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EDITORIAL COMMENT

# Long-Term Results With Left Atrial Appendage Closure

## Watching the Watchman*

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Local mechanical strategies to exclude the left atrial appendage (LAA) as a source of thrombi with nonvalvular atrial fibrillation (AF) have been explored for >5 decades. Early attempts at surgical LAA excision/exclusion were limited by incomplete exclusion, leading to poor efficacy and high stroke rates (1). Minimally invasive approaches using endocardial and epicardial percutaneous techniques were subsequently developed and investigated in the last 20 years. Tremendous strides have been made with several options of left atrial appendage closure (LAAC) devices now commercially available, parallel with in-depth research evaluations of these devices in randomized controlled trials (RCTs) and observational registries. To date, Watchman (Boston Scientific, Natick, Massachusetts) is the percutaneous device with the most clinical experience, having been implanted in >30,000 patients in >75 countries, and with the most extensive clinical trial data, with >3,000 patients studied with a cumulative ~7,000 patient-years of follow-up. However, despite the broad enthusiasm in the clinical community to adopt this novel therapy as an alternative to oral anticoagulation (OAC) for stroke prophylaxis with AF, several controversies and unanswered questions remain. Amongst these, the most noteworthy criticism relates to the uncertain evidence supporting the safety and efficacy of LAAC for stroke prevention; this concern led to 3 extensive panel deliberations by the U.S. Food and Drug Administration (FDA) prior to final approval of the device in March 2015. Therefore, an in-depth discussion of this best-available clinical evidence is explored here.

The landmark PROTECT AF (WATCHMAN Left Atrial Appendage System for Embolic Protection in Patients With Atrial Fibrillation) and PREVAIL (Evaluation of the WATCHMAN LAA Closure Device in Patients With Atrial Fibrillation Versus Long Term Warfarin Therapy) RCTs using the Watchman device were designed in the era where warfarin was considered the treatment of choice for AF stroke prophylaxis; PROTECT AF enrolled patients from 2005 to 2008, and PREVAIL from 2010 to 2012. Reddy et al. (2) now report the protocol-defined maximum 5-year results of both studies in this issue of the *Journal*. Both studies enrolled patients with nonvalvular AF who were eligible for warfarin, and randomized them 2:1 to the device or warfarin. There are a few important differences between these 2 studies that merit clarification.

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PROTECT AF was a prospective, multicenter RCT designed to establish whether the device was noninferior to warfarin for the composite primary efficacy endpoint of stroke, systemic embolism (SE), or cardiovascular/unexplained death. A Bayesian model was used for the primary analysis, stratified for $CHADS_2$ score (congestive heart failure, hypertension, 75 years of age or older, diabetes mellitus, and previous stroke or transient ischemic attack) using data from this study only, and assumed a constant hazard rate with the number of events following a Poisson

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distribution. The primary composite safety endpoint consisted of serious bleeding or procedure-related complications (e.g., serious pericardial effusion, device embolization, or procedure-related stroke). This study enrolled 707 patients with $CHADS_2 \geq 1$ and met the noninferiority criteria for the primary efficacy endpoint at 1,065 patient-years, 1,588 patient-years, 2,621 patient-years, and 2,717 patient-years. Watchman also met the pre-specified superiority criteria against warfarin in the latest 2 follow-ups. However, the early safety event rates were higher with the device (rate ratio: 1.69) at 1,065 patient-years, including serious pericardial effusion (4.8%) and procedural ischemic stroke (1.1%). Furthermore, the robustness of PROTECT AF results was limited by the enrollment of patients with a $CHADS_2$ score of 1, the number of subjects who did not receive protocol treatment per randomization, and a higher than expected hemorrhagic stroke rate in the warfarin group. Thus, the FDA requested a second RCT to primarily confirm the safety and effectiveness of Watchman in a higher-risk cohort.

Accordingly, PREVAIL enrolled patients from the United States with $CHADS_2 \geq 2$ or $CHADS_2 \geq 1$ plus at least 1 high-risk characteristic. PREVAIL also employed a Bayesian methodology, but was allowed an informative prior to include data (down-weighted 50%) from PROTECT AF subjects who met the inclusion/exclusion criteria for PREVAIL, allowing a smaller-sized trial with the caveat that the results of the PREVAIL-only patients were not powered for these endpoints. In addition to this complex statistical model, the study incorporated 3 primary endpoints: 1) primary efficacy composite of stroke, SE, and cardiovascular/unexplained death; 2) ischemic efficacy of ischemic stroke and SE beyond 7 days; and 3) early safety composite endpoint. PREVAIL enrolled 407 patients who had a higher risk profile than PROTECT AF patients, with an older mean age (74.3 years vs. 72.0 years) and higher $CHA_2DS_2$-VASc scores (congestive heart failure, hypertension, 75 years of age and older, diabetes mellitus, previous stroke or transient ischemic attack, vascular disease, 65 to 74 years of age, female) (4.0 vs. 3.5). In the 5-year analysis (1,626 patient-years), the 18-month first coprimary efficacy endpoint did not meet the noninferiority criteria (0.066 vs. 0.051; rate ratio: 1.33; 95% credible interval: 0.78 to 2.13; posterior $p = 0.884$; pre-specified noninferiority margin 1.75), but the second coprimary ischemic efficacy endpoint met noninferiority criteria (0.025 vs. 0.013; posterior $p = 0.975$). Early safety events occurred in 2.2% with Watchman, satisfying the pre-specified safety performance goal (3).

How do clinicians reconcile these disparate findings? Critics no doubt will hang on the failure of the PREVAIL trial to prove noninferiority for the key primary efficacy endpoint. Furthermore, there was a numerically higher signal of ischemic stroke with Watchman (1.68% vs. 0.73%), although this did not meet statistical significance ($p = 0.13$). Three explanations forwarded to explain the negative results were: 1) the PREVAIL trial lacked independent statistical power on its own; 2) the warfarin group ($n = 138$) in PREVAIL had an unusually low ischemic stroke rate of 0.73% (much lower than contemporary OAC stroke prevention trials) due to small sample size; and 3) the Watchman arm in PREVAIL had similar ischemic stroke reduction with warfarin in imputed placebo analysis from 2 large population databases. Although the consummate clinical trialist would demand a more robust study methodology, it is reasonable to accept the available data from PREVAIL despite these potential flaws. Furthermore, the second coprimary efficacy endpoint does support the proof-of-concept of LAAC in preventing future ischemic stroke and systemic embolization.

The patient-level meta-analysis of PROTECT AF and PREVAIL provides additional data that helps to address the limitations of the PREVAIL trial. It includes the 5-year outcomes of 1,114 patients (4,343 patient-years) randomized to Watchman versus warfarin. The composite endpoint of stroke, SE, and cardiovascular death was similar between groups (hazard ratio [HR]: 0.82; $p = 0.27$), as were stroke and SE (HR: 0.96; $p = 0.87$). The ischemic stroke and SE rate was numerically higher with Watchman, but did not reach statistical significance (HR: 1.71; $p = 0.08$). Importantly, there was an 80% decrease in hemorrhagic stroke, 59% decrease in disabling stroke, 41% decrease in cardiovascular death, 27% decrease in all-cause death, and 52% decrease in post-procedure bleeding with Watchman. The reduction in disabling strokes with Watchman serves as a reminder of the differential functional impact of ischemic and hemorrhagic strokes. Intracranial hemorrhage is a known and accepted complication with OAC, with an annual rate of 0.3% to 0.5% even with direct OACs (4), and it is reassuring to observe a dramatic reduction with LAAC. The substantial reductions of life-threatening bleeds after Watchman implantation beyond the period of antithrombotic requirement likely have substantially contributed to the mortality benefit seen in this analysis. Reduction of cardiovascular and all-cause mortality is a remarkable feat with this device therapy, and emphasizes 1 of the key benefits with LAAC: reduction

of major bleeding and associated complications with lifelong OAC administration.

The authors and investigators of both the PROTECT AF and PREVAIL trials should be commended for their contribution in establishing Watchman therapy as safe and effective in stroke prevention for patients with nonvalvular AF compared with warfarin. Percutaneous and surgical LAAC is increasingly being adopted as a strategy to reduce the cardioembolic risk associated with AF. How should a clinician decide on the preventative therapy of choice, especially given the wide availability of more tolerable and efficacious direct OAC? First, guidelines relegate LAAC for patients with contraindications to OAC (Class IIb recommendation) (5). OAC, especially novel agents, remains the treatment of choice for patients with a low bleeding-risk profile given the extensive supportive randomized trial data (4), and the additional systemic thromboembolic protection beyond the LAA. In the United States, based on FDA approval and CMS (Centers for Medicare & Medicaid Services) final coverage determination, Watchman devices are implanted in AF patients with $CHADS_2$ scores ≥2 or $CHA_2DS_2$-VASc scores ≥3 who are suited to short-term OAC but have other medical concerns that may affect their ability to safely tolerate these agents long-term. Outside of the United States, LAAC is performed primarily in patients with OAC contraindications, although there are no randomized data supporting this approach. Important ongoing RCTs should hopefully elucidate the efficacy of LAAC in OAC-contraindicated populations where antiplatelet therapy is used post-LAAC (e.g., ASAP-TOO [Assessment of the WATCHMAN™ Device in Patients Unsuitable for Oral Anticoagulation; NCT02928497] and STROKE-CLOSE [Prevention of Stroke by Left Atrial Appendage Closure in Atrial Fibrillation Patients After Intracerebral Hemorrhage; NCT02830152]). Second, the safety and efficacy of stroke prevention with non-Watchman devices have not been established in RCT, and the proof-of-concept of LAAC may not extend to these devices due to differences in device design, safety and success of implant, residual device leak, and device-associated thrombosis. Several non-inferiority comparative trials are ongoing or will be launched imminently comparing Watchman against other percutaneous LAAC devices (Amulet [Abbott Vascular, Santa Clara, California], WaveCrest [Coherex, Salt Lake City, Utah], LAmbre [Lifetech, Shenzhen, China]). Third, large, prospective, real-world registries will need to confirm the long-term procedural safety and efficacy of these devices in commercial use. Early data from a few such registries have shown promising procedural safety results (e.g., EWOLUTION [Registry on WATCHMAN Outcomes in Real-Life Utilization; NCT01972282], Amulet Post-Marketing Registry), although longer-term efficacy data are still forthcoming. Finally, studies are needed to examine the safety and efficacy of LAAC against direct OACs, and one such study (PRAGUE-17 [Left Atrial Appendage Closure vs. Novel Anticoagulation Agents in Atrial Fibrillation; NCT02426944]) is ongoing.

In summary, the 5-year combined data from the PROTECT AF and PREVAIL trials confirmed the safety and efficacy of Watchman in stroke prevention. Enrollment of appropriate patients in ongoing RCTs and prospective registries is still needed to further scientifically understand the role of LAAC device therapies in the contemporary era of direct OAC.

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