Cardiovascular Therapeutics

New Oral Anticoagulants for Stroke Prevention in Atrial Fibrillation: More Choices Bring More Challenges

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Abstract

For patients with atrial fibrillation, anticoagulant therapy is essential to reduce the risk of ischemic stroke that is associated with this arrhythmia. Historically, warfarin has been the preferred treatment for patients at moderate to high risk despite many potential limitations. With the development of newer oral anticoagulants, clinicians now have 3 additional options: dabigatran, rivaroxaban, and apixaban. Although these agents clearly offer some advantages over warfarin, they may not be appropriate for all patients. This article will discuss factors that should be considered when selecting among these various anticoagulants.

Key Words—anticoagulation, atrial fibrillation, stroke prevention

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Atrial fibrillation (AF) increases the risk of ischemic stroke approximately 5-fold.¹ Whereas the average annual risk of stroke for AF patients averages 5%, the presence of additional risk factors such as heart failure, hypertension, diabetes, prior stroke, or age over 75 years increases this risk.² To reduce this risk, guidelines from the American College of Chest Physicians for stroke prevention in AF strongly recommend an oral anticoagulant for patients at moderate to high risk for stroke (CHADS₂ ≥ 1).³

For decades warfarin has been the only available oral anticoagulant. An impressive body of clinical trial evidence has definitively shown that warfarin reduces the risk of ischemic stroke in AF patients by approximately two-thirds.² However, long-term warfarin therapy also carries a substantial burden for the patient including a narrow therapeutic window, need for routine laboratory monitoring, and significant potential for drug and food interactions. These limitations likely account for the suboptimal utilization of warfarin in eligible patients with AF. For example, a recent population-based retrospective cohort study of 41,447 Medicare beneficiaries aged 66 years and older reported an overall warfarin use rate of 66.8%, a finding consistent with that of prior studies.⁴

Three novel oral anticoagulant drugs have been approved for stroke prevention in AF. Dabigatran,

a direct thrombin inhibitor, and rivaroxaban, a factor Xa inhibitor, were approved in 2010 and 2011, respectively. In 2012, another factor Xa inhibitor, apixaban, received US Food and Drug Administration (FDA) approval. Although the availability of these newer oral anticoagulant drugs increases the therapeutic options for patients, it also presents challenges for clinicians who must now choose among the 4 agents. This article will discuss the advantages and disadvantages of these newer agents and their possible role in therapy.

CLINICAL EFFICACY OF THE NEWER ORAL ANTICOAGULANTS

The FDA approvals of all 3 of the newer oral anticoagulant drugs were based on the findings of large comparative clinical trials with warfarin in patients with nonvalvular AF.

The efficacy of dabigatran was demonstrated in the Randomized Evaluation of Long-term Anticoagulation Therapy (RE-LY) trial, which compared 2 fixed doses of dabigatran (110 or 150 mg twice daily) to open-label adjusted-dose warfarin.⁵ This was a non-inferiority trial involving 18,113 patients with a mean age of 71 years and a mean CHADS₂ score of 2.1. The primary endpoint was stroke or systemic embolism and the median follow-up was 2.0 years. The mean time in therapeutic range for warfarin patients

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was 64%. Based on the findings of the trial, only the 150 mg dosing regimen received FDA approval. The annual rates for the primary endpoint in patients receiving dabigatran 150 mg twice daily were 1.11% versus 1.69% for warfarin (relative risk [RR] 0.66; 95% CI, 0.53-0.82; $P = .003$). Rates of major bleeding were similar for dabigatran and warfarin (3.11% per year vs 3.36% per year; $P = .31$). Hemorrhagic stroke, however, occurred less frequently in dabigatran patients with an annual rate of 0.10% versus 0.38% with warfarin ($P < .001$). Conversely, an increased rate of gastrointestinal (GI) bleeding was reported with dabigatran (1.51% per year vs 1.02% per year; RR 1.50; 95% CI, 1.19-1.89; $P < .001$).

Overall, dabigatran was well tolerated by most patients. However, dyspepsia was more common with dabigatran than with warfarin (11.3% vs 5.8%; $P < .001$) resulting in more patients discontinuing therapy (2.1% vs 0.5%, respectively). Additionally, an unexpected red flag was raised with the initial analysis of RE-LY when an increased rate of myocardial infarction (MI) was seen with dabigatran compared to warfarin (0.74% per year vs 0.53% per year; RR 1.38; 95% CI, 1.00-1.91; $P = .048$). Subsequently, the FDA allowed a reanalysis of the RE-LY data that identified 28 additional cases of silent MI in trial patients. Inclusion of these events eliminated the statistically significant difference between dabigatran and warfarin for this outcome (0.81% per year vs 0.64% per year; RR 1.27; 95% CI, 0.94-1.71; $P = .12$).⁶

Since dabigatran's approval, reports of serious and potentially life-threatening bleeding have emerged.⁷ Boehringer Ingelheim has confirmed that between March 2008 and October 31, 2011, there were 260 fatal bleeding events worldwide. These concerns have already led to safety advisories in Japan, New Zealand, and Australia as well as labeling updates in Europe and the United States that focus on the need for regular assessment of renal function. In addition, the FDA has examined insurance claims and administrative data to access the comparative risk of serious bleeding associated with both dabigatran and warfarin.⁸ In a recent safety advisory, the FDA states that its initial findings indicate that the bleeding rates associated with dabigatran do not appear to be higher than those associated with warfarin. While this safety review is ongoing, the FDA advises AF patients who are taking dabigatran to continue therapy or consult their health care professional and recommends that dosing guidelines be closely followed when dabigatran is prescribed.

The comparative efficacy of rivaroxaban was evaluated in 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).⁹ This non-inferiority trial, which included 14,264 patients who were median age 73 years, compared rivaroxaban 20 mg daily to adjusted-dose warfarin. The mean CHADS₂ score was 3.5, indicating a population at higher risk for stroke as compared to patients in the RE-LY trial. The primary endpoint was stroke or systemic embolism. The mean time in therapeutic range for warfarin patients was 55%, suggesting less than optimal control. After a median follow-up of 1.6 years, the rates for the primary endpoint were 1.7% per year versus 2.2% per year for rivaroxaban and warfarin respectively (hazard ratio [HR] 0.79; 95% CI, 0.66-0.96; $P < .001$, for noninferiority). Major and nonmajor clinically relevant bleeding occurred at similar rates with the 2 drugs. Major bleeding from GI sites, however, was more common with rivaroxaban (3.2% vs 2.2%; $P < .001$). Conversely, significant reductions were seen with rivaroxaban for both intracranial hemorrhage (0.5% vs 0.7%; $P = .02$) and fatal bleeding (0.2% vs 0.5%; $P = .003$).

Apixaban's approval was based primarily on the results of the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) study, a large randomized clinical trial involving 18,201 patients.¹⁰ Trial patients had a median age of 70 years and a mean CHADS₂ score of 2.1 indicating moderate to high risk for stroke similar to those evaluated in RE-LY. The trial compared apixaban 5 mg twice daily to adjusted-dose warfarin. The primary outcome was stroke or systemic embolism. This was a noninferiority trial with secondary objectives to test superiority for the primary outcome as well as rates of major bleeding or death. Patients were followed for a median period of 1.8 years. For warfarin patients, the mean time in therapeutic range was 62.2%. For the primary outcome, the annual rates were 1.27% for apixaban compared to 1.60% for warfarin (HR with apixaban, 0.79; 95% CI, 0.66-0.95; $P < .001$, for noninferiority, $P = .01$, for superiority). Major bleeding was reported in 2.13% of apixaban patients per year compared to 3.09% of the warfarin patients per year (HR 0.69; 95% CI, 0.60-0.80; $P < .001$). The rates of death from any cause were 3.52% and 3.94%, respectively (HR 0.89; 95% CI, 0.80-0.99; $P = .047$). Hemorrhagic stroke, generally the most feared outcome of anticoagulant therapy, was reported in 0.24% per year of the apixaban group compared to 0.47% per year of the warfarin group (HR 0.51; 95% CI, 0.35-0.75; $P < .001$).

Rates of GI bleeding were similar for the 2 drugs (0.76% with apixaban vs 0.86% with warfarin; HR 0.89; 95% CI, 0.70–1.15; $P = .37$).

SELECTING AN ORAL ANTICOAGULANT FOR PATIENTS WITH AF

With the availability of 4 oral anticoagulant drugs, clinicians now have the opportunity to tailor therapy based on patient-specific factors. In terms of their efficacy for reducing the risk of ischemic stroke, all of the newer drugs appear to be comparable to warfarin. Thus, warfarin remains an appropriate choice for those patients who are comfortable taking the drug and able to maintain a stable international normalized ratio (INR). Warfarin is also an attractive choice for those who are concerned about drug costs. Additionally, warfarin is the only oral anticoagulant with proven efficacy for patients who have both AF and valvular heart disease. In particular, patients with mechanical heart valves should not be treated with the newer drugs until safety and efficacy data are available. A phase 2 dose-ranging study of dabigatran (RE-ALIGN), which was initiated in patients with mechanical aortic heart valves, has been halted early due to concerns of increased valve thrombosis compared to warfarin and more bleeding after valve surgery.¹¹ Following this, the FDA issued a safety communication informing health care professionals and patients that dabigatran should not be used to prevent thromboembolic events in patients with mechanical prosthetic heart valves.¹²

The newer oral anticoagulants, however, do offer clinically significant advantages for selected patients. All 3 of the newer agents appear to be slightly more effective than warfarin for reducing the risk of intracranial hemorrhage and hemorrhagic stroke.^{5,9,10} While this is clearly advantageous, it should also be noted that the absolute rates of intracranial hemorrhage within the warfarin arms of all 3 comparative clinical trials were very low, ranging from 4 to 8 events per 1,000 patients annually. The newer agents also provide an alternative for patients who cannot or will not comply with laboratory monitoring or those with complex drug regimens and a high potential for warfarin drug interactions. It is important to note, however, that while the lack of required laboratory testing may be desirable, it is also potentially dangerous in patients who are noncompliant with their regimen. Even one missed dose of the newer drugs may theoretically increase thrombotic risk due to the drugs' shorter half-life and rapid offset compared to warfarin. In addition, the lack of simple monitoring tests may complicate the management of patients prior to surgery or other invasive procedures.

When selecting the most appropriate drug for a specific patient, comorbidities should always be considered. Because all 3 of the newer agents are highly dependent upon renal elimination, dosing adjustments are needed for those with mild to moderate renal dysfunction.^{13–15} Moreover, all of the newer drugs are contraindicated in patients with severe renal failure. For patients with concerns about GI bleeding, apixaban appears to be the safest alternative among the newer drugs, although any anticoagulant must be used with caution in these patients. For patients with coronary heart disease, the long-term safety of dabigatran remains unclear. Whereas the reanalysis of the RE-LY data provided some assurance that MI risk was not increased, other studies have failed to support this conclusion. A meta-analysis of 7 noninferiority trials found an increased risk for MI in patients receiving dabigatran compared to control patients or those on warfarin.¹⁶ However, the absolute increase in risk was relatively small (0.27%). Whether this is truly reflective of an increased risk of MI with dabigatran or perhaps is a protective effect of warfarin remains unknown. No similar concerns have been raised with either rivaroxaban or apixaban.

Like all anticoagulants, special precautions must be taken when any of the newer agents are used in patients who may undergo neuraxial anesthesia (spinal/epidural anesthesia). These patients are at risk for developing an epidural or spinal hematoma, which can result in long-term or permanent paralysis.¹⁷ Product information for the newer agents includes specific guidelines for timing the removal of epidural catheters and subsequent doses.^{13–15}

A major disadvantage of warfarin is the large number of interactions with various drugs and herbals. Even though this is clearly less of a concern with the newer drugs, none are completely free of potential interactions. Dabigatran requires an acidic environment for maximal absorption. Because acid-suppressing drugs may be coadministered to offset dyspepsia with dabigatran, these agents could theoretically reduce dabigatran's bioavailability. However, to date no studies have shown decreased efficacy and concomitant use is not contraindicated. Unlike warfarin, dabigatran is not metabolized by the CYP450 enzymes.¹⁸ However serum levels may be altered by drugs that impact the p-glycoprotein (P-gp) drug transport system. Thus, dabigatran should not be administered with potent P-gp inducers such as rifampin. Caution is also advised for concomitant use with P-gp inhibitors. In particular, if dabigatran is coadministered with ketoconazole or dronedarone in patients with moderate renal impairment

(CrCl 30-50 mL/min), the product information recommends a dosage reduction to 75 mg bid.¹³ It should be noted, however, that the efficacy of this dose for stroke prevention in AF has not been studied. The factor Xa inhibitors are substrates for both the CYP450 3A4 enzyme and P-gp.¹⁹⁻²¹ Thus coadministration of either rivaroxaban or apixaban with strong dual inhibitors or inducers of CYP3A4 and P-gp such as ketoconazole, itraconazole, ritonavir, or clarithromycin should be avoided.^{14,15} It is important for pharmacists to be aware that our current understanding of the interaction potential for all of the new oral anticoagulants is very limited. Specifically, additional studies are needed to assess the potential impact of coadministration of these new agents with more moderate inhibitors or inducers of P-gp and CYP3A4. Until more data are available, patients on complex drug regimens should be monitored closely.

Because the pharmacokinetic and pharmacodynamic responses for the new oral anticoagulants are predictable in patients with adequate renal function, the drugs can be prescribed in fixed doses with no routine laboratory monitoring. In some clinical situations, however, it may be desirable to measure the degree of anticoagulation such as in cases of overt bleeding or prior to surgery and other invasive procedures. Unfortunately, none of the routine coagulation tests can specifically assess the plasma levels and antithrombotic effect of these drugs. However, the International Society on Thrombosis and Haemostasis has developed recommendations for using a number of currently available tests to estimate the presence of anticoagulant.²² For dabigatran, the activated partial thromboplastin time (aPTT) can be used to estimate the relative intensity of anticoagulation. Laboratories must first assess the sensitivity of their aPTT assays to dabigatran, which can be achieved using commercially available dabigatran plasma calibrants. If available, the thrombin time (TT) can also be measured; when TT is normal, it indicates a very low or undetectable level of dabigatran. Neither of these tests is as sensitive or linearly related to dabigatran concentrations as the ecarin clotting time (ECT); however, this test is not widely available. For patients on factor Xa inhibitors, the prothrombin time (PT) can be used to estimate the relative intensity of anticoagulation provided that laboratories have ensured their thromboplastin reagent is sensitive to the presence of factor Xa drugs. Anti-factor Xa assays may also be helpful in determining drug levels. Although these various assays may be helping in verifying the presence or absence of oral anticoagulant, the lack of defined target ranges as well as variability between

reagents and institutions significantly limit their clinical utility.

Because dabigatran and the factor Xa inhibitors have no direct reversal agents, overdosage with major bleeding presents a difficult challenge.²³⁻²⁵ A preliminary study in 12 healthy volunteers found that prothrombin complex concentrate reversed the effects of rivaroxaban but not dabigatran.²⁴ Further study is needed to evaluate the feasibility of using this and various other potential reversal agents in clinical cases of bleeding. Current strategies for managing overdoses of dabigatran include the use of activated charcoal and hemodialysis, which has been shown to remove approximately 50% to 60% of the drug over 4 hours depending on dialyzer flow rates.^{13,25}

SWITCHING BETWEEN ORAL ANTICOAGULANTS

Because AF is a chronic condition requiring lifelong anticoagulation, switching from one oral anticoagulant to another is likely. To avoid placing the patient at risk for thrombosis or bleeding, pharmacists are encouraged to refer to specific product information when recommending these changes.¹³⁻¹⁵ In general, because the newer drugs have a rapid onset, switching from warfarin is relatively easy. However, switching from the new agents to warfarin is more problematic because of the slow onset of warfarin and lack of clinical trial data. This point was illustrated by a post hoc analysis of data from ROCKET AF examining the 30-day risk of stroke or non-central nervous system embolism after end-of-study transition to open-label warfarin therapy.²⁶ An increased risk of thrombosis was observed for rivaroxaban-treated patients transitioning to warfarin compared to patients who continued on warfarin (HR 3.72%; 95% CI, 1.51-9.16; $P = .0044$). Although this study was limited by its observational nature, the investigators attributed the increased thrombotic risk to delays in reaching a therapeutic INR for those switching from rivaroxaban. Concerns of this potential antithrombotic gap suggest that bridging with a parenteral anticoagulant during the initial titration phase of warfarin may be warranted in high-risk patients.

CONCLUSION

For patients with AF, the availability of newer oral anticoagulant drugs has provided a much needed alternative to conventional warfarin therapy for stroke prevention. The convenience of fixed daily doses with no need for routine laboratory monitoring may result in a greater percentage of AF patients receiving this potentially life-saving therapy. Despite these advantages,

the new agents have important limitations that must be considered when therapy is tailored to an individual patient. Moreover, it must be kept in mind that all of these drugs are potent anticoagulants and carry a substantial risk for bleeding. Thus ongoing patient education and assessment are essential.

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