Editorial

Secondary Stroke Prevention in Atrial Fibrillation
New Insights Into an Old Problem

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The detection and treatment of nonvalvular atrial fibrillation (NVAF) constitute areas of active research yielding novel technologies that result in lively debates among general medicine, cardiology, and neurology specialists. Non–vitamin K antagonist oral anticoagulants (NOAC), approved by Food and Drug Administration (FDA) within the first half of this decade, have been increasingly adopted as first-line agents for stroke prevention in NVAF.[1] These medications have shown noninferiority for stroke prevention against warfarin arms with suboptimal international normalized ratio control in patient populations with low mean embolic risk scores for ≈2 years of follow-up. Except ROCKET-AF (Rivaroxaban; The Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation) that enrolled a large patient population (55%) presenting after an ischemic stroke or transient ischemic attack, the phase III studies of NOACs mostly included primary prevention cohorts (≈80%).[2] The mean time in therapeutic range of patients enrolled in warfarin arms of the 3 most commonly used NOACs was in the 55% to 62% range (rivaroxaban, dabigatran, and apixaban). Comparing NOACs to warfarin in that setting suggested equivalent benefit for embolic prevention and a lower risk of intracerebral hemorrhage (ICH) favoring NOACs in patients who were at low ICH risk during study enrollment. Real-world experience with NOACs has been positive to date when used in patient populations similar to their phase III studies, that is, patients with good kidney function, no prior history of ICH, and no perceived high risk for major hemorrhage. A specific reversal agent for dabigatran was FDA approved for use in emergency procedures or in uncontrolled bleeding, and another drug is awaiting approval for the more commonly used Factor Xa inhibitors. These are good news as reversal of anticoagulation can make a difference for large-volume hemorrhages, such as gastrointestinal bleeds, although it is unlikely that we will ever see good quality data from adequately powered randomized controlled trials (RCT) regarding their clinical efficacy, especially for ICH. The overall experience with NOACs is increasing. Rapid onset of action, fewer drug/food interactions, the lack of need for blood draws/monitoring are other advantages of NOACs. Despite concerns of high cost, compliance issues, elevated risk of gastrointestinal hemorrhage, and the inconvenience of lifelong anticoagulant use with its associated risks, these medications now constitute the first-line drugs for stroke prophylaxis in NVAF.[1]

The NVAF patients managed by general and vascular neurologists constitute a special group. Stroke doctors rarely see a noncomplicated NVAF patient to discuss primary prevention strategies. Instead, the NVAF patients evaluated by the majority of the readers of *Stroke* typically have suffered an embolic stroke or transient ischemic attack with or without oral anticoagulant use. Another major category is the patient population with NVAF at high ICH risk, either the lucky patients who have been able to survive an ICH or a much larger group who were found to have risk markers of ICH including but not limited to brain microbleeds, cortical superficial siderosis, or leukoaraiosis on magnetic resonance imaging. Many of the NVAF patients seen by neurologists are frail, not uncommonly with some cognitive or motor problems with fall risk. These issues further increase hemorrhagic risk and make strict compliance more difficult. I commonly get the following question during meetings from well-meaning non-neurologist colleagues: "if ICH is such a big problem, why don't we see these patients more often?". The answer is simple: >50% of patients who sustain an anticoagulant-related ICH die within the first 3 months, and only ≈20% of them are independent in activities of daily living.[2] Based on unbiased RCT data, the outcomes of NOAC-related ICH are no better, with mortality rates >45% for both apixaban- and rivaroxaban-related ICHs, the 2 most commonly used NOACs. At a time when the NOAC trials smartly exclude not only patients with past history of ICH but also patients with any feature that might constitute a high ICH risk from these studies, the stroke neurologists should be familiar with different management options for their NVAF patients who commonly have high embolic and hemorrhagic risks.

One stroke prophylaxis alternative that obviates the need for lifelong anticoagulation in NVAF is left atrial appendage closure (LAAC). Based on the data showing that >90% of thrombi originate from the left atrial appendage in NVAF, procedures that can exclude this unused cardiac appendix were developed. There are different LAAC devices and procedures each with particular advantages and disadvantages. WATCHMAN (a nitinol cage device from Boston Scientific, Marlborough, MA) and AMPLATZER AMULET (a nitinol plug from St Jude Medical/Abbott, Minneapolis, MN) require pure endovascular procedures for LAAC. The LARIAT suture delivery system (SentreHeart, Redwood City, CA) uses a hybrid endovascular and epicardial approach to exclude left

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atrial appendage from the outside. Finally, the AtriClip LAA Occlusion System (AtriCure, Inc, West Chester, OH) uses a clip during open cardiac surgeries to exclude left atrial appendage externally. Among these devices/procedures, WATCHMAN is the only one that was tested against warfarin in RCTs for clinical end points of stroke/embolism prevention in NVAF. The PROTECT AF study (WATCHMAN Left Atrial Appendage System for Embolic Protection in Patients With Atrial Fibrillation) was performed in a NVAF population similar to NOAC studies, with a mean $CHADS_2$ of 2.2 (congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke [double weight]) and 19% of patients with prior ischemic stroke or transient ischemic attack, but none had a prior ICH. Despite relatively high procedural complication rates during early phases of operator formation, the PROTECT AF study showed noninferiority of WATCHMAN against an average performing warfarin arm (mean time in therapeutic range 66%). Specifically, the ischemic stroke rates were similar, but ICH risk was decreased by 91% in the WATCHMAN arm compared with warfarin.[3] Cardiovascular and unexplained death rates were also significantly lower for WATCHMAN arm, rate ratio 0.26 (95% credible interval 0.08–0.77). Further follow-up of this trial population for a mean duration of 3.8 years showed superiority of WATCHMAN against warfarin.[2] Because of the high procedural complication rates in PROTECT AF, FDA mandated another RCT, also requiring the enrollment of a higher embolic risk population. The PREVAIL study (Prospective Randomized Evaluation of the WATCHMEN Left Atrial Appendage Closure Device in Patients With Atrial Fibrillation Versus Long-Term Warfarin Therapy), that used a Bayesian design, enrolled a smaller number of patients but with higher embolic risks (28% with past stroke/transient ischemic attack, mean CHA_2DS_2-VASc of 4; congestive heart failure, hypertension, age ≥75 years [double weight], diabetes mellitus, stroke [double weight],vascular disease [coronary artery disease, peripheral artery disease, aortic atherosclerosis], age 65-74 years, and female sex).[4] One interesting result was that only 1 out of 138 patients enrolled in the warfarin arm had an ischemic stroke. Mainly because of this overperforming warfarin arm, this trial failed to show noninferiority of WATCHMAN against warfarin, failing one of the 3 predetermined coprimary end points. The other 2 coprimary end points were successfully achieved, stroke >7 days postrandomization for efficacy and the prespecified safety performance goals. The warfarin arm of PREVAIL continued to perform perfectly well in longer follow-up, making one wonder whether any NOAC could have achieved noninferiority if their warfarin arms did similarly to PREVAIL in terms of stroke prevention. PROTECT AF and PREVAIL were performed in the United States, whereas only up to 35% to 40% of NOAC RCT enrollment were from the North America and Western Europe. Not unexpectedly, most of the data showing superiority of NOACs over warfarin come from the groups of participants from Asia and Latin America, whenever these subgroup analyses are provided. These facts are important to keep in mind whenever one evaluates the potential benefits of a novel therapeutic tested against an existing agent, such as warfarin, that requires meticulous dose adjustments to maintain a good benefit–risk ratio.

Based on the pivotal studies and other registry-based data, FDA approved WATCHMAN as a stroke prevention option in NVAF patients who are candidates for oral anticoagulants but who have a rationale to avoid their long-term use. LAAC with WATCHMAN is increasingly used for the FDA-approved indications, and the safety of the procedure has improved significantly based on data obtained from prospective US and European postmarketing registries.[2] LAAC still requires an intervention, so concerns about proper patient selection remain in view of both procedural success/complication issues and long-term outcomes. To date, there had been no RCT directly comparing LAAC to NOACs. The study by Reddy et al[5] in this issue of the journal provides important insights in selection of optimal secondary stroke prevention approach in NVAF patients. The authors built a detailed Markov decision model using a 70-year-old stroke survivor with a CHA_2DS_2-VASc score of 7 (annual stroke risk 9.60%) and a HAS-BLED score of 3 (annual bleeding risk 3.74%; hypertension, abnormal renal and liver function, stroke, bleeding, labile INR, elderly, drugs or alcohol) as the base case. This is a case scenario matching the average patient population seen in stroke clinics. Data from the secondary prevention subgroup analyses of the NOAC and LAAC pivotal trials were used for these analyses, whereas costs were calculated from 2016 US Medicare reimbursement rates. As expected, upfront procedure costs make WATCHMAN LAAC more expensive during the first few years, but then LAAC achieves cost-effectiveness in 5 to 6 years compared with both warfarin and NOACs. At 10 years, LAAC provides more quality-adjusted life years and lower costs compared with warfarin/NOACs and remains as the better strategy over the lifetime analysis.

This article adds valuable insights to our understanding of secondary stroke prevention strategies in NVAF. The FDA labeling of WATCHMAN suggests preferential benefit in patients who have a higher than usual hemorrhagic risk with long-term anticoagulation.[2] The current analysis shows that LAAC might be a viable option in NVAF patients even at high embolic and low-to-moderate bleeding risks. The problems associated with the need for lifelong strict compliance with NOACs (increasing hemorrhagic risks with aging, heightened embolic risk even when 1–2 doses are missed) should be compared with the operator dependence of LAAC (periprocedural complication risks) when discussing optimal prevention strategies. We will need carefully designed RCTs that include head to head comparison of NOACs and LAAC in well-characterized NVAF patient populations to better clarify the merits of these treatments. While such data are awaited, the stroke neurologists should become familiar with strengths and weaknesses of the available options to hold informed shared decision-making discussions with patients, cardiologists, and other specialists.

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Disclosures

None.

References

1. Steffel J, Verhamme P, Potpara TS, Albaladejo P, Antz M, Desteghe L, et al. The 2018 European Heart Rhythm Association practical guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation. *Eur Heart J*. 2018;39:1330–1393. doi: 10.1093/eurheartj/ehy136.
2. Gurol ME. Nonpharmacological management of atrial fibrillation in patients at high intracranial hemorrhage risk. *Stroke*. 2018;49:247–254. doi: 10.1161/STROKEAHA.117.017081.
3. Holmes DR, Reddy VY, Turi ZG, Doshi SK, Sievert H, Buchbinder M, et al; PROTECT AF Investigators. Percutaneous closure of the left atrial appendage versus warfarin therapy for prevention of stroke in patients with atrial fibrillation: a randomised non-inferiority trial. *Lancet*. 2009;374:534–542. doi: 10.1016/S0140-6736(09)61343-X.
4. Holmes DR Jr, Kar S, Price MJ, Whisenant B, Sievert H, Doshi SK, et al. Prospective randomized evaluation of the Watchman Left Atrial Appendage Closure device in patients with atrial fibrillation versus long-term warfarin therapy: the PREVAIL trial. *J Am Coll Cardiol*. 2014;64:1–12. doi: 10.1016/j.jacc.2014.04.029.
5. Reddy VY, Akehurst RL, Amorosi SL, Gavaghan MB, Hertz DS, Holmes DR Jr. Cost-effectiveness of left atrial appendage closure with the Watchman device compared with warfarin or non–vitamin K antagonist oral anticoagulants for secondary prevention in nonvalvular atrial fibrillation. *Stroke*. 2018;49:xxx–xxx. doi: 10.1161/STROKEAHA.117.018825.

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