Will the new target-specific oral anticoagulants improve the treatment of venous thromboembolism?

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The current treatment of venous thromboembolism (VTE, i.e. deep-vein thrombosis [DVT] and pulmonary embolism [PE]), is challenging because of the need for a two drug regimen, parenteral therapy, followed by an oral vitamin K antagonist (VKA). The former often requires hospitalisation or complex arrangements for outpatient administration. The latter is associated with the complexity of transitioning to the VKA and the complexity and inconvenience of managing the VKA, most often warfarin. Warfarin has repeatedly been shown to be the drug most commonly associated with adverse events, emergency room visits, and hospitalisation (1). As a result, VKA therapy is often under-prescribed for patients who might benefit, such as those with atrial fibrillation (AF) (2). VTE therapy is also associated with a number of unresolved issues including determining the optimal duration of therapy in order to balance the benefit of preventing recurrence versus the risk of bleeding (3), and preventing the long-term sequelae of thrombosis such as post-thrombotic syndrome (4) or chronic thromboembolic pulmonary hypertension (5). The advent of the low molecular weight heparins and fondaparinux in the last two decades has significantly improved the initial treatment of VTE by allowing outpatient therapy with drugs that do not need monitoring, but this is not without difficulty. Little has changed with oral VKA therapy.

We are now on the verge of a new era in anticoagulant therapy based on the development of target-specific oral anticoagulants (6). Of these, the oral direct thrombin and factor (F)Xa inhibitors are the agents most advanced in development. These drugs differ from the VKAs in that they directly and reversibly inhibit a specific coagulation factor, they have rapid onset of action and short half-lives, they achieve predictable drug levels and anticoagulant effect eliminating the need for monitoring, and they have minimal drug interactions and virtually no dietary interactions (Table 1). Unfortunately, they do not have proven antidotes, and the metabolic and elimination pathways differ for each agent with varying dependency on renal excretion (7).

Four target-specific oral anticoagulants have either completed or are in the process of completing phase III trials in the secondary prevention of acute or chronic recurrent VTE. In this issue of Thrombosis and Haemostasis, Cohen and Dobromirski (8) review the results of one of these agents, rivaroxaban, and discuss the potential implications. Studies with dabigatran etexilate for this indication have been completed and published, while apixaban and edoxaban trials are ongoing. These trials have many similarities, but one essential difference is the point at which randomisation is initiated.

In the RE-COVER trial (9), dabigatran etexilate (150 mg twice daily) was compared to warfarin therapy for patients with acute DVT with or without PE (approx. 20% with PE), but patients were randomised only after all enrolled patients were treated with standard heparin or low-molecular-weight heparin (LMWH) for the first several days (median 9 days). In 2,539 patients randomised, dabigatran was found to be non-inferior to warfarin (event rate 2.4% vs. 2.1% respectively; hazard ratio [HR] 1.10 (95% confidence interval [CI], 0.65 – 1.84). Major bleeding in the dabigatran group was reduced (1.6% vs. 1.9%), and major plus clinically relevant non-major bleeding was significantly reduced compared to warfarin (16.1% vs. 21.9%; HR 0.71; 95% CI, 0.59 – 0.85; p <0.001). In the RE-SONATE trial (10), extended dabigatran therapy was compared with placebo in patients with VTE who had completed 6–18 months of therapy and the decision to continue or stop therapy was at clinical equipoise. Over the next six months, dabigatran significantly reduced the rate of recurrent VTE compared to placebo (event rate 0.4% vs. 5.6%; HR 0.08; 95% CI 0.02–0.025; p<0.0001) with a major bleeding rate of 0.39% (2 patients) versus no major bleeding in the placebo group (p =0.05). Clinically relevant non-major bleeding was significantly increased in the dabigatran group (HR 2.9; 95% CI 1.5–5.6; p=0.001).

Cohen and Dobromirski (8) summarise the EINSTEIN-DVT trial results (11) with rivaroxaban, where 3,449 patients with acute DVT were randomised between rivaroxaban, 15 mg twice daily for three weeks followed by 20 mg once daily for six months, and standard therapy with enoxaparin followed by a VKA. Randomisation and study treatment occurred at the time of diagnosis. Rivaroxaban proved to be non-inferior to standard therapy (HR 0.68; 95% CI, 0.44 – 1.04; p<0.001 for non-inferiority) with a similar major and clinically relevant non-major bleeding rate (HR 0.97; 95% CI 0.76–1.22; p=0.77). The follow-up EINSTEIN-EXT study randomised 1,196 patients who had completed 6–12 months of standard or rivaroxaban therapy for VTE and then randomised between rivaroxaban (20 mg once daily) or placebo and followed for an additional 6–12 months. Rivar-
oxaban was superior in reducing recurrent VTE (1.3% vs. 7.1%; HR 0.18; 95% CI, 0.09–0.39; p<0.001), but with four nonfatal major bleeding events versus none in the placebo group (p=0.11).

Similar trials are being conducted with apixaban and edoxaban (12, 13), both direct FXa inhibitors, where all patients are treated initially with a standard heparin product and then randomised to study drug or warfarin as was done in the RECOVER trial. These studies are still ongoing.

A major advantage of these new agents is their rapid onset of action, equivalent to the onset of action of the LMWHs, allowing them to be used up front at the time of diagnosis. Why did the dabigatran, apixaban and edoxaban investigators opt to treat all patients initially with standard heparin or LMWH before randomisation to the new agent or to warfarin? Clinical experience and previous studies tell us that patients with acute VTE have a heightened degree of thrombogenesis, and if the process is not adequately suppressed the risk of recurrence is increased. The rate of recurrent disease is highest in the first three months, especially within the first few weeks. Studies by Hull et al. (14) showed that failure to rapidly achieve a therapeutic aPTT on heparin during initial therapy led to a greater incidence of recurrent VTE later on. Similar outcomes were seen when a VKA was used up front without a rapidly acting anticoagulant like heparin in a trial by Brandjes et al. (15) More recently, the trial of ximelagatran for the treatment of acute VTE (16) suggested that the dose used

Table 1: Important pharmacokinetic parameters and selected management guidelines for new oral anticoagulants.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Edoxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Target</td>
<td>Factor IIa (thrombin)</td>
<td>Factor Xa</td>
<td>Factor Xa</td>
<td>Factor Xa</td>
</tr>
<tr>
<td>T_{1/2}</td>
<td>2 hours</td>
<td>2.5–4 hours</td>
<td>3 hours</td>
<td>1–2 hours</td>
</tr>
<tr>
<td>Half-life</td>
<td>12–14 hours</td>
<td>9–13 hours</td>
<td>8–11 hours</td>
<td>6–11 hours</td>
</tr>
<tr>
<td>Metabolism/ Elimination</td>
<td>80% renal</td>
<td>33% renal (unchanged)</td>
<td>25% renal (mostly unchanged)</td>
<td>35% renal&lt;br&gt;65% fecal&lt;br&gt;&lt; 4% CYP metabolism</td>
</tr>
<tr>
<td></td>
<td>20% biliary</td>
<td>33% renal (inactive)</td>
<td>55% fecal (metabolites)</td>
<td>15% CYP metabolism</td>
</tr>
<tr>
<td></td>
<td>No CYP metabolism</td>
<td>33% CYP dependent metabolism</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dose frequency</td>
<td>QD/BID</td>
<td>QD/BID</td>
<td>QD/BID</td>
<td>QD/BID</td>
</tr>
<tr>
<td>Monitoring</td>
<td>Not needed</td>
<td>Not needed</td>
<td>Not needed</td>
<td>Not needed</td>
</tr>
<tr>
<td>Recommended assay to detect drug</td>
<td>aPTT</td>
<td>PT (not INR)³</td>
<td>PT</td>
<td>Anti Xa assay calibrated for apixaban</td>
</tr>
<tr>
<td></td>
<td>Thrombin time²</td>
<td>Anti Xa assay that is calibrated for rivaroxaban</td>
<td></td>
<td>Not reported but PT, INR, aPTT and anti Xa elevations correlate with edoxaban concentrations</td>
</tr>
<tr>
<td></td>
<td>Dilute thrombin time²</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ecarin clotting time</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug Interactions</td>
<td>Potent P-gp inhibitors; PP inhibitors may decrease absorption</td>
<td>Potent P-gp inhibitors; Potent CYP3A4 inhibitors</td>
<td>Potent P-gp inhibitors; Potent CYP3A4 inhibitors</td>
<td>Not reported</td>
</tr>
<tr>
<td></td>
<td>No specific antidote; Suggested: Graded response to degree of bleeding; short half-life favors rapid drug elimination; supportive measures for all patients; for major or life-threatening bleeding animal studies are variably supportive of activated or non-activated prothrombin complex concentrates and/or rFVIIa⁴</td>
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</tr>
<tr>
<td>Antidote/Reversal</td>
<td>Activated charcoal for acute ingestion</td>
<td>Activated charcoal for acute ingestion</td>
<td>Activated charcoal for acute ingestion</td>
<td>Activated charcoal for acute ingestion</td>
</tr>
</tbody>
</table>

CYP = cytochrome oxidase hepatic enzymes; QD = once daily; BID = twice daily; aPTT = activated partial thromboplastin time; PT = prothrombin time; INR = international normalised ratio; P-gp = P glycoprotein; PP = proton pump; rFVIIa = recombinant factor VIIa. ¹Half-life dependent on renal function to greater or lesser degree depending on agent. ²aPTT recommended in package insert; thrombin time or dilute thrombin time most linear, but thrombin time may be too sensitive. ³Dose dependent elevation of PT; sensitivity may vary with thromboplastin reagents. ⁴Prothrombin complex concentrates are factor concentrates of the vitamin K factors (II, VII, IX, X) with variable concentrations of factor VII. Some preparations contain activated forms of these factors. rFVIIa is an activated factor VII concentrate. Note: PCCs and rFVIIa have a risk of inducing thrombosis (~1% and 7–10% respectively).
throughout the treatment course was insufficient to prevent an initial up-tick in recurrent VTE in the first 30 days compared to standard therapy.

The problem is one of deciding on the correct dose of the new agent to suppress heightened coagulation early on without causing an increase in bleeding. The EINSTEIN investigators should be credited with their decision to take full advantage of rivaroxaban’s pharmacokinetics and to randomise patients at the time of diagnosis with the study drug versus standard therapy. They made the correct decision to increase the dose of rivaroxaban for the first three weeks before settling on the long-term dose of 20 mg once daily. As a result, rivaroxaban sets a new standard for the acute treatment of DVT and will allow the stable patient with DVT to be easily treated without hospital admission and without the need to transition to another drug.

The decision to extended therapy is based not only on a risk/benefit assessment of continued therapy, but other factors also come into consideration such as the impact of the VKA on quality of life with regard to frequent monitoring, dietary adjustments, co-medications, lost time from work, etc. A drug that significantly reduces recurrence of VTE without the need for monitoring and without other characteristics that impinge on the quality of life is of great value but only if safety can be guaranteed. Both dabigatran and rivaroxaban seem to achieve that goal with positive net clinical benefits. Of course, these results are from only one phase III trial in each case, and more experience will be needed to know how they translate into clinical practice (17). For instance, since rivaroxaban and dabigatran have very short half-lives compared to warfarin, poor drug adherence might predispose to a higher rate of recurrent VTE than that seen in the phase III trials. In this case, a once daily medication compared to a twice daily medication might reduce concerns about adherence.

Finally, the trade-off between major bleeds and recurrent DVT is tricky business. If the major bleed is an intracranial haemorrhage or a life-threatening gastrointestinal bleed, how does that compare to a simple recurrent DVT? The opposite can be said if the recurrent thrombosis is a fatal PE.

Other than the issues reviewed above, little can be said about the results of these studies without extensive speculation, which is what Cohen and Dobromirski do in their paper (8). They review the results of the EINSTEIN studies published previously and then speculate about the potential advantages of rivaroxaban, many of which have not been proven, nor even tested in the trials. How this drug will impact the long-term outcome of post-thrombotic syndrome or chronic thromboembolic pulmonary hypertension is unknown. The post-thrombotic syndrome occurs with a frequency of 10–40% after the first DVT event (4) which is also influenced by other underlying risk factors, and one would not expect rivaroxaban to alter that outcome once the initial event has occurred.

There is great optimism about the value of these new agents, and rightfully so. But optimism must be tempered with reality (18, 19), and only long-term experience of using these drugs for these indications will let us know that they have fulfilled their potential.

Conflict of interest
J. Ansell is a consultant for BMS, Boehringer Ingelheim, Janssen and Daiichi-Sankyo. He serves on Data Safety Boards for BMS.

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References