**Left Atrial Appendage Closure for Stroke Prevention in Atrial Fibrillation**

**Response to an Unmet Need With an Unclear Direction**

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Stroke is the fourth leading cause of death in the United States. Atrial fibrillation (AF) increases the risk of ischemic stroke 5-fold.1 Strokes associated with AF are more severe when compared with non-AF strokes with a 30-day mortality of 25%.2 As such, a crucial component of AF management is stroke prevention. Oral anticoagulation therapy with warfarin effectively reduces the rate of stroke by 64% when compared with placebo and by 37% when compared with antiplatelet agents alone.3 Non–vitamin K antagonist oral anticoagulants have been shown to dramatically reduce the risk of intracranial hemorrhage when compared with warfarin and are guideline-sanctioned alternatives.4–6 However, similar or higher rates of gastrointestinal hemorrhage and medication adherence constitute longer term challenges with anticoagulant drugs. An alternative method of stroke prevention is needed for high-risk patients with refractory bleeding, untenable bleeding risk,7 or persistent medication nonadherence despite multiple interventions.

The rationale behind left atrial appendage (LAA) closure stems from the observation that among individuals in whom left atrial thrombus can be visualized, 90% are located in the LAA.8 The Watchman Left Atrial Appendage System for Embolic Protection in Patients with Atrial Fibrillation (PROTECT AF) trial demonstrated the device to be noninferior to warfarin for the primary efficacy end point comprised ischemic and hemorrhagic stroke, cardiovascular or unexplained death, or systemic embolism (3.0 for the device versus 4.9 for warfarin; rate ratio, 1.21; 95% confidence interval, 0.69–2.05) and no longer met its second primary end point of ischemic stroke or systemic embolism 8 days after randomization (18-month rate, 0.065 for the device versus 0.057 for warfarin; rate ratio, 1.2; 95% confidence interval, 0.69–2.05) and no longer met its second primary end point of ischemic and hemorrhagic stroke, cardiovascular or unexplained death, or systemic embolism (3.0 for the device versus 4.9 for warfarin per 100 patient-years, rate ratio, 0.62; 95% confidence interval, 0.35–1.25).9,10 However, the trial had several limitations, and the device was not approved by the Food and Drug Administration.11–13 The efficacy data in the trial were confounded by the different extent of antithrombotic use in both treatment arms. Although the device is intended for the use in high-risk patients with contraindications to oral anticoagulant therapy, warfarin eligibility was a trial inclusion criterion and nearly one third of the enrolled patients had a CHADS2 score of 1. In addition, periprocedural complications (eg, pericardial effusion with cardiac tamponade, cardiac perforation, device embolization leading to explantation, and procedure-related ischemic stroke) raised serious questions on device safety.

The Prospective Randomized (2:1) Evaluation of the Watchman LAA Closure Device in Patients with Atrial Fibrillation Versus Long Term Warfarin Therapy (PREVAIL) trial was designed to address limitations of the previous trials with 3 coprimary end points.14 The trial randomized patients with CHADS2 score ≥2 or CHADS2 score of 1 with additional risk factors, eg, female sex, age 65 to 74 years with either diabetes mellitus or coronary disease, to the device (n=269) or warfarin (n=138). Mean follow-up was 25.9±9.7 months.15 The results presented at the October 2014 meeting of the Food and Drug Administration panel included a total of 13 ischemic strokes in the Watchman group (1 within 7 days of implantation) versus 1 in the warfarin group.15 The study did not meet its first primary end point of ischemic and hemorrhagic stroke, cardiovascular or unexplained death, or systemic embolism (18-month rate, 0.065 for the device versus 0.057 for warfarin; rate ratio, 1.21; 95% confidence interval, 0.69–2.05) and no longer met its second primary end point of ischemic stroke or systemic embolism 8 days after randomization (18-month rate, 0.029 for the device versus 0.013 for warfarin; rate ratio, 2.8; 95% confidence interval, 0.9–7.3). Of particular concern was the occurrence of late ischemic strokes (10 observed >1 year post device implantation), which raised the question about the long-term efficacy of stroke prevention with the device.

In this issue, Badhke et al16 report the rates of adverse outcomes associated with percutaneous LAA closure in clinical practice across the United States. Using the Nationwide Inpatient Sample database from 2006 to 2010, the authors report a 24% complication rate, >10-fold higher than the complication rates reported in the PREVAIL trial14 and submitted to the Food and Drug Administration.13 An objective interpretation of this rate requires scrutiny of the study’s methodology. Of the patients included in this retrospective cohort, 18% were admitted on an emergent or urgent basis (28% of patients were missing this important data element). Therefore, it is difficult, if not impossible, to discern attribution of complications to the procedure or underlying clinical condition that prompted urgent admission. The indication for LAA occlusion in these settings is not provided. In addition, administrative data obscure temporal relationships so it is difficult to establish causative associations. These points are particularly salient given the broad spectrum of nontrial
designated complications included in the rate calculation, eg, respiratory complications, renal and metabolic complications, postoperative arrhythmias. Because none of these International Classification of Disease-Ninth revision coded events is independently adjudicated and validated, inclusion of more subjective events such as transient ischemic attack is an additional limitation. Inclusion of hemorrhage is also problematic as the laboratory, blood bank, or hemodynamic elements to determine severity, ie, decrement in hemoglobin or number of packed cells transfused, are not available in these datasets. For comparative purposes, it would be most informative to restrict analyses to trial protocol and Food and Drug Administration defined complications in the elective population. For example, in the PREVAIL trial, the third coprimary end point was a composite of early adverse events, including open cardiac surgery or major endovascular interventions.14 The trial reported a 2.2% rate of early adverse events that included device embolization, arteriovenous fistula, cardiac perforation, pericardial effusion with cardiac tamponade, and major hemorrhage requiring transfusion. Even with the use of broader definitions to include ischemic stroke and other vascular complications, the complication rate is significantly lower than that reported by Badheka et al.16 4.2% versus 24%, which is at least partly explained by the methodological issues noted. Finally, as noted by the authors, the study is further limited by the inability to identify complication rates for each individual device.

Despite its limitations, the study highlights several important issues. Given the serious periprocedural complications, how much operator experience and provider training should be required prior to performing LAA closure? Although the PREVAIL trial did not report any difference in periprocedural complication rates between experienced operator sites and new operator sites, fewer complications were seen with the later experience reported with the Watchman device and an inverse relationship with volume was reported in the current study.14,17 Will the next generation of devices have more favorable profiles, and how do we best study and incorporate evolving intracardiac echocardiography?

Acknowledging the currently untimed clinical need for alternatives to anticoagulation for stroke prevention, the European Society of Cardiology recommends percutaneous LAA closure device (Watchman and Amplatzer) use in high stroke risk patients with contraindications to long-term oral anticoagulation (class IIb recommendation, level of evidence: B).18 The American Heart Association/American College of Cardiology/Heart Rhythm Society currently only recommends surgical excision of the LAA in patients undergoing cardiac surgery (class IIb recommendation, level of evidence: C).19 Although LAA closure may have a role in individuals at the highest risk for stroke and bleeding, additional studies are needed to elucidate its long-term efficacy and justify its use despite the potential adverse outcomes.20 The future challenge will lie in the alignment of parallel breakthroughs in coagulation science and advances with occlusive technology. Previously, we did not think it possible to prevent thrombosis without a concomitant increase in hemorrhage. Recent discoveries have challenged this paradigm.20


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