Net Clinical Benefit of Left Atrial Appendage Closure Versus Warfarin in Patients With Atrial Fibrillation: A Pooled Analysis of the Randomized PROTECT-AF and PREVAIL Studies

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Background—The PROTECT-AF (Watchman Left Atrial Appendage Closure Technology for Embolic Protection in Patients With Atrial Fibrillation) and PREVAIL (Evaluation of the Watchman LAA Closure Device in Patients With Atrial Fibrillation Versus Long Term Warfarin Therapy) trials demonstrated noninferiority of left atrial appendage closure (LAAC) to warfarin for the composite end point of stroke, systemic embolism, or cardiovascular death. This study aims to quantify the net clinical benefit (NCB) of LAAC versus warfarin, accounting for differences in clinical impact of different event types.

Methods and Results—We performed a post hoc analysis of the PROTECT-AF and PREVAIL trials, which randomized atrial fibrillation patients to LAAC or warfarin in a 2:1 fashion. The trials enrolled patients in the United States and Europe between 2005 and 2012 with paroxysmal, persistent, or permanent atrial fibrillation and CHADS2 risk scores ≥1. Relative to an index weight for death (1.0), events were assigned weights based on their disabling effect: (1) stroke event weights were based on modified Rankin scores in the base case analyses, and (2) major bleed (0.05) and pericardial effusion (0.05). NCB was calculated as the sum of weight-adjusted events per 100 patient-years. Among 1114 randomized subjects, the NCB of LAAC was 1.42% per year (95% CI 0.01–2.82, P=0.04) and a relative risk of 0.74 (95% CI 0.56–1.00). NCB point estimates favored warfarin early in follow-up, but trended in favor of LAAC after 1 to 2 years. The benefit of LAAC was preserved across subgroups, with particular benefit observed in the subgroup of prior stroke and without diabetes mellitus.

Conclusions—This analysis demonstrates long-term NCB of LAAC with Watchman over warfarin therapy, as the upfront risk of periprocedural events is counterbalanced over time by reduced bleeding events and mortality.

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Key Words: anticoagulation • atrial fibrillation • left atrial appendage

Anticoagulation with warfarin, and more recently nonwarfarin oral anticoagulants (NOACs), has been the mainstay of therapy to prevent stroke in patients with atrial fibrillation (AF). However, long-term warfarin therapy confers an increased risk of major bleeding events including intracranial hemorrhage. In 2 randomized trials, PROTECT-AF (Watchman Left Atrial Appendage Closure Technology for Embolic Protection in Patients With Atrial Fibrillation) and PREVAIL (Evaluation of the Watchman LAA Closure Device in Patients With Atrial Fibrillation Versus Long Term Warfarin Therapy), left atrial appendage closure (LAAC) was compared with warfarin for stroke prevention and, in the most recent meta-analysis of these studies, had similar overall risk for the primary composite end point of stroke, systemic embolism, and cardiac death. But the relative rates of the primary stroke subtypes favored opposite study arms: a trend toward higher risk of ischemic stroke in the LAAC arm was counterbalanced by a significantly reduced risk of hemorrhagic stroke.

Clinicians are often in situations where they need to choose between therapies that result in multiple heterogeneous consequences. Net clinical benefit (NCB) analyses can be helpful to provide a more clinically relevant assessment of
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Clinical Perspective

What Is New?

• This study compared the net clinical benefit of left atrial appendage closure versus warfarin therapy using the composite cardiovascular end point of stroke, systemic embolism, or cardiovascular death, and accounting for the clinical impact of events based on the severity of postevent disability.

What Are the Clinical Implications?

• Left atrial appendage closure had a statistically significant net clinical benefit over warfarin of 1.42% events per year.

• In the first year after device implantation, there was a nonsignificant benefit of warfarin therapy because of periprocedural complications of left atrial appendage closure. However, the balance shifted between 1 to 2 years follow-up in favor of left atrial appendage closure.

treatments by synthesizing multiple effects into a single scalar outcome. In a previous net clinical benefit (NCB) analysis, we used data from the PROTECT-AF study and the CAP (Continued Access Protocol) device registry, specific weights were applied to account for disability caused by different events and demonstrated that LAAC conferred clinical benefit of 1.73% to 4.97% per year.9 However, at the time of that analysis, the PROTECT-AF study was only approximately midway in its planned 5-year follow-up (≈28 months mean follow-up); now, in addition to PROTECT-AF completing 5-year follow-up, PREVAIL is also available (also with 5-year follow-up).

In this present analysis, we sought to provide clinical context about the long-term impact of LAAC by incorporating patient-level 5-year data from both randomized trials of Watchman in the NCB analysis. In addition, we performed NCB analyses using alternative approaches to account for disability from stroke. Our goal was to provide a comprehensive estimate of the NCB of LAAC compared with warfarin therapy over time and to identify patient characteristics that maximize NCB.

Methods

The authors declare that all supporting data are available within the article (and its online supplementary files).

Study Design

The PROTECT-AF trial enrolled 707 patients with nonvalvular AF at 59 sites in the United States and Europe between February 2005 and June 2008.7,10 Patients aged 18 years or older with paroxysmal, persistent, or permanent AF and CHADS2 risk scores ≥1 were eligible. Exclusions included the following: absolute contraindications to warfarin, comorbidities other than AF requiring anticoagulation, LAA thrombus, patent foramen ovale with atrial septal aneurysm and right-to-left shunt, mobile aortic atheroma, and symptomatic carotid artery disease. In PREVAIL, 407 patients with nonvalvular AF were enrolled at 50 sites in the United States between November 2010 and July 2012. Eligibility criteria included CHADS2 score ≥2 or a CHA2DS2-VASc score ≥1 with 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 mellitus 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. Both studies were approved by the local institutional review boards and patients signed informed consent before enrollment.

Patients in both trials were randomly assigned to the intervention or control groups in a 2:1 ratio. After implantation, patients were treated with warfarin for 45 days to allow endothelialization of the device, followed by clopidogrel (75 mg daily) plus aspirin (81–325 mg daily) until completion of the 6-month follow-up visit, and aspirin alone thereafter. The control group was assigned chronic warfarin therapy with a target international normalized ratio of 2.5, range 2.0 to 3.0.

Outcome Assessment

The end points in this NCB analysis included all death events irrespective of cause (DE), ischemic stroke (IS), intracranial hemorrhage (ICH), major extracranial bleeding (MB), and the major procedural complication, pericardial effusion (PE). Assessment of the outcomes was identical in both studies and an independent Clinical Events Committee adjudicated all events. MB was defined as those bleeds that required transfusion of ≥2 units of packed red blood cells or surgical intervention. Patients underwent screening for PE by transthoracic/transesophageal echocardiography before and within 2 days after device implantation. PE was considered an end point event when it resulted either in hemodynamic compromise or drainage and included cardiac perforation causing cardiac tamponade.

IS was defined as the sudden onset of a focal neurological deficit in the distribution of a single brain artery with symptoms and/or signs persisting ≥24 hours or when ≤24 hours if accompanied by the evidence of tissue loss without hemorrhage based on computed tomography or magnetic resonance brain imaging. Diagnosis of ICH was based on the sudden onset of neurological deficit with computed tomography or magnetic resonance evidence of hemorrhage. Stroke events were assessed using the National Institutes of Health Stroke Scale at set intervals and within 48 hours after the onset of
symptoms suggestive of stroke or transient ischemic attack. The modified Rankin score (mRS) and the Barthel index were measured at 6-, 9-, and 18-month telephone follow-up contacts, at all clinic visits, and within 90 days of stroke or transient ischemic attack. Patients were referred for neurological evaluation if there was an increase in the National Institutes of Health Stroke Scale score of ≥2 points, increase in the mRS ≥1 point, or increase in Barthel index ≥15 points. Per-protocol patients were followed for a maximum duration of 5 years.

Net Clinical Benefit Calculation

The NCB analysis of LAAC versus warfarin used weights for each end point reflecting the severity of postevent disability relative to death. We defined the NCB of LAAC as the sum of the differences between the annualized rates of DE, ICH, IS, MB, and PE occurring in the LAAC versus the warfarin group, with weights for each event reflecting the severity of functional impact relative to DE (unity). To avoid double counting of events, for patients who experienced more than 1 event, the event with the highest weight was used. We used 2 alternate methods to calculate NCB that reflected different weighting schemes. In the base case, subject-level stroke severity was incorporated into the model by utilizing the mRS values after IS or ICH in the following equation to calculate NCB:

\[
NCB = (DE_{warfarin} - DE_{LAAC}) + \sum_{i=0}^{6} |Weight_i| (mRS Score_i_{warfarin} - mRS Score_i_{LAAC}) + 0.05 \times (MB_{warfarin} - MB_{LAAC}) + 0.05 \times (PE_{warfarin} - PE_{LAAC}).
\]

where \(i = 0\) to 6, \(Weight_0 = 0\), \(Weight_1 = 0.046\), \(Weight_2 = 0.212\), \(Weight_3 = 0.331\), \(Weight_4 = 0.652\), \(Weight_5 = 0.944\), \(Weight_6 = 1\).\(^{11}\)

Briefly, the disability weight (“Weight”) for each possible mRS score from 0 to 6 was derived from a World Health Organization Global Burden of Disease Project study of disability according to mRS that used a Delphi process among a 9-member panel of stroke experts.\(^{11}\) The weights for death, PE, and MB were fixed at 1.0 (reference), 0.05, and 0.05, respectively, and were consistent with our previous analysis.\(^{9}\) The value of 0.05 represents a 5% decrement from a year of life with perfect health. We doubled and tripled the weights assigned to PE and MB in sensitivity analyses.

As a point of comparison with our prior NCB analysis based on the PROTECT-AF trial, we also performed a sensitivity analysis using the equation from the previous study:

\[
NCB = (DE_{warfarin} - DE_{LAAC}) + 0.6 \times (ICH_{warfarin} - ICH_{LAAC}) + 0.2 \times (IS_{warfarin} - IS_{LAAC}) + 0.05 \times (MB_{warfarin} - MB_{LAAC}) + 0.05 \times (PE_{warfarin} - PE_{LAAC}).
\]

The difference compared with our base case analysis was that fixed weights were used for ICH (0.60) and IS (0.20)—consistent with the NCB analysis of the ACTIVE (Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events Trials) that showed the adjusted hazard ratio for death after hemorrhagic stroke was 3.08 compared with ischemic stroke.\(^{12}\) Again, MB requiring transfusion and PEs requiring intervention were both assigned impacts of 0.05, consistent with our previous analysis.\(^{9}\) Lastly, we artificially lowered the incidence of PE because the implanters’ experience at the time of the PROTECT-AF and PREVAIL trials was limited, since most implanters were still early in their learning/experience curve. The PE incidence for this sensitivity analysis was lowered from 3% to 1%, in line with the US postapproval study.\(^{13}\)

Statistical Analysis

Baseline characteristics were presented as mean±SD or median (25th, 75th) depending on distribution, and dichotomous variables as number and percentage. NCB in weight-adjusted events per 100 person-years of follow-up was presented as absolute risk differences and compared between the LAAC and warfarin arms using the Mantel–Haenszel χ² test. NCB was additionally estimated for subgroups based on age, sex, prior ischemic stroke, hypertension, diabetes mellitus, heart failure, and CHADS² score. Statistical significance was accepted at the 95% CI (2-sided \(P \leq 0.05\)) without adjustment for multiple comparisons. Analyses were performed using the R and RStudio software, version 3.4.4 (R Foundation, Vienna, Austria).\(^{14}\)

Results

Baseline Characteristics

Patients were enrolled across 79 hospitals in the United States and Europe between 2005 and 2012 (Table 1). The pooled cohort consisted of 1114 patients, of whom 732 were randomized to LAAC with Watchman and 382 were treated with warfarin (Table 1). The baseline characteristics were well balanced with a mean age of 73±8 years and 30% of the subjects were female. The median CHA²DS²-VASc score was 2 (2, 3) and 252 (23%) patients had a stroke or transient ischemic attack before enrollment. The most common AF subtype was paroxysmal (45%), followed by permanent (28%) and persistent (24%). Patients in both trials were followed for a mean duration of 48 months adding up to a total 4343 patient years.

Net Clinical Benefit

Table 2 presents the NCB estimates over the course of follow-up using the combined PROTECT-AF and PREVAIL
data. In the base case analysis, which incorporated mRS-based stroke severity and fixed weights for MB and PE at 0.05, patients in the LAAC arm had 4.11 weight-adjusted events per 100 patient-years during the overall follow-up period, versus 5.53 weight-adjusted events in the warfarin arm. This resulted in a NCB of 1.42% for LAAC over warfarin (95% CI 0.01–2.82%, \( P=0.04 \)) and a relative risk of 0.74 (95% CI 0.56–1.00).

**Sensitivity Analyses**

As a sensitivity analysis, when the weights of MB and PE were increased to 0.10 there were 4.21 weight-adjusted events per 100 patient-years in the LAAC arm and 5.59 in the warfarin arm; thus, the NCB continued to favor LAAC at 1.38% (0.04–2.80) and RR 0.75 (0.57–1.01), \( P=0.05 \). When the weights for MB and PE were further increased to 0.15, there were 4.32 weight-adjusted events per 100 patient-years in the LAAC arm and 5.73 in the warfarin arm, again resulting in a NCB of 1.41 (0.02–2.85) and RR of 0.75 (0.57–1.00), \( P=0.05 \).

Instead of a graded scale for stroke based on mRS scores, when we used fixed weights for IS (weight of 0.2) and ICH (weight of 0.6) events as per our prior NCB analysis, the results remained similar to the primary analysis (Figure 1): there were 4.18 weight-adjusted events per 100 patient-years in the LAAC arm and 5.66 in the warfarin arm, resulting in a NCB of 1.48% for LAAC over warfarin (95% CI 0.06–2.90%, \( P=0.04 \)) and a relative risk of 0.74 (95% CI 0.56–0.99). When the weights for IS and ICH were changed to 0.10 and 0.30, respectively, the NCB remained positive at 1.45% (95% CI 0.05–2.85%, \( P=0.04 \)) with 4.07 weight-adjusted events per 100 patient-years in the LAAC arm and 5.53 in the warfarin arm. The lowered incidence rate of PE from 3% to 1% resulted in a smaller advantage of warfarin over LAAC at 90 days follow-up of 3.89% versus 4.47% original data (Figure S1), with a similar overall NCB for LAAC during the course of complete 5-year follow-up compared with the base case analysis.

**NCB Over Time**

In the base case, the NCB during early follow-up was nonsignificantly in favor of the warfarin arm, reflecting periprocedural events associated with LAAC (Figure 1). Between 1 and 2 years follow-up, the NCB was neutral, but then shifted toward LAAC during long-term follow-up (Figure 2). In this clinical benefit analysis, death events were the primary driver of the overall result because they accounted for 179 (93%) out of 192 total weight-adjusted events. This time dependence of the NCB was preserved in the various sensitivity analyses: varying the weights of MB

### Table 1. Baseline Characteristics

|                   | Warfarin | LAAC  | \( P \) Value |
|-------------------|----------|-------|---------------|
| N                 | 382      | 732   |               |
| Age, y, mean (SD) | 73.47 (8.60) | 72.56 (8.38) | 0.09          |
| CHADS2 Score, median (25th, 75th) | 2.00 [2.00, 3.00] | 2.00 [1.00, 3.00] | 0.06          |
| Risk factors      |          |       |               |
| Female, n (%)     | 108 (28.3) | 224 (30.6) | 0.46          |
| Age >75 y, n (%)  | 192 (50.3) | 330 (45.1) | 0.11          |
| Congestive heart failure, n (%) | 98 (25.7) | 187 (25.5) | 1             |
| Hypertension, n (%) | 354 (92.7) | 653 (89.2) | 0.08          |
| Prior TIA or stroke, n (%) | 90 (23.6) | 162 (22.1) | 0.64          |
| Diabetes mellitus, n (%) | 113 (29.6) | 204 (27.9) | 0.60          |
| Coronary artery disease, n (%) | 192 (50.3) | 325 (44.4) | 0.08          |
| Prior gastrointestinal bleed, n (%) | 41 (10.7) | 73 (10.0) | 0.77          |
| AF pattern        |          |       |               |
| Paroxysmal        | 170 (44.5) | 331 (45.2) | 0.82          |
| Persistent        | 89 (23.3) | 182 (24.9) | 0.56          |
| Permanent         | 115 (30.1) | 202 (27.6) | 0.38          |
| Unknown           | 3 (0.8) | 10 (1.4) | 0.56          |
| Paced             | 5 (1.3) | 7 (1.0) | 0.56          |

Baseline characteristics of the pooled cohorts of the PROTECT-AF and PREVAIL studies. AF indicates atrial fibrillation; LAAC, left atrial appendage closure; TIA, transient ischemic attack.

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and PE, and using fixed weights for IS and ICH (Figures S2 and S3).

Subgroups

Although the 95% CIs were wide, the NCB of LAAC compared with warfarin was positive across subgroups (Figure 3) including both men and women. Patients with a history of stroke or transient ischemic attack comprised the subgroup with the largest NCB from LAAC, with a point estimate of the absolute risk reduction of 4.25% (95% CI 0.80–7.91%, \( P=0.02 \)).

Discussion

Main Findings

Through this NCB analysis, we incorporated the differential clinical impact of heterogeneous events to assess the overall effect of LAAC compared with warfarin therapy. This analysis utilizes 5-year randomized trial data involving LAAC with the Watchman device and indicates that, in the long-term, LAAC is likely to provide positive NCB compared with warfarin. Early on in follow-up, there is a nonsignificant expected negative effect of LAAC because of periprocedural complications, but the balance shifts between 1 to 2 years follow-up in favor of LAAC with Watchman.

Clinical Benefit Analysis

Clinical trials commonly use combined end points, recognizing that there are often more than 1 clinically relevant outcome type, while at the same time increasing the statistical power. However, it is widely acknowledged that the individual components of combined end points are clinically not equally important. In this NCB analysis, events were weighted based on the disability level after each event, recognizing that clinical importance of a PE resolved by drainage is different from a stroke resulting in severe disability or death. In order to reduce the subjectivity of assigning weights, stroke events were assigned weights based on stroke severity—that is, the difference between pre- and poststroke disability according to mRS scores.\(^\text{11} \) PE and MB were assigned relatively low weights (both 0.05) because of their transient nature and the fact that if they result in death, this would be captured in the death end point. All told, death events were the primary driver of this NCB analysis.

Periprocedural Complications

As shown in Figure 2, there is an initial increase in events during early follow-up caused by periprocedural complications of LAAC, while there were few events immediately after initiation of long-term warfarin therapy. Both trials represent the earliest experience of implanters with LAAC since they were Food and Drug Administration approval studies. But as expected, with additional experience, implanters have become
more adept with the LAAC implant procedure, and several studies such as the EWOLUTION (Evaluating Real-Life Clinical Outcomes in Atrial Fibrillation Patients Receiving the WATCHMAN Left Atrial Appendage Closure Technology) registry have demonstrated markedly reduced periprocedural complication rates, including a pericardial tamponade rate <1%.15 It is important to recognize that this reduction in periprocedural complications will result in clinical equivalence and benefit of LAAC earlier during follow-up.

Long-Term Outcomes

The concept of LAAC closure provides benefit during long-term follow-up for several reasons. There is no associated long-term bleeding risk. It is well recognized that intracranial bleeding is associated with significantly greater morbidity than ischemic events. Also, there is no interaction with other drugs or therapeutic range that needs to be maintained.

Patient behavior and the ability to remain fully adherent to their medication regimen are important limitations of any long-term preventive strategy. While patients in the NOAC trials were selected based on their ability to adhere to their drug regimen, the time in therapeutic range in the warfarin arm varied between 60% and 70%.16–19 It has been shown in many studies that adherence decreases both over time and with each drug added to the medication regimen.20–23 Given the fact that patients with AF often have a life expectancy of many years at the time of diagnosis and comorbidities such as hypertension, heart failure, and diabetes mellitus requiring drugs as well, long-term adherence to warfarin is often suboptimal in clinical practice. The fact that the chronic efficacy of LAAC is not dependent on adherence issues may be a plausible explanation as to why the clinical benefit of LAAC continues to increase over time.

Limitations

Limitations of our analysis include the lack of data about NOACs. After the advent of the PROTECT-AF and PREVAIL studies, NOACs have been widely adopted because of the reduced risk of intracranial hemorrhage and much simpler dosing. This rendered warfarin a suboptimal comparator to inform clinicians in many patients with AF. The relative efficacy of LAAC versus NOACs is currently unknown, and is the subject of ongoing clinical trials including PRAGUE-17 (Left Atrial Appendage Closure vs. Novel Anticoagulation Agents in Atrial

Figure 2. Net clinical benefit of LAAC compared with warfarin therapy over time. The figure presents the absolute risk difference at different time points during follow-up. Below zero reflects a benefit of warfarin, whereas above zero reflects a benefit of LAAC. The dotted lines reflect the 95% CI. LAAC indicates left atrial appendage closure.
Fibrillation) (NCT# 02426944), CLOSURE-AF (Left Atrial Appendage Closure in Patients With Atrial Fibrillation Compared to Medical Therapy) (NCT# 03463317), Occlusion-AF (Left Atrial Appendage Occlusion Versus Novel Oral Anticoagulation for Stroke Prevention in Atrial Fibrillation) (NCT# 03642509) and STROKECLOSE (Prevention of Stroke by Left Atrial Appendage Closure in Atrial Fibrillation Patients After Intracerebral Hemorrhage) (NCT# 02830152), but these trials are somewhat limited by sample size.

A second limitation is that we did not account for uncertainty in the weights used for the events in our analysis. We did perform sensitivity analyses for the assigned weights and attempted to account for stroke based on actual measurements of disability associated with IS and ICH. These variations in the inputs for the NCB analysis did not materially change the conclusions.

Lastly, the implanters’ experience at the time of the PROTECT-AF and PREVAIL trials was limited, since most implanters were still in their learning phase. This assumption is confirmed by the fact that since the PROTECT-AF and PREVAIL trials, the periprocedural complication rate of Watchman implantation has come down substantially in registries such as the US postapproval registry and EWOLUTION.13,15 In the current clinical benefit analysis, this would translate to smaller difference in the absolute difference in events rate between both groups and reversal of the clinical benefit earlier during follow-up.

Conclusions
This clinical benefit analysis of the PROTECT-AF and the PREVAIL studies demonstrates that when weights are used for each end point reflecting the severity of postevent disability, there is a significant long-term benefit of LAAC with Watchman over warfarin therapy. However, in the first year after device implantation, there is a nonsignificant benefit of long-term warfarin therapy because of periprocedural complications.

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Disclosures

Reddy has received research grant support from and has been a consultant to Boston Scientific, the manufacturer of the Watchman device. In addition, he has conflicts with manufacturers of other LAAC devices: grant support and consultant to Abbott and Biosense-Webster, and equity ownership in Surecor Inc; Brouwer has received research grant support from Boston Scientific, the manufacturer of the Watchman device. Halperin has received consulting fees for advisory activities and studies involving anticoagulant drugs: Bayer HealthCare, Boehringer Ingelheim, Ortho-McNeil-Janssen Pharmaceuticals, and Medtronic. The remaining authors have no disclosures to report.

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| Hospital Name | Protect-AF | PREVAIL |
|---------------|------------|---------|
| Advanced Cardiac Specialists | 1 | |
| Arizona Arrhythmia | 1 | 1 |
| Mercy Gilbert Medical Center | 1 | |
| Foundation for Cardiovascular Medicine | 1 | 1 |
| Los Angeles Cardiology Associates | 1 | |
| Cedars-Sinai Medical Center | 1 | 1 |
| El Camino Hospital | 1 | |
| Orange County Heart | 1 | 1 |
| UC Davis Medical Center | 1 | |
| St. John’s Hospital / Pacific Heart | 1 | 1 |
| Scripps Green | 1 | |
| Washington Hospital Center | 1 | |
| University of Miami | 1 | |
| Baptist Cardiac and Vascular Institute | 1 | 1 |
| Bay Heart Group | 1 | |
| Zasa Clinical Research | 1 | |
| Florida Hospital | 1 | |
| Emory University Midtown Hospital | 1 | 1 |
| Piedmont Hospital | 1 | |
| Emory University Hospital | 1 | |
| University of Chicago | 1 | |
| North Shore University | 1 | 1 |
| Loyola University Medical Center | 1 | |
| Prairie Education Research Cooperative | 1 | |
| Iowa Heart Center | 1 | |
| Baptist Hospital West | 1 | |
| University of Kentucky | 1 | |
| Central Baptist Hospital | 1 | |
| Terrebonne General Medical Center | 1 | |
| Ochsner Clinic | 1 | |
| United States, Massachusetts | Massachusetts General Hospital | 1 | 1 |
| United States, Massachusetts | Lahey Clinic | 1 |
| United States, Michigan | University of Michigan Medical Center | 1 | 1 |
| United States, Michigan | William Beaumont | 1 | 1 |
| United States, Minnesota | Abbott Northwestern Hospital | 1 | 1 |
| United States, Minnesota | Mayo Clinic | 1 | 1 |
| United States, Minnesota | St. Paul Heart Clinic | 1 |
| United States, Mississippi | University of Mississippi Healthcare Center | 1 |
| United States, Mississippi | Cardiology Associates of N. Mississippi | 1 |
| United States, Missouri | St. Luke’s Hospital | 1 | 1 |
| United States, Missouri | St. John’s Mercy | 1 |
| United States, Nebraska | Nebraska Heart Institute | 1 |
| United States, Nebraska | Bryan LGH | 1 |
| United States, New Jersey | Cooper University Hospital | 1 |
| United States, New Jersey | Englewood Hospital and Medical Center | 1 |
| United States, New Mexico | New Mexico Heart Institute | 1 |
| United States, New York | New York University Medical Center | 1 | 1 |
| United States, New York | Columbia University Medical Center | 1 | 1 |
| United States, North Carolina | Carolinas Medical Center | 1 |
| United States, North Carolina | | |
| United States, Ohio | Summa Health System | 1 |
| United States, Ohio | Lindner Clinical Trial Center | 1 | 1 |
| United States, Ohio | Cleveland Clinic Foundation | 1 | 1 |
| United States, Ohio | Ohio State University | 1 |
| United States, Ohio | Riverside Methodist Hospital | 1 |
| United States, Pennsylvania | Geisinger Medical Center | 1 |
| United States, Pennsylvania | Harrisburg Hospital / Associated | 1 |
| Location                  | Hospital Name                                    | 1 |
|---------------------------|--------------------------------------------------|--|
| Allegheny General Hospital|                                                 | 1 |
| Presbyterian University   |                                                 | 1 |
| Moffitt Heart & Vascular  |                                                 | 1 |
| Hospital of the University of Pennsylvania |                             | 1 |
| United States, Tennessee  | Mercy Medical Center West                        | 1 |
|                           | St. Thomas Research Institute                    | 1 |
| United States, Texas      | Texas Cardiac Arrhythmia                         | 1 |
|                           | St. Lukes Episcopal Hospital                     | 1 |
|                           | Baylor Research Institute                        | 1 |
|                           | Methodist Hospital                               | 1 |
| United States, Utah       | Intermountain Medical Center                     | 1 |
| United States, Virginia   | University of Virginia                           | 1 |
|                           | Inova Fairfax Hospital                           | 1 |
|                           | Sentara Norfolk General Hospital                 | 1 |
| United States, Vermont    | Fletcher Allen                                   | 1 |
| United States, Washington | Swedish Medical Center                           | 1 |
| United States, Wisconsin  | Marshfield Clinic                                | 1 |
|                           | St. Luke's Hospital                              | 1 |
| Czech Republic            | Na Homolce                                       | 1 |
| Germany                   | Krankenhaus der Barmherzige Bruder               | 1 |
|                           | Cardiovasculares Centrum Frankfurt - Sankt Katharinen | 1 |
|                           | Herzzentrum                                      | 1 |
Figure S1. Net clinical benefit of LAAC compared with warfarin therapy over time in the artificially lower PE incidence scenario.

**Lowered PE incidence**: scenario where the PE incidence is artificially lower to 1% from 3%. mRS score for ischemic and hemorrhagic stroke are used and fixed weights for major bleed and pericardial effusion of 0.05.
Figure S2. Absolute risk difference using mRS weights for ischemic and hemorrhagic stroke and fix weights of 0.10 for major bleed and pericardial effusion events.
Figure S3. Absolute risk difference using mRS weights for ischemic and hemorrhagic stroke and fix weights of 0.15 for major bleed and pericardial effusion events.