New Frontiers for Stroke Prevention in Atrial Fibrillation

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Key Words

Stroke prevention · Atrial fibrillation · Anticoagulation

Abstract

Atrial fibrillation (AF) is the most common sustained arrhythmia, affects over 2.5 million people in the USA and is responsible for one fifth of the 700,000 ischemic strokes per year. For the last 50 years, long-term anticoagulation with warfarin has been the most effective therapy for preventing stroke in patients with AF and other risk factors. However, many AF patients are poor candidates for this treatment, and management of the drug can be challenging. Such challenges include the need for frequent monitoring, interactions with food and other medications, variability in metabolism and a delayed onset of action. Antiplatelet therapy has also been evaluated, and though it is not as effective at preventing ischemic strokes, it may provide some benefit for patients who cannot tolerate warfarin. Recent clinical trials have tested pharmacologic alternatives to warfarin, and new treatment options have emerged. Of these alternatives, the direct oral thrombin inhibitor dabigatran and the oral factor Xa inhibitor rivaroxaban, which have minimal interactions and require no INR monitoring, have already been approved by the FDA. The field may soon be further expanded as the oral factor Xa inhibitor apixaban has shown promise in its recent phase 3 trial and is under consideration for FDA approval. Nonpharmacologic approaches to stroke prevention in AF are under development as well. These approaches focus on occlusion or ligation of the left atrial appendage, which is frequently the location of thrombus formation. While such

procedures have been done often during other cardiac surgeries, newer methods have focused on percutaneous techniques, including ones that may not require anticoagulation afterwards. In addition, new diagnostic modalities may detect paroxysmal AF with more sensitivity, potentially expanding the population to be treated and the potential impact of stroke preventive strategies on the population. This review provides a practical guide to current treatment and diagnostic options and focuses on emerging therapies.

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Introduction

Affecting nearly 2.5 million people, atrial fibrillation (AF) is the most common sustained arrhythmia encountered in clinical practice [1]. AF is independently associated with a 5-fold increased risk of stroke and, as such, is estimated to account for more than 140,000 instances of ischemic stroke per year in the USA [2–4]. Strokes that occur due to AF are particularly severe and disabling; therefore, stroke prevention is of great importance in this population [5, 6].

Anticoagulation with the vitamin K antagonist warfarin has been the optimal therapy for the prevention of stroke in moderate- to high-risk patients with AF. Pooled data from pivotal trials found that dose-adjusted warfarin reduced the risk of stroke by 68%, from an annual risk of 4.5% (placebo) to 1.4% (warfarin) [7]. In a similar patient population, aspirin showed a more modest effect, reducing the risk of stroke by a relative factor of 21% [8].

Other studies have extended these findings to the very elderly, a patient population frequently undertreated with warfarin [9].

Although warfarin is effective in preventing ischemic stroke in patients with moderate- to high-risk AF, its use can be challenging. Warfarin therapy is complicated by interactions with food and other drugs, variability in metabolism, a delayed onset of action and requirement for regular monitoring [10, 11]. The therapeutic index is narrow, with an increased risk of stroke when the INR falls below 2 and an increased risk of hemorrhage when the INR rises above 3 [12]. Patients who were monitored by specialized anticoagulation clinics were out of the therapeutic range about 37% of the time, and warfarin patients monitored in community-based settings were out of the therapeutic range 49% of the time [13, 14]. Warfarin-associated hemorrhage results in a mortality of 42% with another 34% of patients suffering from major disability [15]. While this risk is greater at INR values over 3.5, there is still a risk of intracerebral hemorrhage at therapeutic INR levels and even at subtherapeutic levels [16]. For these reasons and others, only half of the patients with AF who are appropriate candidates are prescribed warfarin in retrospective analyses of outpatient records [17, 18].

Alternatives to warfarin have been actively sought, and several will be reviewed here. Recent trials of alternate drug regimens, devices and interventions shed light on the promise and difficulties of these efforts. Other avenues of research are being pursued with respect to stroke and AF. A basic review of the pathophysiology of AF may serve as a foundation for these attempts.

Basic Mechanisms

AF causes stroke by formation of thrombus in the left atrium, usually the left atrial appendage (LAA), and subsequent embolism to the brain [19]. A growing body of evidence supports the link between AF and endothelial dysfunction, which may in part explain the relationship between AF, cardiovascular risk factors and stroke [20].

Endothelial dysfunction is a maladaptive state of endothelial cells, characterized by a constellation of impaired physiologic responses including: poor regulation of arterial tone, increased proinflammatory and prothrombotic mediators, overexpression of adhesion molecules and impaired endothelium-dependent vasodilation [20]. Experimental AF has been associated with these features and additionally enhanced platelet activation [20, 21]. Takahashi et al. [22] measured forearm blood

flow before and after acetylcholine (a vasodilator) in patients with AF and controls. They then repeated the measurements after cardioversion to sinus rhythm in the AF group. Compared with controls, they found smaller increases in forearm blood flow during the AF state. They subsequently noted improved responsiveness to acetylcholine after cardioversion to sinus rhythm. This observation suggests that the fibrillatory state is associated with systemic changes in vasoreactivity that may contribute to thrombus formation. Others have extended these findings, noting that when AF is accompanied by underlying comorbidities (such as diabetes and hypertension), the improvement in forearm blood flow after cardioversion is smaller than among those without comorbidities [23, 24].

Endothelial dysfunction may thus be particularly relevant in patients with other underlying disorders, such as hypertension and diabetes, and may offer some explanation as to why AF patients without other risk factors (i.e. those with 'lone AF') have a low risk of stroke. Because of this research, improved risk stratification schemes are already being pursued, which aim to more accurately delineate the risk of stroke. Markers of endothelial dysfunction such as von Willebrand's factor have been found to be elevated in AF patients as compared to patients with other forms of supraventricular tachyarrhythmias [25]. Levels of von Willebrand's factor have been used in risk stratification for AF patients and were shown to be an independent risk factor for adverse events in these patients [26].

Risk Factors

Major risk factors for stroke in the setting of AF include age greater than 75 years, congestive heart failure, hypertension, diabetes, smoking and other structural lesions of the heart [8]. Most prominently, patients with a prior stroke or transient ischemic attack (TIA) and AF face the highest risk, more than twice that of AF patients without such a history. These factors have been incorporated into risk stratification tools such as the commonly used CHADS₂ score (C = congestive heart failure, H = history of hypertension, A = age ≥ 75 years, D = diabetes, S = prior stroke or TIA). Stroke or prior TIA is assigned 2 points, while the other risk factors count for 1 point each. This 0- to 6-point scale can be used to quantify the patient's risk of stroke and thus guide decision making regarding the need for anticoagulation. As a CHADS₂ score of 2 is generally accepted as the level at which anticoagulation should be administered, it should be noted

that any patient with a history of stroke or TIA has automatically reached this threshold. More modest risk factors include female gender, and presence of coronary artery disease or peripheral vascular disease [27]. Age is a critical risk factor as the risk of stroke due to AF increases from an absolute risk of 2.2 for individuals aged 60–69 to 4.2 (ages 70–79) and 5.1 (ages 80–89) [28]. These additional factors are included in the scoring system CHA₂DS₂-VASc which also considers the presence of vascular disease (V), age between 65 and 74 years and female gender (Sc) [26]. This expanded scoring system is most useful at risk-stratifying those patients at the lower end of the CHADS₂ spectrums [29]. Additional risk factors include echocardiographic findings of complex aortic plaque or functional left atrial abnormalities, such as presence of thrombus, diminished peak blood flow velocities and dense spontaneous echo contrast [30].

The relationship between the duration of AF episodes and the risk of stroke is also a subject of increasing interest. Though paroxysmal and persistent AF have similar stroke risks, there is no clear threshold for the AF duration necessary to form a thrombus in the left atrium [8]. A period of 48 h has generally been accepted as the period before which cardioversion can be performed without the need for prior anticoagulation or transesophageal echocardiography, but studies of patients being continually monitored via their implanted cardiac rhythm management devices – i.e. pacemakers and defibrillators – render this threshold questionable.

Capucci et al. [31] studied 725 pacemaker patients with a history of atrial tachyarrhythmias, two thirds of whom were receiving antithrombotic therapy. The risk of embolism, adjusted for known risk factors, was increased 3-fold in patients with device-detected AF episodes longer than 24 h. The Mode Selection Trial studied 312 patients with permanent pacemakers and found that atrial tachyarrhythmias lasting more than 5 min were associated with a 2.8-fold increase in the risk of stroke [32]. A retrospective analysis of pacemaker patients by Botto et al. [33] found that patients at low risk (CHA₂DS₂ = 0) had a low risk of stroke regardless of their AF burden. Likewise, patients at a high risk (CHA₂DS₂ ≥ 3) have a high risk of stroke even with no documented AF. For the intermediate-risk group, however, the risk of stroke depended on the patient's AF burden as patients with more AF were found to have an increased risk of stroke. This study also compared traditional methods of monitoring patients for AF episodes with recordings from the implanted devices, noting that the occasional Holter monitoring typically done to assess AF burden had low sensitivity and poor

negative predictive value [33]. In sum, these studies highlight the uncertainty surrounding the minimum AF duration needed to cause a stroke and raise important questions as to the appropriate threshold for anticoagulation therapy in patients in whom the duration of AF can be reliably measured.

Antiplatelet Therapy as an Alternative to Warfarin

Warfarin has been shown to be superior to aspirin monotherapy as well as combination antiplatelet therapy of aspirin plus clopidogrel in preventing stroke and systemic embolism in patients with AF [34]. Some patients with AF and concomitant stroke risk factors may be unsuitable for anticoagulation because of refusal to comply with regular INR monitoring, fall risk or prior major hemorrhage due to an irreversible cause. For these patients, the standard therapy is aspirin, though aspirin has not been found to be superior to placebo [35]. The Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events compared aspirin with combined aspirin and clopidogrel in patients with AF who were judged to be warfarin ineligible [36]. The combination therapy resulted in a 0.9% decrease in the absolute risk of stroke and an increase in the risk of major bleeding (2.0 vs. 1.3%). Though this result suggests that the bleeding risks of combination therapy outweigh its benefits in most patients, such therapy may be sufficient in patients who are already receiving it following a coronary intervention, are at a lower stroke risk or are warfarin ineligible.

New Anticoagulants

Warfarin's many disadvantages have prompted a search for oral anticoagulants that are more predictable in their anticoagulant effects, easier to administer and potentially safer. Other oral vitamin K antagonists are being explored, as well as two alternate classes of anticoagulants: the direct thrombin inhibitors (DTIs) and factor Xa inhibitors. DTIs and factor Xa inhibitors have minimal drug and food interactions, and they require no dosage adjustments or hematologic monitoring.

Direct Thrombin Inhibitors

The DTIs include ximelagatran and dabigatran, the first new anticoagulant to receive FDA approval. The earliest member of this class to be studied extensively was ximelagatran. Ximelagatran was proven noninferior to

dose-adjusted warfarin, with a similar rate of major bleeding with the two treatments [37, 38]. However, the hepatotoxicity of ximelagatran led to its withdrawal prior to FDA review. The value of ximelagatran, however, was proof of principle that a DTI could be at least as effective as warfarin in high-risk AF patients, without the logistic drawbacks of warfarin.

More recently, the RE-LY (Randomized Evaluation of Long-Term Anticoagulant Therapy, Warfarin, Compared with Dabigatran) trial compared the DTI dabigatran with dose-adjusted warfarin in 18,113 patients with nonvalvular AF [39]. The end point was stroke (ischemic and hemorrhagic) and systemic embolism. Two doses of dabigatran were compared with warfarin and though the dose of dabigatran was double-blinded, assignment to warfarin or dabigatran was not blinded.

Low-dose dabigatran (110 mg twice daily) was shown to be noninferior to warfarin for the primary end point of all stroke and systemic embolism (1.53% per year for dabigatran vs. 1.69% per year for warfarin; p for noninferiority <0.001). High-dose dabigatran (150 mg twice daily) was superior to warfarin for the primary end point (1.11 vs. 1.69% per year; p for superiority <0.001). Most of the benefits of high-dose dabigatran over warfarin were for stroke prevention, with a 36% relative risk (RR) reduction in favor of the former ($p < 0.001$). Conversely, low-dose dabigatran demonstrated safety superior to that of warfarin, with significantly less major bleeding (2.71 vs. 3.36% per year; $p = 0.03$). The risk of major bleeding (intracranial and extracranial hemorrhage) with high-dose dabigatran was nonsignificantly lower than that with warfarin (3.11 vs. 3.36% per year; $p = 0.31$). Although all anticoagulant-associated bleeding has the potential to be life-threatening, anticoagulation-associated hemorrhagic stroke carries a 76% risk of death or permanent disability and is the most feared complication of this therapy [15]. Importantly, the risk of hemorrhagic stroke with both dosages of dabigatran was significantly lower than with warfarin (high-dose dabigatran vs. warfarin – RR reduction, 74%; low-dose dabigatran vs. warfarin – RR reduction, 69%), although the difference between the two doses was not statistically significant itself. There was a slightly higher, though statistically nonsignificant, risk of myocardial infarction in patients taking dabigatran than in those on warfarin (RR = 1.29, $p = 0.09$, and RR = 1.27, $p = 0.12$ for dabigatran, respectively), and there were more medication discontinuations with dabigatran than warfarin, which were largely the result of dyspepsia in patients receiving dabigatran [40].

A subsequent analysis of the RE-LY data regarding the bleeding risks associated with either dose of dabigatran demonstrated that rates of extracranial bleeding increased with age and were comparable to or slightly higher than the rates of extracranial bleeding with warfarin in patients over 75 years of age. Rates of intracranial bleeding, though, were significantly lower than with warfarin and were not affected by age (RR for 150 mg dabigatran compared to warfarin: 0.43 in patients under the age of 75 and 0.42 in patients 75 or older) [41].

A cost-effectiveness analysis of dabigatran compared to warfarin by Shah and Gage [42] concluded that dabigatran was cost-effective for patients at a high risk for ischemic strokes (defined as CHADS₂ ≥ 3). For patients at moderate risk of stroke (CHADS₂ ≥ 2), warfarin was more cost-effective provided that the time in the therapeutic range was greater than 57.1% [42]. This analysis determined that dabigatran was not cost-effective for patients with a CHADS₂ score of 1, though an analysis by Freeman et al. [43] concluded otherwise, primarily due to differences in their analyses. Both of these analyses were conducted based on cost data in the USA and therefore may not be applicable in other countries.

Based on the results of the RE-LY trial, dabigatran (Pradaxa, Boehringer-Ingelheim) was approved by the FDA in October 2010 for stroke prevention in patients with nonvalvular AF at a dose of 150 mg twice a day in patients with creatinine clearance >30 ml/min and 75 mg twice a day in patients with creatinine clearance between 15 and 30 ml/min. The 110-mg dose tested in the RE-LY trial was not approved for use in the USA as it did not improve the risk-benefit profile of dabigatran in any subgroup. Even among patients with moderate renal impairment, defined as creatinine clearance between 30 and 50 ml/min, the 150-mg dose of dabigatran was more effective than the 110-mg dose as it decreased the rate of strokes by almost half (1.3 vs. 2.4 events/100 patient-years) while not increasing the rate of major bleeding (5.3 vs. 5.7 events/100 patient-years) [44, 45]. However, the 110-mg dose is approved in most other countries, including all of Europe.

As a DTI, dabigatran has several lifestyle benefits as compared to warfarin in that it is not known to interact with any foods, has consistent dosing and does not require hematologic monitoring. It also has a much more rapid effect than warfarin, with an onset of action just 0.5–2 h and a half-life of 12–17 h [46]. Dabigatran has significant interactions with several antiarrhythmic drugs such as amiodarone and dronedarone. As the latter two inhibit the p -glycoprotein efflux transporter, concurrent

use with dabigatran may lead to high serum levels of dabigatran and patients should be monitored, though no dose adjustments are recommended at this time. In Europe, however, patients taking verapamil are recommended to receive the 110-mg dose of dabigatran. An advantage of warfarin over dabigatran is that there is currently no antidote to dabigatran, so in the case of severe hemorrhage or overdose, supportive therapy is the only option. Recently, however, an antibody has been under development that may in the future be an effective and rapid antidote for dabigatran [47].

New Vitamin K Antagonists

Tecarfarin is a novel oral vitamin K epoxide reductase antagonist [48]. It is a structural analog of warfarin, highly protein bound (99%) and metabolized by carboxylesterases in the hepatic microsomes. It has a mechanism of action identical to that of warfarin, though it differs substantially in that it is not metabolized by the CYP450 system. In theory then, it offers the possibility of effective anticoagulation that can be monitored by INR, but with fewer CYP450-mediated drug-drug and drug-food interactions. As such it is expected to surpass warfarin in the percentage of time in the therapeutic range. Trials have yet to compare it with warfarin.

Factor Xa Inhibitors

Two oral factor Xa inhibitors, rivaroxaban and apixaban, have recently been studied as alternatives to warfarin for stroke prevention in high-risk patients with AF. Both agents offer potential advantages over warfarin similar to those of DTIs, namely consistent dosing without significant food or drug interactions or the need for monitoring. Rivaroxaban was compared with warfarin in patients with high-risk AF in 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), a randomized, double-blind, double-dummy trial of 14,269 patients. The end point was any type of stroke or systemic embolism. A once daily dose of 20 mg rivaroxaban was compared with warfarin titrated to an INR of 2.5. Notably, the mean CHADS₂ score in this study was 3.5, much higher than for other studies in AF patients including RE-LY where the mean CHADS₂ score was 2.1 [49]. The ROCKET-AF trial demonstrated that rivaroxaban was noninferior to warfarin for the prevention of stroke or systemic embolism, but unlike dabigatran, rivaroxaban did not decrease the risk of ischemic stroke. The overall risk of bleeding, both major and nonmajor clinically rel-

evant bleeding, was comparable, but there was a decreased risk of intracranial and fatal bleeding in the rivaroxaban group [50].

Apixaban has been compared to aspirin in the study AVERROES (Apixaban versus Acetylsalicylic Acid to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment). This randomized double-blind study involved 5,599 patients with a mean CHADS₂ score of 2.0 and compared a twice daily dose of 5 mg apixaban with 81–324 mg aspirin. This trial was terminated early due to the clear benefit of apixaban over aspirin in reduction of strokes (0.45, 95% CI = 0.32–0.62, $p < 0.001$) in this population [51]. Apixaban has recently been compared to warfarin in the ARISTOTLE trial (Apixaban for the Prevention of Stroke in Subjects with Atrial Fibrillation). This trial involved 18,201 patients with a mean CHADS₂ of 2.1 and a median duration of 1.8 years of follow-up. Patients were randomized to a twice daily dose of apixaban (5 mg) or warfarin titrated to an INR of 2.0–3.0. Apixaban was found to be superior to warfarin for the prevention of stroke and systemic embolism (hazard ratio = 0.79, $p = 0.01$) while also demonstrating a decreased risk of bleeding (hazard ratio = 0.69, $p < 0.001$). Importantly, the rate of intracranial hemorrhage was significantly lower for apixaban (0.24 vs. 0.47% per year for warfarin, $p < 0.001$), and overall mortality was also reduced (hazard ratio = 0.89, $p = 0.047$) [52].

Several other factor Xa inhibitors are currently in development. Edoxaban (DU-176b) is currently in a phase 3 trial (ENGAGE-AF-TIMI 48; Global Study to Assess the Safety and Effectiveness of DU-176b versus Standard Practice of Dosing with Warfarin in Patients with Atrial Fibrillation) estimated to be completed in March 2012 [53, 54]. Betrixaban and YM150 have recently finished phase 2 trials [53].

Occlusion Devices

Autopsy studies suggest that more than 90% of cerebral emboli in patients with AF originate in the LAA [19]. For this reason, it is theoretically desirable to isolate the LAA from the circulation, presumably preventing embolism from this site, even after anticoagulation has been discontinued. Percutaneous devices deliverable via transseptal catheters have been developed for this purpose. For example, LAA closure with the Watchman device (Atri-tech, Plymouth, Minn., USA) was compared with warfarin in 707 high-risk AF patients; the patients were fol-

lowed up for the primary end point of stroke, cardiovascular death, or systemic embolism. There were fewer primary end points in the device arm than in the warfarin arm of this study, but the results were statistically nonsignificant. This result was sufficient to establish the device's noninferiority to warfarin. However, there were significantly more safety end points with device implantation, including pericardial effusion requiring drainage, and device embolization [55]. A review of the results from the nonrandomized Continued Access Protocol registry for the Watchman device showed a lower rate of complications such as pericardial effusion, suggesting that greater operator experience decreased the rate of major complications [56]. Additionally, patients who received the Watchman device remained on warfarin anticoagulation for at least 45 days after implantation. After 45 days, 14% of the patients had to continue warfarin, and 8% had to continue warfarin beyond 6 months because of incomplete closure of the LAA [55]. In a 6-year follow-up of 75 patients who had received the Watchman device, 91% remained off warfarin. In a total of 368 patient-years of follow-up, there were 2 embolic strokes (0.5% actual stroke rate), compared with the 5.75% rate that would be expected based on the mean CHADS₂ score of 1.8 for these patients [57].

Because of the requirement for at least short-term warfarin therapy after implantation of the device, LAA occlusion has not yet been an option for patients with contraindications to anticoagulation. Recently, the Watchman device was implanted in 92 patients unable to take warfarin in the ASA and Plavix registry. After implantation, these patients received clopidogrel for 6 months and lifelong aspirin. At 6 months of follow-up, 2 patients had experienced ischemic strokes, though imaging studies did not detect a thrombus on the device. Follow-up is ongoing, but the initial results suggest that implantation of the Watchman device may be possible even in a subset of patients who are unable to take anticoagulants [58].

A second type of LAA occlusion device, the Amplatzer Cardiac Plug (AGA, Minneapolis, Minn., USA) has been implanted in patients with contraindications to warfarin in Asia and Europe. Postimplantation treatment was 1–3 months of clopidogrel and lifelong aspirin. Initial results from the 19 patients who received the device in the Asia study showed no residual leakage around the device and no cases of stroke or systemic embolism at a mean follow-up of 12.7 months [59]. Of the 132 patients who received the device in Europe, there was a 7% rate of major complications including pericardial effusion and stroke. In view of the relatively high risk of

stroke during device implantation, Park et al. [60] concluded that Amplatzer implantation in patients with a CHADS₂ of 1 is not recommended as the rate of strokes during the procedure (2.0%) approaches the rate of strokes for that group in general (2.8%). For higher-risk patients, however, the Amplatzer device may prove beneficial, especially in those patients unable to take anticoagulation [60].

The role of LAA occlusion is unclear [61]. It may be a viable alternative to long-term anticoagulation in high-risk AF patients who can tolerate short-term anticoagulation but in whom long-term anticoagulation is unadvisable. Such patients might include those with cerebral amyloid angiopathy and high-risk AF or those with recent AF-associated ischemic stroke who have a very high risk of gastrointestinal hemorrhage. There is evidence that LAA occlusion devices may become neo-endothelialized over time, and anticoagulation may be safe to discontinue [62]. LAA closure may also be a viable treatment for patients with an absolute contraindication to any anticoagulation, but further research is necessary to confirm these hypotheses.

Surgical ligation and, in certain cases, amputation of the LAA has also been attempted. Given the invasiveness of the approach, it is limited to patients who are already undergoing open-heart surgery. One retrospective study of 205 patients with previous mitral valve replacement contained 58 patients who had undergone ligation of the left atrial appendage at the time of surgery [63]. In multivariate analysis, the only independent predictors of a future embolic event were absence of LAA ligation or presence of left atrial thrombus on echocardiography. The incidence of an embolic event among those with LAA ligation was significantly lower than among those without it (3 vs. 17%). Because of these findings, the 2006 American College of Cardiology/American Heart Association guidelines on the management of valvular heart disease recommended amputation of the LAA at the time of mitral valve surgery [64]. A recent analysis of multiple trials involving LAA ligation, however, is less optimistic as ligation is often incomplete, resulting in a substantial risk of strokes [65]. In the future, more effective methods of ligating the LAA could result in a decreased stroke risk.

One method currently being studied involves a minimally invasive thoroscopically guided endoloop snare and has been described in 15 patients with AF [66]. The authors note that the procedure was successful in 14 patients, while 1 had severe bleeding requiring open conversion. At a follow-up of 42 months, there were 2 strokes, a rate of 4% a year. Recently, percutaneous ligation of the LAA has

been accomplished using the LARIAT snare (SentreHeart Inc., Palo Alto, Calif., USA). In a study of 82 patients who underwent the procedure, ligation of the LAA was successfully performed in 78 of them, and 73/78 patients had acute closure of the LAA while the remaining 5 had a <3-mm jet identified by color flow Doppler sonography. At 1 month, 67/70 had complete closure and 3 patients had a <2-mm jet on Doppler sonography. At the 3-month follow-up, 37/37 patients had complete closure of the LAA. There were no device-related complications in this study, but several patients were excluded from the procedure due to having a superiorly oriented LAA, a thrombus in the LAA, or LAA size greater than 40 mm [67]. An earlier study involving the LARIAT snare encountered complications when performing the procedure on patients with pectus excavatum [68]. Use of the LARIAT snare did not require the patients to take anticoagulants, and a study of 10 AF patients intolerant to oral anticoagulants who underwent the procedure found no cases of postdevice thrombus in the early follow-up [69]. These results suggest that percutaneous closure of the LAA may in the future provide an alternative to oral anticoagulants for stroke prevention, but further studies are required.

Intermittent Antithrombotic Therapy

Alternate stroke prevention strategies are being developed that might spare patients with infrequent or short-lived paroxysms of AF the risks and inconveniences of continuous anticoagulation. These strategies are being examined in individuals with dual-chamber pacemakers, cardioverter-defibrillator and cardiac resynchronization therapy defibrillator devices. As current device technology allows for nearly real-time continuous remote monitoring, it is conceivable that patients with infrequent AF episodes may start and stop anticoagulation only around the time of an AF episode. This theory is currently being examined in the Impact of Biotronic Home Monitoring Guided Anticoagulation on Stroke Risk in Patients with Implanted Cardioverter-Defibrillator and Cardiac Resynchronization Therapy Defibrillator Devices study and the Tailored Anticoagulation for Noncontinuous AF trial [70].

Sinus Rhythm to Prevent Stroke

A final strategy to prevent strokes in AF patients is to maintain them in sinus rhythm ('rhythm control'). Although it seems logical that maintaining normal sinus

rhythm would result in a reduced risk of stroke, there are few data at this time to support this assumption. The issue is complicated by the fact that much AF is asymptomatic, symptoms are unreliable measures of rhythm control in those patients who do have them, antiarrhythmic drugs are often unsuccessful at maintaining sinus rhythm, and symptomatic episodes of AF can be converted into asymptomatic episodes by drug or ablation therapy [71]. Furthermore, external monitoring has limited sensitivity for detecting AF and long-term external monitoring of patients is impractical. These points underscore the unreliable nature of self-reported or periodic monitoring for recurrences of AF, making it difficult to determine whether a rhythm control strategy is effectively preventing AF. This caveat supports the current practice of continuing anticoagulation in most AF patients treated with a rhythm control strategy using antiarrhythmic agents. There is growing interest in the possibility that newer approaches to AF treatment may provide sufficient rhythm control to allow anticoagulation to be discontinued. If so, such treatments might be attractive alternatives for AF patients who are at risk for thromboemboli but are poor anticoagulation candidates. Pulmonary vein isolation procedures are being used increasingly for treating AF and may provide superior rhythm control compared with antiarrhythmic therapy [72]. Uncontrolled data suggest AF ablation may be associated with a decreased risk of stroke and may allow for the safe cessation of anticoagulation therapy in some patients [73, 74]. Newer antiarrhythmic agents have also been associated with a reduced risk of stroke [75]. In the A Trial with Dronedarone to Prevent Hospitalization or Death in Patients with Atrial Fibrillation study, dronedarone was found to reduce the risk of stroke in AF patients. Potential mechanisms for this reduction include decreasing blood pressure and lowering heart rate. Although it is possible that the reduction in strokes was due to the patients having better rhythm control, even patients who were often found to be in AF exhibited this decrease in stroke rate [75]. The efficacy of dronedarone for preventing cardiovascular events was being studied in the Permanent Atrial Fibrillation Outcome Study Using Dronedarone on Top of Standard Therapy, but this trial was terminated early due to an increase in cardiovascular events in this population [76]. These findings suggest that rhythm control with medication may not alone reduce the risk of stroke, but more definitive treatments such as ablation may allow for safe discontinuation of anticoagulants.

Conclusions

With the recent approval of dabigatran and rivaroxaban, patients with high-risk AF who can tolerate anticoagulation now have three options for stroke prevention. Warfarin, dabigatran and rivaroxaban each have individual risks and lifestyle benefits that must be considered with each patient.

However, for those unable or unwilling to use anticoagulants indefinitely, recent clinical trial data suggest that in some patients, the risk-benefit ratio may favor the combination of aspirin and clopidogrel, or percutaneous occlusion of the LAA, for better stroke prevention than aspirin monotherapy. The advent of less cumbersome,

more predictable and safer oral anticoagulants may decrease the proportion of high-risk AF patients unable to comply with anticoagulation therapy. Finally, new cardiac monitoring technology offers clinicians the ability to detect AF and offer selective anticoagulation. These advances improve the outlook for preventing both first and recurrent stroke in patients at risk for AF-related stroke.

Disclosure Statement

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