Progress for Stroke Prevention With Atrial Fibrillation
Emergence of Alternative Oral Anticoagulants

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Atrial fibrillation (AF) is both a common cardiac arrhythmia and a frequent cause of cardioembolic strokes. The prevalence of AF markedly increases with age and with the current population trends, the number of patients with AF is expected to continue to grow and may reach 12 million in the United States by 2050. AF accounts for up to 20% of all ischemic strokes and independently increases the risk of these events by up to 5-fold. Various cardiovascular risk factors do increase the risk of AF and given the continuing rise of obesity and resultant hypertension and diabetes, the future healthcare burden of AF-related strokes is likely to greatly increase.

AF is arguably 1 of the best-studied causes of stroke with dozens of randomized trials that have led to well-established evidence-based recommendations regarding effective treatment modalities. Warfarin, a vitamin K antagonist, is currently the most commonly used oral anticoagulant. It has been used for decades, is inexpensive, and has standardized laboratory monitoring and reversal protocols. Warfarin is also exceedingly effective; a recent meta-analysis has shown it to reduce stroke by almost two thirds compared with placebo therapy, particularly among elderly patients. Maintaining most patients within that therapeutic window is challenging due to numerous drug and diet interactions and requires frequent and inconvenient blood testing and monitoring. Due to these difficulties, a portion of patients and physicians has never adequately adopted this therapy, which means that many patients with AF are likely undertreated and at risk of stroke. Even in clinical trials with selected, closely monitored patients over a median follow-up period of 2.0 years, the study’s mean TTR was 64% with half of the patients being naïve to vitamin K antagonists is 66.4% in 1 meta-analysis, whereas only 56.7% are in range in the community setting. The underuse of warfarin has been well documented. The underuse of warfarin has been well documented.

Warfarin, however, has several limitations that have led to its use gap for warfarin, evolution of the medical treatment of AF would require newer agents that are just as effective, have a better side effect profile, and are easier to monitor. No other oral anticoagulant has been approved by the Food and Drug Administration (FDA) until recently. Now, 2 new agents are FDA-approved. Another agent has promising Phase III data published and is poised to be considered for approval, whereas others are in development. The aims of this review are to evaluate the properties of these new agents, compare the details of the randomized trial designs supporting their use, assess and compare the efficacy and safety results of these trials, and discuss the impact they will have on primary care providers, cardiologists, and neurologists caring for patients with AF.

New Oral Anticoagulants

Dabigatran

Dabigatran, a direct thrombin inhibitor, was the first new oral anticoagulant to be FDA-approved after successful results from a large randomized clinical trial. It is predominantly excreted through the kidney, has no known food and few drug–drug interactions, a rapid onset of action (1–2 hours), a short half-life (12–17 hours), and requires no routine laboratory monitoring. The Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial used a PROBE (prospective, randomized, open-label, blinded end point evaluation) protocol of dabigatran (110 mg or 150 mg twice daily in a blinded fashion) and adjusted-dose warfarin in 18,113 patients over a median follow-up period of 2.0 years. The subjects’ mean age was 71.5 years and the Congestive Heart Failure, Hypertension, Age ≥75, Diabetes and Stroke/TIA Score (CHADS2) was 2.1 (with only one third having a CHADS2 ≥3). Stroke (of any type) and systemic embolism were the primary study outcomes with any major hemorrhage being the primary safety outcome. The study’s mean TTR was 64% with half of the patients being naïve to vitamin K antagonists. Both doses were noninferior to warfarin for preventing primary outcomes, and the higher dose was superior to warfarin. Both doses were also noninferior to warfarin for ischemic strokes with the higher dose again...
being superior. Hemorrhagic strokes were significantly lower with both 110-mg and 150-mg doses compared with warfarin. Rates of major bleeding were also statistically decreased with the lower dose but not with the higher dose. Both doses had lower associated rates of intracranial bleeding and life-threatening bleeding, but both doses were statistically more likely to cause dyspepsia as compared with warfarin. Rates of death were not statistically different with either dose compared with warfarin, although there was a trend toward a lower mortality rate with the higher dose. The higher dose improved vascular mortality compared with warfarin but also was associated with higher rates of myocardial infarction and major gastrointestinal bleeding. Subsequent subanalysis has shown that the concerns about myocardial infarction in RE-LY were unfounded, although questions about dabigatran and risk of myocardial infarctions in other patient populations still remain.

A subgroup analysis was undertaken to assess the efficacy of dabigatran in those who have had a previous transient ischemic attack or stroke and it disclosed similar results. In this subpopulation, however, dabigatran did not significantly reduce ischemic strokes in patients with higher risk scores at either dose compared with warfarin. The drug’s bleeding complications were also compared in different age groups; dabigatran was associated with lower intracranial bleeding than warfarin at any age and at both doses. For those ≥75 years, the drug had similar gastrointestinal bleeding rates compared with warfarin at the lower dose and statistically higher gastrointestinal bleeding rates at the higher dose.

Impaired renal function was found to be a significant predictor for bleeding on dabigatran (RE-LY excluded patients with creatinine clearance <30 mL/min) and it may have similar effects on those taking warfarin, requiring lower dosing. Dabigatran was investigated against warfarin with different levels of center TTR with the findings supporting the general conclusions reached by RE-LY. Dabigatran at a dose of 150 mg twice a day (75 mg twice a day for those with severe renal impairment) was approved in many countries worldwide and by the FDA in October 2010 for the prevention of stroke and blood clots from AF. Renal function should be assessed before treatment with dabigatran to determine the appropriate dose and should be reassessed during treatment if clinically indicated. The FDA also issued a warning about packaging and storage with the recommendation of use within 60 days of original package opening.

**Rivaroxaban**

Rivaroxaban, a direct factor Xa inhibitor, has a time to peak of 3 hours and a half-life of 6 to 10 hours with two thirds of it excreted by the kidney. Rivaroxaban versus Warfarin in Nonvalvular Atrial Fibrillation (ROCKET AF) was a double-blind, randomized trial of 14 264 patients comparing rivaroxaban (20 mg daily [15 mg if creatinine clearance was 30–49 mL/min]) to dose-adjusted warfarin with a mean follow-up of 1.94 years. The mean age was 73 years, 60.3% of subjects were men, and the mean CHADS2 score was 3.47 (87% of the participants had a CHADS2 of ≥3). The ROCKET-AF trial differed from the others because it required at least 90% of patients with AF to have ≥3 risk factors or a previous thromboembolism, whereas the other trials only required 1 risk factor and included a more modest number of stroke survivors. The primary outcome of the study was any stroke or systemic embolism with the principal safety outcome being clinically relevant bleeding events. The mean and median study TTR were only 55% and 58%, respectively, among the warfarin-treated patients. The results demonstrated the noninferiority of rivaroxaban compared with warfarin in the intention-to-treat analysis as well as the per-protocol (or as treated) analysis. Superiority was not achieved (P=0.12) in the intention-to-treat analysis for the primary outcome but was found in the per-protocol as-treated population. Patients on rivaroxaban had similar rates of strokes and major bleeding (with more major bleeding from a gastrointestinal source) but less fatal and intracranial bleeding compared with those taking warfarin. Subanalysis of patients with different warfarin TTRs showed no statistical difference in rivaroxaban effects compared with the amount of time spent in a therapeutic international normalized ratio.

**Apixaban**

Apixaban is also a direct factor Xa inhibitor, which is 25% excreted by the kidney, has a high bioavailability, and a half-life of 8 to 15 hours. It has been investigated in 2 clinical trials. The first, Apixaban versus Acetylsalicylic Acid to Prevent Strokes (AVERROES), was a double-blind study of 5599 patients deemed unsuitable for vitamin K antagonist therapy. Subjects were randomized to apixaban 5 mg twice daily (2.5 mg for those older, with a low body mass index, or who have a renal impaired) or aspirin (81 mg or 324 mg). The average age of the patients was 70 years with 58.5% being male and a mean CHADS2 of 2.1 (with <28% having a CHADS2 ≥3). Patients with creatinine clearance of <25 mL/min were excluded as those with significantly elevated liver function assays. The primary outcome of the study was the occurrence of any stroke or systemic embolism. The study was stopped early by the Data and Safety Monitoring Board after a mean follow-up of 1.1 years due to apixaban being substantially more effective than aspirin in preventing the primary outcome. Ischemic and overall strokes were also significantly decreased with apixaban. The overall, intracranial, extracranial, and fatal bleeding events were similar between the 2 medications. Patients treated with apixaban were significantly less likely to have a major adverse event and discontinue medication compared with aspirin.

Apixaban versus Warfarin in Patients with Atrial Fibrillation (ARISTOTLE) was the second double-blind, randomized trial of apixaban, comparing a 5-mg twice-daily dose with warfarin in 18 201 patients with AF and a mean CHADS2 of 2.1 for a mean follow-up of 1.8 years. The mean age of the study subjects was 70 years and 64.7% were men; in the warfarin arm, TTR was achieved 62% of the time. Similar to the other trials, the primary study outcome was any stroke or systemic embolism and the primary safety outcome was major bleeding. Apixaban was superior to warfarin; patients on apixaban had fewer overall strokes or systemic emboli, fewer strokes (both ischemic and hemorrhagic), and fewer major bleeding events compared with warfarin. Patients on
apixaban had a similar risk of ischemic or uncertain strokes compared with those on warfarin but significantly fewer intracranial bleeds. Gastrointestinal bleeding complications were comparable between the 2 study groups. Patients on apixaban had fewer bleeding events and deaths. The discontinuation rate for apixaban was less than for warfarin.

**Comparing the Agents and Trials**

These 3 novel oral anticoagulants represent important advances over warfarin. They all exhibit a stable pharmacological profile, have less drug–drug interactions, and are virtually unaffected by a patient’s diet (besides some delay in absorption; Table 1). They require no regular monitoring for a vast majority of patients, although dose adjustments may be warranted for those with renal impairment or body weight extremes. These newcomers appear to be as effective, or in some cases superior, to warfarin with an overall better side effect profile. Like with any oral anticoagulant, bleeding is still an issue, but significantly less intracranial bleeding was seen compared with warfarin. A reliable and easy-to-execute reversal protocol still needs to be developed and disseminated for these medications as they gain adoption in community settings. These new agents will likely transform how we treat patients with AF and hopefully lead to greater reductions in cardioembolic strokes in the future.

These trials also highlight some important differences between the new agents (Table 2). Both apixaban and rivaroxaban were investigated with a double-blind study design, whereas dabigatran was studied in a PROBE manner, which is sometimes considered less rigorous and more prone to certain investigator biases. Looking back on the older trials that were done to prove warfarin’s efficacy, however, similar findings were found with the open-label and blinded trials. Both dabigatran and apixaban require twice-daily doses, which allows for a more even drug plasma concentration but arguably is less ideal for patients’ compliance when compared with once-daily dosing. Rivaroxaban offers once-daily dosing, but there is also a concern that it may not confer sufficient protection in between doses given its half-life.

The primary outcome of all of these trials was any stroke, ischemic or hemorrhagic, or systemic embolism (Figure). Stroke greatly outnumbered systemic emboli and ischemic strokes were more frequent than hemorrhages. When comparing the efficacy of these agents, we have relied on the more rigorous intent-to-treat findings (Table 3). Although noninferiority compared with warfarin was found for all 3 agents in the intent-to-treat analyses, both dabigatran and apixaban were superior to warfarin. Rivaroxaban showed superiority in the per-protocol as-treated analysis and not the intent-to-treat. Mean study TTR was similar in RE-LY and ARISTOTLE but lower in ROCKET-AF indicating that warfarin treatment may have been less optimal. Another concerning finding was the increased event rate after the trial was over among those who stopped the rivaroxaban and transitioned to warfarin; however, these patients also took longer to reach therapeutic international normalized ratios. The warfarin arm of this trial also seemed to have the greatest absolute risk of stroke; however, ROCKET-AF enrolled older subjects with a higher CHADS2 score (3.47 versus 2.1) compared with the other studies, therefore exploring a more vulnerable and at-risk population. The results demonstrate rivaroxaban to be noninferior to warfarin and potentially a less risky alternative for those who are older, sicker, and have arguably the most to gain from an effective and safe medication.

Dissecting the effects on ischemic and hemorrhagic stroke subtypes offers some other contrasts in these trials. All 3 study drugs have shown clear evidence of both less intracranial bleeding and hemorrhagic strokes (arguably the 2 most-feared complications of anticoagulants) compared with warfarin. Dabigatran at 150 mg was the only medication to show a significant decrease in ischemic strokes compared with warfarin. AVERROES demonstrated apixaban to be as safe as aspirin for bleeding events, and ARISTOTLE showed it to be as effective as warfarin for ischemic stroke prevention. Apixaban was also the only drug with statistically significant

### Table 1. Comparisons of the Properties of the New Oral Anticoagulants

<table>
<thead>
<tr>
<th></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>Direct factor Xa inhibitor</td>
<td>Direct factor Xa inhibitor</td>
</tr>
<tr>
<td>Half-life</td>
<td>12–17 h</td>
<td>6–10 h</td>
<td>8–15 h</td>
</tr>
<tr>
<td>Excretion</td>
<td>Kidney—80%</td>
<td>Kidney—66%, liver—28%</td>
<td>Kidney—25%</td>
</tr>
</tbody>
</table>

### Table 2. Comparison of the Design of Phase III Trials of New Oral Anticoagulants

<table>
<thead>
<tr>
<th></th>
<th>RE-LY</th>
<th>ROCKET-AF</th>
<th>ARISTOTLE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inclusion criteria</td>
<td>AF and at least 1 additional risk factor for stroke</td>
<td>AF and at least ≥3 or more risk factors or previous thromboembolism (90% of subjects)</td>
<td>AF and at least 1 additional risk factor for stroke</td>
</tr>
<tr>
<td>Exclusion criteria</td>
<td>CrCl &lt;30 mL/min, liver disease, recent stroke</td>
<td>CrCl &lt;30 mL/min, Ptt &lt;90 000, uncontrolled HTN, recent stroke</td>
<td>CrCl &lt;25 mL/min, mitral valve stenosis, recent stroke</td>
</tr>
<tr>
<td>Design</td>
<td>PROBE</td>
<td>Randomized double-blind, double dummy</td>
<td>Randomized double-blind</td>
</tr>
<tr>
<td>Primary stroke</td>
<td>Any stroke or systemic embolism</td>
<td>Any stroke or systemic embolism</td>
<td>Any stroke or systemic embolism</td>
</tr>
<tr>
<td>Mean age, y</td>
<td>71.5</td>
<td>73</td>
<td>70</td>
</tr>
<tr>
<td>Mean time in</td>
<td>64%</td>
<td>55%</td>
<td>62%</td>
</tr>
<tr>
<td>treatment range TTR</td>
<td></td>
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RE-LY indicates Randomized Evaluation of Long-Term Anticoagulation Therapy; ROCKET-AF, Rivaroxaban versus Warfarin in Nonvalvular Atrial Fibrillation; ARISTOTLE, Apixaban versus Warfarin in Patients with Atrial Fibrillation; AF, atrial fibrillation; CrCl, creatine clearance; PROBE, prospective, randomized, open-label, blinded end point evaluation; Ptt, platelets; HTN, hypertension.
decreases in mortality ($P=0.047$), although dabigatran was borderline ($P=0.051$) and rivaroxaban trending in that direction ($P=0.073$). Apixaban was also the only agent to be tested among patients deemed not eligible for vitamin K antagonists and found to be as safe as aspirin (See Table 3 for a more detailed comparison.).

RE-LY demonstrated a higher rate of gastrointestinal bleeding with a higher dose of dabigatran and more dyspepsia with both doses, whereas ROCKET-AF had a higher rate of major gastrointestinal bleeding and epistaxis with rivaroxaban. These findings warrant further investigations. Both apixaban and rivaroxaban were well tolerated, whereas dabigatran had a statistically higher dropout rate compared with warfarin.

These trials show many similarities in design and inclusion and exclusion criteria and readers are often tempted to make indirect comparisons to judge differential efficacy. Such comparisons are fraught with problems and can lead to misinterpretations. Although the relative risk reduction was greatest for 150 mg dabigatran (34%) compared with rivaroxaban (21%) and apixaban (21%), the CIs overlapped and the differential efficacy of these agents is likely to be similar. Only a direct head-to-head comparison trial would be able to conclusively compare the efficacy of these agents. The completed trials demonstrate dabigatran to be the most effective in decreasing ischemic stroke, apixaban superior to warfarin with statistically lower mortality, and rivaroxaban no worse than warfarin for those with higher CHADS$_2$ scores. All 4 trials excluded patients within 7 to 14 days of stroke and further research on the safety and efficacy of the drugs during the acute period is needed.

**Guidelines**

The US FDA has approved dabigatran at 150 mg twice-a-day dosing and 75 mg twice-a-day dosing for those with severe renal impairment (a dose that was not investigated in RE-LY). The approval of dabigatran by the FDA was followed by a strong debate on why the lower dose (110 mg) was not approved. The justification given was based on the superiority of the 150-mg dose in preventing ischemic stroke and on the fact that after a detailed analysis, there were no subgroups of patients in whom the use of a lower dose would have resulted in a better benefit/risk ratio. In contrast, approval of the 75-mg dose for patients with severe renal impairment was based on pharmacokinetic data and corresponding pharmacodynamic modeling rather than on efficacy data. The European Society of Cardiology recommends a (150 mg) higher dose of dabigatran for patients with a HAS-BLED score of 0 to 2 (HAS-BLED is a bleeding stratification score for patients with AF) and a 110-mg dose for those HAS-BLED scores of $\geq3$. A 2011 American College of Cardiology Foundation/American Heart Association/Heart Rhythm Society focused update to American College of Cardiology/American Heart Association/European Society of Cardiology guidelines recommends 150 mg dabigatran twice daily as an alternative to warfarin for patients with nonvalvular AF and without severe renal (creatinine clearance $<15$ mL/min) or liver disease. The Canadian Cardiovascular Society has come out with perhaps the boldest statement, recommending 150 mg dabigatran twice daily over warfarin with some exceptions (dyspepsia, gastrointestinal bleeding, etc). The Society did recommend a lower dose (110 mg) for those $>80$ years.

Rivaroxaban has recently received FDA approval with a warning regarding an increased risk of stroke when discontinuing the drug. Approval for apixaban is still pending at the time of this writing.

**Remaining Questions**

Provided all 3 alternative oral anticoagulants get FDA approval, there will be more work to do and questions to answer regarding the most effective use of these agents in the community. Some potential questions and issues include the following.

1. **How Do the Results From These Studies Translate to Real-World Community Practice? Will the Efficacy and Safety Observed in These Studies Be Similar to the Risks of Bleeding Observed in Community Settings? Will Compliance in the Community Be Similar to That Observed in Randomized Trials? Will Acceptance by Patients Be Better Because of the Decreased Need for Frequent Blood Tests?**

Meta-analyses will be needed to evaluate any heterogeneity across risk groups. Phase IV studies and community patient registries will be required to enhance our knowledge base on
the outcomes associated with these agents, identify areas of controversy, and establish greater certainty regarding maximizing benefit and minimizing risk by efficient selection of patients.

The studies have recruited patients with different stroke risks and variable compliance with warfarin. The 3 agents were used in a wide spectrum of patients with AF ranging from those at highest risk who had already had a stroke to those with the lower CHADS2 scores. Most required at least 1 risk factor with AF, so the benefits of these agents in the lowest risk groups are still unknown. ROCKET-AF specifically demonstrated that patients taking rivaroxaban with higher risk of stroke had similar risks of stroke compared with those taking warfarin at the same time as sustaining less intracranial hemorrhages and hemorrhagic strokes. Subgroup analyses regarding the highest risk groups (with a CHADS2 ≥3) in each of these trials showed the patients taking the new anticoagulants to be as safe, if not safer, compared with those taking warfarin.

Compliance with these agents should be more acceptable than warfarin. They offer fixed dosing and arguably are less “work” to take. Many common drugs are successful despite twice-daily dosing (required for dabigatran and apixaban), whereas rivaroxaban allows for once-daily dosing. A shorter half-life makes these new medications less forgiving of missed doses; however, sporadic dosing of warfarin also pushes the patient outside the therapeutic window. Although gastrointestinal and other extracranial bleeding is a concern, AVERROES demonstrated that apixaban is as safe as aspirin, a drug that is used widely and with less trepidation, even by the elderly. Although aspirin is used in some patients with AF mainly because of the bleeding risk with oral anticoagulants, these newer agents should provide reasonably safe and more efficacious alternatives to aspirin.

Postmarketing surveillance...
will be critical in further assessing safety in the real world. As of the writing of this review, there have been several fatal bleeding events reported worldwide with dabigatran (in RE-LY, life-threatening bleeds did occur but were significantly fewer than with warfarin). Whether these events are happening at a higher rate than what was expected on the basis of clinical trial data will be the object of careful future analysis by the FDA.28

2. Should Patients Who Are Currently on Warfarin Be Switched to These Newer Agents?
Most of these trials included warfarin-naive as well as prior warfarin users. According to subgroup analyses, prior warfarin users did better with dabigatran (150 mg) and apixaban and no worse with rivaroxaban. Switching patients from warfarin to another agent will depend on a variety of factors including prior compliance with international normalized ratio monitoring, TTR, any prior bleeding complications, convenience, and the variability of the patient’s diet. Caution will be needed in switching patients to any new regimen. For example, based on the results from the ROCKET-AF trial, the FDA has issued a warning regarding a greater risk of thrombotic events after rivaroxaban’s discontinuation, a concern that will need to be further studied. In our own opinion, a very stable patient on warfarin who has been doing well for quite some time should probably remain on warfarin, which has an established track record and strong evidence-based recommendations.

3. How Will Cost Factor Into Decisions Regarding Use Any of These Agents?
The new anticoagulants are expensive, particularly compared with warfarin, and their market penetration will likely be gradual. Costs will likely decrease with increasing competition and market forces. Moreover, these newcomers will likely accumulate cost savings by decreasing the frequency of laboratory and clinician monitoring dictated by warfarin. Dabigatran may already be an economically viable contender with reasonable cost-effectiveness.29 Poorly controlled patients would likely benefit from an alternative to warfarin.

4. What Treatment Should Be Initiated for a Newly Diagnosed Patient With AF?
These trials have included a large proportion of new patients with AF who were warfarin-naive who will be the most likely candidate for these agents. Effectiveness, novelty, cost, side effect profile, ease of reversal, and convenience will likely influence physician decisions. In our opinions, unless there are major cost considerations limiting the choices for a given patient, we would recommend starting a new patient with AF on 1 of these new agents. At present, we believe that dabigatran (150 mg twice a day) has a slight edge over rivaroxaban because it was found to be superior to warfarin and significantly reduced ischemic stroke risk; however, in a poorly compliant patient, a once-a-day regimen could tip the scale toward rivaroxaban. If apixaban gets FDA approval, the choices will only be more difficult and largely based on subjective differences, physician preferences, and their own personal experiences and comfort using these agents. Until more evidence becomes available to help differentiate choices between these agents, they are all likely to be recommended as alternatives to warfarin for the prevention of stroke among patients with AF.

Conclusions
The oral anticoagulants presented here, as a group, are at least as effective as warfarin in preventing cardioembolic stroke among patients with AF and appear safer with less intracranial bleeding complications or hemorrhagic strokes. They offer a more convenient and potentially safer way of maintaining optimal antiocoagulation. These drugs provide a new answer for a large subset of patients with AF who have not been protected with oral anticoagulation due to reluctance, fear, or misconceptions about the risks and benefits of optimal therapy for their cardiac arrhythmias. These safer alternatives to warfarin should encourage physicians to more widely use these agents among patients with AF. These new oral anticoagulants offer certain advantages but, more importantly, a greater choice of treatment options and alternatives to vitamin K antagonists and real progress for stroke prevention.

Disclosures
Dr Sacco served on the Data and Safety Monitoring Board for the Apixaban versus Acetylsalicylic Acid to Prevent Strokes (AVERROES) Trial and reported to the Population Research Institute at McMaster University.

References

**Key Words:** anticoagulation ■ atrial fibrillation ■ novel anticoagulants ■ warfarin
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