New Oral Anticoagulants for Atrial Fibrillation: A Review of Clinical Trials

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ABSTRACT

Background: Warfarin had been the only oral anticoagulant for stroke prevention in patients with atrial fibrillation (AF) for decades. Direct thrombin inhibitors and factor Xa inhibitors are new anticoagulants recently approved for prevention of stroke or systemic embolism in patients with AF.

Objective: The aim of this article was to provide a systematic review of recently published clinical data on the direct thrombin inhibitors and factor Xa inhibitors in the management of AF.

Methods: A search of the ClinicalTrials.gov registry was conducted using the subject terms dabigatran, rivaroxaban, and apixaban. Each search was limited to clinical trials that included patients with AF. Completed studies with warfarin as the main comparator were identified. From the yielded results, the national clinical trial identifier was inputted in PubMed (1966–November 2011) for a search of published literature.

Results: Three Phase III clinical trials reported the efficacy of each agent in patients who have AF and risk factors for stroke or embolic complications. The Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) study reported dabigatran 150 mg was associated with a lower rate of stroke and systemic embolism, whereas dabigatran 110 mg was associated with a similar rate for such events when compared with warfarin (relative risk = 0.66; 95% confidence interval [CI], 0.53–0.82; P < 0.001; and relative risk = 0.91; 95% CI, 0.74–1.11; P = 0.34, respectively). From the intention-to-treat analysis of the 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) study, rivaroxaban was reported to be noninferior to warfarin in reducing stroke or systemic embolism (2.1% vs 2.4% per year; hazard ratio = 0.88; 95% CI, 0.75–1.03; P < 0.001). The Apixaban for Reduction in Stroke and Other Thrombotic Events in Atrial Fibrillation (ARISTOTLE) trial reported that apixaban reduced stroke or systemic embolic events by 21% when compared with warfarin (1.27% vs 1.60% per year, respectively; hazard ratio = 0.79; 95% CI, 0.66–0.95; P < 0.001). All 3 agents were associated with similar bleeding when compared with warfarin.

Conclusions: Published data suggest that all 3 agents are at least as efficacious as dose-adjusted warfarin, with similar major bleeding profiles. For patients who are unwilling to adhere to regular coagulation monitoring or whose therapeutic effect using warfarin is not optimal despite adequate monitoring and management, the inhibitors of direct thrombin or factor Xa may provide alternative choices in anticoagulation.

Key words: anticoagulants, apixaban, dabigatran, direct thrombin inhibitors, factor Xa inhibitors, rivaroxaban.

INTRODUCTION

Atrial fibrillation (AF) is a common cardiac arrhythmia affecting approximately 2.2 million Americans in 2010 and may exceed 12 million people by 2050, according to the American Heart Association.1 Ischemic stroke is a primary concern, occurring in 15% of patients with AF.2

The major risk factor for thromboembolic complications in a patient with AF is previous history of stroke or transient ischemic attack (TIA). Other risk factors include the presence of left ventricular systolic dysfunction with or without heart failure, hypertension, age ≥75 years, and diabetes mellitus. Stroke risk stratification is based on the CHADS2 score, which is calculated by assigning 1 point each to the presence of heart failure, hypertension, age ≥75 years, and diabetes mellitus; history of stroke or TIA is allocated 2
points. The American College of Chest Physicians currently recommends that warfarin (target international normalized ratio [INR] = 2.5; range = 2.0–3.0) should be used for long-term anticoagulation in patients with AF who have had prior ischemic stroke, TIA, or systemic embolism or who are at high risk for such events (CHADS2 ≥ 2). In patients with moderate risk (CHADS2 = 1), the use of either warfarin or aspirin is recommended. In patients at the lowest risk (CHADS2 = 0), long-term antiplatelet therapy with aspirin is recommended.2

The vitamin K antagonist warfarin had been the only oral anticoagulant available in the United States for stroke prevention in patients with AF.3 Warfarin works by binding to vitamin K epoxide reductase to inhibit vitamin K–dependent coagulation factors II, VII, IX, and X. For all its extensive use, warfarin has many clinical considerations associated with it, including variable pharmacokinetic and pharmacodynamic properties, a narrow therapeutic index range, and numerous interactions with certain foods and drugs. All of these factors contribute to the need for frequent coagulation laboratory monitoring and dosage adjustments.3 Recently, direct thrombin inhibitors and factor Xa inhibitors have been added to the armamentarium for anticoagulation in AF.4 Dabigatran is an oral, reversible, direct competitive inhibitor of thrombin, which prevents the conversion of fibrinogen to fibrin within the coagulation cascade, thereby inhibiting thrombus formation. Rivaroxaban and apixaban are 2 oral agents that work through selective inhibition of factor Xa. Because factor Xa is positioned at the convergence of the intrinsic and extrinsic pathways within the coagulation cascade, inhibiting factor Xa prevents the conversion of prothrombin to thrombin, thus also halting the conversion of fibrinogen to fibrin.4,5

Within the past 2 years, dabigatran and rivaroxaban were approved by the US Food and Drug Administration (FDA) for the prevention of stroke and systemic embolism in patients with nonvalvular AF, and a third agent, apixaban, was submitted for FDA review.6–8 Literature has been published about the roles of direct thrombin and factor Xa inhibitors as anticoagulants for the treatment of venous thromboembolism. However, there is a need to add further to the literature of recently published clinical data on these agents in AF management. Our objective was to provide a systematic review of published data from completed Phase III clinical trials that compared direct thrombin inhibitors and factor Xa inhibitors with dose-adjusted warfarin in AF patients with risk factors for stroke or thromboembolism.

DATA COLLECTION

A search of the ClinicalTrials.gov registry was conducted using the subject terms dabigatran, rivaroxaban, and apixaban. Each search was limited to clinical trials that included patients with AF. Completed Phase III studies with warfarin as the main comparator to the studied agent were identified for further evaluation. Ongoing studies were excluded. From the yielded results, the national clinical trial identifier was input into PubMed (1966–November 2011) for a search of published literature. Additional publications and meeting abstracts were identified by review of the references and bibliographies. For agents approved for use in the United States, the manufacturers’ prescribing information was consulted for dosing and administration considerations.

RESULTS

Three Phase III clinical trials met the criteria of the literature search. Each of the identified studies compared the efficacy of dabigatran, rivaroxaban, or apixaban with that of dose-adjusted warfarin in patients with AF and risk factors for stroke or thromboembolism (Table I).9–11

The Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial was a noninferiority study that compared dabigatran at 2 fixed doses (150 mg twice daily and 110 mg twice daily) with dose-adjusted warfarin (target INR range = 2.0–3.0).9 It was a randomized, open-label, multicenter study, in which 18,113 patients who had AF as well as increased risk of stroke were assigned to 1 of the treatment arms. Exclusion criteria were major heart valve disease, stroke in the last 14 days or severe stroke in the previous 6 months, any risk factor for hemorrhage,
Table I. Comparison of clinical trials of the direct thrombin inhibitors and factor Xa inhibitors for anticoagulation in patients with atrial fibrillation.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>RE-LY&lt;sup&gt;a&lt;/sup&gt;</th>
<th>ROCKET AF&lt;sup&gt;b&lt;/sup&gt;</th>
<th>ARISTOTLE&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study characteristics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment groups</td>
<td>Dabigatran 150 mg BID; dabigatran 110 mg BID</td>
<td>Rivaroxaban 20 mg/d (15 mg/d for CrCl 30–49 mL/min)</td>
<td>Apixaban 5 mg BID</td>
</tr>
<tr>
<td>Control group</td>
<td>Dose-adjusted warfarin (INR = 2.0–3.0); TTR = 64%</td>
<td>Dose-adjusted warfarin (INR = 2.0–3.0); TTR = 55%</td>
<td>Dose-adjusted warfarin (INR = 2.0–3.0); TTR = 62%</td>
</tr>
<tr>
<td>Study design</td>
<td>Randomized, open-label</td>
<td>Randomized, double-blind, double-dummy</td>
<td>Randomized, double-blind, double-dummy</td>
</tr>
<tr>
<td>Sample size</td>
<td>18,113</td>
<td>14,264</td>
<td>18,201</td>
</tr>
<tr>
<td>Patients’ characteristics at baseline</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diagnosis</td>
<td>AF and ≥1 risk factor*</td>
<td>AF and ≥2 risk factors*</td>
<td>AF and ≥1 risk factor*</td>
</tr>
<tr>
<td>Mean CHADS&lt;sub&gt;2&lt;/sub&gt; score&lt;sup&gt;+&lt;/sup&gt;</td>
<td>2.1</td>
<td>3.5</td>
<td>2.1</td>
</tr>
<tr>
<td>Mean age, y</td>
<td>71.5</td>
<td>73.0</td>
<td>70.0</td>
</tr>
<tr>
<td>Aspirin treatment, %</td>
<td>39.8</td>
<td>36.5</td>
<td>30.9</td>
</tr>
<tr>
<td>Outcomes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke and systemic embolism</td>
<td>Dabigatran 150 mg: 1.11% (&lt;i&gt;P&lt;/i&gt; &lt; 0.001&lt;sup&gt;‡&lt;/sup&gt; and &lt;i&gt;P&lt;/i&gt; &lt; 0.001&lt;sup&gt;§&lt;/sup&gt;); dabigatran 110 mg: 1.53% (&lt;i&gt;P&lt;/i&gt; &lt; 0.001&lt;sup&gt;‡&lt;/sup&gt; and &lt;i&gt;P&lt;/i&gt; = 0.34&lt;sup&gt;‡&lt;/sup&gt;); warfarin: 1.69%</td>
<td>Rivaroxaban: 2.1% (&lt;i&gt;P&lt;/i&gt; &lt; 0.001&lt;sup&gt;‡&lt;/sup&gt; and &lt;i&gt;P&lt;/i&gt; = 0.12&lt;sup&gt;‡&lt;/sup&gt;); warfarin: 2.4%</td>
<td>Apixaban: 1.27% (&lt;i&gt;P&lt;/i&gt; &lt; 0.001&lt;sup&gt;‡&lt;/sup&gt; and &lt;i&gt;P&lt;/i&gt; = 0.01&lt;sup&gt;‡&lt;/sup&gt;); warfarin: 1.60%</td>
</tr>
<tr>
<td>Death from any cause</td>
<td>Dabigatran 150 mg: 3.64% (&lt;i&gt;P&lt;/i&gt; = 0.051); dabigatran 110 mg: 3.75% (&lt;i&gt;P&lt;/i&gt; = 0.13); warfarin: 4.13%</td>
<td>Rivaroxaban: 4.5% (&lt;i&gt;P&lt;/i&gt; = 0.15); warfarin: 4.9%</td>
<td>Apixaban: 3.52% (&lt;i&gt;P&lt;/i&gt; = 0.047); warfarin: 3.94%</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>Dabigatran 150 mg: 3.11% (&lt;i&gt;P&lt;/i&gt; = 0.31); dabigatran 110 mg: 2.71% (&lt;i&gt;P&lt;/i&gt; = 0.003); warfarin: 3.36%</td>
<td>Rivaroxaban: 3.6% (&lt;i&gt;P&lt;/i&gt; = 0.58); warfarin: 3.4%</td>
<td>Apixaban: 2.13% (&lt;i&gt;P&lt;/i&gt; &lt; 0.001); warfarin: 3.09%</td>
</tr>
<tr>
<td>Intracranial bleeding</td>
<td>Dabigatran 150 mg: 0.30% (&lt;i&gt;P&lt;/i&gt; &lt; 0.001); dabigatran 110 mg: 0.23% (&lt;i&gt;P&lt;/i&gt; &lt; 0.001); warfarin: 0.74%</td>
<td>Rivaroxaban: 0.5% (&lt;i&gt;P&lt;/i&gt; = 0.02); warfarin: 0.7%</td>
<td>Apixaban: 0.33% (&lt;i&gt;P&lt;/i&gt; &lt; 0.001); warfarin: 0.80%</td>
</tr>
</tbody>
</table>

AF = atrial fibrillation; ARISTOTLE = Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation; CHADS = Congestive heart failure, hypertension, age, diabetes, prior stroke; CrCl = creatinine clearance; INR = international normalized ratio; RE-LY = Randomized Evaluation of Long-Term Anticoagulation in Therapy; ROCKET AF = Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation; TTR = time in therapeutic range.

<sup>a</sup>Risk factors: age ≥75 y; history of stroke, transient ischemic attack, or systemic embolism; symptomatic heart failure and/or left-ventricular ejection fraction <40%; diabetes mellitus; and/or need for antihypertensive treatment.

<sup>b</sup>Primary outcome for noninferiority.

<sup>c</sup>Primary outcome for superiority.
creatinine clearance of 30 mL per minute, active hepatic disorder, and pregnancy.

The study included approximately one third of patients with a CHADS2 score of at least 3 (mean CHADS2 score = 2.1). Median duration of patient follow-up time was 2.0 years. Mean age of study patients was 71 years; approximately 63.6% were male. Concurrent aspirin therapy was used in 21.1%, 19.6%, and 20.8% of patients assigned to dabigatran 110 mg, dabigatran 150 mg, and warfarin, respectively. The time in therapeutic range that was achieved by the warfarin group was 64%.9

Primary efficacy outcome was stroke (categorized as ischemic, hemorrhagic, or unspecified) or systemic embolism. Primary safety outcome was major bleeding. Dabigatran 150 mg and 110 mg significantly reduced strokes or systemic embolism by 34% and 9%, respectively. Rates of strokes or thromboembolism were 1.69% per year, 1.11% per year, and 1.53% per year in the warfarin, dabigatran 150 mg, and dabigatran 110 mg groups, respectively. Dabigatran 150 mg and 110 mg were considered noninferior to warfarin (relative risk [RR] = 0.66; 95% confidence interval [CI], 0.53–0.82; P < 0.001; and RR = 0.91; 95% CI, 0.74–1.11; P = 0.34, respectively). Major bleeding was reported at 3.36% per year, 3.11% per year, and 2.71% per year for groups that received warfarin, dabigatran 150 mg (RR = 0.93; 95% CI, 0.81–1.07; P = 0.31), and dabigatran 110 mg (RR = 0.80; 95% CI, 0.69–0.93; P = 0.003), respectively. In addition, intracranial hemorrhage (ICH) was less frequently associated with dabigatran 150 mg (RR = 0.26; 95% CI, 0.14–0.49; P < 0.001) and dabigatran 110 mg (RR = 0.31; 95% CI, 0.17–0.56; P < 0.001) than with warfarin. Dabigatran 150 mg was associated with lower incidence of stroke and thromboembolism but with similar major bleeding when compared with warfarin, whereas dabigatran 110 mg was associated with a similar rate of stroke and embolic occurrence and a reduced incidence of major bleeding.9

The 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) study was a randomized, double-blind, double-dummy, multicenter study with 14,264 AF patients assigned to either rivaroxaban 20 mg daily (15 mg daily for patients with creatinine clearance 30–49 mL/min) or dose-adjusted warfarin (target INR range = 2.0–3.0).10 Owing to its double-dummy study design, an independent study monitor provided either actual INR results of the warfarin patients for dosage adjustments or sham INR results of the rivaroxaban group. Included patients were: those who had prior stroke, TIA, or systemic embolism or had at least 2 other risk factors, including heart failure or left ventricular ejection fraction ≤35%, hypertension, at least 75 years of age, or diabetes mellitus. Excluded patients were: those diagnosed with significant mitral stenosis, severe stroke, active bleeding, history of ICH, or transient AF caused by a reversible underlining disorder.

The study enrolled patients who had moderate-to-high risk of stroke, with approximately 87% of patients having a CHADS2 score of at least 3 (mean CHADS2 score = 3.5). The median time for patient follow-up was 1.9 years. Median age was 73 years, and approximately 60.3% were men. Concomitant aspirin therapy was observed in 34.9% and 36.2% of the rivaroxaban and warfarin groups, respectively. The INR values were within therapeutic range for an average of 55% of the time.10

Primary efficacy outcome was stroke or systemic embolism, and primary safety outcome was major and nonmajor clinically relevant bleeding. From the intention-to-treat analysis, rivaroxaban was noninferior to warfarin in reducing stroke or systemic embolism (2.1% vs 2.4% per year; hazard ratio [HR] = 0.88; 95% CI, 0.75–1.03; P < 0.001). Clinically relevant bleeding was also similar between the rivaroxaban and warfarin groups (14.9% vs 14.5% per year, respectively; HR = 1.03; 95% CI, 0.96–1.11; P = 0.44), as was any major bleeding event (3.6% vs 3.4% per year, respectively; HR = 1.04; 95% CI, 0.90–1.20; P = 0.58). Intracranial hemorrhage occurred less frequently with rivaroxaban than with warfarin (0.5% vs 0.7% per year; HR = 0.67; 95% CI, 0.47–0.93; P = 0.02). The differences between rivaroxaban and warfarin did not reach the level of statistical significance in stroke or thromboembolism reduction in the study patients. Similarly, the differences in major and nonmajor hemorrhage also did not achieve a level of statistical significance between rivaroxaban and warfarin.10

The Apixaban for Reduction in Stroke and Other Thrombotic Events in Atrial Fibrillation (ARISTOTLE) trial was a randomized, double-blind, multicenter, noninferiority study, which compared apixaban 5 mg twice daily (2.5 mg twice daily for elderly patients or those with renal insufficiency) to dose-adjusted warfarin (target INR range = 2.0–3.0) in 18,201 patients.
with AF and at least 1 other risk factor. Enrolled patients were those with documented AF based on an electrocardiographic finding or the occurrence of at least 1 of the following in the previous 12 months: stroke, TIA or thromboembolic event, symptomatic heart failure exacerbation in the prior 3 months or left ventricular ejection fraction <40%, diabetes mellitus, hypertension, or age of at least 75 years. Exclusion criteria were major heart valve disease, stroke in the last 7 days or severe stroke in the previous 6 months, requirement for aspirin dose of >165 mg per day or both aspirin and clopidogrel therapies, or creatinine clearance of <25 mL per minute.

Approximately 30% of patients enrolled in this study had a CHADS2 score of at least 3 (mean CHADS2 score = 2.1). Median duration of patient follow-up time was 1.8 years. Median age of enrolled patients was 70 years, and approximately 64.7% were men. The warfarin group achieved an average time within therapeutic INR range of 62%.

The primary efficacy outcome was ischemic or hemorrhagic stroke or systemic embolism, and the primary safety outcome was major bleeding. Apixaban reduced stroke or systemic embolic events by 21% when compared with warfarin (1.27% vs 1.60% per year, respectively; HR = 0.79; 95% CI, 0.66–0.95; P < 0.001). The annual rate of major bleeding was 2.13% in the apixaban group and 3.09% in the warfarin group (HR = 0.69; 95% CI, 0.60–0.80; P < 0.001). Intracranial hemorrhage and mortality from any cause were also reduced in the apixaban group (0.33% per year and 3.52% per year, respectively) when compared with warfarin (0.88% per year and 3.94% per year, respectively; P < 0.001 for ICH and P = 0.047 for mortality from any cause). The ARISTOTLE study reported that in patients with AF, apixaban was superior to warfarin in preventing stroke or thromboembolism, reducing major bleeding, and decreasing ICH and mortality.

DISCUSSION

For decades, warfarin had been the recommended oral agent for the prevention and treatment of thromboembolism associated with AF. Within the past 2 years, dabigatran and rivaroxaban were approved by the FDA as anticoagulants for the prevention of stroke or systemic embolism in nonvalvular AF. The identified Phase III clinical (Table I) trials have suggested that all 3 agents are at least as efficacious as dose-adjusted warfarin and have a similar bleeding profile. However, the data are based on limited Phase III studies, and the results from long-term studies of dabigatran, rivaroxaban and apixaban are not yet available to evaluate their true potential impact when compared with that of warfarin. Currently, no direct comparisons exist among dabigatran, rivaroxaban, and apixaban; therefore, no valid conclusion can be extrapolated based on the available clinical studies as to which agent is preferred in certain AF patients.

Despite positive results reported from the clinical trials, there were some noteworthy clinical issues and implications related to the use of these agents (Table II). Patients in the ROCKET AF study had greater risk factors for stroke (mean CHADS2 score = 3.5) than those from RE-LY (mean CHADS2 score = 2.1) or ARISTOTLE (mean CHADS2 score = 2.1).9–11 The high-risk patients in ROCKET AF could be a contributing factor for its noninferiority result when compared with those in the dose-adjusted warfarin group. In a subgroup analysis of the RE-LY study, dabigatran 150 mg did not demonstrate superiority but did show noninferiority to dose-adjusted warfarin in patients with CHADS2 ≥3.15

Management of warfarin therapy in the control arm of the ROCKET AF trial seemed to have been suboptimal relative to other studies, in which the time in therapeutic range was 55%, compared with 64% and 62% in the RE-LY and ARISTOTLE trials, respectively.9–11 Of the 45% of the time outside therapeutic INR, twice as much time was subtherapeutic (INR <2.0) than supratherapeutic (INR >3.0). The amount of time spent in the subtherapeutic range suggests that the warfarin patients might have been at increased risk for ischemic strokes, thereby potentially increasing the chance to demonstrate rivaroxaban to be similar to warfarin in preventing stroke and thromboembolism.16

Currently, no routine standardized laboratory monitoring test is being recommended for these new oral agents. The thrombin time and ecarin clotting time, which directly measure the thrombin activity from the plasma in a concentration-dependent linear relationship, may be used to estimate the anticoagulant effect of dabigatran. Similarly, the prothrombin time has a positive correlation with rivaroxaban’s plasma concentration. However, none of these laboratory measures has been validated as an optimal test of dabiga-
Although no coagulation monitoring is a marketing advantage of these agents, such lack of monitoring may become an issue if the patient were to experience a thromboembolic event; there is no way to ascertain whether the event was due to a subtherapeutic dose or to therapeutic failure of the anticoagulants. In contrast, hemorrhagic events cannot be attributed to supratherapeutic or toxic effects due to lack of standardized methods of monitoring such drugs.

When bleeding events are associated with the new oral drugs, the lack of proven agents to reverse their anticoagulant effects is a clinical issue for consideration. 

A Phase IV clinical study, is being planned to evaluate the ability of coagulation factors such as prothrombin complex concentrate and activated factor VIIa to reverse the anticoagulant effects of these new agents. 

The 3 new agents are administered using fixed doses. The daily dosing frequency of these anticoagulants in AF patients is either twice daily (dabigatran and apixaban) or once daily (rivaroxaban). 

A pharmacokinetic simulation study by Clemens et al. showed that twice daily dosing of dabigatran in AF patients reduced the variations in plasma drug concentrations and maintained a trough level to prevent thrombus formation. Owing to the relative shorter half-life of these oral agents when compared with that of warfarin, the anticoagulant effect of warfarin generally lasts longer than those of the direct thrombin and factor Xa inhibitors. Therefore, patients who suddenly stop taking the new oral agents may be at increased risk for thromboembolic events. 

Table II. Comparison of direct thrombin inhibitors and factor Xa inhibitors for anticoagulation in patients with atrial fibrillation. 

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mechanism of action</td>
<td>Direct thrombin inhibitor</td>
<td>Factor Xa inhibitor</td>
<td>Factor Xa inhibitor</td>
</tr>
<tr>
<td>Approved indication</td>
<td>Prevention of stroke and embolism in nonvalvular AF</td>
<td>Prevention of stroke and embolism in nonvalvular AF; thromboprophylaxis following hip or knee replacement surgery</td>
<td>Not yet FDA approved</td>
</tr>
<tr>
<td>Dosing and frequency</td>
<td>AF: 150 mg BID</td>
<td>AF: 20 mg/d; VTE prophylaxis: 10 mg/d</td>
<td>AF: 5 mg BID</td>
</tr>
<tr>
<td>Renal dosage adjustment</td>
<td>Yes; 75 mg BID</td>
<td>Yes; 15 mg once daily</td>
<td>Yes; 2.5 mg BID</td>
</tr>
<tr>
<td>Bioavailability, %</td>
<td>3–7</td>
<td>80–100</td>
<td>66</td>
</tr>
<tr>
<td>$T_{\text{max}}$, h</td>
<td>1</td>
<td>2–4</td>
<td>3–4</td>
</tr>
<tr>
<td>$t_{1/2}$, h</td>
<td>12–17</td>
<td>5–9</td>
<td>12</td>
</tr>
<tr>
<td>Protein binding, %</td>
<td>35</td>
<td>92–95</td>
<td>87</td>
</tr>
<tr>
<td>Common adverse events*</td>
<td>Dyspepsia</td>
<td>Elevated hepatic GGT</td>
<td>Nausea</td>
</tr>
<tr>
<td>Reversal agent</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
</tbody>
</table>

AF = atrial fibrillation; FDA = US Food and Drug Administration; GGT = γ-glutamyl transpeptidase; VTE = venous thromboembolism.

*Other than bleeding.
increased risk for systemic thromboembolism in a shorter time period relative to that for warfarin discontinuation. In patients who are being switched from dabigatran to warfarin, the vitamin K antagonist should be initiated for 3 days before stopping dabigatran, provided that they have normal renal function (creatinine clearance of at least 50 mL/min). Similarly, patients who need to discontinue dabigatran temporarily for invasive procedures are recommended to stop the drug for 1 to 2 days before such intervention.6

The clinical benefits observed from the clinical trials were based on strict inclusion and exclusion criteria for study enrollment. Such results may not be extrapolated to the generalized population. A subset of patients who were excluded from the studies were patients with renal insufficiency; thus, the direct thrombin and factor Xa inhibitors require dosage adjustments in patients with renal insufficiency and are contraindicated in patients with severe renal impairment. Postmarket surveillance studies for dabigatran are planned or are enrolling patients to further detect long-term outcomes in AF patients.25,26

Warfarin has clinical evidence to support its use and is recommended for anticoagulation in patients with AF who have moderate-to-high risk for thromboembolism. The respective noninferiority clinical trials have reported the 3 agents to be associated with a similar rate of stroke or thromboembolism as dose-adjusted warfarin and a similar or better major bleeding profile. Warfarin is marketed in generic form and is considerably cheaper than the newer oral anticoagulants, even with the associated costs of regular coagulation monitoring included. Until direct head-to-head studies are available for the new oral anticoagulants, the selection may depend on other factors related to each agent’s adverse effect profile, dosing schedule, and cost.

**CONCLUSION**

The inhibitors of direct thrombin and factor Xa represent a new approach to anticoagulation in patients with AF who have risk factors for stroke or thromboembolism. For patients who are unwilling to adhere to regular coagulation monitoring or whose warfarin therapeutic effect is not optimal despite adequate monitoring and management, the inhibitors of direct thrombin or factor Xa may provide alternative choices in anticoagulation.

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**CONFLICTS OF INTEREST**

The authors have indicated that they have no conflicts of interest regarding the content of this article.

**REFERENCES**


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