A Pilot Randomized Study of Atorvastatin As Adjunct Therapy in Patients with Acute Venous Thromboembolism

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Abstract

Background: Venous thromboembolism (VTE) is a considerable public health threat. Improving the management of VTE may achieve better long-term outcomes. In this single-center pilot study, we sought to investigate the effects of statins in addition to anticoagulation in patients with acute VTE.

Methods: We enrolled patients over the age of 18 presenting with an acute proximal lower extremity deep vein thrombosis with or without pulmonary embolism. Patients were randomized to anticoagulation alone (with either warfarin or rivaroxaban) or anticoagulation plus atorvastatin 40 mg daily and followed for 9 months. The primary objective was to determine if adjunct atorvastatin reduced thrombin generation, estimated by endogenous thrombin potential and/or peak thrombin concentration. Secondary endpoints included recurrent VTE, arterial thrombosis, bleeding events, and more.

Results: A total of 21 patients (11 randomized to anticoagulation only and 10 to anticoagulation plus atorvastatin) were enrolled over 3.5 years. The addition of atorvastatin significantly reduced the mean low-density lipoproteins at 3 months, but did not reduce either endogenous thrombin potential, peak thrombin, D-dimer, or high sensitivity-C reactive protein. Given the low recruitment rate, continuation of the study was deemed futile and the study was terminated early. Barriers to enrollment and completion of study included the many ineligible patients due to the exclusion criteria (e.g. pre-existing statin use, active malignancy, etc) and high rate of lost follow-up.

Conclusions: The pilot study did not enroll sufficient number of patients, but was able to inform obstacles for future similar studies investigating the effects of statins in the management of patients with VTE.

Trial registration: The study was registered with ClinicalTrials.gov (NCT02331095), January 6, 2015. https://clinicaltrials.gov/ct2/show/NCT02331095

Introduction

Venous thromboembolism (VTE) has an estimated incidence of 1–2 per 1000 in the general population, and increases to over 1% in the elderly (1). It is the third most common acute cardiovascular disease (after myocardial infarction and stroke) (2). According to the data from the Nationwide Inpatient Sample Database from the Healthcare Cost and Utilization Project, approximately 30,044 patients were hospitalized in the United States with a primary diagnosis of VTE in 2011, corresponding to over $11 billion dollars of healthcare cost (3). The one-year mortality risk could be as high as 20% after a pulmonary embolism (PE), and one third of survivors could suffer from long-term morbidity (4).

Anticoagulation is the standard of care for acute VTE. However, even with a course of standard anticoagulation, 30% of patients have VTE recurrence within 5–10 years after an unprovoked VTE (5), and 25–50% of patients could develop post-thrombotic syndrome (PTS), causing long-term morbidity (6, 7). In addition, long-term anticoagulation is associated with an increased risk of bleeding (8). Therefore, ongoing efforts are needed to optimize the management of VTE and improve outcomes.

Statins are effective in the prevention of arterial thrombosis (9). Arterial and venous thrombosis have been shown to share common pathophysiological mechanisms (10). Thus, effective therapies for arterial thrombosis may provide benefits in VTE. Several observational studies and the JUPITER trial, a large, randomized, placebo-controlled trial, demonstrated that statins significantly reduce the risk of first VTE by 40–50% (11–15). Additionally, as few as 3 days of atorvastatin has been shown to increase fibrin clot permeability and susceptibility to fibrinolysis (16). A study in patients with atrial fibrillation on warfarin showed a 40% reduction in endogenous thrombin potential (ETP) (the area under the thrombin generation curve) with only three months of intensive cholesterol-lowering treatment including statins (17). Similar effects could be seen in patients with acute VTE. In addition, previous studies evaluating the effects of statins on the reduction of D-dimer or inflammatory cytokines revealed promising results but were not focused on patients with acute VTE (18, 19). Unlike anticoagulation, statins are not associated with risks of bleeding. As a result, we hypothesized that statins could be a feasible adjunct therapy for patients with an acute VTE to inhibit thrombin generation and reduce inflammation, which may translate into pertinent clinical outcomes including reduction of recurrent VTE and/or PTS.

We therefore designed this pilot study to evaluate the effects of atorvastatin on thrombin generation, lipidomic profiles, and clinical outcomes in patients with an acute VTE receiving anticoagulation. We randomized patients with acute proximal lower extremity deep vein thrombosis (DVT) with or without PE to anticoagulation only vs. anticoagulation plus atorvastatin 40 mg daily. The study duration is 9 months. Our primary objective is to determine if adjunct atorvastatin reduces thrombin generation, estimated by ETP and/or peak thrombin concentration.

Methods

Study procedures

In this prospective pilot study, we enrolled patients presenting to a major tertiary care academic medical center (The Ohio State University Wexner Medical Center) in the Midwestern United States from January 2015 to August 2018 and followed all patients for a pre-defined 9-month study period.

Patients were eligible if they were ≥ 18 years old presenting with an acute proximal lower extremity DVT (thrombus involving popliteal, femoral, iliac veins or inferior vena cava) with or without PE within the preceding 3 weeks and treated with standard-of-care anticoagulation with either warfarin or rivaroxaban (20). The protocol initially only allowed patients on warfarin, then was amended in September 2015 to include patients on either warfarin or rivaroxaban. The diagnosis of VTE was confirmed by objective imaging studies. Patients were excluded if they received thrombolytic therapy, were administered any statins within 6 weeks of enrollment, had known allergy or intolerance to statins, baseline liver enzymes over two times of the upper limit of normal, were pregnant or breast feeding, or had a malignancy diagnosed within the preceding two years (except squamous or basal cell of the skin treated with local resection and carcinoma *in situ* of the prostate or cervix). The study was approved by the institutional review board of The Ohio State University and was registered at ClinicalTrials.gov (NCT02331095).

Enrolled patients were randomized 1:1 to anticoagulation alone or anticoagulation plus atorvastatin 40 mg daily. The study biostatistician implemented the random allocation sequence in REDCap and the sequence was concealed to the research staff and clinician. Patients were enrolled within 3 weeks of the acute VTE diagnosis. Fasting blood samples were drawn on enrollment and at 3 and 9 months. Clinical outcomes were monitored throughout the study and during the three study visits, including recurrent venous or arterial thrombosis, major bleeding events, and PTS symptoms evaluated by the Villalta score (21). Consistent with previous studies, recurrent PE was defined as new filling defect(s) seen on CT angiogram or a new high-probability ventilation-perfusion lung scan (22, 23). Recurrent DVT was defined as new uncompressible segments seen on vascular Doppler ultrasonography in a previously uninvolved limb, clearly extending from the prior thrombosis, or a new venous segment in a previously involved limb. Arterial thromboembolism was defined as a new myocardial infarction (based on typical electrocardiographic findings and/or elevation of cardiac enzymes) or cerebral vascular accident (based on clinical syndrome of development of focal or global loss of brain function thought to be vascular in origin, confirmed by appropriate standard imaging studies). Major bleeding events were defined by the International Society on Thrombosis and Haemostasis (ISTH) criteria, with overt bleeding in critical organs (e.g. central nervous system, retroperitoneum), a > 2 gram/dL drop in hemoglobin from baseline, or requiring at least two units of packed red blood cell transfusion meeting the criteria for major bleeding (24). Clinically relevant, non-major bleeding (CRNMB) events were defined as any other bleeding events reported by patients but not otherwise meeting the above listed criteria for major bleeding.

The primary objective was to determine if adjunct statin therapy reduces ETP and/or peak thrombin concentration at 3 months, parameters derived from thrombin generation assays (TGA), which are known surrogate markers of recurrent VTE (25). Secondary endpoints included recurrent VTE, arterial thrombosis, major bleeding and CRNMB events, PTS, residual venous obstruction, as assessed by Doppler ultrasonography at 3 months, and changes in other pre-specified inflammatory and lipidomic biomarkers (see below) at 3 and 9 months.

Laboratory Methods

Thrombin Generation Assay (TGA)

Blood samples were drawn in vacutainer tubes containing 3.2% sodium citrate and processed within an hour. The samples were centrifuged at 2500 g for 15 minutes (min). Plasma was transferred into plastic tubes, and re-centrifuged at 2500 g for 15 min (26, 27). The resulting Platelet Poor Plasma was aliquoted to 0.2 mL increments, snap frozen and stored at -80 °C until tested in batch runs.

TGA assays were performed in duplicate on PPP using the Technothrombin TGA Kit (Technoclone, Vienna, Austria) and TGA RC Low Reagent, according to manufacturer's instructions. Fluorescence was read on a Spectramax M2 Fluorescent Plate Reader (Molecular Devices, Sunnyvale, CA). Relative fluorescence units (RFUs) were converted to thrombin (nanomolar) generation curves using Technoclone Evaluation Software, which also calculates characteristic parameters, including peak thrombin concentration and ETP.

Lipidomic assessment

Blood samples were drawn in polyester gel separators to allow separation of serum. Lipidomic profiles were obtained on blood samples using a Lipidyzer (SCIEX, Framingham, MA, USA) triple quadrupole mass spectrometry platform which was enabled through ion mobility hardware. This assay covers 13 different lipid classes and uses 54 stable isotope internal standards to provide quantitative results for as many as 1,100 lipid species. A separate LCMS panel will be utilized to determine eicosanoid profiles in blood.

Statistical analysis

In the original design, at least 66 evaluable patients were planned to be randomized (1:1 allocation, 33 evaluable patients in each arm) into “anticoagulation only” versus “anticoagulation plus atorvastatin” arms. The primary endpoint is to determine the differences in ETP and/or thrombin peak concentration at 3 months between the anticoagulation only arm and the anticoagulation plus atorvastatin arm. Based on published data (17, 28), we anticipated an 80% power to detect an effect size of 0.7 standard deviations in the reduction of thrombin peak or thrombin generation between the two arms with two-side alpha of 0.05 using a two-sample t test. An overall alpha of 0.1 for this pilot study was split into 0.05 for each endpoint (thrombin peak and thrombin generation) using Bonferroni method. Considering possible drop-outs, our target enrollment will be 80 patients, with 40 on each arm.

For blood collected from enrolled patients at each visit, ETP and thrombin peak concentration at 3 months were tested for normality using Kolmogorov-Smirnov test and they were not normally distributed. Therefore, Wilcoxon rank-sum test was used to test ETP and thrombin peak concentration between the two arms. ETP and thrombin peak concentration at other time points were also summarized and compared. Descriptive statistics was used for demographics, clinical outcomes, laboratory results, and adverse events for each arm. The secondary categorical endpoints were compared between the two arms using chi- square test or Fisher’s exact test, whichever is appropriate. The secondary continuous endpoints were compared between the two arms using two sample t-test or Wilcoxon rank sum test if not normally distributed. For the lipidomic profiles, the changes in each lipid class in both arms were summarized as medians and ranges. The percentage change were not normally distributed in some lipid class (using Kolmogorov-Smirnov test). Therefore, Wilcoxon rank-sum test was used to test the difference and percentage change between the two arms. *P*-values were not adjusted for multiple comparisons. *P*-values < 0.05 were considered statistically significant. All analyses were conducted in SAS version 9.4 (SAS Institute, Cary, North Carolina).

Results

From February 2015 to August 2018, more than 500 patients were screened, but only 21 patients were enrolled. The most common reasons for screen failures included active cancer (26.6%), contemporaneous statin treatment (20%), and chronic DVT (16.3%). Given the low recruitment rate and lack of funding support, continuing the study was futile and the trial was thus prematurely ended.

Ten (47.6%) of the enrolled patients were randomized to anticoagulation plus atorvastatin arm and 11 (52.4%) to the anticoagulation only arm. The baseline characteristics of the patients are summarized in Table 1. The median age was 55 years (range: 22–72), 48% (10 of 21) were female, and 81% were Caucasians. All patients had proximal lower extremity DVT, while 4 (19%) had concurrent PE. All 21 patients completed 3 month follow-up and 16 (76%) completed the 9 month visit. Five patients were lost to follow-up at 9 months and two additional patients declined the 9-month blood draw, but their clinical assessments were completed. Although patients were allowed to be enrolled within the 3 week window after an acute VTE, the majority of patients (17/21, 81%) were enrolled within the second week (day 8–14) after VTE. Eleven patients (52%) were treated with warfarin, the remainder with rivaroxaban. Duration of anticoagulation was at the discretion of the treating physician, 5 of 16 patients (31%) remained on anticoagulation at the 9-month visit. The median duration of anticoagulation for the entire cohort was 6.45 (range 3.3–9.9) months. No patient had recurrent VTE or major bleeding events during the 9-month study period.

Table 1
Baseline patient characteristics

	Anticoagulation + atorvastatin (N = 10)	**Anticoagulation only (N = 11)**	**Overall (N = 21)**
Age (years) (median, range)	57.5 (48–72)	54 (22–63)	55 (22–72)
Female sex, number (%)	7 (70%)	3 (27%)	10 (48%)
Race/ethnic group, number (%) Caucasians African Americans	7 (70%) 3 (30%)	10 (90%) 1 (10%)	17 (81%) 4 (19%)
PE (in addition to DVT)	2 (20%)	2 (18%)	4 (19%)
Provoked, N (%)	6 (60%)	8 (73%)	14 (67%)
Hemoglobin (g/dL) (median, range)	12.1 (9.4–15.5)	13.7 (10.3–16)	13.4 (9.4–16)
Platelet count (K/uL) (median, range)	301 (165–608)	276 (194–664)	290 (165–664)
Creatinine (mg/dL)	0.74 (0.4–0.91)	0.82 (0.52–1.34)	0.77 (0.4–1.34)

DVT: deep vein thrombosis; PE: pulmonary embolism

The mean LDL at 3 months was significantly reduced in patients on the anticoagulation plus atorvastatin arm (76.1 ± 26.02) compared to anticoagulation only arm (115.9 ± 30.63) ($p = 0.008$), while other markers including triglycerides, D-dimer, and high sensitivity C-reactive protein (hs-CRP) were not significantly different (Table 2). Only three patients in the atorvastatin arm remained on atorvastatin at the month 9

study visit. Laboratory data from the 9-month visit thus had limited utility and the analysis was concentrated on data from 3-month visit. Eight patients (80%) in each arm had residual chronic DVT (to any degree) noted on ultrasound at 3 months. The median and range of Villalta scores were summarized in Table 2. The median Villalta score was numerically higher in the lower extremity affected by DVT compared to the unaffected contralateral extremity, and decreased with time in both treatment arms, but not statistically significant between study arms.

Table 2
Selected lipid panel, inflammatory markers, and Villalta score by study arms at different time points

	Anticoagulation + Atorvastatin (N = 10)	Anticoagulation only (N = 11)
LDL (mg/dL), mean (SD)		
Enrollment	116.9 (43.07)	123.8 (22.73)
3 months	76.1 (26.02)*	115.9 (30.63)*
TG (mg/dL), mean (SD)		
Enrollment	157.9 (83.06)	130.5 (47.69)
3 months	135.3 (83.79)	127.4 (60.45)
D-dimer (mcg/mL FEU), median (range)[#]		
Enrollment	2.2 (0.6–5.42)	2.12 (0.88–13.76)
3 months	0.59 (< 0.27–1.23)	0.36 (< 0.27–0.71)
hs-CRP (mg/L), median (range)^		
Enrollment	7.0 (2-42.4)	5.5 (2-51.4)
3 months	5.1 (0.9–21.1)	3.9 (0.6–15.7)
Villalta score (median)[‡]		
Affected leg		
Enrollment	4.5 (2–21)	7 (0–18)
3 months	3.5 (0–15)	6 (1–13)
Unaffected leg		
Enrollment	1.5 (0–6)	1 (0–13)

LDL: low-density lipoprotein; SD: standard deviation; TG: triglyceride; hs-CRP: high sensitivity C-reactive protein

*The mean LDL at 3 months is significantly lower in the anticoagulation + atorvastatin arm compared to the anticoagulation only arm, p = 0.008. No other parameters are significantly different between the two arms.

[#]D-dimer reference range: <0.50 mcg/mL FEU

^hs-CRP reference range: <3.0 mg/L

[‡]None of the p-values were significant between the two study arms

	Anticoagulation + Atorvastatin (N = 10)	Anticoagulation only (N = 11)
3 months	2.5 (0–9)	1 (0–9)
LDL: low-density lipoprotein; SD: standard deviation; TG: triglyceride; hs-CRP: high sensitivity C-reactive protein		
*The mean LDL at 3 months is significantly lower in the anticoagulation + atorvastatin arm compared to the anticoagulation only arm, p = 0.008. No other parameters are significantly different between the two arms.		
#D-dimer reference range: <0.50 mcg/mL FEU		
^hs-CRP reference range: <3.0 mg/L		
‡None of the p-values were significant between the two study arms		

Table 3 summarizes the data of ETP and peak thrombin. There were no significant differences between the two arms for either variable at both enrollment and 3 months (Table 3). For lipidomic profiles, we obtained the difference of lipid concentration in each lipid class between 3 months (visit 2, v2) and baseline (visit 1, v1) and calculated the percentage change ([v2-v1]/v2). Figure 1 showed the percentage change of median concentration in each lipid class in two study arms. Patients receiving atorvastatin in addition to anticoagulation had reduced CE (cholesterol ester), CER (ceramides), PC (phosphatidylcholine), and SM (sphingomyelin). LCER (lactosyl ceramides) was increased in the atorvastatin arm at 3 months. Other classes of lipids were not significantly different between the study arms. The *p*-values between arms were not adjusted for multiple comparisons.

Table 3
Primary outcome [peak thrombin and endogenous thrombin potential] by study arms at different time points

Time points	Outcomes	Median (range)		p-value
		Anticoagulation + atorvastatin (N = 10)	Anticoagulation only (N = 11)	
Enrollment	Peak thrombin	67.32 (0–122.89)	37.45 (0–157.28)	0.273
	ETP	1440.27 (0–3190.13)	1155.35 (0–1852.64)	0.245
3 months	Peak thrombin	47.87 (11.02–253.15)	54.25 (0 - 149.17)	0.862
	ETP	1142.80 (60.45–3766.25)	1274.82 (0–2562.06)	0.603
ETP: endogenous thrombin potential				

Discussion

In this pilot study of patients with acute proximal DVT and/or PE, the addition of atorvastatin (40 mg daily) to standard anticoagulation therapy did not significantly reduce either ETP or peak thrombin at 3 months. However, the study was underpowered due to early termination for futility. Therefore, we could not fully evaluate the potential effects of statins on thrombin generation in this study. The mean LDL was significantly reduced at 3 months in patients receiving atorvastatin. Other biomarkers such as D-dimer and hs-CRP were not significantly reduced with atorvastatin.

Our study was limited by the small sample size. Although a total of 80 patients were originally planned, over the course of 3.5 years, only 21 patients consented to enrollment, despite screening over 500 potentially eligible patients. We limited the type of anticoagulants allowed due to the effort to minimize the impact of different anticoagulants on thrombin generation assays. We initially included only patients on warfarin. However, direct oral anticoagulants quickly became the anticoagulant of choice for VTE afterwards, which limited enrollment. The protocol was amended in September 2015 to include patients on both warfarin and rivaroxaban. The research staff routinely screened Doppler ultrasound reports on a daily basis to identify potential study participants. We also worked with Emergency Department to encourage referrals of patients with newly diagnosed VTE. Despite these efforts, recruitment remained slow, and eventually continuation of the study was deemed futile and the study was terminated early. The most common reasons for ineligibility included active cancer, current statin treatment, and chronic DVT. The most common reasons for non-consent in eligible patients included refusal of additional medication and discomfort with randomization and clinical research protocols. This highlights the need for alternative eligibility criteria and/or study design.

In this pilot study, we chose to use surrogate endpoints such as thrombin generation based on previous report of a positive association between thrombin generation and recurrent VTE (25). We acknowledged that surrogate endpoints had limitations and may or may not correlate with clinical outcomes. Ultimately, clinical outcomes including recurrent VTE and bleeding events are the gold standard, which would require a much larger sample size. In addition, long-term compliance with medications was problematic in our cohort. There was a significant reduction of LDL at 3 months in patients on the atorvastatin plus anticoagulation arm compared to the anticoagulation only arm, indirectly indicated compliance to atorvastatin at least at 3 months. However, only three patients on atorvastatin self-reported continued adherence to statin therapy at 9 months, and more-than-expected number of patients were lost to follow up or declined study blood draw (N = 7) at 9 months. The low adherence could be partially due to participants' relative young age on minimal medications prior to the VTE event. To ensure adequate compliance monitoring, future studies could consider incorporating the use of smartphone applications or pill bottle caps with a radio frequency identification (RFID) reader.

The START (The STAtins Reduce Thrombophilia) trial published in 2019 randomized 245 patients with a history of VTE (48.6% unprovoked) who have completed a course of anticoagulation to rosuvastatin 20 mg daily or no statin for 4 weeks (29). All patients stopped vitamin K antagonists for one month prior to enrollment. Patients on rosuvastatin had a significantly reduced ETP by 10% and peak thrombin by 5% at 4 weeks (29). Our results are different for a few reasons. First, we used atorvastatin instead of

rosuvastatin, and the potency can vary among different statins (30). We chose atorvastatin because it was widely available as a generic compound (whereas rosuvastatin was a brand-name only compound during the time of study period). Moreover, atorvastatin had previously been shown to reduce thrombin generation in patients with cardiovascular disease or diabetes (28, 31). Second, we started atorvastatin within 3 weeks of the index acute VTE, along with anticoagulation, instead of waiting until after patients had stopped anticoagulation. We chose to add atorvastatin up front to investigate the effects of early addition of statins and their potential long-term benefits. In addition, prior study in patients on warfarin for atrial fibrillation had shown that 3 months of statins could cause a reduction in ETP (17). However, anticoagulation itself can reduce thrombin generation. Our original goal was to determine if early adjunct atorvastatin could also reduce post-anticoagulation thrombin generation at the 9-month visit, assuming that most patients would be prescribed a standard 3- or 6-month anticoagulant regimen for their VTE, as recommended in VTE guidelines (20). Unfortunately, due to the significant loss of follow up at 9 months, the data on thrombin generation could only be analyzed on 3-month samples, and all patients remained on anticoagulation at that time. Therefore, we suspect that the effects of statin on thrombin generation were obscured by the presence of anticoagulation. Nonetheless, atorvastatin did not appear to enhance the inhibition of thrombin generation in the presence of anticoagulation, suggesting that adjuvant atorvastatin would not increase the risk of bleeding associated with anticoagulation. This was supported by the lack of major bleeding in our cohort, although we acknowledge that the number of patients was small and the observation was preliminary. Larger trials will be needed to determine the safety and efficacy of adjunct statin therapy.

Our study included exploratory lipidomic profile analyses. Lipidomics is a mean of global mapping of lipid metabolites which may provide further detailed information of the effects of atorvastatin in patients with VTE, which has not been published previously. Previous studies have evaluated detailed lipidomic profiles as effects of simvastatin or rosuvastain in patients with hyperlipidemia (32, 33). We found in our study that VTE patients receiving atorvastatin in addition to anticoagulation had reduced CE (cholesterol ester), CER (ceramides), PC (phosphatidylcholine) and SM (sphingomyelin), as well as increased LCER (lactosyl ceramide) at 3 months. Other lipid classes did not show significant changes with or without 3 months of statins. The statistical analysis was not adjusted for multiple comparisons, so this analysis was exploratory in nature, but it could provide insights into mechanisms and be hypothesis generating. While anticoagulation is generally not considered to cause significant alterations on lipid profiles, whether there are interactions between anticoagulation and statin agents on lipid profile warrants further investigation.

Although our study was terminated early for low accrual and funding issues, we believe that it provides insights into strategies needed for future trials of statin therapy in patients with VTE. Our study showed that multiple adjustments in the current study design are needed to improve feasibility. These could include: expansion of eligibility criteria (such as inclusion of patients with different types of VTE, provoked, unprovoked, cancer-associated, etc), relaxation of time frame for enrollment after index VTE, inclusion of all care settings for enrollment including primary care and subspecialty clinics, and utilization of established network for multicenter collaboration. The ongoing SAVER (StAtins for Venous

Event Reduction in patients with venous thromboembolism) pilot trial (NCT02679664) aims to investigate the feasibility of recruitment in this population and the effects of rosuvastatin for prevention of PTS. The upcoming SAVER full trial will further investigate the use of rosuvastatin for secondary prevention of VTE. These important trials will shed lights on the use of statins in patients with VTE.

Conclusions

In this small pilot study, atorvastatin 40 mg daily did not reduce thrombin generation at 3 months when used in combination with standard anticoagulation as treatment for an acute VTE. The study was limited by the small sample size and early termination due to futility. Atorvastatin was associated with reduced LDL at 3 months and may alter selected lipidomic profiles. Future large randomized controlled trials to investigate the role of statins in the reduction of recurrent VTE and/or PTS are forthcoming and results could be practice changing.

List Of Abbreviations

VTE: Venous thromboembolism

PE: Pulmonary embolism

PTS: Post-thrombotic syndrome

ETP: Endogenous thrombin potential

DVT: Deep vein thrombosis

LDL: Low-density lipoprotein

CRNMB: Clinically relevant non-major bleeding

TGA: Thrombin generation assays

Declarations

Ethics approval and consent to participate

The study was approved by the institutional review board of The Ohio State University. All participants provided written informed consent.

Consent for publication

Not applicable

Availability of data and materials

The protocol and datasets generated and/or analyzed are available from the corresponding author on reasonable request.

Competing Interests

BAK is, or has been, a site primary investigator in multiple clinical trials for Bayer Healthcare, CSL Behring, Novo Nordisk A/S, and Bioverativ and has received consultant fees or honoraria from Bayer Healthcare, Novo Nordisk A/S, and CSL Behring.

All other authors declare that there is no conflict of interests.

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Authors' contributions

TW wrote the study protocol, obtained the funding, performed the research, patient recruitment, analyzed data, and wrote the first draft of the manuscript. APW performed the research, data analysis, reviewed, edited, and approved the manuscript. EL performed the research, data analysis, reviewed, edited, and approved the manuscript. LW analyzed the data, reviewed, edited, and approved the manuscript. AB performed the research, reviewed, edited, and approved the manuscript. KR performed the research, data analysis, reviewed, edited, and approved the manuscript. BAK performed the research, data analysis, reviewed, edited, and approved the manuscript. All authors read and approved the final manuscript for submission.

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Figures

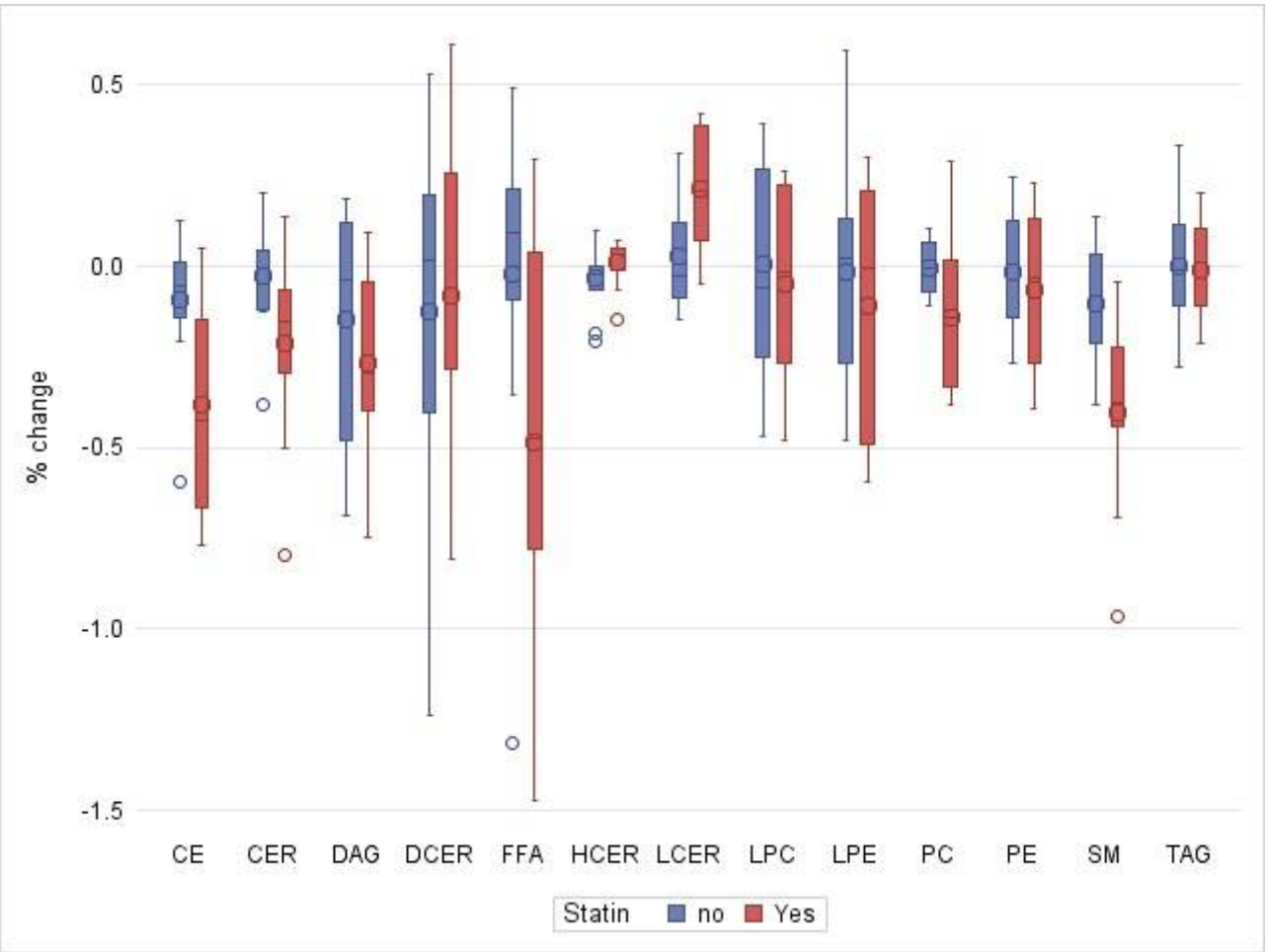

Figure 1

The percentage change of median concentration in the lipidomic profiles by study arms CE: cholesterol ester; CER: ceramides; DAG: diacylglyceride; DCER: dihydroceramides; FFA: free fatty acids; HCER: hexosylceramides; LCER: lactosylceramides; LPC: lysophosphatidylcholine; LPE: lysophosphatidylethanolamine; PC: phosphatidylcholine; PE: phosphatidylethanolamine; SM: sphingomyelin; TAG: triacylglyceride.

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