VTE-Pulmonary Embolism
Contemporary Management

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Disclosures

Investigator:
- Boehringer-Ingelheim [RELY]
- Daiichi Sankyo [ENGAGE]

Speakers Bureau:
- Janssen
VTE

Definitions
Diagnosis
Management: Conventional NOACs
VTE

VTE: Venous thromboembolism – deep vein thrombosis (DVT) to pulmonary embolism (PE)

*Note: most patients with PE have DVT...many patients with DVT have asymptomatic PE*
DVT, DVT, died of PE
PE

200,000 deaths/year

30% mortality if diagnosis is missed
Etiology of VTE

- Immobilization: hospitalized patients
- Post operative (esp knee/hip surgery)
- Cancer
- Genetic (protein C and S deficiency, Factor V Leiden)
- Trauma
Virchow’s Triad > thrombus formation

Rudolf Virchow 1856
Diagnosis of VTE

- Clinical suspicion
- Clinical exam (unilateral swelling)
- D-dimer
- Clinical algorithm (Wells, Geneva)
- LE Doppler
- Imaging: CTA, VQ scan
Diagnosis of DVT

- Clinical exam – swollen leg, cord, Homan’s sign
Diagnosis of DVT

- Clinical exam – swollen leg, cord, Homan’s sign
- Venous ultrasound

Compression

Augmentation
Pulmonary Emboli

Nomenclature

Chronicity (Acute, subacute, chronic)
Hemodynamic Stability (Submassive vs Massive)
Anatomic Location (Saddle, Segmental, Subsegmental)
Symptoms
Diagnosis of PE

- Clinical suspicion
- Clinical algorithms
- D-Dimer
- Imaging
Clinical algorithms

Wells [ < 2 low probability, > 4 PE likely ]

<table>
<thead>
<tr>
<th>Condition</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>PE more likely than alternatives:</td>
<td>3.0</td>
</tr>
<tr>
<td>Deep Vein Thrombosis (DVT) suspected:</td>
<td>3.0</td>
</tr>
<tr>
<td>Tachycardia (pulse &gt;100 beats per minute):</td>
<td>1.5</td>
</tr>
<tr>
<td>Surgery or immobilization in last 4 weeks:</td>
<td>1.5</td>
</tr>
<tr>
<td>Prior DVT or Pulmonary Embolism:</td>
<td>1.5</td>
</tr>
<tr>
<td>Hemoptysis:</td>
<td>1.0</td>
</tr>
<tr>
<td>Active malignancy:</td>
<td>1.0</td>
</tr>
</tbody>
</table>

**Clinical algorithms**

**Simplified Geneva**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt;65</td>
<td>1</td>
</tr>
<tr>
<td>Previous DVT or PE</td>
<td>1</td>
</tr>
<tr>
<td>Surgery or fracture within 1 month</td>
<td>1</td>
</tr>
<tr>
<td>Active malignancy</td>
<td>1</td>
</tr>
<tr>
<td>Unilateral lower limb pain</td>
<td>1</td>
</tr>
<tr>
<td>Hemoptysis</td>
<td>1</td>
</tr>
<tr>
<td>Pain on deep vein palpation of lower limb</td>
<td>1</td>
</tr>
<tr>
<td>and unilateral edema</td>
<td></td>
</tr>
<tr>
<td>Heart rate 75 to 94 bpm</td>
<td>1</td>
</tr>
<tr>
<td>Heart rate greater than 94 bpm</td>
<td>2</td>
</tr>
</tbody>
</table>
How good are clinical algorithms?

277 patients ER

- Geneva
- Wells
- Geneva “overridden by implicit clinical judgment” [in 21% of patients]

- Similar proportion of patients classified as low (53-58%), intermediate (37-41%) and high (4-10%).

- +PE: low = 5-13%, intermediate = 38-40%, high = 67-91%

**D-Dimer**

- use if low probability of PE
- NPV = 99.5% +
- positive D-Dimer does NOT raise probability of PE
- normal < 500 ng/ml, but age-related (higher cutoff if age > 80)

+ Wells, Ann Int Med 2001
CTA
V/Q scan

Ventilation (V): Xenon [or technetium labelled carbon nanoparticles]
Perfusion (Q): technetium or gallium labeled albumin
Hemodynamic alterations in massive PE (that you need to worry about)
Fibrinolysis or anti-coagulation in massive/sub-massive PE

Submassive pulmonary embolism

↑Cardiac biomarkers with:
-RV dysfunction on echocardiography OR
-RV enlargement on CT

Contraindications to fibrinolysis?
-Yes
-Contraindications to catheter-assisted embolectomy
-Yes
-Contraindications to surgical embolectomy?
-Yes
-Anticoagulation +/- IVC filter insertion

-No
-Consider fibrinolysis
-Consider catheter-assisted embolectomy
-Consider surgical embolectomy

Anticoagulation alone
Treatment of Venous Thromboembolism - acute

Patient with objectively confirmed segmental or larger PE or proximal DVT of the upper or lower extremity

Does the patient have (1) a PE with severe cardiopulmonary compromise; or (2) a DVT with high risk of limb loss?

Yes

Administer thrombolytic therapy followed immediately by anticoagulation therapy (unfractionated heparin or low-molecular weight heparin).

No

Is the patient actively bleeding or at high risk of bleeding or is anticoagulation contraindicated?

Yes

Place inferior vena cava filter (lower extremity DVT only). Begin anticoagulation therapy when active bleeding stops (see text).

No

Prognostic risk?

DVT or PE with good prognosis (see Table 4)

Outpatient treatment

PE with poor prognosis (see Table 4)

Consider initial hospitalization

No

Does the patient have renal insufficiency (creatinine clearance <30 mL/min)?

No

Initial treatment with 1 of the following:
- Low-molecular weight heparin
- Fondaparinux
- Rivaroxaban
- Apixaban

Yes

Initial treatment with subcutaneous unfractionated heparin
Confirmed segmental or > PE or proximal DVT
Confirmed segmental or > PE or proximal DVT

\[\downarrow\]

CV compromise or threatened limb loss \[\rightarrow\] tPA
“There is a distinct regional pattern of right ventricular dysfunction, with akinesia of the mid free wall but normal motion at the apex”

McConnell's sign

“There is a distinct regional pattern of right ventricular dysfunction, with akinesia of the mid free wall but normal motion at the apex”

McConnell's sign

Pulmonary Emboli

Thrombolytic therapy –

- leads to early hemodynamic improvement
- increased risk of major bleeding
  “Major bleeding” 9.2% - 20%
  Intracranial bleeding 3% - 5%

2008 American College of Chest Physicians’ guidelines: “
fibrinolysis as an option for patients with submassive PE
who are judged to have a low risk of bleeding (grade 2B)”.
The decrease in mean pulmonary artery systolic pressure was sustained from baseline to 48 h, as estimated by trans-thoracic echocardiography (51.4 mm Hg vs. 36.9 mm Hg; mean difference, 14.4; p < 0.0001). Mean modified Miller angiographic obstruction index decreased from 22.5 at baseline to 15.8 at 48 h (mean difference, 6.6; p < 0.0001).

An analysis was conducted to determine whether there was any difference in the change in RV/LV diameter ratio between patients who had a follow-up CT scan performed within the 48 h window and those who had a follow-up CT scan performed but it fell outside of the 48 h window. There was no difference in the change in RV/LV diameter ratio patients who had a follow-up CT scan performed within the 48 h window and those who had a follow-up CT scan performed but it fell outside of the 48 h window (mean percentage of change, 24% vs. 29%; p = 0.29). Similarly, there was no difference in the change in pulmonary artery systolic pressure in patients who had follow-up echocardiography performed within the 48 h window and those who had echocardiography performed outside of the 48 h window (mean percentage of change, 14.4 mm Hg vs. 17.5 mm Hg; p = 0.24).

A random-effect model analysis was performed to assess whether there was significant variance in the change in RV/LV diameter ratio according to study site. There was no indication of significant study site variance (p = 0.24), and the 2-sided p value for comparing the mean change in RV/LV diameter ratio with the pre-specified control value of 0.2 remained significant (p < 0.0001).

SAFETY OUTCOMES.

Three patients died while hospitalized, and 1 patient died after hospital discharge within 30 days of the procedure (Table 5). One patient died of massive PE before the procedure could be completed; 1 patient changed her code status and elected to receive hospice care after multisystem organ failure developed during a prolonged admission; 1 patient died of sepsis unrelated to the procedure; and 1 patient died of PE resulting in progressive respiratory failure. The patient who died before the procedure could be completed was a 61-year-old woman with diabetes, obesity, and recent infectious illness who presented hemodynamically stable with...
Confirmed segmental or > PE or proximal DVT

↓

CV compromise or threatened limb loss → tPA

↓

bleeding or high-risk anticoag → IVC filter
Confirmed segmental or > PE or proximal DVT

CV compromise or threatened limb loss → tPA

bleeding or high-risk anticoag → IVC filter
Confirmed segmental or > PE or proximal DVT

CV compromise or threatened limb loss → tPA

bleeding or high-risk anticoag → IVC filter
Confirmed segmental or > PE or proximal DVT

\[ \downarrow \]

CV

\[ \downarrow \]

bleeding

\[ \downarrow \]

prognosis

\[ \downarrow \]

good \hspace{1cm} poor
Confirmed segmental or > PE or proximal DVT

CV

bleeding

prognosis

good

poor

hospitalization
Confirmed segmental or > PE or proximal DVT

CV

bleeding

prognosis

→

good

→

outpatient tx

poor

→

hospitalization
Confirmed segmental or > PE or proximal DVT

CV

bleeding

prognosis

good

outpatient tx

poor

hospitalization

CrCl < 30 ?
Confirmed segmental or > PE or proximal DVT

CrCl < 30 ?

- no
  - LMWH
  - fondaparinux
  - NOAC
- yes
  - UFH
Schematic representation of the coagulation cascade including our improved understanding of the role of the tissue factor (TF) pathway in initiating clotting; interactions between pathways; and the role of thrombin in sustaining the cascade by feedback activation of coagulation factors.

HK: high-molecular-weight kininogen; PK: prekallikrein; PL: phospholipid; PT: prothrombin; TH: thrombin.

Adapted from Ferguson et al, Eur Heart J 1998; Suppl 19:8.
Schematic representation of the coagulation cascade including our improved understanding of the role of the tissue factor (TF) pathway in initiating clotting; interactions between pathways; and the role of thrombin in sustaining the cascade by feedback activation of coagulation factors. HK: high-molecular-weight kininogen; PK: prekallikrein; PL: phospholipid; PT: prothrombin; TH: thrombin.

Adapted from Ferguson et al, Eur Heart J 1998; Suppl 19:8.
for reference only….pharmacology of warfarin and NOACs

<table>
<thead>
<tr>
<th>Mode of action</th>
<th>Warfarin</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Edoxaban</th>
<th>Direct Thrombin Inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inhibition of hepatic synthesis of vitamin K-dependent coagulation factors</td>
<td>Inhibition of FXa</td>
<td>Direct inhibition of FXa</td>
<td>Direct inhibition of FXa</td>
<td>Direct inhibition of clot-bound and free thrombin (FIIa)</td>
<td>Direct inhibition of thrombin (FII)</td>
</tr>
<tr>
<td>Time to peak effect (hours)</td>
<td>72–96</td>
<td>0.5–3</td>
<td>3</td>
<td>1.5</td>
<td>2–3</td>
</tr>
<tr>
<td>Half-life hours</td>
<td>20–60</td>
<td>5–9 (9–13 in elderly)</td>
<td>8–13</td>
<td>9–11</td>
<td>14–17</td>
</tr>
<tr>
<td>Bioavailability %</td>
<td>100</td>
<td>80</td>
<td>66</td>
<td>50</td>
<td>65</td>
</tr>
<tr>
<td>Recommended therapeutic dose and frequency</td>
<td>Adjusted-dose based on INR; once daily</td>
<td>20 mg; once daily</td>
<td>5 mg; twice daily</td>
<td>30 mg or 60 mg; once daily</td>
<td>150 mg; twice daily</td>
</tr>
<tr>
<td>Monitoring</td>
<td>Required using INR</td>
<td>Not required</td>
<td>In case of hemorrhage or renal impairment, FXa-dependent assays may be used</td>
<td>Not required due to predictable pharmacokinetics</td>
<td>In hemorrhage or renal impairment, FXa-dependent assays may be used</td>
</tr>
<tr>
<td>Renal excretion</td>
<td>1% excreted unchanged in the urine</td>
<td>66% renal elimination</td>
<td>50% renal elimination</td>
<td>45% renal elimination</td>
<td>80% renal elimination</td>
</tr>
<tr>
<td>Interactions</td>
<td>CYP2C9, CYP1A2, CYP3A4 inhibitors</td>
<td>Potent CYP3A4 inhibitors and P-glycoprotein inhibitors</td>
<td>Potent CYP3A4 inhibitors</td>
<td>P-glycoprotein inhibitors</td>
<td>P-glycoprotein inhibitors</td>
</tr>
<tr>
<td>Drug reversal</td>
<td>Vitamin K, fresh frozen plasma, prothrombin complex concentrate, recombinant FVIIa</td>
<td>FVIIa partially reverses rivaroxaban anticoagulant effect</td>
<td>Prothrombin complex concentrate completely reverses its anticoagulant effect</td>
<td>No available antidote</td>
<td>No available antidote</td>
</tr>
<tr>
<td>Precautions</td>
<td>Severe active bleeding, pregnancy, breast feeding, documented hypersensitivity</td>
<td>Severe active bleeding; severe renal impairment</td>
<td>Severe active bleeding; severe renal impairment</td>
<td>Severe active bleeding; severe renal impairment</td>
<td>Severe active bleeding; severe renal impairment</td>
</tr>
<tr>
<td></td>
<td>Severe renal impairment (glomerular filtration rate &lt;30 mL/min/1.73m²)</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
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<td></td>
</tr>
</tbody>
</table>
NOACs - key points

Specific targets (Xa, IIa)
Rapid onset, short half-life
Primary renal excretion
No monitoring
No reversal (coming*)
Interactions with CYP3A, Pgp

* NEJM 2015
RCTs: NOACs in treatment of VTE

**Switch therapy:** Initial heparin [all] followed by warfarin or dabigatran or edoxaban

**Mono therapy:** apixaban or rivaroxaban vs heparin + warfarin

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1 RE-COVER, RE-COVER II [NEJM 2009]  
Hokusai-VTE [edoxaban]  
2 AMPLIFY  
EINSTEIN-DVT and EINSTEIN-PE
Dabigatran versus Warfarin in the Treatment of Acute Venous Thromboembolism

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

Oral Rivaroxaban for Symptomatic Venous Thromboembolism

The EINSTEIN Investigators*

Edoxaban versus Warfarin for the Treatment of Symptomatic Venous Thromboembolism
dabigatran: RE-COVER

- N = 2564, Follow-up 6 months, double-blind
- Inclusion: DVT or PE with planned tx for 6 months
- Randomized to 150 mg dabigatran BID vs warfarin
- Primary outcome: symptomatic VTE or death 2/2 VTE
### Table 2. Efficacy and Bleeding Outcomes.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Dabigatran (N = 1274)</th>
<th>Warfarin (N = 1265)</th>
<th>Hazard Ratio (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Efficacy analysis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary end point of venous thromboembolism or related death</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>— no. of subjects (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>During the study period</td>
<td>30 (2.4)</td>
<td>27 (2.1)</td>
<td>1.10 (0.65–1.84)</td>
</tr>
<tr>
<td>During the study period plus an additional 30-day follow-up†</td>
<td>34 (2.7)</td>
<td>32 (2.5)</td>
<td>1.05 (0.65–1.70)</td>
</tr>
<tr>
<td><strong>Secondary end point — no. of subjects (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptomatic deep-vein thrombosis</td>
<td>16 (1.3)</td>
<td>18 (1.4)</td>
<td>0.87 (0.44–1.71)</td>
</tr>
<tr>
<td>Symptomatic nonfatal pulmonary embolism</td>
<td>13 (1.0)</td>
<td>7 (0.6)</td>
<td><strong>1.85 (0.74–4.64)</strong></td>
</tr>
<tr>
<td>Death related to venous thromboembolism</td>
<td>1 (0.1)</td>
<td>3 (0.2)</td>
<td><strong>0.33 (0.03–3.15)</strong></td>
</tr>
<tr>
<td>All deaths</td>
<td>21 (1.6)</td>
<td>21 (1.7)</td>
<td>0.98 (0.53–1.79)</td>
</tr>
</tbody>
</table>
## RE-COVER outcomes

<table>
<thead>
<tr>
<th>Safety analysis§</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Major bleeding event — no. of subjects (%)</td>
<td>20 (1.6)</td>
<td>24 (1.9)</td>
<td>0.82 (0.45–1.48)</td>
</tr>
<tr>
<td>Fatal event — no. of events</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Bleeding into critical organ — no. of events</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>Hemoptysis</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Event resulting in fall in hemoglobin level or need for blood transfusions — no. of subjects (%)¶</td>
<td>20 (1.6)</td>
<td>18 (1.4)</td>
<td></td>
</tr>
<tr>
<td>Major or clinically relevant nonmajor bleeding event — no. of subjects (%)</td>
<td>71 (5.6)</td>
<td>111 (8.8)</td>
<td>0.63 (0.47–0.84)</td>
</tr>
<tr>
<td>Any bleeding event — no. of subjects (%)</td>
<td>205 (16.1)</td>
<td>277 (21.9)</td>
<td>0.71 (0.59–0.85)</td>
</tr>
</tbody>
</table>

### Site of bleeding event — no. of events

<table>
<thead>
<tr>
<th>Site</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Intracranial</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Intraocular**</td>
<td>8</td>
<td>9</td>
</tr>
<tr>
<td>Retroperitoneal**</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Intraarticular or intramuscular</td>
<td>8</td>
<td>27</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>53</td>
<td>35</td>
</tr>
<tr>
<td>Urogenital</td>
<td>53</td>
<td>95</td>
</tr>
<tr>
<td>Nasal**</td>
<td>40</td>
<td>107</td>
</tr>
<tr>
<td>Other</td>
<td>137</td>
<td>205</td>
</tr>
</tbody>
</table>
Oral Rivaroxaban for Symptomatic Venous Thromboembolism

The EINSTEIN Investigators*
Rivaroxaban: EINSTEIN-DVT

- N = 3449, most tx for 6 months, open-label
- Inclusion: DVT w/o PE
- Randomized to rivaroxaban at 15 mg BID for 3 weeks then 20 mg daily for 3, 6, or 12 months vs warfarin
- Primary outcome: symptomatic recurrent VTE
Rivaroxaban: EINSTEIN-DVT

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Rivaroxaban</th>
<th>Enoxaparin–VKA</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Efficacy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intention-to-treat population</td>
<td>1731 (100%)</td>
<td>1718 (100%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recurrent VTE</td>
<td>36 (2.1%)</td>
<td>51 (3.0%)</td>
<td>0.68 (0.44–1.04)</td>
<td>&lt;0.001†</td>
</tr>
<tr>
<td><strong>Type of recurrent VTE</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatal PE</td>
<td>1</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PE could not be ruled out</td>
<td>3</td>
<td>6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonfatal PE</td>
<td>20</td>
<td>18</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recurrent DVT plus PE</td>
<td>1</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recurrent DVT</td>
<td>14</td>
<td>28</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Net clinical benefit in terms of VTE plus major bleeding</td>
<td>51 (2.9%)</td>
<td>73 (4.2%)</td>
<td>0.67 (0.47–0.95)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

*Table 3. Clinical Outcomes in the Acute DVT Study.*
<table>
<thead>
<tr>
<th>Outcome</th>
<th>Rivaroxaban</th>
<th>Enoxaparin–VKA</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Safety</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Safety population</td>
<td>1718</td>
<td>1711</td>
<td></td>
<td></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>
<td>0.97 (0.76–1.22)</td>
<td>0.77</td>
</tr>
<tr>
<td>Major bleeding</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Contributing to death</td>
<td>1 (&lt;0.1)</td>
<td>5 (0.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>In a critical site</td>
<td>3 (0.2)</td>
<td>3 (0.2)</td>
<td></td>
<td></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>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinically relevant nonmajor bleeding</td>
<td>126 (7.3)</td>
<td>119 (7.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total deaths through end of intended treatment period</td>
<td>38 (2.2)</td>
<td>49 (2.9)</td>
<td>0.67 (0.44–1.02)</td>
<td>0.06</td>
</tr>
<tr>
<td><strong>Cause of death</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PE, or PE not ruled out</td>
<td>4</td>
<td>6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bleeding</td>
<td>2‡</td>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cancer</td>
<td>25</td>
<td>20</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>2</td>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>6</td>
<td>14</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Adverse events</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any event emerging during treatment</td>
<td>1078 (62.7)</td>
<td>1080 (63.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any serious event emerging during treatment</td>
<td>201 (12.0)</td>
<td>233 (13.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any event resulting in permanent discontinuation of study drug</td>
<td>85 (4.9)</td>
<td>81 (4.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any event leading to or prolonging hospitalization</td>
<td>193 (11.2)</td>
<td>211 (12.3)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Oral Apixaban for the Treatment of Acute 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., Urszula Masiukiewicz, M.D., Raphael Pak, Ph.D., John Thompson, Ph.D., Gary E. Raskob, Ph.D., Jeffrey I. Weitz, M.D., for the AMPLIFY Investigators

N Engl J Med
Volume 369(9):799-808
August 29, 2013
Apixaban: AMPLIFY

5395 pts

initial Rx – apixaban 10 BID for 7 days, then 5 mg BID or LMWH/warfarin
Edoxaban versus Warfarin for the Treatment of Symptomatic Venous Thromboembolism

The Hokusai-VTE Investigators*
Hokusai VTE: LMW heparin followed by edoxaban vs. initial LMW heparin followed by warfarin only
Hokusai VTE: Primary Efficacy Outcome

<table>
<thead>
<tr>
<th></th>
<th>hep / edoxaban (n / N)</th>
<th>hep / warfarin (n / N)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>mITT Overall</td>
<td>130 / 4,118</td>
<td>146 / 4,122</td>
<td>0.89 (0.70 – 1.13)</td>
</tr>
<tr>
<td>mITT On-Rx</td>
<td>66 / 4,118</td>
<td>80 / 4,122</td>
<td>0.82 (0.60 – 1.14)</td>
</tr>
</tbody>
</table>

Time to Event (days)

Overall

On-Rx

TTR: 63.5%

Cumulative Event Rate (%)

Edoxaban superior

Edoxaban non-inferior
Hokusai VTE: Bleeding

<table>
<thead>
<tr>
<th></th>
<th>warfarin</th>
<th>edoxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>n / N</td>
<td>4122</td>
<td>4118</td>
</tr>
<tr>
<td>349 / 4,118</td>
<td>349 / 4,118</td>
<td></td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.81 (0.71–0.94)</td>
<td></td>
</tr>
</tbody>
</table>

Number of patients at risk:

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>30</th>
<th>60</th>
<th>90</th>
<th>120</th>
<th>150</th>
<th>180</th>
<th>210</th>
<th>240</th>
<th>270</th>
<th>300</th>
<th>330</th>
<th>360</th>
</tr>
</thead>
<tbody>
<tr>
<td>warfarin</td>
<td>4122</td>
<td>3757</td>
<td>3627</td>
<td>3522</td>
<td>3313</td>
<td>3218</td>
<td>2979</td>
<td>2165</td>
<td>2007</td>
<td>1883</td>
<td>1754</td>
<td>1613</td>
<td>1212</td>
</tr>
<tr>
<td>edoxaban</td>
<td>4118</td>
<td>3840</td>
<td>3695</td>
<td>3587</td>
<td>3382</td>
<td>3308</td>
<td>3038</td>
<td>2192</td>
<td>2043</td>
<td>1904</td>
<td>1767</td>
<td>1650</td>
<td>1241</td>
</tr>
</tbody>
</table>
### RCTs: NOACs in *acute* treatment of VTE

<table>
<thead>
<tr>
<th></th>
<th>dabigatran</th>
<th>rivaroxaban</th>
<th>apixaban</th>
<th>edoxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Efficacy</strong></td>
<td>=</td>
<td>=</td>
<td>=</td>
<td>=</td>
</tr>
<tr>
<td><strong>Safety</strong></td>
<td>less bleeding</td>
<td>less bleeding</td>
<td>less bleeding</td>
<td>less bleeding</td>
</tr>
</tbody>
</table>

dabigatran: RE-COVER, RE-COVER II  
edoxaban: Hokusai-VTE  
apixaban: AMPLIFY  
rivaroxaban: EINSTEIN–DVT and EINSTEIN-PE
Evaluation of **medical costs** associated with use of new oral anticoagulants compared with standard therapy among venous thromboembolism patients

As a result of the reduction in clinical event rates, the overall medical cost differences were:

- dabigatran $-146$
- rivaroxaban $-482$
- apixaban $-918$
- edoxaban $-344$

for VTE patients vs patients treated with standard therapy.

Amin et al J Medical Economics 2014
NOACs in extended treatment of VTE

Problem: recurrent VTE occurs in many patients following discontinuation of anti-thrombotic therapy

Question: Can extended treatment of VTE (>6 months) reduce incidence of recurrent VTE??
Cumulative incidence of recurrent thromboembolism separately in patients with idiopathic (unprovoked) and secondary VTE.

<table>
<thead>
<tr>
<th>months</th>
<th>N. of VTE</th>
<th>Cum Incid (%)</th>
<th>95% CI</th>
<th>N. of VTE</th>
<th>Cum Incid (%)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>85</td>
<td>10.0</td>
<td>8.0-12.0</td>
<td>32</td>
<td>4.2</td>
<td>2.8-8.7</td>
</tr>
<tr>
<td>12</td>
<td>99</td>
<td>15.0</td>
<td>12.6-17.4</td>
<td>17</td>
<td>5.5</td>
<td>4.8-6.4</td>
</tr>
<tr>
<td>26</td>
<td>74</td>
<td>26.3</td>
<td>23.0-29.6</td>
<td>34</td>
<td>12.3</td>
<td>9.8-14.8</td>
</tr>
<tr>
<td>60</td>
<td>96</td>
<td>40.3</td>
<td>36.5-45.1</td>
<td>14</td>
<td>16.1</td>
<td>13.0-19.2</td>
</tr>
<tr>
<td>96</td>
<td>9</td>
<td>46.4</td>
<td>41.1-51.8</td>
<td>6</td>
<td>20.3</td>
<td>15.8-24.8</td>
</tr>
<tr>
<td>120</td>
<td>5</td>
<td>52.6</td>
<td>45.6-59.5</td>
<td>2</td>
<td>22.5</td>
<td>17.2-27.8</td>
</tr>
</tbody>
</table>
NOACs in extended treatment of VTE

dabigatran: vs warfarin or placebo

rivaroxaban: vs placebo

apixaban: vs placebo

1 RE-MEDY, RE-SONATE
2 EINSTEIN-Extension
3 AMPLIFY-EXT
Cumulative Risk of Recurrent Venous Thromboembolism or Related Death (or Unexplained Death in the Placebo-Control Study).

Dabigatran: vs warfarin vs placebo

Dabigatran: Cumulative Risk of Any Bleeding.

vs warfarin

vs placebo

## EINSTEIN-Extension: Primary Efficacy Outcome Analysis

**ITT population**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Rivaroxaban (n=602)</th>
<th>Placebo (n=594)</th>
<th>Hazard ratio (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptomatic recurrent VTE</td>
<td>8 (1.3)</td>
<td>42 (7.1)*</td>
<td>0.18 (0.09–0.39)</td>
<td>&lt;0.001†</td>
</tr>
<tr>
<td>Recurrent DVT</td>
<td>5</td>
<td>31</td>
<td>-----</td>
<td>-----</td>
</tr>
<tr>
<td>Non-fatal PE</td>
<td>2</td>
<td>13</td>
<td>-----</td>
<td>-----</td>
</tr>
<tr>
<td>Fatal PE</td>
<td>0</td>
<td>1</td>
<td>-----</td>
<td>-----</td>
</tr>
<tr>
<td>PE cannot be ruled out</td>
<td>1</td>
<td>0</td>
<td>-----</td>
<td>-----</td>
</tr>
</tbody>
</table>

*Some patients experienced more than 1 event

†p<0.001 for superiority

CI=confidence interval; DVT=deep vein thrombosis; ITT=intent-to-treat; PE=pulmonary embolism; VTE=venous thromboembolism

NOACs in extended treatment of VTE

dabigatran: 95% reduction vs placebo \(^1\)
rivaroxaban: 82% reduction vs placebo \(^2\)
apixaban: 67% reduction vs placebo \(^3\)

\(^1\) RE-MEDY, RE-SONATE
\(^2\) EINSTEIN-Extension
\(^3\) AMPLIFY-EXT
Evaluation of Oral Anticoagulants for the Extended Treatment of Venous Thromboembolism Using a Mixed-Treatment Comparison, Meta-Analytic Approach

Rollins et al: Clinical Therapeutics, 2014
In the present meta-analysis, efficacy end points in the extended treatment of VTE with apixaban, dabigatran, rivaroxaban, warfarin (conventional and low dose) … were not significantly different.

The assessment of non-major or clinically relevant bleeding did not identify any meaningful differences between these agents.
Extended treatment of VTE – NOACS, warfarin and aspirin

Comparative efficacy and safety of anticoagulants and aspirin for extended treatment of venous thromboembolism: A network meta-analysis

Thrombosis Research 2015
Extended treatment of VTE – NOACS, warfarin and aspirin

Comparative efficacy and safety of anticoagulants and aspirin for extended treatment of venous thromboembolism: A network meta-analysis
Treatment of Venous Thromboembolism – long-term

Patient with PE or proximal upper or lower extremity DVT stable on acute phase treatment (see Figure 1)

Etiology of VTE?

Transient risk factor
- Treatment with 1 of following:
  - Vitamin K antagonist
  - Rivaroxaban
  - Apixaban
  - Edoxaban
  - Dabigatran
- Discontinue treatment after 3 mo.

Unprovoked VTE
- Treatment with 1 of following:
  - Vitamin K antagonist
  - Rivaroxaban
  - Apixaban
  - Edoxaban
  - Dabigatran
- Consider extended treatment (> 6 mo.)
- Low to moderate bleeding risk?
  - Continue treatment indefinitely with 1 of following:
    - Vitamin K antagonist
    - Rivaroxaban
    - Apixaban
    - Edoxaban
    - Dabigatran
  - Consider discontinuing treatment in women at low risk of VTE recurrence or if strong patient preference to discontinue.
  - High bleeding risk?
    - Discontinue treatment after 3 to 6 mo.

Malignancy
- Treatment with low molecular weight heparin
- Consider extended treatment (> 6 mo.)
- VTE recurrence risk?
  - High VTE recurrence risk
    - Continue low molecular weight heparin or switch to 1 of the following: rivaroxaban, apixaban, edoxaban, dabigatran, or a vitamin K antagonist.
  - Low VTE recurrence risk or high bleeding risk
    - Discontinue anticoagulation or continue low molecular weight heparin or switch to 1 of the following: rivaroxaban, apixaban, edoxaban, dabigatran, or a vitamin K antagonist.
NOACs in prophylaxis of VTE for knee/hip surgery

dabigatran: vs warfarin or placebo

rivaroxaban: vs placebo

apixaban: vs placebo

1 RE-MEDY, RE-SONATE
2 EINSTEIN-Extension
3 AMPLIFY-EXT
Comparative Effectiveness of New Oral Anticoagulants and Standard Thromboprophylaxis in Patients Having Total Hip or Knee Replacement: A Systematic Review

FXa Inhibitors vs. LMWH:

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total Studies (Patients), n (n)</th>
<th>Events/Total, n/N</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>10 (22 838)</td>
<td>31/12 384</td>
<td>0.95 (0.55–1.63)</td>
</tr>
<tr>
<td>Symptomatic DVT</td>
<td>12 (22 877)</td>
<td>41/12 993</td>
<td>0.46 (0.3–0.7)</td>
</tr>
<tr>
<td>Nonfatal PE</td>
<td>20 (26 998)</td>
<td>44/15 187</td>
<td>1.07 (0.65–1.73)</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>21 (31 424)</td>
<td>192/18 307</td>
<td>1.27 (0.98–1.65)</td>
</tr>
</tbody>
</table>

Dabigatran vs. LMWH:

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total Studies (Patients), n (n)</th>
<th>Events/Total, n/N</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>4 (10 264)</td>
<td>10/6508</td>
<td>1.54 (0.38–6.33)</td>
</tr>
<tr>
<td>Symptomatic DVT</td>
<td>4 (10 264)</td>
<td>34/6508</td>
<td>0.82 (0.17–3.99)</td>
</tr>
<tr>
<td>Nonfatal PE</td>
<td>4 (10 264)</td>
<td>14/6508</td>
<td>0.69 (0.31–1.54)</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>4 (10 264)</td>
<td>81/6508</td>
<td>0.94 (0.58–1.52)</td>
</tr>
</tbody>
</table>

Summary

VTE diagnosis relies on clinical suspicion, exam, assessment of risk (D-dimer, Geneva or Wells score), imaging

VTE treatment depends on risk, including concurrent conditions, thrombus burden, and hemodynamics

NOACs can safely treat VTE with reduced bleeding, and will likely, IMHO, replace heparin/warfarin
Hanging chads
(with apologies to Kathleen Harris)

Role of NOACs in massive PE?

Extended treatment (> 6 months) for some/all?