New oral anticoagulants: not quite there yet

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KEY WORDS
apixaban, dabigatran, oral anticoagulants, rivaroxaban, vitamin K antagonists (VKA)

ABSTRACT
The results of 3 large randomized trials of activated factor X inhibitors, for the prevention of venous thromboembolism, recently became available. Similar data for orally active thrombin inhibitors is also available from recent trials. In this review, we attempt to provide a balanced perspective on the relative merits and demerits of the new, orally active anticoagulants, and speculate on the future of these agents in clinical practice.

Anticoagulants are pivotal agents in the prevention and treatment of thromboembolic disorders.1,2 Currently, parenteral agents are used to prevent and treat acute thromboembolic disorders, often in hospital, while oral agents (coumarins) are used for long-term anticoagulation.2

For over the past 65 years, the vitamin K antagonists (VKA), such as warfarin have been the only oral anticoagulants available. Vitamin K antagonists are effective for the prevention and treatment of venous thromboembolism (VTE), for the prevention of systemic embolism from a cardiac source (e.g. in atrial fibrillation and valvular heart disease) and for the extended treatment of myocardial infarction.3 These agents, however, have important limitations, including drug and food interactions that lead to a variable anticoagulant response, which in turn leads to the requirement for frequent anticoagulant monitoring.3 Anticoagulant monitoring is labor intensive and can be stressful for a patient and health care professional. For this reason, there is an important need for a replacement for VKA, which can be administered orally without the need for anticoagulant monitoring. This need has stimulated the development of orally-active, synthetic small molecules that target specific clotting enzymes.

Three obstacles had to be overcome before new oral anticoagulants that do not require coagulation monitoring could be developed. The first was to elucidate the structure of the active site of clotting enzymes and design small molecules to fit into the active site like a key into a lock. The second was to design ways to protect these small molecules from inactivation while they were being absorbed from the gastrointestinal tract. And the third was to ensure that safe and effective levels of the drug could be achieved without routine dose adjustment.

Several small molecular weight oral inhibitors that either target thrombin or factor Xa are in advanced stages of clinical development.4 These compounds do not appear to be affected by food intake, have a low potential for drug interactions and, because they have a much more predictable dose response than VKAs, they are administered in fixed doses without anticoagulant monitoring. Results of earlier clinical trials with direct parenteral5 and oral thrombin inhibitors6 and indirect parenteral factor Xa inhibitors7 have validated both thrombin and activated factor X as promising targets for new oral anticoagulants. More recently, the results of phase 3 clinical trials with these new oral inhibitors suggest that these oral agents are likely to be safe and effective when used in fixed doses without routine anticoagulant monitoring.8-10 These recent clinical findings provide hope that more convenient, effective and safe oral anticoagulants will soon be available to replace VKAs.

The greatest need for new oral anticoagulants is for prevention of cardioembolism in patients with atrial fibrillation (AF) or prosthetic heart valves.5 Since, however, the cost to develop a new anticoagulant is high, clinical drug development often starts with studies in the prevention of venous thrombosis because the required sample size is much smaller and the duration of follow-up is shorter. Such an approach presupposes that
In the remainder of this review we will discuss the current status of the three most advanced new oral anticoagulants, two factor Xa inhibitors and a factor IIa inhibitor, and speculate on their future role in clinical practice.

**Current status dabigatran etexilate**

Dabigatran etexilate is an oral direct thrombin inhibitor, which is converted into its active metabolite, dabigatran, after absorption from the gastrointestinal tract. Bioconversion begins in the gut and is completed in the liver. The drug has low oral bioavailability (about 6%), and relatively high doses need to be given to achieve adequate plasma concentrations. Absorption is dependent upon an acid environment and is reduced by 20–25% if proton pump inhibitors are given concomitantly.

Plasma levels of dabigatran peak 2 hours after oral administration and the half-life is 12 to 17 hours in patients with preserved renal function making single daily dosing possible.

About 20% of the drug is conjugated and excreted via the biliary system and the remaining 80% is excreted unchanged by the kidneys. Dabigatran etexilate is therefore contraindicated in patients with renal insufficiency. The cytochrome P450 system is not involved in the metabolism of dabigatran etexilate. Dabigatran etexilate is a substrate for the efflux transporter P-glycoprotein and reduced doses are recommended in patients treated with amiodarone. Quinidine is contraindicated in patients treated with dabigatran etexilate.

An early dose ranging study of dabigatran etexilate in patients undergoing hip replacement surgery found the drug to be effective over a wide spectrum of doses between 12.5 mg to 300 mg per day. A subsequent large phase II study success in the prevention of VTE predicts success for other indications.

The first orally-active drug to be evaluated clinically was the thrombin inhibitor ximelagatran, which is a pro-drug that after absorption from the small intestine undergoes rapid bio-transformation to melagatran, the active agent. Ximelagatran has a plasma half-life of 4 to 5 hours and is administered orally twice daily. Based on its predictable anticoagulant response, ximelagatran was administered in fixed doses without coagulation monitoring and evaluated in large phase 3 trials for thromboprophylaxis in high-risk orthopedic patients, for treatment of VTE and for prevention of cardioembolic events in patients with non-valvular atrial fibrillation. These studies showed that ximelagatran:

1. administered post-operatively is safe and effective for the prevention of venous thrombosis in patients undergoing elective orthopedic surgical procedures
2. is an effective and safe alternative to low molecular-weight heparin (LMWH) followed by warfarin, for acute treatment of VTE
3. is as effective and safe as warfarin for the prevention of stroke in patients with atrial fibrillation.

Unfortunately, because of hepatic toxicity, the clinical development of ximelagatran was discontinued. However, the results of the clinical trials with ximelagatran were ground-breaking because, for the first time they showed that a rapidly acting oral anticoagulant can be used without coagulation monitoring, and that when used in such a manner, it had the potential to replace coumarins, and so greatly improve the convenience of long-term anti-coagulant therapy.

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**TABLE 1** Phase III studies comparing dabigatran and enoxaparin in patients undergoing joint replacement surgery

<table>
<thead>
<tr>
<th>Surgery</th>
<th>REMODEL8</th>
<th>RENOVATE9</th>
<th>REMOBILIZE10</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dabigatran – dose and timing of administration</strong></td>
<td>220/150 mg/d 1–4 hours after surgerya</td>
<td>220/150 mg/d 1–4 hours after surgerya</td>
<td>220/150 mg/d 6–12 hours after surgerya</td>
</tr>
<tr>
<td><strong>Enoxaparin – dose and timing of administration</strong></td>
<td>40 mg once daily, evening before surgery</td>
<td>40 mg once daily, evening before surgery</td>
<td>30 mg twice daily, 12–24 hours after surgery</td>
</tr>
<tr>
<td><strong>Duration of study treatment</strong></td>
<td>6–10 days</td>
<td>28–35 days</td>
<td>12–15 days</td>
</tr>
<tr>
<td>**Primary outcome (%)**b</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dabigatran 220 mg</td>
<td>36.4</td>
<td>6.0</td>
<td>31.1</td>
</tr>
<tr>
<td>Dabigatran 150 mg</td>
<td>40.5</td>
<td>8.6</td>
<td>33.7</td>
</tr>
<tr>
<td>Enoxaparin arm</td>
<td>37.7</td>
<td>6.7</td>
<td>25.3</td>
</tr>
<tr>
<td>**Major bleeding (%)**c</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dabigatran 220 mg</td>
<td>1.5</td>
<td>2.0</td>
<td>0.6</td>
</tr>
<tr>
<td>Dabigatran 150 mg</td>
<td>1.5</td>
<td>1.3</td>
<td>0.6</td>
</tr>
<tr>
<td>Enoxaparin arm</td>
<td>1.3</td>
<td>1.6</td>
<td>1.4</td>
</tr>
<tr>
<td><strong>Trial result (efficacy)</strong></td>
<td>Dabigatran non-inferior to enoxaparin</td>
<td>Dabigatran non-inferior to enoxaparin</td>
<td>Dabigatran inferior to enoxaparin</td>
</tr>
</tbody>
</table>

a Started at half the dose
b Composite of total VTE and all-cause mortality
c The definitions of major bleeding were different in the dabigatran studies and the rivaroxaban studies, contributing to the large differences in bleeding
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### TABLE 2 Phase III studies comparing rivaroxaban and enoxaparin in patients undergoing joint replacement surgery

<table>
<thead>
<tr>
<th>Surgery</th>
<th>RECORD 1</th>
<th>RECORD 2</th>
<th>RECORD 3</th>
<th>RECORD 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rivaroxaban – dose and timing of administration</td>
<td>10 mg once daily 6–8 hours after wound closure</td>
<td>10 mg once daily 6–8 hours after wound closure</td>
<td>10 mg once daily 6–8 hours after wound closure</td>
<td>10 mg once daily 6–8 hours after wound closure</td>
</tr>
<tr>
<td>Enoxaparin – dose and timing of administration</td>
<td>40 mg enoxaparin once daily, 12 hours before surgery</td>
<td>40 mg enoxaparin once daily, 12 hours before surgery</td>
<td>40 mg enoxaparin once daily, 12 hours before surgery</td>
<td>30 mg twice daily, 12–24 hours after surgery</td>
</tr>
<tr>
<td>Duration of study treatment</td>
<td>31–39 days</td>
<td>Rivaroxaban 31–39 days Enoxaparin 10–14 days</td>
<td>10–14 days</td>
<td>10–14 days</td>
</tr>
<tr>
<td>Primary outcome (%)</td>
<td>Rivaroxaban 1.1</td>
<td>2.0</td>
<td>9.6</td>
<td>6.9</td>
</tr>
<tr>
<td>Enoxaparin</td>
<td>3.7</td>
<td>9.3</td>
<td>18.9</td>
<td>10.1</td>
</tr>
<tr>
<td>Major bleeding (%)</td>
<td>Rivaroxaban 0.3</td>
<td>&lt;0.1</td>
<td>0.6</td>
<td>0.7</td>
</tr>
<tr>
<td>Enoxaparin</td>
<td>0.1</td>
<td>&lt;0.1</td>
<td>0.5</td>
<td>0.3</td>
</tr>
<tr>
<td>Trial result (efficacy)</td>
<td>Rivaroxaban superior</td>
<td>Rivaroxaban superior</td>
<td>Rivaroxaban superior</td>
<td>Rivaroxaban superior</td>
</tr>
</tbody>
</table>

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*Composite of total VTE and all-cause mortality*  
*The definitions of major bleeding were different in the dabigatran studies and the rivaroxaban studies, contributing to the large differences in bleeding*
increase in the risk of bleeding. The optimal dose was considered to be between 5 and 20 mg/d. In another phase II study in patients undergoing hip replacement, similar results were found, thereby leading to evaluation of a dose of 10 mg/d in phase III trials.22

To date, 4 phase-III trials of rivaroxaban in VTE prophylaxis have been completed, and all of them have demonstrated superiority of rivaroxaban over enoxaparin in preventing VTE.23–26 Meta-analysis of the available data (7 studies and over 7000 patients) with rivaroxaban indicates that it is superior to enoxaparin in preventing VTE (RR 0.48, 95% CI 0.41–0.57, p <0.001) but that rivaroxaban increases clinically relevant non-major bleeding (unpublished data). Similar to the trials of dabigatran, the rivaroxaban trials differed substantially in terms of the populations studied, the dose and timing of administration of the study drugs, and the duration of study therapy (TABLE 2). The shorter duration of treatment specified for the enoxaparin arm compared to the rivaroxaban arm in the RECORD 2 study contributed to the large difference in treatment effect in this trial (TABLE 2).24 The observed benefits of rivaroxaban compared with enoxaparin were less in the RECORD 4 study where the (higher) North American twice-daily dosing regimen for enoxaparin was used. Further, the much lower than usual rates of VTE in control patients undergoing knee replacement in the RECORD 3 study and the occurrence of the primary endpoint (which was a composite of VTE diagnosed by mandatory venography, and all cause mortality). There was a dose-dependent increase in efficacy, but also a significant dose-related increase in the incidence of total adjudicated bleeding events. Based on the results of this study, a dose of 2.5 mg twice daily or 5 mg once daily has been selected for investigation in phase III trials. Apixaban has also been evaluated in a dose ranging study among patients with symptomatic DVT. In this study apixaban (5 mg bd, 10 mg bd or 20 mg qd) was compared with LMWH followed by oral VKA therapy for a total of 84–91 days.31 The occurrence of the primary outcome event (a composite of recurrent symptomatic venous thromboembolism and asymptomatic deterioration of bilateral compression ultrasound or perfusion lung scan) was similar in the apixaban and the LMWH/VKA group with no evidence of a dose-response relationship with apixaban. The occurrence of the principal safety outcome (a composite of major and clinically relevant non-major bleeding) was also similar in the two treatment groups.31

In the only completed phase III study of apixaban for VTE prevention involving 3195 patients undergoing knee replacement surgery, apixaban 2.5 mg given twice daily compared with enoxaparin 30 mg twice daily did not meet statistical criteria for noninferiority but significantly reduced bleeding. The rates of the composite primary end-point (any VTE or all-cause death) were numerically similar between the two treatments (9.0% vs. 8.9%). Major bleeding was less frequent (0.7% vs. 1.4%, p = 0.053) and clinically relevant bleeding was significantly lower among patients receiving apixaban (2.9% vs. 4.3%, p = 0.034).32 Further details are expected when the study results will be presented later this year.

Apixaban Apixaban is a small molecule which selectively and reversibly inhibits factor Xa. Like rivaroxaban, it inhibits both free and bound factor Xa. The drug has an oral bioavailability of 50% which is unaffected by food, and a terminal plasma half-life of 9–14 hours after repeated dosing.29 It is metabolized in the liver by both CYP3A4 and CYP-independent mechanisms. The drug is mainly excreted in the feces, with the renal route accounting for about 25% of elimination.24 The potential for drug interactions with apixaban is similar to that with rivaroxaban. A phase II, dose-ranging study compared apixaban with enoxaparin or warfarin in patients undergoing knee replacement surgery.30 This study included 1238 patients who were randomized in a double-blind manner to 1 of 6 apixaban doses (5, 10 or 20 mg/d administered as a single or a twice-daily divided dose), enoxaparin (30 mg twice daily) or open-label warfarin (titrated to an INR of 1.8–3.0). Apixaban and enoxaparin were initiated 12–24 hours after surgery and warfarin was started on the evening before surgery. Treatment was continued for 10–14 days. Compared to enoxaparin or warfarin, all doses of apixaban reduced the occurrence of the primary endpoint (which was a composite of VTE diagnosed by mandatory venography, and all cause mortality). There was a dose-dependent increase in efficacy, but also a significant dose-related increase in the incidence of total adjudicated bleeding events. Based on the results of this study, a dose of 2.5 mg twice daily or 5 mg once daily has been selected for investigation in phase III trials. Apixaban has also been evaluated in a dose ranging study among patients with symptomatic DVT. In this study apixaban (5 mg bd, 10 mg bd or 20 mg qd) was compared with LMWH followed by oral VKA therapy for a total of 84–91 days.31 The occurrence of the primary outcome event (a composite of recurrent symptomatic venous thromboembolism and asymptomatic deterioration of bilateral compression ultrasound or perfusion lung scan) was similar in the apixaban and the LMWH/VKA group with no evidence of a dose-response relationship with apixaban. The occurrence of the principal safety outcome (a composite of major and clinically relevant non-major bleeding) was also similar in the two treatment groups.31

The future of oral factor Xa and thrombin inhibitors The results of phase III trials of dabigatran etexilate, rivaroxaban and apixaban are promising for VTE prevention in patients undergoing orthopedic surgery. Unlike VTE prevention in orthopedic surgery where parenteral agents are likely to retain a major role, orally administered VKAs are the antithrombotics of choice in patients with AF, in those with prosthetic heart valves, and in those requiring continued out-of-hospital treatment for secondary prevention of VTE. Therefore, a clearer picture of the clinical utility of new oral anticoagulants will become apparent only when the results of the large ongoing phase III trials
in patients with AF and in those with established VTE become available. Based on experience with VKAs, it is likely that an oral agent that is effective for any one of these indications has the potential to be effective and safe for the others. Since, however, the optimal dosing regimens for the various anticoagulants are likely to vary from one indication to the next, a potentially valuable drug could be discarded and lost from clinical practice if it is evaluated using a sub-optimal dose. Past experience with parenteral inhibitors indicates that both oral factor Xa and thrombin inhibitors will be effective for most indications. An exception might exist for prosthetic heart valves in which the contact activation pathway is likely to contribute to thrombogenesis. This prediction is based on the failure of fondaparinux (a parental factor Xa inhibitor) to prevent catheter-related thrombosis in the acute coronary syndrome trials.33,34 and its parallel inability to inhibit contact pathway activation of the coagulation cascade.35 On the other hand, thrombin inhibition (using bivalirudin) does not appear to be associated with catheter-related thrombosis.36 On the basis of these observations, it is conceivable that factor Xa inhibitors might be less effective than thrombin inhibitors (like dabigatran) in preventing thromboembolic complications in patients with mechanical heart valves.

In addition to the efficacy and safety demonstrated in the VTE prevention trials, the long-term safety and cost will also determine the acceptance and uptake of new oral anticoagulants into clinical practice. Dabigatran etexilate and rivaroxaban have been approved for use in Europe and Canada and are priced similarly to prophylactic doses of LMWH. Additional efficacy data as well as long-term safety data will be obtained from phase III trials in patients with AF and VTE that are either in the later stages of completion or currently ongoing.

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