

EDITORIAL COMMENT

Left Atrial Appendage Closure to Reduce the Risk of Thromboembolic Complications in Atrial Fibrillation

Pay Now and Possibly Pay Later?*

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Atrial fibrillation (AF) is the most common sustained arrhythmia and currently afflicts 5 million Americans (1). The treatment of AF and its complications costs the United States health-care system \$26 billion annually (2). Due to aging of the population and an increasing incidence of AF risk factors, by the year 2050, >12 million Americans will have this arrhythmia (2). Thromboembolism and its associated morbidity and mortality is the most dreaded complication of AF, and AF has been implicated in up to one quarter of all strokes in patients >80 years of age (2). Anticoagulation has been shown to reduce the risk of AF-associated stroke by 64% and is therefore the current standard of care for thromboembolic prophylaxis in the vast majority of AF patients (3).

Despite the proven efficacy of anticoagulation with both warfarin and recently available non-vitamin K oral anticoagulants, the use, safety and efficacy of chronic anticoagulation therapy is limited by bleeding complications, medication compliance, costs, and interactions with food and other medications (1). Additionally, some patients are not candidates for long-term anticoagulation due to a prohibitive bleeding risk. In patients with nonvalvular AF, up to

91% of left atrial thrombi have been localized to the left atrial appendage (LAA) (4,5), and the presence of LAA thrombus, depressed LAA mechanical function, and spontaneous echo contrast on transesophageal echocardiogram (TEE) identify patients at increased risk for stroke (6). As a result, LAA surgical ligation or mechanical occlusion has emerged as a potential alternative to oral anticoagulation to reduce the risk of AF-related stroke without a concomitant increase in bleeding risk.

The PROTECT AF (Watchman Left Atrial Appendage System for Embolic Protection in Patients with Atrial Fibrillation) randomized control trial (RCT) compared the Watchman LAA closure (LAAC) device (Boston Scientific, Natick, Massachusetts) and short-term warfarin followed by antiplatelet therapy to chronic warfarin (international normalized ratio goal 2 to 3) in 707 nonvalvular AF patients (42% paroxysmal, 36% permanent) with at least 1 CHADS₂ risk factor (mean score 2.2 ± 1.2 with 90% hypertension and 43% ≥ 75 years of age). The Watchman was successfully implanted in 88% of patients, and LAAC efficacy was 86% at 45 days and 92% at 6 months. After a mean follow-up of 18 months, Watchman LAAC was found to be non-inferior to warfarin (time in therapeutic range 66%) for the composite primary endpoint of stroke, systemic embolism, and cardiovascular death (3.0 vs. 4.9 events per 100 patient-years, respectively), although there were significantly more adverse events (primarily periprocedural complications) in the Watchman group (1.1% periprocedure stroke and 4.8% pericardial effusion requiring percutaneous or surgical drainage) (7). Of note, 26% of Watchman patients remained on anticoagulation 45 days after implant, whereas

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27% of warfarin patients interrupted warfarin during follow-up (8). In both groups, all patients with ischemic strokes who had international normalized ratio measured at the time of their ischemic event were subtherapeutic or not taking warfarin (7). Based on these results, concerns about the risk factor profiles of enrolled patients, confounding by chronic antiplatelet therapy, and poor compliance with protocol mandated anticoagulation strategies (8), the Watchman device was not approved by the U.S. Food and Drug Administration (FDA), and the PREVAIL RCT was designed in concert with the FDA to address these concerns.

The PREVAIL (Prospective Randomized Evaluation of the Watchman LAA Closure Device In Patients With Atrial Fibrillation Versus Long Term Warfarin Therapy) trial randomized 407 nonvalvular AF patients (50% paroxysmal, 16% permanent) with higher CHADS₂ score (mean 2.6 ± 1.0 ; 91% hypertension, 54% ≥ 75 years of age), used the same Watchman device and anticoagulation protocol as in the PROTECT AF trial, excluded patients on chronic clopidogrel therapy, and followed patients for a mean of 12 months. Notably, to improve the power of the PREVAIL study, some data from the PROTECT AF trial was included in the PREVAIL analysis using a Bayesian informative prior analysis. In the PREVAIL trial, procedure-related adverse events improved to 2.2% and successful device implantation increased to 95% with LAAC efficacy of 92% at 45 days and 98% at 6 months. The Watchman failed to demonstrate noninferiority to long-term warfarin for the composite coprimary endpoint of stroke, systemic embolism, and cardiovascular or unexplained death. In the Watchman group, however, at 18 months, the coprimary endpoint of ischemic stroke or systemic embolism occurring *after* 7 days post-randomization was noninferior to long-term therapy with warfarin (event rate of 0.025 vs. 0.020, respectively). Importantly, late ischemic stroke events in the Watchman arm were suggested after 14 months (9).

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In this issue of the *Journal*, Holmes et al. (10) present the results of a patient level meta-analysis of the PROTECT AF and PREVAIL RCTs and their respective registries. This meta-analysis represents the most comprehensive and long-term evaluation of the Watchman LAAC device to date, and includes data on 1,877 patients treated with Watchman and 382 control patients treated with long-term warfarin, totaling 5,931 patient-years of follow-up. The average CHADS₂ score was >2 , and 90% of patients were at a moderate to high risk of bleeding (HAS-BLED score

of ≥ 1). Mean follow-up varied between 0.6 years in patients enrolled in the higher CHADS₂ risk PREVAIL registry, and 4.0 years for the lower CHADS₂ risk PROTECT AF RCT patients (10).

Meta-analysis of the 2 RCTs revealed that Watchman implantation was noninferior to long-term warfarin for the composite outcome of stroke, systemic embolism, and cardiovascular/unexplained death (2.72 vs. 3.50 events per 100 patient-years, respectively; $p = 0.22$). There was no difference in all-cause stroke or systemic embolism (1.75 vs. 1.87 events per 100 patient-years for Watchman and warfarin respectively; $p = 0.94$), or all-cause major bleeding ($p = 0.95$). When stroke etiology was evaluated there was a borderline increase in *ischemic* stroke or systemic embolism in Watchman patients (1.62 vs. 0.89 events per 100 patient-years; HR: 1.95; $p = 0.05$) with reduced *hemorrhagic* stroke (0.15 vs. 0.96 events per 100 patient-years; HR: 0.22; $p = 0.004$) (10). Notably, the rate of hemorrhagic stroke in warfarin-treated patients was nearly double the rate reported in other contemporary AF warfarin studies (8,11,12).

When procedure-related events were excluded, there was no difference between Watchman and warfarin in the rate of ischemic stroke (1.4 vs. 0.89 events per 100 patient-years, respectively; $p = 0.21$) or major bleeding (HR: 0.51; $p = 0.02$). The authors also found a 52% reduction in cardiovascular death in patients treated with Watchman compared with warfarin (1.1 vs. 2.3 events per 100 patient-years; $p = 0.006$). Results were similar when patients in the PROTECT AF and PREVAIL nonrandomized registries were included in the analysis (10). These data support the use of the Watchman as an alternative to warfarin for thromboembolic prophylaxis in AF. However, uncertainty remains regarding the overall safety and *late* efficacy of the Watchman device.

Chronic anticoagulation is associated with an increased risk of bleeding complications, and LAAC is, in theory, an excellent solution for reducing the risk of LAA mediated thromboembolism in patients who are not candidates for chronic anticoagulation. However, all patients in the PROTECT AF and PREVAIL trials had to be eligible to take warfarin to enroll in these studies, and all Watchman-implanted patients were required to take warfarin for at least 45 days post-implantation (longer for the 8% to 14% of patients without adequate LAAC), dual antiplatelet therapy with aspirin and clopidogrel between 45 days and 6 months after implantation (for patients with closure), and aspirin indefinitely (7,9). The safety of the Watchman in patients who are poor candidates for even short-term anticoagulant or antiplatelet therapy is currently unknown. Patients with residual

leakage into the LAA at 6 months may need to be on warfarin indefinitely with perhaps an increased risk of thromboembolism (versus no Watchman) if warfarin needs to be held/stopped. This is unfortunate, as patients who are unable or unwilling to take warfarin are the patient populations that would likely derive the greatest benefit from Watchman.

The authors refer to a small, nonrandomized trial (Aspirin Plavix Registry) using the Watchman in 150 patients who were not eligible for long-term anticoagulation, which demonstrated a reasonable safety profile over short-term follow-up (13). Even these patients, however, were treated with 6 months of dual antiplatelet therapy and lifelong aspirin. At this point in time, Watchman implantation without peri-implant anticoagulation/antiplatelet therapy cannot be recommended.

Data on the long-term safety of the Watchman are also incomplete and particularly concerning. In the original PREVAIL publication, there were similar rates of 18-month freedom from stroke and systemic embolism starting 7 days after randomization (9). With continued follow-up, however, there were ongoing late strokes in the Watchman group (10 of 13 total ischemic strokes occurred *after* 1 year), but no new strokes in the warfarin group. With this late increase in Watchman-associated thromboembolic events, the Watchman lost its non-inferiority compared to warfarin for non-procedure related ischemic events (event rate 0.029 vs. 0.013, respectively) (8). Of particular concern, these late ischemic strokes may be related to late thrombus formation on the Watchman device in the absence of anticoagulation (14).

Although LAA thrombi have been implicated in a majority of AF-related strokes, it is important to realize that not all strokes in AF patients are necessarily related to the presence of AF and/or LAA thrombi, and Watchman LAAC would not be expected to have any beneficial effect on these types of strokes. In 2 studies evaluating the correlation between AF burden and thromboembolism using implantable pacemakers and defibrillators with atrial leads to accurately and continuously record AF burden, only 10% to 30% of patients who developed thromboembolism had AF detected within 1 month of their event (15,16). Patients with AF can have ischemic strokes independent of their cardiac rhythm

(e.g., from hypertension or carotid artery atherosclerosis), and, in 1 study of 860 patients with AF and stroke, 27% had a possible atheroembolic stroke etiology (17). AF may also be associated with a systemic inflammatory and hypercoagulable state (18). In the current meta-analysis, ~90% of patients had hypertension, the most frequent stroke risk factor. Without a method of accurately adjudicating stroke etiology, it is possible that many strokes were unrelated to LAA thrombi.

The Watchman has been approved in Europe since 2005. In March 2015 it was FDA approved for use in the United States. In a select group of patients, it may be safe, effective, and preferable to chronic warfarin therapy for thromboembolic prophylaxis in AF, but at this point many questions surrounding its safety and long-term efficacy remain unanswered. Additionally, the meta-analysis's unusually high rate of hemorrhagic strokes in the warfarin-treated group may limit the beneficial effect of LACC in the general population.

As with most new technologies, over time, procedural success and safety will likely continue to improve, and future iterations of the Watchman or similar LAAC devices might allow safe deployment without the need for any anticoagulant or antiplatelet therapy. At the same time, however, pharmaceutical approaches to AF stroke prevention are not stagnant with the increasing use of non-vitamin K oral anticoagulants demonstrating improved efficacy and lower bleeding rates vs. warfarin. This might further reduce the benefit of mechanical LAAC compared to pharmacologic stroke prophylaxis. At this point in time, it appears that patients treated with Watchman may pay early (procedural complications) and may also possibly pay later (late thromboembolism). The jury is still out as we await clarity from long-term efficacy data.

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