In the past decades, the two-stage treatment of initial parenteral heparin followed by vitamin K antagonists has been the standard therapy for patients with acute venous thromboembolism (VTE). With the advent of direct oral anticoagulants (DOACs), previously known as new oral anticoagulants, this era has come to an end.

The RE-COVER II study not only concludes the clinical development program of dabigatran, it is also the last of a series of phase III trials in the acute treatment of VTE with the 4 newcomers (ie, dabigatran, rivaroxaban, apixaban, and edoxaban). Whereas the RE-COVER study was the first reported study in VTE, RE-COVER II closes the circle. The results of all 4 DOACs for the acute treatment of VTE are summarized in the Table.5-8

These results deserve some clinically important comments. First, all DOACs were shown consistently to be non-inferior compared with well-managed warfarin. The high quality of warfarin management, with a superior time in international normalized ratio target range compared with daily clinical practice, strengthens both the internal and external validity of these studies but also underscores that well-managed warfarin is an effective therapy for preventing recurrent VTE.

Second, all DOACs caused less bleeding. Importantly, the shift in the bleeding pattern that is observed in patients with atrial fibrillation, with less intracranial, less life-threatening, and less critical site bleedings, is also seen in patients with VTE. DOACs cause less major (Table) and less intracranial bleedings in patients with VTE, but caution remains, in particular for patients at risk for gastrointestinal bleeding.

Third, the new regimens differ in their initial treatment approach. The first couple of weeks are of particular interest because of the high risk for recurrence and bleeding. The dual-drug bridging period with overlapping heparin and vitamin K antagonists constitutes a risk for overtreatment and undertreatment and requires intensive international normalized ratio monitoring that is labor- and time-consuming and costly. Furthermore, lessons have been drawn from the observation that ximelagatran7 and idraparinux,10 administered without heparin lead-in and without initial intensified dosing, caused more early recurrence compared with heparin/vitamin K antagonists. This helps to explain the 2 different strategies of DOACs for acute VTE (ie, including a heparin lead-in or starting with an intensified dose).

In the clinical studies with dabigatran and edoxaban, the initial treatment was open-label parenteral heparin overlapping with warfarin or sham warfarin. On discontinuation of the parenteral heparin (ie, when the [sham] international normalized ratio was in the therapeutic range), double-blind therapy was continued with warfarin or the DOAC under investigation.

In the clinical trials with apixaban and rivaroxaban, a single-drug approach was examined but with an intensified dose for 1 or 3 weeks, respectively.

The convenience of an oral-only monotherapy without laboratory monitoring is particularly attractive for patients with DVT.
and pulmonary embolism for whom outpatient treatment is feasible, and this is likely to further facilitate outpatient treatment when observational registries are supportive of such a strategy.

Parenteral heparin will remain a preferred treatment option for many patients, especially those with more severe clinical presentations and patients with high thrombus burden who are admitted to the hospital. When parenteral heparin has been administered for 5 to 10 days, peroral anticoagulation with dabigatran or edoxaban can be continued.

For most cancer patients, the continued treatment with LMWH is currently the recommended and preferred therapy. Patients with active cancer for whom long-term treatment with LMWH was anticipated were not eligible for the phase III trials. Hence, additional studies are needed in cancer patients with continued LMWH and not warfarin as the comparator before DOACs can be considered an alternative standard to continued LMWH in these patients.

The subgroup analyses of the pooled study results of the RE-COVER and RE-COVER II studies support a broad applicability of 150 mg of dabigatran twice daily for patients with acute VTE. However, caution is needed for patient populations not appropriately represented in the clinical studies. Of note, only 150 mg of dabigatran twice daily was evaluated in the RE-COVER studies, whereas the Randomized Evaluation of Long-Term Anticoagulant Therapy (RE-LY) study investigated both 110 and 150 mg of dabigatran in patients with nonvalvular atrial fibrillation.

Very elderly patients have a high risk for adverse outcomes, yet the reduction in clinically relevant bleeding with dabigatran was observed until the age of approximately 85 years with age analyzed as a continuous variable.1

Elderly patients do differ with respect to renal function, body weight, and frailty. Additional study is warranted to examine whether the standard dose of 150 mg of dabigatran twice daily should be adjusted in some patient populations (eg, in patients with increased drug exposure as a result of impaired renal function). This issue is of particular importance for the thrombin inhibitor dabigatran that is mainly eliminated via the kidney, contrary to the 3 factor Xa inhibitors.

Reassuring observational studies and registries are needed to support and confirm the improved benefit/risk profile in the real world. Additional studies should provide more insights on the efficacy and safety of all 4 DOACs in special populations, such as elderly patients but also adolescents, patients with impaired renal function, patients with extreme body weight, and patients with interfering medications, such as NSAIDs and antiplatelet therapy.

Besides particular patient characteristics, also less common clinical manifestations of VTE require our attention. DOACs have only been studied in patients with proximal DVT of the lower limb or hemodynamically stable pulmonary embolism. Patients with distal DVT, DVT of the upper limb, superficial thrombophlebitis, or catheter-related thrombosis, patients who underwent thrombolysis, and patients with cerebral vein or mesenteric vein thrombosis have not been studied yet. Efforts from both the academia and the pharmaceutical industry are needed to evaluate whether DOACs can improve the clinical outcomes in these less common clinical entities of the VTE superfamily.

Although phase III trials have included >27000 patients (Table), clinical trials differ from clinical practice in many ways. Rigorous adherence to therapy and therapy monitoring are typical features of clinical trials. The periodical follow-up to check and reinforce adherence to therapy will also be a prerequisite to translate the improved outcomes in clinical trials to our patients and to completely close the circle.

In conclusion, the availability of DOACs that do not require monitoring will be a treatment shift for patients with VTE. DOACs have challenges to overcome but offer patients, physicians, and healthcare systems an effective, safer, and more convenient treatment for acute VTE. The circle is almost closed.

**Disclosures**

Dr Verhamme received a research grant, speaker’s fees, and honoraria for studies with dabigatran from Boehringer-Ingelheim, a research grant, speaker’s fees, and honoraria for studies with rivaroxaban from Bayer Healthcare, speaker’s fees from Pfizer, speaker’s fees and honoraria for a study with edoxaban from Daiichi-Sankyo, and a research grant, speaker’s fees for a study with apixaban from Bayer Healthcare, speaker’s fees from Janssen, and honoraria for a study with dabigatran from Boehringer-Ingelheim.

### Table. Recurrent Venous Thromboembolism and Bleeding Outcomes in Phase III Trials of Acute Venous Thromboembolism Treatment

<table>
<thead>
<tr>
<th>Name of the Trial</th>
<th>RE-COVER I and II</th>
<th>EINSTEIN DVT and PE&lt;sup&gt;a-d&lt;/sup&gt;</th>
<th>AMPLIFY&lt;sup&gt;c&lt;/sup&gt;</th>
<th>Hokuriku VTE&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug</td>
<td>Dabigatran</td>
<td>Rivaroxaban</td>
<td>Apixaban</td>
<td>Edoxaban</td>
</tr>
<tr>
<td>Study duration</td>
<td>6 mo</td>
<td>3, 6, or 12 mo</td>
<td>6 mo</td>
<td>≤12 mo</td>
</tr>
<tr>
<td>Patients, n</td>
<td>5153</td>
<td>8282</td>
<td>5395</td>
<td>8292</td>
</tr>
<tr>
<td>Recurrent VTE, %</td>
<td>2.4</td>
<td>2.2</td>
<td>2.1</td>
<td>2.3</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>1.09 (0.76–1.57)</td>
<td>0.89 (0.66–1.19)</td>
<td>0.84 (0.60–1.18)*</td>
<td>0.82 (0.60–1.14)</td>
</tr>
<tr>
<td>Major bleeding, %</td>
<td>1.4</td>
<td>2.0</td>
<td>1.0</td>
<td>1.7</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.73 (0.48–1.11)</td>
<td>0.54 (0.37–0.79)</td>
<td>0.31 (0.17–0.55)*</td>
<td>0.84 (0.59–1.21)</td>
</tr>
<tr>
<td>Major + CRNMB, %</td>
<td>5.3</td>
<td>8.5</td>
<td>9.4</td>
<td>10.0</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.62 (0.50–0.76)</td>
<td>0.93 (0.81–1.06)</td>
<td>0.44 (0.36–0.55)*</td>
<td>0.81 (0.71–0.94)</td>
</tr>
</tbody>
</table>

<sup>a</sup>Indicates apixaban; CI, confidence interval; CRNMB, clinically relevant nonmajor bleeding; D, dabigatran; E, edoxaban; HR, hazard ratio; PE, pulmonary embolism; VTE, venous thromboembolism; and W, warfarin.

<sup>*Relative risks are reported for the AMPLIFY study.
†Recurrent VTE during on-treatment period.
grant from Sanofi-Aventis. Dr Bounameaux received a research grant, speaker’s fees, and honoraria for studies with edoxaban from Daiichi-Sankyo, a research grant, speaker’s fees, and honoraria for studies with rivaroxaban from Bayer Healthcare, and honoraria from Sanofi-Aventis.

References


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