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# 5-Year Outcomes After Left Atrial Appendage Closure

## From the PREVAIL and PROTECT AF Trials

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## ABSTRACT

**BACKGROUND** The PROTECT AF (WATCHMAN Left Atrial Appendage System for Embolic Protection in Patients With Atrial Fibrillation) trial demonstrated that left atrial appendage closure (LAAC) with the Watchman device (Boston Scientific, St. Paul, Minnesota) was equivalent to warfarin for preventing stroke in atrial fibrillation, but had a high rate of complications. In a second randomized trial, PREVAIL (Evaluation of the WATCHMAN LAA Closure Device in Patients With Atrial Fibrillation Versus Long Term Warfarin Therapy), the complication rate was low. The warfarin cohort experienced an unexpectedly low ischemic stroke rate, rendering the efficacy endpoints inconclusive. However, these outcomes were based on relatively few patients followed for a relatively short time.

**OBJECTIVES** The final results of the PREVAIL trial, both alone and as part of a patient-level meta-analysis with the PROTECT AF trial, are reported with patients in both trials followed for 5 years.

**METHODS** PREVAIL and PROTECT AF are prospective randomized clinical trials with patients randomized 2:1 to LAAC or warfarin; together, they enrolled 1,114 patients for 4,343 patient-years. Analyses are by intention-to-treat, and rates are events per 100 patient-years.

**RESULTS** For the PREVAIL trial, the first composite coprimary endpoint of stroke, systemic embolism (SE), or cardiovascular/unexplained death did not achieve noninferiority (posterior probability for noninferiority = 88.4%), whereas the second coprimary endpoint of post-procedure ischemic stroke/SE did achieve noninferiority (posterior probability for noninferiority = 97.5%); the warfarin arm maintained an unusually low ischemic stroke rate (0.73%). In the meta-analysis, the composite endpoint was similar between groups (hazard ratio [HR]: 0.820; p = 0.27), as were all-stroke/SE (HR: 0.961; p = 0.87). The ischemic stroke/SE rate was numerically higher with LAAC, but this difference did not reach statistical significance (HR: 1.71; p = 0.080). However, differences in hemorrhagic stroke, disabling/fatal stroke, cardiovascular/unexplained death, all-cause death, and post-procedure bleeding favored LAAC (HR: 0.20; p = 0.0022; HR: 0.45; p = 0.03; HR: 0.59; p = 0.027; HR: 0.73; p = 0.035; HR: 0.48; p = 0.0003, respectively).

**CONCLUSIONS** These 5-year outcomes of the PREVAIL trial, combined with the 5-year outcomes of the PROTECT AF trial, demonstrate that LAAC with Watchman provides stroke prevention in nonvalvular atrial fibrillation comparable to warfarin, with additional reductions in major bleeding, particularly hemorrhagic stroke, and mortality. (WATCHMAN Left Atrial Appendage System for Embolic Protection in Patients With Atrial Fibrillation; NCT00129545; and Evaluation of the WATCHMAN LAA Closure Device in Patients With Atrial Fibrillation Versus Long Term Warfarin Therapy; NCT01182441) (J Am Coll Cardiol 2017;■:■–■) © 2017 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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**ABBREVIATIONS AND ACRONYMS**

**AF** = atrial fibrillation

**CI** = confidence interval

**FDA** = U.S. Food and Drug Administration

**HR** = hazard ratio

**INR** = international normalized ratio

**LAA** = left atrial appendage

**LAAC** = left atrial appendage closure

**NOAC** = nonwarfarin oral anticoagulation

**OAC** = oral anticoagulation

**PY** = patient-years

**RCT** = randomized control trial

For decades, oral anticoagulation (OAC) (initially warfarin, and more recently, the nonwarfarin oral anticoagulants [NOACs]) has been the therapeutic mainstay for stroke prophylaxis in atrial fibrillation (AF) (1,2). However, many patients cannot or will not tolerate long-term OAC because of a personal history of bleeding, risk for bleeding (e.g., elderly with fall risk or cerebral amyloid angiopathy), a high-risk occupation with safety hazards, documented noncompliance, or simply a desire to avoid OAC (3). Because thrombi typically occur in the left atrial appendage in nonvalvular AF, mechanical left atrial appendage closure (LAAC) has emerged as an alternative to OAC in selected patients (4,5).

Neither warfarin nor NOACs completely abolish ischemic stroke in AF because clots can still form in the face of OAC therapy, and there may be other stroke mechanisms at work. Similarly, it is unreasonable to expect LAAC to abolish all strokes in AF patients. Accordingly, the Watchman device (Boston Scientific, St. Paul, Minnesota) was studied against warfarin in randomized clinical trials (RCTs), and ultimately received U.S. Food and Drug Administration (FDA) approval. The first RCT, PROTECT AF (WATCHMAN Left Atrial Appendage System for Embolic Protection in Patients With Atrial Fibrillation), randomized AF patients with a $CHADS_2$ score (congestive heart failure, hypertension, 75 years of age or older, diabetes mellitus, and previous stroke or transient ischemic attack) ≥1 to either Watchman implantation or warfarin (6). At 3.8 years of follow-up (2,621 patient-years [PY]), LAAC was: 1) superior to warfarin for the primary endpoint of stroke, systemic embolism, or cardiovascular mortality; 2) equivalent for preventing stroke; and 3) superior for preventing cardiovascular and all-cause mortality. However, a high complication rate prompted initiation of a second randomized trial, PREVAIL (Evaluation of the WATCHMAN LAA Closure Device in Patients With Atrial Fibrillation Versus Long Term Warfarin Therapy), which maintained a similar design to PROTECT AF with slight modifications to the inclusion criteria (7,8). As the PREVAIL trial was primarily directed toward assessing safety, 1 major difference was that PREVAIL's statistical plan employed Bayesian statistics incorporating efficacy outcomes from PROTECT AF.

Herein, we report the final results of PREVAIL with follow-up to the protocol maximum of 5 years. Furthermore, as the PROTECT AF cohort has also completed the maximum follow-up of 5 years, we evaluated the totality of the randomized data, with a patient-level meta-analysis in which all patients from both PROTECT AF and PREVAIL are combined and the data analyzed using "traditional" frequentist statistical methods.

## METHODS

PREVAIL (NCT01182441) and PROTECT AF (NCT00129545) are prospective, multicenter, open-label, randomized FDA clinical trials (6-8). The institutional review boards at each participating center approved the trials. In both trials, patients were randomized 2:1 to either LAAC with the Watchman device (Boston Scientific, St. Paul, Minnesota) or warfarin. As previously described, the self-expanding Watchman device has a nitinol frame with fixation barbs and a permeable polyester fabric, is available in 5 sizes

clinical trials were funded by Boston Scientific, the manufacturer of the Watchman LAA closure device used in this trial (which acquired the company that initiated these trials, Atritech). Dr. Reddy has received research grant support from and has been a consultant for Abbott, Biosense Webster, and Boston Scientific. Dr. Doshi has received research grants and consulting fees from Abbott, Biosense Webster, Boston Scientific, and SentreHeart; and is the national principal investigator of the Continuous Access Registry (CAP2). Dr. Kar has received research grants from and served as a consultant for Abbott Vascular and Boston Scientific; has served as a member of the advisory board for left atrial appendage closure; is the national principal investigator of the Continuous Access Registries (CAP and CAP2); and has served as a proctor for Boston Scientific. Dr. Gibson has received speaker and proctoring fees from SentreHeart and Boston Scientific. Dr. Price has received consulting honoraria from Abbott Vascular, Boston Scientific, W.L. Gore, Medtronic, and AstraZeneca; has received speaker honoraria from Abbott Vascular, Medtronic, Terumo, and AstraZeneca; has served as a site investigator for trials involving the Watchman device; has received honoraria as a proctor for Abbott Vascular and Boston Scientific; and is a member of the Steering Committee for the National Cardiovascular Data Registry Left Atrial Appendage Occlusion Registry. Dr. Huber has served on the Watchman Advisory Board for Boston Scientific. Dr. Horton has received consulting fees from Boston Scientific. Dr. Buchbinder has received research grant support from and has been a consultant for Boston Scientific. Dr. Neuzil has received grant support and consulting fees from Abbott, Biosense Webster, and Boston Scientific. Nicole T. Gordon is a salaried employee of and owns stocks in Boston Scientific. Dr. Holmes and Mayo Clinic have a financial interest in technology related to this research; that technology has been licensed to Boston Scientific. Deepak L. Bhatt, MD, MPH, served as Guest Editor-in-Chief for this paper. Jacqueline Saw, MD, served as Guest Editor for this paper.

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ranging from 21 to 33 mm diameter to accommodate varying left atrial appendage (LAA) ostia, and is percutaneously delivered through a transseptal puncture approach using a 12-F sheath under transesophageal guidance (9). After implantation, patients were treated with an antithrombotic regimen to allow time for device endothelialization: 1) warfarin with a goal international normalized ratio (INR) between 2.0 to 3.0 and aspirin (81 mg) for 45 days; 2) following transesophageal echocardiography demonstrating adequate LAAC (no peridevice leak >5 mm width), warfarin was discontinued, and clopidogrel (75 mg) and aspirin (81 to 325 mg) were instituted until the 6-month timepoint; and then, 3) clopidogrel was discontinued and aspirin (325 mg) was continued indefinitely. In the warfarin arms, the target INR remained between 2.0 to 3.0 throughout follow-up. Follow-up visits occurred at 45 days; at 6, 9, and 12 months; and twice yearly thereafter.

The bleeding risk score, HAS-BLED (hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly, drugs/alcohol concomitantly), was not prospectively captured in these trials. However, many of the components of this score were captured as a part of the routine data collection; abnormal liver function tests and labile INR were not captured. Accordingly, a modified HAS-BLED score was determined using these available data.

For both trials, patients were followed for a maximum of 5 years, and all safety and efficacy events were independently adjudicated by an unblinded clinical events committee. An independent data and safety monitoring board oversaw trial conduct.

**THE PROTECT AF TRIAL.** As previously described, qualifying patients included adults with nonvalvular paroxysmal, persistent, or permanent AF with $CHADS_2$ score ≥1; with a preserved left ventricular ejection fraction (≥30%); and without absolute contraindication to warfarin, LAA thrombus, patent foramen ovale with atrial septal aneurysm, mobile aortic atheroma, or symptomatic carotid disease (6,7). The primary efficacy endpoint was a composite of stroke, systemic embolism, or cardiovascular/unexplained death. A Bayesian statistical model was employed to test for noninferiority and superiority.

**THE PREVAIL TRIAL.** The eligibility criteria were similar to PROTECT AF, but modified to: 1) include $CHADS_2$ ≥2 or =1 plus at least 1 of the following high-risk characteristics: female age ≥75 years, ejection fraction ≥30% but <35%, age 65 to 74 years plus either diabetes or coronary artery disease, and age ≥65 years with heart failure; and 2) exclude patients in whom chronic clopidogrel therapy was otherwise clinically indicated (8). There were 2 coprimary efficacy endpoints: 1) a composite efficacy endpoint identical to that in PROTECT AF; and 2) a composite of ischemic stroke or systemic embolization beyond 7 days post-randomization; this criterion aimed to isolate the mechanism of LAAC on embolic protection without the potential confounding influence of procedural complications. The PREVAIL trial also mandated the inclusion of new operators into the trial to assess procedural performance.

**STATISTICAL METHODOLOGY—PREVAIL.** The PREVAIL trial's statistical design was previously reported (8). Briefly, PREVAIL employed a Bayesian statistical methodology that allowed an informative prior—that is, data was "borrowed" from PREVAIL-eligible PROTECT AF trial patients at 1,500 PY of follow-up. By using this informative prior, a smaller size was possible for the confirmatory PREVAIL trial, but with the limitation that the results of the PREVAIL-only patients are not powered for these endpoints.

The endpoint data at 1,500 PY of follow-up from PROTECT AF subjects meeting PREVAIL's eligibility criteria were used in a historical previous distribution, with 50% discounting to moderate the influence of these earlier data. The primary study model was a piecewise exponential model with 4 time periods (0 to 7, 8 to 60, 61 to 182, and ≥183 days) and conjugate gamma priors with parameters based on the follow-up time and events from PROTECT AF. The primary treatment comparison was made by calculating the posterior distributions for the 18-month event rates and calculating the probability of noninferiority.

For the first efficacy endpoint, the rate ratios of 18-month event rates of the 2 arms were compared, and 1.75 as the upper bound for the ratio was used to define noninferiority. The second efficacy endpoint was based on a 1-tailed test, in which the null hypothesis would be rejected if either the ratio or the difference between rates in the 2 arms satisfied the noninferiority criteria, using 95% upper credible intervals <2.0 and <0.0275, respectively, and posterior probability for noninferiority ≥97.5%. No adjustment was made for multiple comparisons. All analyses were by intention to treat, and rates are events per 100 PY (indicated for simplicity by %).

**STATISTICAL METHODOLOGY: META-ANALYSIS.** Because of identical efficacy endpoint definitions in both the PROTECT AF and PREVAIL trials, and the near-identical eligibility criteria, data from both trials were pooled for a patient-level meta-analysis as previously described (10). Briefly, the datasets were combined with all available follow-up and analyzed

**TABLE 1 Patient Demographics**

| | PROTECT AF | | | PREVAIL | | | Combined Cohort | | |
|---|---|---|---|---|---|---|---|---|---|
| | Device (n = 463) | Control (n = 244) | p Value | Device (n = 269) | Control (n = 138) | p Value | Device (n = 732) | Control (n = 382) | p Value |
| Age, yrs | 71.7 ± 8.8 | 72.7 ± 9.2 | 0.18 | 74.0 ± 7.4 | 74.9 ± 7.2 | 0.26 | 72.6 ± 8.4 | 73.5 ± 8.6 | 0.09 |
| Male | 70.4 | 70.1 | 0.93 | 67.7 | 74.6 | 0.15 | 69.4 | 71.7 | 0.42 |
| $CHADS_2$ score | 2.2 ± 1.2 | 2.3 ± 1.2 | 0.07 | 2.6 ± 1.0 | 2.6 ± 1.0 | 0.48 | 2.3 ± 1.1 | 2.4 ± 1.2 | 0.06 |
| Risk factors | | | | | | | | | |
| CHF | 26.8 | 27.0 | 0.94 | 23.4 | 23.2 | 0.96 | 25.5 | 25.7 | 0.97 |
| Hypertension | 89.6 | 90.2 | 0.82 | 88.5 | 97.1 | 0.003 | 89.2 | 92.7 | 0.06 |
| Age ≥75 yrs | 36.9 | 41.4 | 0.25 | 46.5 | 46.4 | 0.99 | 40.4 | 43.2 | 0.38 |
| Diabetes | 24.4 | 29.5 | 0.14 | 33.8 | 29.7 | 0.4 | 27.9 | 29.6 | 0.55 |
| Prior stroke/TIA | 17.7 | 20.1 | 0.44 | 29.7 | 29.7% | 1.0 | 22.1 | 23.6 | 0.59 |
| $CHA_2DS_2$-VASc score | 3.4 ± 1.5 | 3.7 ± 1.6 | 0.02 | 4.0 ± 1.2 | 4.1 ± 1.2 | 0.4 | 3.6 ± 1.4 | 3.9 ± 1.5 | 0.02 |
| AF pattern | | | | | | | | | |
| Paroxysmal | 43.2 | 40.6 | 0.50 | 48.7 | 51.4 | 0.6 | 45.2 | 44.5 | 0.82 |
| Persistent | 21.0 | 20.5 | 0.89 | 31.6 | 28.3 | 0.49 | 24.9 | 23.3 | 0.56 |
| Permanent | 34.6 | 38.1 | 0.35 | 15.6 | 15.9 | 0.93 | 27.6 | 30.1 | 0.38 |
| Unknown | 1.3 | 0.8 | 0.72 | 1.5 | 0.7 | 0.5 | 1.4 | 0.8 | 0.56 |
| Paced | 0 | 0 | – | 2.6 | 3.6 | 0.55 | 1.0 | 1.3 | 0.56 |

Values are mean ± SD or n/N (%).

CHF = congestive heart failure; $CHADS_2$ = congestive heart failure, hypertension, 75 years of age or older, diabetes mellitus, and previous stroke or transient ischemic attack; $CHA_2DS_2$-VASc = 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; PREVAIL = Evaluation of the WATCHMAN LAA Closure Device in Patients With Atrial Fibrillation Versus Long Term Warfarin Therapy; PROTECT AF = WATCHMAN Left Atrial Appendage System for Embolic Protection in Patients With Atrial Fibrillation; TIA = transient ischemic attack.

to provide a more robust exploration of the role of covariates. The baseline risk profile in the combined population included a somewhat higher risk profile for the PREVAIL cohort; subgroup analyses were performed to assess for potential differences in outcome by baseline risk. Analyses were intent-to-treat, censoring data from patients without events at the time of the last known status. Strokes were classified as disabling if associated with an increase in the Modified Rankin Score by at least 2 points. A Cox proportional hazards model with confidence intervals (CIs) was used for comparison of event rates. This model was stratified by study (PROTECT AF or PREVAIL) to account for differences in risk profiles. Kaplan-Meier curves were used for graphical assessment of time-dependent events. Results are presented using frequentist statistics and 2-sided p values nominally significant at $p < 0.05$, without adjustment for multiple comparisons.

## RESULTS

**BASELINE CHARACTERISTICS.** The PROTECT AF and PREVAIL trials enrolled patients at 59 U.S. and European centers between 2005 and 2008, and at 41 U.S. centers between 2010 and 2012, respectively. As shown in Table 1, the trials enrolled 707 and 407 patients, respectively, with randomization in a 2:1 fashion to the LAAC and warfarin arms. In both trials, patients were followed for the protocol-defined maximum time period of 5 years, ending in 2013 and 2017, respectively. The mean follow-up in PROTECT AF was 47.6 ± 21.3 months to yield 2,717 PY, and for PREVAIL was 47.9 ± 19.4 months for 1,626 PY. The combined follow-up of both trial cohorts was 4,343 PY.

Within each study, the baseline characteristics were similar between treatment arms (Table 1). The risk profile of the PROTECT AF cohort was somewhat lower than that of PREVAIL's cohort: mean ages were 72.0 ± 8.9 years and 74.3 ± 7.4 years, and $CHA_2DS_2$-VASc (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) scores were 3.5 ± 1.6 and 4.0 ± 1.2, respectively. Most patients in both trials were at high risk for stroke: 93% and 100% of the patients in PROTECT AF and PREVAIL had $CHA_2DS_2$-VASc scores ≥2. The modified HAS-BLED scores were elevated in both the PROTECT AF and PREVAIL trials, with only 6.4% and 1.7%, respectively, considered at low risk (HAS-BLED score = 0); 73.7% and 68.6%, respectively, at moderate risk (HAS-BLED score = 1 to 2); and 19.9% and 29.7%, respectively, at high risk (HAS-BLED score ≥3).

**PREVAIL PRIMARY EFFICACY ENDPOINTS.** For the PREVAIL trial, the calculated 18-month rate of the first coprimary efficacy endpoint (composite of stroke,

**TABLE 2 PREVAIL Primary Efficacy Endpoints**

| Dataset | Device 18-Month Rate | Control 18-Month Rate | 18-Month Rate Ratio (95% CrI) | Criteria Met? 95% CrI Upper Bound <1.75 | | | Posterior Probability Noninferiority ($P_{NI}$ ≥97.5%) |
|---|---|---|---|---|---|---|---|
| **First Primary Endpoint (ITT)—Stroke, SE, and CV/Unexplained Death** | | | | | | | |
| Primary analysis (January 2013) | 0.064 | 0.063 | 1.07 (0.57 to 1.89) | No | | | 93% |
| First post hoc analysis (June 2014) | 0.065 | 0.057 | 1.21 (0.69 to 2.05) | No | | | 93% |
| Final 5-year analysis (September 2017) | 0.066 | 0.051 | 1.33 (0.78 to 2.13) | No | | | 88.4% |
| | | | | | 18-Month Rate Difference (95% CrI) | Criteria Met? 95% CrI Upper Bound <0.0275 | |
| **Second Primary Endpoint (ITT)—Ischemic Stroke or SE >7 Days Must Meet Either the 18-Month Rate Ratio OR 18-Month Rate Difference Criteria** | | | | | | | |
| Primary analysis (January 2013) | 0.0253 | 0.0200 | 1.6 (0.5 to 4.2) | No | 0.0053 (−0.0190 to 0.0273) | Yes | 97.6% |
| First post hoc analysis (June 2014) | 0.0294 | 0.0131 | 2.8 (0.9 to 7.3) | No | 0.0163 (−0.0023 to 0.0342) | No | 89.2% |
| Final 5-year analysis (September 2017) | 0.0255 | 0.0135 | 2.2 (0.8 to 4.9) | No | 0.0120 (−0.0036 to 0.0275)* | Yes | 97.5% |

*Upper credible interval (CrI) is displayed as 0.0275, but if all significant digits were displayed, it is less than upper bound of 0.0275.

ITT = intention to treat; PREVAIL = Evaluation of the WATCHMAN LAA Closure Device in Patients With Atrial Fibrillation Versus Long Term Warfarin Therapy; SE = systemic embolism.

systemic embolism, and cardiovascular/unexplained death) was 0.066 with LAAC versus 0.051 for warfarin, yielding a mean 18-month rate ratio of 1.33 (95% credible interval: 0.78 to 2.13). Because the upper bound of 2.13 was not lower than the pre-specified noninferiority margin of 1.75, statistical noninferiority was not achieved (Table 2). The posterior probabilities for noninferiority and superiority were 88.4% and 15.8%, respectively. None of the components of the primary efficacy endpoint were significantly different between treatment arms (Table 3). The rate of ischemic stroke with warfarin (0.73%) was lower than expected for a warfarin-treated cohort with a mean $CHA_2DS_2$-VASc score of 4.0 ± 1.2. Analyses of this coprimary endpoint at earlier timepoints of the study also failed to demonstrate noninferiority.

The calculated 18-month rate for the second coprimary efficacy endpoint (ischemic stroke or systemic embolism >7 days post-randomization) was 0.0255 in the LAAC group versus 0.0135 in the warfarin group (rate difference 0.0120; 95% credible interval: −0.0036 to 0.0275) (Table 2). Because the posterior probability for noninferiority was 97.5% for the risk difference, noninferiority of the device to warfarin was achieved.

**META-ANALYSIS OF ALL RANDOMIZED PATIENTS.** In a patient-level meta-analysis of all patients enrolled in the PROTECT AF and PREVAIL trials (Table 4, Central Illustration), the composite of stroke, systemic embolism, or cardiovascular/unexplained death occurred with similar frequency in the LAAC and warfarin groups (hazard ratio [HR]: 0.82; 95% CI: 0.58 to 1.17; p = 0.27). The Kapan-Meier estimate of this endpoint is shown in Figure 1. Subgroup analysis of this composite endpoint revealed no significant interaction with clinical characteristics such as age dichotomized at 75 years, sex, baseline $CHA_2DS_2$-VASc score and modified HAS-BLED score (Figure 2).

**TABLE 3 Efficacy Rates at 5 Years (2:1 Randomization)**

| | PROTECT AF Subjects | | | | | PREVAIL-Only Subjects | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Device Group (n = 463) | | Control Group (n = 244) | | | Device Group (n = 269) | | Control Group (n = 138) | | |
| | No. of Events | Rate* | No. of Events | Rate* | p Value | No. of Events | Rate* | No. of Events | Rate* | p Value |
| Primary efficacy: stroke/SE/CV death | 40/1,787.7 | 2.24 | 34/929.4 | 3.66 | 0.04 | 37/1,038.3 | 3.65% | 15/530.4 | 2.94% | 0.47 |
| All stroke | 26/1,781.7 | 1.46 | 20/929.4 | 2.15 | 0.23 | 19/1,042.4 | 1.97% | 7/530.4 | 1.29% | 0.32 |
| Ischemic stroke | 24/1,781.7 | 1.35 | 10/932.8 | 1.07 | 0.49 | 17/1,043.1 | 1.68% | 4/533.3 | 0.73% | 0.13 |
| Hemorrhagic stroke | 3/1,837.7 | 0.16 | 10/945.6 | 1.06 | 0.005 | 2/1,084.6 | 0.18% | 3/538.0 | 0.54% | 0.23 |
| Systemic embolism | 3/1,837.1 | 0.16 | 0 | N/A | N/A | 1/1,080.6 | 0.09% | 0/540.9 | N/A | N/A |
| CV/unexplained death | 19/1,843.2 | 1.03 | 22/948.9 | 2.32 | 0.009 | 18/1,084.7 | 1.79% | 10/540.9 | 1.98% | 0.76 |

*Events are per 100 patient-years.

CV = cardiovascular; SE = systemic embolism; other abbreviations as in Table 1.

**TABLE 4 5-Year Patient-Level Meta-Analysis of PROTECT AF and PREVAIL (2:1 Randomization)**

| | Device Group (n = 732) | | Control Group (n = 382) | | | |
|---|---|---|---|---|---|---|
| | No. of Events | Rate (per 100 PY) | No. of Events | Rate (per 100 PY) | Hazard Ratio (95% Confidence Interval) | p Value |
| Efficacy: stroke/SE/CV death | 79/2,856.0 | 2.8% | 50/1,472.8 | 3.4% | 0.82 (0.58–1.17) | 0.27 |
| All stroke or SE | 49/2,849.4 | 1.7% | 27/1,472.9 | 1.8% | 0.96 (0.60–1.54) | 0.87 |
| Ischemic stroke or SE | 45/2,850.2 | 1.6% | 14/1,479.1 | 0.95% | 1.71 (0.94–3.11) | 0.08 |
| Hemorrhagic stroke | 5/2,954.8 | 0.17% | 13/1,499.0 | 0.87% | 0.20 (0.07–0.56) | 0.0022 |
| Ischemic stroke or SE >7 days | 37/2,862.1 | 1.3% | 14/1,479.1 | 0.95% | 1.40 (0.76–2.59) | 0.28 |
| Disabling stroke | 13/2,943.0 | 0.44% | 15/1,493.8 | 1.0% | 0.45 (0.21–0.94) | 0.03 |
| Nondisabling stroke | 31/2,879.1 | 1.1% | 12/1,484.3 | 0.81% | 1.38 (0.71–2.68) | 0.35 |
| CV/unexplained death | 39/2,960.5 | 1.3% | 33/1,505.2 | 2.2% | 0.59 (0.37–0.94) | 0.027 |
| All-cause death | 106/2,961.6 | 3.6% | 73/1,505.2 | 4.9% | 0.73 (0.54–0.98) | 0.035 |
| Major bleeding, all | 85/2,748.4 | 3.1% | 50/1,414.7 | 3.5% | 0.91 (0.64–1.29) | 0.60 |
| Major bleeding, non-procedure-related | 48/2,853.6 | 1.7% | 51/1,411.3 | 3.6% | 0.48 (0.32–0.71) | 0.0003 |

Two strokes in PREVAIL are excluded because the baseline MRS score was unavailable. Disabling stroke is defined as a stroke that increases the Modified Rankin Score by ≥2.
PY = patient-years. Other abbreviations as in Table 3.

A consistent treatment effect was also observed in patients with prior stroke or transient ischemic attack—patients who enrolled in the trials for secondary prevention of stroke.

The rate of all-stroke or systemic embolism was also similar between groups (HR: 0.96; 95% CI: 0.60 to 1.54; p = 0.87). However, there were directional variations in the individual components of this endpoint: the rate of ischemic stroke or systemic embolism was numerically (but not statistically significantly) higher with LAAC (HR: 1.71; 95% CI: 0.94 to 3.11; p = 0.08). If procedure-related strokes were excluded, the difference in ischemic stroke or systemic embolism remained nonsignificant (HR: 1.40; 95% CI: 0.76 to 2.59; p = 0.28). On the other hand, there was a large and statistically-significant decrease in hemorrhagic stroke with LAAC (HR: 0.20; 95% CI: 0.07 to 0.56; p = 0.0022). Kaplan-Meier estimates of these stroke components are shown in Figure 1.

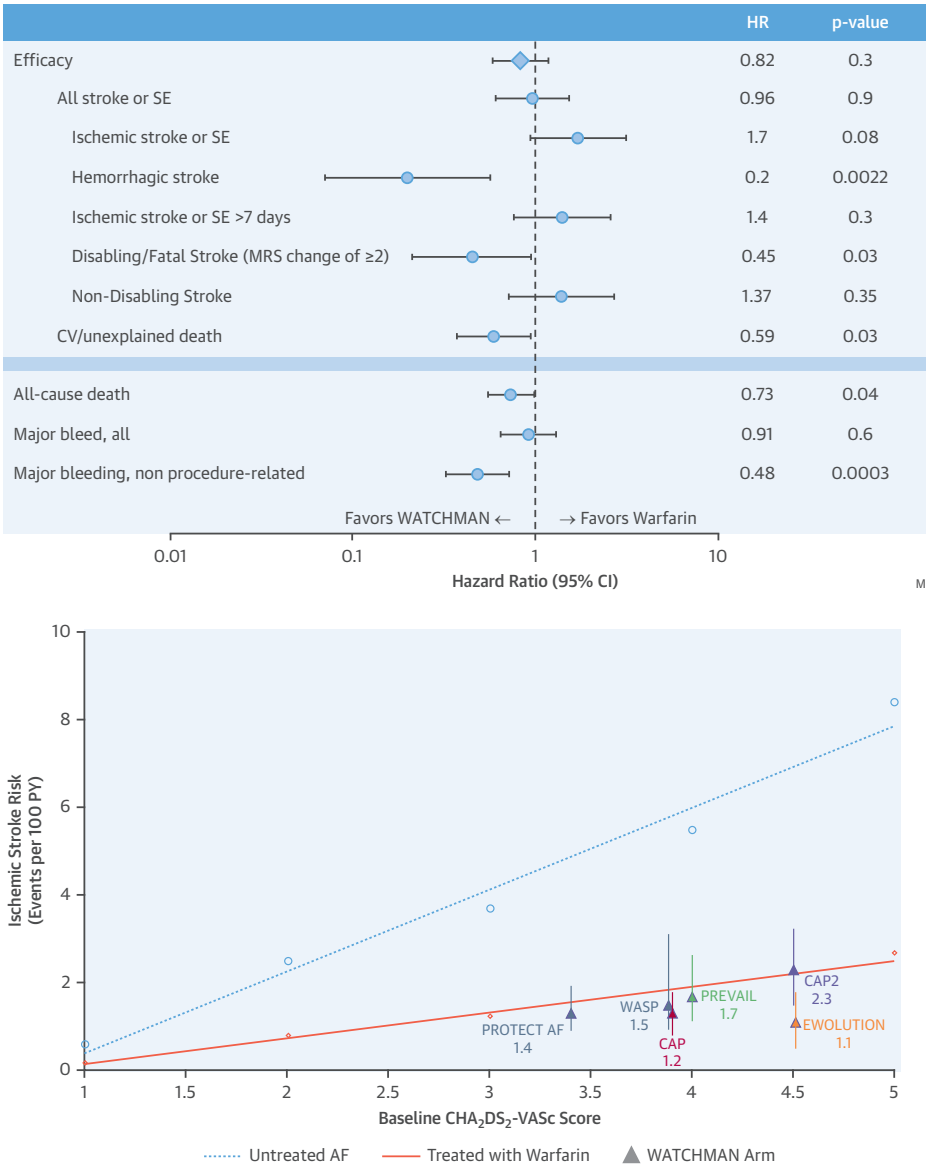
In addition to partitioning the strokes by type, the strokes were also subdivided by clinical severity. Although there was no statistical difference in the rate of nondisabling strokes, there were substantially fewer disabling/fatal strokes with LAAC (HR: 0.45; 95% CI: 0.21 to 0.94; p = 0.034). LAAC was also associated with statistically-significantly lower rates of cardiovascular or unexplained death (HR: 0.59; 95% CI: 0.37 to 0.94; p = 0.027).

Beyond the composite efficacy endpoint and its individual components, additional analyses included all-cause death and major bleeding (Table 4, Central Illustration). Consistent with cardiovascular death, the HR for all-cause death also significantly favored LAAC (HR: 0.73; 95% CI: 0.54 to 0.98; p = 0.035). The Kaplan-Meier estimate of all-cause death is shown in Figure 1. For major bleeding, including those bleeds occurring at the time of the procedure such as pericardial effusions and vascular access complications, there was no significant difference between LAAC and warfarin (HR: 0.91; 95% CI: 0.64 to 1.29; p = 0.60). But excluding procedure-related events, consistent with the absence of chronic OAC treatment, LAAC patients experienced substantially fewer major bleeds (HR: 0.48; 95% CI: 0.32 to 0.71; p = 0.0003).

## DISCUSSION

Beyond the PROTECT AF trial, PREVAIL is the only other randomized clinical trial comparing a LAAC device with any oral anticoagulant. The 5-year outcomes of the PREVAIL trial revealed that: 1) for the first coprimary composite endpoint of stroke, systemic embolism, or cardiovascular/unexplained death, LAAC did not meet the noninferiority endpoint; and 2) LAAC achieved noninferiority to warfarin for the second coprimary endpoint of ischemic stroke or systemic embolism (>7 days post-procedure), consistent with the mechanistic hypothesis of LAAC. Furthermore, in a patient-level meta-analysis combining the 5-year outcomes of the PREVAIL and PROTECT AF trials, compared with warfarin, LAAC provided equivalent rates of all-cause stroke, with reductions in hemorrhagic stroke and disabling/fatal stroke. There were no significant differences in ischemic stroke, but LAAC was associated with significant reductions in both cardiovascular and all-cause mortality.

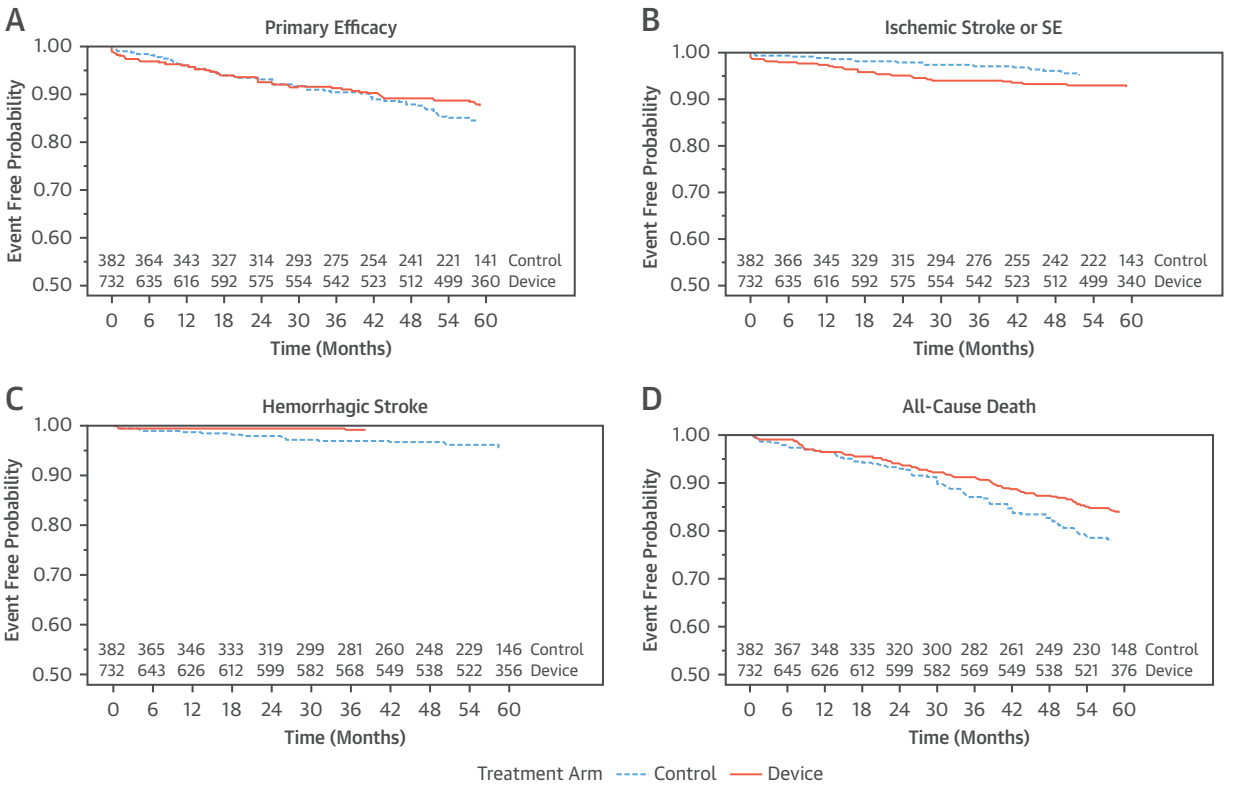
## CENTRAL ILLUSTRATION Stroke Prevention in Nonvalvular Atrial Fibrillation With LAA Closure




**Reddy, V.Y. et al. J Am Coll Cardiol. 2017;■(■):■–■.**

**(Top)** In a patient-level meta-analysis combining the randomized PROTECT AF and PREVAIL trial cohorts, patients receiving the Watchman device were compared with patients receiving chronic warfarin for major clinical endpoints. Disabling was defined as an increase in the Modified Rankin Score by at least 2 points. **(Bottom)** The ischemic stroke rates of nonvalvular atrial fibrillation patients are shown as a function of the baseline $CHA_2DS_2$-VASc score using 2 large population databases (11,12). The **dotted line** represents untreated patients, whereas the **solid line** represents OAC-treated patients, largely warfarin. On this graph, the ischemic stroke rates and 95% confidence intervals of the LAAC arms from various clinical trials are shown. Because the baseline $CHA_2DS_2$-VASc scores for CAP and WASP were identical, they are arbitrarily offset for clarity; CAP2 and EWOLUTION were similarly offset for clarity. This imputed placebo analysis demonstrates the consistent performance of LAA closure with the Watchman device in preventing ischemic stroke across the various clinical studies. CAP = Continued Access to PROTECT AF registry; CAP2 = Continued Access to PREVAIL; $CHA_2DS_2$-VASc = 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; CI = confidence interval; CV = cardiovascular; EWOLUTION = Registry on Watchman Outcomes in Real-Life Utilization; HR = hazard ratio; LAA = left atrial appendage; MRS = Modified Rankin Score; PY = patient years; SE = systemic embolism; WASP = Registry on Watchman Outcomes in Real-Life Utilization WASP Registry.

**FIGURE 1 PROTECT AF/PREVAIL Combined: Kaplan-Meier Curves of the Major Efficacy Endpoints**



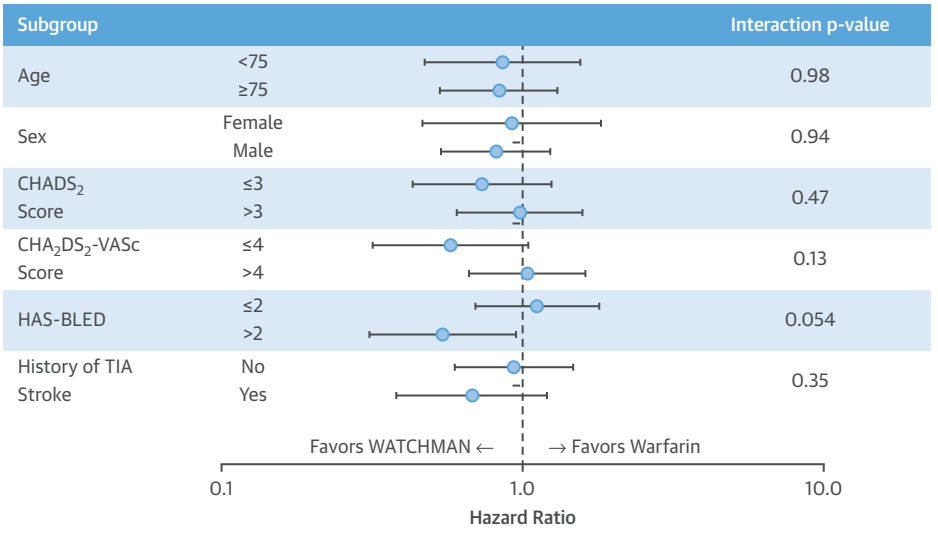

**(A)** Freedom from composite efficacy events—stroke, systemic embolism (SE), or cardiovascular/unexplained death (hazard ratio [HR]: 0.82; p = 0.27). **(B)** Freedom from ischemic stroke (HR: 1.7; p = 0.08). **(C)** Freedom from hemorrhagic stroke (HR: 0.20; p = 0.0022). **(D)** Freedom from all-cause death (HR: 0.73; p < 0.04). PREVAIL = Evaluation of the WATCHMAN LAA Closure Device in Patients With Atrial Fibrillation Versus Long Term Warfarin Therapy; PROTECT AF = WATCHMAN Left Atrial Appendage System for Embolic Protection in Patients With Atrial Fibrillation.

**PREVAIL EFFICACY OUTCOMES.** We previously reported at the pre-specified time of the primary analysis in 2013 at 11.8 ± 5.8 months of follow-up (396 PY), LAAC met noninferiority for 1 of the 2 coprimary efficacy endpoints (the rate ratio difference for post-procedure ischemic stroke or systemic embolism, but not the rate ratio for stroke, systemic embolism, or cardiovascular death) (8). Herein, we now report that with continued follow-up in the PREVAIL trial until patients reached the protocol maximum 5 years of follow-up, LAAC continued to meet non-inferiority criteria for the same 1 of the 2 coprimary endpoints (post-procedure ischemic stroke or system embolism).

Given the striking results for LAAC in the larger PROTECT AF trial, why were the PREVAIL results less positive? First, PREVAIL enrolled fewer patients and was not statistically powered to "stand on its own." Instead, PREVAIL's Bayesian statistical design incorporated an informative prior and "borrowed" data from PROTECT AF. Thus, the lack of statistical significance in any of the components of the composite endpoints of the newly enrolled PREVAIL-only patients (Table 3) is not surprising. After incorporating the pre-specified statistical methodology, the second coprimary endpoint (post-procedure ischemic stroke or system embolism) met the criteria for non-inferiority. But, although the statistical significance criteria were met, it is still worth evaluating the clinical significance of the numerically greater number of ischemic strokes with LAAC in the newly enrolled PREVAIL patients. Although PREVAIL was not powered to examine differences in ischemic stroke, the question nonetheless remains: why the difference? Did LAAC perform worse than expected or warfarin better than expected (or both)?

The former was addressed in an imputed placebo analysis of PREVAIL. In the Central Illustration, the

**FIGURE 2** **PROTECT AF/PREVAIL Combined: Primary Efficacy by Subgroup**




For the composite efficacy endpoint of stroke, systemic embolism, or cardiovascular/unexplained death, the effect of LAAC versus warfarin was calculated for the different subsets of patients enrolled. There was no significant difference in outcomes by patient subset. $CHADS_2$ = congestive heart failure, hypertension, 75 years of age or older, diabetes mellitus, and previous stroke or transient ischemic attack; $CHA_2DS_2$-VASc = 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; HAS-BLED = hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly, drugs/alcohol concomitantly; TIA = transient ischemic attack; other abbreviations as in Figure 1.

ischemic stroke rates of untreated AF patients (dotted line) and warfarin-treated patients (solid line) are plotted as a function of the baseline $CHA_2DS_2$-VASc score using 2 large population databases (11,12). The ischemic stroke point estimate and 95% CIs of the LAAC arm of PREVAIL overlapped the solid line, thereby demonstrating that the LAAC arm in PREVAIL performed as expected in providing ischemic stroke reduction similar to that observed with warfarin. This consistency of ischemic stroke reduction was also observed with LAAC arms of other large prospective trials: 1) PROTECT AF; 2) the nonrandomized prospective FDA registries, CAP (Continued Access to PROTECT AF) and CAP2 (Continued Access to PREVAIL); 3) the prospective 1,021-patient EWOLUTION (Registry on Watchman Outcomes in Real-Life Utilization) conducted in Europe, Russia, and the Middle East; and 4) the prospective multicenter 201-patient WASP (Registry on Watchman Outcomes in Real-Life Utilization) conducted in Asia and Australia (10,13,14). Together, these data further corroborate the critical role of the LAA in stroke pathogenesis in AF.

However, PREVAIL's warfarin group had an unusually low ischemic stroke rate of 0.73%, a rate superior to that observed for warfarin in other stroke prevention trials: in RE-LY (Randomized Evaluation of Long-Term Anticoagulation Therapy), ROCKET-AF (Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation), ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation), ENGAGE-AF TIMI-48 (Effective Anticoagulation with Factor Xa [Next Generation in Atrial Fibrillation-Thrombolysis in Myocardial Infarction]-48), and PROTECT AF, warfarin's ischemic stroke rates were 1.2 (95% CI: 1.00 to 1.39), 1.42 (95% CI: 1.20 to 1.63), 1.05 (95% CI: 0.92 to 1.24), 1.25 (95% CI: 1.05 to 1.36), and 1.1 (95% CI: 0.6 to 2.0), respectively (15-18). That is, despite the expected differences in population characteristics across this range of trials, the warfarin arms exhibited similar ischemic stroke rates—with the notable exception being the warfarin arm of PREVAIL. This low rate is not due to a lower risk cohort—the $CHA_2DS_2$-VASc score in PREVAIL was 4.0 ± 1.2. Rather, the answer is likely found in the wide 95% CIs (0.27% to 1.95%): the small size of PREVAIL's warfarin arm (n = 138) resulted in a point estimate with low confidence—that is, chance.

Indeed, if warfarin's ischemic stroke rate was truly 0.73% in an AF population with a $CHA_2DS_2$-VASc = 4.0, there is no known therapy that would be equivalent, including any NOAC.

**5-YEAR META-ANALYSIS: STROKE EFFICACY OUTCOMES.** To fully appreciate the relative efficacy of LAAC versus warfarin, a 5-year patient-level meta-analysis was performed including all randomized patients from the PREVAIL and PROTECT AF trials. Despite including PREVAIL's overperforming warfarin arm, this intention-to-treat analysis revealed 18% fewer primary efficacy events (stroke, systemic embolism, or cardiovascular/unexplained death) with LAAC, but this did not reach statistical significance (**Table 4, Central Illustration**). The overall stroke or systemic embolism rates were also similar between groups, but there was a divergence when examining stroke type.

The rate of ischemic stroke or systemic embolism was numerically higher with LAAC, although the magnitude of this difference was further attenuated when procedure-related strokes were excluded (again, neither difference reached statistical significance). On the other hand, the rate of hemorrhagic stroke was 80% less with LAAC, a value that was both statistically significant and clinically significant because it is well-appreciated that hemorrhagic strokes are associated with high morbidity and mortality (19). An analysis of stroke severity strongly and significantly favored LAAC—there were 55% fewer disabling/fatal strokes with LAAC ($p = 0.03$). Thus, although the overall stroke rates between LAAC with the Watchman device and warfarin are similar, the former strokes are less often disabling or fatal.

Although the present paper only focuses on Watchman, there are nonrandomized data using other LAAC strategies that further buttress the pathophysiological basis of mechanical appendage closure for stroke prevention. First, in a 1,047-patient multicenter registry of AF patients ($CHA_2DS_2$-VASc 4.5 ± 1.6) followed for 13 months after receiving an alternative LAAC device, the Amplatzer Cardiac Plug (St. Jude Medical, St. Paul, Minnesota), the observed thromboembolism rate (2.3%) was 59% less than expected if untreated (20). Second, a comparative effectiveness analysis of surgical LAAC using the Society of Thoracic Surgeons database (n = 10,524; $CHA_2DS_2$-VASc = 4; surgical LAAC in 37%), the thromboembolism rates at 1 year were 1.6% and 2.5% with and without LAAC, respectively ($p = 0.001$) (21).

**5-YEAR META-ANALYSIS: MORTALITY OUTCOMES.** At 5 years, LAAC with Watchman was associated with a statistically significant 41% decrease in cardiovascular mortality and a 27% decrease in all-cause mortality. These observations are particularly striking when one considers that the elderly patients enrolled in these randomized trials are likely to have competing mortality risks. The mechanism of mortality benefit is driven in part by the 80% decrease in hemorrhagic stroke with LAAC. In addition, it is possible that some of the mortality benefit may also be driven by reduced noncranial bleeding. That is, the primary benefit of LAAC is the ability to avoid OAC and its associated bleeding risk. Indeed, the meta-analysis revealed a 52% decrease in post-procedure major bleeding with LAAC. Also, a recent subanalysis of major bleeding in the ARISTOTLE trial revealed that in addition to the expected increase in subsequent 30-day mortality associated with cranial bleeding (HR: 121.5), noncranial bleeding also conferred high 30-day mortality (HR: 11.57) (22).

Mortality alone was not a primary endpoint in either trial. However, cardiovascular mortality was a component of the primary efficacy endpoint of both trials. Second, in virtually all stroke prevention trials, mortality is an important secondary endpoint with a clinical relevance that is undisputed. Third, mortality reduction is mechanistically congruent with avoiding warfarin. Indeed, the ~10% mortality benefit conferred by NOACs over warfarin was also driven by a reduction in hemorrhagic stroke with NOACs (2).

**CLINICAL IMPLICATIONS.** In the translation of these trial results to clinical practice, it is important to recognize the patient populations enrolled in these trials. All enrolled patients had nonvalvular AF—that is, no rheumatic heart disease or mechanical heart valves. The PROTECT AF and PREVAIL trials also excluded patients who were at higher risk of harboring thrombi outside of the LAA—in particular, patients with severely reduced ventricular function (left ventricular ejection fraction <30%) or a large atrial septal aneurysm. Patients were all at elevated stroke risk: 93% and 100% of the patients in the PROTECT AF and PREVAIL trials had a $CHA_2DS_2$-VASc score of 2 or greater, respectively.

It is also worth considering that when deciding which patients to consider for enrollment in these trials of cardiovascular intervention, physicians likely also incorporated other factors not necessarily captured by the $CHA_2DS_2$-VASc score. For example, if clinicians had preferentially chosen patients considered to be at higher fall risk, this would not have been captured in the baseline characteristics. Clinical judgment is a quality that is difficult to characterize or quantify, but certainly should be employed to determine which AF patients are likely to be poor candidates for long-term OAC because of a propensity for bleeding or poor drug compliance, and

thus should preferentially be considered for LAAC. Finally, procedural complications are important factors in determining the risk-benefit calculation for LAAC.

**STUDY LIMITATIONS.** Although the PREVAIL trial was designed for a total of 5 years of follow-up, the primary efficacy endpoints were pre-specified to only be evaluated at the time of the initial analysis: when the last patient enrolled reached 6 months of follow-up. Thus, the current analysis should be considered post hoc. In addition, the pre-specified informative prior for PREVAIL was at 1,500 PY of follow-up in PROTECT AF only, and the additional 3 years of PROTECT AF follow-up were not incorporated into further analyses, including the current one. However, this was the more conservative approach, because use of the full 5-year PROTECT AF data for the informative prior would have further favored the LAAC group.

Per the eligibility criteria, patients who enrolled in these trials had to be able to tolerate OAC. This is underscored by the fact that Watchman implantation was followed by a short-term antithrombotic regimen: warfarin for 6 weeks and dual antiplatelet therapy until 6 months. Thus, these results do not necessarily apply to patients with true contraindications to OAC. However, an ongoing RCT of LAAC versus antiplatelet therapy (ASAP-TOO [Assessment of the WATCHMAN Device in Patients Unsuitable for Oral Anticoagulation]; NCT02928497) has been designed to evaluate this strategy.

After these LAAC RCTs were initiated, NOACs became clinically available and are now routinely used in clinical practice. It should be remembered that LAAC with the Watchman device has not been tested against these agents. RCTs of LAAC versus NOACs are likely to be conducted in forthcoming years; indeed, a small such study (PRAGUE-17 [Left Atrial Appendage Closure vs. Novel Anticoagulation Agents in Atrial Fibrillation]; NCT02426944) is currently ongoing.

Finally, the patient populations in real-world clinical practice may differ from those enrolled during clinical trials. Forthcoming results from the National Cardiovascular Data Registry should provide further insight on this issue.

## CONCLUSIONS

The long-term 5-year outcomes of the PREVAIL trial, combined with the 5-year outcomes of the PROTECT AF trial, demonstrate that LAAC with the Watchman device provides stroke prevention in nonvalvular AF patients to a similar degree as OAC with warfarin. Furthermore, by virtue of its ability to minimize major bleeding, particularly hemorrhagic stroke, LAAC results in less disability or death than warfarin.

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## PERSPECTIVES

**COMPETENCY IN MEDICAL KNOWLEDGE AND PATIENT CARE:** In patients with AF undergoing LAA occlusion using the Watchman device, protection against ischemic stroke and systemic embolism was similar to that achieved with warfarin anticoagulation, but LAA closure was associated with substantial reductions in hemorrhagic, disabling and fatal stroke, favorably influencing survival.

**TRANSLATIONAL OUTLOOK:** Further studies are needed to compare the benefit of LAA occlusion against oral anticoagulants other than warfarin in patients with AF, and to assess advantages for those with contraindications to anticoagulation.

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**KEY WORDS** atrial fibrillation, left atrial appendage, left atrial appendage closure, oral anticoagulation, stroke prevention, warfarin, Watchman