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.
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). Non-inferiority 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.

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
echocardiography was performed. If there was complete LAAC or if residual peridevice flow was <5 mm in width, warfarin was discontinued and the patient was treated with clopidogrel 75 mg and aspirin 81 to 325 mg until 6 months following implantation, at which time clopidogrel was discontinued and 325 mg of aspirin was used indefinitely. In the control (warfarin) limb, INR was monitored every 2 weeks to achieve an INR of 2 to 3. All patients had follow-up visits at 45 days, and at 6, 9, and 12 months, and then twice yearly.

All 4 datasets included a primary efficacy composite of all cause stroke (both hemorrhagic and ischemic), systemic embolization, and CV death. Any death of unknown origin was included as CV. Safety endpoints varied slightly between the 2 randomized trials and included bleeding as well as all cause stroke (ischemic and hemorrhagic). To be a candidate for the device, all patients had to be able to take warfarin for 45 days following implantation.

Because of the identical efficacy endpoint definitions in both randomized trials, the data from both trials were pooled for this meta-analysis (1,4).

**PROTECT AF STUDY.** Eligibility criteria included ≥18 years of age with paroxysmal persistent or permanent AF with a CHADS2 risk score ≥1. Exclusion criteria included absolute contraindications to warfarin, LAA thrombus, a patent foramen ovale with an atrial septal aneurysm and right to left shunt, mobile aortic atheroma, or symptomatic carotid disease. The primary composite safety endpoint included excessive bleeding or procedural-related complications (e.g., pericardial effusion requiring intervention, device embolization, or procedural-related stroke). A Bayesian statistical model (12) was used for noninferiority trial design, and pre-specified endpoint analysis of observed event rates after 600 follow-up PY and after each additional 150 PY, up to 1,500.

**PREVAIL TRIAL.** Selection criteria were modified to include higher risk patients: a CHADS2 score ≥2 or a CHADS2 score ≥1 with more than 1 of the following higher risk characteristics; female ≥75 years of age, baseline ejection fraction ≥30% but <35%, 65 to 74 years of age with either diabetes or coronary artery disease, and ≥65 years of age with heart failure. Exclusion criteria were similar to the PROTECT AF trial, except patients in whom clopidogrel therapy was indicated were excluded because of the potential confounding influence of this drug on efficacy outcome.

There were 3 coprimary endpoints: 1) a composite efficacy endpoint identical to the PROTECT AF trial; 2) a second, “late ischemic efficacy endpoint”—a composite of ischemic stroke or systemic embolization excluding the first 7 days post-randomization, which aimed to isolate the mechanism of LAAC and its potential effect on outcomes without the confounding influence of procedural complications; and 3) a composite of early safety—death, ischemic stroke, systemic embolization, device-/procedural-related events requiring open CV surgery or a major endovascular intervention between randomization and 7 days post-procedure or during the index hospitalization.

Inclusion of new operators was mandated to assess procedural performance. Trial design recognized the utility of the available efficacy data from the PROTECT AF trial, and used Bayesian statistical methodology that allowed “borrowing” some data on PREVAIL-eligible PROTECT AF trial patients at 1,500 PY of follow-up as an informative prior. Incorporation of the informative prior allowed for a smaller confirmatory PREVAIL trial, but results in the fact that the confirmatory trial by itself is not powered to reach robust conclusions. The PROTECT AF trial results were combined with the small sample size of the PREVAIL trial to confirm device safety and collect additional efficacy data on LAAC. The resulting study requirements were such that follow-up with the new PREVAIL trial patients was limited to 6 months minimum in order for the endpoint to occur using the modeled 18-month event rates against pre-specified performance boundaries.

**REGISTRIES.** The registries (3) were designed to treat patients with similar baseline characteristics according to the same protocols after the specific trial enrollment had been completed—CAP following PROTECT AF and CAP2 following the PREVAIL trial. Procedural performance and adjunctive medications were identical in each registry and the respective randomized trials except registries did not mandate 1-year neurological assessment required in both randomized trials.

**DEFINITIONS.** For all data sets, the CHADS2 score (1,4) was used for patient entry. Because the CHA2DS2-VASc score has largely supplanted CHADS2 (13-16), risk prediction was reported using both. Assessment of bleeding risk was a clinical site determination. Though not prospectively captured in the Watchman studies, many components of the HAS-BLED (13,15) score were captured as a part of routine data collection. A conservative bleeding score was determined using the available case report form data and points were assigned per the HAS-BLED score. Abnormal liver function and labile INR were not captured and were consequently assigned a score of zero. An independent Clinical Events Committee
adjudicated strokes in all trials and registries. Ischemic stroke was defined as sudden onset of a focal neurological deficit with symptoms and/or signs persisting >24 h, or symptoms <24 h with computed tomography or magnetic resonance imaging evidence of tissue loss without hemorrhage. Although hemorrhagic stroke definitions varied slightly from the PROTECT AF trial to the PREVAIL trial, they included sudden onset of a focal neurological deficit with computed tomography or magnetic resonance imaging evidence of tissue loss with evidence of blood vessel and/or intracranial hemorrhage with symptomatic focal neurological deficit. Subdural hematomas with evidence of parenchymal involvement such as parenchymal extensions or contusion were adjudicated as a hemorrhagic stroke, unless confined exclusively to the subdural space.

**STATISTICAL ANALYSIS FOR META-ANALYSIS.** This patient level meta-analysis had 3 components: 1) assessment of the device outcomes including all primary efficacy components, all-cause mortality, and major bleeding versus warfarin control in patients randomized in both the PROTECT AF and PREVAIL; 2) the primary composite efficacy rates of patients receiving the Watchman device in both randomized controlled trials and registries; and 3) comparison of the device performance in each of the 4 trials.

Both randomized trials were designed to establish noninferiority of a device-based strategy versus warfarin for a composite primary efficacy endpoint. To evaluate benefit-risk ratio, the PROTECT AF and PREVAIL data sets were combined with all available follow-up and analyzed as a traditional patient-level meta-analysis. Fully utilizing the data from both trials while accounting for the fact that they are different studies facilitates more robust exploration of the role of covariates. This meta-analysis of these 2 studies is appropriate because both studies randomized subjects to the same treatment strategies (Watchman vs. warfarin) and primary efficacy endpoint definitions. The baseline risk profile in the combined the PROTECT AF and PREVAIL trial population included a somewhat higher risk profile for the PREVAIL trial; subgroup analyses by CHADS2 and CHA2DS2-VASc scores were performed to assess differences in outcome by baseline risk profile. Further, results were stratified with Cox proportional hazards modeling, adjusting for potential baseline risk differences. In addition, the device patients from the registry data were combined with all randomized data in the same fashion. Though registries had no control group, the same criteria around device and primary efficacy definitions apply. Given the variable initiation of recruitment, the PROTECT AF trial patients have the longest follow-up, but registry patients provide the largest number of patients.

Analyses were intent-to-treat, censoring data from patients without events at the time of the last known status. A Cox proportional hazards model with confidence intervals (CIs) was used for comparison of event rates. For the analysis including the randomized trials, this model was stratified by study (PROTECT AF or PREVAIL) in order to account for differences in risk profiles. For the analysis including all 4 data sets, studies were treated as “clusters” in order to account for correlation among patients within studies. The Kaplan-Meier method was used for graphical assessment of time-dependent events. Results are presented using frequentist statistics and 2-sided p values nominally significant at p < 0.05 with no adjustments for multiple comparisons.

**RESULTS**

**PATIENT CHARACTERISTICS.** Four clinical trials enrolled 2,406 patients from 2005 to 2014; 1,877 were treated with Watchman (1,145 Registry patients) and 382 (the control limbs in the 2 randomized clinical trials) received warfarin. Mean follow-up depended on when the patients were enrolled; there were a total of 5,931 PY follow-up available (Table 1). Patient follow-up for CAP2 was the shortest by virtue of enrollment initiation (mean follow-up of 0.58 years vs. 4.0 for the PROTECT AF trial and 3.7 years for CAP). There was a progressive increase in patient risk over the course of these data sets (Table 2); mean patient age ranged from 72.0 ± 8.9 years of age in the PROTECT AF trial to 75.3 ± 8.0 years of age in CAP2. The CHADS2 score similarly ranged from 2.2 ± 1.2 to 2.7 ± 1.1 (p < 0.0001) as did the CHA2DS2-VASc score 3.5 ± 1.6 to 4.5 ± 1.3 (p < 0.0001). On the basis of these scores, the total predicted annualized risk for stroke, if untreated with anticoagulation, ranged from 5.7% to 7.6% annually.

The distribution of both CHADS2 and CHA2DS2-VASc scores documented the majority of patients were high risk for stroke and all were eligible for warfarin (Figures 1A and 1B). Conversely, 90% of patients were moderate to high risk of bleeding using the estimated HAS-BLED score; 61% had a moderate risk of increased bleeding. The PROTECT AF trial had the highest prevalence of a low-risk HAS-BLED score, but even in this study, this only constituted 6.4% of the study. Between 93.2% and 98.7% of patients were able to discontinue warfarin at 1 year.

**LAAC VERSUS WARFARIN—META-ANALYSIS OF RANDOMIZED CLINICAL TRIALS.** Both the PROTECT AF and PREVAIL trials shared the primary efficacy
endpoint of stroke, systemic embolism, and CV death. The meta-analysis of the randomized clinical trial cohorts reveals that the hazard ratio (HR) for this composite efficacy endpoint was 0.79 (95% CI: 0.53 to 1.2; p = 0.22) (Figure 2) meeting noninferiority of LAAC versus warfarin. Event rates per 100 PY were 2.72 (95% CI: 2.29 to 3.24) and 3.50 (95% CI: 2.60 to 4.72) for device and warfarin, respectively. But for the individual endpoint components, there were significant differences. Although all-cause stroke or systemic embolism rates per 100 PY were virtually identical between the 2 strategies (device: 1.75; 95% CI: 1.41 to 2.17; warfarin: 1.87; 95% CI: 1.41 to 2.17; HR: 1.02; 95% CI: 0.62 to 1.7; p = 0.94), there were differences when strokes were subdivided into ischemic versus hemorrhagic. Though there were more ischemic strokes in the device group (1.6 vs. 0.9 events/100 PY; HR: 1.95; p = 0.05) once procedure-related strokes were excluded, the rates of ischemic stroke were no longer significantly different between the device and warfarin (HR: 1.40 [95% CI: 1.10 to 1.78] and HR: 0.89 [95% CI: 0.50 to 1.61]; HR: 1.56; 95% CI: 0.78 to 3.09; p = 0.21). In contrast, hemorrhagic stroke occurred significantly less frequently in the LAAC treated patients at a rate of 0.15 per 100 PY (95% CI: 0.07 to 0.4) for device versus 0.96 (95% CI: 0.55 to 1.70) for warfarin (HR: 0.22; 95% CI: 0.08 to 0.61; p = 0.004). There were also significantly fewer CV deaths in the LAAC cohort (HR: 0.48; 95% CI: 0.28 to 0.81; p = 0.006).

Subgroup analysis of the composite efficacy endpoint revealed no significant interaction with clinical characteristics such as age dichotomized at 75 years of age, sex, or the CHADS2 and CHA2DS2-VASc risk scores (Figure 3). The p value for interaction of the estimated HAS-BLED score was 0.098. Finally, the presence or absence of a history of transient ischemic attack or stroke before entering the clinical trial also failed to affect outcomes.

Beyond the composite efficacy endpoint and its individual components, 2 additional analyses were performed: all-cause mortality and major bleeding (Figure 2). Consistent with CV mortality, the HR for all-cause mortality also favored LAAC, but did not reach statistical significance (HR: 0.73; 95% CI: 0.52 to 1.00; p = 0.07). For total major bleeding including the index implantation period, there was no significant difference between LAAC and warfarin (HR: 1.00; 95% CI: 0.69 to 1.40; p = 0.95). However, for non-procedure-related major bleeding occurring after the first 7 days post-implantation, there was a highly significant reduction in events in the LAAC arm (HR: 0.51; 95% CI: 0.33 to 0.77; p = 0.02).

### TABLE 2 Patient Demographics Across Trials

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<th>PROTECT AF</th>
<th>PREVAIL</th>
<th>CAP</th>
<th>CAP2</th>
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<tr>
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<td>(N = 707)</td>
<td>(N = 407)</td>
<td>(N = 566)</td>
<td>(N = 579)</td>
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<td>Age, yrs</td>
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<td>75.3 ± 8.0</td>
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<td>CHADS2 score</td>
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<td>2.4 ± 1.2</td>
<td>2.7 ± 1.1</td>
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<tr>
<td>CHA2DS2-VASc</td>
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<td>4.0 ± 1.2</td>
<td>3.9 ± 1.5</td>
<td>4.5 ± 1.3</td>
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<td>19.9</td>
<td>29.7</td>
<td>36.2</td>
<td>28.3</td>
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</table>

Values are mean ± SD or %.

CHF = congestive heart failure; other abbreviations as in Table 1.
stroke seen in the LAAC group is counterbalanced by a highly significant reduction in hemorrhagic stroke; 3) there were significantly fewer CV deaths with LAAC; 4) all-cause mortality favored LAAC, but was not statistically significant; and 5) major bleeding was similar between groups, but non-procedure-related bleeds occurred with significantly greater frequency with warfarin treatment.

DISCUSSION

In patients with NVAF, the totality of the Watchman data from 2 randomized clinical trials and 2 non-randomized registries demonstrates: 1) local therapy with LAAC provides similar benefit to warfarin for the composite efficacy endpoint of stroke, systemic embolism, or CV death; 2) compared with long-term warfarin, patients randomized to LAAC have a significantly different pathophysiology of stroke was significantly different; more warfarin patients experiencing hemorrhagic strokes and more device patients experiencing ischemic strokes; 4) by 1 year, approximately 95% of device patients discontinued warfarin; 5) although all-cause bleeding was similar between groups, when peri-procedural bleeding was excluded, bleeding rates were significantly higher in patients treated with chronic warfarin; 6) device performance was consistent over the entire data set—both randomized clinical trials and registries, the latter of which are likely to more closely resemble real world experience.

The relationship between the increasing incidence of NVAF and consequent stroke is well described: stroke rates are increased 4- to 5-fold, larger and more debilitating with hemorrhagic conversion, and higher recurrence rates (13,17–20). In patients >80 years of age, AF is believed to be responsible for 15% to 30% of strokes (20). Although warfarin has been the mainstay for stroke prevention, reducing it by approximately 65%, its disadvantages are well appreciated including drug-drug interactions, the need for frequent monitoring and dose adjustment, and the potential for bleeding. In addition, when a stroke occurs in the setting of anticoagulant therapy, mortality rates approximate 50%. In the National Electronic Injury Surveillance System project that included 99,682 emergency hospitalizations, warfarin was the most commonly implicated medication, constituting 33% of cases (21). Combined with the anxiety provoked by the fear of bleeding, these reasons have led to the fact that over 40% of patients with NVAF at risk for stroke do not receive warfarin, either because of absolute or relative contraindications, as perceived by patients or physicians (10,13,22–24).

Warfarin limitations have led to the development of new oral anticoagulant agents (NOACs), such as Factor II and Xa inhibitors, which have now been studied in comparison to warfarin in large randomized trials (25–30). In a meta-analysis of trials randomizing NOACs to warfarin, NOACs were associated with a significant decrease in stroke (RR: 0.81; 95% CI: 0.73 to 0.91), primarily driven by a reduction in hemorrhagic stroke (RR: 0.48; 95% CI: 0.39 to 0.59). There was also a significant decrease in all-cause mortality (RR: 0.99; 95% CI: 0.85 to 0.95), but a significant increase in gastrointestinal bleeding (RR: 1.25; 95% CI: 1.01 to
The LAA has been implicated as the source of embolism in ~90% of patients with NVAF (7); strategies to isolate or occlude the LAA have been developed with initial studies demonstrating feasibility and safety. LACC may have competing influences on stroke rates: on the one hand, local therapy with LAAC would not attenuate stroke arising from other vascular sources such as aortic atheroma or carotid disease, but on the other hand, truncating exposure to anticoagulant agents should minimize the risk for hemorrhagic complications, including stroke. To evaluate the risk/benefit ratio of local therapy, the PROTECT AF and PREVAIL trials were performed. Taken together, the 2 randomized trials included 1,114 randomized patients with 3,577 PY of follow-up. By virtue of trial enrollment dates, the PROTECT AF data represents 75% of all of the available follow-up. Although not dictated by trial design, the majority of patients enrolled in these trials were at moderate to high risk for bleeding on the basis of the estimated HAS-BLED score.

For this meta-analysis of the randomized clinical trials, the composite efficacy endpoint favored the Watchman patients (HR: 0.79), albeit without reaching statistical significance (p = 0.22). The individual components of this composite endpoint, however, were quite different between groups. The 3 most striking differences were in hemorrhagic stroke (HR: 0.22; p = 0.004), CV/unexplained death (HR: 0.48; p = 0.006), and major non-procedural bleeding (HR: 0.51; p = 0.002). The reduction in hemorrhagic stroke and major nonprocedural bleeding could have been anticipated because device patients were not chronically exposed to a continued incremental bleeding risk from anticoagulation. Between 93.2% and 98.7% of patients had been able to discontinue warfarin after 1 year.

The reduction in hemorrhagic stroke with LAAC was balanced by a relative increase in ischemic stroke or systemic embolism with rates per 100 years for device and warfarin of 0.15 and 0.96 (hemorrhagic), respectively, and 1.62 and 0.89 (ischemic, including procedure related), respectively. As mentioned this may relate to the fundamental observation that local device therapy does not prevent strokes from other causes. Alternatively, the higher ischemic stroke rate may relate to possible technical failures of the device: failure to completely obliterate LAA flow, anatomical remodeling of the LAA ostium over time resulting in more leaks, or the development of thrombus on the device. Although small series have raised questions about the embolic potential of these small leaks (<5 mm), the only large patient dataset evaluated to address this question indicated that small residual leaks are not associated with increased stroke rates (31).

The combined data set of all PROTECT AF and PREVAIL Watchman patients versus chronic warfarin patients documented: 1) similarity in overall stroke or systemic embolism; 2) ischemic stroke slightly increased with Watchman but hemorrhagic stroke significantly decreased with warfarin; and 3) all-cause mortality and major nonprocedural bleeding both significantly improved with Watchman. CI — confidence interval; CV — cardiovascular; HR — hazard ratio; SE — systemic embolism; other abbreviations as in Figure 1.

FIGURE 3 pooled Watchman Efficacy Performance in Randomized Clinical Trials (PROTECT AF/PREVAIL)

<table>
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<th>Subgroup</th>
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Documentation of the effect of Watchman versus chronic warfarin on the different subsets of patients enrolled. There was no significant difference in Watchman effect by patient subset. TIA — transient ischemic attack; other abbreviations as in Figure 1.
The dramatic reduction in CV/unexplained death with Watchman (HR: 0.48; p = 0.006) is one of the most significant findings. This mortality benefit may be multifactorial, but is likely at least in part a result of the reduced rate of hemorrhagic stroke and is completely consistent with the ~10% to 15% mortality benefit that NOACs confer over warfarin—a benefit also driven by the reduction in hemorrhagic stroke with NOACs (26–28). However, it should also be noted that the PROTECT AF and PREVAIL trial patients had multiple comorbidities. In this setting, one cannot rule out the possibility that a small amount of bleeding in a warfarin-treated patient could have had significant clinical implications, or resulted in discontinuation of other beneficial medications because of postulated drug-drug interactions. Also, some of the deaths in the warfarin arm may have resulted from undetected ischemic stroke with hemorrhagic transformation.

The addition of the CAP and CAP2 registries to the meta-analysis added important information to the totality of the Watchman data. In these registries, 1,145 patients were enrolled and the procedural performance
and follow-up schedules were similar. The absence of trial randomization in these registries was associated with a patient cohort at somewhat higher risk for both stroke and hemorrhage. Although a warfarin control cohort for the registries was also not available for inclusion into the meta-analysis, this additional bias favoring the warfarin group did not appreciably alter any of the conclusions derived from the randomized clinical trial—alone meta-analysis. The LAAC and warfarin groups performed similarly for the composite efficacy endpoint; the advantage seen with warfarin for ischemic stroke was counterbalanced by improved rates of hemorrhagic stroke and CV death with LAAC, and major non-procedure-related bleeding was significantly less frequent with LAAC. Thus, device performance was consistent across all 4 clinical trial datasets.

An important consideration revolves around patient selection criteria. With that in mind, the risk benefit of an invasive procedure must be balanced against the longer term issues of continued exposure to anticoagulation and bleeding. In patients who are excellent candidates for an anticoagulant agent, or who have uncomplicated success with anticoagulant agents for stroke prevention, an LAAC device may not be needed. In other patients, careful consideration of LAAC versus long-term anticoagulant agents warrants an individualized discussion between physician and patient.

**STUDY LIMITATIONS.** There are important considerations that these analyses do not address. By trial design, all device patients were treated with aspirin and warfarin until the 45 day transesophageal echocardiogram, and thereafter acetylsalicylic acid and Plavix for 6 months followed by acetylsalicylic acid alone. An important question relates to the population of “contraindicated” patients, those with NVAF at risk of stroke but who are either not prescribed, or do not take, oral anticoagulation. Although all 4 Watchman studies excluded these contraindicated patients, in the Aspirin Plavix Registry (8), the device was implanted in 150 NVAF patients ineligible for warfarin. As compared to the expected stroke rates in this population, there were 77% fewer ischemic strokes observed with device.

Another question not answered by these analyses is the relative effect of the device compared to currently approved NOACs. Currently, there are no data comparing LAAC to any of the NOACs. It must be remembered that even in the randomized NOAC trials, the 2-year drug discontinuation rates ranged between 21% and 33%, and for these patients, the protective effect of the drug would accordingly be lost (26-28).

Though warfarin has been extensively studied and has well-characterized efficacy rates, it should be noted that the Watchman trials were randomized in a 2-to-1 fashion, thus resulting in a limited number of warfarin patients with whom to compare the device, and the majority of device patients in this analysis (62%) were registry patients.

**CONCLUSIONS**

In the setting of NVAF with increased stroke risk, systemic embolism, or CV death, patients who are treated with the Watchman device for LAAC have marked reduction in hemorrhagic stroke, CV death, and major non-procedural-related bleeding compared to patients treated with chronic warfarin. This is balanced by a smaller magnitude increase in ischemic stroke in device treated patients that may reflect the diverse etiology of stroke in this population.

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**PERSPECTIVES**

**COMPETENCY IN MEDICAL KNOWLEDGE:** Cardioembolic strokes in patients with nonvalvular atrial fibrillation typically arise from the left atrial appendage, and are associated with high rates of recurrence, morbidity, and mortality. Although systemic anticoagulation can reduce the risk of stroke in patients with atrial fibrillation, this form of therapy carries a risk of bleeding and a large proportion of patients are undertreated.

**COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS:** In patients at elevated risk of stroke and bleeding with suitable anatomy, occlusion of the left atrial appendage with the catheter-deployed Watchman device is associated with lower risks of major bleeding post procedure, hemorrhagic stroke, and mortality than long-term warfarin therapy.

**TRANSLATIONAL OUTLOOK:** Further studies are needed to define risk thresholds for thromboembolism and bleeding at which patients with atrial fibrillation benefit from left atrial appendage occlusion therapy for stroke prevention and to compare the safety and efficacy of this strategy with target-specific oral anticoagulant agents.
REFERENCES


KEY WORDS: appendage occlusion, long-term warfarin, stroke prevention, thromboembolism, warfarin alternative