Comparative Patient Impact of Venous Thromboembolic Disease Prophylaxis Following Foot & Ankle Surgery

The PIVoTED Trial

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Orthopaedic Foot & Ankle Outcomes Research
Stepping forward into the future with patient-reported outcomes
The VTE Problem

- Left untreated, can be serious or fatal
- Efforts to avoid can have equally serious consequences

WHERE DO WE DRAW THE LINE?
The Foot & Ankle Conundrum

*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)*
  - **ULTIMATELY**: who benefits from Rx (or not), and who is hurt by treatment (or not)
Are there F/A Risk Factors?

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 Hx of VTED in F/A Surgery?

- “Presumed rare”; relationship to prophylaxis unclear
- Sx DVT & PE rates @ 1%-10% & 0.2-0.6%
- ASx DVT & PE rates @ 20-36% & 1-3%
- Statistically, Sx VTED impacts 65,000 U.S. F/A pts/yr
“OUR” THOUGHTS

- Complication rates may be *markedly* higher for *some*?
  - certain F/A patient subgroups
  - side effects of chemoprophylactic Rx
  - impact of “silent” disease

→ *ALL POORLY MEASURED* in our literature

- **Hypothesis**: looking only at averages is a disservice!
  - when viewed *in aggregate*, F/A VTED numbers are “very low” vs other groups; when viewed as subgroups, *likely some quite low & high risk pts*!
Guidelines

“There remains insufficient data to recommend for or against routine anti-thrombotic prophylaxis for patients undergoing foot and ankle surgery”

- No better guidelines from any official body
  - AOFAS
  - AAOS
  - AAOS
  - ACCP
  - NICE
  - SQIP
OUR CLINICAL NEED

- Generate powered, Level I VTE data for F/A pts

→ We need to focus more on THE TRIPLE AIM
  Patient experience (shared, data driven decision)
  Improve the health of this population
  Optimize harm/benefit = ↑↑ outcomes
  Lower cost
“THE OFAR ADVANTAGE”

- Established nationwide member network & database
- Patient-reported outcomes (PRO) data to improve foot and ankle care
- Infrastructure for future Level I translational research!

- Extensive AOFAS member participation & data sharing
- Eventual registry status for pt safety and post-market device surveillance
- Support for AOFAS members in meeting requirements for ABOS Maintenance of Certification, Part IV MOC Performance in Practice

- Coordinated data collection with EMR
- Potential framework for international collaboration
Evolution of This Study

- Industry, insurance, NIH (NHLBI): either unable or uninterested in funding as designed
- Only agency big enough: PCORI → Patient Centered Outcomes Research Institute
- July 2015: first full submission
- PCORI feedback: implement reviewer comments and submit revision application for Dec 2016 cycle
TRIAL DESIGN

- Prospective, randomized, multicenter, pragmatic
- 26,700 F/A pts, very few excl criteria

- 3 Rx arms, beginning AM after foot/ankle surgery
  1. “MECH” = TED/SCD in house, then education protocol x 35d
  2. “AP” = Arm (1) + ASA at surgeon directed dose x 35d
  3. “AC” = Arm (1) + daily oral or injectable anticoagulant regimen per surgeon preference x 35d

- All pts followed for 6 mos (pre-op, 2, 6, 12, 24 wks)
- Primary outcome: VTE/BAE
- Secondary outcomes: PROs, disease specific measures
STUDY AIMS

- We plan to compare the effectiveness of three prophylactic strategies in preventing VTED through the following aims:

  - **Specific Aim #1:** Determine the impact of each prophylactic strategy on the incidence of VTE and BAE

  - **Specific Aim #2:** Measure the effect of prophylactic strategy and VTED/BAE occurrence on PROs

  - **Specific Aim #3:** Evaluate the heterogeneity of treatment effects across different populations, surgery types, and VTE risk groups
Enrollment and Data Collection

- Based on 80% statistical power & therapeutic effect of 30%, we calculated that we must enroll 26,700 patients

- Plan @ 50 sites throughout North America, avg @ 2-3 investig/site

- Enrollment phase expected to span @ 18-24 mos
  - Screening 30 pts per investigator per month (80% inc/excl)
  - 24 patients per investigator per month (65% enrolled)
  - Expect @ 16 pts per investigator per month
  - Requirement: min 12, max 35

- OFAR/M2S will serve as the study’s database repository

- Estimated cost $14,000,000
Primary Outcome Measure

- Incidence of clinically evident (Sx) DVT/PE as identified by the provider and confirmed by appropriate testing (Duplex U/S, Spiral CT) within 6 mo study period
Site/Investigator Expectations

- **Site PI**: active/candidate member of AOFAS or COFAS board eligible/certified MD or DO
  
  foot/ankle fellowship trained, or ≥ 15 yr membership in AOFAS/COFAS and ≥ 50% practice dedicated to F/A

- **Participant Investigators**:

  AAOS member & board eligible/certified MD or DO

  AOFAS member or applying for membership, with demonstrated expertise in F/A surg per site PI and ≥ 50% of practice dedicated to F/A

- Agree to OFAR approved expectation summary

- Demographics (per PCORI)
INCLUSION CRITERIA

- Any patient $\geq 18$ yrs who undergoes a below-knee surgical procedure by any approved investigator/site 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) Poly trauma involving either more than one organ system or involving musculoskeletal injuries beyond the involved lower leg, foot, and/or ankle
7) Unable to discontinue a current aspirin, antiplatelet, or anticoagulation regimen
8) Are pregnant or suspected of being pregnant
9) Renal and hepatic insufficiency to a level that precludes anticoagulant use
10) Allergic to any component of the treatment agents
11) Likely to require more than one leg/foot/ankle surgery within the 90-day study timeframe
12) Minor procedure that requires none of the following: tourniquet use, post-operative immobilization, post-operative weight bearing restriction

*NOTE: ANY PATIENT DEFINED “MIN OR MAX RISK” FOR VTED EXCLUDED*
Overall Study Period

- All enrolled pts seen pre-op, 2/6/12 wks, 6mo
- MINIMAL distraction from your regular, day to day patient care activities!
- VTE/BAE disease-specific questionnaires (@D1, 12wks, 6mo)
- PROMIS questionnaires (all pts pre-op, 2, 6, 12wks, 6mo)
  - Physical Function CAT
  - Anxiety CAT
  - Depression CAT
  - Pain Interference CAT
  - Global Health short form
  - Pain Intensity short form
Stratification of enrolled patients

Post enrollment but pre surgery, the *Caprini Risk Assessment Tool* will be used for each pt to categorize enrollees into one of four “risk” groups.

1. **Low VTE risk (0-1p)**
2. **Moderate VTE risk (2p)**
3. **High VTE risk (3-4p)**
4. **Highest VTE risk (>5p)**
2° Outcome Measures

- Bleeding adverse event
- All-cause mortality
- Fatal and non-fatal PE rates
- Characterization & rate: proximal DVT (at or above knee) distal DVT (below knee)
- Clinical outcome/impact of VTED on pain, function, depression, global health compared to non-VTED
- Any other unexpected Sx, sign, or AE in post-op period, identified by the clinical investigator to be outside the normal course of recovery
Other 2° Outcome Measures

- In order to better characterize the risk factors for symptomatic VTE, we intend to screen all patients dx with VTE via additional bloodwork to assess for potentially hidden/under-appreciated coagulopathic conditions.
  - Factor V Leiden, Protein C, Protein S, anti-thrombin III, prothrombin G20210A, lupus anticoagulant, antiphospholipid antibody, Beta-2 glycoproteins (IgG, IgM)
- Also capturing all imaginable potential risk factors for every enrolled patient → can later stratify these risk factors with Odds Ratios.
Site Reimbursement

- Payment will be received after all required data related to each enrolled patient has been completed and verified to be accurate.

- $125 per site per pt who does not get VTE or BAE

- $1000 per site per pt who develops VTE or BAE
The Defined Stakeholders

- **Patient Steering Committee**
  Consists of @ 9 patients who have suffered various complications (DVT, PE, post-thrombotic syndrome, bleeding, etc) related to VTED and/or its chemoprophylaxis after having undergone F/A surgery

- **AOFAS/OFAR**

- **Support?** YES!!
  - IFFAS, COFAS, AAOS, ABOS, ACS, OTA, NATF, MGH pt advisory group, PCNA, NAON, BCPSQC, ISTH
WHAT’S EXPECTED FROM THIS STUDY?

- 1st attempt by our society to perform a major US/Canada Level I Study thru AOFAS/OFAR!
- Reliable algorithm to guide proper VTE management and provide a powerful shared decision making model
- Future path for AOFAS/OFAR/COFAS/?other collaboration to answer our important Q’s with Level I data
- Define the feasibility and utility of various outcomes measures in F/A, as well as their role in daily use
- Generate huge database for answering other questions about how to improve the care of our pts