Direct Oral Anticoagulants for Acute Venous Thromboembolism:

Closing the Circle?

Running title: Verhamme et al.; DOACs for acute venous thromboembolism

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Key words: Editorial, anticoagulation, warfarin, venous thromboembolism
In the past decades, the two-stage treatment of initial parenteral heparin followed by vitamin K antagonists (VKA) has been the standard therapy for patients with acute venous thromboembolism (VTE). With the advent of direct oral anticoagulants (DOACs), previously known as new or non-VKA oral anticoagulants (NOACs), 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 (PE) who were treated for 6 months with dabigatran 150 mg twice daily or warfarin targeted to an international normalized ratio (INR) 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 to 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.\textsuperscript{3}

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, i.e. 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 Table 1.\textsuperscript{4-8}

These results deserve some clinically important comments. First, all DOACs were consistently shown to be non-inferior compared to well-managed warfarin. The high quality of warfarin management, with a superior time in INR-target range compared to 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 1) and less intracranial bleedings in patients with VTE, but caution remains, in particular for patients at risk for gastro-intestinal 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 VKA constitutes a risk for over- and undertreatment, and requires intensive INR-monitoring that is labor- and time-consuming, and costly. Furthermore, lessons have been drawn from the observation that ximelagatran\textsuperscript{9} and idraparinux\textsuperscript{10}, administered without heparin lead-in and without initial intensified dosing, caused
more early recurrence compared to heparin/VKA. This helps to explain the 2 different strategies of DOACs for acute VTE, i.e. 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. Upon discontinuation of the parenteral heparin, i.e. when the (sham) INR 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 DVT and PE patients 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 study support a broad applicability of dabigatran 150 mg twice daily for patients with acute VTE.
However, caution is needed for patient populations not appropriately represented in the clinical studies. Of note, only dabigatran 150 mg twice daily was evaluated in the RE-COVER studies whereas the RE-LY study investigated both dabigatran 110 mg and 150 mg in patients with non-valvular 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. Further study is warranted to examine whether the standard dose of dabigatran 150 mg twice daily should be adjusted in some patient populations, e.g. in patients with increased drug exposure due to 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 and/or hemodynamically stable PE. Patients with distal DVT, with DVT of the upper limb, with superficial thrombophlebitis, with 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.

Even though phase III trials have included more than 27,000 patients (Table 1), clinical trials differ from clinical practice in many ways. Rigorous adherence to therapy and the monitoring hereof is a typical feature 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.

**Conflict of Interest Disclosures:** Dr. Peter Verhamme has 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. Henri Bounamaux has 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:**


Table 1. Recurrent VTE and bleeding outcomes in phase III trials of acute VTE treatment

<table>
<thead>
<tr>
<th>Name of the trial</th>
<th>Drug</th>
<th>Study Duration</th>
<th>Patients</th>
<th>Recurrent VTE (%)</th>
<th>HR (95% CI)</th>
<th>Major-GRNMB (%)</th>
<th>HR (95% CI)</th>
<th>Major Bleeding (%)</th>
<th>HR (95% CI)</th>
<th>Major+CRNMB (%)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RE-COVER I &amp; II</td>
<td>Dabigatran</td>
<td>6 months</td>
<td>5153</td>
<td>2.4</td>
<td>1.09 (0.76-1.57)</td>
<td>5.3</td>
<td>0.62 (0.50-0.76)</td>
<td>1.0</td>
<td>1.4</td>
<td>0.73 (0.48-1.11)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Rivaroxaban</td>
<td>3, 6 or 12 months</td>
<td>8282</td>
<td>2.2</td>
<td>0.89 (0.66-1.19)</td>
<td>8.5</td>
<td>0.73 (0.48-1.11)</td>
<td>2.0</td>
<td>2.0</td>
<td>1.4 (0.66-1.19)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Apixaban</td>
<td>6 months</td>
<td>5395</td>
<td>2.1</td>
<td>0.84 (0.60-1.18)</td>
<td>10.0</td>
<td>0.54 (0.37-0.79)</td>
<td>1.7</td>
<td>1.0</td>
<td>0.54 (0.37-0.79)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Edoxaban</td>
<td>up to 12 months</td>
<td>8292</td>
<td>2.3</td>
<td>0.84 (0.60-1.18)</td>
<td>4.3</td>
<td>0.31 (0.17-0.55)</td>
<td>18.0</td>
<td>1.0</td>
<td>0.31 (0.17-0.55)</td>
<td></td>
</tr>
</tbody>
</table>

VTE indicates venous thromboembolism. HR Hazard Ratio, CI confidence interval, CRNMB clinically relevant nonmajor bleeding.

* Relative risks are reported for the Amplify study.
# Recurrent VTE during on-treatment period.
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Circulation. published online December 16, 2013;
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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