Acute and extended treatment of venous thromboembolism – the role of the NOACs

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Disclosures Menno Huisman

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Significant morbidity and mortality of VTE\(^1\)–\(^4\)

**Morbidity**
- Without extended treatment after unprovoked VTE, a recurrence may occur in:\(^1\)
  - 11% of patients within 1 year
  - 29.1% of patients within 5 years
- VTE is associated with long-term, clinically significant complications, including post-thrombotic syndrome and chronic thrombo-embolic pulmonary hypertension\(^2\)

**Mortality**
- Approximately 550,000 annual deaths due to VTE across the EU\(^3\)
- PE may be responsible for 1 in \(~\)10 hospital deaths\(^4\)

EU: European Union; PE: pulmonary embolism; VTE: venous thromboembolism.


Phases of anticoagulation treatment for DVT and PE\(^1\),\(^2\)

![Diagram showing phases of anticoagulation treatment for DVT and PE](image)

DVT: deep vein thrombosis; LMWH: low molecular weight heparin; NOACs: non-VKA oral anticoagulants; PE: pulmonary embolism; SmPC: summary of product characteristics; VKA: vitamin K antagonist; VTE: venous thromboembolism.

Overview of NOAC trials in VTE\(^1\)–\(^8\)

<table>
<thead>
<tr>
<th>Initial</th>
<th>Long-term</th>
<th>Extended</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>LMWH</strong></td>
<td><strong>VKA</strong></td>
<td>Dabigatran (RE-SONATE and RE-MEDY)(^3)</td>
</tr>
<tr>
<td>LMWH</td>
<td>Dabigatran (RE-COVER and RE-COVER II)(^1,2)</td>
<td></td>
</tr>
<tr>
<td>LMWH</td>
<td>Edoxaban (Hokusai-VTE)(^4)</td>
<td></td>
</tr>
<tr>
<td>Rivaroxaban (EINSTEIN-DVT and EINSTEIN-PE)(^5,6)</td>
<td>Rivaroxaban (EINSTEIN-Extension)(^3)</td>
<td></td>
</tr>
<tr>
<td>Apixaban (AMPLIFY)(^7)</td>
<td>Apixaban (AMPLIFY-EXT)(^8)</td>
<td></td>
</tr>
</tbody>
</table>

All four NOACs are licensed for the treatment of DVT and PE, and prevention of recurrent DVT and PE in adults. Please refer to individual SmPCs for further information.

DVT: deep vein thrombosis; NOAC(s): non-VKA oral anticoagulant(s); PE: pulmonary embolism; SmPCs: Summary of Product Characteristics; VTE: venous thromboembolism; VKA: vitamin K antagonist.


Acute DVT and PE treatment: NOAC trial designs

Head-to-head studies do not exist, therefore comparisons between agents cannot be made

<table>
<thead>
<tr>
<th>NOAC</th>
<th>Trial</th>
<th>Number of patients</th>
<th>Design</th>
<th>Parenteral required before NOAC?</th>
<th>NOAC dosing</th>
<th>Treatment length (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Apixaban</strong></td>
<td>AMPLIFY(^1)</td>
<td>5,395 DVT: 3,532 PE: 1,863*</td>
<td>Double-blind</td>
<td>No</td>
<td>Apixaban 10 mg BID for 7 days, then 5 mg BID</td>
<td>6</td>
</tr>
<tr>
<td><strong>Rivaroxaban</strong></td>
<td>EINSTEIN-DVT(^2)</td>
<td>DVT: 3,449</td>
<td>Open-label</td>
<td>No</td>
<td>Rivaroxaban 15 mg BID for 21 days, then 20 mg once daily</td>
<td>3, 6 or 12(^7)</td>
</tr>
<tr>
<td></td>
<td>EINSTEIN-PE(^3)</td>
<td>PE: 4,832</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Dabigatran</strong></td>
<td>RE-COVER(^4)</td>
<td>2,539</td>
<td>Double-blind</td>
<td>LMWH, UFH, or fondaparinux ≥5 days</td>
<td>Dabigatran 150 mg BID</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>RE-COVER II(^5)</td>
<td>2,568</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Edoxaban</strong></td>
<td>Hokusai-VTE(^6)</td>
<td>8,240 DVT: 4,921 PE: 3,319*</td>
<td>Double-blind</td>
<td>Enoxaparin or UFH ≥5 days</td>
<td>Edoxaban 60 mg OD(^8)</td>
<td>3–12(^8)</td>
</tr>
</tbody>
</table>

*Patients presenting with PE may also present with concomitant DVT.
\(^1\)Duration of treatment was determined by the treating physician before randomisation. Most patients received 6 or 12 months of therapy.
\(^2\)Patients with a body weight ≤60 kg or CrCl 30–50 mL/min, or patients receiving concomitant potent P-gp inhibitors received edoxaban 30 mg OD.
\(^3\)Duration of treatment was determined by the treating physician based on the patient’s clinical features and patient preference.

BID: twice daily; CrCl: creatinine clearance; DVT: deep vein thrombosis; LMWH: low molecular weight heparin; NOAC: non-VKA oral anticoagulant; OD: once daily; P-gp: P-glycoprotein; PE: pulmonary embolism; UFH: unfractionated heparin; VTE: venous thromboembolism.

AMPLIFY: 6-month double-blind active-controlled non-inferiority treatment study¹

**Patient population:**
- Patients with confirmed symptomatic proximal DVT or PE requiring treatment for ≥6 months

n=5,395 (randomised)

n=2,704

- Apixaban
  - 10 mg BID
  - 5 mg BID
  - 6 months

n=2,691

- Warfarin (INR 2–3)
  - Enoxaparin (1 mg/kg) BID SC*

30-day safety follow-up

End of treatment

End of treatment

**Stratification based on DVT and PE; randomisation target was two thirds DVT and one third PE**

*For at least 5 days and then discontinued if blinded INR was 2.0 or higher.

BID: twice daily; D: day; DVT: deep vein thrombosis; INR: international normalised ratio; R: randomisation; PE: pulmonary embolism; SC: subcutaneous.

Created from Agnelli et al. 2013³

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AMPLIFY: Baseline patient characteristics*

<table>
<thead>
<tr>
<th></th>
<th>Apixaban (n=2691)</th>
<th>Conventional therapy (n=2704)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, years (±SD)</strong></td>
<td>57 ±16.0</td>
<td>56.7 ±16.0</td>
</tr>
<tr>
<td><strong>Male, no. (%)</strong></td>
<td>1569 (58.3)</td>
<td>1598 (59.1)</td>
</tr>
<tr>
<td><strong>Weight, kg (mean)</strong></td>
<td>84.6 ±19.8</td>
<td>84.6 ±19.8</td>
</tr>
<tr>
<td><strong>Creatinine clearance, no. (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤30 mL/min</td>
<td>14 (0.5)</td>
<td>15 (0.6)</td>
</tr>
<tr>
<td>&gt;30 – ≤50 mL/min</td>
<td>161 (6.0)</td>
<td>148 (5.5)</td>
</tr>
<tr>
<td>&gt;50 – ≤80 mL/min</td>
<td>549 (20.4)</td>
<td>544 (20.1)</td>
</tr>
<tr>
<td>&gt;80 mL/min</td>
<td>1721 (64.0)</td>
<td>1757 (65.0)</td>
</tr>
<tr>
<td>Data missing</td>
<td>246 (9.1)</td>
<td>240 (8.9)</td>
</tr>
<tr>
<td><strong>Qualifying diagnosis, no. (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DVT</td>
<td>1749 (65.0)</td>
<td>1783 (65.9)</td>
</tr>
<tr>
<td>PE</td>
<td>678 (25.2)</td>
<td>681 (25.2)</td>
</tr>
<tr>
<td>PE with DVT</td>
<td>252 (9.4)</td>
<td>225 (8.3)</td>
</tr>
<tr>
<td><strong>Risk factors for recurrent VTE, no. (%)†</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previous VTE</td>
<td>463 (17.2)</td>
<td>409 (15.1)</td>
</tr>
<tr>
<td>Known thrombophilia</td>
<td>74 (2.8)</td>
<td>59 (2.2)</td>
</tr>
<tr>
<td>Active cancer</td>
<td>66 (2.5)</td>
<td>77 (2.8)</td>
</tr>
</tbody>
</table>

*Plus–minus values are means ±SD. Percentages may not total 100 because of rounding. VTE denotes venous thromboembolism. There were no significant differences between the study groups in the baseline characteristics listed here. †Patients may have undergone more than one imaging test.

DVT: deep vein thrombosis; PE: pulmonary embolism; SD: standard deviation; VTE: venous thromboembolism.

Created from Agnelli et al. 2013³

First recurrent VTE/VTE-related death: apixaban non-inferior to enoxaparin/warfarin

\[ \text{RR}=0.84 \text{ (95\% CI: 0.60–1.18)} \]
\[ p<0.001 \text{ non-inferiority} \]

Adapted from Agnelli et al. 2013

Apixaban significantly reduced major bleeding by 69\% vs enoxaparin/warfarin

\[ \text{ARR}=1.2, \text{ RR } = 0.31 \text{ (95\% CI: 0.17–0.55)} \]
\[ p<0.001 \text{ superiority} \]

Adapted from Agnelli et al. 2013
Meta-analysis DOAC efficacy in VTE


Non inferior in efficacy

Meta-analysis of NOAC safety in VTE


Significantly less major and fatal bleeding
Prevention of recurrent DVT and PE: NOAC trial designs

Head-to-head studies do not exist, therefore comparisons between agents cannot be made

<table>
<thead>
<tr>
<th>Study drug</th>
<th>Trial</th>
<th>Number of patients</th>
<th>Treatment before randomisation</th>
<th>Study drug dosing</th>
<th>Comparator</th>
<th>Treatment length (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran</td>
<td>RE-SONATE1</td>
<td>1,343</td>
<td>6–18 months of VKA or dabigatran</td>
<td>Dabigatran 150 mg BID</td>
<td>Placebo</td>
<td>6</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>EINSTEIN-EXT2</td>
<td>1,196</td>
<td>6 or 12 months of VKA or rivaroxaban</td>
<td>Rivaroxaban 20 mg OD</td>
<td>Placebo</td>
<td>6 or 12</td>
</tr>
<tr>
<td>Apixaban</td>
<td>AMPLIFY-EXT3</td>
<td>2,482</td>
<td>6–12 months of standard therapy or apixaban</td>
<td>Apixaban 2.5 mg or 5 mg BID*</td>
<td>Placebo</td>
<td>12</td>
</tr>
<tr>
<td>Dabigatran</td>
<td>RE-MEDY4</td>
<td>2,856</td>
<td>3–12 months of VKA or dabigatran</td>
<td>Dabigatran 150 mg BID</td>
<td>Warfarin INR 2.0–3.0</td>
<td>6–36</td>
</tr>
</tbody>
</table>

*Only apixaban 2.5 mg BID is licensed for prevention of recurrent DVT/PE*4

BID: twice daily; DVT: deep vein thrombosis; INR: international normalized ratio; NOAC: non-VKA oral anticoagulant; OD: once daily; PE: pulmonary embolism; VKA: vitamin K antagonist.


AMPLIFY-EXT: 12-month double-blind placebo-controlled extended treatment study1

Patient population:
* Patients with confirmed DVT/PE who have completed 6–12 months of standard anticoagulation

The n value for each study arm was based on the calculation that 810 patients were required in each group for the study to have 90% power to show the superiority of apixaban over placebo (~60% RRR), at a two-sided alpha level of 0.05

*Only apixaban 2.5 mg BID is licensed for prevention of recurrent DVT/PE in those who have been treated for 6 months.2

BID: twice daily; DVT: deep vein thrombosis; RRR: relative risk reduction PE: pulmonary embolism.

VTE/VTE-related death: apixaban demonstrated superior efficacy to placebo

Apixaban demonstrated a similar incidence of major/CRNM bleeding as placebo

Study Limitations:
- Only 15% of the patients in this study were >75 yr
- Few had a body weight <60kg or moderate/severe renal impairment
AMPLIFY-EXT: clinical interpretation

A potential strategy for the long-term treatment of VTE: a dichotomised approach

- In patients with proximal DVT/PE: 3 months anticoagulant therapy recommended vs no therapy (Grade 1B)
- In patients with DVT of the leg and PE, and no cancer*: NOAC recommended vs VKA for long-term anticoagulant therapy (first 3 months)(Grade 2B)
  - If not NOAC: VKA therapy suggested over LMWH (Grade 2C)
- Not necessary to change OAC choice after 3 months in patients with DVT/PE who receive extended therapy (Grade 2C)

DVT: deep vein thrombosis; NNH: number needed to harm; NNT: number needed to treat; PE: pulmonary embolism; VTE: venous thromboembolism.


*Only apixaban 2.5 mg BID is licensed for prevention of recurrent DVT/PE in patients who have been treated for 6 months
†Only 15% of patients were ≥75 years of age and few had a body weight ≤60 kg or moderate or severe renal impairment.

A potential strategy for the long-term treatment of VTE:

- In patients with proximal DVT/PE: 3 months anticoagulant therapy recommended vs no therapy (Grade 1B)
- In patients with DVT of the leg and PE, and no cancer*: NOAC recommended vs VKA for long-term anticoagulant therapy (first 3 months)(Grade 2B)
  - If not NOAC: VKA therapy suggested over LMWH (Grade 2C)
- Not necessary to change OAC choice after 3 months in patients with DVT/PE who receive extended therapy (Grade 2C)

*There is no data to support the use of NOACs for treatment of VTE in patients with active cancer.
†Licensed NOACs for the treatment of VTE include apixaban, rivaroxaban, dabigatran or edoxaban

DVT: deep vein thrombosis; LMWH: low molecular weight heparin; NOACs: non-VKA oral anticoagulants; PE: pulmonary embolism; VKA: vitamin K antagonist; VTE: venous thromboembolism.

Conclusions (1)

- NOAC trials in acute treatment of DVT and PE:
  - Differences exist in the design of the trials, mainly with respect to initial parenteral anticoagulation, and duration and dosing frequency for all-oral treatments\(^1\)
  - All NOACs were non-inferior to the standard of care for reducing the risk of recurrent VTE and related death, but they have varied bleeding profiles\(^1\)
- NOAC trials vs placebo in prevention of recurrent DVT and PE:
  - All NOACs studied in this setting were superior to placebo for reducing the risk of their primary efficacy endpoints; safety outcomes suggest varied bleeding profiles\(^2-4\)


DVT: deep vein thrombosis; NOAC(s): non-VKA oral anticoagulant(s); PE: pulmonary embolism; VTE: venous thromboembolism.

Conclusions (2)

- In the AMPLIFY trial, apixaban showed comparable efficacy and significantly lower major bleeding (69% RRR, 1.2% ARR) vs LMWH/warfarin\(^1\)
- In the AMPLIFY-EXT trial, apixaban 2.5 mg BID demonstrated superior efficacy with a similar incidence of major and major and clinically relevant bleeding vs placebo\(^2\)