Update on the Prevention of VTE (Thromboprophylaxis), 2012

Peter Kouides MD
Associate Professor of Medicine
University of Rochester School of Medicine
Attending Hematologist, Rochester General Hospital
Rochester NY
peter.kouides@rochestergeneral.org
Scope of the Problem

- 350,000 to 650,000 with VTE per year
- 100,000 to > 200,000 deaths per year
- Most are hospital related-10% of hospital deaths
  - More deaths than HIV, MVAs, Breast CA combined
  - Equals 1 jumbo jet crash / day
- The #1 preventable cause of hospital deaths!!
- In addition, huge costs and morbidity (recurrence, post- thrombotic syndrome, chronic PAH)

*Surgeon General’s Call to Action to Prevent DVT and PE 2008 DHHS*
Post-thrombotic Syndrome...in 1/3rd-1/2th of DVTs....

1. Venous obstruction
2. Inflammatory response to thrombosis → valve and adjacent vessel wall injury → valvular reflux
   • 1 + 2 = venous hypertension →
     - Edema
     - Tissue hypoxia and injury
     - Progressive calf pump dysfunction
     - Subcutaneous fibrosis
     - Skin ulceration
CASE #1

The patient is a 72 year-old female, with history of htn, CHF, RA, admitted for CHF exacerbation. Labs reveal Hb 10.1, Plt 112,000, and normal renal fxn.

What prophylaxis regimen, if any, would you choose?
1. Encourage ambulation
2. GCS or IPC device
3. SC heparin
4. LMWH
Risk Factors to Clot: Remembering Virchow’s Triad

- History of conditions promoting venous stasis: advanced age, immobility (long car ride, bed-ridden), obesity, post-operative state, pregnancy (also promotes coagulation) varicose veins
- History of recent trauma or surgery

**Hypercoaguuable State**

- History to suggest congenital disorder:
  - Thrombosis at an early age (<45 yrs)
  - Thrombosis at unusual sites
  - Thrombosis in other family members
  - Thrombosis despite adequate anticoagulation
Who is at Risk?
Venous Stasis

- Age > 40
- Immobilization
- Obesity
- Varicose veins
- MI
- CHF
- Stroke
- Paralysis
- Spinal cord injury
- Hyperviscosity syndromes
- Polycythemia vera
- Severe COPD
- Anesthesia

Thrift Consensus Group. BMJ:1992
Joint Effect of Obesity with Other Risk Factors for VTE- MEGA Study

<table>
<thead>
<tr>
<th>BMI (kg/m²)</th>
<th>OC use</th>
<th>Patients</th>
<th>Controls</th>
<th>Odds Ratio</th>
<th>95% CI</th>
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<tbody>
<tr>
<td>&lt;25</td>
<td>No</td>
<td>51</td>
<td>167</td>
<td>1</td>
<td></td>
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<tr>
<td>&gt;25&lt;30</td>
<td>No</td>
<td>27</td>
<td>34</td>
<td>2.52</td>
<td>1.38-4.57</td>
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<tr>
<td>≥ 30</td>
<td>No</td>
<td>28</td>
<td>30</td>
<td>3.04</td>
<td>1.66-5.57</td>
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<tr>
<td>&lt;25</td>
<td>Yes</td>
<td>260</td>
<td>233</td>
<td>4.15</td>
<td>2.85-6.03</td>
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<tr>
<td>&gt;25&lt;30</td>
<td>Yes</td>
<td>178</td>
<td>55</td>
<td>11.63</td>
<td>7.46-18.14</td>
</tr>
<tr>
<td>≥ 30</td>
<td>Yes</td>
<td>132</td>
<td>19</td>
<td>23.78</td>
<td>13.35-42.34</td>
</tr>
</tbody>
</table>

Who is at Risk? Hypercoaguable

*Congenital*
- **Deficiency** of naturally occurring anti-coagulant factor
  - Protein C
  - Protein S
  - Anti-thrombin III
- **Excess** of naturally occurring pro-coagulant factor
  - Prothrombin-”Hyperprothrombinemia” AKA PT 20,210
  - Homocysteine- “Hyperhomocysteinemia”
  - Probably-plasminogen activator inhibitor, FVIII,FIX,FXI
- **Resistance** to naturally occurring anti-coagulant:
  - “Resistance to activated Protein C”- Factor V Leiden

*Acquired*
- Numerous disease states can be associated with hypercoaguable
  - “V” “I” “C” “T” “I” “M”
“Anti-clotting” proteins

“Pro-clotting” proteins

“Normal”

Excess of a “Pro-clotting” protein

Deficiency of a “Anti-clotting” protein

Thrombophilia

Anti-thrombin III Deficiency (1:5000)

Protein S Deficiency (1:2000)

Protein C (1:1000)

PTG mutation (1:50)

Factor V Leiden (1:20)

FVIII Excess

Hyperhomocysteinemia, APAS, Ca
“Anti-clotting” proteins

“Pro-clotting” proteins

“Normal”

Deficiency of a “Anti-clotting” protein

Excess of a “Pro-clotting” protein

Thrombophilia

Anti-thrombin III Deficiency (1:5000)
Protein S Deficiency (1:2000)
Protein C (1:1000)

• Long ride
• Surgery
• Pregnancy, OC, ERT

PTG mutation (1:50)
Factor V Leiden (1:20)
FVIII Excess
Hyperhomocysteinemia, APAS, Ca

CLOT!!!
Thrombosis = Hurricane Sandy, AKA The Perfect Storm
VTE in Hospitalized Patients in the Absence of Thromboprophylaxis

• **Past**: VTE incidence of 10-80%
  – Estimate probably too high because of the increasing use of early ambulation and shorter lengths of hospitalization.

• **Present**: data from audits and registries demonstrate that the incidence of VTE, and in particular fatal pulmonary embolism, remains excessively high in hospitalized patients
VTE in Hospitalized Patients in the Presence of Thromboprophylaxis

• Meta-analysis of 36 randomized trials comparing the ability of the various pharmacological agents to prevent VTE, the following observations were made (Wein L et al, Arch Intern Med. 2007;167(14):1476):
  
  – Compared with placebo, UFH was associated with a significantly reduced risk of deep venous thrombosis (risk ratio [RR] 0.33) and pulmonary embolism (RR 0.64), as was LMW heparin (RR 0.56 and RR 0.37, respectively).
  
  – When compared with placebo, UFH given in a dose of 5000 units three times daily (RR 0.27) was significantly more effective in preventing DVT than UFH given in a dose of 5000 units twice daily (RR 0.52). Neither UFH nor LMW heparin reduced mortality.
  
  – When directly compared with UFH, LMW heparin was associated with a significantly lower risk of DVT (RR 0.68) and injection site hematoma (RR 0.47), but no difference was seen between the two agents in the risk of bleeding or thrombocytopenia.
Take Home Points, So Far…. 

• In general, VTE prophylaxis should be considered in medical patients older than age 40 who have limited mobility for ≥3 days, and have at least one thrombotic risk factor.

• All patients admitted to intensive care units are considered high risk for VTE, even after routine prophylactic anticoagulation.

Underuse of Prophylaxis Medical/Surgical Patients

- ENDORSE Registry
- 68,103 patients at 358 hospitals

<table>
<thead>
<tr>
<th></th>
<th>Appropriate Prophylaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgical patients</td>
<td>58%</td>
</tr>
<tr>
<td>Medical patients</td>
<td>39%</td>
</tr>
</tbody>
</table>

Adherence to Prophylaxis Guidelines

- Premier database; 429 hospitals; 2005 & 2006
- Age $\geq 40$ and LOS $\geq 6$ days and $\geq 1$ risk factor for VTE and no contraindications to anticoagulant prophylaxis
- Appropriate prophylaxis = type, dose, daily, duration according to 7th ACCP (2004)

<table>
<thead>
<tr>
<th>Prophylaxis</th>
<th>Medical (N=201,224)</th>
<th>Surgical (N=188,800)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any (&gt;1 dose)</td>
<td>66%</td>
<td>78%</td>
</tr>
<tr>
<td>Appropriate</td>
<td>13%</td>
<td>16%</td>
</tr>
</tbody>
</table>

Why Can’t We Do Better?

- Competing Priorities

- National Policies / Incentives / Initiatives / Accreditation not all in place

- Lack of awareness of guidelines, battling guidelines

- Underestimation of clot risk, overestimation of bleeding risk

- Validated *and practical* risk assessment models needed

- Measurement Issues

- Translating complicated guidelines into everyday practice is difficult

- Medical training failures (QI and systems re-design)
SCIP-VTE

• Guideline jointly developed by CMS and the Joint Commission

surgery patients who received appropriate venous thromboembolism prophylaxis within 24 hours prior to surgery to 24 hours after surgery = $$$

all surgical patients
No Pay for Performance

- Mandated revision of the IPPS by DRA of 2005
- Hospital-acquired conditions for which CMS will not reimburse hospitals
- Oct 2008
  - Object inadvertently left in after surgery
  - Air embolism
  - Blood incompatibility
  - Catheter associated urinary tract infection
  - Pressure ulcer
  - Vascular catheter associated infection
  - Mediastinitis after CABG
  - Falls
No Pay for Performance. . .

HACs 2009

- Surgical site infections following elective procedures
- Legionnaires’ disease
- DKA
- Iatrogenic pneumothorax
- Delirium
- Ventilator-associated pneumonia
- **DVT / PE**
- *Staphylococcus aureus* septicemia
- *Clostridium difficile*
1. Recommends assessment of risk for TE and bleeding in medical and stroke
2. Recommends pharmacologic prophylaxis with heparin or related drug unless the risks outweigh the benefits
3. ACP does not support performance measures promoting universal VTE prophylaxis

Qaseem A. Ann Intern Med. 2011;155:625-32
1. For acutely ill hospitalized medical patients at increased risk of thrombosis, we recommend anticoagulant prophylaxis (1B)

2. Recommends LMWH, UFH 5000u BID or TID, or fondaparinux (1B)

Go With This Assessment?

### Contraindications to Anticoagulants:

**Relative:** (check if applicable)
- Cerebral hemorrhage at any time
- GI, GU bleed or stroke in last 6 months
- Platelet count < 10,000
- Severe peripheral artery disease
- History of cancer
- Prognosis for surgery
- Unfractionated or Low Molecular Weight Heparin use in Heparin induced Thrombocytopenia

**Absolute:** (check if applicable)
- Active hemorrhage from wounds, drains, lesions
- Unfractionated or Low Molecular Weight Heparin use in Heparin Induced Thrombocytopenia
- Severe trauma to head, spinal cord, abdomen with spleen or liver laceration or hemorrhage in last 4 weeks
- Spinal or epidural anesthesia planned or performed, discuss with anesthesiologist
- Warfarin use in pregnancy

### Contraindication(s) to pharmacological prophylaxis with anticoagulants?

Yes: If yes explain and choose non pharmacological method unless also contraindicated (Peripheral vascular disease or wounds)

### Risk Factors Associated with Clinical Setting:

<table>
<thead>
<tr>
<th>Score 1 point</th>
<th>Score 2 points</th>
<th>Score 3 points</th>
<th>Score 5 points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minor Surgery</td>
<td>Major Surgery</td>
<td>Major surgery with:</td>
<td>Elective lower extremity amputation</td>
</tr>
<tr>
<td>Trauma</td>
<td>Patients contacts to bed &gt; 24 hr</td>
<td>- myocardial infarction</td>
<td>Hip, pelvis or leg fracture</td>
</tr>
<tr>
<td>Observation</td>
<td>Immobilizing plaster cast</td>
<td>- congestive heart failure</td>
<td>Stroke new onset</td>
</tr>
<tr>
<td>Bed rest &gt; 12 hours</td>
<td>Central Venous Access</td>
<td>- severe sepsis infection</td>
<td>Multiple trauma</td>
</tr>
</tbody>
</table>

**BASELINE RISK SCORE (IF SCORE = 5, GO TO STEP 4) → □**

### Risk Factors Associated with the Patient:

CLINICAL (1 point each unless otherwise indicated)

- Varicose veins
- Inflammatory Bowel disease
- History of DVT/PE
- Active Mallory
- Pregnancy or postpartum < 1 month
- Stroke, history of (5 points)
- Current tobacco use

### TOTAL ADDITIONAL RISK POINTS → □

### DVT/PE Prophylaxis Orders

- Score of 1 or less: Low Risk
  - Early ambulation
- Score of 2: Moderate Risk
  - Sequential compression device and/or Heparin 5000 units q 12 hrs Subcut
- Score of 3-4: High Risk
  - Sequential compression device and/or Heparin 5000 units q 8 hrs Subcut
- Score of 5 or more: Highest Risk
  - Sequential compression device AND at least one of the following
    - Heparin 5000 units q 8 hrs subcut
    - Enoxaparin 40 mg subcut daily
    - Enoxaparin 30 mg subcut q 12 hrs
    - Warfarin daily with goal INR 2-3 (see warfarin orders) along with Heparin or Enoxaparin as above due to concerns for Hypercoagulable states and Warfarin Alone

**PHYSICIAN SIGNATURE Date/Time**
<table>
<thead>
<tr>
<th>Risk Level</th>
<th>Low Risk</th>
<th>Moderate Risk</th>
<th>Highest Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observation patients, expected LOS &lt; 48 hrs: Minor/Ambulatory surgery or Age &lt; 50 and NO other risk factors, or Already on therapeutic anticoagulation</td>
<td>Early ambulation, education</td>
<td>Education</td>
<td>CHOOSE ONE PHARMACOLOGIC option</td>
</tr>
<tr>
<td>Highest Risk</td>
<td>Elective hip or knee arthroplasty</td>
<td>CHOOSE ONE PHARMACOLOGIC option</td>
<td>Enoxaparin 40 mg SC q day</td>
</tr>
<tr>
<td></td>
<td>Acute spinal cord injury with paresis</td>
<td></td>
<td>Enoxaparin 30 mg SC q 24 hrs (for renal insufficiency)</td>
</tr>
<tr>
<td></td>
<td>Multiple major trauma</td>
<td></td>
<td>Heparin 5000 units SC q 8 hrs (End stage renal disease only)</td>
</tr>
<tr>
<td></td>
<td>Abdominal or pelvic surgery for cancer</td>
<td></td>
<td>Enoxaparin 30 mg SC q 12 hrs (knee replacement)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Fondaparinux 2.5 mg SC q day</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>AND Sequential compression device</td>
</tr>
<tr>
<td></td>
<td></td>
<td>OR</td>
<td>The risk of adverse effects of pharmacologic prophylaxis outweighs the risk of DVT / PE</td>
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<tr>
<td></td>
<td></td>
<td>Contraindication to pharmacologic prophylaxis (see reverse):</td>
<td>Mechanical prophylaxis with sequential compression device OR</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Contraindicated (peripheral vascular disease or wounds)</td>
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SIGNATURE / PROVIDER ID ___________________________________ DATE / TIME __________________________
## Keeping Thromboprophylaxis Simple

<table>
<thead>
<tr>
<th>Patient Group</th>
<th>Prophylaxis</th>
<th>Duration</th>
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<tbody>
<tr>
<td>Medical</td>
<td>LMWH or UFH</td>
<td>Discharge</td>
</tr>
<tr>
<td>General surgical</td>
<td>LMWH or UFH</td>
<td>Discharge</td>
</tr>
<tr>
<td>Orthopedics</td>
<td>LMWH, Rivaroxaban plus mech</td>
<td>25 days, 15 days</td>
</tr>
<tr>
<td>Trauma / SCI</td>
<td>LMWH plus mech</td>
<td>Rehab discharge</td>
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<tr>
<td>ICU</td>
<td>LMWH plus mech</td>
<td>discharge</td>
</tr>
<tr>
<td>High bleeding risk</td>
<td>Mechanical until risk diminishes, then LMWH</td>
<td></td>
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What’s New in the ACCP Guidelines, 9th ed., 2/2012

• Decrease in 1A recommendations

• Ortho prophylaxis

• Mechanical Prophylaxis

• VTE prophylaxis in hospitalized medical patients
<table>
<thead>
<tr>
<th>Year</th>
<th>Pages</th>
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<td>2004</td>
<td>123</td>
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<td>2008</td>
<td>182</td>
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<tr>
<td>2012</td>
<td>29</td>
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Why a Dramatic Decrease in IA Recommendations?

Readers of AT9 will find many weak recommendations replacing the strong recommendations of AT8.

1. More critical look at the evidence and the resulting inferences that some evidence is lower quality than previously believed.

2. Recognition of variability in values and preferences.

3. Small number of controversial recommendations that came to a formal vote using anonymous electronic voting, required the endorsement of > 80% of panelists to make a strong recommendation.

4. Exclusion of conflicted experts, who often hold strong opinions about optimal management approaches, from final decisions regarding quality of evidence and strength of recommendations also may have contributed.
• Decrease in 1A recommendations

• Ortho prophylaxis

• Mechanical Prophylaxis

• VTE prophylaxis in hospitalized medical patients
2012 ACCP Guideline

• 2.3.1. In patients undergoing THA or TKA, irrespective of the concomitant use of an IPCD or length of treatment, we suggest the use of LMWH in preference to the other agents we have recommended as alternatives: fondaparinux, apixaban, dabigatran, rivaroxaban, LDUH (all Grade 2B), adjusted-dose VKA, or aspirin (all Grade 2C)

• Allow ASA as a choice (split decision)

• Allows IPC as stand alone option (with caveats)
What’s New in the ACCP Guidelines, 9th ed., 2/2012

Continued

• Decrease in 1A recommendations

• Ortho prophylaxis

• **Mechanical Prophylaxis**

• VTE prophylaxis in hospitalized medical patients
Mechanical Prophylaxis

2008

• Mechanical methods of VTE prophylaxis should be used in patients who are at high risk of bleeding [1C+], or

• As an adjunct to anticoagulant-based prophylaxis [2A] Surgery patients with multiple risk factors

• Careful attention should be directed toward ensuring the proper fit and optimal compliance when using mechanical devices

2012

• endorses a specific SCD type as stand alone-

• ActiveCare+SFT Portable Compression device for both in-hospital and home use
What’s New in the ACCP Guidelines, 9th ed., 2/2012
Cont. . .

• Decrease in 1A recommendations

• Ortho prophylaxis

• Mechanical Prophylaxis

• VTE prophylaxis in hospitalized medical patients
### 2008 ACCP

6.0.1. For acutely ill medical patients admitted to hospital with congestive heart failure or severe respiratory disease, or who are confined to bed and have one or more additional risk factors, including active cancer, previous VTE, sepsis, acute neurologic disease, or inflammatory bowel disease, we recommend thromboprophylaxis with LMWH (Grade 1A), LDUH (Grade 1A), or fondaparinux (Grade 1A).

### 2012 ACCP

2.3. For acutely ill hospitalized medical patients at increased risk of thrombosis, we recommend anticoagulant thromboprophylaxis with LMWH, UFH or fondaparinux (Grade 1B).

2.4. For acutely ill hospitalized medical patients at low risk of thrombosis, we recommend against the use of pharmacologic prophylaxis or mechanical prophylaxis (Grade 1B).

- But “low risk” in 2012 is per the Padua model but that “low risk” group not truly representative of the more acutely US population.
CASE # 2. . .

• A 35-year-old man is admitted to the hospital for management of hepatic failure.

• He has a history of gastrointestinal bleeding within the past three months, no prior VTE, thrombophilia, or malignancy

• His admission platelet count is 40,000/microL
Definitions:

1. **Previous VTE is defined as**: Evidence of previous episode(s) of acute venous thromboembolic episodes in patient history (prior to current admission).

2. **Thrombophilia is defined as**: Familial or acquired disorders of the hemostatic system that result in an increased risk of thrombosis. Examples include, antithrombin III deficiency, resistance to activated protein C, protein C and protein S deficiencies, prothrombin gene mutation, Factor V Leiden, antiphospholipid syndrome.

3. **Cancer is defined as**: Evidence of active malignancy (treated or untreated) within the past 6 months.

This tool is intended for educational purposes only.

For information about the IMPROVE database, please visit [www.outcomes.org](http://www.outcomes.org).
Prophylactic anticoagulation would not be appropriate for this individual, while mechanical means of prophylaxis might be considered.
CASE # 3

• A 65-year-old woman is admitted to the hospital for treatment of an active malignancy.

• She has a history of prior VTE but no history of bleeding, hepatic, or renal failure.

• Her platelet count is 150,000/microL
Prophylactic anticoagulation would be appropriate for this woman.
CASE # 4

• An 86-year-old man is admitted to the hospital for treatment of community-acquired pneumonia.
• He has a history of a duodenal ulcer which has not bled in the past two years.
• He also has a history of an episode of VTE five years ago at which time he was found to be heterozygous for factor V Leiden.
• He has a moderate degree of renal insufficiency, with an estimated glomerular filtration rate of 50 mL/min/m².
As the risks of both bleeding and thrombosis are high in this patient, a decision to employ or not employ prophylactic anticoagulation will depend upon the clinician’s clinical judgment as well as input concerning the patient’s values and preferences.
Anticoagulants In Development

Unfractionated Heparin

Low Molecular Weight Heparin

New Oral Xa Inhibitors
- Rivaroxaban
- Apixaban
- Edoxaban

New Oral IIa Inhibitors
- Ximelagatran
  *Dabigatran etexilate

Fibrin Clot
### Comparative Features of Warfarin and New Oral Anticoagulants

<table>
<thead>
<tr>
<th></th>
<th>Warfarin</th>
<th>Dabigatran etexilate</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Target</strong></td>
<td>VKORC1 Factors II, VII, IX, X</td>
<td>Thrombin</td>
<td>Factor Xa</td>
<td>Factor Xa</td>
</tr>
<tr>
<td><strong>T (max)</strong></td>
<td>72-96 h</td>
<td>2 h</td>
<td>2.5-4 h</td>
<td>3 h</td>
</tr>
<tr>
<td><strong>Half-life</strong></td>
<td>40 h</td>
<td>14-17 h</td>
<td>5-9 h healthy, 9-13 h elderly</td>
<td>8-15 h</td>
</tr>
<tr>
<td><strong>Monitoring</strong></td>
<td>INR-adjusted</td>
<td>Not needed</td>
<td>Not needed</td>
<td>Not needed</td>
</tr>
<tr>
<td><strong>Administration</strong></td>
<td>Once daily</td>
<td>Once or twice daily</td>
<td>Once daily</td>
<td>Twice daily</td>
</tr>
<tr>
<td><strong>Metabolism</strong></td>
<td>Cytochrome P450</td>
<td>80% renal, 20% fecal</td>
<td>66% renal, 33% fecal</td>
<td>25% renal, 75% fecal</td>
</tr>
<tr>
<td><strong>Assay</strong></td>
<td>PT/INR</td>
<td>Ecarin clotting time, Thrombin time</td>
<td>Anti-factor Xa, PiCT®, HepTest®</td>
<td>Anti-factor Xa</td>
</tr>
</tbody>
</table>
Kaplan–Meier Curves for Adjudicated Symptomatic Venous Thromboembolism or Death Related to Venous Thromboembolism during the Treatment Period.

Kaplan–Meier Curves for the Composite of Major and Clinically Relevant Non major Bleeding Events during the Treatment Period.