NOACs in VTE
drug selection according to
patient’s risk profile and
duration of therapy

João Morais
Head of Cardiology Division and Research Centre
Leiria Hospital Centre
Portugal
Disclosures

João Morais

On the last year JM received honoraria for consultant activities and invited speaker for pharmaceutical and device’s companies

Astra Zeneca
Bayer Healthcare
BMS / Pfizer
Boehringer Ingelheim
Boston Scientific
Daiichi Sankyo
Merck Sharp and Dhome
Goals of VTE treatment

Initial Treatment

Acute Clot:
- Stop propagation
- Prevent embolism
- Protect pulmonary circulation
- Restore venous return

Minimize Bleeding Risk

Long-term Prevention

Prevent Recurrent VTE
Postthrombotic syndrome
CTEPH

CTEPH = chronic thromboembolic pulmonary hypertension
New concepts in anticoagulation therapy

Conventional therapy

• Heparin plus VKA

New therapy

• Single drug approach
• Higher initial dose
Individualized therapy

Based on the clinical setting

Based on patient’s characteristics

Based on the individual prognosis
Classification of lower limb DVT

**Proximal DVT**
- Popliteal
- Femoral
- Deep femoral
- Common femoral
- Iliac

**Distal DVT**
- Gastrocnemius
- Tibial (ant/post)
- Soleus
- Peroneal

**Superficial vein**
- Great saphenous

*www.escardio.org*

*Chest 2012;141:e419S-e494S*
Classification of lower limb DVT

Proximal DVT
Early treatment
Anticoagulants
Agressive
Parenteral $R_x$

Distal DVT
Gastrocnemius
Tibial (ant/post)
Soleus
Peroneal

Superficial vein
Great saphenous

www.escardio.org

Chest 2012;141:e419S-e494S
Classification of lower limb DVT

**Proximal DVT**
- Early treatment
- Anticoagulants
- Aggressive
- Parenteral $R_x$

**Distal DVT**
- Conservative treatment
- Delayed oral $R_x$

**Superficial vein**
- Great saphenous

*www.escardio.org*

*Chest 2012;141:e419S-e494S*
Classification of lower limb DVT

Proximal DVT
- Early treatment
  - Anticoagulants
- Agressive Parenteral $R_x$

Distal DVT
- Conservative treatment
  - Delayed oral $R_x$

Superficial vein
- Prophylatic treatment

References:

Chest 2012;141:e419S-e494S
Clinical trigger

**Unprovoked**

DVT or PE in patients with no recently occurring major clinical risk factors for venous embolism or patients with active cancer, thrombophilia or family history of DVT

**Provoked**

DVT or PE in patients with recent occurrence of a major clinical risk factor such as embolism from trauma, immobilization, pregnancy, oral contraceptive use or hormone replacement therapy
## Bleeding risk assessment

### Risk factors

- Age ≥ 65 y\textsuperscript{17-23}
- Age ≥ 75 y\textsuperscript{17-21,23,25-34}
- Previous bleeding\textsuperscript{18,24,25,30,33-36}
- Cancer\textsuperscript{20,24,30,37}
- Metastatic cancer\textsuperscript{36,38}
- Renal failure\textsuperscript{18,24,25,28,30,33}
- Liver failure\textsuperscript{19,21,27,28}
- Thrombocytopenia\textsuperscript{27,36}
- Previous stroke\textsuperscript{18,25,27,39}
- Diabetes\textsuperscript{18,19,25,32,34}
- Anemia\textsuperscript{18,21,27,30,34}
- Antiplatelet therapy\textsuperscript{19,27,28,34,40}
- Poor anticoagulant control\textsuperscript{22,28,35}
- Comorbidity and reduced functional capacity\textsuperscript{24,28,36}
- Recent surgery\textsuperscript{21,41,b}
- Frequent falls\textsuperscript{27}
- Alcohol abuse\textsuperscript{24,25,27,34}

### Risk assessment

- **Low risk**
  - 0 risk factors

- **Moderate risk**
  - 1 risk factor

- **High risk**
  - > 2 risk factors

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Chest 2012;141:e419S-e494S

www.escardio.org
## Bleeding risk assessment

### Anticoagulation 0 - 3 months

<table>
<thead>
<tr>
<th>Categorization of Risk of Bleeding</th>
<th>Low Risk&lt;sup&gt;d&lt;/sup&gt; (0 Risk Factors)</th>
<th>Moderate Risk&lt;sup&gt;d&lt;/sup&gt; (1 Risk Factor)</th>
<th>High Risk&lt;sup&gt;d&lt;/sup&gt; (≥ 2 Risk Factors)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anticoagulation 0-3 mo&lt;sup&gt;e&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline risk (%)</td>
<td>0.6</td>
<td>1.2</td>
<td>4.8</td>
</tr>
<tr>
<td>Increased risk (%)</td>
<td>1.0</td>
<td>2.0</td>
<td>8.0</td>
</tr>
<tr>
<td>Total risk (%)</td>
<td>1.6&lt;sup&gt;e&lt;/sup&gt;</td>
<td>3.2</td>
<td>12.8&lt;sup&gt;f&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

### Anticoagulation after 3 months

<table>
<thead>
<tr>
<th></th>
<th>Baseline risk (%)/y</th>
<th>Moderate Risk&lt;sup&gt;d&lt;/sup&gt; (1 Risk Factor)</th>
<th>High Risk&lt;sup&gt;d&lt;/sup&gt; (≥ 2 Risk Factors)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline risk (%)/y</td>
<td>0.3&lt;sup&gt;h&lt;/sup&gt;</td>
<td>0.6</td>
<td>≥2.5</td>
</tr>
<tr>
<td>Increased risk (%)/y</td>
<td>0.5</td>
<td>1.0</td>
<td>≥4.0</td>
</tr>
<tr>
<td>Total risk (%)/y</td>
<td>0.8&lt;sup&gt;i&lt;/sup&gt;</td>
<td>1.6&lt;sup&gt;i&lt;/sup&gt;</td>
<td>≥6.5</td>
</tr>
</tbody>
</table>
Targets for anticoagulants

Factor Xa inhibitors:
- Apixaban
- Edoxaban
- Rivaroxaban
- Fondaparinux (indirect)

Direct thrombin inhibitors:
- Dabigatran
- Bivalirudin
- Hirudin
- Argabatran

VKAs inhibit synthesis of FII, VII, IX, X

Adapted from Weitz JI, et al.¹
Current and evolving anticoagulant regimen

- **Current standard of care**
  - LMWH or Fondaparinux s.c.
  - VKA

- **VKA**
  - Day 1
  - Day 5 - 11
  - At least 3 months

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Treatment of acute DVT/PE: NOACs non-inferior to warfarin for prevention of recurrent DVT/PE in Phase III trials

Direct comparisons cannot be made as no head-to-head data are available

*Pooled data from RE-COVER™ and RE-COVER™ II; †Pooled analysis; ‡On treatment

Treatment of acute DVT/PE: NOACs associated with less major bleeding than warfarin in Phase III trials

HR: 0.60 (95% CI: 0.36–0.99)
HR: 0.54 (95% CI: 0.37–0.79)
HR: 0.31 (95% CI: 0.17–0.55)
HR: 0.84 (95% CI: 0.59–1.21)

Direct comparisons cannot be made as no head-to-head data are available
*Statistically significant reductions for dabigatran, rivaroxaban, and apixaban vs warfarin, numerical reduction for edoxaban vs warfarin; †Pooled data from RE-COVER™ and RE-COVER™ II; oral drug treatment period only; ‡Pooled analysis; §On treatment
Efficacy and Safety of the New Oral Anticoagulants Dabigatran, Rivaroxaban, Apixaban, and Edoxaban in the Treatment and Secondary Prevention of Venous Thromboembolism: A Systematic Review and Meta-analysis of Phase III Trials

S.K. Kakkos *, G.I. Kirkilesis, I.A. Tsolakis

Department of Vascular Surgery, University Hospital of Patras, Patras, Greece

European Journal of Vascular and Endovascular Surgery (2014),
http://dx.doi.org/10.1016/j.ejvs.2014.05.001
Major bleeding

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>NOAs</th>
<th>VKAs</th>
<th>Risk Ratio</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
<td>Total</td>
</tr>
<tr>
<td>RE-COVER</td>
<td>20</td>
<td>1274</td>
<td>24</td>
<td>1265</td>
</tr>
<tr>
<td>EINSTEIN-DVT</td>
<td>14</td>
<td>1718</td>
<td>20</td>
<td>1711</td>
</tr>
<tr>
<td>EINSTEIN-PE</td>
<td>26</td>
<td>2412</td>
<td>52</td>
<td>2405</td>
</tr>
<tr>
<td>AMPLIFY</td>
<td>15</td>
<td>2676</td>
<td>49</td>
<td>2689</td>
</tr>
<tr>
<td>Hokusai-VTE</td>
<td>56</td>
<td>4118</td>
<td>66</td>
<td>4122</td>
</tr>
<tr>
<td>RE-COVER II</td>
<td>15</td>
<td>1280</td>
<td>22</td>
<td>1288</td>
</tr>
</tbody>
</table>

Total (95% CI) 13478 13480 100.0% 0.63 [0.51, 0.77]

Heterogeneity: Chi² = 10.65, df = 5 (P = 0.06); I² = 53%
Test for overall effect: Z = 4.46 (P < 0.00001)

Net clinical benefit

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>NOAs</th>
<th>VKAs</th>
<th>Risk Ratio</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
<td>Total</td>
</tr>
<tr>
<td>RE-COVER</td>
<td>50</td>
<td>1274</td>
<td>51</td>
<td>1265</td>
</tr>
<tr>
<td>EINSTEIN-DVT</td>
<td>51</td>
<td>1731</td>
<td>73</td>
<td>1718</td>
</tr>
<tr>
<td>EINSTEIN-PE</td>
<td>83</td>
<td>2419</td>
<td>96</td>
<td>2413</td>
</tr>
<tr>
<td>AMPLIFY</td>
<td>74</td>
<td>2676</td>
<td>120</td>
<td>2689</td>
</tr>
<tr>
<td>Hokusai-VTE</td>
<td>120</td>
<td>4118</td>
<td>144</td>
<td>4122</td>
</tr>
<tr>
<td>RE-COVER II</td>
<td>45</td>
<td>1279</td>
<td>50</td>
<td>1289</td>
</tr>
</tbody>
</table>

Total (95% CI) 13497 13496 100.0% 0.79 [0.70, 0.90]

Heterogeneity: Chi² = 5.49, df = 5 (P = 0.36); I² = 9%
Test for overall effect: Z = 3.65 (P = 0.0003)

www.escardio.org

European Journal of Vascular and Endovascular Surgery (2014), http://dx.doi.org/10.1016/j.ejvs.2014.05.001
What long-term data exist for NOACs compared with warfarin in secondary prevention of VTE?

- **RE-COVER™ II**
  - Dabigatran 150 mg BID vs warfarin

- **RE-MEDY™**
  - Dabigatran 150 mg BID vs warfarin

- **RE-SONATE™**
  - Dabigatran 150 mg BID vs placebo

- **AMPLIFY**
  - Apixaban vs warfarin

- **AMPLIFY-EXT**
  - Apixaban vs placebo

- **EINSTEIN DVT/PE**
  - Rivaroxaban vs VKA

- **EINSTEIN-EXT**
  - Rivaroxaban vs placebo

- **HOKUSAI-VTE**
  - Edoxaban vs warfarin

*Original protocol, 3–6 months pretreatment, 18 months on study drug; amendment allowed 3–12 months pretreatment, then up to 36 months on study drug.

## Risk of recurrent VTE or VTE-related death: NOACs vs placebo

<table>
<thead>
<tr>
<th>Study</th>
<th>% Patients</th>
<th>HR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NOAC</td>
<td>Placebo</td>
<td></td>
</tr>
<tr>
<td>RE-SONATE™¹*</td>
<td>0.4</td>
<td>5.6</td>
<td>0.08 (0.02–0.25)</td>
</tr>
<tr>
<td>EINSTEIN-EXT²</td>
<td>1.3</td>
<td>7.1</td>
<td>0.18 (0.09–0.39)</td>
</tr>
<tr>
<td>AMPLIFY-EXT³†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.5 mg BID</td>
<td>1.7</td>
<td>8.8</td>
<td>0.19 (0.11–0.33)</td>
</tr>
<tr>
<td>5 mg BID</td>
<td>1.7</td>
<td>8.8</td>
<td>0.20 (0.11–0.34)</td>
</tr>
</tbody>
</table>

Direct comparisons cannot be made as no head-to-head data are available
*Unexplained death also included in primary efficacy outcome; †All-cause death also included in primary efficacy outcome
**REMEDY: efficacy and safety of long-term treatment**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Dabigatran (N = 1430) no. of patients (%)</th>
<th>Warfarin (N = 1426) no. of patients (%)</th>
<th>HR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary endpoint of recurrent or fatal VTE</td>
<td>26 (1.8)</td>
<td>18 (1.3)</td>
<td>1.44 (0.78-2.64)</td>
<td>.01*</td>
</tr>
<tr>
<td>Secondary endpoints</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptomatic DVT</td>
<td>17 (1.2)</td>
<td>13 (0.9)</td>
<td>1.32 (0.64-2.71)</td>
<td>.46</td>
</tr>
<tr>
<td>Symptomatic nonfatal PE</td>
<td>10 (0.7)</td>
<td>5 (0.4)</td>
<td>2.04 (0.70-5.98)</td>
<td>.19</td>
</tr>
<tr>
<td>Major bleeding event</td>
<td>13 (0.9)</td>
<td>25 (1.8)</td>
<td>0.52 (0.27-1.02)</td>
<td>.06</td>
</tr>
<tr>
<td>Major or clinically relevant bleeding event</td>
<td>80 (5.6)</td>
<td>145 (10.2)</td>
<td>0.54 (0.41-0.71)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

*The P value for the primary outcome is for noninferiority*

### VTE trials: proportions of patients with PE

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Drug/Control, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rivaroxaban</td>
<td></td>
</tr>
<tr>
<td>- EINSTEIN-PE</td>
<td>100/100</td>
</tr>
<tr>
<td>Dabigatran</td>
<td></td>
</tr>
<tr>
<td>- RE-COVER</td>
<td>21.2/21.4</td>
</tr>
<tr>
<td>- RE-MEDY</td>
<td>22.7/23.5</td>
</tr>
<tr>
<td>- RE-SONATE</td>
<td>26.9/26.9</td>
</tr>
<tr>
<td>Apixaban</td>
<td></td>
</tr>
<tr>
<td>- AMPLIFY</td>
<td>25.2/25.2</td>
</tr>
<tr>
<td>- AMPLIFY-Extension</td>
<td>35.2/33.5</td>
</tr>
<tr>
<td>Edoxaban</td>
<td></td>
</tr>
<tr>
<td>- Hokusai-VTE</td>
<td>40/40</td>
</tr>
</tbody>
</table>

VTE extension studies

**AMPLIFY-Extension**

- Apixaban 2.5 mg: 3.8%
- Apixaban 5 mg: 4.2%
- Placebo: 11.6%

- \( P < .001 \)

**EINSTEIN-Extension**

- Rivaroxaban: 1.3%
- Placebo: 7.1%

- \( P < .001 \)

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NOACs in cancer patients (limitations)

- Paucity of clinical trial data
  (< 10% of the populations in RCTs)
- No comparison with LMWH
- Patients were not representative of cancer patients
- Drug interaction may be clinically relevant
- Liver and renal dysfunction are common in cancer patients
NOACs in cancer patients

**Efficacy data**

<table>
<thead>
<tr>
<th>Study ID</th>
<th>OR (95% CI)</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>vs LMWH</td>
<td>0.98 (0.52, 1.85)</td>
<td>36.38</td>
</tr>
<tr>
<td>MAGELLAN</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ADOPT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subtotal (I-squared = 0.0%, p = 0.786)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>vs VKI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EINSTEIN</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EINSTEIN PE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AMPLIFY</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RECOVER I &amp; II</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RE-MEDY</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HOKUSAI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subtotal (I-squared = 0.0%, p = 0.947)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall (I-squared = 0.0%, p = 0.981)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Safety data**

<table>
<thead>
<tr>
<th>Study ID</th>
<th>OR (95% CI)</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>vs LMWH</td>
<td>3.14 (1.12, 8.75)</td>
<td>5.43</td>
</tr>
<tr>
<td>MAGELLAN</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ADOPT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subtotal (I-squared = 0.0%, p = 0.352)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>vs VKI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EINSTEIN</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EINSTEIN PE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AMPLIFY</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RECOVER I &amp; II</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RE-MEDY</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HOKUSAI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subtotal (I-squared = 0.0%, p = 0.947)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall (I-squared = 43.9%, p = 0.036)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Meta-analysis**

* N = 1952

[www.escardio.org](http://www.escardio.org)
SELECT-D
Study Design

Prospective, randomized, open label, multicenter, pilot trial in selected cancer patients at risk of VTE recurrence
Estimated enrollment: 530 patients

Rivaroxaban
15 mg orally twice daily x 3 wk
20 mg once daily x 6 mo

Dalteparin
200 IU/kg daily SC x 1 mo
150 IU/kg mo 2-6

Residual vein thrombosis (RVT) positive patients

Rivaroxaban
20 mg once daily

Placebo

6 month vs 12 month treatment

Primary efficacy: incidence of recurrent VTE
Secondary outcomes: safety, acceptability, biomarker identification, and health economics

EINSTEIN pooled analysis

- Elderly (>75 years)
- Body weight < 50 kg
- Renal failure (CrCl < 50 mL/min)
- n = 790

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Rivaroxaban, %</th>
<th>Enoxaparin/VKA, %</th>
<th>HR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrence of thromboembolism</td>
<td>2.7</td>
<td>3.8</td>
<td>0.68 (0.39 - 1.18)</td>
<td>-</td>
</tr>
<tr>
<td>Overall</td>
<td>2.1</td>
<td>2.3</td>
<td>0.89 (0.66 - 1.19)</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>1.3</td>
<td>4.5</td>
<td>0.27 (0.13 - 0.54)</td>
<td>-</td>
</tr>
<tr>
<td>Overall</td>
<td>1.0</td>
<td>1.7</td>
<td>0.54 (0.37 - 0.79)</td>
<td>.002</td>
</tr>
</tbody>
</table>

Büller HR, et al. 54th Annual ASH Annual Meeting and Exposition; 2012.[6]
Key messages

- The paradigm of DVT treatment is rapidly changing. The evidence for NOACs is strong enough to spread the use of these drugs instead of VKAs.

- A single drug approach is very attractive and very useful for an outpatient management of patients with DVT.

- More data is needed in patients with massive pulmonary embolism (after lytics ?).

- Extended treatment is the rule for unprovoked DVT/PE but no firm recommendations about when to stop.
NOACs in VTE
drug selection according to patient’s risk profile and duration of therapy

João Morais
Head of Cardiology Division and Research Centre
Leiria Hospital Centre
Portugal