A pilot study of using statins in patients with acute venous thromboembolism

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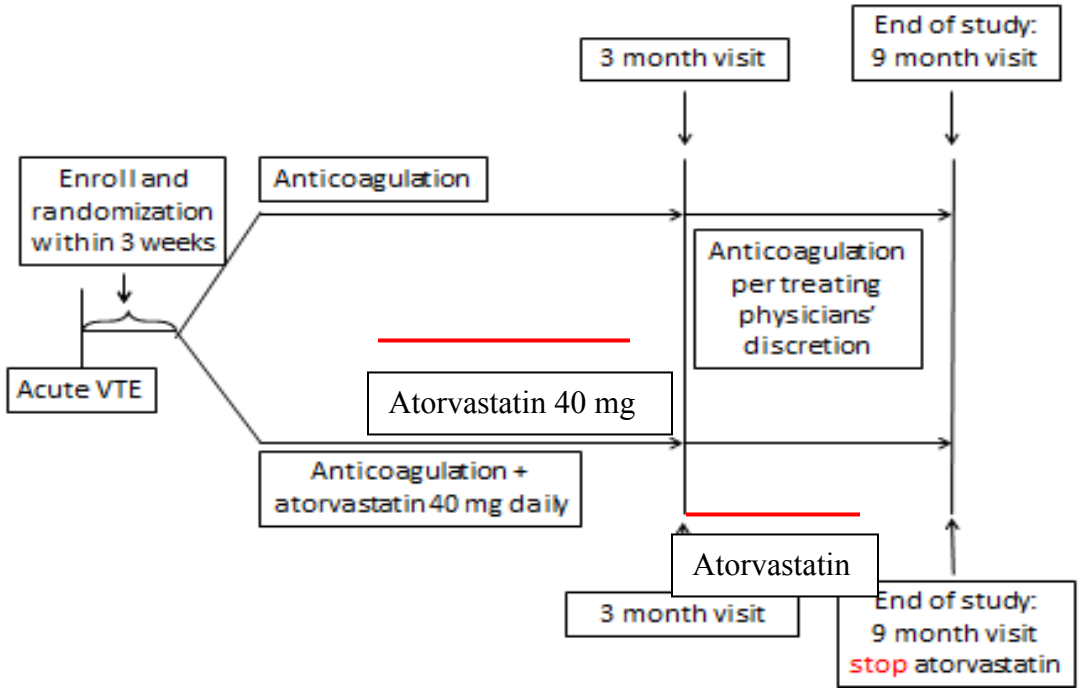
Study drug(s): Atorvastatin

Clinical Trials.gov #: NCT02331095

Schema



1.0 Objectives

This will be a single-center, open-labelled, pilot study. This study has the following objectives:

1.1 Primary Objective

1.1.1 To determine the reduction of thrombin peak concentration and/or endogenous thrombin potential measured by Thrombin Generation Assay (TGA) at 3 months in the "anticoagulation +atorvastatin" arm as compared to the "anticoagulation" arm.

1.2 Secondary Objectives

1.2.1 To determine the composite rate of recurrent VTE and VTE related mortality in patients in the statin arm as compared to no statin arm.

1.2.2 To determine the rate of arterial thrombotic events in patients in the statin arm as compared to no statin arm.

1.2.3 To determine the rate of major, non-major, and all hemorrhages defined by the ISTH (International Society on Thrombosis and Haemostasis) criteria (see section 7.3) in patients in the statin arm as compared to no statin arm.

1.2.4 To evaluate the changes in proposed hemostatic, inflammatory, and lipidomic biomarkers at 3 and 9 months compared to upon enrollment in patients in both arms.

1.2.5 To determine the rate of residual vein obstruction by Doppler ultrasound at 3 months in patients in the statin arm as compared to no statin arm.

1.2.6 To determine the rate of clinical post-thrombotic syndrome (PTS), as objectively evaluated with Villalta scoring system in patients in the statin arm as compared to no statin arm.

2.0 Background

Venous thromboembolism (VTE) refers to the formation of pathological blood clots in extremity veins (deep vein thrombosis, DVT) and/or pulmonary arteries (pulmonary embolism, PE). VTE is common, with an estimated incidence of 1-2 per 1000 in the general population, and increases to over 1% in the elderly.[1] VTE is a considerable public health threat. Approximately 300,000-600,000 patients develop VTE in the United States each year, accounting for 60,000-100,000 deaths. According to the Healthcare Cost and Utilization Project, about 350,000 hospital admissions were due to VTE, costing over three billion dollars in 2011 alone. In addition, approximately one third of patients die within one year of their initial VTE, and one third of survivors suffer from long-term morbidity.

Anticoagulation is the current standard of care for acute VTE. However, even after a course of anticoagulation, 30% patients have VTE recurrence in 10 years after an unprovoked VTE,[2] and 25-50% patients will develop post-thrombotic syndrome (PTS), causing long-term morbidity. [3,4] Therefore, there is significant room for improvement. To accomplish this, it is crucial to have a better understanding of the pathophysiology of VTE and its complications. Although some important biomarkers in VTE were identified, [12-14] the detailed hemostatic, inflammatory, and lipidomic biomarker profiles in patients after an acute VTE and their evolution and interplay in relation to treatments are unclear. A better understanding can help to identify promising targets to develop novel therapy.

The first aim of the study is to investigate important biomarkers in acute VTE as below:

1) *Hemostatic profile:*

In acute VTE, patients' pro-coagulation, anti-coagulation, and fibrinolytic systems are highly activated. The routine clinical coagulation assays such as prothrombin time and activated partial thromboplastin time terminate at initial clot formation, and are inadequate for comprehensive assessment of the coagulation system. In contrast, thrombin generation assays are increasingly used to assess the global hemostatic status. High thrombin generation potential or high thrombin peak concentration was correlated with increased risk of first and recurrent VTE.[15-17] However, the thrombin generation profiles in acute VTE and their changes with anticoagulation have not been solidified. Therefore, thrombin generation will be used as our primary biomarker of interest. Secondly, a product of fibrinolysis, D-dimer, indicates ongoing fibrin formation and degradation. Elevated D-dimer after the completion of anticoagulation has been shown to predict increased risk of recurrent VTE.[18,19] Therefore, we will also follow D- dimer during and after acute VTE. Thirdly, tissue factor (TF) and

tissue factor pathway inhibitor (TFPI) play essential roles in the initiation and modulating of blood coagulation cascade and are of interest in the process of venous thrombosis. We therefore plan to study these biomarkers in our patient population as well.[36]

2) *Inflammatory profiles:*

Inflammation and coagulation are closely interwined.[20] Inflammatory diseases are associated with increased risk of VTE,[21] and thrombosis is associated with release of inflammatory cytokines. [22]However, their changes in relates to anticoagulation and statins are unclear, and therefore selected inflammatory biomarkers including IL-6, IL-8, tumor necrosis factor (TNF)-α, high sensitivity C-reactive protein (hs-CRP) will be evaluated.

3) *Lipidomic profiles:*

Serum phospholipids play crucial roles in inflammation and serve as the substrate for phospholipase A_2 (PLA_2), which subsequently liberates arachidonic acid for cyclooxygenase (COX) and lipoxygenase (LOX) to generate eicosanoids.[23]In addition, these bioactive phospholipids play a major role in inflammation and repair.[24] However, the quantification of these bioactive lipids and the process of their modulation of inflammation during acute VTE are unclear, and this study intends to clarify it. Lipid biomarkers of inflammation that will be analyzed in the study include free fatty acids and eicosanoids.

Statins are effective in the prevention of arterial thrombosis.[25] Recently, arterial and venous thrombosis are shown to share common pathophysiological mechanisms,[26] and effective therapies for arterial thrombosis could provide benefits in VTE. Several observational studies and the JUPITER trial, a large, randomized, placebo-controlled study, demonstrates that statins significantly reduce the risk of first VTE by 40-50%.[7, 27-30] Additionally, as few as 3 days of atorvastatin increase plasma fibrin clot permeability and susceptibility to lysis.[31]These promising results, as well as their safety profiles, make statins an attractive potential addition to the standard anticoagulation for treating acute VTE, in an effort to reduce long-term morbidity.

Our second aim is to determine the actions of statins on the proposed biomarkers in acute VTE because: First, the effects of statins on thrombin generation in patients with acute VTE have not been studied. A study in patients with atrial fibrillation on warfarin showed a 40% reduction in endogenous thrombin potential with only three months of intensive cholesterol-lowering treatment including statins.[8] 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.[32,33] Therefore, this study will generate important information for acute VTE patients.

3.0 Patient Selection

3.1 Inclusion of Women and Minorities

Entry to this study is open to both men and women ages 18 and older, of all racial and ethnic subgroups. This study will be conducted in accordance with the International Conference on Harmonisation and Helsinki Guidelines.

3.2 Inclusion Criteria

3.2.1 At least 18 years old

3.2.2 A diagnosis of proximal DVT (proximal to and including popliteal vein), with or without PE, confirmed by objective imaging studies, such as Doppler ultrasound, venograms (for DVT) and/or computer tomography, angiograms, ventilation-perfusion scan (for PE)

3.2.3 Treated with warfarin or rivaroxaban as anticoagulation (short-term bridging with heparin or lovenox, if needed is allowed)

3.3 Exclusion Criteria

3.3.1 Thrombolysis within 6 weeks prior to enrollment

3.3.2 Patients with statin use within 6 weeks of enrollment

3.3.3 Patients with known allergy or intolerance to statins or statins are contraindicated for any other reasons

3.3.4 Patients with baseline aspartate aminotransferase (AST), alanine aminotransferase (ALT), or total bilirubin ≥2.0 x ULN (upper limit of normal)

3.3.5 Pregnant or breastfeeding females are excluded

3.3.6 Any malignancy diagnosed within the preceding 2 years, except for squamous cell carcinoma or basal cell carcinoma of skin treated with local resection only, or carcinoma *in situ* of the cervix

3.3.7 Incarcerated patients are excluded from the study due to the inherent difficulties in maintaining close follow-up for study purposes in patients who are incarcerated.

3.4 Enrollment/registration of patients

3.4.1 Patients must give written informed consent prior to enrollment on this study. Informed consent may be obtained by the principal investigator, co-investigators, or one of their designees.

4.0 Randomization of Patients

Patients will be randomized at the time of registration/enrollment on this clinical trial via contact with the study nurse/coordinator at the time of the initial registration of the subject. The study nurse/coordinator will conduct the randomization on the REDCap Data Capture system and relay this information to the treating/enrolling physician so that the appropriate medication (atorvastatin) can be started.

5.0 Treatment plan: atorvastatin vs placebo

After randomization, patients on the statin arm will start the assigned study drug (atorvastatin) for a total of 9 months, in addition to the standard of care (anticoagulation). Atorvastatin will be prescribed through patients' pharmacy of choice. It will be taken once a day in a tablet form. Pill count and patient self-report compliance diary will be reviewed at each visit. All the attempts will be made to continue atorvastatin for entire 9 months, however, if a patient needs to stop atorvastatin prior to the intended period for any reasons (for example, side effects), it will be documented, but they are allowed to remain in the study for blood tests and clinical follow up. At the end of the study, the decision of whether patients should remain on atorvastatin or not will be left to the treating physicians.

6.0 Study calendar

	Initial visit	3 month[1]	9 month[1]
Singed informed consent	**x**		
Medical/treatment history	**x**	**x**	**x**
Physical examination	**x**	**x**	**x**
Vital signs	**x**	**x**	**x**
CBC with diff[2]	**x**	**x**	**x**
Chemistry[3], including liver function tests	**x**	**x**	**x**
Fasting lipid profiles	**x**	**x**	**x**
hs-CRP	**x**	**x**	**x**
D-dimer	**x**	**x**	**x**
Urine β-hCG[4]	**x**		
Thrombin generation assay	**x**	**x**	**x**
IL-6, IL-8, TNF-α	**x**	**x**	**x**
Lipidomic profiles[5]	**x**	**x**	**x**
Doppler ultrasound of bilateral lower extremities		**x**	
Prescription of statins[6]	**x**	**x**	

[1]All scheduled visits are allowed a window of +/- 21 days
[2]CBC includes: white blood cells with differential, hemoglobin, red blood cells, and platelets
[3]Chemistry and liver function tests include: sodium, potassium, carbon dioxide, glucose, BUN, creatinine, calcium, total protein, albumin, bilirubin, alkaline phosphatase, AST and ALT
[4]Required only in women of child-bearing potential
[5]Lipidomic profiles includes free fatty acids, lipoprotein-associated phospholipase A2, pro-inflammatory eicosanoids
[6]Prescription of statins only in the statin arm

7.0 Outcome Criteria

7.1 Recurrent venous thromboembolism

7.1.1 Recurrent pulmonary embolism will be diagnosed when:

a) New filling defect(s) is/are seen in CT angiogram of chest or pulmonary angiography
b) A new high probability on ventilation-perfusion lung scan.

7.1.2 Recurrent deep vein thrombosis will be diagnosed when:

a) New filling defect(s) is/are seen in venography or new uncompressible segments seen on vascular Doppler ultrasound in a previously uninvolved limb
b) In the limb with a previous VTE, new filling defect(s) in venography or new uncompressible segments in vascular Doppler ultrasound that is clearly extending from the prior thrombosis or involving a new venous segment

7.2 Arterial thromboembolism

7.2.1 Myocardial infarction:

Myocardial infarction will be diagnosed if at least two of the following criteria are met: a history of typical ischemic pain lasting for at least 20 minutes and unresponsive to sublingual nitrates (if given), new elevation of cardiac enzymes (creatinine kinase or its MB fraction) to more than twice the ULN or troponin value, new EKG changes including new persistent ST/T changes, new bundle branch block or new Q waves in at least two consecutive leads.

7.2.2 Cerebral vascular accidents:

Cerebral vascular accidents (CVA) is a clinical syndrome of rapid development of focal or global loss of brain function, lasting more than 24 hours, thought to be vascular in origin, and/or leading to neurological damages or early death. It is expected that CT or MRI scans will be performed to confirm the diagnosis in most cases.

7.3 Bleeding

7.3.1 Major bleeding will be defined as:

a) Bleeding into critical organs such as central nervous system, retroperitonium
b) Bleeding requiring emergent intervention or surgery for hemostasis
c) Bleeding requiring at least 2 units of packed red blood cell transfusion
d) Bleeding leading to at least 2 points drop in hemoglobin from baseline
e) Bleeding requiring hospital admission for intervention

7.3.2 Non-major bleeding is defined as any other bleeding reported by patients but not otherwise meeting the above listed criteria for major bleeding

8.0 Treatment after Recurrences of VTE

Patients suffering a recurrent VTE on either arm will stop study drugs and but will continue to be followed on the study. The management of recurrent VTE will be left to the discretion of the treating physician.

9.0 Correlative Studies

9.1 Laboratory Studies at Enrollment

9.1.1 The initial laboratory tests will be obtained at the time of enrollment on this study. Blood will be collected after overnight fasting for at least 9 hours. Laboratory tests will include:

- CBC (complete blood count)
- chemistry panel (Na, K, Cl, CO2, Cr, BUN, Ca, and glucose),
- liver function tests (AST, ALT, ALP, total and direct bilirubin)
- D-dimer
- high-sensitivity C-reactive protein (hs-CRP)
- fasting lipid profiles (LDL, HLD, TG, total cholesterol
- β-hCG is required only in women of child-bearing potential

Research labs:

- thrombin generation assay
- IL-6, IL-8, tumor necrosis factor (TNF)-α
- lipidomic profiles including free fatty acids, lipoprotein-associated phospholipase A2, pro-inflammatory eicosanoids
- plasma levels and RNA expression of tissue factor (TF), tissue factor pathway inhibitor (TFPI), and other clotting factors

9.2 Subsequent Follow-up and Correlative Laboratory Studies

9.2.1 All enrolled patients will be seen on enrollment and at month 3 and 9.

9.2.2 The following laboratory studies will be obtained at each follow-up visit:

- CBC (complete blood count), platelet count
- chemistry panel (Na, K, Cl, CO2, Cr, BUN, Ca, and glucose),
- liver function tests (AST, ALT, ALP, total and direct bilirubin)
- d-dimer
- high-sensitivity C-reactive protein (hs-CRP)
- fasting lipid profiles (LDL, HLD, TG, total cholesterol)

Research labs:

- thrombin generation assay
- IL-6, IL-8, tumor necrosis factor (TNF)-α
- lipidomic profiles including free fatty acids, lipoprotein-associated phospholipase A2, pro-inflammatory eicosanoids
- plasma levels and RNA expression of tissue factor (TF), tissue factor pathway inhibitor (TFPI), and other clotting factors

9.2.3 A follow up Doppler ultrasound will be obtained at month 3 as standard of care in all patients to evaluate residual vein thrombosis.

10.0 Outpatient Visits

Patients will be seen in the outpatient thrombosis clinic at least on enrollment, month 3, and month 9 (conclusion of the study), at each time side effects of drugs, symptoms of bleeding and recurrent VTE, post thrombotic syndrome will be assessed. Pill count and drug compliance will be assessed as well. Enrollees will be given $6 dollar food vouchers to be used in the cafeteria for each of the scheduled study visit (enrollment, 3 and 9 months) to compensate their efforts of fasting prior to lab drawn.

11.0 Safety Monitoring During Study

11.1 To ensure the safety of all patients enrolled on this study, careful monitoring and follow-ups for all patients will be important aspects of this study. Patients will be monitored closely with laboratory and clinical evaluations at regular intervals defined in the study protocol.

11.2 At each visit (enrollment, 3 and 9 months), patients will be evaluated by physicians and study personnel for side effects of statins and anticoagulation. The management of side effects from statins will follow the routine practice for patients who are prescribed with statins for other medical problems, and will be left to the discretion of the treating physicians, but the study team and PI will be available for any assistance if questions of the optimal management of adverse events were to arise. Live function tests will be obtained prior to and at each follow-up visit. Creatitine kinase (CK) test will not be collected without symptoms, but will be collected if patients were to develop symptoms of muscle pain or weakness. Patients with new onset of transaminitis or CK above three times of upper limit of normal or significant symptoms will be taken off statins. Their abnormal laboratory tests will be monitored at least every 2 weeks, more frequently if needed, until the abnormalities resolve. Patients will only resume statins if their symptoms resolve, blood tests normalize, and if patients are willing to resume treatment. Recurrent test abnormality or symptoms will require permanent discontinuation of statins.

12.0 Adverse Events/Severe Adverse Events

12.1 *Definition:* Adverse events as defined in the International Council on Harmonisation Guidelines for Good Clinical Practice are described as "an untoward medical occurrence in a patient or clinical investigation administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment."

12.2 A serious adverse event is an adverse event that:

- Is fatal
- Is life threatening (places the subject at immediate risk of death)
- Results in inpatient hospitalization or prolonged existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Includes other significant hazard

12.3 *Grading of Adverse Events* – Events will be graded by using the Common Terminology Criteria for Adverse Events (CTCAE) Criteria version 4.0.

12.4 *Attribution* – the determination and documentation of whether an adverse event is related to a medical procedure.

Attribution Categories:

1. Not Related –Event clearly related to other factors (e.g., clinical state, other therapies; concomitant drugs)
2. Possible Related – Sequence of event is compatible with study drug, device, or procedure, but could have been produced by other factors
3. Probably Related - Sequence of event is compatible with study drug, or procedure and cannot be explained by other factors without much doubt
4. Definitely Related - Sequence of event is compatible with study drug, or procedure and beyond doubt cannot be explained by other factors

12.5 *Reporting of Adverse Events:* Adverse events must be recorded within 7 days of the occurrence using the "Adverse Event" form (see Appendix). The principal investigator will review all adverse event forms every month or more frequently if needed. All serious or unexpected adverse events must be communicated to the principal investigator immediately and will be reported to the IRB within 24 hours of learning of the event's occurrence by phone, email, or SAE for regardless of attribution. Using these mechanisms of rapid reporting, we will be able to rapidly evaluate and minimize the potential risks to patients from the occurrence of these events. Subjects will be instructed to report any adverse event(s) during the study and post-study. The investigator will notify the IRB of any unanticipated death or adverse event occurring after a participant has discontinued or terminated study participation that may reasonably be related to the study.

12.6 *Follow-up of Adverse Events:* Patients experiencing an adverse event will continue to be followed and carefully monitored until the resolution of the adverse event. This applies whether the patient continues on study or is removed from the study for any reason.

12.7 While no formal stopping rules are deemed necessary due to the well-known safety and tolerability of statins, the PI will be informed of any SAE immediately, determine correlation, and report to IRB. The PI is responsible to continuously evaluate the safety for study continuation based on regular review of AE reports.

13.0 Sample Procurement

Both plasma and blood samples will be taken as a part of this protocol. Theses samples will be obtained at the same time that standard clinical samples or procedures are being performed so patients will not be exposed to additional venipunctures or procedures by their participation in this study.

14.0 Sample Storage and Handling

At the time of enrollment and registration with the coordinating institution, arrangements will be made for the research blood samples to be delivered to the laboratory of Dr. Bryce Kerlin, Dr. Mark Hall, and Dr. Kenneth Riedl for processing and analysis. Research blood samples will be labeled with a unique identification number so that the data obtained may be correlated with the patient's clinical course by the investigators at the end of the study, while the laboratory personnel performing the research testing will not be able to identity each individual patient. This will help ensure patient confidentiality, as the investigators will be the only people to know the patient name and medical record number that correspond with the identification number. Samples to be used for future study will be frozen at -80°C and be stored in the benign hematology research office at the James Cancer Hospital, and in the laboratory of Dr. Kerlin, depending on the designated research testing to be done: thrombin generation assays will be performed in Dr. Kerlin's laboratory at Nationwide Children's. Inflammatory markers will be done in Dr. Mark Hall's laboratory at Nationwide Children's and lipidomic profiles will be performed at Dr. Kenneth Riedl's laboratory at Ohio State. At the end of the study, at least one aliquot of each plasma and RNA samples will be delivered to Dr. Alan Mast's laboratory at the Blood Center of Wisconsin for testing including TF, TFPI, and other clotting factors. Samples will be sent on dry ice via commercial carriers overnight.

15.0 Risks Associated with Testing of Patient Samples

A breach of confidentiality is the most serious risk which patients may be exposed to regarding to research testing of biologic samples. Confidentiality will be maintained by labeling the patient samples with only an identification number and not their name or medical record number. By using this approach, patient samples may be tied to clinical information by the investigators but will preserve the confidentiality of patients. Only the principal investigator, co-investigator, and the study nurse/coordinator will have access to both the study number and the corresponding patient identification information. Clinical

information or laboratory data used for publication will not identify patients in any way that could potentially breach patient confidentiality. The samples sent to BloodCenter of Wisconsin will be coded and all PHI will be removed so the laboratory personnel there will have no access to the PHI. The samples need to be coded and not de-identified, so the principal and co-investigators can correlate clinical with research laboratory findings. Even though more research laboratory tests are planned in this protocol amendment, it will be accomplished within the same amount of blood that was originally planned to be drawn and therefore expose no additional risks to subsequent enrollees.

16.0 Thrombin generation assay

Blood samples for measurement of thrombin generation will be drawn in vacutainer tubes containing 3.2% sodium citrate with and without corn trypsin inhibitor (CTI) and be processed appropriately within an hour prior to storage. Blood samples will be centrifuged at 2500g (relative centrifugal force) for 15 minutes (min). Plasma will be transferred into plastic tubes, and re-centrifuged at 2500g for 15 min. Plasma will be decanted again after second spin and stored in aliquots of 0.2 mL (platelet poor plasma). The platelet poor plasma will then be snap frozen and stored at -70°C until testing as bulk at the end of the study.
The thrombin generation assays will be performed using a commercial kit (TECHNOTHROMBIN® TGA, Technoclone, Vienna, Austria) according to the manufacturer's instructions in Dr. Kerlin's laboratory. The assays are performed based on monitoring the fluorescence generated by thrombin cleavage of a fluorogenic substrate over time, after the activation of the coagulation cascade by tissue factor. At least two reagents will be used. Parameters that will be recorded include: lag phase, time to peak thrombin concentration, peak thrombin concentration, and endogenous thrombin potential (measured by area under the curve).

17.0 Inflammatory marker assessment

Serum IL-6, IL-8, and TNF-α levels will be measured using commercial enzyme-linked immunosorbent assay (ELISA) according to the manufacturer's instructions in Dr. Mark Hall'slaboratory.

18.0 Lipodomic profiles

18.1 Lipidomic profiles will be done in Dr. Riedl's laboratory. Blood samples for measurement of lipidomic profiles will be drawn in two vacutainer tubes, one containing 3.2% sodium citrate and the other being a serum separator tube.

After collection, blood will be separated into individual constituents including serum. Lipidomic profiles will be collected on blood samples using a triple quadrupole mass spectrometry platform called Lipidyzer which is enabled through ion mobility hardware. This assay covers 13 different lipid classes and uses 56 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. Both of these

assays will be conducted in the Nutrient & Phytochemical Analytic Shared Resource (NPASR) of the OSU Comprehensive Cancer Center under the direction of Acting Director, Ken Riedl..

19.0 Plasma levels and RNA expression of tissue factor (TF), tissue factor pathway inhibitor (TFPI), and other clotting factors

19.1 These tests will be done in Dr. Alan Mast's laboratory at BloodCenter of Wisconsin according to their standard protocol. The plasma samples will be frozen and stored at -80°C at the Ohio State University until the end of the study, when samples will be delivered to Dr. Mast's lab to perform the research testing.

19.2 After plasma was removed from each tube as per protocol above, the buffy coats in the tubes will be collected as much as possible and stored in RNAlater® reagent as per manufacturer's protocol. These buffy coats will be used for analysis of RNA expression in Dr. Mast's laboratory at the end of the study, according to their standard protocol.

20.0 Statistical Analysis

At least 66 evaluable patients will be randomized (1:1 allocation, 33 evaluable patients in each arm) into "anticoagulation" versus "anticoagulation +atorvastatin" arms. The primary endpoints are thrombin peak and thrombin generation. Based on the published data,[8,9] we anticipate 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.

All data will be collected on study-approved data collection forms and entered into Research Electronic Data Capture (REDCap), which is a secure, web-based application designed to support data capture for research studies by building and managing online surveys and databases. The system was built with the help of the OSU Research Informatics Services.

Descriptive statistics (i.e. means, standard deviations, 95% confidence intervals for continuous variables, and frequencies for discrete data) and graphical analyses will be used for all clinical outcomes, demographics, VTE related events, laboratory results, and adverse events for each arm. The secondary endpoints will be compared between the two arms using chi- square test or Fisher's exact test, whichever is appropriate. The associations between treatment type and the change in biomarkers will be evaluated using two-sample t test. Log-transform will be used if necessary. Linear mixed models will be used to study the associations between the primary endpoints and treatment, and trend across time. The interaction term "arm x time" will be included in the model to study whether the two treatment arms have different "behavior" across time. Potential confounders will be included in the models. Thrombin peak concentration and

endogenous thrombin potential at 9 months will be compared between the patients on anticoagulation and those off anticoagulation.

21.0 Costs of the Study

Given the fact that all patients will be receiving standard therapy for VTE (anticoagulation), either the patient or their insurance carrier will be responsible for all of the medical expenses associated with the treatment and follow up of their VTE. The costs associated with the research laboratory studies will be paid by the study researchers and will not be passed on to patients or their insurance carriers. The cost of atorvastatin will be reimbursed by the study researchers. Patients enrolled on this study will not incur any additional expenses as a result of enrolling on this protocol.

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