DOAC’s in the Management of Deep Vein Thrombosis and Pulmonary Embolus

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Relevant Disclosures:

• Janssen Pharmaceutical- Speaker
• Daiichi-Sankyo- Speaker
VTE-Scope of the Problem

- Annual Incidence: 900,000 cases per year
- Annual Mortality: 60,000 – 100,000
- Long term morbidity
  - Recurrent VTE: 33% in 10 years
  - Post Thrombotic Syndrome: 40-50% DVT patients

Goals of Treatment - VTE

- Prevent Death from Pulmonary Embolus
- Prevent Symptomatic Recurrent VTE
- 25% risk symptomatic recurrent VTE during 1st 3 months of inadequate therapy
- Prevent/Reduce morbidity from:
  - Post Thrombotic Syndrome (PTS)—at least 25% at 2 yrs
  - Chronic Thromboembolic Pulmonary hypertension- 4% at 2 years
- Minimize Bleeding
Figure. What is PTS? A, Valves in the leg veins help blood flow in the right direction.


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Post Thrombotic Syndrome

Figure 3. Venogram of severely stenotic iliac vein in 40-year-old female with significant edema and varicose veins of left thigh and calf. Retrograde filling of internal iliac vein with pelvic collaterals and ascending lumbar vein is seen (A). Percutaneous transluminal angioplasty (PTA) of iliac vein (B). Post-PTA venography with significant residual stenosis due to elastic recoil (C). Venogram following successful revascularization of iliac vein with Wallstent (Boston Scientific) (D).
Warfarin: A “Gold Standard” Since 1954

Image courtesy of Nick H. Kim, MD.
Rudolph Virchow:

- The elements comprising Virchow’s Triad were never proposed by Virchow.
- Decades following Virchow’s death before consensus was reached that thrombosis was the result of alteration of blood flow/vascular endothelial injury/alterations of constitution of blood.
- Liberal opponent of Bismark and his military budget.
- Bismark challenged him to the legendary “Sausage Dual”.
- Two sausages one loaded with Trichinella Larvae.
ACCP Guidelines:

1. In Patients with Proximal DVT or PE:
   - We Recommend Long Term Anticoagulation (3 months)
   - Over No Such Therapy
ACCP Guidelines:

- In Patients with DVT of the Leg or Pulmonary Embolus AND NO CANCER as Long Term Anticoagulation We Suggest:
  - Dabigatran, Rivaroxaban, Apixaban or Edoxaban over VKA therapy (Grade 2B)
- In Patients with DVT of the Leg or Pulmonary Embolus AND NO CANCER not treated with Dabigatran, Rivaroxaban, Apixaban or Edoxaban, We Suggest:
  - VKA therapy over LMWH (Grade 2C)

RE-COVER Study

Dabigatran versus Warfarin in the Treatment of Acute Venous Thromboembolism

Sam Schulman, M.D., Clive Kearon, M.D., Ajay K. Kakkar, M.D., Patrick Mismetti, M.D., Sebastian Schellong, M.D., Henry Eriksson, M.D., David Baanstra, M.Sc., Janet Schnee, M.D., and Samuel Z. Goldhaber, M.D., for the RE-COVER Study Group

Dabigatran 150 mg, BID for 6 months
Double Blind, Double Dummy, Non-Inferiority

Schulman S. et al NEJM 2009;361:2342-2352
“NOACs in the Management of DVT/PE”
Bryan W. Kluck, D.O.

![Diagram of RE-COVER Study](image1)

**RE-COVER Study**

<table>
<thead>
<tr>
<th>VTE</th>
<th>Dabigatran 150 mg, BID</th>
<th>2.4%</th>
<th>1.6%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Warfarin INR 2-3</td>
<td>2.1%</td>
<td>1.9%</td>
</tr>
</tbody>
</table>

**Parenteral Anticoagulant**
Median 9 days

**Warfarin TTR= 60%**


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![Diagram of RE-COVER Study Index Events](image2)

**RE-COVER Study**

**Index Events**

<table>
<thead>
<tr>
<th>Type of index event — no. (%)</th>
<th>Dabigatran 1273</th>
<th>Warfarin 1266</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deep-vein thrombosis only</td>
<td>880 (69.1)</td>
<td>869 (68.6)</td>
</tr>
<tr>
<td>Pulmonary embolism only</td>
<td>270 (21.2)</td>
<td>271 (21.4)</td>
</tr>
<tr>
<td>Both deep-vein thrombosis and pulmonary embolism</td>
<td>121 (9.5)</td>
<td>124 (9.8)</td>
</tr>
<tr>
<td>Neither deep-vein thrombosis nor pulmonary embolism</td>
<td>2 (0.2)</td>
<td>2 (0.2)</td>
</tr>
<tr>
<td>Cancer — no. (%)</td>
<td>64 (5.0)</td>
<td>57 (4.5)</td>
</tr>
<tr>
<td>Previous venous thromboembolism — no. (%)</td>
<td>327 (25.7)</td>
<td>322 (25.4)</td>
</tr>
</tbody>
</table>


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POMA 108th Annual Clinical Assembly
May 4-7, 2016
RE-COVER Study

Major Bleeding

<table>
<thead>
<tr>
<th>Safety analysis</th>
<th>Dabi (1.6)</th>
<th>Warfarin (1.9)</th>
<th>p-value (0.45–1.48)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major bleeding event</td>
<td>20</td>
<td>24</td>
<td>0.82</td>
</tr>
<tr>
<td>Fatal event</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Bleeding into critical organ</td>
<td>1</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Intracranial</td>
<td>0</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Hemarthrosis</td>
<td>1</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Hemothysis</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Event resulting in fall in hemoglobin level or need for blood transfusions</td>
<td>20</td>
<td>18</td>
<td>0.63</td>
</tr>
<tr>
<td>Major or clinically relevant nonmajor bleeding event</td>
<td>71</td>
<td>111</td>
<td>0.63</td>
</tr>
</tbody>
</table>

Schulman S, et al. NEJM 2009;361:2342-2352

Dabigatran = 150mg, BID

INR = 60% TTR

HR = 1.1 (0.65–1.84)

TTR = Therapeutic Time in Range

Schulman S, et al. NEJM 2009;361:2342-2352
A limitation of the study is that the first dose of dabigatran, was given only after initial parenteral anticoagulation therapy had been administered for median of 9 days.

“There is no data to support the use of dabigatran monotherapy for acute venous thromboembolism”
Rivaroxaban 15 mg, PO, BID x 3 weeks then 20 mg, Qday
Enoxaparin 1mg/kg/Q12hrs bridge to Warfarin INR 2-3
Open Label, Non-Inferiority trial

Einstein DVT

Rivaroxaban 15 mg, BID x 3 wks
20 mg, Qday
VTE Major Bld
2.1% 8.1%

Enoxaparin
Warfarin INR 2-3
3.0% 8.1%

3, 6, 12 months

Warfarin TTR = 57.7%
**Einstein Acute DVT Study**

**Causes of VTE**

<table>
<thead>
<tr>
<th>Cause of DVT or PE — no. (%)</th>
<th>Riva (no. (%))</th>
<th>Standard (no. (%))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unprovoked</td>
<td>1055 (60.9)</td>
<td>1083 (63.0)</td>
</tr>
<tr>
<td>Recent surgery or trauma</td>
<td>338 (19.5)</td>
<td>335 (19.5)</td>
</tr>
<tr>
<td>Immobilization</td>
<td>265 (15.3)</td>
<td>260 (15.1)</td>
</tr>
<tr>
<td>Estrogen therapy</td>
<td>140 (8.1)</td>
<td>115 (6.7)</td>
</tr>
<tr>
<td>Active cancer</td>
<td>118 (6.8)</td>
<td>89 (5.2)</td>
</tr>
<tr>
<td>Puerperium</td>
<td>6 (0.3)</td>
<td>11 (0.6)</td>
</tr>
<tr>
<td>Known thrombophilic condition — no. (%)</td>
<td>107 (6.2)</td>
<td>116 (6.8)</td>
</tr>
<tr>
<td>Previous VTE — no. (%)</td>
<td>336 (19.4)</td>
<td>330 (19.2)</td>
</tr>
</tbody>
</table>

*Einstein Investigators NEJM 2010;363:2499-2510*
**Einstein Acute DVT Study**

**Safety Outcomes**

<table>
<thead>
<tr>
<th>Safety</th>
<th>Riva</th>
<th>Standard</th>
</tr>
</thead>
<tbody>
<tr>
<td>Safety population</td>
<td>1718</td>
<td>1711</td>
</tr>
<tr>
<td>First major or clinically relevant nonmajor bleeding occurring during treatment</td>
<td>139 (8.1)</td>
<td>138 (8.1)</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>14 (0.8)</td>
<td>20 (1.2)</td>
</tr>
<tr>
<td>Contributing to death</td>
<td>1 (&lt;0.1)</td>
<td>5 (0.3)</td>
</tr>
<tr>
<td>In a critical site</td>
<td>3 (0.2)</td>
<td>3 (0.2)</td>
</tr>
<tr>
<td>Associated with a fall in hemoglobin of ≥2 g per deciliter, transfusion of ≥2 units, or both</td>
<td>10 (0.6)</td>
<td>12 (0.7)</td>
</tr>
<tr>
<td>Clinically relevant nonmajor bleeding</td>
<td>126 (7.3)</td>
<td>119 (7.0)</td>
</tr>
</tbody>
</table>

HR = 0.97 (95% CI, 0.76 to 1.22, P=0.77)
Oral Rivaroxaban for the Treatment of Symptomatic Pulmonary Embolism

The EINSTEIN-PE Investigators*

Rivaroxaban 15 mg, PO, BID x 3 weeks then 20 mg, Qday
Enoxaparin 1mg/kg/Q12hrs bridge to Warfarin INR 2-3
Open Label, Non-Inferiority

Einstein Investigators NEJM 2012;366:1287-1297

Einstein PE

Rivaroxaban
15 mg, BID x 3 wks
20 mg, Qday

Enoxaparin
Warfarin INR 2-3

VTE | Major Bld
---|---
2.1% | 1.1%
1.8% | 2.2%

Non-Inferior

3, 6, 12 months

Warfarin TTR = 62.7%

Einstein-PE Investigators NEJM 2012;366:1287-1297
NOACs in the Management of DVT/PE
Bryan W. Kluck, D.O.

Einstein Investigators NEJM 2012;366:1287-1297

Einstein PE

A Primary Efficacy

INR = 62.7% TTR

Einstein Investigators NEJM 2012;366:1287-1297

Einstein PE

Major Bleeding

Einstein Investigators NEJM 2012;366:1287-1297
## Einstein PE

### Causes

<table>
<thead>
<tr>
<th>Cause of pulmonary embolism — no. (%)</th>
<th>Riva</th>
<th>Standard</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unprovoked</td>
<td>1566 (64.7)</td>
<td>1551 (64.3)</td>
</tr>
<tr>
<td>Recent surgery or trauma</td>
<td>415 (17.2)</td>
<td>398 (16.5)</td>
</tr>
<tr>
<td>Immobilization</td>
<td>384 (15.9)</td>
<td>380 (15.7)</td>
</tr>
<tr>
<td>Estrogen therapy</td>
<td>207 (8.6)</td>
<td>223 (9.2)</td>
</tr>
<tr>
<td>Active cancer</td>
<td>114 (4.7)</td>
<td>109 (4.5)</td>
</tr>
<tr>
<td>Known thrombophilic condition — no. (%)</td>
<td>138 (5.7)</td>
<td>121 (5.0)</td>
</tr>
<tr>
<td>Previous venous thromboembolism — no. (%)</td>
<td>455 (18.8)</td>
<td>489 (20.3)</td>
</tr>
</tbody>
</table>

Einstein Investigators NEJM 2012;366:1287-1297

### Anatomical Extent

<table>
<thead>
<tr>
<th>Anatomical extent of pulmonary embolism — no. (%)</th>
<th>Riva</th>
<th>Standard</th>
</tr>
</thead>
<tbody>
<tr>
<td>Limited: ≤25% of vasculature of a 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 (59.0)</td>
</tr>
<tr>
<td>Extensive: multiple lobes and &gt;25% of entire pulmonary vasculature</td>
<td>597 (24.7)</td>
<td>576 (23.9)</td>
</tr>
</tbody>
</table>

Einstein Investigators NEJM 2012;366:1287-1297
Apixaban

- Amplify trial

AMPLIFY

Study Treatment

- Apixaban group
  - 10 mg apixaban twice daily, first 7 days
  - 5 mg twice daily for 6 months
  - Placebo enoxaparin injections
  - Placebo warfarin tablets

- Conventional therapy
  - Enoxaparin 1mg/kg q12 hours for 5 days
  - Warfarin continued for 6 months
  - Placebo apixaban tablets

- Blinded monthly INR monitoring with encrypted results
Figure 1. Enrollment and Outcomes.
All five patients who were excluded from all the analyses owing to absent source documentation were enrolled at the same center.
A fixed-dose Regimen of Apixaban alone was noninferior to conventional therapy for the treatment of acute venous thromboembolism and was associated with significantly less bleeding.
Hokusai VTE Study Design

Objective confirmed VTE
Stratified randomization:
PE or DVT
Risk factors
Edoxaban dose adjustment

edoxaban 60 mg/30 mg

Sham/RR
RR
Warfarin

Days 1-5
Day 6-12
3 Months
12 Months

HOKUSAI-VTE: edoxaban non-inferior to warfarin in prevention of recurrent VTE

Adjudicated Recurrent VTE (%)


Buller et al., NEJM 2013
HOKUSAI-VTE: fewer bleedings after edoxaban vs. warfarin in patients with VTE or PE

Buller et al., NEJM 2013

HOKUSAI

Edoxaban administered once daily after initial treatment with heparin was non-inferior to high quality standard therapy and caused significantly less bleeding in a broad spectrum of patients with venous thromboembolism including those with severe pulmonary embolism
"NOACs in the Management of DVT/PE"
Bryan W. Kluck, D.O.

Comparisons of Designs of Phase III Acute VTE Trials

<table>
<thead>
<tr>
<th>RE-COVER&lt;sup&gt;a,b&lt;/sup&gt;</th>
<th>EINSTEIN&lt;sup&gt;c,d&lt;/sup&gt;</th>
<th>AMPLIFY&lt;sup&gt;e&lt;/sup&gt;</th>
<th>HOKUSAIf</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug</td>
<td>Dabigatran</td>
<td>Rivaroxaban</td>
<td>Apixaban</td>
</tr>
<tr>
<td>N</td>
<td>5173</td>
<td>8281</td>
<td>5395</td>
</tr>
<tr>
<td>Design</td>
<td>Double blind</td>
<td>PROBE</td>
<td>Double blind</td>
</tr>
<tr>
<td>Indication</td>
<td>VTE</td>
<td>DVT or PE</td>
<td>VTE</td>
</tr>
<tr>
<td>Heparin bridge</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Duration (mo)</td>
<td>6</td>
<td>3, 6, 12</td>
<td>6</td>
</tr>
</tbody>
</table>


First Recurrent VTE or VTE Related Death

<table>
<thead>
<tr>
<th>DOAC (n/N)</th>
<th>VKA (n/N)</th>
<th>Risk ratio (95% CI)</th>
<th>RR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>AMPLIFY</td>
<td>59/2669 (2.3%)</td>
<td>71/2635 (2.7%)</td>
<td>0.84 (0.60-1.18)</td>
<td>0.31</td>
</tr>
<tr>
<td>EINSTEIN-VVT</td>
<td>30/1731 (2.1%)</td>
<td>53/1718 (3.0%)</td>
<td>0.70 (0.46-1.07)</td>
<td>0.10</td>
</tr>
<tr>
<td>EINSTEIN-PE</td>
<td>50/2419 (2.1%)</td>
<td>44/2413 (1.8%)</td>
<td>1.13 (0.70-1.69)</td>
<td>0.54</td>
</tr>
<tr>
<td>Hokusai-VTE</td>
<td>66/4116 (1.6%)</td>
<td>80/4122 (1.9%)</td>
<td>0.83 (0.60-1.14)</td>
<td>0.25</td>
</tr>
<tr>
<td>RE-COVER</td>
<td>30/1274 (2.4%)</td>
<td>27/1265 (2.1%)</td>
<td>1.10 (0.65-1.84)</td>
<td>0.71</td>
</tr>
<tr>
<td>RE-COVER II</td>
<td>30/1279 (2.3%)</td>
<td>28/1289 (2.2%)</td>
<td>1.08 (0.65-1.80)</td>
<td>0.77</td>
</tr>
<tr>
<td>Combined (random)</td>
<td>271/13430 (2.0%)</td>
<td>301/13442 (2.2%)</td>
<td>0.90 (0.77-1.06)</td>
<td>0.21</td>
</tr>
</tbody>
</table>

Major Bleeding


Bleeding Breakdown

Clinical VTE

- Provoked (70% of all patients)
  - Associated with known risk factors
  - Hospital, Surgery, cancer, medical illness
  - Risk factors may be ongoing (CA, APLA)
  - If risk factor reversible/transient - 2%/yr recurrence after 3 months of A/C
- Unprovoked (30% of all patients)
  - Absence of identifiable risk factors
  - 7-11% per year recurrence for DVT/PE if anticoagulation stopped 3, 6, 12, 24 months

ACCP Guidelines:

- In Patients with DVT of the Leg or Pulmonary Embolus Provoked By Surgery, We Recommend:
  - Treatment With Anticoagulation for 3 Months over (1) Treatment of shorter duration (Grade 1B) or (2) Treatment over Longer (6, 12, 24 m.) Duration (Grade 1B) or (3) Extended Therapy (no stop date) (Grade 1B)
ACCP Guidelines:

• In Patients with Distal DVT of Leg Provoked by Surgery or Nonsurgical Transient Risk Factors, We suggest:

• Anticoagulation for 3 Months over (1) shorter (2C) (2) Longer (6,12,24) (1B) or Extended (no stop date) (1B)

ACCP Guidelines:

• In Patients with Unprovoked DVT of the Leg or Pulmonary Embolus We Recommend:

• At Least 3 months of Anticoagulation over (1)shorter (1B) or (2)Longer (6,12,24) (1C)

• But...
ACCP Guidelines:

1. In Patients with a First Unprovoked DVT or Pulmonary Embolus who have Low to Moderate Bleeding Risk: We Suggest:
   - Extended Anticoagulation (No Stop Date) over 3 Months of Anticoagulation

2. In Patients with a First Unprovoked DVT or Pulmonary Embolus who have High Bleeding Risk, We Recommend:
   - 3 Months of Anticoagulation over Extended Therapy (No Scheduled Stop Date)
   - Periodic (Annual) Clinical Reassessment

ACCP Guidelines:

2nd Unprovoked:

- Low Bleeding Risk: Extended Therapy over 3M
- Moderate Bleeding Risk: Extended Tx over 3M
- High Bleeding Risk: 3M over Extended Tx
**VTE Treatment Paradigms**

- **Mono Therapy**
  - NOAC Started (rivaroxaban, apixaban)
- **Bridge Therapy**
  - BRIDGE
  - VKA AC Monitoring Required
- **Switch Therapy**
  - UFH/LMWH
  - NOAC Started (dabigatran, edoxaban)

- New oral anticoagulant
- IV or subcutaneous anticoagulant
- IV or subcutaneous + VKA oral anticoagulant
- VKA oral anticoagulant

- Parenteral Discontinued

---

**Einstein Continued Treatment study**

- 1,197 Patients underwent randomization
- 602 Were assigned to receive rivaroxaban
  - 620 Were included in intention-to-treat analysis
  - 4 Did not receive rivaroxaban
  - 598 Were included in safety analysis
- 595 Were assigned to receive placebo
  - 594 Were included in intention-to-treat analysis
  - 590 Were included in safety analysis
  - 1 Was excluded because informed consent was invalid
  - 4 Did not receive placebo
Einstein DVT-Extend

DVT

<table>
<thead>
<tr>
<th>Rivaroxaban 20 mg, Qday</th>
<th>VTE</th>
<th>Major Bld</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Rxed</td>
<td>1.3%</td>
<td>0.7%</td>
</tr>
<tr>
<td>Placebo</td>
<td>7.1%</td>
<td>0%</td>
</tr>
</tbody>
</table>

3, 6, 12 mo
6-12 mo

Einstein Investigators NEJM 2010;363:2499-2510

Extended Use of Dabigatran, Warfarin, or Placebo in Venous Thromboembolism

Sam Schulman, M.D., Ph.D., Clive Kearon, M.D.,
Ajay K. Kakkar, M.B., B.S., Ph.D., Sebastian Schellong, M.D.,
Henry Eriksson, M.D., Ph D., David Banstra, M.Sc.,
Anne Mathilde Vrannme, M.Sc. Pharm., Jeffrey Friedman, M.D.,
Patrick Mismetti, M.D., and Samuel Z. Goldhaber, M.D.,
for the RE-MEDY and the RE-SONATE Trials Investigators*

Schulman S. et al NEJM 2013;368:709-718

Double Blind, Randomized Trial
NOACs in the Management of DVT/PE

Bryan W. Kluck, D.O.

POMA 108th Annual Clinical Assembly
May 4-7, 2016

**RE-MEDY**

- **VTE**
  - Dabigatran 150 mg, BID: 1.8% for VTE, 0.9% for Major Bld
  - Warfarin INR 2-3: 1.3% for VTE, 1.8% for Major Bld

- **Patient Rx** 3 to 12 months

**RE-SONATE**

- **DVT**
  - Dabigatran 150 mg, BID: 0.4% for VTE, 0.3% for Major Bld
  - Placebo: 5.6% for VTE, 0% for Major Bld

- **Patient Rx** 6 to 18 months

Schulman S, et al NEJM 2013;368:709-718
**RE-MEDY Study**

A. Recurrent Venous Thromboembolism or Related Death in the Active-Control Study

![Graph showing estimated cumulative risk over months since randomization for Dabigatran and Warfarin.](Schulman_S_et_al_NEJM_2013;368:709-718)

- **Dabigatran**: 1.8%
- **Warfarin**: 1.3%

No. at Risk:
- **Dabigatran**: 1420, 1409, 1389, 1259, 1087, 995, 852, 793, 723, 670, 600, 539, 492, 449, 403, 362, 321, 282, 243, 205, 168, 131, 97, 68, 39, 31, 0
- **Warfarin**: 1426, 1420, 1388, 1253, 1081, 997, 913, 839, 765, 691, 618, 545, 472, 400, 330, 258, 188, 118, 50, 3, 0

P=0.01 for noninferiority

**RE-SONATE Study**

B. Recurrent Venous Thromboembolism, Related Death, or Unexplained Death in the Placebo-Control Study

![Graph showing estimated cumulative risk over months since randomization for Placebo and Dabigatran.](Schulman_S_et_al_NEJM_2013;368:709-718)

- **Placebo**: 5.6%
- **Dabigatran**: 0.4%

No. at Risk:
- **Dabigatran**: 681, 677, 653, 631, 591, 557, 508, 461, 186
- **Matching placebo**: 682, 615, 586, 537, 502, 463, 171

P=0.001 at 6 mo
P=0.006 at 12 mo
P=0.03 at 18 mo

Schulman S, et al NEJM 2013;368:709-718
**RE-MEDY Study**

- **Any Bleeding**
  - Dabigatran: 19.4%
  - Warfarin: 26.2%

**Major Bleeding**
- Dabigatran: 0.9%
- Warfarin: 1.3%

Schulman S, et al. NEJM 2013;368:709-718

**RE-SONATE Study**

- **Any Bleeding**
  - Dabigatran: 10.5%
  - Placebo: 5.9%

**Major or Clinically Relevant Bleeding**
- Dabigatran: 5.3%
- Placebo: 1.8%

Schulman S, et al. NEJM 2013;368:709-718
Apixaban for Extended Treatment of Venous Thromboembolism

Giancarlo Agnelli, M.D., Harry R. Buller, M.D., Ph.D., Alexander Cohen, M.D., Madelyn Curto, D.V.M., Alexander S. Gallus, M.D., Margot Johnson, M.D., Anthony Porcari, Ph.D., Pharm.D., Gary E. Raskob, Ph.D., and Jeffrey I. Weitz, M.D., for the AMPLIFY-EXT Investigators*

Agnelli G, et al NEJM 2012;1-10

AMPLIFY-EXT

<table>
<thead>
<tr>
<th>VTE</th>
<th>VTE</th>
<th>Major Bld</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apixaban 2.5 mg, BID</td>
<td>1.7%</td>
<td>0.2%</td>
</tr>
<tr>
<td>Apixaban 5.0 mg, BID</td>
<td>1.7%</td>
<td>0.1%</td>
</tr>
<tr>
<td>Placebo</td>
<td>8.8%</td>
<td>0.5%</td>
</tr>
</tbody>
</table>

Rx 6-12 mo

12 months

### AMPLIFY-EXT

#### Risk factors for recurrent VTE — no. (%)†

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Apixaban 2.5</th>
<th>Apixaban 5</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active cancer</td>
<td>15 (1.8)</td>
<td>9 (1.1)</td>
<td>18 (2.2)</td>
</tr>
<tr>
<td>Persistent or permanent immobilization</td>
<td>19 (2.3)</td>
<td>29 (3.6)</td>
<td>22 (2.7)</td>
</tr>
<tr>
<td>Previous deep-vein thrombosis or pulmonary embolism</td>
<td>99 (11.8)</td>
<td>118 (14.5)</td>
<td>99 (11.9)</td>
</tr>
<tr>
<td>Known prothrombotic genotype</td>
<td>32 (3.8)</td>
<td>26 (3.2)</td>
<td>36 (4.3)</td>
</tr>
<tr>
<td>Use of antiplatelet agents‡</td>
<td>120 (14.3)</td>
<td>96 (11.8)</td>
<td>107 (13.0)</td>
</tr>
</tbody>
</table>


---

### AMPLIFY-EXT

**Symptomatic Recurrent VTE or VTE Related Death**

**AMPLIFY-EXT**

Major-Clinical Relevant Non-Major Bleeding

![Graph showing cumulative event rate (%) over months](image)


**ACCP Guidelines:**

- In Patients with Isolated Distal DVT of the Leg Without Severe Symptoms or risk for extension **We Recommend:**
  - Serial Imaging over Anticoagulation
  - In Patients with Isolated Distal DVT of the Leg With Severe Symptoms or risk for extension **We Recommend:**
  - Anticoagulation over Serial Imaging
ACCP Guidelines:

• In Patients with Acute DVT of the Leg We Suggest NOT using compression stockings to Prevent PTS

VTE and Cancer

• “There appears in the cachexiae...a particular condition of the blood that predisposes it to spontaneous coagulation”

• Armand Trousseau, 1865
VTE and Cancer

• Cancer is independent and major risk factor for VTE
• Up to 20% of patients with cancer have VTE
• CA+VTE: Risk of Recurrent VTE, bleeding and morbidity
• VTE Recurrence with D/C A/C=15%/Y
• VTE is second leading cause of death in cancer patients
ACCP Guidelines:

- In Patients with DVT of the Leg or Pulmonary Embolus And Active Cancer We Recommend:

  - (1) No High Bleeding Risk: Extended Therapy over 3M
  - (2) High Bleeding Risk: Extended Therapy over 3 M
    Reassess Annually
ACCP Guidelines:

- In Patients with DVT of the Leg or Pulmonary Embolus and Cancer, We Suggest:
- Low Molecular Weight Heparin over VKA therapy, Dabigatran, Rivaroxaban, Apixaban, or Edoxaban (All Grade 2C)

DOACs in Cancer Patients
Outpatient Treatment of VTE

- REITE Registry:
  - 13,493 patients – 1/3 treated at home
    - 0.2% PE
    - 0.09% recurrent DVT
    - 0.38% Major Bleeding
    - 0.59% Death

Patients at home had similar VTE rates and lower bleeding

Lozano, F J VascSurg 2014, 59 1362-1367
Current guidelines recommend initial treatment at home over treatment in-hospital (Grade 1B)

Current guidelines recommend early discharge over standard discharge (Grade 2B)

These recommendations are contingent on adequate home circumstances, including:

- Well-maintained living conditions
- Strong support network
- Phone access
- Patient feeling well enough for home treatment
- Ability to be promptly rehospitalized

These recommendations are contingent on adequate home circumstances, including:

- Controlled clinical trials suggest that outpatient management is at least as effective as inpatient management for acute DVT

<table>
<thead>
<tr>
<th>Study</th>
<th>VTE Recurrence (%)</th>
<th>Major Bleeding (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ramacciotti et al, 2004</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>Daskalopoulos et al, 2005</td>
<td>9.1</td>
<td>3.6</td>
</tr>
<tr>
<td>Chong et al, 2005</td>
<td>2.7</td>
<td>7.5</td>
</tr>
<tr>
<td>Boccalon et al, 2000</td>
<td>9.5</td>
<td>2</td>
</tr>
</tbody>
</table>

**Controlled clinical trials suggest that outpatient management is at least as effective as inpatient management for acute DVT**
Considerations for Patient Selection for Outpatient Therapy

- 60%-95% of patients with acute, proximal DVT may be eligible for outpatient therapy
- Exclusion criteria on institutional protocols include:
  - Comorbid illness requiring hospitalization
  - Active or high risk for bleeding
  - Severe hypertension
  - Catheter-associated DVT
  - Recent surgery
  - Morbid obesity
  - Hypercoagulable state
  - Pregnancy

Risk Stratification DVT

- 1.) Bilateral DVT
- 2.) Renal Insufficiency
- 3.) Body Wgt < 70 kg
- 4.) Recent Immobility
- 5.) CHF
- 6.) CA

- <2 1.0% adverse events
- >2 4.7% adverse events

• Trujillo-Santos et al J Vasc Surg 2006
Outpatient PE

- Meta-analysis -1258 patients
- Recurrent VTE: 1.47%
- Major Bleeding: 0.81%
- ICH: 0.29%
- 3 Month Mortality: 1.5%
  - Piran S et al. Thromb Res 2013

Considerations for Identifying Patients With Low-Risk PE

- Risk stratification tools may help to identify patients with low-risk PE who may be candidates for outpatient therapy
- Potential candidates include patients with acute PE who are clinically/hemodynamically stable with good cardiopulmonary reserve
  - No hypoxia
  - Systolic BP ≥100
  - No recent bleeding
  - No severe chest pain
  - Platelet count ≥70,000/mm³
  - No severe liver or renal disease
  - PE did not occur while on anticoagulant therapy
Eligible for Outpatient treatment?

Clinical Scores

- **PESI**: Well validated; 11 variables increasing mortality
- **Simplified PESI**: Bedside using 6/11 variables
- **Hestia**: Detects patients at low risk of adverse events; may identify RVD
- **Grace**: Detects Low risk patients with high accuracy
PESI and simplified PESI

<table>
<thead>
<tr>
<th>Variable</th>
<th>Score</th>
<th>PESI</th>
<th>sPESI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt;80 years</td>
<td>Age in years</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Male sex</td>
<td>10</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>History of cancer</td>
<td>30</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>History of heart failure</td>
<td>10</td>
<td>1*</td>
<td></td>
</tr>
<tr>
<td>History of chronic lung disease</td>
<td>10</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Pulse ≥110 bpm</td>
<td>20</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Systolic BP &lt;100 mm Hg</td>
<td>30</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Respiratory rate ≥30 breaths/min</td>
<td>20</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Temperature &lt;36°C</td>
<td>20</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Altered mental status†</td>
<td>60</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>SaO₂ &lt;90%‡</td>
<td>20</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

*Heart failure or history of chronic lung disease combined into a single category of chronic cardiopulmonary disease.
†Disorientation, lethargy, stupor, or coma.
‡With or without the administration of supplemental oxygen.

Classification by Total Score

<table>
<thead>
<tr>
<th>PESI</th>
<th>sPESI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I ≤65</td>
<td>Low risk=0</td>
</tr>
<tr>
<td>Class II 66-85</td>
<td></td>
</tr>
<tr>
<td>Class III 86-105</td>
<td></td>
</tr>
<tr>
<td>Class IV 106-125</td>
<td>High risk≥1</td>
</tr>
<tr>
<td>Class V &gt;125</td>
<td></td>
</tr>
</tbody>
</table>

Other Factors – Home Treatment

- No severe comorbidity
- No Bleeding Risk
- Mental Status
- Access/Transportation- follow up Visits
- Patient Motivation (CA; Young)
- Family Support
DOACs-Patient Concerns

• DOACs have similar adverse effects as VKAs (bleeding)
• Lack of Reversal Agents engenders reluctance
• Life threatening/Fatal bleeding reduced up to 50% with DOACs
• Outcomes with DOAC associated major bleeding no worse than Warfarin
• No true reversal agents for Warfarin (4F PCC does not significantly ↑ hemostatic efficacy or ↓ mortality)

Reversal of DOACs

KEEP CALM AND STOP BLEEDING
Reversal of DOACs

Where Reversal Needed

- Life Threatening or Uncontrolled Bleeding
- Emergency Surgery/Urgent Procedures
First Things First
Supportive Measures:

• All DOACs have short half lives (≈12h)
• Assess for contributory medications (antiplatelet tx)
• Maintain BP, monitor comorbidities
• Resuscitation (IV Fluids, Blood Products)
• Maintain Diuresis –drug clearance
• Mechanical Compression/Surgery to stop bleeding

Idarucizumab- available

• Humanized Fab fragment
• Specific- high affinity for Dabigatran
• Renal Excretion
• Short Half Life
• No intrinsic procoagulant or anticoagulant activity
• Immediate, complete and sustained reversal of Dabigatran
Idarucizumab Is a True, Specific Antidote to Dabigatran

Development
- Monoclonal mouse antibody developed with high dabigatran binding affinity
- Monoclonal antibody then humanized and directly expressed as a Fab fragment in hamster cells

Properties
- Potent binding affinity ~350 x higher than binding of dabigatran to thrombin
- No procoagulant or anticoagulant effects expected
- Short half-life
- Intravenous administration, immediate onset of action

Expected Low Risk of Adverse Reactions
- No Fc receptor binding
- No endogenous targets


Andexanet Alfa-In Development

Andexanet at a glance

- Mechanism of action: Recombinant and inactivated form of factor Xa
- Binds factor Xa inhibitors: apixaban, rivaroxaban, and edoxaban
- Proposed dose: 400 mg IV bolus ±2 hours infusion at 4 mg/min
- Time to effect: 2 minutes; 94% decrease in anti Xa activity
- Adverse effects: No known prothrombotic effect – tissue factor pathway inhibitor interaction deserves further investigation
- Possible indications: Life-threatening hemorrhage, Emergent surgery
Andexanet alfa
Antidote for Factor Xa Inhibitors

Properties
- An engineered version of human FXa, lacking the direct catalytic activity of the native protein
- Acts as a Factor Xa decoy. Binds with high-affinity, blocking inhibition of FXa

Clinical Development
- Pre-clinical data collected in numerous models
- Phase 2 dose response assessments in 144 healthy volunteers indicated initial significant, dose-dependent decreases in anti-Xa activity are followed by slow increases in anti-Xa activity to high levels
- Two studies in healthy subjects aged 50-75 investigating the reversal of rivaroxaban, and apixaban
- Phase 3 study in healthy volunteers: reversed the anticoagulation of apixaban and rivaroxaban


PER977- In Development

<table>
<thead>
<tr>
<th>Ciraparantag (PER977) at a glance</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mechanism of action</strong></td>
</tr>
<tr>
<td>Synthetic molecule binds:</td>
</tr>
<tr>
<td>Direct Xa inhibitors (apixaban, rivaroxaban, and edoxaban)</td>
</tr>
<tr>
<td>Direct thrombin inhibitors (dabigatran)</td>
</tr>
<tr>
<td>Unfractionated and low molecular weight heparin</td>
</tr>
<tr>
<td><strong>Proposed dose</strong></td>
</tr>
<tr>
<td><strong>Time to effect</strong></td>
</tr>
<tr>
<td><strong>Adverse effects</strong></td>
</tr>
<tr>
<td>PT remains elevated</td>
</tr>
<tr>
<td>Does not appear to be sensitive marker for PER977-mediated anticoagulation reversal</td>
</tr>
<tr>
<td>No prothrombotic effect</td>
</tr>
<tr>
<td><strong>Possible indications</strong></td>
</tr>
<tr>
<td>Emergent surgery</td>
</tr>
<tr>
<td>Elective procedures to minimize time off anticoagulation</td>
</tr>
</tbody>
</table>
Specific antidotes to NOACs

<table>
<thead>
<tr>
<th></th>
<th>Idarucizumab</th>
<th>PER977</th>
<th>Andexanet alpha</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Structure</strong></td>
<td>Humanized Fab fragment</td>
<td>Synthetic small molecule</td>
<td>Human rXa variant</td>
</tr>
<tr>
<td><strong>Target</strong></td>
<td>Dabigatran</td>
<td>Universal</td>
<td>FXa inhibitors</td>
</tr>
<tr>
<td><strong>Binding</strong></td>
<td>Non-competit., High affinity</td>
<td>?</td>
<td>Competitive</td>
</tr>
<tr>
<td><strong>Clinical studies</strong></td>
<td>Rapid complete reversal</td>
<td>?</td>
<td>Rapid, near complete reversal</td>
</tr>
</tbody>
</table>

“NOACs in the Management of DVT/PE”
Bryan W. Kluck, D.O.