VTED Prophylaxis after Foot and Ankle Surgery: A Randomized, Controlled, Double Blinded Comparative Trial

Christopher W. DiGiovanni, MD
Bart Lubberts, MD-PhD Candidate
Dept.Orthopaedics, MGH, Boston, MA

Orthopaedic Foot & Ankle Outcomes Research
Stepping forward into the future with patient-reported outcomes
The VTED Problem in foot & ankle

- Left untreated, can be serious or fatal

- Efforts to avoid can have equally serious consequences

WHERE DO WE DRAW THE LINE?
What has remained elusive, on a worldwide scale:

- **Understanding**
  - **Who** we need to Rx (risk factors)
  - **What** we need to use, or not (prophylaxis)
  - **How long** we need to give anything (duration)
A number of published studies talk about RFs, but few have actually studied them—and none have been properly powered to do so.

- Post-op immobilization: 4/16
- Hindfoot surgery: 1/16
- Tourniquet time: 1/16
- Advanced age: 6/16
- NWB status: 2/16
- RA: 1/16
- Recent air travel: 1/16
- Male: 1/16
- Female: 2/16
- Obesity: 3/16
- h/o malignancy: 0/16
- Ethnic background: 1/16
- Higher ISS (trauma): 1/16
- Multiple comorbidities: 1/16
- Smoking: 0/16
- + Hx VTE: 1/16
- + Thrombophilia: 0/16
- + FHx: 0/16
What is the natural history of VTED in foot and ankle surgery?

- Supposedly “rare”; unclear how this relates to prophylaxis

- Sx DVT and PE rates @ 1%-10% and 0.2-0.6%, respectively

- ASx DVT and PE rates @ 20-36% and 1-3%, respectively

- Sx VTED statistically impacts nearly 65,000 American foot and ankle pts per year
  - we surmise that these numbers would at least triple if the side effects/complications of chemoprophylactic Rx and the impact of “initially silent” disease were to be included
Currently Available Guidelines

- To date, there remain insufficient data to recommend for or against routine anti-thrombotic prophylaxis for almost any patient undergoing foot and ankle surgery.

- No attention/advice from any official body:
  - AAOS
  - ACCP
  - NICE
  - SQIP
  - Etc…
OUR CLINICAL NEED

Generate powered VTE data for F/A pts:

- Optimize risk (harm)/benefit
  - improve care
  - improve outcomes
  - prevent complications
  - lower cost
THE OFAR ADVANTAGE

- Establishing a nationwide member network and database
- Collecting patient-reported outcomes (PRO) data to improve foot and ankle pt care
- Expanding our infrastructure for future comparative pt outcomes research
- Continued growth of the nationwide, multi-site OFAR network
- AOFAS member participation and data sharing
- Eventual registry status
- Support for AOFAS members in meeting requirements for ABOS Maintenance of Certification, Part IV MOC Performance in Practice
- Coordinate data collection with EMR systems
- Collaborate with industry for pt safety and post-market device surveillance
- Collaborate with international data collection and registry networks
Evolution of Study

- 18-20 months of work, numerous rejections
  - Neither industry, insurance, nor NHLBI (NIH) have been interested in funding as designed

- Only interested grant source: Patient Centered Outcomes Research Institute (PCORI)

- October 2014: submitted Letter of Intent accepted by PCORI
STUDY PURPOSES

1) Identify true rates of Sx VTED in F/A

2) Define optimal Rx

3) Stratify at-risk pts (who needs, who not)

4) ? Characterize proper duration
STUDY DESIGN

- Prospective, randomized, controlled, double blinded, multicenter, comparative trial

- 3 Rx arms, beginning AM after surgery x 6 wks
  - No prophylaxis = placebo pill 2x/d (control)
  - ASA (162 mg po 2x/d)
  - Apixaban (2.5 mg po 2x/d)
    - Factor Xa inhibitor; most likely chemoprophylactant in future

- Pills hopefully manufactured to appear identical
  - 2.4 million pills (800,000 of each)
Enrollment and Data Collection

- Based on 80% statistical power & therapeutic effect of 30%

Data Collection through REDCap
- A mature, secure web application for building and managing online surveys and databases, supported by OFAR

### Table 1: Amount of DVT and minimum amount of cases based on study sample size

<table>
<thead>
<tr>
<th>sympt DVT(%)</th>
<th>n per group</th>
<th>Total sample size</th>
<th>n sympt DVT*</th>
<th>n enrollment/18 months*</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5</td>
<td>30844</td>
<td>102813</td>
<td>514</td>
<td>48</td>
</tr>
<tr>
<td>1</td>
<td>15258</td>
<td>50860</td>
<td>509</td>
<td>24</td>
</tr>
<tr>
<td>1.5</td>
<td>10197</td>
<td>33990</td>
<td>510</td>
<td>16</td>
</tr>
<tr>
<td><strong>2</strong></td>
<td><strong>7616</strong></td>
<td><strong>25387</strong></td>
<td><strong>508</strong></td>
<td><strong>12</strong></td>
</tr>
<tr>
<td>3</td>
<td>5035</td>
<td>16783</td>
<td>503</td>
<td>8</td>
</tr>
<tr>
<td>4</td>
<td>3722</td>
<td>12407</td>
<td>496</td>
<td>6</td>
</tr>
</tbody>
</table>

*Enrollment per surgeon per month (based on 40 sites and an average of 3 surgeons per site)*
*\( n \) sympt DVT; estimated amount of symptomatic DVT in total group*
Inclusion Criteria

Sites/Investigators:
- Fellowship-trained orthopaedic foot and ankle specialist
- AOFAS Active Member
- U.S. based program (under review)
- Agree to OFAR-approved expectation summary

Patients:
- Any patient 18 years of age or older who undergoes a below-knee surgical procedure by one of the sites’ approved investigators during enrollment period
Exclusion Criteria

1) Age < 18
2) Prior personal history of DVT/PE, active malignancy, spinal cord injury resulting in paralysis
3) Known coagulopathy
4) Major bleeding disorder such as hemophilia and von Willebrand’s Disease, significant risk of bleeding from intracranial hemorrhage or gastrointestinal bleeding, platelet count < 75 x 10^9 /L
5) Unable to take medication in tablet form
6) Deemed unable to d/c a preoperative aspirin regimen in the perioperative period by PCP
7) On anticoagulation therapy prior to surgery for other medical reasons
8) Pregnancy
9) Renal insufficiency
10) Allergic to any component of the treatment agents
11) Subject to lumbar puncture/spinal/epidural anesthesia within 12 hrs before or after planned surgical procedure
12) Diagnosed with uncontrolled hypertension
13) Known to be clinically non-compliant or a transient
14) Any multi-trauma patient who, in addition to the reason for which the patient requires a below-knee surgical procedure, has presence of significant injury involving another extremity or injury involvement of any major organ system
Overall Study Period

- 3 month f/u for DVT (primary outcome)
- 6-12 month f/u for secondary outcomes (under review)
- LITTLE distraction from your regular day to day patient care activities required

Perioperative Demographics

- Tourniquet size, location, time, pressure
- All co-morbidities (ex, nicotine, DM, age, FHx, etc)
- Exact type of procedure & anaesthesia
- Length/type of immobilization, pre and post op
- Onset and duration of PT, use of specific AD
- Work status
Questionnaires

- Custom surveys being developed by pt collaborators
  - will include questions deemed important to pts/families

- PROMIS mobility/PF CAT/depression CAT/Pain interference CAT/Pain intensity CAT

- EQ-5D

- Patient satisfaction questionnaire

- VAS pain scale
Primary Outcome Measure

- Incidence of clinically evident (Sx) DVT/PE
  - As identified by the provider
    - Clinical signs/sx as guidelines to follow (under review)
  - As confirmed by appropriate testing (Duplex U/S, Spiral CT)
  - Within the defined study period
Secondary Outcome Measures

- All-cause mortality
- Fatal and non-fatal PE rates
- Characterization & rate of proximal (at or above knee) and distal (below knee) DVT
- All post-operative complications
- Clinical outcome, including impact of DVT on pain, function, depression, global health compared to non-DVT
- Any other unexpected symptom, sign, or AE in the post-operative period as identified by the clinical investigator to be outside the normal course of recovery
Other Secondary Outcome Measures

- In order to better characterize the risk factors for Sx VTE, we intend to screen **all patients dx w/VTE event using additional bloodwork as a screening panel** to assist in identifying potentially hidden coagulopathic risk factors:

  - Factor V Leiden, Protein C, Protein S, anti-thrombin III, prothrombin gene mutation, lupus anticoagulant, and antiphospholipid antibody
PCORI Requirements

- All successful studies must be carefully configured as a shared decision making process on behalf of all stakeholders.

- Every stakeholder must complete a “Needs Assessment” survey. This survey must assess the priorities and preferences of all stakeholders with respect to study objectives, design, and execution.
The Defined Stakeholders

- **Patient Steering Committee**
  Consists of 7-10 patients who have suffered various complications (DVT, PE, post-thrombotic syndrome, bleeding, death) related to VTED and/or its chemoprophylaxis after having undergone F/A surgery

- **AOFAS**

- **OFAR**

- **Advocacy Groups**
  - MGH Patient and Family Advisory Committees for the Institute for Heart, Vascular, and Stroke Care
  - The North American Thrombosis Forum
Clinician Stakeholders

- Andrew Nierenberg, MD
  - Clinical Director of the Bipolar and Research clinic at MGH

- David Kuter, MD
  - Director of Clinical Hematology at MGH and renowned expert on VTED

- Stephan Wicky Van Doyer, MD
  - Director of the Vascular Imaging & Intervention Division at MGH

- Robert Schainfeld, DO
  - Associate Director of Vascular Medicine at MGH

- David Zurakowski, PhD
  - Director of Biostatistics at MGH

- Joseph Caprini, MD
  - Chair/Clinical Professor of Surgery at U. Chicago/NorthShore Health System

- Maurizio Fava, MD
  - Director, Clinical Research Program at MGH
Executive Summary

- Plan to recruit @ 40 sites across U.S.A.
  - Planning average of 3 investigators per site
  - Overall patient enrollment @ 25,000
  - All patients followed for 6-12 mos
  - AOFAS/OFAR discussing help with logistics, IRBs, etc

- Expected study duration @ 18-24 months
  - This would mean 200+ pts per investigator, which would equal @ 12 or 17 pts per month (18 vs 12 mos)

- Estimated costs: $13-15,000,000.00
  - These costs will cover a site coordinator for each site
Conclusions

- We expect this study to generate the following:
  
  - Creation of a properly powered and reliable algorithm to guide VTED management for our future F/A pts
  
  - A much better understanding for OFAR/AOFAS regarding how we as an organization can collectively answer singularly important societal questions with reliable Level I data—instead of the Level III-V data we now act on 95% of time
  
  - Defining the feasibility and utility of various outcomes measures as well as their role in daily use
  
  - Generating the beginnings of a huge registry database for future mining of many different aspects of foot & ankle care
Questions?

- Due date for final grant application is Feb 1, 2105
- Subject to further discussion/agreement @ OFAR
- Given that the framework of our investigation and grant remain somewhat in evolution, we are unlikely to have all the answers this evening...but we are definitely open to any constructive suggestions beforehand!
- Thank you