Texas Heart Institute Journal

Ali Massumi Cardiac Arrhythmia Symposium

Medical and Device Therapy for Stroke Prevention in Patients With Atrial Fibrillation

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Atrial fibrillation (AF) is the most common arrhythmia, affecting an estimated 2.2 million people in the United States (US) and 4.5 million people in the European Union.[1,2] It accounts for a third of hospitalizations for cardiac rhythm disturbances.[2] During the last 2 decades, as the population has aged and the incidence of chronic heart disease has increased, hospitalizations for AF have increased by 66%.[2] As a result, AF has been called a "disease of the elderly." Atrial fibrillation is responsible for 1 in 6 strokes in the general population and for 1 in 3 strokes in the elderly (≥65 yr).[1] Strokes related to AF are typically more severe than other types of stroke.[1]

Stroke and AF are strongly associated. Atrial fibrillation impairs atrial contraction, which can disrupt coordinated myocyte activity, thus promoting hemostasis and increasing thromboembolic risk. A stroke can trigger AF by disrupting cerebral autonomic centers. Also, AF has been associated with other factors that contribute to strokes, including hypertension, coronary heart disease, valvular heart disease, and heart failure. Atrial fibrillation commonly coexists with other atrial abnormalities, including impaired myocyte contractility, left atrial appendage (LAA) mechanical dysfunction, and chamber dilation.[3] The LAA, a trabeculated cul-de-sac, is where 90% of clots that cause AF-related stroke form.[4]

Preventing AF-related stroke is a major aspect of AF management. Warfarin and novel oral anticoagulants (NOACs) are very effective at preventing AF-related stroke.[5] When these agents are contraindicated or not tolerated, LAA closure is an option.[4] We review these and other current options for preventing stroke in patients with AF.

Anticoagulants

Warfarin

Anticoagulation with warfarin at a target international normalized ratio (INR) of 2.0 to 3.0 reduces stroke risk by 67%.[6] However, warfarin is used in only about half of appropriate candidates because of the need for serial monitoring, a slow onset of action, genetic variation in metabolism, multiple food and drug interactions, and a narrow therapeutic index,[7] as well as poor adherence by physicians to guidelines and by patients to treatment regimens.[8] The risk of major bleeding, which increases with age, is compounded by use of warfarin.[8]

Novel Oral Anticoagulants

Novel oral anticoagulants provide an alternative medical approach to stroke prevention in AF. Compared with warfarin, they are given on a fixed dosing schedule and need no monitoring; they also have a more rapid onset of action, no food and few drug interactions, and a broad therapeutic window.[9] However, NOACs have a short half-life.[9] Novel oral anticoagulants approved by the US Food and Drug Administration (FDA) include direct inhibitors of factor II (dabigatran) and factor Xa (rivaroxaban, apixaban, and edoxaban).[9]

★ ***CME Credit***

Citation:
Huang S, Safavi-Naeini P, Rasekh A. Medical and device therapy for stroke prevention in patients with atrial fibrillation. Tex Heart Inst J 2021;48(4):e217549. doi: 10.14503/THIJ-21-7549

Key words:
Anticoagulants/administration & dosage/therapeutic use; atrial appendage/therapy; atrial fibrillation/complications/therapy; factor Xa inhibitors; left atrial appendage/ligation; non-vitamin K antagonist oral anticoagulants; stroke/prevention & control/treatment outcome

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Dabigatran. Dabigatran, a direct, competitive inhibitor of factor IIa (thrombin), is administered as a prodrug. The prodrug is converted by serum esterase into its active form, which has a bioavailability of 6.5% and a serum half-life of 12 to 17 hours. Dabigatran is not metabolized by the cytochrome P450 system.[10] In the long-term RE-LY trial,[11] dabigatran was compared with warfarin. A 150-mg dose of dabigatran taken twice daily significantly reduced the rate of stroke without increasing major bleeding. A twice-daily dose at 110 mg did not affect the stroke rate but significantly reduced major bleeding. Both doses markedly reduced intracranial and life-threatening hemorrhage. Both also appeared to be free of liver and other toxicity, although they did increase the rates of dyspepsia and gastrointestinal bleeding.

Rivaroxaban. Rivaroxaban is a direct factor Xa inhibitor metabolized by the cytochrome P450 system, with a bioavailability of 70% and a serum half-life of 5 to 9 hours.[10] The ROCKET AF trial,[12] a double-blind noninferiority study, compared rivaroxaban and warfarin in 14,264 patients with nonvalvular AF at moderate risk of stroke. Rivaroxaban was noninferior to warfarin in preventing stroke and non–central nervous system embolism. In an intention-to-treat analysis, rivaroxaban was noninferior to warfarin but did not achieve superiority. However, in an analysis of patients who received at least one dose of a study drug and were monitored for events during treatment, rivaroxaban was superior. Both drugs were associated with similar rates of bleeding and adverse events, although rivaroxaban was associated with less frequent intracranial hemorrhage and fatal bleeding.

Apixaban. Apixaban is a direct factor Xa inhibitor metabolized by the cytochrome P450 system, with a bioavailability of 50% and a serum half-life of 8 to 15 hours.[10] In the randomized phase 3 ARISTOTLE trial,[13] the efficacy of apixaban was compared with that of warfarin in preventing stroke. Apixaban significantly reduced the rates of stroke and systemic embolism by 21% (P=0.01), major bleeding by 31% (P <0.001), and death by 11% (P=0.047). Apixaban had consistent effects across all major subgroups; it was also better tolerated and discontinued less frequently than warfarin.

Edoxaban. Edoxaban is a direct factor Xa inhibitor. In a double-blind, double-dummy trial in 21,105 patients with AF,[14] edoxaban was noninferior to warfarin in preventing stroke and systemic embolic events. Both high-dose (60 mg/d) and low-dose (30 mg/d) edoxaban significantly reduced the frequency of major bleeding, intracranial hemorrhage, hemorrhagic stroke, and cardiovascular (CV) death. Overall, edoxaban therapy resulted in superior net clinical outcomes with no increase in stroke or bleeding during the transition to an oral anticoagulant (OAC) at the end of the trial.[14]

Left Atrial Appendage Closure

Several LAA closure devices have been developed over the years, ranging from first- and next-generation closure devices to epicardial catheter–based devices. In addition, several clinical studies have evaluated LAA closure in patients with and without contraindications to OACs.

Endocardial Devices

First-generation devices include the Percutaneous LAA Transcatheter Occlusion System (PLAATO) (ev3 Inc.), the Watchman Left Atrial Appendage Closure Implant (Boston Scientific Corporation), and the Amplatzer Cardiac Plug (Abbott).[15] The PLAATO, the first endocardial LAA closure device, is no longer commercially available. The Watchman, designed to provide flexibility, control, and sealing, can treat a wide range of patient anatomies. As of 15 February 2020, the Watchman and the Watchman FLX were the only LAA closure devices approved by the FDA for use in the US.[15]

Next-generation endocardial closure devices include the WaveCrest Left Atrial Appendage Occlusion System (Coherex Medical, Inc.), the LAmbre LAA Closure System (Lifetech Scientific Corporation), and the Occlutech LAA Occluder (Occlutech International AB).[15] The WaveCrest has retractable anchors, which enable safer repositioning. Approved in Europe, it is still under investigation for approval in the US.

Epicardial Catheter–Based Devices

Epicardial catheter–based LAA closure devices include the Lariat Suture Delivery System (AtriCure, Inc.)[15] and the Sierra Ligation System (Aegis Medical Innovations).[16] The Lariat combines endocardial and epicardial approaches to AF management. It is commercially available outside the US and available under an FDA-approved continued-access protocol in the US. The ongoing aMAZE trial continues to evaluate the safety and efficacy of the Lariat while its premarket approval application is under review.[17] The Sierra uses a strictly epicardial approach and is currently under investigation for approval in the US and Canada.[16]

Left Atrial Appendage Closure Without Contraindications to Anticoagulant Use

PROTECT AF. The prospective, randomized PROTECT AF trial[7] evaluated whether the Watchman was noninferior to anticoagulation with warfarin in patients with no contraindications to OACs. After 5 years of follow-up, the device was superior to warfarin in preventing the primary composite efficacy endpoint of stroke, CV death, and systemic embolism, as well as all-cause and CV death. Procedural complications and major bleeding occurred at similar rates in both treatment groups, but usually occurred earlier after de-

vice treatment. Concerns raised by the PROTECT AF study include a high initial rate of procedural complications, failure of device implant in some patients, and low $CHADS_2$ scores.[7]

PREVAIL. The PREVAIL trial[18] demonstrated the superior efficacy, reduced mortality, and similar overall safety of the Watchman procedure for LAA closure when compared with warfarin.

5-Year Outcomes. A meta-analysis of 5-year follow-up data from the PROTECT AF and PREVAIL trials[19] showed that treatment with the Watchman device resulted in a similar rate of all-cause stroke and a lower rate of CV deaths when compared with warfarin. The Watchman was also associated with substantially lower bleeding-related costs in OAC-eligible populations.[19]

Left Atrial Appendage Closure With Contraindications to Anticoagulant Use

Separate multicenter, prospective studies of the PLAATO[20] and Watchman[21] devices showed that each significantly reduced the rates of stroke and ischemic attack in patients with contraindications to OACs. The PLAATO device effected a 59% reduction in annual risk of stroke or transient ischemic attack (TIA)[20]; the Watchman device, a 77% reduction.[21]

In several studies, the outcomes of LAA occlusion with the Amplatzer Cardiac Plug have been assessed. Tzikas and colleagues[22] compared stroke and bleeding risk after treatment in 198 patients with previous intracranial bleeding and AF. They observed a significant reduction in the risk of stroke and TIA (75%) and major bleeding (89%) at an average follow-up time of 1.3 years. Freixa and associates[23] evaluated stroke severity after LAA occlusion in 1,001 patients who had an absolute or relative contraindication to OACs. The annual stroke rate was 0.8%, and most strokes (81%) were nondisabling. Kefer and colleagues[24] evaluated the safety and efficacy of LAA occlusion in preventing stroke in 375 patients with chronic kidney disease (defined as a glomerular filtration rate <60) and AF. Regardless of disease stage, the occlusion procedure was safe and markedly reduced the frequency of persistent stroke and TIA.

Interventional Treatment Versus Novel Oral Anticoagulants in High-Risk Patients

In the PRAGUE-17 study,[25] an investigator-initiated, multicenter, open-label, randomized trial conducted in 10 Czech cardiac centers, LAA closure was evaluated for its noninferiority to NOACs. The trial's primary composite endpoint was stroke, TIA, systemic embolism, CV death, clinically significant bleeding, and periprocedural or device-related complications. In the LAA-closure arm, 187 patients were treated with the Amplatzer Amulet (Abbott), Watchman, or Watchman FLX device. In the NOAC arm, 192 patients received apixaban. Among high-risk patients with AF, LAA closure was noninferior to NOACs in preventing major CV or neurologic events. However, safety issues related to the closure procedure revealed the need for improvements in device technology and operator technique. Moreover, the PRAGUE-17 trial was insufficiently powered to evaluate separately differences in the efficacy and safety components of the primary composite endpoint. Larger trials comparing LAA closure and NOACs are warranted.

Ongoing Studies

CATALYST. The purpose of the prospective, randomized, multicenter CATALYST study[26] is to evaluate the safety and effectiveness of LAA closure with the Amplatzer Amulet device versus NOACs in a planned population of 2,650 patients with nonvalvular AF. The choice of NOAC is at the physician's discretion.

CHAMPION-AF. This prospective, multicenter randomized trial[27] is designed to evaluate whether LAA closure with the Watchman FLX device is an acceptable alternative to non-vitamin K oral anticoagulants in patients with nonvalvular AF. This study will recruit approximately 3,000 patients with a CHA_2DS_2-VASc score ≥2 from approximately 150 global sites.

Device Approval Status

The Watchman and Watchman FLX are the only LAA closure devices approved for LAA exclusion in the US. As of 15 February 2020, the Amplatzer Cardiac Plug and WaveCrest devices were under investigation in clinical trials in the US. No devices have been approved for use in the US in patients with AF and an absolute contraindication to OACs.

Published: 15 October 2021

Section editor: Mohammad Saeed, MD, FACC

Meeting presentation: Presented at The Ali Massumi Cardiac Arrhythmia Symposium; Houston, 15 February 2020.

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