Medical Treatment of PE: When, Why, for How Long and How Can I Remember How Long?

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Professor Medicine & Surgery
Sidney Kimmel Medical College
Thomas Jefferson University Hospitals

Session 17
11/13/18
7:35-7:50 AM

- Janssen: Research MARINER Study
- Bristol-Meyer Squibb: ADIOS Study
- Portola: APEX Study
- LoweRisk LLC, Co-Chief Development Officer

Disclosure
Financial Relationships
Geno J. Merli, MD, MACP, FHM, FSVM

Risk Stratification PE

<table>
<thead>
<tr>
<th>Early Mortality Risk</th>
<th>Risk Parameters and Scores</th>
<th>Risk Parameters and Scores</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Neck or Hypoplasia</td>
<td>RES (possibly or definitely high)</td>
</tr>
<tr>
<td>High</td>
<td>+ (+)</td>
<td>+ (+)</td>
</tr>
<tr>
<td>Intermediate-High</td>
<td>= +</td>
<td>= +</td>
</tr>
<tr>
<td>Intermediate</td>
<td>= +</td>
<td>= +</td>
</tr>
<tr>
<td>Low</td>
<td>= =</td>
<td>= =</td>
</tr>
</tbody>
</table>

Konstantinides S, et al JACC 2016;67:976

Initiation DOAC Acute PE

<table>
<thead>
<tr>
<th>Study</th>
<th>Initiation DOAC</th>
</tr>
</thead>
<tbody>
<tr>
<td>AMPLIFY</td>
<td>At randomization (Exclusion Criteria: 2 doses LMWH or 36 hrs of UFH)</td>
</tr>
<tr>
<td>EINSTEIN PE</td>
<td>At randomization (Exclusion Criteria: LMWH or UFH for 48 hrs)</td>
</tr>
<tr>
<td>RECOVER/RECOVER II</td>
<td>DOAC started after 5 days LMWH or UFH</td>
</tr>
</tbody>
</table>

Hokusai
DOAC started after 5 days LMWH or UFH

Einstein Investigators NEJM 2010;363:2499
Einstein Investigators NEJM 2012;366:1287-1297
Schulman S, et al NEJM 2009;361:2342
The Hokusai-VTE Investigators, NEJM 2013;369:1406

Einstein PE & AMPLIFY

Anatomical Extent PE

<table>
<thead>
<tr>
<th>Anatomical Extent PE</th>
<th>Rivaroxaban</th>
<th>Standard</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 25% vasculature of single lobe</td>
<td>309 (12.8%)</td>
<td>299 (12.4%)</td>
</tr>
<tr>
<td>Intermediate</td>
<td>1392 (57.5%)</td>
<td>1424 (59%)</td>
</tr>
<tr>
<td>Multiple Lobes &amp; &gt; 25% entire pulmonary vasculature</td>
<td>897 (34.7%)</td>
<td>576 (23.9%)</td>
</tr>
</tbody>
</table>

Anatomic Extent PE

<table>
<thead>
<tr>
<th>Anatomic Extent PE</th>
<th>Apixaban</th>
<th>Standard</th>
</tr>
</thead>
<tbody>
<tr>
<td>Limited</td>
<td>79 (8.5%)</td>
<td>89 (9.8%)</td>
</tr>
<tr>
<td>Intermediate</td>
<td>392 (42.2%)</td>
<td>395 (43.6%)</td>
</tr>
<tr>
<td>Extensive</td>
<td>357 (38.4%)</td>
<td>326 (38%)</td>
</tr>
</tbody>
</table>

Einstein Investigators NEJM 2013;366:1287-1297

Acute Treatment VTE

Direct Oral Anticoagulants

<table>
<thead>
<tr>
<th>Anticoagulant</th>
<th>Duration</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rivaroxaban</td>
<td>15 mg, Q12hrs, 21 days</td>
<td>20mg, Q day</td>
</tr>
<tr>
<td>Apixaban</td>
<td>10mg, Q12hrs, 7 days</td>
<td>5 mg, Q12hrs</td>
</tr>
<tr>
<td>Edoxaban</td>
<td>30 mg, Q day</td>
<td>UFH or LMWH 5-10 days</td>
</tr>
<tr>
<td></td>
<td>20 mg, Q day, if OAC 15-50, Wt &lt; 60 kg, P-gp inhibitor</td>
<td></td>
</tr>
<tr>
<td>Dabigatran</td>
<td>150 mg, Q12hrs</td>
<td>UFH or LMWH 5-10 days</td>
</tr>
</tbody>
</table>

Rosovsky & Merli, Tech Vasc Interven Rad. 2017;20:141
**Primary Efficacy Outcomes in DOAC VTE Treatment Trials**

**EINSTEIN-DVT**
Noninferior
HR (95% CI): 0.68 (0.44, 1.04)

**EINSTEIN-PE**
Noninferior
HR (95% CI): 1.12 (0.75, 1.68)

**AMPLIFY**
Noninferior
RR (95% CI): 0.84 (0.60, 1.18)

**RE-COVER**
Noninferior
HR (95% CI): 1.05 (0.65, 1.70)

**Hokusai-VTE**
Patients With VTE or VTE-Related Death, %
Einstein Investigators. NEJM 2010;363:2499
Einstein Investigators. NEJM 2012;366:1287
Schulman S, et al. NEJM 2009;361:2342
The Hokusai-VTE Investigators. NEJM 2013;369:1406

**Major Bleeding Outcomes in DOAC VTE Treatment Trials**

**EINSTEIN-DVT/EINSTEIN-PE Pooled Analysis**
RE-COVER/RE-COVER II Pooled Analysis
P=0.35 (for superiority)
HR (95% CI): 0.84 (0.59, 1.21)

**AMPLIFY**
P<0.0001 (for superiority)
RR (95% CI): 0.31 (0.17, 0.55)

**ACCP Guidelines 2016**

- **PE: No Cancer**, 3 months anticoagulant therapy, suggest dabigatran, rivaroxaban, apixaban, or edoxaban over vitamin K antagonist (VKA) therapy (all Grade 2B).
- **PE: “Cancer-Associated Thrombosis”**, 3 months or longer, suggest LMWH over VKA therapy, dabigatran, rivaroxaban, apixaban or edoxaban (all Grade 2C).
- **PE: Unprovoked with a low/moderate bleeding risk**, suggest extended anticoagulant therapy over 3 months therapy (Grade 2B), and high bleeding risk, 3 months of anticoagulant therapy over extended therapy (Grade 1B).


**Cancer-Associated VTE New Treatment Guidelines**

**NCCN 2018**
- Treatment options for Cancer Associated VTE include
  - Monotherapy: LMWH (preferred, category 2A); dalteparin, 1; rivaroxaban (2A); fondaparinux (2A); UFH (2B); apixaban for patients who refuse or have compelling reasons to avoid LMWH (2A)
  - Combination therapy: LMWH + edoxaban (category 1); LMWH + warfarin, fondaparinux + warfarin, UFH + warfarin, UFH + edoxaban, LMWH + dabigatran, UFH + dabigatran (all category 2A)

**ISTH 2018**
- Patients with Cancer Associated VTE, low bleeding risk, and no drug-drug interactions with concomitant medications: edoxaban or rivaroxaban
- Patients with cancer, acute VTE diagnosis, and high bleeding risk: LMWH; edoxaban or rivaroxaban can be used if no drug-drug interactions with concomitant medications

**Extended VTE Prevention**

<table>
<thead>
<tr>
<th>Group</th>
<th>Recurrent VTE</th>
<th>Hazard Ratio</th>
<th>Major Bleed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran 150mg Q12</td>
<td>0.4%</td>
<td>0.08 (0.02-0.25)</td>
<td>0.3%</td>
</tr>
<tr>
<td>Placebo</td>
<td>5.6%</td>
<td>-</td>
<td>0.0%</td>
</tr>
<tr>
<td>Apix 5 mg Q12h</td>
<td>1.7%</td>
<td>0.2 (0.11-0.34)</td>
<td>0.1%</td>
</tr>
<tr>
<td>Apix 2.5 mg Q12h</td>
<td>1.7%</td>
<td>0.19 (0.11-0.33)</td>
<td>0.2%</td>
</tr>
<tr>
<td>Placebo</td>
<td>8.5%</td>
<td>-</td>
<td>0.5%</td>
</tr>
<tr>
<td>Riv 20mg Qday</td>
<td>1.3%</td>
<td>0.18 (0.09-0.39)</td>
<td>0.7%</td>
</tr>
<tr>
<td>Placebo</td>
<td>7.1%</td>
<td>-</td>
<td>0.9%</td>
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<tr>
<td>Riv 20mg, Qday</td>
<td>1.5%</td>
<td>0.34 (0.20-0.59)</td>
<td>0.5%</td>
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<tr>
<td>Placebo</td>
<td>4.4%</td>
<td>-</td>
<td>0.3%</td>
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<tr>
<td>ASA 10mg, Qday</td>
<td>1.2%</td>
<td>0.26 (0.14-0.47)</td>
<td>0.4%</td>
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Sedlacek S, et al. NEJM 2012;366:1371-1380
Weitz J, et al. NEJM 2017;376:1211-1220

**Cancer-Associated VTE**

- New Treatment Guidelines
- **Provoked**
- **Unprovoked**
  - Bleeding Risk
  - Renal Status
  - Liver Status
- **Pulmonary Embolism**
  - Cancer Thrombophilia
  - Surgery
  - Trauma
  - Immobility
  - Pregnancy
  - OC
  - Estrogen
- **Extended Rxment**

Vienna Prediction Model VTE
Predicting Unprovoked VTE Recurrence

Risk factors:
- Patient sex — Male > female
- Event type — Pulmonary embolism > proximal DVT > distal DVT
- D-dimer — (drawn 3 weeks after discontinuation of anticoagulation) — higher value = higher risk


DASH Score VTE
Predicting Unprovoked VTE Recurrence

Risk factor Points
- D-dimer abnormal* 2 points
- Age < 50 years 1 point
- Male sex 1 point
- Hormone-associated VTE − 2 points

Eichinger S, et al Circulation 2010;121:1630

MEN Continue and HER DOO2
Predicting Unprovoked VTE Recurrence

Risk factors:
- Post-thrombotic syndrome signs (hyperpigmentation, edema, redness of either leg)
- D-dimer ≥ 230 µg/L (on anticoagulation)
- Body mass index ≥ 30 kg/M²
- Age ≥ 65 years

Women with 0 or 1 of these risk factors have a low annual risk for recurrence (1.6%)

Annual Risk Recurrence higher in Men (13.7%) than Women (5.5%).
Identifies 52.2% of women as being low risk. Could not identify men.

Rodger M et al CMAJ 2008;179:417

Extended VTE Prevention

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Weitz J, et al. NEJM 2017;376:1211

How I Treat PE

Acute PE (1-2 days)
- UFH LMWH

Acute PE (3-5 days)
- UFH LMWH
- Apixaban
- Rivaroxaban
- Dabigatran
- Edoxaban

Post Acute PE (3-6 months)
- Apixaban
- Rivaroxaban
- VKA
- LMWH

Extended Rx PE (No Stop Date)
- Geno.Merli@Jefferson.Edu

# 5 days UFH or LMWH then Rx Dabigatran or Edoxaban