Dabigatran, ROCKET Atrial Fibrillation, and Beyond
Basic Science, Mechanisms of Agents, Monitoring, and Reversal

Kenneth A. Bauer, MD

For >50 years, vitamin K antagonists (eg, warfarin) were the only available oral anticoagulants. Warfarin, however, is associated with >10-fold interindividual variation in dose to achieve therapeutic anticoagulation. The pharmacokinetics and pharmacodynamics of warfarin are influenced by genetic polymorphisms (CYP 2C9 and VKORC1), dietary vitamin K intake, concomitant medications, alcohol use, patient age, body weight, and various disease states, necessitating regular coagulation monitoring to ensure that each patient’s international normalized ratio (INR) remains within the target range.

New oral anticoagulants that selectively inhibit either thrombin or factor Xa, via reversible binding to their active enzymatic sites, have been developed. Thrombin plays a central role as a procoagulant by converting fibrinogen to fibrin as well as by activating its other substrates, including factor V, factor VIII, factor XI, factor XIII, and the platelet protease-activated receptors (PAR-1 and PAR-4). The substrate specificity of thrombin derives from specific surface binding sites (eg, exosite 1 for fibrin) for its substrates. Factor Xa is also an attractive target for the design of new anticoagulants because factor Xa is positioned at the start of the common pathway of coagulation.

Dabigatran etexilate is an oral prodrug that is converted to dabigatran, a competitive direct thrombin inhibitor (Kᵢ 4.5 nmol/L), by hydrolytic cleavage mediated by plasma esterases in vivo. It is not metabolized by the cytochrome P450 enzymes or oxidoreductases. Dabigatran etexilate has relatively low oral bioavailability and is encapsulated with tarteric acid to facilitate absorption in the gastrointestinal tract; consistent absorption of dabigatran etexilate, however, is not dependent on overall gastrointestinal acidity, and dose modifications are not required with the use of proton pump inhibitors. There is no specific antidote to reverse the anticoagulant effect of dabigatran; approaches for managing serious bleeding and monitoring the anticoagulant activity of the drug in such situations have been published. Hemodialysis is effective in removing ≈60% of the dabigatran in the blood over 2 to 3 hours and can be used to treat dabigatran toxicity. Several synthetic small molecules that directly inhibit factor Xa have been developed that are orally bioavailable; they are not prodrugs. Rivaroxaban (Kᵢ 0.4 nmol/L) and apixaban (Kᵢ 0.08 nmol/L) bind competitively to the active site of factor Xa. Edoxaban is another oral factor Xa inhibitor. The pharmacological properties of these agents are summarized in Table 1. These new oral anticoagulants have been evaluated in clinical trials for the prevention and treatment of arterial and venous thrombosis.

Although the new oral anticoagulants have been developed without the need for laboratory monitoring, assays to assess drug levels will be helpful when major bleeding occurs to determine whether it results from high-drug levels or another pathogenesis (eg, bleeding from a discrete anatomic site, coagulopathy resulting from liver disease, or disseminated intravascular coagulation). For dabigatran, assays using the ecarin clotting time seem to be the most sensitive and accurate assay; however, this test is not available routinely in clinical practice. Thrombin time determinations are more widely available but are generally too sensitive for the clinically relevant plasma drug concentration range. Dabigatran prolongs the partial thromboplastin time, but the effects are not dose-dependent; although a prolonged partial thromboplastin time may indicate the presence of dabigatran, it will not provide an exact level of anticoagulant activity. Prothrombin time assays used with rivaroxaban calibrators (expressed in ng/mL) have been evaluated to measure levels of rivaroxaban. Anti-factor Xa chromogenic assays used with rivaroxaban calibrators, however, are more sensitive and specific for measurement of drug concentrations. The assay results, however, need to be interpreted in relation to timing of drug administration and its pharmacokinetics.

Warfarin prevents >60% of strokes in patients with atrial fibrillation and has been the recommended treatment for those with this rhythm abnormality and 1 additional risk factor. Failure to maintain the INR in the therapeutic range can either reduce its benefit or increase the risk of major hemorrhage. As a result, many patients with atrial fibrillation at risk for stroke are either not started on warfarin or discontinue therapy after it is started. Thus, many patients with atrial fibrillation at risk of stroke could potentially benefit from one of the new oral anticoagulants, which have more predictable pharmacological behavior.

Three of these agents, dabigatran etexilate, rivaroxaban, and apixaban have gained approval from the US Food and Drug Administration for stroke prevention in atrial fibrillation. Edoxaban is in very advanced stages of development for this indication.

The Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial compared 2 doses of dabigatran...
etexilate (110 or 150 mg twice daily) to adjusted dose warfarin in 18113 patients with nonvalvular atrial fibrillation. The median CHADS$_{2}$ (a scoring system for stroke risk ranging from 0 to 6) score of the population was 2.1, and the achievement of therapeutic INRs was 64% in the warfarin arm. The stroke or systemic embolism rate was significantly lower with dabigatran etexilate at a dose of 150 mg twice daily (1.11%; risk ratio, 0.66; 95% confidence interval, 0.53–0.82; P<0.001 for superiority) compared with warfarin. The rate of major bleeding with the 150 mg dose was not different from that with warfarin (3.11% vs 3.36%; risk ratio, 0.93; 95% confidence interval, 0.81–1.07; P=0.31). The hemorrhagic stroke rate with the 150 mg dabigatran etexilate dose (0.10%) was significantly lower than with warfarin (0.38%) of the RE-LY trial. A subgroup analysis of the warfarin arm according to INR control (based on time on therapeutic range) showed that the advantages of dabigatran were greater at sites with poorer INR control; these data suggest that patients on warfarin with excellent INR control (>72.6% time in therapeutic range) have less to gain by switching to dabigatran from warfarin.

Although the 110 and 150 mg dosing schedules of dabigatran were approved in some countries, only the higher dose was approved in the United States in patients with a creatinine clearance ≥30 mL/min; a dose of 75 mg twice daily, however, gained approval in the United States for patients with a creatinine clearance of 15 to 29 mL/min.

In the double-blind Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF) trial containing >14000 patients, rivaroxaban at a dose of 20 mg once daily was noninferior to warfarin in reducing stroke and systemic embolism with a similar rate of major bleeding. The median CHADS$_{2}$ score of the population was just <3.5. Although the on-treatment analysis did show superiority, superiority was not achieved in the intention-to-treat analysis. Therapeutic INRs were achieved in 58% of patients in the warfarin arm, and the rate of intracranial hemorrhage was significantly lower in patients randomized to rivaroxaban. The approved dose of rivaroxaban for stroke prevention in atrial fibrillation; 20 mg once daily with a reduction to 15 mg once daily for patients with renal dysfunction (creatinine clearance, 15–49 mL/min).

The Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) study compared apixaban at a dose of 5 mg twice daily to warfarin, for stroke prevention in >18000 patients with atrial fibrillation with 1 additional risk factor for stroke (median CHADS$_{2}$ score of 2.1); the dose was reduced to 2.5 mg in patients with two or more of the following criteria: serum creatinine ≥1.5mg/dL, age ≥80 years, body weight ≤60kg. This double-blind study found that apixaban reduced stroke and systemic embolism by 21% (P<0.01), major bleeding by 31% (P<0.001), and overall mortality by 11% (P<0.047). The rate of hemorrhagic stroke was reduced by 49% (P<0.001) in patients randomized to apixaban compared with warfarin.

Oral direct thrombin and factor Xa inhibitors offer advantages over vitamin K antagonists. In the real-world setting, the new agents could lead to better clinical outcomes and greater use of anticoagulants in patients with atrial fibrillation. However, there are significant issues that must be recognized with the new oral agents. Patient education and medication compliance will be extremely important to attain good clinical outcomes, especially in atrial fibrillation, in which therapy is often in the absence of an antecedent thrombotic event. The lack of a requirement for regular coagulation monitoring may limit the initial and continuing education that is currently provided to patients on warfarin along with early detection of medication nonadherence. The long half-life of warfarin of ≥40 hours may actually be an advantage for patients who occasionally miss doses of medication compared with one of the new oral anticoagulants that have a much shorter half-life. Furthermore, the twice daily dosing schedules of some of the new agents will be more difficult for some patients to adhere to than a once daily regimen.

### Table 1. Properties of Warfarin and Oral Inhibitors of Thrombin and Factor Xa Inhibitors Approved for Use or in Advanced Stages of Development

<table>
<thead>
<tr>
<th>Property</th>
<th>Warfarin</th>
<th>Dabigatran Etexilate</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Edoxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Target</td>
<td>Vitamin K epoxide reductase VKORC1-reducing the functional levels of vitamin K–dependent coagulation factors</td>
<td>Thrombin</td>
<td>Factor Xa</td>
<td>Factor Xa</td>
<td>Factor Xa</td>
</tr>
<tr>
<td>Prodrug</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Bioavailability</td>
<td>&gt;95%</td>
<td>6.5%</td>
<td>80%</td>
<td>=66%</td>
<td>50%</td>
</tr>
<tr>
<td>T (max), h</td>
<td>72–96</td>
<td>2</td>
<td>2.5–4</td>
<td>3</td>
<td>1–3</td>
</tr>
<tr>
<td>Half-life, h</td>
<td>40</td>
<td>12–14</td>
<td>7–13</td>
<td>8–13</td>
<td>9–11</td>
</tr>
<tr>
<td>Protein binding</td>
<td>&gt;95%</td>
<td>35%</td>
<td>90%</td>
<td>87%</td>
<td>…</td>
</tr>
<tr>
<td>Dosing (atrial fibrillation)</td>
<td>Once daily (INR-adjusted)</td>
<td>Fixed, twice daily</td>
<td>Fixed, once daily</td>
<td>Fixed, twice daily</td>
<td>Fixed, once daily</td>
</tr>
<tr>
<td>Elimination</td>
<td>None</td>
<td>80%</td>
<td>67% renal (half is inactive drug), 33% fecal</td>
<td>25% renal, 75% fecal</td>
<td>35% renal, 65% fecal</td>
</tr>
<tr>
<td>Potential drug interactions</td>
<td>CYP 2C9, 3A4, and 1A2</td>
<td>Potent P-gp inhibitors</td>
<td>Potent CYP 3A4 and P-gp inhibitors</td>
<td>Potent CYP 3A4 inhibitors</td>
<td>Potent CYP 3A4 and P-gp inhibitors</td>
</tr>
</tbody>
</table>

Adapted from Eriksson et al$^{2,3}$ and Bauer.$^{4}$

CYP indicates cytochrome P; INR, international normalized ratio; P-gp transporters, P-glycoprotein transporters; and T (max), peak plasma levels.
Another challenge is difficulty in determining whether one of the new anticoagulants has failed when patients develop an initial or recurrent thrombotic event. If a thromboembolic event occurs on warfarin, INR levels can be reviewed to determine whether they were in the therapeutic range at the time of the event or whether it is actually a therapeutic failure or a consequence of subtherapeutic dosing of the medication. In the latter case, dosing can be adjusted to increase the INR and measures put in place to improve monitoring or medication compliance. With the use of nonmonitored drugs, such as the oral thrombin and factor Xa inhibitors, such determinations cannot readily be made at the present time. Other considerations for the new oral agents include contraindications in renal dysfunction and the current absence of specific antidotes when patients taking these drugs develop major bleeds. Until specific antidotes for the new oral agents become available, some reversal strategies, such as prothrombin complex concentrates, have shown promising results for reversing anticoagulant effect of rivaroxaban in vitro and could provide a useful option for the management of severe bleeding episodes in clinical practice (Table 2).

Table 2. Use of Coagulation Factor Concentrates for the Management of Life-Threatening Bleeds in Association With Novel Oral Anticoagulants

<table>
<thead>
<tr>
<th>Fresh frozen plasma</th>
<th>Dabigatran Etexilate</th>
<th>Factor Xa Inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recombinogen factor VIIa</td>
<td>Efficacy unclear</td>
<td>Efficacy unclear</td>
</tr>
<tr>
<td>Prothrombin complex concentrates (3-factor)</td>
<td>Efficacy unclear</td>
<td>Efficacy unclear</td>
</tr>
<tr>
<td>Prothrombin complex concentrates (4-factor)</td>
<td>Efficacy unclear</td>
<td>Efficacy unclear</td>
</tr>
<tr>
<td>Factor VIII inhibitor bypassing activity</td>
<td>Efficacy unclear</td>
<td>Efficacy unclear</td>
</tr>
</tbody>
</table>

Specific antidotes for novel oral anticoagulants are in preclinical development. A monoclonal antibody completely inhibits dabigatran activity in vitro and in vivo. A modified FXa molecule lacking catalytic and membrane-binding activities has high affinity for FXa inhibitors in vitro.

Disclosures

Dr. Bauer has served as a consultant to Bayer HealthCare Pharmaceuticals, Janssen Research & Development, Bristol Myers Squibb, Pfizer, Boehringer Ingelheim, Baxter Healthcare, and Instrumentation Laboratory.

References


Key Words: apixaban ▪ atrial fibrillation ▪ dabigatran ▪ international normalized ratio ▪ prothrombin time ▪ rivaroxaban ▪ vitamin K antagonists
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