New oral anticoagulants in development

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Summary
Although currently available anticoagulants are effective for the prevention and treatment of thromboembolic disorders, they have several drawbacks. Low-molecular-weight heparins and fondaparinux produce a predictable level of anticoagulation that obviates the need for coagulation monitoring, but they must be given parenterally, which renders them inconvenient for long-term use. Vitamin K antagonists, such as warfarin, are administered orally, but produce a variable anticoagulant response because genetic polymorphisms, dietary vitamin K intake and multiple drug-drug interactions affect their metabolism. Consequently, coagulation monitoring and frequent dose adjustments are needed to ensure that a therapeutic level of anticoagulation is achieved. This is burdensome for patients and physicians, and costly for the healthcare system. These limitations have prompted the development of new oral anticoagulants that target thrombin or factor Xa and can be given in fixed doses without coagulation monitoring. This paper focuses on the new oral anticoagulants in the most advanced stages of development.

Keywords
Anticoagulants, arterial thromboembolism, direct factor Xa inhibitors, direct thrombin inhibitors, venous thromboembolism

Introduction
Arterial and venous thrombosis are major causes of morbidity and mortality and, with an aging population, their incidence is likely to increase. Anticoagulants are widely used for the prevention and treatment of venous thromboembolism (VTE) (1), the acute management of patients with acute coronary syndromes (ACS) and for stroke prevention in patients with atrial fibrillation (AF) or mechanical heart valves (2). Although vitamin K antagonists (VKAs) are also effective for the prevention of recurrent ischaemia after acute myocardial infarction, they are not widely used for this indication (3) because of their limitations (Table 1).

Currently available parenteral anticoagulants, including low-molecular-weight heparin (LMWH) and fondaparinux, are effective for the prevention and initial treatment of VTE and for the management of ACS, but the need for subcutaneous injection renders them inconvenient for long-term or home use. This drawback may contribute to the poor compliance with guidelines that recommend extended thromboprophylaxis for patients undergoing major orthopaedic surgery (4). Prophylaxis is often stopped at the time of hospital discharge, which places patients at risk for VTE when they are in outpatient settings. This is particularly problematic with the shortening of hospital stays because patients remain at risk for VTE for several weeks after surgery (5).

The risk of stroke is increased five-fold in patients with AF (6). Although VKAs are more effective than acetylsalicylic acid (ASA) at lowering this risk (7), VKA therapy is underused. This underuse reflects, at least in part, the many drawbacks of VKA therapy, particularly the variable anticoagulation response, which necessitates frequent coagulation monitoring and dose adjustments (8). A recent meta-analysis showed that, in community-based practice in the US, AF patients spent on average only 51% of their time within the therapeutic international normalised ratio (INR) range (9). Although specialised anticoagulation clinics do somewhat better, even these units achieve a therapeutic INR in only 63% of patients, with the remainder either under- or over-anticoagulated (9), which places them at risk for thromboembolic events or bleeding, respectively.

The limitations of VKAs have prompted the development of new oral anticoagulants. In contrast to VKAs, these drugs have a rapid onset and offset of action, a low propensity for food and drug

<table>
<thead>
<tr>
<th>Limitation</th>
<th>Consequence</th>
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<tr>
<td>Slow onset of action</td>
<td>Overlap with a parenteral anticoagulant</td>
</tr>
<tr>
<td>Genetic variation in metabolism</td>
<td>Variable dose requirements</td>
</tr>
<tr>
<td>Multiple food and drug interactions</td>
<td>Frequent coagulation monitoring</td>
</tr>
<tr>
<td>Narrow therapeutic window</td>
<td>Frequent coagulation monitoring</td>
</tr>
</tbody>
</table>

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Mechanistic advantages of the new oral anticoagulants

The new oral anticoagulants in the most advanced stages of development are specific and direct inhibitors of either thrombin or FXa. As the final effector in blood coagulation, thrombin is a logical target for new anticoagulants. Thrombin not only converts fibrinogen to fibrin, but also amplifies its own generation by feedback activation of factors (F) V, VIII and IX. Therefore, thrombin inhibition not only attenuates fibrin formation, but also reduces thrombin generation (10). In addition, thrombin also activates platelets.

Direct thrombin inhibitors have potential efficacy advantages over indirect inhibitors, such as heparin or LMWH. Whereas indirect thrombin inhibitors are limited in their capacity to inhibit fibrin-bound thrombin, direct thrombin inhibitors inactivate fibrin-bound thrombin and free thrombin equally well (11). This endows direct thrombin inhibitors with the capacity to better suppress thrombus growth because thrombolytic activity is rapid and complete. Furthermore, direct thrombin inhibitors retain their activity in the vicinity of platelet-rich thrombi. In contrast, heparin and LMWH are neutralised by platelet factor 4 and von Willebrand factor released from activated platelets (13). The evidence supporting thrombin as a target for new oral anticoagulants comes from studies with ximelagatran, an oral direct thrombin inhibitor. Ximelagatran underwent extensive phase III evaluation for several indications, including the prevention and treatment of VTE, and stroke prevention in patients with ACS (19–24). The results from these studies provided proof-of-principle for selective FXa inhibition as an attractive target. However, the need for subcutaneous injection renders fondaparinux inconvenient for long-term and home use. Direct FXa inhibitors may have advantages over indirect inhibitors, because direct FXa inhibitors inactivate both prothrombinase-bound FXa and free FXa (25, 26). In contrast, indirect inhibitors (such as heparin, LMWH and fondaparinux), which must interact with antithrombin to exert their anticoagulant effects, are limited in their capacity to inhibit FXa within the prothrombinase complex (27–29). This may reflect, at least in part, the inability of antithrombin to compete effectively with the substrate prothrombin for the active site of FXa when the enzyme is incorporated within the prothrombinase complex (30). The capacity to inhibit prothrombinase-bound FXa may endow direct FXa inhibitors with an advantage over indirect inhibitors because it is FXa assembled within the prothrombinase complex that propagates coagulation by converting prothrombin to thrombin (30).

Pharmacological properties of the new oral anticoagulants

The new oral anticoagulants in the most advanced stages of development include dabigatran etexilate, which targets thrombin, and rivaroxaban and apixaban, which target FXa. The pharmacological properties of each of these agents are described separately and their main pharmacological profiles are summarised in Table 2.

Dabigatran etexilate

Dabigatran etexilate, a prodrug of dabigatran, has an oral bioavailability of ~6% (11). After oral administration, dabigatran etexilate is rapidly and completely converted by esterases to dabigatran.

Table 2: Comparison of the characteristics of new oral anticoagulants in advanced stages of clinical development.

<table>
<thead>
<tr>
<th></th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Dabigatran etexilate</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Target</strong></td>
<td>Factor Xa</td>
<td>Factor Xa</td>
<td>Factor IIa</td>
</tr>
<tr>
<td><strong>Molecular weight</strong></td>
<td>436</td>
<td>460</td>
<td>628</td>
</tr>
<tr>
<td><strong>Prodrug</strong></td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Bioavailability (%)</strong></td>
<td>~80</td>
<td>~50</td>
<td>6–7</td>
</tr>
<tr>
<td><strong>Time to peak (h)</strong></td>
<td>2–3</td>
<td>1–2</td>
<td>1.5</td>
</tr>
<tr>
<td><strong>Half-life (h)</strong></td>
<td>7–11</td>
<td>8–14</td>
<td>14–17</td>
</tr>
<tr>
<td><strong>Renal excretion (%)</strong></td>
<td>66*</td>
<td>~25</td>
<td>&gt;80</td>
</tr>
<tr>
<td><strong>Antidote</strong></td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
</tbody>
</table>

*Approximately 33% as unchanged drug, the remainder as inactive metabolites.
Plasma levels of dabigatran peak 2 hours (h) after drug administration. Dabigatran has a half-life of 14–17 h, which permits once daily (od) or twice daily (bid) administration. The elimination of dabigatran occurs predominantly via the kidneys, with approximately 80% of the drug excreted unchanged in the urine. Dabigatran has predictable pharmacokinetics and pharmacodynamics, and no clinically relevant interactions with atorvastatin or with the non-steroidal anti-inflammatory drug diclofenac (31). Therefore, combination therapy with these agents is feasible. However, the P-glycoprotein (P-gp) inhibitor quinidine is contraindicated (32).

**Rivaroxaban**

Rivaroxaban, an oral direct Factor Xa inhibitor, is an active compound that exhibits high oral bioavailability (approximately 80%), and a rapid onset and offset of action. Plasma levels of rivaroxaban peak 2–3 h after administration and the terminal half-life is 7–11 h (33, 34). Rivaroxaban has a dual mode of elimination: one-third of the administered drug is cleared as unchanged active drug by the kidneys, one-third is metabolised by the liver via CYP3A4-dependent and independent pathways and then excreted in faeces, and one-third is metabolised to inactive metabolites and then excreted by the kidneys (35). Rivaroxaban was found to exhibit a predictable and dose-dependent pharmacokinetic and pharmacodynamic profile that is not influenced by age, gender or body weight (36–38). Rivaroxaban can be co-administered with ASA or clopidogrel and non-steroidal anti-inflammatory drugs (39–41). Potent inhibitors of both CYP3A4 and P-gp, such as ketoconazole or ritonavir, are contraindicated because they increase plasma drug concentrations (34).

**Apixaban**

Apixaban is an oral, direct FXa inhibitor (42, 43). In healthy males, apixaban, a selective and reversible inhibitor of FXa (43), is absorbed rapidly, with maximal plasma concentrations reached 3 h after oral administration, and the drug is cleared with a terminal plasma half-life of 8–14 h. Apixaban is eliminated via multiple pathways, including oxidative metabolism, renal and intestinal routes (44).

**Clinical trial results**

Dabigatran etexilate, rivaroxaban and apixaban are undergoing extensive phase II and III evaluation for several indications, which include the prevention of VTE, VTE treatment, stroke prevention in patients with AF and the prevention of recurrent ischaemic events in ACS patients. The trials with each of the agents will be described separately. Phase III trial results with dabigatran etexilate and rivaroxaban, which are licensed in many countries for the prevention of VTE after total hip replacement (THR) or total knee replacement (TKR) surgery, are presented in Tables (Tables 3 and 4).

<table>
<thead>
<tr>
<th>RE-NOVATE (THR)</th>
<th>Dabigatran etexilate (150 mg od) % (n/N)</th>
<th>Dabigatran etexilate (220 mg od) % (n/N)</th>
<th>Enoxaparin (40 mg od [RE-NOVATE; RE-MODEL]; 30 mg bid [RE-MOBILIZE]) % (n/N)</th>
<th>P-values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total VTE</td>
<td>8.6 (75/874)*</td>
<td>6.0 (53/880)*</td>
<td>6.7 (60/897) *</td>
<td>p&lt;0.0001 for non-inferiority vs. enoxaparin</td>
</tr>
<tr>
<td>Major VTE</td>
<td>4.3 (38/888)</td>
<td>3.1 (28/909)</td>
<td>3.9 (36/917)</td>
<td></td>
</tr>
<tr>
<td>Major bleeding</td>
<td>1.3 (15/1,163)</td>
<td>2.0 (23/1,146)</td>
<td>1.6 (18/1,154) *</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>RE-MODEL (TKR)</th>
<th>Dabigatran etexilate (150 mg od) % (n/N)</th>
<th>Dabigatran etexilate (220 mg od) % (n/N)</th>
<th>Enoxaparin (40 mg od [RE-NOVATE; RE-MODEL]; 30 mg bid [RE-MOBILIZE]) % (n/N)</th>
<th>P-values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total VTE</td>
<td>40.5 (213/526)*</td>
<td>36.4 (183/503)**</td>
<td>37.7 (193/512) *</td>
<td>p=0.017; **p=0.0003 for non-inferiority vs. enoxaparin</td>
</tr>
<tr>
<td>Major VTE</td>
<td>3.8 (20/527)</td>
<td>2.6 (13/506)</td>
<td>3.5 (18/511)</td>
<td></td>
</tr>
<tr>
<td>Major bleeding</td>
<td>1.3 (9/703)</td>
<td>1.5 (10/679)</td>
<td>1.3 (9/694)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>RE-MOBILIZE (TKR)</th>
<th>Dabigatran etexilate (150 mg od) % (n/N)</th>
<th>Dabigatran etexilate (220 mg od) % (n/N)</th>
<th>Enoxaparin (40 mg od [RE-NOVATE; RE-MODEL]; 30 mg bid [RE-MOBILIZE]) % (n/N)</th>
<th>P-values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total VTE</td>
<td>33.7 (219/649)*</td>
<td>31.1 (188/604)**</td>
<td>25.3 (163/643) *</td>
<td>p=0.0009; **p=0.02 vs. enoxaparin</td>
</tr>
<tr>
<td>Major VTE</td>
<td>3.0 (20/656)</td>
<td>3.4 (21/618)</td>
<td>2.2 (15/668)</td>
<td></td>
</tr>
<tr>
<td>Major bleeding</td>
<td>0.6 (5/871)</td>
<td>0.6 (5/857)</td>
<td>1.4 (12/868)</td>
<td></td>
</tr>
</tbody>
</table>

bid, twice daily; od, once daily; THR, total hip replacement; TKR, total knee replacement; VTE, venous thromboembolism.

Table 3: Key outcomes in phase III studies investigating dabigatran etexilate for the prevention of venous thromboembolism in patients undergoing total hip or knee replacement surgery [46, 47, 79].
Dabigatran etexilate

Prevention of VTE

Based on the results of a phase II dose-ranging study (BISTRO II) [45], two doses of dabigatran etexilate were evaluated in three double-blind, randomised phase III trials (Table 3). In all three trials, dabigatran etexilate (at doses of 150 or 220 mg od, starting with a half-dose on the day of surgery) was compared with subcutaneous enoxaparin. The primary efficacy endpoint was total VTE (a composite of venographically detected or symptomatic deep-vein thrombosis [DVT] and/or symptomatic pulmonary embolism [PE], and all-cause mortality). The primary safety endpoint was major bleeding (defined as fatal bleeding; clinically overt bleeding associated with a fall in haemoglobin of ≥2 g/dl; clinically overt bleeding leading to a transfusion of ≥2 units of blood; or retroperitoneal, intracranial, intraocular or intraspinal bleeding).

In the RE-MODEL trial in patients undergoing TKR (treatment duration 6–10 days), both doses of dabigatran etexilate (started 1–4 hours after surgery) were non-inferior to enoxaparin (40 mg od, with the first dose given the evening prior to surgery) for the primary efficacy endpoint. The incidence of major VTE (a composite of proximal DVT and PE) was similar between both doses of dabigatran etexilate and enoxaparin (46). In the RE-NOVATE trial in patients undergoing THR, extended prophylaxis (28–35 days) with dabigatran etexilate was compared with extended prophylaxis with enoxaparin. Both doses of dabigatran etexilate were again non-inferior to enoxaparin (40 mg od) for the primary efficacy endpoint (47). The incidence of major VTE was similar between both doses of dabigatran etexilate and enoxaparin. However, in the RE-MOBILIZE trial (48) in patients undergoing TKR, both doses of dabigatran etexilate failed to achieve non-inferiority compared with enoxaparin (30 mg bid) for the primary efficacy endpoint (Table 3). The design of this trial differed from that of the RE-MODEL trial in several ways. Firstly, the initial dose of dabigatran etexilate was given later at 6–12 h after surgery instead of 1–4 h. Secondly, the dose of enoxaparin was higher: a 30 mg bid regimen was used instead of the 40 mg od regimen. Thirdly, the treatment duration was 12–15 days instead of 6–10 days. Therefore, the different results from the two trials in TKR patients (RE-MODEL and RE-MOBILIZE) may reflect the higher daily dose of enoxaparin used as a comparator and/or the delayed start of dabigatran etexilate in the RE-MOBILIZE trial (48).

A meta-analysis of the results of the RE-MODEL and RE-NOVATE trials (two-trial analysis), and also including those of RE-MOBILIZE (three-trial analysis), did not find any significant differences between dabigatran and enoxaparin in any of the endpoints analysed, either in the two-trial (all p>0.15), or in the three-trial analysis (all p>0.30) (49). The meta-analysis of RE-MODEL and RE-NOVATE trials supports the conclusions of the individual trials that dabigatran etexilate is non-inferior to enoxaparin 40 mg od, and has a similar safety profile.

Dabigatran etexilate was approved for the prevention of VTE after THR or TKR in adult patients in the European Union and Canada in 2008. The 220 mg od dose is recommended for most patients, and the 150 mg od dose is reserved for elderly patients and those with moderate renal impairment (creatinine clearance of 30–50 ml/min). Treatment in patients with severe renal impairment (creatinine clearance <30 ml/minute) is contraindicated (32).

Treatment of VTE

Ongoing phase III trials are evaluating dabigatran etexilate for the treatment of acute symptomatic VTE (RE-COVER-1; www.clinicaltrials.gov; NCT00291330) and for the long-term secondary prevention of recurrent VTE in patients who have completed a course of conventional anticoagulant treatment with a VKA for 6–18 months (RE-MEDY; www.clinicaltrials.gov; NCT00538259), or 3–6 months (RE-SOLVE; www.clinicaltrials.gov; NCT00329238). The RE-COVER-1 trial has been completed and results will be reported in 2009. A second trial with the same study design has been initiated.

Stroke prevention in AF

In a phase II study (PETRO) in patients with AF, three doses of dabigatran etexilate (50, 150 or 300 mg bid), with or without ASA , were compared with dose-adjusted warfarin (50). Excess bleeding

Table 4: Key outcomes in phase III studies investigating rivaroxaban for the prevention of venous thromboembolism in patients undergoing total hip or knee replacement surgery [57–59, 80].

<table>
<thead>
<tr>
<th></th>
<th>Rivaroxaban (10 mg od)</th>
<th>Enoxaparin (40 mg od)</th>
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<tbody>
<tr>
<td></td>
<td>% (n/N)</td>
<td>% (n/N)</td>
</tr>
<tr>
<td>Total VTE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RECORD1 (THR)</td>
<td>1.1 (18/1,595)</td>
<td>3.7 (58/1,558)</td>
</tr>
<tr>
<td>Major VTE</td>
<td>0.2 (4/1,686)</td>
<td>2.0 (33/1,678)</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>0.3 (6/2,209)</td>
<td>0.1 (2/2,224)</td>
</tr>
<tr>
<td></td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>RECORD2 (THR)</td>
<td>2.0 (17/864)</td>
<td>9.3 (81/869)</td>
</tr>
<tr>
<td>Major VTE</td>
<td>0.6 (6/961)</td>
<td>5.1 (49/962)</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>0.1 (1/1,228)</td>
<td>0.1 (1/1,229)</td>
</tr>
<tr>
<td></td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>RECORD3 (TKR)</td>
<td>9.6 (79/824)</td>
<td>18.9 (166/878)</td>
</tr>
<tr>
<td>Major VTE</td>
<td>1.0 (9/908)</td>
<td>2.6 (24/925)</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>0.6 (7/1,220)</td>
<td>0.5 (6/1,239)</td>
</tr>
<tr>
<td></td>
<td>0.01</td>
<td>0.77</td>
</tr>
<tr>
<td>RECORD4 (TKR)</td>
<td>6.9 (67/965)</td>
<td>10.1 (97/959)</td>
</tr>
<tr>
<td>Major VTE</td>
<td>1.2 (13/1,122)</td>
<td>2.0 (22/1,112)</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>0.7 (10/1,526)</td>
<td>0.3 (4/1,508)</td>
</tr>
<tr>
<td></td>
<td>0.11</td>
<td>0.124</td>
</tr>
</tbody>
</table>

Note: bid, twice daily; od, once daily; THR, total hip replacement; TKR, total knee replacement; VTE, venous thromboembolism.
was observed in patients receiving the highest dose of dabigatran etexilate in conjunction with ASA, leading to the discontinuation of ASA in these patients. Building on the results of the PETRO study, dose changes were made for the open-label extension PETRO-Ex study. The 50 mg bid and the 150 mg od groups were discontinued because of the stroke rates, and patients were transferred to the 150 mg bid or 300 mg od group. Later, it was observed that the stroke rate in patients receiving the dabigatran etexilate 300 mg od regimen was similar to that with placebo (51). Based on these data, the phase III RE-LY trial compared dabigatran etexilate doses of 110 or 150 mg bid with open-label, dose-adjusted warfarin in 18,113 patients with AF. Dabigatran etexilate 110 mg bid was non-inferior, whereas 150 mg bid was superior to warfarin for the prevention of stroke and systemic embolism (p<0.001), with a significantly lower rate of major bleeding in the 110 mg dose group. The annual rate of haemorrhagic stroke was reduced from 0.38% with warfarin to 0.12% and 0.10% with 110 and 150 mg bid of dabigatran etexilate, respectively (p<0.001). The incidence of dyspepsia was higher in both dabigatran etexilate dose groups, leading to significantly higher rates of treatment discontinuation (p<0.001) (52).

ACS
A phase II dose-finding study in ACS patients (RE-DEEM) has been completed (www.clinicaltrials.gov; NCT00621855). This trial will determine whether the addition of dabigatran etexilate to dual antiplatelet therapy with ASA and clopidogrel reduces the risk of recurrent ischaemia in ACS patients.

Rivaroxaban
Prevention of VTE
Phase IIb studies in patients undergoing THR or TKR showed that 5–20 mg total daily doses of rivaroxaban had efficacy and safety similar to those of enoxaparin (53,54). The 10 mg od regimen appeared to provide the optimal balance between efficacy and safety, and was selected for the phase III REGulation of Coagulation in Orthopaedic surgery to prevent DVT and PE (RECORD program) (55,56). In all of the RECORD studies, the primary efficacy endpoint was total VTE (a composite of symptomatic or asymptomatic DVT detected by mandatory, bilateral venography, non-fatal PE and all-cause mortality), and the secondary efficacy endpoint was major VTE (a composite of proximal DVT, non-fatal PE and VTE-related death). The primary safety endpoint was major bleeding, defined as fatal bleeding, bleeding into a critical organ, bleeding requiring re-operation and clinically overt extra-surgical-site bleeding associated with a fall in haemoglobin ≥2 g/dl or requiring transfusion of ≥2 units of blood.

The RECORD1 trial compared rivaroxaban (10 mg od) with enoxaparin (40 mg od) in patients undergoing THR (57). Both treatments were given for 31–39 days. There was a significant reduction in the primary efficacy endpoint in the rivaroxaban group compared with the enoxaparin group (relative risk reduction [RRR] 70%; p<0.001). Rivaroxaban also significantly reduced the incidence of major VTE compared with enoxaparin (RRR 88%; p<0.001). The incidence of major bleeding was not significantly different between the two groups (Table 4).

RECORD2 compared extended prophylaxis with rivaroxaban (31–39 days) with short-term prophylaxis with enoxaparin (10–14 days followed by placebo) in patients undergoing THR (58). Rivaroxaban (10 mg od) significantly reduced the incidence of the primary efficacy endpoint compared with short-term enoxaparin (40 mg od; RRR 79%; p<0.0001). This result confirms the benefit of extended over short-term prophylaxis in THR patients. The incidence of symptomatic VTE was also lower with rivaroxaban (RRR 80%; p=0.004), and the rate of major bleeding was low and not significantly different between the two groups (Table 4).

The efficacy and safety of rivaroxaban have also been investigated in patients undergoing TKR and compared with enoxaparin 40 mg od (RECORD3) or 30 mg bid (RECORD4). Treatments were given for 10–14 days. In the RECORD3 trial, rivaroxaban (10 mg od, beginning 6–8 h postoperatively) was superior to enoxaparin (40 mg od, beginning preoperatively), with significant reductions in the incidence of the primary efficacy endpoint (RRR 49%; p<0.001) and major VTE (RRR 62%; p=0.02). Moreover, symptomatic VTE (any symptomatic DVT or symptomatic non-fatal or fatal PE) occurred significantly less frequently in rivaroxaban-treated than enoxaparin-treated patients (RRR 66%; p=0.008). There was no significant difference in major bleeding rates between the two treatment groups (Table 4) (59). RECORD4 compared rivaroxaban (10 mg od, beginning 6–8 h postoperatively) with enoxaparin (30 mg bid, initiated 12–24 h postoperatively) (60). Rivaroxaban was more effective than enoxaparin in reducing the primary efficacy endpoint (RRR 31%; p=0.016). There was no significant difference in the incidence of major VTE or major bleeding between the two groups (Table 4).

A prespecified pooled analysis of the four RECORD studies was performed to evaluate the effect of rivaroxaban on the composite of symptomatic VTE and all-cause mortality, and bleeding. The results showed that rivaroxaban significantly reduced the incidence of symptomatic VTE and death compared with enoxaparin regimens (RRR 52%; p=0.001) at day 12 ± 2 in the active treatment pool (i.e. during the enoxaparin-controlled period common to all studies), and for the total study duration pool (double-blind treatment period plus the 30–35 day follow-up period; RRR 51%; p<0.001). The pooled analysis showed that there was no significant difference between the rivaroxaban regimens and enoxaparin regimens in the rates of treatment-emergent major bleeding or any bleeding. The composite of major and clinically relevant non-major bleeding rate was 2.55% and 3.19% for enoxaparin and rivaroxaban regimens, respectively (p=0.039), for the total treatment duration pool (planned treatment period of each study). This difference arose in a comparison that included the placebo phase in RECORD2, during which patients in the rivaroxaban arm continued to receive active medication, whereas those in the enoxaparin arm received only placebo (61).
Based on the results of the RECORD programme, rivaroxaban was approved in 2008 in the European Union, Canada and several other countries for the prevention of VTE in adult patients undergoing THR or TKR.

To determine the efficacy and safety of rivaroxaban for the prevention of VTE in other patient groups, a phase III trial (MAGELLAN; www.clinicaltrials.gov; NCT00571649) is comparing extended prophylaxis with rivaroxaban (10 mg od for 35 days) with short-term prophylaxis with enoxaparin (40 mg for 10 days) in hospitalized, medically ill patients.

**Treatment of VTE**

The efficacy and safety of rivaroxaban for the treatment of VTE was evaluated in two phase II studies (62, 63). In the ODIXa-DVT study, an improvement in thrombotic burden at 21 days was achieved in patients receiving rivaroxaban (10, 20, or 30 mg bid, or 40 mg od; respectively), compared with standard therapy (enoxaparin 1 mg/kg bid and a VKA). Major bleeding occurred in 1.7%, 1.7%, 3.3% and 1.7%, respectively, compared with none in the standard-therapy group (62). In the EINSTEIN DVT study, rivaroxaban (20, 30 or 40 mg od) was compared with standard therapy (LMWH and a VKA) (63). An improvement of thrombotic burden was also observed in patients receiving rivaroxaban 20, 30 and 40 mg, respectively, compared with those receiving standard therapy. The incidence of any clinically relevant bleeding ranged between 2.2% and 6.0% for the rivaroxaban groups and was 8.8% for the LMWH and VKA group.

EINSTEIN DVT (www.clinicaltrials.gov; NCT00440193) and EINSTEIN PE (www.clinicaltrials.gov; NCT00439777) are multicentre, randomised, open-label phase III trials currently ongoing in patients with confirmed, acute symptomatic DVT or PE, respectively. The rivaroxaban regimen used in these trials consists of 15 mg bid for the first three weeks, followed by 20 mg od for a predefined treatment period of 3, 6 or 12 months. The EINSTEIN EXT (www.clinicaltrials.gov; NCT00439725) trial recruited VTE patients who completed a 6– or 12-month course of treatment with rivaroxaban or a VKA. Such patients were then randomised to receive either rivaroxaban (20 mg od) or placebo for an additional six or 12 months. The results of this trial will be presented later this year.

**Stroke prevention in AF**

The results of the phase II VTE treatment studies were used to select the 20 mg od dose of rivaroxaban for the investigation of stroke prevention in patients with AF. The ROCKET trial is a multicentre, double-blind phase III trial comparing rivaroxaban (20 mg od or 15 mg od for patients with moderate renal impairment, as defined by a creatinine clearance between 30 and 49 ml/min at screening) with dose-adjusted warfarin (www.clinicaltrials.gov; NCT00403767).

**ACS**

A phase IIb study (ATLAS ACS-TIMI-46) explored the utility of rivaroxaban in combination with ASA or ASA plus a thienopyridine for secondary prevention in patients with ACS (64). The results indicate that the use of rivaroxaban (in combination with antiplatelet therapy) increases bleeding in a dose-dependent manner and may reduce the risk of important clinical events (death, myocardial infarction, or stroke). Based on the sum of safety, efficacy, and net clinical outcomes data, doses of 2.5 mg bid and 5 mg bid have been selected for further evaluation in a large international randomised phase III trial (Anti-Xa Therapy to Lower Cardiovascular events in Addition to aspirin with/without thienopyridine therapy in Subjects with Acute Coronary Syndrome [ATLAS ACS TIMI 51]) of high-risk ACS patients (www.clinicaltrials.gov; NCT00809965).

**Apixaban**

**Prevention of VTE**

In a phase IIb study in patients undergoing TKR (APROPOS) (65), apixaban (at total daily doses of 5–20 mg, given od or bid) was compared with enoxaparin (30 mg bid) or open-label warfarin (dose-adjusted to an INR of 1.8–3.0). Exposure-clinical outcome modelling using the results of this study identified the 2.5 mg bid dosing regimen as optimal, and this dose was selected for the phase III VTE prevention trials (66).

Three phase III trials are evaluating the efficacy and safety of apixaban for the prevention of VTE after major orthopaedic surgery (the ADVANCE programme). ADVANCE-1 compared apixaban (2.5 mg bid, with the first dose started on the morning of the day after surgery) with subcutaneous enoxaparin (30 mg bid, started 12–24 h after surgery) in patients undergoing TKR. Both treatments were given for 12 ± 2 days. Although the primary efficacy endpoint (a composite of total VTE and all-cause mortality) in the apixaban and enoxaparin groups occurred in 9.0% and 8.9%, respectively, because of the low overall event rates, apixaban did not meet the prespecified non-inferiority criteria (67). Rates of major bleeding with apixaban and enoxaparin were 0.7% and 1.4%, respectively (p=0.053). ADVANCE-2 compared the same apixaban regimen with enoxaparin (40 mg od) in patients undergoing THR. The incidence of the primary endpoint was 15.1% and 24.4% for the apixaban and enoxaparin groups, respectively (p<0.001). Major VTE (a composite of proximal DVT, symptomatic non-fatal PE, and VTE-related death) occurred less frequently in the apixaban group (1.1%) compared with the enoxaparin group (2.2%; p=0.019). The rate of major or clinically relevant non-major bleeding was numerically lower in the apixaban group (3.5% vs. 4.8%), but this did not reach statistical significance (68). ADVANCE-3 is comparing a 35-day course of either apixaban (2.5 mg bid) or enoxaparin (40 mg od) in patients undergoing THR (www.clinicaltrials.gov; NCT00423319). This trial will be completed in 2009.

Apixaban is also being evaluated for thromboprophylaxis in medical patients. In the ADAPT trial, a 30-day regimen of apixaban (2.5 mg bid) is being compared with enoxaparin (40 mg od, given for at least seven days) in acutely ill medical patients (www.clinicaltrials.gov; NCT00457002). A phase II pilot study is
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investigating apixaban for the prevention of VTE in patients with metastatic cancer (www.clinicaltrials.gov; NCT00320255).

Treatment of VTE

The efficacy and safety of apixaban for VTE treatment was explored in the phase II BOTTICELLI study (69). Patients with confirmed DVT were randomised to receive either apixaban (5 or 10 mg bid, or 20 mg od) or conventional therapy (LMWH or fondaparinux, followed by a VKA) for 84–91 days. The primary efficacy endpoint (a composite of recurrent VTE and compression ultrasound or perfusion lung scan evidence of progressive thrombosis) occurred in 4.2% of patients receiving conventional therapy, and was similar in the apixaban 5 mg and 10 mg bid groups (6.0% and 5.6%, respectively), and lower in the apixaban 20 mg od group (2.6%). The rate of major and clinically relevant non-major bleeding was also similar between apixaban and conventional therapy. Building on these results, phase III trials (AMPLIFY and AMPLIFY-EX) are evaluating apixaban for VTE treatment (www.clinicaltrials.gov; NCT00633893, NCT00643201).

Stroke prevention in AF

Two phase III trials are underway; the first, the ARISTOTLE trial, is comparing apixaban (5 mg bid) with warfarin (dose adjusted to achieve an INR of 2.0 to 3.0) in AF patients with at least one additional risk factor for stroke (www.clinicaltrials.gov; NCT00412984), and the second (AVERROES) is comparing the same apixaban regimen with ASA in AF patients who are ineligible for VKA treatment or have not tolerated previous VKA treatment (www.clinicaltrials.gov; NCT00496769).

ACS

The APPRAISE-1 study was a phase II, randomised, double-blind, dose-ranging, placebo-controlled, six-month safety trial of apixaban 2.5 mg bid, 10 mg od, 10 mg bid or 20 mg od vs. placebo in ACS patients receiving antiplatelet therapy (70). The two highest doses were prematurely discontinued due to excess bleeding in patients receiving apixaban and dual antiplatelet therapy. There was a dose-dependent increase in bleeding events and a dose-dependent reduction in ischaemic events with apixaban in combination with antiplatelet therapy compared with placebo (70).

Conclusions and future directions

For more than 65 years, VKAs have been the only available oral anticoagulants. Although effective, the need for dose adjustment and frequent coagulation monitoring renders them difficult to manage. Consequently, despite current guidelines, a large proportion of patients do not receive appropriate prophylaxis, particularly those with AF (71). Thus, there is a clear unmet need for oral anticoagulants that can be given in fixed doses without the need for routine coagulation monitoring. The promising results with the new oral thrombin and FXa inhibitors in patients undergoing TKR or THR have already streamlined clinical practice in countries where dabigatran etexilate and rivaroxaban have been licensed. With od oral administration and no need for monitoring, these agents are ideal for out-of-hospital use and potentially simplify adherence to guidelines that recommend extended prophylaxis. With evidence of superiority over a LMWH, rivaroxaban may also confer economic benefits due to reduced costs associated with VTE management (72–74).

Without head-to-head trials, direct comparisons of the efficacy and safety of the various new oral anticoagulants cannot be made, particularly with regard to bleeding rates because different definitions were used. Nevertheless, the superior efficacy of rivaroxaban over enoxaparin in the RECORD studies, and the superior efficacy of the 150 mg bid dabigatran etexilate regimen and the superior safety of the 110 mg bid dabigatran etexilate regimen over warfarin in the RE-LY trial, highlight the potential of these new agents as better anticoagulant therapies. The results of trials comparing other new oral agents with warfarin for the prevention of stroke and systemic embolism in patients with AF, and for treatment of VTE are eagerly awaited. New oral anticoagulants that are more convenient to use, safer, and more effective than VKA might soon be available for a variety of indications.

Although routine coagulation monitoring is not required with new agents such as rivaroxaban and dabigatran, a simple test for monitoring would be useful in some circumstances. For example, monitoring might be required prior to surgery to ensure that these drugs no longer have any clinically relevant anticoagulant effect before the operation. Similarly, if patients taking these new agents present with a haemorrhagic or thrombotic event, coagulation testing would be useful to determine whether patients are over- or under-anticoagulated. Periodic coagulation testing may also be helpful to assess compliance. The oral FXa inhibitors have variable and transient effects on the prothrombin time. Although assays measuring FXa activity may be useful (75), such tests have not yet been standardised. Dabigatran etexilate can be monitored with the activated partial thromboplastin time (aPTT) (11), but the aPTT reaches a plateau at higher drug concentrations. Although the ecarin clotting time is more linear, this test is not widely available. Therefore, further research to identify reproducible and convenient assays for monitoring the effects of these new drugs may be beneficial. Regardless, they constitute an advance in terms of ease of use, as they do not require routine coagulation monitoring and subsequent dose adjustments, as is the case with warfarin.

Another potential drawback of the new oral anticoagulants is the lack of specific antidotes. Although the short half-lives of these new agents relative to warfarin are likely to limit the need for antidotes, there will be instances when immediate reversal is needed. Dialysis or haemofiltration may remove drugs such as dabigatran, which are not highly protein-bound. Encouraging preclinical results have been obtained with procoagulants such as recombinant FVIIIa or activated prothrombin complex concentrates (76, 77), but the effectiveness of these agents in patients with bleeding in association with oral direct FXa or thrombin inhibitors has yet to be
established. Recently, an active-site-blocked recombinant FXa mut- tant lacking the membrane-binding domain was shown to reverse the anticoagulant effects of FXa inhibitors in vitro and in animals by competing with endogenous FXa for the inhibitor (78). These promising results may prompt the development of specific anti-
dotes.

In summary, emerging evidence suggests that new oral agents may change the future of anticoagulation therapy and provide im-
proved patient care. With the new opportunities will come new
challenges, but the benefits of the new oral anticoagulants far out-
weigh any disadvantages.

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References

boembolic disease: American College of Chest Physicians Evidence-Based
2. Singer DE, Albers GW, Dalen JE, et al. Antithrombotic therapy in atrial fibril-
lation: American College of Chest Physicians Evidence-Based Clinical Practice
3. Anand SS, Yusuf S. Oral anticoagulant therapy in patients with coronary artery
for deep-vein thrombosis prevention in total hip and knee arthroplasty. Curr Med
5. Warwick D, Friedman RJ, Agnelli G, et al. Insufficient duration of venous throm-
boembolism prophylaxis after total hip or knee replacement when compared with
the time course of thromboembolic events: findings from the Global Orthopaedic
6. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor
7. Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to pre-
vent stroke in patients who have nonvalvular atrial fibrillation. Ann Intern Med
antagonists: American College of Chest Physicians evidence-based clinical prac-
rin control in atrial fibrillation patients in the United States. J Manag Care Pharm
10. Mann KG, Brummell K, Butenas S. What is all that thrombin for? J Thromb
and tolerability of dabigatran etexilate, a new oral direct thrombin inhibitor, in
12. Kumar K, Beguin S, Hemker HC. The effect of fibrin clots and clot-bound throm-
bin on the development of platelet procoagulant activity. Thromb Haemost 1995;
74: 962–968.
V275–V284.
14. Francis CW, Berkowitz SD, Comp PC, et al. Comparison of ximelagatran with
warfarin for the prevention of venous thromboembolism after total knee replace-
ximelagatran compared with warfarin for the prevention of venous thromboem-
16. Fiessinger JN, Huismann MV, Davidson BL, et al. Ximelagatran vs low-molecular-
weight heparin and warfarin for the treatment of deep vein thrombosis: a ran-
thromboembolism with the oral direct thrombin inhibitor ximelagatran. N Engl J
18. Albers GW, Diener HC, Frison L, et al. Ximelagatran vs warfarin for stroke pre-
vention in patients with nonvalvular atrial fibrillation: a randomized trial. J Am
19. Eriksson BI, Bauer KA, Lassen MR, et al. Fondaparinux compared with enoxapa-
rin for the prevention of venous thromboembolism after hip fracture surgery. N
20. Turpie AG, Bauer KA, Eriksson BI, et al. Fondaparinux vs enoxaparin for the pre-
vention of venous thromboembolism in major orthopedic surgery: a meta-analys-
21. Lassen MR, Bauer KA, Eriksson BI, et al. Postoperative fondaparinux versus pre-
operative enoxaparin for prevention of venous thromboembolism in elective hip
replacement surgery: a randomised double-blind comparison. Lancet 2002; 359:
1715–1720.
22. Bauer KA, Eriksson BI, Lassen MR, et al. Fondaparinux compared with enoxapa-
rin for the prevention of venous thromboembolism after elective major knee sur-
23. Buller HR, Davidson BL, Decousus H, et al. Subcutaneous fondaparinux versus
intravenous unfractionated heparin in the initial treatment of pulmonary embol-
24. Buller HR, Davidson BL, Decousus H, et al. Fondaparinux or enoxaparin for the
initial treatment of symptomatic deep venous thrombosis: a randomized trial.
antithrombotic agent BAY 59–7939 ‘an oral, direct Factor Xa inhibitor. J Thromb
27. Brufatto N, Nesheim ME. The use of prothrombin(5253C) labeled with fluores-
cein to directly study the inhibition of prothrombinase by antithrombin during
28. Brufatto N, Ward A, Nesheim ME. Factor Xa is highly protected from antithrom-
29. Rezaie AR. Prothrombin protects factor Xa in the prothrombinase complex from
30. Mann KG, Jenny RJ, Krishnaswamy S. Cofactor proteins in the assembly and ex-
32. Pradaxa® (dabigatran etexilate): Summary of product characteristics. Available at:
http://www.pradaxa.com/Include/media/pdf/Pradaxa_SPC_EMEA.pdf. Ac-
cessed May 18, 2009.
33. Kubista D, Becka M, Voith B, et al. Safety, pharmacodynamics, and pharmacoki-
netics of single doses of BAY 59–7939, an oral, direct Factor Xa inhibitor. Clin
34. Xarelto® Summary of Product Characteristics. Available at: http://www.xarelo-
35. Weine C, Schwarz T, Kubista D, et al. Metabolism and excretion of rivaroxaban,
an oral, direct Factor Xa inhibitor, in rats, dogs and humans. Drug Metab Dispos
36. Kubista D, Becka M, Rueck W, et al. The effect of extreme age, and gender, on the
pharmacology and tolerability of rivaroxaban ‘an oral, direct Factor Xa inhibitor.
oral, direct Factor Xa inhibitor – in subjects with extreme body weight. Blood
and pharmacodynamics of rivaroxaban in healthy elderly subjects. Curr Med Res
Opin 2008; 24: 2757–2765.

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