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# Left Atrial Appendage Closure as an Alternative to Warfarin for Stroke Prevention in Atrial Fibrillation

## A Patient-Level Meta-Analysis

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**ABSTRACT**

**BACKGROUND** The risk-benefit ratio of left atrial appendage closure (LAAC) versus systemic therapy (warfarin) for prevention of stroke, systemic embolism, and cardiovascular death in nonvalvular atrial fibrillation (NVAF) requires continued evaluation.

**OBJECTIVES** This study sought to assess composite data regarding left atrial appendage closure (LAAC) in 2 randomized trials compared to warfarin for prevention of stroke, systemic embolism, and cardiovascular death in patients with nonvalvular AF.

**METHODS** Our meta-analysis included 2,406 patients with 5,931 patient-years (PY) of follow-up from the PROTECT AF (Watchman Left Atrial Appendage System for Embolic Protection in Patients with Atrial Fibrillation) and PREVAIL (Prospective Randomized Evaluation of the Watchman LAA Closure Device In Patients With Atrial Fibrillation Versus Long Term Warfarin Therapy) trials, and their respective registries (Continued Access to PROTECT AF registry and Continued Access to PREVAIL registry).

**RESULTS** With mean follow-up of 2.69 years, patients receiving LAAC with the Watchman device had significantly fewer hemorrhagic strokes (0.15 vs. 0.96 events/100 patient-years [PY]; hazard ratio [HR]: 0.22; $p = 0.004$), cardiovascular/unexplained death (1.1 vs. 2.3 events/100 PY; HR: 0.48; $p = 0.006$), and nonprocedural bleeding (6.0% vs. 11.3%; HR: 0.51; $p = 0.006$) compared with warfarin. All-cause stroke or systemic embolism was similar between both strategies (1.75 vs. 1.87 events/100 PY; HR: 1.02; 95% CI: 0.62 to 1.7; $p = 0.94$). There were more ischemic strokes in the device group (1.6 vs. 0.9 and 0.2 vs. 1.0 events/100 PY; HR: 1.95 and 0.22, respectively; $p = 0.05$ and 0.004, respectively). Both trials and registries identified similar event rates and consistent device effect in multiple subsets.

**CONCLUSIONS** In patients with NVAF at increased risk for stroke or bleeding who are candidates for chronic anticoagulation, LAAC resulted in improved rates of hemorrhagic stroke, cardiovascular/unexplained death, and nonprocedural bleeding compared to warfarin. (J Am Coll Cardiol 2015;65:2614–23) © 2015 by the American College of Cardiology Foundation.

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Left atrial appendage closure (LAAC) has been investigated intensely for stroke prevention as an alternative to systemic oral anticoagulation in selected patients with high-risk nonvalvular atrial fibrillation (NVAF) (1–11). The PROTECT AF (Prospective Randomized Evaluation of the Watchman LAA Closure Device In Patients With Atrial Fibrillation Versus Long Term Warfarin Therapy) trial was a multicenter, randomized controlled trial in NVAF patients comparing the Watchman device to warfarin for a composite primary endpoint of stroke, systemic embolism, and cardiovascular (CV) death (1,9). Noninferiority to warfarin was documented early and long term (2,621 patient-years [PY]), LAAC demonstrated a significant (40%) relative risk reduction to warfarin for the primary efficacy endpoint (1,5), an 85% relative risk reduction in hemorrhagic stroke, a 60% relative reduction in CV mortality (absolute annual risk reduction of 1.4%), and a 34% relative reduction in all-cause mortality (absolute annual risk reduction of 1.6%) (5). Despite a positive vote from the Center for Devices and Radiological Health (CDRH) Panel in 2009, the U.S. Food and Drug Administration (FDA) issued a nonapprovable letter on the basis of concerns of procedural complications, the risk profile of patients, and the confounding use and effect of clopidogrel following implant. To address these, the device manufacturer worked with the FDA for a confirmatory randomized trial (PREVAIL [Prospective Randomized Evaluation of the Watchman LAA Closure Device In Patients With Atrial Fibrillation Versus Long Term Warfarin Therapy] trial) comparing LAAC with the Watchman device to warfarin, which mandated inclusion of new operators, slight modifications in inclusion criteria, and elimination of clopidogrel 7 days before implant. Bayesian statistical methodology was agreed upon using informative prior data from the PROTECT AF trial (see Methods section). At the pre-defined evaluation time point, the PREVAIL trial demonstrated improved safety compared to the PROTECT AF trial, and noninferiority of 1 of 2 coprimary efficacy endpoints; an 18-month rate ratio (RR) for primary efficacy, and an 18-month rate ratio difference for post-procedure ischemic stroke and systemic embolism. After review of these data in December 2013, the FDA panel returned a positive vote for safety, efficacy, and benefit/risk. However, after this panel, an updated data set to FDA as part of routine regulatory filings raised further efficacy concerns, resulting in a third panel to evaluate the totality of data.

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To evaluate the totality of data, this patient level meta-analysis was performed in which: 1) all randomized patients from the PROTECT AF and PREVAIL trials are combined and the data analyzed using "traditional" frequentist statistical methods; and 2) patients from 2 nonrandomized registries of LAAC with the device (the CAP [Continued Access to PROTECT AF registry] and the CAP2 [Continued Access to PREVAIL registry]) are included. (3) By including these data from over 2,200 patients and ~6,000 PY of follow-up, we provide the most comprehensive assessment to date of the efficacy of Watchman LAAC for stroke prevention.

## METHODS

Local institutional review board approval was obtained for each dataset. All clinical trials were registered on ClinicalTrials.gov (1,3,4). The specific Watchman device was identical throughout; a self-expanding nitinol framed structure positioned at LAA ostium with diameter ranges from 20 to 33 mm and fixation barbs to prevent embolization (9). Implant protocols were identical. As previously described (1,4,9), after implantation, patients were treated with warfarin with an international normalized ratio (INR) goal of 2.0 to 3.0 and aspirin (81 mg) for 45 days; at that time, transesophageal

### ABBREVIATIONS AND ACRONYMS

**CI** = confidence interval
**CV** = cardiovascular
**HR** = hazard ratio
**INR** = international normalized ratio
**LAA** = left atrial appendage
**LAAC** = left atrial appendage closure
**NOAC** = new oral anticoagulant agent
**NVAF** = nonvalvular atrial fibrillation
**PY** = patient-years
**RR** = rate ratio

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