Atrial Fibrillation

Recent Developments in the Prevention of Thromboembolism from Atrial Fibrillation: Novel Oral Anticoagulants and Left Atrial Appendage Occlusion Devices

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Introduction

Atrial fibrillation (AF) is the most commonly diagnosed adult arrhythmia in the United States and worldwide.1,2 Owing to an aging population and increasing incidence, the prevalence of AF in the United States is projected to reach 12–15 million patients by the year 2050.3-4 AF is a major risk factor for stroke, accounting for 15% of all strokes and more than a third of strokes among patients above 80 years of age.5-10 AF-related strokes are more frequently fatal and disabling than non-AF-related strokes, and they carry a worse prognosis than embolic events from other causes.11-13 The majority of embolic strokes from AF result from thrombus formation in the left atrial appendage (LAA) due to stasis and reduced contractile activity (Figure 1), although stroke in AF can also result from cerebrovascular disease or aortic pathology.1

Current American College of Cardiology/American Heart Association/Heart Rhythm Society (ACC/AHA/HRS) guidelines stress the critical role of antithrombotic therapy for the prevention of stroke and systemic embolism, with aspirin therapy recommended only for low-risk patients.1 Patients are categorized into low, intermediate, and high risk for stroke according to the presence or absence of risk factors.14-20 (Figure 2). The vitamin K epoxide reductase inhibitor warfarin has been demonstrated to dramatically reduce the incidence of ischemic stroke in patients with AF21 and it has until recently been the only antithrombotic therapy approved for this indication. However, its use can be challenging because of its variable pharmacokinetic and pharmacodynamic profile, numerous drug and dietary interactions, delayed onset of action, need for substantial laboratory monitoring and dosage titrations, and, most importantly, bleeding complications.12,22-24 Variations in international normalized ratio (INR) values are ubiquitous, and even the best centers keep patients’ INR values in the therapeutic range less than 70% of the time.25 In addition, 30–50% of AF patients do not receive warfarin because of relative or absolute contraindications or other barriers,26,27 and its use even among stroke patients for secondary prevention declines rapidly within 2 years.28

These disadvantages have engendered great interest in the development of alternative therapies that may overcome these limitations. In this article, we review the data supporting new therapeutic strategies, including dual antiplatelet agents, direct thrombin inhibitors, factor Xa inhibitors, and LAA occlusion devices.

Dual antiplatelet therapy

The above-mentioned limitations of warfarin therapy, particularly its need for laboratory monitoring and
In the ACTIVE-W trial, 6706 high-risk AF patients were randomized to either dual antiplatelet therapy (clopidogrel 75 mg and aspirin 81 mg) or warfarin (INR 2.0–3.0). The trial was discontinued early for safety reasons when interim analysis revealed a significant 44% relative increase in the rate of stroke, non-central-nervous system (CNS) embolus, myocardial infarction, or vascular death among those treated with dual antiplatelet therapy (relative risk (RR) 1.44, 95% confidence interval (CI) 1.18–1.76; \( p = 0.0003 \)). Rates of major bleeding were similar. Thus, warfarin was clearly superior in this study, and there is currently no role for dual antiplatelet therapy as an acceptable alternative among warfarin-eligible AF patients with risk factors for embolic stroke. Interestingly, the benefit of warfarin in ACTIVE-W was smaller among warfarin-naïve patients; however, it is unlikely that a trial of warfarin-naïve patients will be conducted in the wake of ACTIVE-W.

The ACTIVE-A trial compared the same dual antiplatelet regimen with aspirin monotherapy among high-risk AF patients who either refused, or were deemed to be poor candidates for, warfarin. There was a significant 28% relative risk reduction in stroke (RR 0.72, 95% CI 0.62–0.83; \( p < 0.001 \)) as well as a non-significant 22% lower rate of myocardial infarction (RR 0.78, 95% CI 0.59–1.03; \( p = 0.08 \)) among those treated with aspirin compared to those treated with warfarin.

### Table: Risk of Stroke in AF Patients

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>Recommended Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Risk Factors</td>
<td>Aspirin, 81-325 mg daily</td>
</tr>
<tr>
<td>One moderate-risk factor</td>
<td>Aspirin, 81-324 mg daily, or warfarin (INR 2.0 to 3.0, target 2.5) or dabigatran</td>
</tr>
<tr>
<td>Any high-risk factor or more than one moderate-risk factor</td>
<td>Warfarin (INR 2.0 to 3.0, target 2.5) or dabigatran</td>
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### Less Validated or Weaker Risk Factors

<table>
<thead>
<tr>
<th>Moderate-Risk Factors</th>
<th>High-Risk Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female gender</td>
<td>Age greater than or equal to 75 y</td>
</tr>
<tr>
<td>Age 65 to 74 y</td>
<td>Hypertension</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>Heart failure</td>
</tr>
<tr>
<td>Thyrotoxicosis</td>
<td>L.V ejection fraction 35% or less</td>
</tr>
<tr>
<td></td>
<td>Diabetes Mellitus</td>
</tr>
<tr>
<td></td>
<td>Prior stroke, TIA, or embolism</td>
</tr>
<tr>
<td></td>
<td>Mitral Stenosis</td>
</tr>
<tr>
<td></td>
<td>Prosthetic heart valve*</td>
</tr>
</tbody>
</table>

*For Mechanical Valves, target INR greater than 2.5
aspirin and clopidogrel at the expense of a 57% higher rate of major hemorrhagic complications (RR 1.57, 95% CI 1.29–1.92; p<0.001). Thus, the ACTIVE trials established that dual antiplatelet therapy is less effective than warfarin, but more effective than aspirin alone, among AF patients with risk factors for stroke. On this basis, a recent guideline update provides a class IIb recommendation for dual antiplatelet therapy only among AF patients who cannot safely sustain anticoagulation using warfarin.33

Direct thrombin inhibitors

A desire for practical and efficient alternatives to warfarin, which inhibits synthesis of multiple molecules in the coagulation cascade, led to interest in agents which inhibit other steps in the formation of a durable thrombus. (Figure 3). The first class to be intensively studied was the direct thrombin inhibitors (DTIs). These agents selectively and reversibly inhibit thrombin, thereby preventing the last step in the coagulation cascade, the transformation of fibrinogen to fibrin.34,35 DTIs also inhibit thrombin-induced platelet aggregation.36 Several DTIs were previously approved in the United States for the treatment of heparin-induced thrombocytopenia,37,38 as an alternative to heparin during coronary artery intervention,39–42 and for thromboembolism prophylaxis after orthopedic surgery.43,44 Compared with warfarin, oral DTIs have a more rapid onset of action, fewer food and drug interactions, a more predictable anticoagulation response, and no need for blood monitoring.

Ximelagatran was the first oral DTI within this class to show potential for treatment of AF. It was studied in the SPORTIF trials, which compared Ximelagatran with warfarin in non-valvular AF.45–50 These trials enrolled over 10,000 patients and found ximelagatran to be non-inferior to warfarin with respect to the incidence of stroke and systemic embolism, with a similar bleeding profile. This engendered great excitement in the AF community regarding the possibility of a convenient oral alternative to warfarin. However, an unacceptably high rate of hepatotoxicity was observed. For example, in SPORTIF V, serum alanine aminotransferase levels rose to greater than three times the upper limit of normal in 6% of patients treated with ximelagatran, with one definite case of documented fatal liver disease and one suspicious case. An even higher rate of abnormal liver function tests was observed in the THRIVE trials of ximelagatran in venous thromboembolism.51–53 This observed hepatotoxicity of ximelagatran led to its rejection by the FDA.54,55

Dabigatran, another DTI, was the first alternative to warfarin to be approved for prevention of stroke in AF patients. It is a competitive direct and reversible thrombin inhibitor which is given as an oral pro-drug that is converted in the liver through esterases to the active compound. It has a rapid onset of action (peak 0.5–4 h), a half-life of 12–17 h, and reaches clinical steady state within 2–2.5 days after initiation. Eighty percent of dabigatran is excreted unchanged by the kidneys.56 The drug acts on platelet-derived thrombin as well as clot-bound and free-floating thrombin, preventing further amplification of the clotting cascade and platelet aggregation.57 Dabigatran was approved based upon a single large study, the RE-LY trial,58 a randomized, phase III, non-inferiority trial in 18,113 patients with non-valvular AF and risk factors for stroke. Patients were randomized to either dabigatran, at a dosage of 110 or 150 mg twice daily, or warfarin titrated to a target INR of 2–3. There was no blinding to agent used (warfarin versus dabigatran), but among patients who received dabigatran the dosage was administered in a double-blind fashion. The primary efficacy end point of the study was a composite of stroke or systemic embolism. Time in therapeutic range (TTR) for the warfarin group was 64%, which compares favorably with other large trials.25,59,60 In the RE-LY trial, the 150-mg dose was found to be superior to warfarin, and the 110-mg dose was non-inferior. Rates of the primary outcome (systemic embolism or stroke) in RE-LY were 1.11% per year with dabigatran 150 mg versus 1.69% per year with warfarin (RR 0.66; 95% CI 0.53–0.82; p<0.001 for superiority). The 110-mg dose was found to be non-inferior, with an event rate of 1.53% per year (RR 0.91; 95% CI 0.74–1.11; p=0.001 for non-inferiority). The annual incidence of non-hemorrhagic stroke was lowest with dabigatran 150 mg (0.92%; RR 0.76 versus warfarin; p=0.03). In terms of safety data, major bleeding (primary safety endpoint) was 3.11% per year in the dabigatran 150-mg group compared with 3.36% per year in the warfarin group (p=0.31) and 2.71% per year in the dabigatran 110-mg group (p=0.003 versus warfarin). A key finding of the RE-LY trial was a dramatic reduction in the rate of intracranial hemorrhage, the most dreaded complication of anticoagulant use, among patients randomized to dabigatran. Rates of hemorrhagic stroke were lower with both dabigatran 150 mg (0.10% per year; RR 0.26; p=0.001) and dabigatran 110 mg (0.12% per year; RR 0.31; p=0.001) compared with the warfarin group (0.38% per year). Dabigatran 150 mg was associated with a lower rate of major bleeding and

Figure 3: The coagulation cascade. Factors whose synthesis is affected by warfarin are depicted in red. The blue and green arrows illustrate steps in the cascade that are inhibited by anti-Xa agents and direct thrombin inhibitors.
life-threatening bleeding than warfarin, but there was a significantly higher rate of major gastrointestinal bleeding with dabigatran 150 mg (1.51% per year) than with warfarin (1.02% per year, p < 0.001). A trend towards higher bleeding risk was seen with advancing age, which became statistically significant with the 150-mg dabigatran dose in patients 80 years of age and older, and among patients with lower creatinine clearance. Among elderly patients, despite an increased risk of gastrointestinal bleeding, the authors reported that a net clinical benefit was still present. Gastrointestinal adverse events (e.g. dyspepsia, gastrointestinal hemorrhage, nausea) occurred more frequently with dabigatran versus warfarin (35% versus 24%) and were the most frequently reported adverse events resulting in treatment discontinuation. Annual rates of discontinuation due to dyspepsia were 2% for dabigatran 150 mg versus 0.6% for warfarin. The risk of dyspepsia with dabigatran was highest within the first few weeks of treatment.

The relationship between bleeding risk and age in the RE-LY trial was subsequently studied by Eikelboom et al. in a highly detailed subgroup analysis. Although, strictly speaking, subgroup analyses should be viewed only as hypothesis-generating, these data are, in our opinion, helpful. Among patients above 75 years of age in RE-LY, dabigatran 150 mg was associated with absolute annual risk reductions for stroke/systemic embolism and intracranial bleeding of 0.7% and 0.6% respectively, at the cost of an increased absolute annual risk of major bleeding of 1.2%. Gastrointestinal bleeding was more frequent with dabigatran 150 mg bid, with an annual absolute increase of 0.73%. Thus, for every 1000 patients above 75 years of age treated with dabigatran 150 mg instead of warfarin, a reduction of 13 events—seven thrombotic events and six intracranial hemorrhages—was achieved at the cost of 12 major bleeds. These numbers do indeed support the notion of a “net clinical benefit” among the elderly on dabigatran therapy. Of note, there is presently no available antidote for dabigatran.

Based upon the results of the RE-LY trial, dabigatran was the first medication to be approved by the FDA as an alternative to warfarin for the prevention of stroke and systemic embolism in patients with non-valvular AF. The 150 mg bid dosage was approved for patients with creatinine clearance above 30 ml/min, and a lower dosage of 75 mg bid was approved, based upon pharmacodynamic modeling, for patients with a creatinine clearance of 15–30 ml/min. The 110-mg formulation, which was found to be non-inferior to warfarin in the RE-LY trial, was not approved by the FDA. An update to the AHA/ACC/HRS guidelines was published shortly after FDA approval, with a class I recommendation for dabigatran use as an alternative to warfarin in non-valvular AF.

Factor Xa inhibitors

The second emerging class of medications for thromboembolism prevention in AF are the factor Xa inhibitors, which inhibit both free and protein-bound factor Xa, as well as phospholipid- and factor V-bound factor Xa. These agents are highly selective and possess high oral bioavailability and a rapid onset of action. They inhibit thrombin formation and therefore the formation of thrombi. Like oral DTIs, oral factor Xa inhibitors have a predictable pharmacokinetic profile, allowing for a fixed dosing schedule without the need for coagulation parameter monitoring. This class includes rivaroxaban, apixaban, edoxaban, betrixaban, TAK-442, and darexaban. Our review will focus upon rivaroxaban, which has received FDA approval, and apixaban, which is highly likely to receive FDA approval in the near future.

Rivaroxaban has a rapid onset of action and high oral bioavailability. It is 67% metabolized by the cytochrome P450 system, with one half of resultant metabolites directly eliminated renally and the other half by the fecal route. The remaining one-third of the drug is directly eliminated via the kidneys. There is no approved antidote for rivaroxaban, although prothrombin complex concentrate may be effective. As with dabigatran, the medication was approved by the FDA based upon a single large randomized trial: The Most Recent 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).

ROCKET-AF was a phase III, randomized, double-blind, double-dummy, event-driven, non-inferiority trial among high-risk patients with non-valvular AF. Patients were randomized to rivaroxaban 20 mg once daily (15 mg among patients with moderate renal impairment) or to dose-adjusted warfarin (target INR of 2.5). Patients in the trial were generally high risk, with 55% having suffered a prior stroke and 90% having hypertension. In addition, 90% of the patients had a CHADS2 score of 3 or higher, which was much higher than the CHADS2 scores among patients enrolled in comparable studies. The primary efficacy end point of ROCKET-AF was a composite of stroke or systemic embolism, and the primary safety end point was a composite of major and non-major clinically relevant bleeding. Of note, the study authors included both intention-to-treat and on-treatment analyses. This resulted from the consideration that non-inferiority trials are best interpreted via on-treatment analyses, but that conclusions of therapeutic superiority are more appropriately drawn based upon intention-to-treat. Unless otherwise stated, this review will focus upon the intention-to-treat analysis.

In ROCKET-AF, rivaroxaban was non-inferior to warfarin with regards to the primary end point of stroke or systemic embolism (2.1% per year versus 2.4%, HR 0.88, p = 0.117). There were similar rates of clinically relevant bleeding (20.7% versus 20.3%) and major bleeding (5.6% versus 5.4%). Rivaroxaban was associated with a statistically significantly higher rate of transfusion (1.6% versus 1.3%, p = 0.04) and decreased hemoglobin > 2 g/dl (2.8% versus 2.3%, p = 0.02), but lower rates of critical bleeding (0.8% versus 1.2%, p = 0.007), and fatal bleeding (0.2% versus 0.5%, p = 0.003) than warfarin. Interestingly, similar to the results observed with dabigatran, the rivaroxaban arm of the study was noted...
to have a statistically significant large reduction in the rate of hemorrhagic stroke (0.41% versus 0.71%, HR 0.57, p=0.024). In fact, when stroke outcomes were subanalyzed in ROCKET-AF, only hemorrhagic strokes, but not ischemic strokes, were observed to be significantly reduced by rivaroxaban compared with warfarin. The low 55% TTR in ROCKET-AF has been considered a potential weakness of the study; however, the authors noted that the relative benefit of the drug did not vary across quartiles of TTR according to study centers.

The authors also performed a prespecified superiority analysis over warfarin. Based upon a traditional intention-to-treat analysis, the medication was non-superior. However, in an on-therapy per-protocol analysis, the medication was found to be superior. Interpretation of these findings is of course challenging, as most clinicians do not accept on-therapy analyses as compelling evidence for clinical superiority. Whatever the case, the medication was clearly non-inferior to warfarin, establishing rivaroxaban as another acceptable alternative in patients who do not tolerate warfarin.

In ROCKET-AF, a significantly increased stroke rate was noted among patients who discontinued the medication and were subsequently transitioned back to warfarin. These events were included in the intention-to-treat analysis, which established non-inferiority, but not the on-treatment analysis, which was truncated 2 days after discontinuation and was significant for superiority. A total of 28 embolic events occurred in the study population within 30 days of end-of-study site notification: 22 in the rivaroxaban arm and six in the warfarin arm.69 Among rivaroxaban patients who were transitioned back to warfarin after the study ended, the median time to reach a therapeutic INR was an inexplicably long 13 days, as opposed to 3 days for the patients who were already on warfarin. Obviously, for the high-risk population studied in ROCKET-AF, this was problematic, and it provides an important context for the interpretation of the on-treatment and intention-to-treat analyses.70 It also underscores the risk of temporarily discontinuing anticoagulation, particularly rivaroxaban, among high-risk AF patients.

Apixaban is another selective reversible oral direct factor Xa inhibitor. It has a rapid onset of action and is metabolized by the kidney, liver (cytochrome P450), and intestine. Apixaban was initially evaluated for stroke prophylaxis in the AVERROES (Apixaban Versus Acetylsalicylic Acid to Prevent Strokes) trial, a double-blinded, randomized, multicenter, phase III trial of 5,599 patients in 36 countries.71 In this study, patients with AF and at least one risk factor for stroke who were ineligible for warfarin were randomized to either aspirin (81 to 324 mg/day) or apixaban (5 mg twice daily). The mean CHADS2 score was 2. There was a clinically significant reduction in stroke and systemic embolism in the apixaban arm (1.6% per year versus 3.5%, HR 0.45, p<0.001). There was a trend towards a decrease in mortality for apixaban (3.5% versus 4.4% per year, HR, 0.79; 95% CI 0.62–1.02; p=0.07). Apixaban did not significantly increase the risk of major bleeding compared with aspirin (1.4% versus 1.2%, HR 1.13; 95% CI 0.74–1.75; p=0.57) or intracranial bleeding (HR 0.85, p=0.69). Because of the favorable outcome, the study was terminated early. This study is the only AF trial to have ever demonstrated an anticoagulant to be superior to aspirin in a head-to-head comparison. If apixaban is eventually approved for AF, it will indeed be interesting to observe how revised guidelines will address aspirin therapy among lower-risk AF patients, since AVERROES found apixaban to be more effective than aspirin without additional bleeding risk. Similarly, the results of AVERROES and ACTIVE-W will need to be accommodated among higher-risk patients who are not candidates for warfarin.

ARISTOTLE (Apixaban for the Prevention of Stroke in Subjects with Atrial Fibrillation) was a landmark randomized, double-blind trial comparing the oral anti-Xa agent apixaban with warfarin in AF patients with at least one risk factor for stroke.59 The trial randomized 18,201 AF patients with at least one risk factor for stroke to apixaban (5 mg bid) or warfarin (target INR 2.0–3.0). The primary end point was stroke or systemic embolism, and the primary safety outcome was major bleeding. The median age of the study population was 70, and the mean CHADS2 score was 2.1. After a median follow-up of 1.8 years, apixaban was associated with reductions in the risk of stroke or systemic embolism, bleeding, and all-cause mortality.

In ARISTOTLE, apixaban reduced the risk of stroke or systemic embolism by 21% compared with warfarin (1.27% versus 1.60% per year; HR 0.79, 95% CI 0.66–0.95; p=0.01 for superiority). Apixaban also reduced major bleeding (2.1% versus 3.1%, HR 0.69, CI 0.6–0.8, p<0.001). The mortality trend originally observed in AVERROES was again seen and was observed to be significant, with a relative reduction of all-cause mortality by 11% (3.5% versus 3.9%, HR 0.89, CI 0.8–0.99, p=0.047). As with the other trials, a reduction in intracranial hemorrhage was again observed (0.24% versus 0.47%, HR 0.51; 95% CI 0.35–0.75; p<0.001) . In summary, apixaban was demonstrated to be superior to warfarin with respect to the rate of stroke or systemic embolism and also, importantly, mortality, and it caused less bleeding. These results, particularly the mortality data, were indeed compelling, and there is currently great enthusiasm regarding the future of Apixaban, which is not yet FDA-approved.

Comparing the trials

It is of course difficult to compare medications in the absence of direct head-to-head trials, and the most important conclusion one can draw from these trials is that excellent alternatives to warfarin have finally arrived. However, there are important similarities and differences between RE-LY, ROCKET-AF, and ARISTOTLE which are worthy of discussion. They are summarized in Table 1. The most important similarity among them is that all three studies showed a substantial and significant decrease in intracranial hemorrhage compared with warfarin therapy. In the case of ROCKET-AF and ARISTOTLE, this
whereas DTIs and anti-Xas do not (Figure 3) inhibiting production of VIIa, reduces the availability setting of vessel injury. It is possible that warfarin, by complexes serve an important hemostatic function in the receptor for factor VIIa in the brain, where TF–VIIa the RE-LY trial. Tissue factor (TF) is a transmembrane may be an important clinical consideration when choosing however, a reduction in ischemic stroke was also seen; this may be an important clinical consideration when choosing an agent for patients who have already suffered prior embolism. The mechanism of this reduction in intracranial hemorrhage among alternative agents is unknown, but an intriguing possible explanation is offered by Eikelbloom et al in their analysis of bleeding rates in the RE-LY trial. Tissue factor (TF) is a transmembrane receptor for factor VIIa in the brain, where TF–VIIa complexes serve an important hemostatic function in the setting of vessel injury. It is possible that warfarin, by inhibiting production of VIIa, reduces the availability of this important protective mechanism in the brain, whereas DTIs and anti-Xas do not (Figure 3).

Another important comparison between the studies pertains to bleeding risk. In RE-LY, although overall bleeding risk was not elevated with dabigatran 150 mg bid, there was an excess in major gastrointestinal bleeding. We believe that trial design played a partial role in this outcome. In RE-LY, "triple therapy"—concomitant anticoagulation with aspirin and clopidogrel—was permitted, unlike in the other two studies. Furthermore, clopidogrel was not permitted in ROCKET-AF, and it was used in only 2% of patients in ARISTOTLE versus 6% in RE-LY. Furthermore, ARISTOTLE AND ROCKET-AF utilized dose reductions among the elderly and among patients with reduced renal function, whereas RE-LY did not. This dosage strategy eventually became part of the prescribing information for rivaroxaban. These trial design issues may have played a role in the subtle differences in results among the trials. Ironically, the lower dose of dabigatran used in RE-LY (110 mg) would probably have provided an optimal balance of risk and benefit among the elderly and among patients with intermediate renal function because of an improved risk–benefit ratio, but the FDA did not approve it.

There were several other important differences between the trials. Firstly, the RE-LY trial was not blinded. This was an important shortcoming of the trial. Secondly, there was a much higher average CHADS2 score in ROCKET-AF than in the other trials; therefore, its results may be more applicable to patients at high risk of embolic stroke due to multiple risk factors. Thirdly, reductions in the primary end point observed in ROCKET-AF and ARISTOTLE were entirely explained by reductions in hemorrhagic stroke, with no observed reduction in embolic stroke, unlike RE-LY, in which reductions were seen in both outcomes. Finally, ARISTOTLE, unlike the other trials, detected a mortality benefit. Interestingly, a similar relative risk for mortality was seen in RE-LY, but the p-value was 0.051, whereas the p-value was 0.047 for ARISTOTLE. This means that the ARISTOTLE result had a one in 19.6 chance of being random, and was therefore not significant.

For the clinician, the decision whether to prescribe warfarin, dabigatran, or rivaroxaban to AF patients at risk for thromboembolism remains complex. The most common barrier to the use of the newer agents is cost. In addition, these agents have no known antidotes, and it is difficult to monitor compliance. Thus, some patients may not be appropriate for these medications. Unlike warfarin, the newer agents are subject to significant renal elimination and are therefore more challenging to prescribe to patients with borderline or variable renal function. For patients on triple therapy, there are as yet no compelling data to guide the choice of anticoagulant.

Table 1: Comparison of the three key studies of newer anticoagulants for atrial fibrillation

<table>
<thead>
<tr>
<th></th>
<th>Re-LY (150 mg)</th>
<th>Rocket-AF</th>
<th>ARISTOTLE</th>
</tr>
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<tbody>
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<td>Blinded</td>
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<td>Yes</td>
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<td>Rivaroxaban</td>
<td>Apixaban</td>
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<td>No</td>
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<tr>
<td>Average CHADS</td>
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<tr>
<td>Stroke or embolism (RR)</td>
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<td>0.79, non-inferior</td>
<td>0.79, superior</td>
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<tr>
<td>Mean TTR for warfarin arm</td>
<td>64%</td>
<td>55%</td>
<td>62%</td>
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<td>IC hemorrhage (RR)</td>
<td>0.72, significant</td>
<td>0.57, significant</td>
<td>0.51, significant</td>
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<tr>
<td>Embolic stroke</td>
<td>0.76, significant</td>
<td>NS</td>
<td>NS</td>
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<td>Death (RR)</td>
<td>0.88, p=0.051</td>
<td>NS</td>
<td>0.89, p=0.047</td>
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<td>Major bleeding (RR)</td>
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<td>0.69, p&lt;0.05</td>
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<td>Major GI bleeding (RR)</td>
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<td>MI</td>
<td>NS*</td>
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<td>“Claim to Fame”</td>
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<td>High-risk population</td>
<td>Mortality benefit</td>
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*Although the Re-LY manuscript reported a small but significant increased rate of myocardial infarction (MI) for the dabigatran arm (0.72% per year versus 0.53%, RR 1.35; CI 0.98–1.87, p=0.048), a subsequent audit of clinical data revealed additional events. Although a trend remained (0.81% versus 0.64%, RR 1.27, CI 0.94–1.71, p=0.12), the difference was found to be non-significant. However, it is important to note that the additional events were all due to new silent Q-waves, while the originally reported events were clinically apparent events. Although the absolute excess of MI events was small, this issue remains an area of potential concern, and a recently presented meta-analysis suggests that this may indeed be a DTI class effect.

DTI: direct thrombin inhibitor; IC: intracranial; GI: gastrointestinal; TTR: time in therapeutic range.
In the case of dabigatran, gastrointestinal intolerance can be a significant challenge. Among patients who require interventional electrophysiologic procedures, it is unknown whether the newer agents can be safely continued, although a limited literature suggests that brief discontinuation with enoxaparin or heparin bridging may be the best strategy for patients undergoing AF ablation who are treated with dabigatran.\textsuperscript{72–74} Finally, among patients who are well controlled on warfarin, there are as yet no compelling data supporting "switching" patients to a newer agent; this consideration is explicitly stated in current guidelines.\textsuperscript{62} On the other hand, as previously stated, these agents offer patients the promise of antithrombotic therapy without myriad dietary and medication interactions or the need for routine blood monitoring and resultant dosage adjustments. In the end, in our view, the most important consideration is that these new agents are all associated with significant reductions in the rate of intracranial hemorrhage without reductions in the rate of thrombotic events, compared with warfarin, making them extremely attractive to clinician and patient alike.

**Interventions targeting the left atrial appendage**

Because the vast majority of thromboembolic strokes in AF are due to thrombi which originate in the LAA, strategies of LAA occlusion, removal, and closure have been developed as possible alternatives to systemic anticoagulation.\textsuperscript{10} This strategy is intrinsically appealing, as it offers the promise of a reduction in embolic events without the need for anticoagulation, thus potentially avoiding the risk of bleeding as a side effect of therapy. Current AHA/ACC guidelines recommend surgical exclusion or obliteration of the LAA among patients undergoing mitral valve surgery or a surgical MAZE procedure.\textsuperscript{75,76} Surgical techniques have not been extensively studied, but there is an established risk of incomplete closure, residual recanalization, and ongoing risk of thromboembolism.\textsuperscript{77,78} A transesophageal echocardiography (TEE)-guided evaluation of three surgical techniques among 137 patients revealed that complete excision of the LAA was superior to either staple exclusion or suture exclusion, with incomplete closure in 0%, 73%, and 23%, of patients, respectively, and LAA thrombi in 41% of patients with incomplete closure.\textsuperscript{79} For this reason, we routinely perform a baseline TEE, to rule out LAA remnants and/or thrombi, among patients who have previously undergone surgical LAA closure prior to proceeding with cardioversion or left atrial ablation.

Several investigational percutaneous LAA occlusion procedures, in which occlusion devices are inserted transvenously and advanced to the left atrium via a transseptal approach, have been studied (Figure 4). The first such device, the PLAATO device, was studied in 111 patients with risk factors for stroke and a contraindication...
to anticoagulation. Device insertion was successful in 108 patients, and periprocedural complications included one death and three pericardiocentesis procedures. Patients subsequently received only antiplatelet therapy and no systemic anticoagulation. At an average follow-up of 9.8 months, two strokes occurred, which was a low rate for this high-risk population who did not receive anticoagulation.⁸⁰ A subsequent observational study of 64 patients who received the PLAATO device and were followed off anticoagulation for 5 years revealed an annual 3.8% rate of stroke or TIA despite an average CHADS² score ≥2 and an expected rate of stroke/TIA of 6.6% off anticoagulation. TEE revealed effective seal of the LAA in 98.2%.⁸¹ Despite these promising initial results, this device is no longer in development.

The Amplatzer septal occluder device, which is FDA-approved for the treatment of atrial septal defect, has also been evaluated as a LAA occlusion device in a small pilot trial of 16 patients with a history of contraindications to warfarin.⁸² No CVA or TIA was reported during an average 4-month follow up, and there was one device embolization requiring surgical removal. The device is currently under investigation in the Amplatzer Cardiac Plug trial, which will compare the device to warfarin.⁸³

The most extensively studied percutaneous left atrial appendage exclusion device is the WATCHMAN device, which is constructed of a nitinol frame and a permeable polyester fabric. The device was evaluated in the PROTECT-AF study,⁸⁴ a randomized trial comparing the WATCHMAN device to warfarin among 707 patients with a mean CHADS² score above 2. Patients who received the device were maintained on warfarin for at least 45 days, and anticoagulation was discontinued if TEE revealed effective LAA closure, which was defined as a residual flow less than 5 mm in diameter as detected by color Doppler imaging. The primary efficacy end point was a composite of stroke, systemic embolism, and cardiovascular death. The device was successfully inserted in 91% of attempted cases, and anticoagulation was discontinued among 92% of device recipients. The mean follow-up was 18 months.

On an intention to treat basis, the WATCHMAN device was found to be non-inferior with respect to the primary efficacy endpoint, with an event rate of three per 100 patient-years versus 4.9 per 100 patient-years for warfarin (RR 0.62, 95% CI 0.35–1.25). Among patients who actually received their assigned therapy, the event rates were more compelling, 1.9 versus 4.6 (RR 0.40, 95% CI 0.19–0.91). The rate of hemorrhagic stroke, as expected, was dramatically lower in the intervention group (0.1 versus 1.6, RR 0.09, CI 0–0.45). The rate of ischemic stroke was actually higher in the intervention group (2.2 versus 1.6, RR 1.34, CI 0.6–4.29), mainly due to periprocedural complications including air embolism. After the periprocedural time period, however, the trend was reversed. PROTECT-AF was an important and groundbreaking study, establishing proof of concept for the first time in a large patient population that the strategy of treating the LAA, rather than the coagulation cascade or a patient’s abnormal rhythm, was non-inferior to anticoagulation.

However, safety analysis of PROTECT-AF revealed an excess of events in the device arm of the trial, with 7.4% of device patients and 4.4% of warfarin patients meeting the primary safety endpoint of excessive bleeding or procedure-related complications (RR 1.69, 95% CI 1.01–3.19). An on-treatment analysis of PROTECT-AF revealed that the primary safety event rate was in fact lower in the intervention group than in the control group (RR 0.35, 95% CI 0.15–0.80). Importantly, more than half of the safety events in the intervention group occurred on the day of the procedure, and they were primarily due to pericardial effusion and air embolism. A substantial learning curve was observed, in which increased operator experience mitigated the up-front risk of device insertion, and this phenomenon was confirmed in a subsequent pooled analysis of over 1000 patients in PROTECT-AF combined with a continued access protocol.⁸⁵ This suggests that the observed up-front risks might be lowered through improvements in technique.

However, substantial concerns remain concerning procedural risk, particularly among new operators, and whether this device can be safely introduced into widespread use. Although an FDA advisory panel voted in favor of approval, the FDA subsequently withheld approval and required the manufacturer to conduct another trial including a substantial proportion of new centers to demonstrate mitigation of the learning curve and an acceptable procedural complication rate. This study, the PREVAIL trial, is currently nearing completion of enrollment.⁸⁶

As with surgical closure or exclusion, percutaneous transcatheter LAA occlusion is associated with a risk of incomplete closure and residual communication. This issue is of even greater potential concern for transcatheter devices than for surgical therapy because all device-treated patients are, by design, left with an intact LAA and the potential for communication. This issue has been well studied in the WATCHMAN population, and the recently reported results are encouraging.⁸⁷ TEE was performed at 3, 6, and 12 months. Residual communication, detected by color Doppler imaging, was present in one third of patients. This was graded as mild (<1 mm, 8%), moderate (1–3 mm, 60%), or severe (>3 mm, 32%). There was no association between residual flow and clinical events. In addition, there was no indication that continued anticoagulation use in such patients affected the low event rate. These results support the strategy, currently followed in PREVAIL,⁸⁶ of anticoagulation discontinuation among patients in whom follow-up echocardiography reveals a residual communication <5 mm.

Conclusions

We have entered a new era in the prevention of stroke due to AF. For over 60 years, only warfarin has been available. Although warfarin has proven to be highly effective in the prevention of embolism, its use is challenging and unpredictable, and clinicians have long hoped for more convenient agents with similar or
improved efficacy. We now have available dabigatran and rivaroxaban, which have been shown to be superior and non-inferior, respectively, to warfarin, and it is likely that apixaban will soon be approved. Mechanical strategies to isolate or eliminate the LAA hold great promise because they remove the need for anticoagulation and its attendant bleeding risk. All of these developments represent great progress in the treatment of patients with AF.

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