Direct Oral Anticoagulants for Acute Venous Thromboembolism
Closing the Circle?

Peter Verhamme, MD; Henri Bounnameaux, MD

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.

In this issue of Circulation, Schulman et al report on the results of the RE-COVER II study that investigated the efficacy and safety of dabigatran for the treatment of acute VTE. The study included patients with acute deep vein thrombosis (DVT) and pulmonary embolism who were treated for 6 months with 150 mg of dabigatran twice daily or warfarin targeted to an international normalized ratio between 2 and 3, after initial parenteral heparin, mostly low-molecular-weight heparin (LMWH). The study shows that parenteral heparin followed by dabigatran was as effective as heparin overlapped with and followed by warfarin. The primary endpoint of recurrent symptomatic VTE occurred in 2.3% of patients randomized to dabigatran and in 2.2% of patients randomized to warfarin. Moreover, bleeding was less frequent in the dabigatran group. Thus, the RE-COVER II study confirms the results of the RE-COVER study with an identical design.

This study completes the phase III clinical development program of dabigatran in VTE, further encompassing 2 studies for the long-term secondary prevention of recurrent VTE, totaling 9372 patients in 4 phase III studies. The RE-MEDY study showed comparable efficacy and less bleeding of dabigatran compared with warfarin in patients with an indication for long-term anticoagulant therapy and is the only warfarin-controlled study evaluating a DOAC for the long-term secondary prevention of VTE. In the RE-SONATE study, a placebo-controlled study, dabigatran was effective in preventing recurrent VTE in patients who completed 6 to 18 months of anticoagulation and who were at risk for recurrence but had no compelling indication for continued anticoagulant therapy.

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.

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 ximelagatran and idraparinux, 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.
Table. Recurrent Venous Thromboembolism and Bleeding Outcomes in Phase III Trials of Acute Venous Thromboembolism Treatment

<table>
<thead>
<tr>
<th>Drug</th>
<th>RE-COVER I and II</th>
<th>EINSTEIN DVT and PE&lt;sup&gt;a&lt;/sup&gt;</th>
<th>AMPLIFY&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Hokurui VTE&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<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>D</td>
<td>2.4</td>
<td>2.2</td>
<td>2.1</td>
<td>2.3</td>
</tr>
<tr>
<td>W</td>
<td>3.8</td>
<td>2.3</td>
<td>2.0</td>
<td>2.7</td>
</tr>
<tr>
<td>R</td>
<td>1.6</td>
<td>1.9</td>
<td>1.4</td>
<td>1.9</td>
</tr>
<tr>
<td>W</td>
<td>1.9</td>
<td>1.9</td>
<td>1.9</td>
<td>2.0</td>
</tr>
</tbody>
</table>

HR (95% CI) 1.09 (0.76–1.57) 0.89 (0.66–1.19) 0.84 (0.60–1.18)* 0.82 (0.60–1.14)

HR (95% CI) 0.73 (0.48–1.11) 0.54 (0.37–0.79) 0.31 (0.17–0.55)* 0.84 (0.59–1.21)

Major + CRNMB, % 5.3 8.5 9.4 10.0 4.3 9.7 8.5 10.3

HR (95% CI) 0.62 (0.50–0.76) 0.93 (0.81–1.06) 0.44 (0.36–0.55)* 0.81 (0.71–0.94)

A 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.

*Relative risks are reported for the AMPLIFY study.
†Recurrent VTE during on-treatment period.

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 >27,000 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 requisite 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 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

KEY WORDS: Editorials • venous thromboembolism • warfarin
Direct Oral Anticoagulants for Acute Venous Thromboembolism: Closing the Circle?
Peter Verhamme and Henri Bounameaux

_Circulation._ 2014;129:725-727; originally published online December 16, 2013;
doi: 10.1161/CIRCULATIONAHA.113.007478
_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2013 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://circ.ahajournals.org/content/129/7/725

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Circulation_ is online at:
http://circ.ahajournals.org/subscriptions/