23 (55)	0.12

DVT: deep vein thrombosis, PE: pulmonary embolism, VTE: venous thromboembolism,

SD: Standard deviation

Table 4: Multivariable analysis

Variable	Thrombus Resolution or Improvement	Recurrent VTE	Mortality
Statin therapy	3.23 [1.32-7.87]*	1.12 [0.55-2.29]	0.79 [0.49-1.27]
Age	0.97 [0.95-0.99]*	1 [0.98-1.01]	1.04 [1.03-1.06]*
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]*
Warfarin vs No anticoagulation	1.71 [0.64-4.58]	1.52 [0.63-3.67]	0.19 [0.12-0.3]*
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]*
Antiplatelet therapy	2.25 [1.05-4.81]*	0.83 [0.46-1.49]	0.57 [0.37-0.87]*
CAD	0.9 [0.33-2.45]	0.65 [0.26-1.61]	3.12 [1.80-5.41]*
History of cancer	0.84 [0.42-1.67]	0.58 [0.32-1.08]	4.26 [2.91-6.25]*

*Statistically significant P < .05; DVT: deep vein thrombosis, PE: pulmonary embolism, LMWH: Low molecular weight heparin, CAD: coronary artery disease, DOAC: direct-acting oral anticoagulant; Odds Ratio [95% Confidence Interval]

Supplement Table 1: Patient characteristics of those who received repeat ultrasound after one month from DVT diagnosis

	Statin group (n = 110) % (n)	**Non-statin group (n = 242) % (n)**	***P* value**
Age (years ± SD)	69 ± 13	58 ± 17	<0.001*
Female	50 (55)	54 (131)	0.47
Hypertension	75 (82)	49 (118)	<0.001*
Diabetes	45 (50)	13 (32)	<0.001*
Hyperlipidemia	75 (82)	11 (27)	<0.001*
CHF	17 (19)	8 (20)	0.013*
CAD	26 (29)	7 (18)	<0.001*
PAD	9 (10)	2 (5)	0.007*
CVD	23 (25)	5 (11)	<0.001*
Hypercoagulable disorder	4 (4)	8 (19)	0.14
History of prior DVT	22 (24)	22 (53)	0.99
History of prior PE	8 (9)	11 (26)	0.46
History of cancer	29 (32)	36 (87)	0.21
History of smoking	51 (56)	54 (130)	0.62
Antiplatelet therapy	48 (53)	21 (50)	<0.001*
Caprini score ± SD	6.3 ± 3.1	6.0 ± 2.8	0.36

*Statistically significant P < .05; SD: standard deviation, DVT: deep vein thrombosis, PE: pulmonary embolism, CHF: congestive heart failure, CAD: coronary artery disease, PAD: peripheral arterial disease, CVD: cerebral vascular disease

Supplement Table 2: DVT characteristics and treatment of patients who received repeat ultrasound after one month from DVT incident

	Statin group (n = 110) % (n)	**Non-statin group (n = 242) % (n)**	***P* value**
Provoked DVT	51 (56)	49 (118)	0.71
DVT location			0.17
Distal	23 (25)	30 (72)	
Proximal	77 (85)	70 (170)	
DVT associated with PE	22 (24)	22 (54)	0.92
Severity of PE			0.33
Low risk	46 (11)	44 (24)	
Intermediate risk	29 (7)	43 (23)	
High risk	25 (6)	13 (7)	
Anticoagulation			0.48
None	11 (12)	10 (24)	
Warfarin	60 (66)	52 (127)	
LMWH	13 (14)	17 (42)	
DOAC	16 (18)	20 (49)	
Duration of anticoagulation			0.69
< 3 months	15 (15)	14 (30)	
3-6 months	22 (22)	28 (62)	
6-12 months	33 (32)	27 (58)	
> 12 months	24 (24)	24 (53)	
Not available	5 (5)	7 (15)	
Placement of IVC filter	32 (35)	29 (70)	0.58
Catheter-directed thrombolysis of DVT	5 (5)	2 (6)	0.33
Catheter-directed thrombolysis of PE	0 (0)	3 (7)	0.1
Systemic administration of thrombolytic agent	2 (2)	2 (4)	1

*Statistically significant P < .05; LMWH: low molecular weight heparin, DOAC: direct-acting oral anticoagulant, IVC: inferior vena cava, DVT: deep vein thrombosis, PE: pulmonary embolism

Supplement Table 3: Long-term outcomes of patients who received repeat ultrasound after one month from DVT incident

	Statin group (n = 110) % (n)	**Non-statin group (n = 242) % (n)**	***P* value**
Days to last follow-up Mean ± SD Median (IQR)	 1042 ± 433 1235 (723–1347)	 1029 ± 432 1200 (697–1337)	0.78 0.51
Surviving patients at last follow up	80 (88)	80 (194)	
New or recurrent DVT	28 (31)	32 (77)	0.49
New or recurrent PE	2 (2)	5 (13)	0.16
Recurrent VTE	29 (32)	33 (81)	0.41
Mortality	20 (22)	20 (48)	0.97

DVT: deep vein thrombosis, PE: pulmonary embolism, VTE: venous thromboembolism, SD: Standard deviation

Supplement Table 4: Patient characteristics of those who received repeat ultrasound after one month from DVT diagnosis versus those who did not

	Repeat US after one month (n = 352) % (n)	**No repeat US after one month (n = 466) % (n)**	***P* value**
Age (years ± SD)	61 ± 16	69 ± 16	<0.001*
Female	53 (186)	50 (232)	0.39
Hypertension	57 (200)	64 (297)	0.04*
Diabetes	23 (82)	25 (115)	0.63
Hyperlipidemia	31 (109)	37 (172)	0.07
CHF	11 (39)	14 (64)	0.25
CAD	13 (47)	22 (102)	0.002*
PAD	4 (15)	5 (21)	0.87
CVD	10 (36)	13 (59)	0.28
Hypercoagulable disorder	7 (23)	5 (21)	0.2
History of prior DVT	22 (77)	16 (73)	0.02
History of prior PE	10 (35)	10 (46)	0.97
History of cancer	34 (119)	49 (229)	<0.001*
History of smoking	53 (186)	58 (271)	0.13
Antiplatelet therapy	29 (103)	34 (158)	0.16
Caprini score ± SD	6.1 ± 2.9	6.7 ± 2.9	0.004*

*Statistically significant P < .05; SD: standard deviation, DVT: deep vein thrombosis, PE: pulmonary embolism, CHF: congestive heart failure, CAD: coronary artery disease, PAD: peripheral arterial disease, CVD: cerebral vascular disease

Supplement Table 5: DVT characteristics and treatment of patients who received repeat ultrasound after one month from DVT incident

	Repeat US after one month (n = 352) % (n)	**No repeat US after one month (n = 466) % (n)**	***P* value**
Provoked DVT	49 (174)	51 (237)	0.66
DVT location			0.4
Distal	28 (97)	25 (116)	
Proximal	72 (255)	75 (349)	
DVT associated with PE	22 (78)	29 (137)	0.02*
Severity of PE			0.2
Low risk	45 (35)	34 (46)	
Intermediate risk	38 (30)	51 (69)	
High risk	17 (13)	15 (21)	
Anticoagulation			<0.001*
None	10 (36)	30 (139)	
Warfarin	55 (193)	43 (200)	
LMWH	16 (56)	18 (82)	
DOAC	19 (67)	10 (45)	
Placement of IVC filter	30 (105)	26 (122)	0.25
Catheter-directed thrombolysis of DVT	3 (11)	1 (3)	0.007*
Catheter-directed thrombolysis of PE	2 (7)	1 (5)	0.28
Systemic administration of thrombolytic agent	2 (6)	2 (8)	0.99

*Statistically significant P < .05; LMWH: low molecular weight heparin, DOAC: direct-acting oral anticoagulant, IVC: inferior vena cava, DVT: deep vein thrombosis, PE: pulmonary embolism

Supplement Table 6: Long-term outcomes of patients who received repeat ultrasound after one month from DVT incident versus those who did not

	Repeat US after one month (n = 352) % (n)	**No repeat US after one month (n = 466) % (n)**	***P* value**
Days to last follow-up ± SD	1033 ± 432	485 ± 541	<0.001*
New or recurrent DVT	31 (108)	2 (10)	<0.001*
New or recurrent PE	4 (15)	2 (9)	0.05
Recurrent VTE	32 (113)	4 (17)	<0.001*
Mortality	20 (70)	52 (242)	<0.001*

DVT: deep vein thrombosis, PE: pulmonary embolism, VTE: venous thromboembolism, SD: Standard deviation

Supplement Table 7: Thrombus resolution or improvement by time to repeat ultrasound

Time to repeat US	Statin group (n = 110)		Non-statin group (n = 242)		Total cases (n = 352)	*P* value
	Resolved / Improved (n = 93) % (n)	Stable / Progression (n = 17) % (n)	Resolved / Improved (n = 187) % (n)	Stable / Progression (n = 55) % (n)	% of total (n)	
< 1 year	59 (10)	41 (7)	65 (20)	35 (11)	13 (48)	0.69
1 – 2 years	91 (10)	9 (1)	58 (18)	42 (13)	12 (42)	0.07
2 – 3 years	85 (11)	15 (2)	83 (25)	17 (5)	12 (42)	1.00
3 – 4 years	87 (48)	13 (7)	83 (104)	18 (22)	51 (181)	0.51
> 4 years	100 (14)	0 (0)	83 (20)	17 (4)	11 (38)	0.28