Venous Thromboembolic Disease Prophylaxis Following Foot & Ankle Surgery: A Randomized Controlled Comparative Trial

Study background:
Venous thromboembolic disease (VTED) is a pathological process that encompasses both deep venous thrombosis (DVT) and pulmonary embolism (PE). The condition, as well as the well-intentioned use of numerous commonly employed prophylactic agents designed to prevent it, can both result in profoundly morbid and sometimes fatal complications following foot and ankle surgery. Although there remains significant controversy as to the ideal application of these various agents as well as the overall nature and prevalence of the disease process amongst foot and ankle post-surgical patients, experts agree that these complications would, with better science, become far more preventable. Current incidence estimates suggest that symptomatic VTED statistically impacts nearly 65,000 American foot and ankle patients every year. When factoring in “silent” DVT and PE rates, these numbers increase three fold—indicating that the true disease process of VTED adversely affects a substantial portion of this patient population in spite of current treatment regimens. The absolute number of patients amongst this group who become negatively affected extends even further when one considers the numerous serious side effects associated with our still poorly directed pharmacologic management of these patients, as this subgroup doesn’t sustain any VTED—but should nonetheless be included. Our goal, therefore, is to create scientifically driven screening and treatment guidelines to help mitigate this persistent and significant quality of life and patient care issue. By using a double blinded, prospective, randomized, controlled, multi-center trial with three commonly employed treatment arms, we aim to define the incidence of VTED in these post-operative patients as a means of characterizing: 1) who actually mandates prophylactic treatment, 2) what regimen represents ideal prophylaxis for a given patient, and 3) how best to avoid related complications by creating an optimized algorithm designed to eliminate over- and under-treatment of this population world wide.

Objectives:
Specific Aim #1: To determine the incidence of VTED (as a proxy for treatment efficacy) in patients who receive one of three currently widely accepted methods of managing perioperative VTED risk in foot and ankle surgical patients: Aspirin, oral factor Xa inhibitor Apixaban (which, according to leading world experts, represents the agent most likely to be used in our future world wide as a chemoprophylactant—and which is soon to have a reversal agent), and no treatment (which given current evidence we view as an ethical and common choice for “treatment” today).
Specific Aim #2: To define the incidence of side effects (treatment complications) associated with VTED prophylaxis and therefore better characterize all risk-benefit tradeoffs.
Specific Aim #3: To categorize the specific VTED risk factors which must be taken into account for individual foot and ankle preoperative patients, and thereafter create an algorithm which enables accurate pre-surgical identification of who should reasonably be prophylaxed in the perioperative setting (or not), and with what agent.
Specific Aim #4: Potential stratification of the ideal duration of anti-thrombotic prophylaxis necessary for these patients in the post-operative setting. (NB: Since our
study duration will be 3 months and our treatment will last 6 weeks, this last hypothesis may or may not be answerable via our dataset).

Population to be studied (including inclusion/exclusion criteria): Any patient presenting to one of the study centers who: 1) is identified as a candidate for foot and/or ankle surgery by one of the investigators, 2) meets all inclusion and exclusion criteria, 3) willingly consents to participate in this study, and 4) then enrolls and completes the study in accordance with study protocol.

Inclusion criteria: All patients 18 years of age or older who undergo a below-knee surgical procedure by one of the investigation’s fellowship trained orthopaedic foot and ankle specialists as part of this enrollment period.

Exclusion criteria: Any patient initially recruited to this study who meets any of the following criteria shall thereafter be excluded from enrollment or eventual data analysis, as appropriate: 1) under age 18; 2) already agreed to be at sufficient risk for developing perioperative VTED by consensus of fellowship trained foot and ankle specialists such that in effectively all cases these patients would be aggressively chemoprophylaxed, to specifically include the following: prior personal history of DVT/PE, active malignancy, known coagulopathy (ie. Factor V Leiden, Prothrombin Gene Mutation, Protein C/S deficiency, anti-thrombin III lupus anticoagulant or anticardiolipin antibody), spinal cord injured patients resulting in paralysis or multitrauma patients having multisystem injury, polyextremity injury, or injuries which extend into or above the ipsilateral knee or anywhere else along the axial or appendicular skeleton; 3) considered at risk for a major bleeding episode that would contraindicate any form of chemoprophylaxis, to specifically include the following: major bleeding disorder such as hemophilia and von Willebrand’s Disease, significant risk of bleeding as a result of intracranial hemorrhage or gastrointestinal bleeding, platelet count < 75 x 10^9 /L; 4) unable to take medication in tablet form; 5) deemed unable to discontinue a preoperative aspirin regimen in the perioperative period by his or her medical provider; 6) on anticoagulation therapy prior to surgery for other medical reasons such as atrial fibrillation, prosthetic valvular disease, coronary artery stent; 8) pregnant or suspected being pregnant; 9) renal insufficiency with creatinine clearance <20% of normal ; 10) allergic to any component of the treatment agents; 11) subject to lumbar puncture/spinal/epidural anesthesia within 12 hours before or after the planned surgical procedure; 12) diagnosed with uncontrolled hypertension (>230/120 mmHg); 13) demonstrated non-compliance with the post-operative protocol as outlined. 14) any multi-trauma patient who has presence of any significant injury involving another extremity or any major organ system other than the injury wherefore the patient needs a below-knee surgical procedure.

Treatment groups:
(for purposes of maintaining a double-blinded status, all pills will be manufactured to appear identical, and two “pills” will be taken every day by every patient)
A. No anti-thrombotic prophylaxis (placebo pill orally 2x daily), beginning the morning after surgery x 6 weeks (control arm)
B. Anti-thrombotic prophylaxis with Aspirin 160 mg orally 2x daily, beginning the morning after surgery x 6 weeks
C. Anti-thrombotic prophylaxis with Apixaban 2.5 mg orally 2x daily, beginning the morning after surgery x 6 weeks

**Primary Outcome measure:**
The incidence of clinically evident (symptomatic) lower extremity DVT and/or PE (VTED) as identified by the provider and confirmed with appropriate testing (bilateral extremity duplex US, and/or spiral CT) within the defined three month post-operative study period for all enrolled patients. The specific nature of all identified DVTs and PEs will be carefully recorded as to exact extent, location(s), and resultant symptomatology.

**Secondary Outcome measures:**
The following parameters will also be tracked for the purposes of this study: 1) all cause mortality; 2) fatal and non-fatal PE rates; 3) characterization and rate of proximal (at, or above, knee) and distal (below knee) DVT; 4) all post-operative complications regardless of etiology, including local (surgical site) or distant (cerebral, gastrointestinal, other) bleeding complications, reoperation for any reason, pharmacological side effects, post-phlebitic syndrome, venous stasis disease, etc; 6) any other unexpected symptom, sign, or adverse event in the post-operative period as identified by the clinical investigator to be outside the normal course of recovery. **Questionnaires:** Custom surveys being developed by patient collaborators will include questions deemed important to patients and families, PROMIS mobility/PF CAT/depression CAT/Pain interference CAT/Pain intensity CAT, EQ-5D, patient satisfaction questionnaire, and VAS pain scale. (*Please note, we are considering including these at various intervals for a total of one year post-operatively for each patient.*)

In order to better characterize the risk factors for symptomatic VTE, we intend to screen each patient who develops any sign or symptom consistent with VTED with a screening panel to assist in identifying potential underlying/hidden coagulopathic risk factors. This will occur via a bloodwork panel that specifically includes Factor V Leiden, Protein C, Protein S, anti-thrombin III, prothrombin gene mutation, lupus anticoagulant, and antiphospholipid antibody. Finally, we will be recording any patient and surgical factors considered potentially related to VTE (but as yet unproven), including all patient demographics and comorbidities (ex, prior smoking history, diabetes, family history, age, etc), type(s) of anaesthesia, exact nature (skin to skin time and type) of the surgical procedure, tourniquet size/type/pressure/location/inflation time, utilization of any contralateral pneumatic mechanical compression device or antithrombotic stocking, length and types of all immobilization pre and post-operatively, sequential perioperative weight-bearing status timeline, assistive device use, onset and duration of physical therapy, smoking/nicotine status, and work status. It should be noted that any patient who is identified by the provider as having a VTE must undergo this additional work up and testing but is thereafter expected to undergo routine post-VTE management for his or her particular problem as indicated.

**Pre-specified subgroup analyses:**
The pre-specified subgroup analyses will consist of risk factors for post-operative DVT, differences in perioperative complication rates based on agent side effects, validity of the Caprini score in association with foot and ankle VTED rates, overall compliance rates,
risk of development of post-thrombotic syndrome in the different treatment groups, satisfaction of patient care and outcome as a result of patient steering committee involvement, and patient assessment regarding adequacy of preoperative educational preparation for making a comfortable and appropriate patient-driven choice for postoperative VTED prophylaxis based on pre-defined risk benefit discussion.

Discussion of proven effectiveness of study interventions

No anti-thrombotic prophylaxis: There is currently insufficient data to recommend for or against routine anti-thrombotic prophylaxis across the entire foot and ankle surgical population. While the dangers of no prophylaxis when prophylaxis is necessary in orthopaedics are well documented, the potentially perilous consequences of chemoprophylaxis itself have also been documented to be equally disastrous (fatal) in some cases. Therefore, various sources continue to recommend no antithrombotic prophylaxis (or simply state there is no basis for formulating any recommendation in this regard) following routine foot and ankle procedures patients (1). For these reasons, incorporating a “no active form” of management serves as both an ethically appropriate treatment arm as well as an outstanding control for this study.

Aspirin: In recent years aspirin has enjoyed a tremendous surge in popularity across almost all areas of orthopaedic surgery, as well as a first ever endorsement by the American College of Chest Physicians (ACCP) and American Academy of Orthopaedic Surgeons (AAOS) in 2012 as acceptable chemoprophylaxis against VTED following hip and knee arthroplasty (no comment of utility has ever been made with respect to foot and ankle surgery) (2). This has been predominantly based on not just its efficacy profile but moreso on its safety-efficacy (harm-benefit) profile.

Apixaban: Use of oral apixaban in patients undergoing knee or hip replacement surgery has been studied extensively and shown to effectively decrease the rate of VTED, even relative to certain other anticoagulation medications, with the added benefit of a potentially significant but comparatively more limited side effect profile (3). It is not only one of the first newer generation agents to enjoy an oral administration but also promises to have a reversal agent on the horizon that has previously been unavailable for similar agents. Many consider this the horizon of “aggressive” chemoprophylactic management.


Sample size

A conservative 2% estimate of previously documented but widely variable symptomatic and asymptomatic VTED rates was used. To estimate the effect size, we utilized the historical orthopaedic data on enoxaparin versus placebo for DVT prophylaxis, which
report a mean effect size of 62.4% (range 33% to 75%)\textsuperscript{7,8} and conclude that the effect size of apixaban is likely to be at least 30% and most likely greater than 60%. In reference to aspirin, two recent investigations identified that risk reduction based on aspirin compared to no treatment was 22% and 37%\textsuperscript{9}. In choosing to be sensitive to an effect size of 30% relative reduction in the incidence of VTED, we will be powered to identify a clinically meaningful difference between the pharmacologic treatment arms (aspirin and apixaban) versus the placebo arm, and also powered to detect a difference of this size or larger between the aspirin and apixaban arms. Furthermore, in order to achieve 80% statistical power based on Fisher’s exact test for capturing a therapeutic effect of 30%, we have calculated the required sample size to be 7,616 patients randomized to each of the three arms, resulting in a total required N of 22,850 patients using a two-tailed significance level of 0.05 (version 7.0, nQuery Advisor, Statistical Solutions, Saugus, MA). Assuming a possible dropout or loss to follow-up rate of 10%, this will require the recruitment of 25,400 patients.

We expect that this entire study will take approximately 18-24 months to complete, although we do not believe it will require significant investigator efforts beyond the routine perioperative patient care that we already provide on a daily basis, which is a wonderful strength of the study.

**Duration:** All enrolled patients will be followed individually for a study period of three months postoperatively. In order to compile the total number of patients necessary to adequately power our study, we estimate that it will take approximately 18-24 months to engage all IRB approved sites and thereafter fully enroll.

**Costs:** Based on lengthy discussion with various world recognized, subspecialty experts in the fields of foot and ankle surgery, vascular surgery, vascular medicine, hematology, statistics, and radiology, we propose an estimated budget of $9.5 million in direct costs and $3 million in indirect costs.

**Contact information principal investigator:**
Christopher W. DiGiovanni, MD  
Visiting Professor, Harvard Medical School  
Chief, Foot and Ankle Service and Fellowship Program, Massachusetts General Hospital  
Director, MGH Comprehensive Foot and Ankle Center, Waltham, MA  
Director, Foot and Ankle Service, Newton-Wellesley Hospital  
Department of Orthopaedic Surgery, Massachusetts General Hospital  
Yawkey Center for Outpatient Care, 3F, Suite 3300  
55 Fruit Street  
Boston, MA 02114

Administrative Contact: PLaliberte@Partners.org  
Work Contact: CWDiGiovanni@MGH.Harvard.edu  
Office Phone: (617) 724-9338  
Office Fax: (617) 726-6161