Cost-Effectiveness of Left Atrial Appendage Closure for Stroke Reduction in Atrial Fibrillation: Analysis of Pooled, 5-Year, Long-Term Data

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Background—Recent publications reached conflicting conclusions about the cost-effectiveness of left atrial appendage closure (LAAC) with the Watchman device (Boston Scientific, Marlborough, MA) for stroke risk reduction in nonvalvular atrial fibrillation (AF). This analysis sought to assess the cost-effectiveness of LAAC relative to both warfarin and nonwarfarin oral anticoagulants (NOACs) using pooled, long-term data from the randomized 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) trials.

Methods and Results—A Markov model was constructed from a US payer perspective with a lifetime (20-year) horizon. LAAC clinical event rates and stroke outcomes were from pooled PROTECT AF and PREVAIL trial 5-year data. Warfarin and NOAC inputs were derived from published meta-analyses. The model was populated with a cohort of 10 000 patients, aged 70 years, at moderate stroke and bleeding risk. Sensitivity analyses were performed. LAAC was cost-effective relative to warfarin by year 7 ($48 674/quality-adjusted life-year) and dominant (more effective and less costly) by year 10. LAAC became cost-effective and dominant compared with NOACs by year 5. Over a lifetime, LAAC provided 0.60 more quality-adjusted life-years than warfarin and 0.29 more than NOACs. In sensitivity analyses, LAAC was cost-effective relative to warfarin and NOACs in 98% and 95% of simulations, respectively.

Conclusions—Using pooled, 5-year PROTECT AF and PREVAIL trial data, LAAC proved to be not only cost-effective, but cost saving relative to warfarin and NOACs. LAAC with the Watchman device is an economically viable stroke risk reduction strategy for patients with AF seeking an alternative to lifelong anticoagulation. (***J Am Heart Assoc***. 2019;8:e011577. DOI: 10.1161/JAHA.118.011577.)

Key Words: anticoagulant • atrial fibrillation • cost-effectiveness • left atrial appendage closure • nonwarfarin oral anticoagulants • Watchman

Atrial fibrillation (AF) has a substantial impact on patient lives and medical costs. It is estimated that treating patients with AF adds $26 billion to US healthcare costs, predominantly caused by AF-related stroke.[1,2] Several stroke prevention strategies now exist for patients with nonvalvular AF, including pharmacotherapies, such as warfarin and the nonwarfarin oral anticoagulants (NOACs), and the device-based strategy of percutaneous left atrial appendage closure (LAAC). Warfarin has been used to treat AF for >50 years and is effective at reducing ischemic stroke risk, but has a narrow therapeutic window in which to achieve maximal risk reduction. It is associated with drug and food interactions and high nonadherence to therapy.[3] NOACs have demonstrated similar efficacy to warfarin for stroke prevention without the need for routine monitoring; however, NOAC-related complications, such as increased risk for gastrointestinal tract bleeding, have been observed in various patient subpopulations.[4–7] And more important, any drug-based therapy is dependent on patient adherence to treatment.

Percutaneous LAAC with the Watchman device (Boston Scientific, Marlborough, MA) was approved for use in the United States on the basis of 2 pivotal, randomized controlled

trials (RCTs): 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).[8–10] Patients in both trials were followed up for 5 years, and the long-term outcomes from these studies have demonstrated LAAC is: as effective as warfarin in preventing all-cause strokes; similar to warfarin in preventing ischemic strokes; superior in preventing hemorrhagic stroke; superior in preventing disabling/fatal stroke; superior in preventing postprocedure major bleeding; and superior in reduction of all-cause mortality.[10] Finally, US real-world clinical experience after US Food and Drug Administration (FDA) approval has been favorable.[11] In 3822 consecutive patients, Watchman implantation was successful in 95.6% of patients and was associated with a favorable safety profile; compared with PROTECT AF/PREVAIL trials, pericardial effusion rates decreased from 3.69% to 1.02% and procedure-related stroke decreased from 0.82% to 0.05%.[10,11]

To ensure patient access to novel therapies, it is becoming increasingly important to demonstrate both clinical and economic value. Published US economic analyses to date have explored the cost-effectiveness of LAAC using either the PROTECT AF or PREVAIL trial data sets separately.[12,13] These analyses yielded conflicting results, thereby leading to

confusion in the clinical and policy community. To further inform the economics of LAAC, this present analysis uses the complete, 5-year RCT evidence in its totality: a patient-level pooled analysis of both PROTECT AF and PREVAIL trials.[10] Herein, we estimate the cost-effectiveness of LAAC with Watchman relative to both warfarin and NOACs for stroke risk reduction in nonvalvular AF. This comprehensive assessment uses the most complete body of clinical evidence for LAAC in an attempt to more definitively evaluate the therapy's economic value and provide guidance for future analyses.

Methods

We evaluated the cost-effectiveness of 3 treatment strategies: (1) LAAC with the Watchman device; (2) NOACs as a class; and (3) adjusted-dose warfarin. This analysis was conducted using an Excel-based (Microsoft, Redmond, WA) Markov model developed to assess the cost-effectiveness of LAAC using pooled PROTECT AF and PREVAIL 5-year, pivotal clinical trial data. Patients were assumed to be 70 years of age and have a mean Congestive Heart Failure, Hypertension, Age≥75 years, Diabetes Mellitus, Prior Stroke or Transient Ischemic Attack, Vascular Disease, Age 65–74 years, Sex Category (CHA_2DS_2-VASc) score of 4.0 (annual stroke risk of 4.8%) and a Hypertension, Abnormal Renal/Liver Function, Stroke, Bleeding History or Predisposition, Labile INR, Elderly, Drugs/Alcohol (HAS-BLED) score of 1.98 (annual risk of bleeding of 1.88%).[8–10] The model was constructed from the perspective of the Centers for Medicare and Medicaid Services with a lifetime horizon (defined as 20 years) and 3-month cycle length. Within each cycle, patients could experience clinical events leading to death, disability, and/or therapy discontinuation and incur associated costs and quality-of-life (QoL) adjustments. Model parameters are available for other researchers on request to the corresponding author. Institutional review board review was not required for this analysis.

Cost-effectiveness was evaluated using the US commonly accepted willingness to pay threshold of $50 000 per quality-adjusted life-year (QALY) gained and reported as the incremental cost-effectiveness ratio (ICER).[14] The ICER provides a standardized approach to measure cost per unit of health improvement in and across health states. Cost-effectiveness was assessed annually to determine at which point in time treatment options achieved accepted levels of cost-effectiveness.

Model Structure and Clinical Pathways

The model began with patients being assigned to LAAC, NOACs, or warfarin (Figure 1). For the base-case analysis, patients in the LAAC arm faced one-time, procedure-related
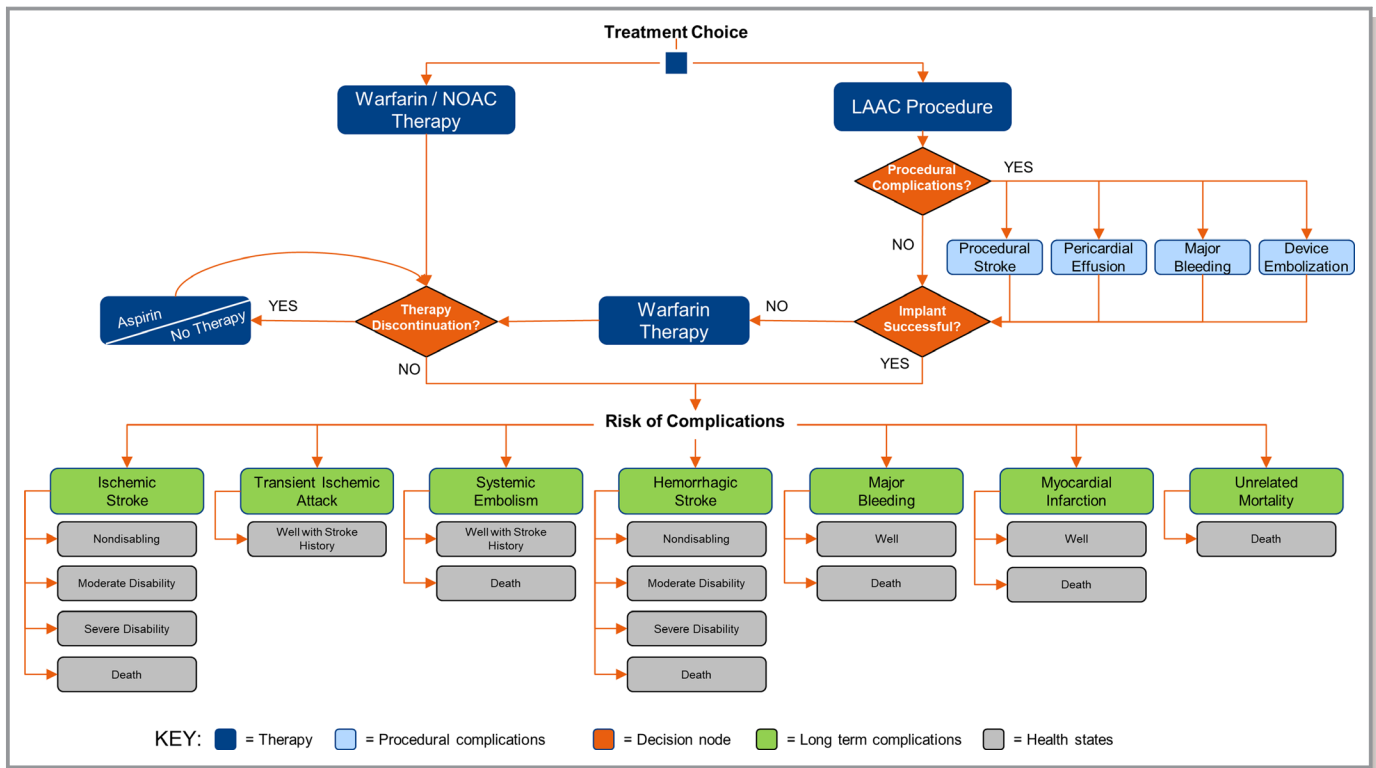
Figure 1. Model schematic depicting left atrial appendage closure (LAAC) and nonwarfarin oral anticoagulant (NOAC) patient pathways. Patient pathways for LAAC and NOAC.

risk of ischemic stroke caused by air embolism (0.82%), major bleeding (0.55%), pericardial effusion (3.69%), and device embolization (0.68%).[15] Patients undergoing LAAC could experience a successful or failed implantation procedure. Successfully implanted patients (92.5%) were assumed to receive warfarin for 45 days, aspirin plus clopidogrel from 46 days to 6 months, and aspirin thereafter in accordance with the treatment algorithms in the LAAC trials.[8,9,15] After a failed procedure, patients were assumed to return to warfarin therapy.[8–10,15] Patients in the warfarin and NOAC arms could discontinue therapy after a bleeding event or for nonclinical reasons. Patients who discontinued primary drug therapy were assumed to switch to aspirin.[4,6,16–19] Discontinuation of second-line therapy was assumed to result in no treatment.

On entering the model, patients were assumed to be "Well" or in normal, good health for an average-aged patient diagnosed with nonvalvular AF. Patients transitioned from Well to different health states after a clinical event or death. Each health state corresponded to an event-specific QoL decrement and cost. Only ischemic and hemorrhagic stroke impacted disability outcomes. Patients undergoing a second stroke could either remain in the same health state or worsen to greater disability. Transient ischemic attack and systemic embolism led to patients being well with a history of stroke, which increased their risk of subsequent stroke.

All events, except transient ischemic attack, could lead to death.

Clinical Inputs

Clinical inputs are presented in Table 1. LAAC procedural complications and clinical event probabilities were derived from pooled PROTECT AF and PREVAIL clinical trial data at 5 years of follow-up.[10,15] Relative risks for postprocedural stroke and bleeding were used to apply a standard efficacy estimate to the derived baseline risks.[10] Warfarin and NOAC clinical inputs were derived primarily from meta-analyses and AF stroke prevention clinical trials.[4,6,16–22] Event probabilities were extrapolated over the lifetime horizon for all treatment strategies. Last, a scenario analysis was conducted to compare LAAC trial-based procedural outcomes to post-FDA, real-world procedural outcomes.[11]

Baseline risk of stroke was assigned on the basis of Congestive Heart Failure, Hypertension, Age≥75 years, Diabetes Mellitus, Prior Stroke or Transient Ischemic Attack, Vascular Disease, Age 65–74 years, Sex Category (CHA_2DS_2-VASc) scores and risk of bleeds on the basis of HAS-BLED scores.[21,23] Stroke risk was estimated by converting Congestive Heart Failure, Hypertension, Age≥65 years, Diabetes Mellitus, Stroke or Transient Ischemic Attack

Table 1. Clinical Inputs Derived From Meta-Analyses and Pivotal Trials

Variable	Value	Range	Distribution	Source
LAAC: clinical trial-based procedural events				
Implantation success	92.50%	85.00%–100.00%	β	15
Procedural risk of ischemic stroke	0.82%	0.66%–0.98%	β	15
Procedural risk of major bleeding	0.55%	0.44%–0.66%	β	15
Procedural risk of pericardial effusion requiring intervention	3.69%	2.95%–4.43%	β	15
Procedural risk of device embolization	0.68%	0.54%–0.82%	β	15
LAAC: post-FDA, real-world procedural events				
Implantation success	95.60%	85.00%–100.00%	β	11
Procedural risk of ischemic stroke	0.05%	0.04%–0.06%	β	11
Procedural risk of hemorrhagic stroke	0.03%	0.02%–0.03%	β	11
Procedural risk of major bleeding*	0.55%	0.44%–0.66%	β	15
Procedural risk of pericardial effusion	1.02%	0.82%–1.22%	β	11
Procedural risk of device embolization	0.24%	0.19%–0.29%	β	11
Procedural risk of death	0.10%	0.08%–0.13%	β	11
LAAC: postprocedural events				
Relative risk of postprocedure ischemic stroke (relative to warfarin)	1.29	1.03–1.54	Lognormal	10
Relative risk of hemorrhagic stroke (relative to warfarin)	0.16	0.12–0.19	Lognormal	10
Relative risk of postprocedure major bleeding (relative to warfarin)	0.60	0.48–0.72	Lognormal	10
Annual risk of systemic embolism	0.10%	0.08%–0.12%	β	10
Relative risk of myocardial infarction (relative to warfarin)	0.50	0.40–0.60	Lognormal	8
Risk of minor bleeding	Based on concomitant drug therapy			
Warfarin				
Relative risk of ischemic stroke (relative to no therapy)	0.33	0.23–0.46	Lognormal	20
Relative risk of major bleeding (relative to HAS-BLED)	1.00	0.80–1.20	Lognormal	21
Percentage of major bleeding that is hemorrhagic stroke	41.80%	33.40%–50.20%	β	22
Annual risk of systemic embolism	0.11%	0.90%–0.11%	β	4,6
Annual risk of myocardial infarction	1.47%	0.53%–1.47%	β	22
Annual risk of minor bleeding	7.70%	0.80%–16.40%	β	20,21
Nonclinical discontinuation rate	4.33%	3.46%–5.19%	Uniform	16–19
NOACs				
Relative risk of ischemic stroke (relative to warfarin)	0.92	0.83–1.02	Lognormal	22
Relative risk of hemorrhagic stroke (relative to warfarin)	0.48	0.39–0.59	Lognormal	22
Relative risk of extracranial hemorrhage (relative to warfarin)	1.25	1.01–1.55	Lognormal	22
Relative risk of systemic embolism	0.92	0.83–1.02	Lognormal	22
Relative risk of myocardial infarction (relative to warfarin)	0.97	0.78–1.20	Lognormal	22
Annual risk of minor bleeding	8.70%	7.00%–10.40%	β	20,21
Nonclinical discontinuation rate	4.18%	3.34%–5.01%	Uniform	4,6
All treatment arms				
Discount rate	3.00%	2.00%–4.00%	β	39

FDA indicates US Food and Drug Administration; LAAC, left atrial appendage closure; NOAC, nonwarfarin oral anticoagulant; HAS-BLED, hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile INR, elderly, drugs/alcohol.
*Major bleeding was not an end point in the post-FDA real-world data study, so we have used the trial-based event rate for this input.

(CHADS$_2$) scores that were prospectively collected during PROTECT AF and PREVAIL trials to Congestive Heart Failure, Hypertension, Age≥75 years, Diabetes Mellitus, Prior Stroke or Transient Ischemic Attack, Vascular Disease, Age 65–74 years, Sex Category (CHA$_2$DS$_2$-VASc).[8–10,23,24] A modified HAS-BLED score, calculated using the available data on 5 of the 7 criteria, was estimated as a weighted mean from PROTECT AF and PREVAIL trials.[8–10,21] To account for increasing risk with age, rates of ischemic and hemorrhagic stroke were increased by 1.4 and 1.97 times per decade, respectively.[25,26] In addition, the impact of advanced age was explored via a scenario analysis with starting ages of 75 and 80 years. Patients experiencing a transient ischemic attack or systemic embolism were assumed to have a 2.6 times increased risk of experiencing a second ischemic event.[25] Healthcare Utilization Project mortality rates were used to inform probabilities of death after systemic embolism, extracranial hemorrhage, or myocardial infarction.[27] Risk of death from unrelated causes was obtained from US life tables, with disabled patients facing a 2.3 times greater risk of death.[28,29]

Health State Utilities and Stroke Outcomes

Patient QoL was captured in the model as health utility. Health utility values were based on a scale of 0 to 1, with 1 representing perfect health and 0 representing death. The baseline utility values used for Well with warfarin (0.987), Well with NOAC (0.994), and Well with aspirin (0.998) are consistent with values used in previously published analyses.[12,30–34] As QoL data were not collected as part of the PREVAIL trial, the utility value for Well with LAAC (0.999) was calculated by applying the Nichol ordinary least squares algorithm to 12-Item Short Form Survey (SF-12) data collected during the PROTECT AF trial.[35,36] The utility weights for all Well–based health states were applied as a multiplying factor to an underlying baseline utility of 0.82, representing QoL at the age of 70 years.[31] The baseline utility was decremented by 2% per decade to account for general decline in QoL with advancing age.[37]

In addition, a series of disutilities were applied in the model for acute clinical events, representing a one-time decrement to QoL experienced for a finite length of time. Utility decrements were assessed for stroke (−0.139), extracranial hemorrhage (−0.181), transient ischemic attack (−0.103), systemic embolism (−0.120), and myocardial infarction (−0.125).[38] A value of −0.0315 was used for the LAAC procedure itself, which is based on a 2-week disruption to healthy life.

QALYs were calculated by multiplying the health state utility value of each health state by the mean time spent in the health state. Future QALYs were discounted at an annual rate of 3%.[39]

Stroke outcomes and resulting disability (Table 2) were assigned using the modified Rankin score (MRS) and characterized as nondisabling (MRS 0–2), moderately disabling (MRS 3), severely disabling (MRS 4–5), and fatal (MRS 6). LAAC stroke outcomes were from pooled PROTECT AF and PREVAIL 5-year trial data.[10] Warfarin stroke outcomes were estimated using a weighted average of outcomes from 4 warfarin trials.[16,17,40,41] For NOACs, the rate of nondisabling strokes was derived from 2 of the 4 pivotal trials.[4,6] As this was the only stroke outcome reported in the NOAC trials, the inverse represented disabling and fatal strokes, with the distribution of moderately disabling, severely disabling, and fatal strokes assumed to be the same as for warfarin.

Costs

The model incorporated all direct healthcare costs for the therapies and treatment of associated acute events, as well as costs for long-term care after a disabling stroke. Costs for acute events were taken from US 2017 diagnosis-related group (DRG) national average values, and costs for poststroke inpatient rehabilitation represent 2017 case-mix group (CMG) reimbursement rates.[12,42,43] Long-term stroke disability costs were from published literature and inflated to 2017 dollars using the Consumer Price Index for medical care published by the US Bureau of Labor Statistics.[32–34,44–47] The cost of the LAAC procedure was calculated as a weighted average of 2 diagnosis-related groups for percutaneous intracardiac procedures (273 and 274) plus the cost of 2 transesophageal echocardiograms.[42,48] The annual cost of warfarin therapy was also applied for patients receiving LAAC who were unable to discontinue warfarin. Warfarin costs were from US pharmaceutical wholesale acquisition cost in combination with reimbursement rates for Current Procedural Terminology (CPT (R)) codes related to international normalized ratio monitoring.[48,49] NOAC costs were calculated as an average of US wholesale acquisition costs for the first 3 approved drugs: dabigatran, rivaroxaban, and apixaban.[49] All costs are in 2017 US dollars and discounted at an annual rate of 3% (Table 3).

Sensitivity Analysis

One-way sensitivity analysis and probabilistic sensitivity analysis were undertaken to assess the impact of parameter uncertainty on model results. Clinical inputs were varied within 95% CIs, where available, and by ±20% where CIs were not published. The ranges and distributions used for clinical inputs are shown in Table 1. Health state utilities were varied by ±5% and assumed a β distribution. Stroke outcomes were varied by ±20% and assumed a Dirichlet distribution. All costs were varied ±20% and assumed a γ distribution. The probabilistic sensitivity analysis followed a standard Monte Carlo approach based on 5000 randomly drawn simulations of parameter values.

Table 2. Stroke Outcomes and Health State Utilities

Stroke Outcome	LAAC, %	Warfarin, %	NOAC, %	Utility Value
Nondisabling stroke (MRS 0–2)	75.0[10]	24.0[16,17,40,41]	44.0[4,6]	0.760[35]
Moderately disabling stroke (MRS 3)	2.8[10]	29.0[16,17,40,41]	21.4*	0.390[35]
Severely disabling stroke (MRS 4–5)	16.7[10]	35.0[16,17,40,41]	25.8*	0.110[35]
Fatal stroke (MRS 6)	5.6[10]	12.0[16,17,40,41]	8.8*	0.000

LAAC indicates left atrial appendage closure; MRS, modified Rankin score; NOAC, nonwarfarin oral anticoagulant.
*NOAC stroke outcomes were assumed to have the same distribution as warfarin across MRS 3 to 6.

Results

LAAC Versus Warfarin

As expected, LAAC is more costly than warfarin in the early years after the procedure (Figure 2). By year 3, patients undergoing LAAC had more QALYs than patients receiving warfarin (2.185 versus 2.170); this trend continued over the lifetime analysis, with patients undergoing LAAC having 0.60 more QALYs than their warfarin counterparts at 20 years (Table 4). LAAC became cost-effective relative to warfarin at year 7 ($48 674/QALY) and less costly than warfarin at year 10 (Figure 2). LAAC was dominant (more effective and less costly) relative to warfarin by year 10. Once achieved, LAAC remained cost-effective and dominant relative to warfarin over the 20-year lifetime horizon (Table 4).

Table 3. Cost Inputs

Acute Events	Costs, $	Code	Reference
LAAC procedure+2 transesophageal echocardiograms*	16 741	DRG 273/274	[42,43]
Fatal ischemic stroke	11 250	DRG 063	[42]
Severe ischemic stroke	48 593	DRG 061/CMG 108-110	[42,43]
Moderate ischemic stroke	33 613	DRG 062/CMG 105-107	[42,43]
Minor ischemic stroke	23 951	DRG 063/CMG 101-104	[42,43]
TIA	4396	DRG 069	[42]
Systemic embolism (nonfatal)	5163	DRG 068	[42]
Systemic embolism (fatal)	7975	DRG 067	[42]
Fatal hemorrhagic stroke	10 446	DRG 064	[42]
Severe hemorrhagic stroke	42 721	DRG 064/CMG 108-110	[42,43]
Moderate hemorrhagic stroke	28 583	DRG 065/CMG 105-107	[42,43]
Minor hemorrhagic stroke	19 001	DRG 066/CMG 101-104	[42,43]
Major bleeding (nonfatal)	5879	DRG 377	[42]
Major bleeding (fatal)	10 572	DRG 378	[42]
Minor bleeding	423	CPT 42970	[48]
Myocardial infarction (nonfatal)	5944	DRG 280, 281, and 282	[42]
Myocardial infarction (fatal)	8821	DRG 283, 284, and 285	[42]
Quarterly costs			
Warfarin+INR monitoring	118	CPT 85610 and 99211	[48,49]
NOAC	1147	...	[49]
Independent after stroke	109	CPT 99214	[48]
Moderately disabled after stroke	9483	...	[44–47]
Severely disabled after stroke	15 441	...	[44–47]

CMG indicates case-mix group; CPT, Current Procedural Terminology; DRG, diagnosis-related group; INR, international normalized ratio; LAAC, left atrial appendage closure; NOAC, nonwarfarin oral anticoagulant; TIA, transient ischemic attack.
*Procedure cost reflects inclusion of 2 transesophageal echocardiograms and is weighted between 2 DRGs to be consistent with previous analysis.[12]
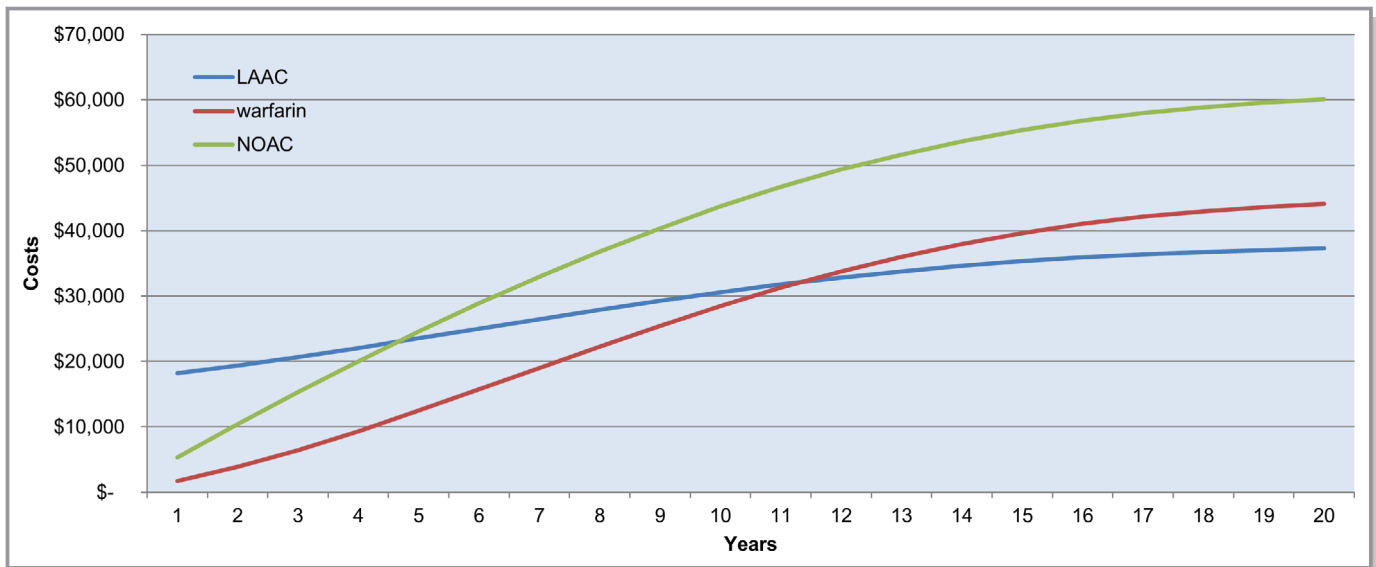
Figure 2. Cumulative cost curve: left atrial appendage closure (LAAC) vs warfarin vs nonwarfarin oral anticoagulant (NOACs). Cumulative costs by year for LAAC, warfarin, and NOACs.

LAAC Versus NOACs

Over the lifetime analysis, patients undergoing LAAC had more QALYs than patients receiving NOACs (7.772 versus 7.481) (Table 4). LAAC had lower costs than NOACs by year 5 ($23 960 versus $25 691) (Figure 2). LAAC became cost-effective and dominant relative to NOACs by year 5 and remained so over the lifetime analysis (Table 4).

Scenario Analysis: Post-FDA, Real-World Procedure Data

When using the real-world procedure data, LAAC provided an additional 0.65 QALYs at year 20 relative to warfarin. This represents a slight increase in QALYs relative to the RCT-based analysis. As in the RCT analysis, LAAC became less costly than warfarin at year 10 (−$2202 versus −$517).

LAAC became cost-effective relative to warfarin at year 7 ($35 051/QALY) and dominant at year 10, and it remained dominant over the 20-year lifetime horizon.

One-Way Sensitivity Analysis

Tornado diagrams illustrating the 10 most impactful variables in descending order of influence at 20 years are depicted in Figure S1. One-way sensitivity analyses of LAAC versus warfarin demonstrated that the health utility value used for Well with LAAC had a significant impact on model results. The baseline risk of stroke and bleeding also influenced the ICER, with higher risks resulting in more favorable cost-effectiveness for LAAC. When comparing LAAC with NOACs, the 20-year results were most sensitive to the utility values for Well with LAAC and Well with NOACs, along with the percentage of nondisabling ischemic strokes experienced by patients with

Table 4. QALYs, Cost, and ICER Results at 10 and 20 Years for LAAC Versus Warfarin and LAAC Versus NOACs

Time	Total QALYs	Incremental QALYs (Relative to OACs)	Total Costs, $	Incremental Costs (Relative to OACs), $	ICER Versus OACs
10 Years					
LAAC	5.77	…	32 769	…	…
Warfarin	5.52	0.25	33 286	−517	Dominant
NOAC	5.68	0.09	48 803	−16 034	Dominant
20 Years					
LAAC	7.77	…	44 894	…	…
Warfarin	7.17	0.60	61 623	−16 729	Dominant
NOAC	7.48	0.29	77 023	−32 129	Dominant

ICER indicates incremental cost-effectiveness ratio; LAAC, left atrial appendage closure; NOAC, nonwarfarin OAC; OAC, oral anticoagulant; QALY, quality-adjusted life-year.
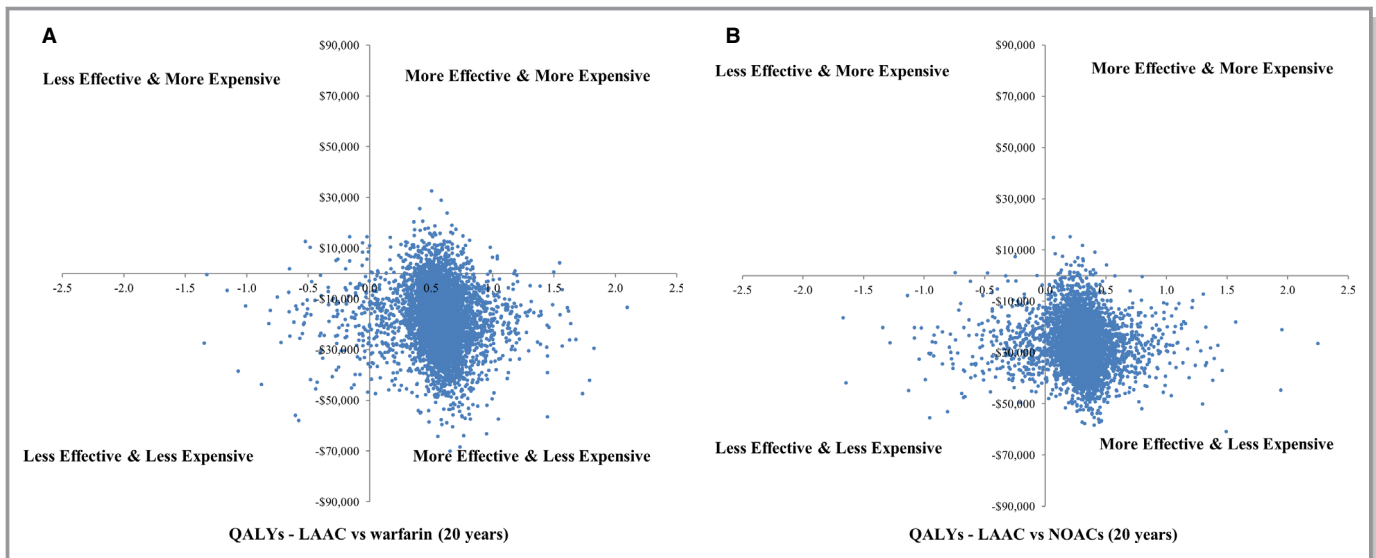
Figure 3. A, Scatter plots of incremental costs and incremental quality-adjusted life-years (QALYs) at 20 years for left atrial appendage closure (LAAC) vs warfarin. Probabilistic sensitivity analysis (PSA) results reflect 5000 model simulations to estimate the effect of uncertainty on model results. **B**, Scatter plots of incremental costs and incremental QALYs at 20 years for LAAC vs nonwarfarin oral anticoagulants (NOACs). PSA results reflect 5000 model simulations to estimate the effect of uncertainty on model results.

LAAC and baseline risk of bleeding; only varying Well with LAAC increased the ICER beyond the $50 000 threshold. Additional results can be found in Data S1.

Probabilistic Sensitivity Analysis

Probabilistic sensitivity analysis simulations (Figure 3) demonstrated that at 20 years, LAAC had lower average total costs than warfarin and NOACs: $44 768 (95% CI, $26 009–$70 566) versus $61 585 (95% CI, $35 999–$98 329) versus $76 985 (95% CI, $44 888–$119 604), closely in line with the deterministic estimates. Relative to warfarin, there was a 97% probability that LAAC provided more QALYs and a 94% probability that LAAC was cost saving over the lifetime analysis. The overall probability of cost-effectiveness was 98%, using a willingness-to-pay threshold of $50 000/QALY. At 20 years, there was a 95% probability that LAAC was cost-effective relative to NOACs.

Discussion

This analysis demonstrates that LAAC with the Watchman device is a cost-effective solution relative to both warfarin and NOACs for stroke risk reduction in patients with nonvalvular AF. Using pooled PROTECT AF and PREVAIL 5-year RCT data, LAAC became cost-effective and dominant (more effective *and* less costly) relative to NOACs at 5 years. LAAC achieved cost-effectiveness relative to warfarin at 7 years, with an ICER of $35 051, and dominance at 10 years. Despite the increase in the risk of ischemic stroke

observed in the pooled data, LAAC proved to be the most cost-effective treatment strategy.

Sensitivity analyses indicate that model results are robust and not overly sensitive to variation in individual parameters. Results of the one-way sensitivity analysis demonstrated that health state utilities (Well with LAAC, Well with NOACs), baseline risk of stroke and/or bleeding, and stroke outcomes had the greatest impact on model results. These findings confirmed the importance of QoL as well as the need to consider the differential stroke outcomes and costs associated with the treatment modalities. Probabilistic sensitivity analysis results confirmed that when using pooled, long-term data, there is a high probability that LAAC is cost-effective relative to warfarin and NOACs at 20 years (98% and 95%, respectively).

In addition to our primary analysis, we conducted a scenario analysis to understand the impact of post-FDA, real-world LAAC procedural data on cost-effectiveness.[11] LAAC procedure-related complications with the Watchman device have continued to decrease since the PROTECT AF trial. Despite 71% of implanting physicians being first-time operators and performing 50% of the procedures in this cohort, the implantation success rate and complication rate both improved. The combination of increased procedural success rates and lower complication rates in the real-world data led to slightly higher QALYs than observed with the trial data. As would be expected, time to cost-effectiveness remained consistent with the trial-based analysis relative to both warfarin and NOACs. This relatively minimal improvement in cost-effectiveness is related to the fact that postprocedural

clinical events, such as stroke and bleeds, constituted the majority of costs accrued over time.

To ensure the generalizability of our findings, we further explored the impact of age on modeled results. The primary analysis considered a baseline patient 70 years of age at moderate risk of stroke and bleeds. Holding all other model inputs constant, we repeated the analysis using a baseline age of 75 and 80 years and found that LAAC remained cost-effective relative to warfarin over the lifetime horizon.

The findings from this pooled analysis are consistent with our previously published data using only PROTECT AF 4-year, follow-up trial data.[12] As expected, given the increased risk of ischemic stroke relative to warfarin in the pooled data, patients receiving LAAC had a modest reduction in QALYs and a slight increase in total costs over the lifetime analysis (7.77 versus 8.03 and $44 894 versus $31 198, respectively). Despite these changes, LAAC time to cost-effectiveness remained the same: LAAC achieved cost-effectiveness relative to warfarin and NOACs by years 7 and 5, respectively. Once achieved, LAAC cost-effectiveness and cost savings were maintained over the lifetime analyses in both studies.

In addition to our PROTECT AF trial 4-year cost-effectiveness analysis, one other recent publication assessed the cost-effectiveness of LAAC compared with warfarin and NOACs from a US payer perspective.[13] Freeman et al[13] examined the cost-effectiveness of LAAC versus OACs 2 ways: first using PROTECT AF 4-year trial data alone and then using PREVAIL 1-year trial data alone. Consistent with our original analysis, the authors found that LAAC was cost-effective relative to warfarin and NOACs when using the clinical results from the PROTECT AF trial ($20 486/QALY and $23 422/QALY, respectively). However, when using the PREVAIL trial, LAAC was dominated by warfarin and NOACs at 20 years. This finding was not unexpected given the PREVAIL trial was primarily designed to assess procedural safety and ultimately achieved noninferiority to warfarin for only 1 of its 2 efficacy end points. However, it must be emphasized that warfarin performance in the PREVAIL trial was atypical, with a substantially lower rate of ischemic stroke (0.7%) than ever reported for warfarin in any other stroke prevention trial.[4–6] This is consistent with the wide CIs attendant with the PREVAIL trial's smaller sample size, which, again, was never intended to be analyzed in isolation. Furthermore, the mean follow-up was much shorter in the PREVAIL trial analysis compared with the PROTECT AF trial analysis, which could account for the lower rate of long-term complications. Last, and more important, the analysis by Freeman et al[13] assumed equivalent QoL and stroke outcomes for all treatments, whereas we have used treatment-specific data for these outcomes.

Taking the limitations of the PREVAIL trial into account but recognizing the importance of assessing the full body of RCT evidence, our analysis sought to provide greater certainty as to the cost-effectiveness of LAAC by using pooled PROTECT AF and PREVAIL trial data over as long a period of follow-up as possible. This approach is in line with best practices recommended by the International Society for Pharmacoeconomics and Outcomes Research.[50] In addition, our analysis differentiated QoL and stroke outcomes by treatment. Patients undergoing LAAC have been shown to have higher QoL and experience fewer disabling strokes compared with patients receiving warfarin.[10,16,17,40,41] Disability after a stroke has substantial implications for patient QoL and costs of care. Furthermore, sensitivity analyses reveal that these variables have notable impact on model results. Given this, one should not understate the importance of using *therapy-specific QoL and stroke outcomes* data in economic evaluations of stroke prevention strategies.

Limitations

Clinical inputs were derived from different sources, including pivotal trials and meta-analyses. No RCT directly comparing LAAC with NOACs exists; indirect comparison techniques were leveraged by necessity. The clinical studies used had different lengths of follow-up, and data were extrapolated to 20 years; however, 5 years of follow-up in the PROTECT AF and PREVAIL clinical trials is substantial by stroke prevention RCT standards. In addition, treatments administered in clinical practice may vary in effectiveness compared with the results observed in RCTs. Clinical inputs reflect the results of the intent-to-treat analyses, but the model allowed for therapy change. The model allowed for OAC switching and discontinuation through 2 years but did not account for patients restarting anticoagulation after discontinuation because of the lack of long-term data on clinical outcomes in these treatment scenarios. Switching, discontinuing, and restarting anticoagulation may impact the stroke and bleeding risk and relative effectiveness of treatment for the warfarin and NOAC treatment arms. In the absence of such data, the results would be speculative at best; restarting OAC use may improve outcomes but allowing for further discontinuation beyond 2 years may lead to worse outcomes. Further research is needed to understand long-term OAC patient adherence and outcomes. The baseline risks of stroke and bleeds were based on modified Congestive Heart Failure, Hypertension, Age≥75 years, Diabetes Mellitus, Prior Stroke or Transient Ischemic Attack, Vascular Disease, Age 65-74 years, Sex Category (CHA$_2$DS$_2$-VASc) and HAS-BLED scores, as not all score components were available in the baseline patient-level data.[8–10] Although we have presented some post-FDA real-world evidence as part of this analysis, these data were limited to procedural outcomes without long-term follow-up. Finally, we used a 3-month cycle length with the chance for

one event per cycle, although in real-world clinical practice, patients may experience >1 event in 3 months.

Conclusion

Despite the increased risk of ischemic stroke observed in the PREVAIL trial, LAAC is cost-effective and cost saving relative to NOACs and warfarin when the full body of RCT data is taken into consideration. LAAC with the Watchman device is an economically viable stroke risk reduction strategy for patients with AF seeking an alternative to lifelong anticoagulation. These findings confirm those of the earlier PROTECT AF trial–based analyses and should be considered when formulating policy and practice guidelines for stroke prevention in AF.

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SUPPLEMENTAL MATERIAL

Data S1.

Supplemental Results

One-way Sensitivity Analysis

LAAC vs. warfarin: Other variables that had a greater than 4% impact on model outcomes were the cost of the LAAC procedure, the percent of ischemic strokes experienced by LAAC patients that were non-disabling, and the long-term disability costs associated with severe strokes.

Figure S1. Tornado plots of one-way sensitivity analyses at 20 years of LAAC versus warfarin and LAAC versus NOACs.
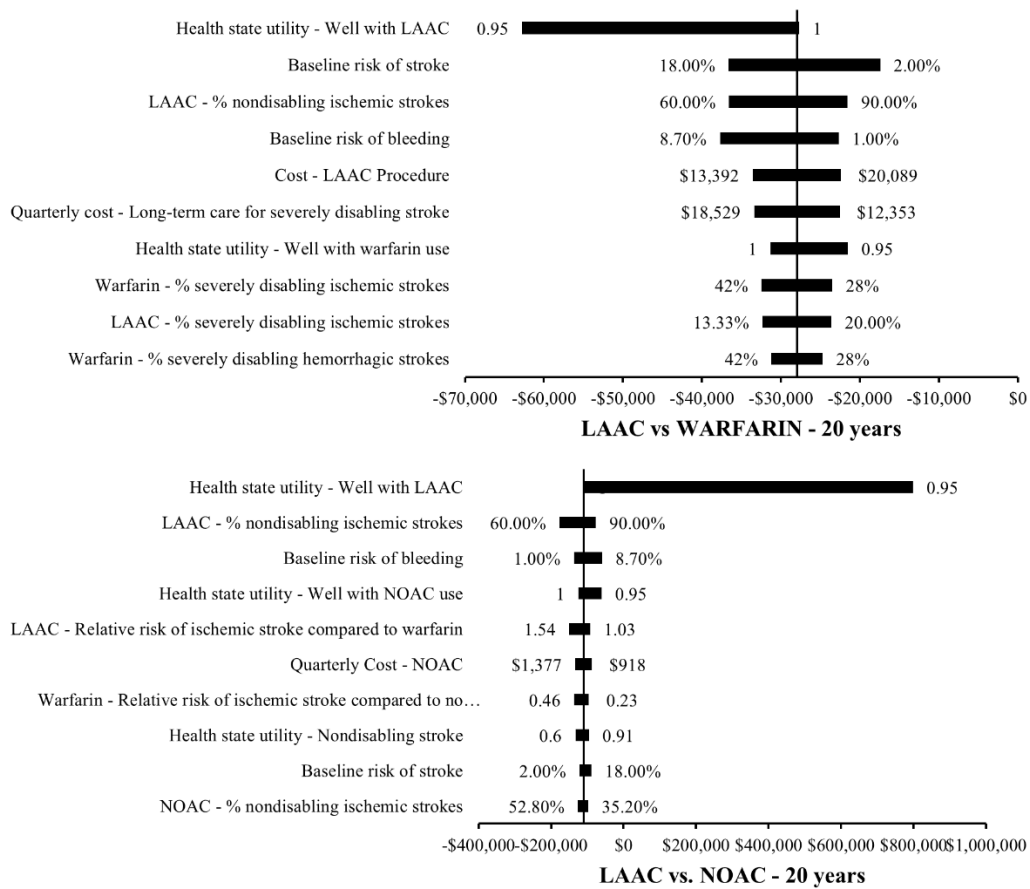
The ten most impactful variables are presented in descending order of influence. All were varied as published 95% confidence intervals or +/- 20%. LAAC=left atrial appendage closure; NOAC=non-warfarin oral anticoagulant.