The Novel Oral Anticoagulants

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Abstract

After the introduction of warfarin, long-term oral anticoagulation treatment remained unchanged for more than 50 years. Most recently, with the development and approval of new oral anticoagulants, the treatment of medical conditions that require thrombosis prophylaxis and long-term anticoagulation has become more complex. In the case of venous thromboembolism (VTE) prevention after orthopedic surgery, the new oral agents will be less costly than the parenteral alternative. In other settings (such as atrial fibrillation or treatment of acute VTE), the new agents will offer additional convenience at higher cost, but the degree to which they will reduce clinically important events such as thrombosis or bleeding will be limited, especially for patients on optimally controlled warfarin. As the use of the new oral anticoagulants becomes more widespread, it will be important for all clinicians to have a basic understanding of their pharmacology, advantages, and limitations. Although the need to measure or reverse the effect of these drugs will arise infrequently, clinicians—especially hematologists—will desire evidence-based recommendations about how to manage such scenarios, which will require research studies.

Keywords

► anticoagulants
► oral anticoagulants
► apixaban
► rivaroxaban
► dabigatran

Three new oral anticoagulant drugs (apixaban, rivaroxaban, and dabigatran) have become available for prophylaxis and treatment of acute venous thromboembolism (VTE), and, since 2010, also for prevention of stroke and systemic embolism in patients with nonvalvular atrial fibrillation (AF). This represents a significant change, because since the introduction of warfarin half a century ago, there had been no significant changes in drugs available for use in long-term anticoagulation. The favorable features of the new oral agents (i.e., less complex drug-to-drug interaction profiles, the lack of need for routine monitoring) make them an attractive option for managing anticoagulation in the inpatient and outpatient settings. On the contrary, the new agents have important limitations (e.g., contraindication in severe renal insufficiency, lack of an antidote in case of bleeding, and higher cost than warfarin) that complicate clinical decisions about when and how to use them. This review describes the landmark clinical trial data as well as practical considerations that are relevant to treating patients with the three new oral agents (apixaban, dabigatran, and rivaroxaban) that are now in advanced stages of clinical development.

Pharmacology

All drug dosage recommendations in this article are for North America, unless otherwise stated. The doses approved may differ in other regions.

Apixaban

Apixaban is a reversible, direct, and highly selective active site inhibitor of factor Xa (FXa). It does not require antithrombin for its anticoagulant activity. Apixaban inhibits free and clot-bound FXa, and prothrombinase activity. Apixaban has no direct effects on platelet aggregation, but indirectly inhibits tissue factor–induced platelet aggregation in vitro, presumably by inhibiting the production of thrombin.1,2

Apixaban is produced as a 2.5 mg film-coated tablet. The bioavailability of apixaban is approximately 50%; it is rapidly absorbed, not affected by food, with maximum concentrations appearing 3 to 4 hours after tablet intake and has a half-life of approximately 12 hours.3 Apixaban is metabolized mainly via the cytochrome P450 (CYP) enzyme 3A4/5.3

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excretion of apixaban accounts for approximately 27% of total clearance with additional contributions from biliary and direct intestinal excretion.3

The recommended apixaban doses for most patients are 5 mg twice daily for stroke prevention in Af and 2.5 mg twice daily for the prevention of VTE after orthopedic surgery. No dose adjustment is necessary in patients with mild renal impairment. There is no clinical experience in patients with creatinine clearance (CrCl) less than 15 mL/min, or in patients undergoing dialysis.4 No dose adjustment is required in patients with mild or moderate hepatic impairment (Child Pugh A or B), but apixaban is contraindicated in patients with hepatic disease associated with coagulopathy.6

No additional adjustment is necessary by body weight or age. There are no data available from the use of apixaban in pregnant women, and apixaban is not recommended during pregnancy. It is unknown whether apixaban or its metabolites are excreted in human milk. Available data in animals have shown excretion of apixaban in milk.5

**Rivaroxaban**

Rivaroxaban is an oral FXa inhibitor that selectively blocks the active site of FXa and, like apixaban, does not require antithrombin for its activity.

Rivaroxaban is manufactured as tablets: 10, 15, and 20 mg. The absolute bioavailability is more than 50% and it is dose-dependent; at 10 mg dose, it is estimated to be 80 to 100% bioavailable. The bioavailability of rivaroxaban is not decreased by food and it is not affected by drugs that alter gastric pH.6,7

The maximum concentrations of rivaroxaban appear 2 to 4 hours after oral intake and the elimination half-life of rivaroxaban is 5 to 9 hours. Rivaroxaban is metabolized mainly via oxidative degradation in the liver.8 In humans, CYP3A4 and CYP2J2 are the two enzymes responsible for its oxidative metabolism.8 Inhibitors and inducers of these CYP enzymes can result in changes in rivaroxaban exposure.

Approximately 40% of the unchanged drug is excreted into the urine due to elimination by active tubular secretion.6 Rivaroxaban is a moderate substrate of the efflux transporter P-glycoprotein (P-gp). Drugs that inhibit both the CYP3A4 enzymes and the P-gp include ketoconazole, ritonavir, clarithromycin, fluconazole, and erythromycin.9 The concomitant use of rivaroxaban and these medications could increase blood levels of rivaroxaban and bleeding risk.9

The recommended postoperative thromboprophylaxis (knee and hip replacement) is 10 mg once daily. The therapeutic dose ranges between 15 and 20 mg once daily, and needs adjustment based on the estimated CrCl. For patients with CrCl > 50 mL/min, 20 mg is the recommended daily dose; with CrCl < 50 mL/min, 15 mg is the recommended daily dose. There is no clinical experience in patients with CrCl < 30 mL/min.7 For the first 21 days of treatment for acute DVT or PE, rivaroxaban is given at a dose of 15 mg orally twice daily.

Rivaroxaban has not been studied in patients with severe hepatic impairment (Child Pugh C). For patients with moderate hepatic impairment (Child Pugh B), the mean rivaroxaban exposure is increased by 2.3-fold.7

The safety and effectiveness of rivaroxaban during labor and delivery have not been studied in clinical trials; it is not known if rivaroxaban is excreted in human milk.

**Dabigatran Eteixlate**

Dabigatran etexilate is a pro-drug that is converted by tissue esterases to dabigatran, a competitive, direct thrombin inhibitor.10 There is an evidence from in vitro experiments that both free and clot-bound thrombin are inhibited by dabigatran.2 Also, there is evidence of inhibition of tissue factor-induced platelet aggregation by this medication.2

Dabigatran is available in the United States as 75 and 150 mg capsules. In many other jurisdictions, dabigatran is available as 110 and 150 mg capsules. The absolute bioavailability of dabigatran following oral administration is approximately 3 to 7%. The absorption is influenced by the intestinal efflux transporter P-gp. The maximum concentration occurs at 1 hour postadministration in the fasted state; and can be delayed by approximately 2 hours if administered with meals, but the presence of food does not change the ultimate bioavailability of dabigatran. The half-life of dabigatran etexilate is 12 to 17 hours.10

Dabigatran is not a substrate, inhibitor, or inducer of CYP450 enzymes and is eliminated primarily in the urine.11 In adults with moderate hepatic impairment (Child Pugh B), there is no evidence of a consistent change in exposure or pharmacodynamics.12

The recommended dose of dabigatran is 150 mg taken orally, twice daily; a dose reduction to 75 mg twice daily is indicated (in the United States) for patients with CrCl < 30 mL/min.12 There is no clinical trial experience in patients with a CrCl < 30 mL/min (the 75 mg dose was approved based on pharmacokinetic modeling) and the manufacturer recommends that dabigatran should not be used in patients with a CrCl < 15 mL/min or in patients who require renal replacement therapy.

The concomitant use of dabigatran etexilate with P-gp inducers (e.g., rifampicin) reduces exposure to dabigatran and should generally be avoided13; although concomitant P-gp inhibitors may increase exposure to dabigatran,14 the prescribing information approved by the U.S. Food and Drug Administration (FDA) does not require a dose adjustments in such situations. There are no well-controlled studies in pregnant women, and it is not known whether dabigatran is excreted in human milk.

**Clinical Trial Evidence**

**Apixaban**

Available phase III clinical trial data support the use of apixaban for VTE prophylaxis after orthopedic surgery and for cardioembolic prophylaxis in Af (→*Tables 1–3*). Phase II studies indicate that apixaban may be a safe and effective option for the treatment of VTE but data from pivotal phase III trials are pending.
**Table 1** Summary of the efficacy and safety data for apixaban, rivaroxaban, and dabigatran in the prevention of venous thromboembolism after major orthopedic surgery

<table>
<thead>
<tr>
<th>Agent (where approved for postoperative VTE prevention)</th>
<th>Trial name</th>
<th>Dose, frequency</th>
<th>Comparator (enoxaparin)</th>
<th>VTE* (%) (vs. LMWH %)</th>
<th>Relative Risk for VTE (95% CI)</th>
<th>Major bleeding (%) (vs. LMWH %)</th>
<th>Relative risk for major bleeding (95% CI)</th>
<th>Number of patients randomized</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apixaban (Europe)</td>
<td>ADVANCE-1: knee</td>
<td>2.5 mg b.i.d.</td>
<td>30 mg b.i.d.</td>
<td>9.0 (vs. 8.8)</td>
<td>1.02 (0.78–1.32)</td>
<td>0.7 (vs. 1.4)</td>
<td>0.65 (0.28–1.49)</td>
<td>3,195</td>
</tr>
<tr>
<td></td>
<td>ADVANCE-2: knee</td>
<td>2.5 mg b.i.d.</td>
<td>40 mg o.d.</td>
<td>15.1 (vs. 24.4)</td>
<td>0.62 (0.51–0.74)</td>
<td>0.6 (vs. 0.9)</td>
<td>1.22 (0.65–2.26)</td>
<td>3,057</td>
</tr>
<tr>
<td></td>
<td>ADVANCE-3: hip</td>
<td>2.5 mg b.i.d.</td>
<td>30 mg b.i.d.</td>
<td>1.4 (vs. 3.9)</td>
<td>0.36 (0.23–0.56)</td>
<td>0.8 (vs. 0.7)</td>
<td>0.5 (0.24–1.02)</td>
<td>5,407</td>
</tr>
<tr>
<td>Rivaroxaban (Europe, Canada, United States)</td>
<td>RECORD-1: hip</td>
<td>10 mg o.d.</td>
<td>40 mg o.d.</td>
<td>1.1 (vs. 3.7)</td>
<td>0.30 (0.18–0.51)</td>
<td>0.3 (vs. 0.1)</td>
<td>3.02 (0.61–14.95)</td>
<td>5,541</td>
</tr>
<tr>
<td></td>
<td>RECORD-2: hip</td>
<td>10 mg o.d.</td>
<td>40 mg o.d.</td>
<td>2.0 (vs. 9.3)</td>
<td>0.21 (0.13–0.35)</td>
<td>0.1 (vs. 0.1)</td>
<td>1.00 (0.06–15.98)</td>
<td>2,509</td>
</tr>
<tr>
<td></td>
<td>RECORD-3: knee</td>
<td>10 mg o.d.</td>
<td>40 mg o.d.</td>
<td>9.6 (vs. 18.9)</td>
<td>0.51 (0.39–0.65)</td>
<td>0.6 (vs. 0.5)</td>
<td>1.19 (0.40–3.53)</td>
<td>2,531</td>
</tr>
<tr>
<td></td>
<td>RECORD-4: knee</td>
<td>10 mg o.d.</td>
<td>30 mg b.i.d.</td>
<td>6.9 (vs. 10.1)</td>
<td>0.69 (0.51–0.92)</td>
<td>0.7 (vs. 0.3)</td>
<td>2.47 (0.78–7.86)</td>
<td>3,148</td>
</tr>
<tr>
<td>Dabigatran (Europe, Canada)</td>
<td>RE-NOVATE: hip</td>
<td>220 mg o.d.</td>
<td>40 mg o.d.</td>
<td>6.0 (vs. 6.7)</td>
<td>0.90 (0.63–1.29)</td>
<td>2.0 (vs. 1.6)</td>
<td>1.29 (0.70–2.37)</td>
<td>3,493</td>
</tr>
<tr>
<td></td>
<td>RE-MODEL: knee</td>
<td>150 mg o.d.</td>
<td>40 mg o.d.</td>
<td>8.6 (vs. 6.7)</td>
<td>1.28 (0.93–1.78)</td>
<td>1.3 (vs. 1.6)</td>
<td>0.83 (0.42–1.63)</td>
<td>2,101</td>
</tr>
<tr>
<td></td>
<td>RE-MOBILIZE: knee</td>
<td>30 mg b.i.d.</td>
<td>30 mg b.i.d.</td>
<td>36.4 (vs. 37.7)</td>
<td>0.97 (0.82–1.13)</td>
<td>1.5 (vs. 1.3)</td>
<td>1.14 (0.46–2.78)</td>
<td>2,615</td>
</tr>
<tr>
<td></td>
<td>RE-COVER</td>
<td>150 mg o.d.</td>
<td>40 mg o.d.</td>
<td>40.5 (vs. 37.7)</td>
<td>1.07 (0.92–1.25)</td>
<td>1.3 (vs. 1.3)</td>
<td>0.99 (0.39–2.47)</td>
<td>3,128</td>
</tr>
<tr>
<td></td>
<td>RE-COVER II</td>
<td>150 mg o.d.</td>
<td>30 mg b.i.d.</td>
<td>31.1 (vs. 25.3)</td>
<td>1.23 (1.03–1.47)</td>
<td>0.6 (vs. 1.4)</td>
<td>0.42 (0.15–1.19)</td>
<td>3,128</td>
</tr>
<tr>
<td></td>
<td>RE-SONATE</td>
<td>150 mg b.i.d.</td>
<td>30 mg b.i.d.</td>
<td>33.7 (vs. 25.3)</td>
<td>1.33 (1.12–1.58)</td>
<td>0.6 (vs. 1.4)</td>
<td>0.42 (0.15–1.17)</td>
<td>3,057</td>
</tr>
</tbody>
</table>

Abbreviations: b.i.d., twice daily; CI, confidence interval; LMWH, low-molecular-weight heparin; o.d., once daily; vs., versus; VTE, venous thromboembolism.

*VTE numbers included asymptomatic events detected by surveillance venography.

**Table 2** Summary of efficacy and safety data for rivaroxaban and dabigatran in the treatment of acute venous thromboembolism

<table>
<thead>
<tr>
<th>Agent</th>
<th>Trial name</th>
<th>Dose, frequency</th>
<th>Comparator (INR indicated if VKA)</th>
<th>Recurrent VTE* (%) (vs. VKA %)</th>
<th>Relative risk for recurrent VTE (95% CI)</th>
<th>Major bleeding (%) (vs. comparator %)</th>
<th>Relative risk for major bleeding (95% CI)</th>
<th>Number of patients randomized</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rivaroxaban</td>
<td>EINSTEIN-DVT</td>
<td>15 mg b.i.d.</td>
<td>INR 2.0–3.0</td>
<td>2.1 (vs. 3.0)</td>
<td>0.70 (0.46–1.07)</td>
<td>0.8 (vs. 1.2)</td>
<td>0.70 (0.35–1.38)</td>
<td>3,449</td>
</tr>
<tr>
<td></td>
<td>EINSTEIN-extension</td>
<td>20 mg o.d.</td>
<td>placebo</td>
<td>1.3 (vs. 7.1)</td>
<td>0.19 (0.09–0.40)</td>
<td>0.7 (vs. 0.1)</td>
<td>0.79 (0.42–148.99)</td>
<td>1,197</td>
</tr>
<tr>
<td></td>
<td>EINSTEIN-PE</td>
<td>15 mg b.i.d.</td>
<td>INR 2.0–3.0</td>
<td>2.1 (vs. 1.8)</td>
<td>1.13 (0.76–1.69)</td>
<td>1.1 (vs. 2.2)</td>
<td>0.50 (0.31–0.80)</td>
<td>4,832</td>
</tr>
<tr>
<td>Dabigatran</td>
<td>RE-COVER</td>
<td>150 mg b.i.d.</td>
<td>INR 2.0–3.0</td>
<td>2.4 (vs. 2.1)</td>
<td>1.10 (0.66–1.84)</td>
<td>1.6 (vs. 1.9)</td>
<td>0.83 (0.46–1.49)</td>
<td>2,539</td>
</tr>
<tr>
<td></td>
<td>RE-COVER II</td>
<td>150 mg b.i.d.</td>
<td>INR 2.0–3.0</td>
<td>2.4 (vs. 2.2)</td>
<td>1.09 (0.65–1.81)</td>
<td>1.2 (vs. 1.7)</td>
<td>0.69 (0.36–1.33)</td>
<td>2,568</td>
</tr>
<tr>
<td></td>
<td>RE-SONATE</td>
<td>150 mg b.i.d.</td>
<td>placebo</td>
<td>0.4 (vs. 5.6)</td>
<td>0.08 (0.02–0.25)</td>
<td>0.3 (vs. 0.1)</td>
<td>3.89 (0.18–86.07)</td>
<td>1,343</td>
</tr>
<tr>
<td></td>
<td>RE-MEDY</td>
<td>150 mg b.i.d.</td>
<td>INR 2.0–3.0</td>
<td>1.8 (vs. 1.3)</td>
<td>1.44 (0.79–2.62)</td>
<td>19.4 (vs. 26.2)</td>
<td>0.74 (0.65–0.85)</td>
<td>2,856</td>
</tr>
</tbody>
</table>

Abbreviations: b.i.d., twice daily; CI, confidence interval; INR, international normalized ratio; o.d., once daily; VKA, vitamin K antagonist; vs., versus; VTE, venous thromboembolism.

*Recurrent VTE was taken as the composite of deep venous thrombosis or nonfatal or fatal pulmonary embolism.
**Table 3** Summary of the efficacy and safety data for apixaban, rivaroxaban, and dabigatran in the prevention of embolism in atrial fibrillation

<table>
<thead>
<tr>
<th>Agent (where approved for stroke prevention in AF)</th>
<th>Trial name</th>
<th>Dose, frequency</th>
<th>Comparator* (INR indicated if VKA)</th>
<th>All stroke or systemic embolism</th>
<th>Relative risk for embolism (95% CI)</th>
<th>Major bleeding (%)</th>
<th>Relative risk for major bleeding/ICH (95% CI)</th>
<th>Number of patients randomized</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Apixaban</strong> (Europe, Canada, United States of America)</td>
<td>ARISTOTLE</td>
<td>5 mg b.i.d.</td>
<td>INR 2.0–3.0 aspirin</td>
<td>2.3 (vs. 2.9)</td>
<td>0.80 (0.67–0.95)</td>
<td>3.6 (vs. 5.1)</td>
<td>0.70 (0.61–0.81)</td>
<td>18,201</td>
</tr>
<tr>
<td></td>
<td>AVERROES</td>
<td>5 mg b.i.d.</td>
<td></td>
<td>1.8 (vs. 4.0)</td>
<td>0.45 (0.32–0.62)</td>
<td>0.6 (vs. 1.3)</td>
<td>0.42 (0.31–0.59)</td>
<td>5,599</td>
</tr>
<tr>
<td><strong>Rivaroxaban</strong> (Europe, Canada, United States of America)</td>
<td>ROCKET-AF</td>
<td>20 mg o.d.</td>
<td>INR 2.0–3.0</td>
<td>3.8 (vs. 4.3)</td>
<td>0.88 (0.75–1.03)</td>
<td>5.6 (vs. 5.4)</td>
<td>1.03 (0.89–1.18)</td>
<td>14,264</td>
</tr>
<tr>
<td><strong>Dabigatran</strong> (Europe, Canada, United States of America)</td>
<td>RE-LY</td>
<td>110 mg b.i.d.</td>
<td>INR 2.0–3.0</td>
<td>3.0 (vs. 3.3)</td>
<td>0.92 (0.75–1.12)</td>
<td>5.4 (vs. 6.6)</td>
<td>0.81 (0.70–0.94)</td>
<td>18,113</td>
</tr>
<tr>
<td></td>
<td></td>
<td>150 mg b.i.d.</td>
<td></td>
<td>2.2 (vs. 3.3)</td>
<td>0.67 (0.54–0.83)</td>
<td>0.4 (vs. 1.4)</td>
<td>0.31 (0.20–0.48)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: b.i.d., twice daily; CI, confidence interval; ICH, intracranial hemorrhage; INR, international normalized ratio; o.d., once daily; VKA, vitamin K antagonist; VTE, venous thromboembolism.
*All embolism was defined as the composite of stroke and non-central nervous system systemic embolism.

Taken together, the clinical trial data for apixaban, rivaroxaban, and dabigatran suggests that these NOACs are as effective as low-dose warfarin (VKA) in patients with symptomatic deep vein thrombosis (DVT). Despite a later start and shorter expected stay of at least 3 days, the primary efficacy outcome of the AVERROES trial (aspirin vs. apixaban in patients who were not suitable for warfarin) was stopped early because of a trend toward higher rate of major bleeding events in the apixaban arm (relative risk [RR], 2.53; 95% confidence interval [CI], 0.98 to 6.50). A subsequent pooled analysis highlights the importance of a prespecified pooled analysis highs.
very low overall rate of serious hemorrhagic events\textsuperscript{28} (\textit{-Table 1}).

The MAGELLAN study, a multicenter randomized controlled trial (RCT), evaluated the efficacy of rivaroxaban for 35 days versus enoxaparin for 10 days in patients hospitalized for various acute medical illnesses with risk factors for VTE. The primary efficacy outcome was the composite of asymptomatic proximal DVT, symptomatic DVT, symptomatic non-fatal PE, and VTE-related death. The primary safety outcome was the composite of major bleeding and clinically relevant nonmajor bleeding.\textsuperscript{29} The modified intent-to-treat analysis showed comparable rates for the primary efficacy outcome (3.0\% in the rivaroxaban group vs. 3.1\% in the enoxaparin group; RR, 0.99; 95\% CI, 0.75 to 1.30; \( p = 0.95 \)), but the safety outcome favored enoxaparin, with a higher rate of bleeding in the rivaroxaban group (4.1 vs. 1.7\%; RR, 2.5; 95\% CI, 1.85 to 3.25; \( p < 0.0001 \)).\textsuperscript{30}

In the DVT treatment setting, the EINSTEIN-DVT study and the EINSTEIN-extension trial\textsuperscript{31} have demonstrated that the efficacy of rivaroxaban for acute treatment and secondary prevention of DVT is comparable to that provided by traditional therapy with LMWH followed by long-term VKA. Furthermore, recent data from the EINSTEIN-PE trial that rivaroxaban is noninferior to standard therapy in patients with symptomatic PE with or without concurrent DVT\textsuperscript{32} (\textit{-Table 2}).

The ATLAS ACS-TIMI 51 study assessed the efficacy of rivaroxaban in the treatment of ACS.\textsuperscript{33} This randomized, double-blind, placebo-controlled trial compared one of two twice-daily doses (2.5 or 5 mg) of rivaroxaban to placebo. All patients received other standard therapy for ACS (e.g., antiplatelet medications) at the discretion of the treating physician. The primary efficacy end point, a composite of death due to cardiovascular causes, myocardial infarction, or stroke, occurred less frequently in the rivaroxaban-treated patients for both 2.5 mg (hazard ratio [HR], 0.84; 95\% CI, 0.72 to 0.97; \( p = 0.02 \)) and 5 mg doses (HR, 0.85; 95\% CI, 0.73 to 0.98; \( p = 0.03 \)). Moreover, the twice-daily 2.5 mg dose of rivaroxaban reduced the rates of death from cardiovascular causes (2.7 vs. 4.1\%; HR, 0.66; 95\% CI, 0.51 to 0.86; \( p = 0.002 \)) and death from any cause (2.9 vs. 4.5\%; HR, 0.68; 95\% CI, 0.53 to 0.87; \( p = 0.002 \)); this survival benefit was not seen with the twice-daily 5 mg dose, perhaps because it caused more major bleeding.

The risk of clinically significant bleeding with rivaroxaban increased among patients with ACS in a dose-dependent manner.\textsuperscript{35} As compared with placebo, rivaroxaban increased the rates of major bleeding not related to coronary artery bypass grafting (2.1 vs. 0.6\%; HR, 3.96; 95\% CI, 2.46 to 6.38; \( p < 0.001 \)) and the rates of intracranial hemorrhage (ICH) (0.6 vs. 0.2\%; \( p = 0.009 \)). The twice-daily 2.5 mg dose resulted in fewer fatal bleeding events than the twice-daily 5 mg dose (0.1 vs. 0.4\%; \( p = 0.04 \)). The ACS population that will derive a clear-cut net clinical benefit from adding rivaroxaban to other antithrombotic therapies has yet to be defined.

The ROCKET AF trial\textsuperscript{34} showed that rivaroxaban was not inferior to warfarin for the prevention of stroke or systemic embolism in patients with high-risk nonvalvular AF; rivaroxaban-treated patients exhibited a statistically significant reduction in the risk of intracranial bleeding (\textit{-Table 3}).

**Dabigatran Etxilate**

The RE-NOVATE, the RE-MODEL, and the RE-MOBILIZE trials have explored the efficacy of dabigatran as VTE prophylaxis following elective hip, elective knee replacement surgery, respectively.\textsuperscript{35–37} Taken together, the results of these trials suggest that dabigatran is an effective and safe VTE prevention option following total joint replacement; however, the RE-MOBILIZE trial, which demonstrated superiority for twice-daily enoxaparin over dabigatran, suggests that the optimal VTE prophylaxis dose of this drug is not yet established\textsuperscript{35–37} (\textit{-Table 1}).

For treatment of acute VTE, dabigatran has been compared with standard therapy in the RE-COVER and RE-COVER II trials.\textsuperscript{38,39} The primary outcome in both studies was the 6 month incidence of recurrent symptomatic VTE and related deaths (\textit{-Table 2}). In both trials, the patients assigned to dabigatran were treated with LMWH or unfractionated heparin for 5 to 11 days prior to the initiation of dabigatran. In the control arm of both studies, parenteral therapy was overlapped with VKA treatment until a therapeutic international normalized ratio (INR) was achieved. These studies showed that dabigatran is as effective as LMWH followed by VKA for secondary VTE prevention, without an increase in the bleeding rate when compared to more traditional pharmacologic measures.\textsuperscript{38,40} Furthermore, the data from the RE-SONATE and RE-MEDY studies have demonstrated the safety and efficacy of continuing dabigatran for at least 6 more months beyond the initial treatment for VTE\textsuperscript{35,41} (\textit{-Table 2}). There was a slightly higher rate of treatment discontinuation in the dabigatran group related to nonhemorrhagic adverse events, mainly dyspeptic symptoms.\textsuperscript{38} In the RE-MEDY study, a higher rate of ACS was observed in the dabigatran arm. The extent to which this difference may be explained by an imbalance in the baseline diabetes and hypertension between the groups assigned to the different treatment arms is not known.\textsuperscript{41}

In patients with recent ACS, dabigatran has been evaluated for the prevention of recurrent cardiovascular ischemic events in a placebo-controlled multicenter phase II dose escalation RCT.\textsuperscript{42} The overall rate of the efficacy outcome was low, with minor differences between the treatment groups. The rate of clinically relevant bleeding was dose-dependent, with 93\% of the events occurring within the first 3 days of therapy; most of the patients who experienced bleeding were receiving concomitant dual antiplatelet therapy (aspirin and clopidogrel or ticlopidine) as part of the standard medical management of ACS at randomization.\textsuperscript{42} Even at the lowest dose of dabigatran, the 1.3\% absolute increase in the 6-month bleeding rate could not be justified by any off-setting benefit from this drug.

For stroke prevention in patients with AF, the RE-LY trial\textsuperscript{43} evaluated patients with nonvalvular AF with an increased risk of stroke, who were randomized to one of two fixed doses of dabigatran, or open-label use of warfarin (\textit{-Table 3}). Concomitant use of antiplatelet agents was discouraged but low-
dose aspirin was permitted in this study, and the median
duration of follow-up was 2 years. Dabigatran 150 mg twice
daily was superior to warfarin, and dabigatran 110 mg twice
daily was noninferior to warfarin for the prevention of stroke
or systemic embolism.

The rates of major and intracranial bleeding were higher
with warfarin than with either the 110 mg dose of dabigatran
or the 150 mg dose of dabigatran (►Table 3). Not surprisingly,
when compared with the 110 mg twice-daily dose, the 150 mg
twice-daily dose of dabigatran was associated with a
higher rate of overall major bleeding (3.31% per year vs.
2.87% per year; RR, 1.16; 95% CI, 1.00 to 1.34; \( p = 0.04 \)),
mainly from the gastrointestinal tract, and a nonsignificant
trend toward more intracranial bleeding (0.19% per year vs.
0.10% per year; RR, 1.90; 95% CI, 0.94 to 3.81; \( p = 0.07 \)). In a
subgroup analysis, the treatment effect of dabigatran appeared
to change based on age; dabigatran-associated major
bleeding was more common than warfarin-associated bleeding
in patients older than 75 years. Dyspeptic symptoms
were significantly more common with dabigatran than with
warfarin (5.8% in the warfarin group; 11.8 and 11.3% in the
110 and 150 mg dabigatran groups, respectively; \( p < 0.001\)
for both comparisons).

Although there was an almost statistically significant trend
toward a higher rate of myocardial infarction with dabigatran at
both doses versus warfarin, a strong trend toward less all-cause
mortality was observed in the 150 mg twice-daily dabigatran
group compared with the warfarin group.

The FDA has not approved the 110 mg dose of dabigatran
because their analyses failed to identify a population where the
“net benefit” would be greater at the lower dose. In other
jurisdictions such as Europe and Canada, the 110 mg dose has
been approved by the applicable regulatory agencies.

**Clinical Application**

The novel oral anticoagulants have a role in the management
of acute VTE, stroke prophylaxis in patients with AF, and in
the primary prevention of VTE after joint replacement surgery.
An effectiveness overview and meta-analysis of the
available data has been recently published for the novel
anticoagulants in the management of VTE and AF. For these
indications, the target-specific oral agents have demonstrated
efficacy and safety that are comparable to more traditional
alternatives, such as LMWH or warfarin (►Figs. 1 and 2). In
the case of VTE prevention after orthopedic surgery, the new

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**Fig. 1** Comparison of outcomes for the treatment of venous thromboembolism with the new oral anticoagulants compared with warfarin. Panels compare the key outcomes of venous thromboembolism including (A) overall death, (B) recurrent deep venous thrombosis and pulmonary embolism, and (C) thromboembolism-related death.
agents will be less costly overall than the parenteral alternative (LMWH or fondaparinux) currently used in many institutions. This cost savings, in light of the oral route of administration and the favorable clinical data, make the novel drugs especially attractive for this indication. In other settings (such as AF or VTE), the new agents will offer additional convenience at higher cost, but the degree to which they reduce clinically important events such as thrombosis or bleeding will be limited, especially for patients on optimally controlled warfarin. We suggest that, pending further evidence, the new oral agents be avoided or used with caution in patients who have highly pro-thrombotic conditions (e.g., patients with cancer-associated VTE or patients with bona fide antiphospholipid syndrome). Patients who, despite adhering to recommendations from their provider, have INR values frequently outside the therapeutic range while on warfarin may stand to gain the most from these newer drugs. That notwithstanding, warfarin-treated patients with low time-in-therapeutic range because of poor compliance are probably not good candidates for the novel oral agents.

The short half-lives of the newer medicines and the infrequent need for outpatient follow-up would make drugs such as apixaban, dabigatran, and rivaroxaban especially problematic for a patient who did not follow instructions on warfarin. Furthermore, the inability to easily measure the anticoagulant effect of the novel agents and the lack of an available antidote or evidence-based reversal strategy are disadvantages to consider.

As patients with severe renal failure or hemodialysis were excluded from the clinical trials on the new oral anticoagu- lants, they should not be started on these medications. Although the U.S. prescribing information for dabigatran includes a dose recommendation for patients with CrCl between 15 and 30 mL/min, the dose (75 mg twice daily) is based on pharmacokinetic modeling and has not been tested in a large clinical trial. Finally, warfarin and other VKA remain the only anticoagulant options for patients with mechanical heart valve replacement because the efficacy of the novel agents has not been evaluated in this setting.

Measuring the Anticoagulant Effect and Managing Hemorrhagic Complications

Apixaban
As a result of FXa inhibition, apixaban can prolong prothrombin time (PT), and the activated partial thromboplastin time (APTT). However, changes observed in these clotting tests at the expected therapeutic dose are often very small and vary significantly depending, in part, on the reagent used in the assay. A properly calibrated anti-FXa chromogenic assay (using
an apixaban standard) can exhibit a close direct linear relationship with apixaban plasma concentration.3

Rivaroxaban
Rivaroxaban causes a dose-dependent prolongation of the PT with most reagents.5 A normal PT measurement can reassure the clinician that little or no rivaroxaban is present, especially if neoplastin is used as the reagent. As with apixaban, the anticoagulant effect of rivaroxaban can be assessed with a properly calibrated chromogenic anti-FXa activity measurement (using a rivaroxaban standard).47

Dabigatran
Dabigatran etexilate prolongs the APTT and the thrombin time (TT). The PT/INR is relatively insensitive to dabigatran, but the APTT can, if it is entirely normal, suggest that very little anticoagulant effect is present.48 The degree of anticoagulant activity can also be assessed by the ecarin clotting time (ECT). This test is a more specific measure of the effect of dabigatran than the APTT.10 The TT assay provides a linear response to dabigatran10,49; modified TT assays to measure dabigatran levels are available in some countries. The HEMOCLOT (HYPHEN BioMed, France) direct thrombin inhibitor assay is a sensitive assay that involves highly purified human thrombin to initiate coagulation and has demonstrated a good correlation with plasma levels of dabigatran.50 The HEMOCLOT assay, which is already registered in the European Union and Canada, could be useful to evaluate for excessive dabigatran activity in patients presenting with bleeding, or in patients undergoing elective surgery.50

The management of clinically significant hemorrhagic complications should include supportive measures: immediately begin resuscitation (e.g., red blood cell transfusions, if required), discontinue the anticoagulant medication, and consider investigations to identify and treat the local source of bleeding. Unfortunately, there is no specific antidote for acute reversal of the effect of these agents. Invasive procedures (e.g., endoscopy) are typically avoided until the anticoagulant effect has worn off.

On the basis of preclinical data, such as animal bleeding models and in vitro coagulation testing, some authors have recommended considering high-dose prothrombin complex concentrates or recombinant factor VIIa in cases of severe, life-threatening bleeding in patients receiving a novel oral anticoagulant. While the rationale for and possible merits of these interventions are discussed in detail elsewhere,51 we remind clinicians that powerful procoagulant agents carry a risk of causing thrombosis and, in patients with normal renal function, the anticoagulant effect of these new oral agents will dissipate quickly.

Hemodialysis should be considered for dabigatran-associated bleeding, since it is only 35% bound to plasma proteins.52 However, dialysis is not a suitable option for removing rivaroxaban or apixaban given their high degree of protein binding (> 95%).6

Other Novel Oral Anticoagulants under Clinical Investigation
The vast majority of the new oral anticoagulants in clinical development are direct FXa inhibitors, many of them with completed phase II clinical trials for prevention of VTE in the orthopedics surgery setting, and one of them (darexaban) in the ACS treatment and AF cardioembolic prevention scenarios. However, the development of darexaban was discontinued in September 2011 ( ¦ Table 4). In addition to FXa and direct thrombin inhibitors, factor IXa and factor Xla53 are among the suitable targets under current clinical investigation.54

Table 4 Oral anticoagulants under clinical development

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism of action</th>
<th>Phase of development</th>
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<tbody>
<tr>
<td>TTP889</td>
<td>FXa inhibitor</td>
<td>Phase II trials in VTE prophylaxis for hip replacement</td>
</tr>
<tr>
<td>Betrixaban</td>
<td>FXa inhibitor</td>
<td>Phase II trials in VTE prophylaxis for knee replacement, AF</td>
</tr>
<tr>
<td>Darexaban</td>
<td>FXa inhibitor</td>
<td>Phase II/III trials in VTE prophylaxis for hip and knee replacement, phase II for ACS and AF</td>
</tr>
<tr>
<td>Edoxaban</td>
<td>FXa inhibitor</td>
<td>Phase II/III trials in VTE prophylaxis for hip and knee replacement, phase II/III for AF</td>
</tr>
<tr>
<td>Eribaxaban</td>
<td>FXa inhibitor</td>
<td>Phase II trials in VTE prophylaxis for hip and knee replacement</td>
</tr>
<tr>
<td>Letaxaban</td>
<td>FXa inhibitor</td>
<td>Phase II trials in VTE prophylaxis for knee replacement, and treatment in ACS</td>
</tr>
<tr>
<td>LY517717</td>
<td>FXa inhibitor</td>
<td>Phase II trial in VTE prophylaxis for knee replacement</td>
</tr>
<tr>
<td>AZD0837</td>
<td>Direct thrombin inhibitor</td>
<td>Phase II trials in cardioembolic prophylaxis for AF</td>
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Abbreviations: ACS, acute coronary syndromes; AF, atrial fibrillation; FXa, activated factor IX; FXa, activated factor X; VTE, venous thromboembolism. Adapted from Ahrens et al (2012).54
disadvantages that will no doubt be addressed in future research. In some instances, the cost of these newer agents will likely be a barrier to their widespread use.

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