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Left Atrial Appendage Occlusion Versus Oral Anticoagulation in Atrial Fibrillation

A Decision Analysis

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Background: Left atrial appendage occlusion (LAAO) is a potential alternative to oral anticoagulants in selected patients with atrial fibrillation (AF). Compared with anticoagulants, LAAO decreases major bleeding risk, but there is uncertainty regarding the risk for ischemic stroke compared with anticoagulation.

Objective: To determine the optimal strategy for stroke prevention conditional on a patient's individual risks for ischemic stroke and bleeding.

Design: Decision analysis with a Markov model.

Data Sources: Evidence from the published literature informed model inputs.

Target Population: Women and men with nonvalvular AF and without prior stroke.

Time Horizon: Lifetime.

Perspective: Clinical.

Intervention: LAAO versus warfarin or direct oral anticoagulants (DOACs).

Outcome Measures: The primary end point was clinical benefit measured in quality-adjusted life-years.

Results of Base-Case Analysis: The baseline risks for stroke and bleeding determined whether LAAO was preferred over anticoagulants in patients with AF. The combined risks favored LAAO for higher bleeding risk, but that benefit became less certain at higher stroke risks. For example, at a HAS-BLED score of 5, LAAO was favored in more than 80% of model simulations for CHA_2DS_2-VASc scores between 2 and 5. The probability of LAAO benefit in QALYs (>80%) at lower bleeding risks (HAS-BLED score of 0 to 1) was limited to patients with lower stroke risks (CHA_2DS_2-VASc score of 2). Because DOACs carry lower bleeding risks than warfarin, the net benefit of LAAO is less certain than that of DOACs.

Results of Sensitivity Analysis: Results were consistent using the ORBIT bleeding score instead of the HAS-BLED score, as well as alternative sources for LAAO clinical effectiveness data.

Limitation: Clinical effectiveness data were drawn primarily from studies on the Watchman device.

Conclusion: Although LAAO could be an alternative to anticoagulants for stroke prevention in patients with AF and high bleeding risk, the overall benefit from LAAO depends on the combination of stroke and bleeding risks in individual patients. These results suggest the need for a sufficiently low stroke risk for LAAO to be beneficial. The authors believe that these results could improve shared decision making when selecting patients for LAAO.

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Left atrial appendage occlusion (LAAO) has emerged as a potential alternative to anticoagulation for preventing stroke in patients with atrial fibrillation (AF) (1). Clinical trials suggest that LAAO is noninferior to oral anticoagulants (OACs), including warfarin and direct OACs (DOACs), with regard to overall clinical benefit (2–4). Compared with warfarin, LAAO is associated with a significant reduction in the risks for intracranial hemorrhage and major bleeding. However, concerns remain over the possible increased risk for ischemic stroke or systemic embolism as well as the procedural risks associated with LAAO (5, 6). Thus, patient selection is influenced by 3 competing hazards: the long-term risk for thromboembolism, the long-term increase in risk for bleeding associated with OAC therapy, and the short-term procedural risks of LAAO.

Although several studies have attempted to determine the preferred strategy for stroke prevention in patients with AF at a cohort level (7, 8), these attempts have not provided enough detail about the net clinical benefit (NCB) of LAAO compared with OACs to inform shared decision making for individual patients.

The objective of this study is to assess the probability of NCB of LAAO versus OACs across a range of individual patient combinations of stroke risk and bleeding risk. Thus, we did a decision analysis to better understand the risk–benefit tradeoffs when choosing between LAAO and OACs contingent on a patient's stroke risk and bleeding risk.

See also:

Editorial comment
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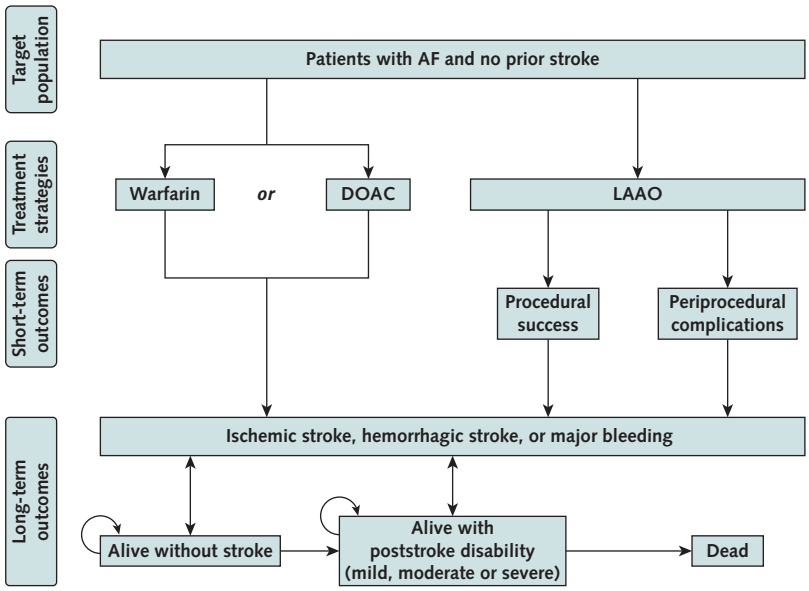
Figure 1. Schematic of Markov model structure.



Note that death may occur from any of the short-term or long-term health outcome states. AF = atrial fibrillation; DOAC = direct oral anticoagulant; LAAO = left atrial appendage occlusion.

METHODS

Model Design and Structure

We constructed a decision analytic Markov model to simulate a virtual clinical trial of stroke prevention strategies in a cohort of 70-year-old women and men with nonvalvular AF and without prior stroke followed over a lifetime horizon. We compared 2 strategies of stroke prevention, LAAO and oral anticoagulation with either warfarin or a DOAC. Formal ethical review was not required by Conjoint Health Research Ethics Board at the University of Calgary for model-based studies using data from the published literature.

The Markov model included 5 categories of health states based on functional status to account for differences in quality of life and life expectancy with and without prior stroke. These health states were 1) alive without prior stroke; alive with prior stroke and 2) mild, 3) moderate, or 4) severe poststroke disability as classified by the modified Rankin Scale (mRS); and 5) death. Mild, moderate, and severe disability were defined as an mRS score of 0 to 2, 3 or 4, and 5, respectively. We further stratified these health states on the basis of stroke prevention therapy with LAAO, OACs, or aspirin.

For the OAC strategy, all patients entered the model in the health state defined by being alive, not having prior stroke, and receiving an OAC. For the LAAO strategy, the proportion of patients in each health state was based on the initial LAAO procedural success (defined as device implantation followed by discontinuation of oral anticoagulation) and periprocedural stroke and bleeding events (9). Patients who could not have successful LAAO placement were assumed to resume OAC therapy.

During every 3-month cycle, patients moved between health states if they had an ischemic stroke, hemorrhagic stroke, or extracranial major bleeding event, which determined their future health state, prognosis, and treatment. For example, patients treated with anticoagulation could discontinue treatment and switch to aspirin if they had a major bleeding event or intracranial hemorrhage. Figure 1 shows the model structure.

Model Assumptions

Consistent with prior modeling analyses of anticoagulants for stroke prevention in AF, we made several assumptions (10–12). First, after an intracranial hemorrhage, all patients receiving anticoagulation switched to aspirin. After a major bleeding event, a quarter of patients discontinued anticoagulation permanently (10, 11). Second, patients who had an ischemic or hemorrhagic stroke could transition only to a health state with similar or greater disability; for example, stroke survivors with moderate disability (mRS score of 3 to 4) could develop severe disability with recurrent stroke (mRS score of 5), but they could not move into a health state with mild disability (mRS score of 0 to 2) (10–12). Third, LAAO was available for those with prior bleeding at baseline—for example, those with a HAS-BLED score of at least 1 (where 1 point is scored for prior major bleeding)—but the model did not allow for crossover to LAAO for those initially allocated to OAC.

Model Inputs

The clinical effectiveness inputs were based on a patient-level meta-analysis using the pooled, long-term data of the PROTECT AF (Watchman Left Atrial Appendage System for Embolic Protection in Patients With Atrial Fibrillation) trial and the PREVAIL (Prospective Randomized Evaluation of the Watchman LAA Closure

Table 1. Clinical Effectiveness and Quality-of-Life Inputs for Markov Model

Variable	Base Case	Range	Distribution	Source
Annual rates: clinical events				
Ischemic stroke	CHA_2DS_2-VASc	–	β	23
Major bleeding	HAS-BLED	–	β	24
All-cause mortality	U.S. life tables	–	NA	20
Lethal extracranial bleeding	0.003	0.002 to 0.004	β	14
LAAO periprocedural events				
LAAO implantation success	95.6%	85.0% to 100%	β	17, 18
Periprocedural risk				
Ischemic stroke	0.05%	0.04% to 0.06%	β	17, 18
Major bleeding	0.55%	0.44% to 0.66%	β	17, 18
Hemorrhagic stroke	0.03%	0.02% to 0.03%	β	17, 18
Death	0.10%	0.08% to 0.13%	β	17, 18
Clinical effectiveness				
RR of ischemic stroke				
Warfarin vs. aspirin	0.48	0.37 to 0.63	Log-normal	14
DOAC vs. warfarin	0.92	0.83 to 1.02	Log-normal	15, 16
LAAO vs. warfarin	1.4	0.76 to 2.59	Log-normal	13
RR of hemorrhagic stroke				
Warfarin vs. aspirin	1.84	0.87 to 3.87	Log-normal	14
DOAC vs. warfarin	0.48	0.39 to 0.59	Log-normal	15
LAAO vs. warfarin	0.2	0.07 to 0.56	Log-normal	13
RR of major bleeding				
Warfarin vs. aspirin	1.71	1.21 to 2.41	Log-normal	14
DOAC vs. warfarin	0.86	0.74 to 1.0	Log-normal	15
LAAO vs. warfarin	0.48	0.32 to 0.71	Log-normal	13
RR of all-cause mortality (AF vs. no AF)	2.84	2.1 to 4.1	Log-normal	19
RR of all-cause mortality (stroke vs. no stroke)				
mRS 0–2 poststroke disability	2.56	±25%	Log-normal	25
mRS 3–4 poststroke disability	4.63	±25%	Log-normal	25
mRS 5 poststroke disability	13.18	±25%	Log-normal	25
Probability of permanently discontinuing anticoagulation after an intracranial hemorrhage	1.0	NA	NA	Assumption
Probability of permanently discontinuing anticoagulation after a GI bleeding event	0.25	NA	NA	Assumption
Utility inputs				
Mild stroke (mRS, 0–2)				
First year	0.73	0.70 to 0.76	β	26
Subsequent years	0.74	0.71 to 0.77	β	26
Moderate stroke (mRS, 3–4)				26
First year	0.5	0.43 to 0.57	β	26
Subsequent years	0.65	0.60 to 0.70	β	26
Severe stroke (mRS, 5)				26
First year	0.13	0.02 to 0.24	β	26
Subsequent years	0.41	0.26 to 0.56	β	26
Major bleeding (disutility deduction per event)	−0.013	−0.016 to −0.009	β	21, 22

AF = atrial fibrillation; DOAC = direct oral anticoagulant; GI = gastrointestinal; LAAO = left atrial appendage occlusion; mRS = modified Rankin Scale; NA = not applicable; RR = risk ratio.

Device in Patients With Atrial Fibrillation Versus Long-Term Warfarin Therapy) trial that compared LAAO with oral anticoagulation (**Table 1**) (13). The LAAO group of that meta-analysis reported pooled relative risks of 1.40 (95% CI, 0.76 to 2.59) for ischemic stroke, 0.48 (CI, 0.32 to 0.71) for non–procedure-related major bleeding, and 0.20 (CI, 0.07 to 0.56) for intracranial hemorrhage. Warfarin and DOAC clinical inputs were obtained primarily from meta-analyses and clinical trials of stroke prevention in AF (14–16).

The risk ratios, comparing LAAO versus OAC, were applied to the 3-month rates of ischemic stroke, hemorrhagic stroke, and major bleeding for the anticoagulation cohort to estimate the outcomes associated with LAAO. Stroke and bleeding event rates associated with the OAC cohort were based on choice of therapy (that is,

warfarin, DOAC, or aspirin) and the combination of risks from the CHA_2DS_2-VASc and HAS-BLED scores (**Supplement Table 1**, available at Annals.org). To account for increasing bleeding and stroke risks with age, the event rates of ischemic stroke were increased by a factor of 1.45 and the event rates of major bleeding and intracranial hemorrhage by a factor of 1.61 per decade (27).

For the LAAO cohort, we also included the periprocedural risks for stroke, major bleeding, and procedural failure in the model informed by PROTECT AF, PREVAIL, and more contemporary cohorts, such as the postapproval LAAO registry (17, 18). We assumed that those without successful implantation of the LAAO device would start anticoagulation. All-cause mortality was obtained from U.S. life tables and adjusted for the presence of AF (19, 20). After a stroke event, the increased risk for death was modeled on the basis of mRS disability (28, 29). To account for fewer fatal strokes associated with LAAO than warfarin (13, 17), we applied the risk ratio of all-cause death, comparing LAAO versus warfarin, from the pooled long-term PREVAIL and PROTECT AF trials to calibrate the LAAO survival curves. Given the uncertainty in survival and in the clinical effectiveness of LAAO beyond the 5-year follow-up of the pooled analysis, we assumed an attenuated benefit of LAAO on mortality, where the risk ratio of all-cause death was set to 1.0.

In sensitivity analyses, our model used the following alternative sources for the clinical effectiveness data (**Supplement Table 2**, available at Annals.org): 1) a network meta-analysis of randomized trials (30) that included a comparison between LAAO and warfarin for stroke prevention in AF and found hazard rates of 0.84 for stroke and systemic embolism, 0.63 for major bleeding, and 0.21 for intracranial hemorrhage and 2) a recent individual patient–level meta-analysis (31) that included the PRAGUE-17 (Left Atrial Appendage Closure vs. Novel Anticoagulation Agents in Atrial Fibrillation) trial, which was the only available trial that directly compared LAAO with DOACs at time of study analysis. We also conducted a sensitivity analysis comparing LAAO versus a strategy of no anticoagulation to assess the clinical situations where anticoagulation may be contraindicated or patients may be nonadherent to anticoagulant therapy.

Patient quality of life was included in the model as a health utility, which is a weighting scale with 1 representing perfect health and 0 representing death. The mean baseline utility for persons with AF and no prior stroke was 0.779 (SD, 0.253), which was obtained from the Euro Heart Survey, which collected EuroQol 5-dimension survey data from 5050 patients with cardiac disease (32). Utility measurements for poststroke health states were obtained from a population-based study of stroke survivors in the United Kingdom (the Oxford Vascular Study) and from previously published models on anticoagulation in AF (21, 22). Short-term, nonfatal major bleeding events involved one-time quality-of-life decrements that could be applied every 3 months (33).

Study End Points

The primary end point was the quality-adjusted life-year (QALY), which is the cumulative survival duration in each health state weighted by the utility. Secondary end points were life expectancy or life-years (LYs) and NCB. There is no widely accepted approach for estimating NCB in this situation, so we used a method from a previous study of LAAO (34). In this method, "clinical benefit" is the sum of the annual rate of ischemic stroke plus 1.5 times the annual rate of intracranial hemorrhage, because of the higher risk for death and functional impairment with hemorrhage. Annual rates are calculated as the total number of events divided by the total person-years at risk. "Net clinical benefit" is then determined by subtracting the clinical benefit with LAAO from the clinical benefit with anticoagulation using the equation

$$\begin{aligned} NCB = &(\textit{annual rate of } IS_{OAC} + 1.5 \\ &\times \textit{annual rate of } ICH_{OAC}) \\ &- (\textit{annual rate of } IS_{LAAO} + 1.5 \\ &\times \textit{annual rate of } ICH_{LAAO}) \end{aligned}$$

where IS indicates ischemic stroke and ICH indicates intracranial hemorrhage.

We also used an alternative method to calculate NCB on the basis of another study of LAAO (35), which defined NCB as the sum of the rate differences of ischemic stroke, intracranial hemorrhage, major bleeding, and all-cause death in the 2 treatment groups, weighted by the relative effect of each event on death and disability.

Statistical Analysis

We calculated the base-case QALYs, NCB, and survival benefit of LAAO versus OACs over a range of risks for ischemic stroke and bleeding based on the CHA_2DS_2-VASc and HAS-BLED scores. We did an additional sensitivity analysis using the ORBIT score as an alternative bleeding score (36). We reported the results of patients with a CHA_2DS_2-VASc score of at least 2 (consistent with the cut point at the time the pivotal LAAO trials were conducted) and at most 7 (the maximal score for patients without a history of stroke). For this analysis, we categorized the risk for an ischemic event into low (CHA_2DS_2-VASc score of 2), intermediate (CHA_2DS_2-VASc score of 3 to 4), and high (CHA_2DS_2-VASc score ≥5) categories and the risk for major bleeding into low (HAS-BLED score of 0 to 1), intermediate (HAS-BLED score of 2 to 4), and high (HAS-BLED score ≥5) categories.

We incorporated uncertainty in the point estimates of all model inputs into base-case results–for example, using 95% CIs. A Monte Carlo simulation of 1000 iterations was used to propagate the uncertainty in individual model parameters to generate a distribution of expected LYs, QALYs, and NCB. We applied log-normal distributions for all hazard ratios and β distributions for all probabilities and utilities. We used ±0.1 LYs or QALYs as a minimum clinically significant gain to consider 1 strategy better than another (37) and calculated the probability of achieving that gain in the 1000 iterations. Analyses were done in TreeAge Pro 2021 (TreeAge Software).

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RESULTS

Model Validation

To assess internal validity, we compared the modeled survival probabilities of the anticoagulation cohort with the reported survival in the long-term pooled analysis of the PREVAIL and PROTECT AF trials. We simulated a cohort of patients with the following similar base characteristics: mean age of 73 years, CHA_2DS_2-VASc score of 4, and warfarin as the choice of anticoagulant. Among the cohort treated with anticoagulation alone, the modeled survival probabilities (92.0% at 1 year, 74.4% at 3 years, and 56.7% at 5 years) were similar to the probabilities estimated from the Kaplan–Meier curves reported in PREVAIL and PROTECT AF (92.8% at 1 year, 74.8% at 3 years, and 57.4% at 5 years) (13). Last, the modeled survival probabilities of the LAAO cohort (94.2% at 1 year, 81.1% at 3 years, and 66.7% at 5 years) were also similar to the Kaplan–Meier estimates from the pooled analysis of PREVAIL and PROTECT AF (93.0% at 1 year, 82.5% at 3 years, and 69.2% at 5 years) (13).

Base-Case Results

In the base case of a 70-year-old patient with AF and prior stroke or transient ischemic attack, we saw clinical benefit (as measured using QALYs, LYs, and NCB) of LAAO over anticoagulation, with higher HAS-BLED scores and lower CHA_2DS_2-VASc scores (**Table 2**; **Supplement Table 3**, available at Annals.org).

Tradeoffs Between Bleeding and Stroke Risk in Selecting Stroke Prevention Therapy

Figure 2 illustrates the information in **Table 2** and adds more detail about the preference for LAAO over OACs when clinical benefit was measured in QALYs. The probability of LAAO being the preferred strategy depended on the combination of stroke and bleeding risks. The preferred strategy was more likely LAAO for patients with higher risk for bleeding and lower risk for stroke, and the clinical benefit of LAAO over OACs was less certain for patients with lower risk for bleeding and higher risk for stroke. For example, at the highest bleeding risk (HAS-BLED score of 5), LAAO was favored in more than 80% of model simulations for CHA_2DS_2-VASc scores between 2 and 5. The probability of LAAO benefit in QALYs at lower bleeding risks was limited to patients with lower stroke risks. When patients had the lowest bleeding risk (HAS-BLED score of 0) and a CHA_2DS_2-VASc score of 2 (*lower left corner*), the probability of LAAO being preferred over warfarin was greater than 80%. However, when patients had the lowest bleeding risk and a CHA_2DS_2-VASc score of 3 or 4, LAAO had only a 60% to 80% probability of being the preferred strategy. For patients with the same low bleeding risk, LAAO had only equivocal benefit at a CHA_2DS_2-VASc score of 5, and warfarin was preferred over LAAO at CHA_2DS_2-VASc scores of 6 or higher.

Table 2. Incremental Benefit of LAAO Versus Anticoagulation,* by Type of Anticoagulant, Risk for Ischemic Stroke, and Risk for Bleeding†, With Benefit Measured in QALYs, LYs, and NCB‡

Bleeding Risk	Ischemic Stroke Risk		
	Low	Intermediate	High
LAAO vs. warfarin			
Low			
QALYs	+0.45	+0.38	UB
LYs	+0.58	+0.51	UB
NCB	UB	UB	OP
Intermediate			
QALYs	+0.74	+0.65	+0.22
LYs	+0.92	+0.82	+0.32
NCB	0.49%/y	0.34%/y	OP
High			
QALYs	+0.92	+0.83	+0.36
LYs	+1.12	+1.03	+0.48
NCB	0.81%/y	0.68%/y	UB
LAAO vs. DOAC			
Low			
QALYs	+0.30	+0.20	OP
LYs	+0.34	+0.32	OP
NCB	OP	OP	OP
Intermediate			
QALYs	+0.43	+0.32	OP
LYs	+0.55	+0.43	UB
NCB	UB	OP	OP
High			
QALYs	+0.50	+0.41	UB
LYs	+0.60	+0.52	UB
NCB	0.09%/y	UB	OP

DOAC = direct oral anticoagulant; LAAO = left atrial appendage occlusion; LY = life-year; NCB = net clinical benefit; OAC = oral anticoagulant; OP = OAC preferred; QALY = quality-adjusted life-year; UB = uncertain benefit.

* Incremental benefits are reported if LAAO was favored over OAC in >60% of simulations. If LAAO was favored over OAC in <40% of simulations, OAC is considered the more beneficial strategy (OP). If LAAO was favored over OAC in 40%–60% of simulations, the relative benefit of LAAO vs. OAC is considered uncertain (UB).

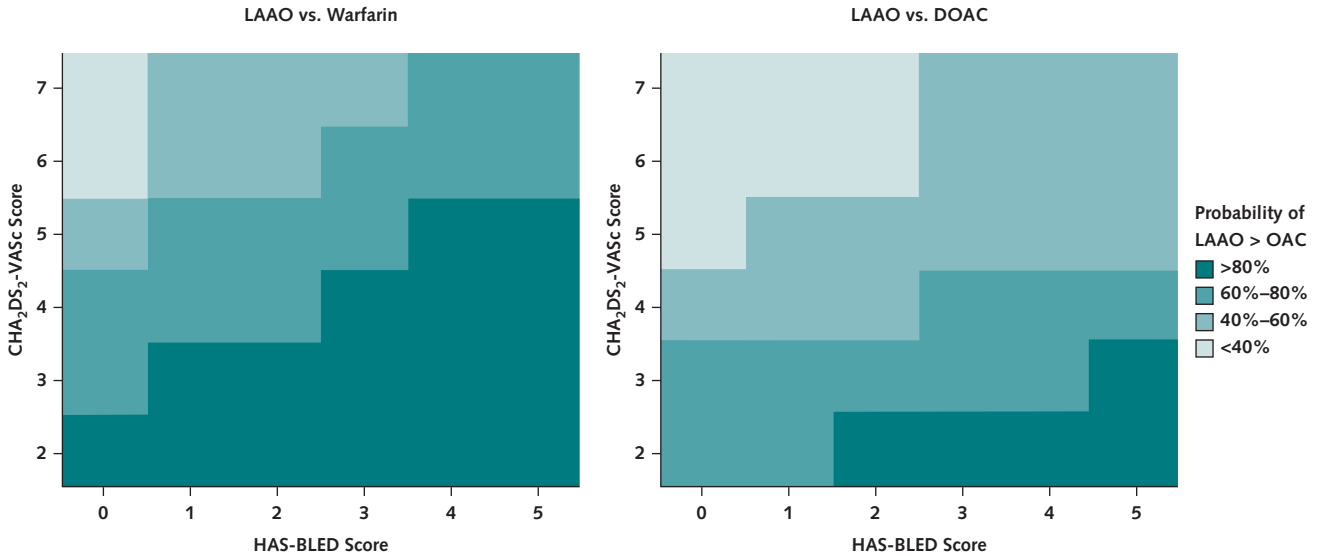
† Ischemic stroke risk is classified as follows: low risk (CHA_2DS_2-VASc score, 2), intermediate risk (CHA_2DS_2-VASc score, 3–4) and high risk (CHA_2DS_2-VASc score ≥ 5). Bleeding risk is classified as follows: low risk (HAS-BLED score, 0–1), intermediate risk (HAS-BLED score, 2–4) and high risk (HAS-BLED score ≥ 5).

‡ NCB is the sum of the rate differences of ischemic stroke and intracranial hemorrhage in the LAAO and OAC treatment groups, weighted by the relative effect of each event on death and disability.

As shown in **Figure 2**, LAAO was preferred less when DOACs were the anticoagulant comparator, given the improved bleeding risk for DOACs. For example, when clinical benefit was measured with QALYs, LAAO was favored over DOACs with at least 80% probability only for patients with a CHA_2DS_2-VASc score of 2 and HAS-BLED score of 2 to 5 and for patients with a CHA_2DS_2-VASc score of 3 and HAS-BLED score of 5.

Figure 3 describes our results for the secondary analyses using LYs and NCB. The results for LYs were similar to those for QALYs. In contrast, for NCB we found fewer combinations of bleeding and stroke risks where LAAO was preferred over warfarin and no combinations where LAAO was preferred over DOACs with at least 80% certainty.

Figure 2. Probability of LAAO being the preferable stroke prevention strategy compared with OAC by QALYs.



DOAC = direct oral anticoagulant; LAAO = left atrial appendage occlusion; OAC = oral anticoagulant; QALY = quality-adjusted life-year.

Because the definition of NCB is not standardized (38), we did a sensitivity analysis using an alternative definition that included mortality events. These results were similar to those of the primary analysis, where benefit was measured in QALYs (**Supplement Figure 1**, available at Annals.org).

Additional Sensitivity Analyses

To verify the relationship between LAAO and OAC over the range of stroke–bleeding risk combinations, we found alternative sources for the clinical effectiveness of LAAO in the decision model. First, we used data from a network meta-analysis of randomized trials that pooled the results of the landmark LAAO and anticoagulation studies. The results of this sensitivity analysis were concordant with those of the primary analysis, where LAAO was the preferred strategy under most stroke–bleeding risk combinations (**Supplement Table 4**, available at Annals.org). The benefit of LAAO was less certain when compared with DOAC among persons with low to intermediate bleeding risk (HAS-BLED score of 0 to 4) and high stroke risk (CHA_2DS_2-VASc score ≥5).

Second, we used clinical effectiveness data from a recent meta-analysis that directly compared LAAO versus DOACs (31). As in the primary analysis, LAAO was the preferred strategy across HAS-BLED bleeding risk categories when the stroke risk was low or intermediate (**Supplement Table 5**, available at Annals.org). When the risk for stroke was high (CHA_2DS_2-VASc score ≥5), LAAO was the preferred strategy when the risk for bleeding was also high (HAS-BLED score of 5); however, the benefit of LAAO over OAC was equivocal at an intermediate bleeding risk, and OAC was preferred at a low bleeding risk.

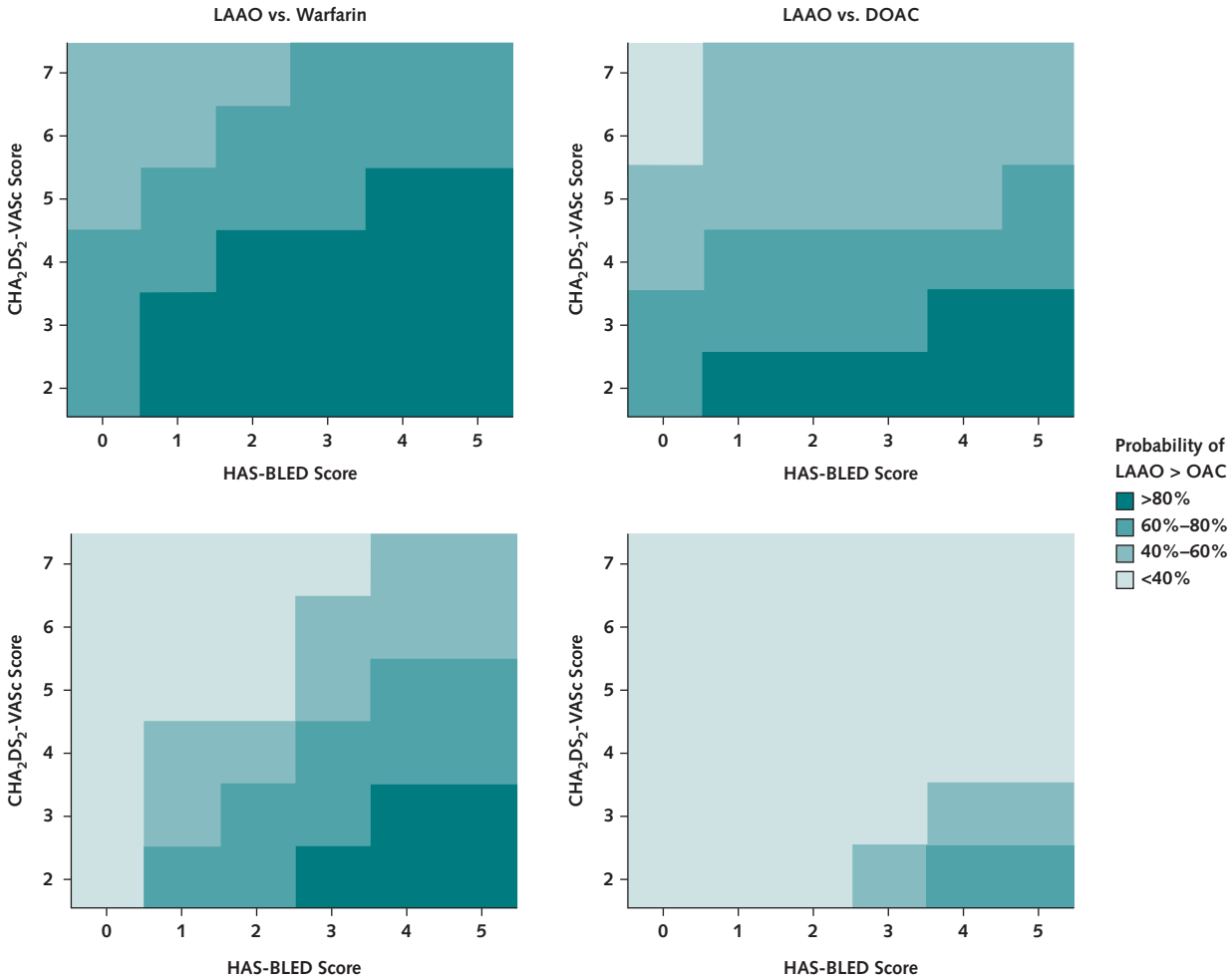
Third, in the sensitivity analysis using an alternative bleeding score, the relationship between LAAO and OAC was similar to that found in the primary analysis, where LAAO was preferred with increasing HAS-BLED scores and decreasing CHA_2DS_2-VASc scores (**Supplement Figure 2**, available at Annals.org).

Finally, we did a sensitivity analysis to assess the relative benefit of LAAO compared with no anticoagulation, which would include patients with contraindications to anticoagulation and those who are nonadherent to prescribed anticoagulant therapy. In this analysis, LAAO was the preferred strategy across the spectrum of HAS-BLED and CHA_2DS_2-VASc scores (**Supplement Table 6**, available at Annals.org).

Discussion

In a simulated cohort of patients with nonvalvular AF and no prior stroke, our study investigated the preferred stroke prevention strategy comparing LAAO and anticoagulation for patients with various combinations of stroke risk and bleeding risk. The study had 3 main findings. First, the likelihood that LAAO was the preferred strategy over warfarin increased with higher HAS-BLED scores and decreased with lower CHA_2DS_2-VASc scores. At the highest bleeding risk (HAS-BLED score ≥5), LAAO was the preferred strategy, but the likelihood of clinical benefit was less certain among patients with high risk for ischemic stroke (CHA_2DS_2-VASc score ≥5). This observation was consistent when clinical benefit was measured in terms of QALYs, LYs, or NCB. Second, the clinical benefit of LAAO included the survival benefit of LAAO compared with warfarin that was observed in clinical trial data (13). Third, LAAO was the preferred strategy across a smaller range of stroke and bleeding risks when a DOAC was the anticoagulant because DOACs are less likely than warfarin to cause bleeding.

Figure 3. Probability of LAAO being the preferable stroke prevention strategy compared with OAC by life-years (*top*) and net clinical benefit (*bottom*).



DOAC = direct oral anticoagulant; LAAO = left atrial appendage occlusion; OAC = oral anticoagulant.

The notable finding of a gradient in LAAO preference across the spectrum of ischemic stroke and bleeding risk is consistent with observations from the PROTECT AF and PREVAIL trials. Analyses of the combined data suggested that LAAO therapy led to less major bleeding and intracranial hemorrhage (13). Thus, those patients at greatest bleeding risk would be expected to maximally benefit from the risk reduction in major bleeding and intracranial hemorrhage conferred by LAAO. Although LAAO therapy was noninferior to dose-adjusted warfarin therapy for the prevention of overall stroke and systemic embolism, the LAAO group had more ischemic strokes than the warfarin group—although this difference in stroke rates was statistically nonsignificant (13). Our model incorporates this uncertainty in the clinical effect of LAAO on ischemic stroke, and the preference for the LAAO strategy is least certain among patients at greatest risk for ischemic stroke. Finally, we note that LAAO would become more favorable in patients who adhere less to their prescribed anticoagulant treatment than the 100% adherence we assumed in this study (39).

Although OAC therapy for stroke prevention in high-risk patients with AF is an established, guideline-indicated therapy (40, 41), LAAO is emerging as a potential alternative in selected persons. The evidence is evolving, and the results of several ongoing randomized clinical trials are expected to refine the indications for LAAO (42). Current suggestions for LAAO are outlined in the 2019 expert consensus statement from the European Heart Rhythm Association and European Association of Percutaneous Cardiovascular Interventions (43); suggested recipients include patients with nonvalvular AF who are eligible for long-term OAC therapy, those with elevated bleeding risk under long-term OAC therapy, those with contraindications to OAC, and nonadherent patients. These categories are broad, and our current analysis provides further insight into the LAAO benefit based on an individual's specific combination of stroke and bleeding risks.

Our baseline analysis addresses the first 2 patient categories suggested by the European Heart Rhythm Association and European Association of Percutaneous Cardiovascular

Interventions, where OAC is more favorable than LAAO in persons at highest stroke risk and low to moderate bleeding risk. The preference for LAAO increases with increasing bleeding risk and decreases with increasing stroke risk, and the benefit of LAAO becomes more uncertain when compared with DOACs with their decreased bleeding risk. Finally, our sensitivity analysis (**Supplement Table 6**) addresses the last 2 categories of patients, who have contraindications or nonadherence to OACs.

Our decision model may help clinicians to further understand and explain to their patients the tradeoffs between ischemic stroke and bleeding events for different treatment options. For patients with low to moderate CHA_2DS_2-VASc scores and high HAS-BLED scores, LAAO may be particularly beneficial. This scenario is not uncommon because 12% of patients had a CHA_2DS_2-VASc score of 1 or 2 and a HAS-BLED score of 3 or higher in a secondary analysis of the ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation) trial (44).

Our study has some limitations. First, clinical effectiveness data were primarily drawn from randomized trials that studied only the Watchman device (Boston Scientific), and thus the results from this study may not apply to other types of LAAO devices, although registry data suggest similar safety characteristics and long-term effectiveness between the 2 most common LAAO devices, Watchman and Amulet (Abbott Medical) (45, 46). The relative efficacy of these devices is currently being investigated in the SWISS-APERO (Comparison of Amplatzer Amulet and Watchman Device in Patients Undergoing Left Atrial Appendage Closure) trial (ClinicalTrials.gov: NCT03399851). In addition, our study's findings cannot be generalized to patients having surgical ligation of the left atrial appendage, those undergoing concomitant AF ablation with or without left atrial appendage electrical isolation, or those who have a stroke while receiving OAC. Second, data on the comparative efficacy of DOACs versus LAAO are limited. Finally, we described stroke and bleeding risk by the CHA_2DS_2-VASc and HAS-BLED scores, and we did a sensitivity analysis using the ORBIT bleeding risk score. Nevertheless, newer scores are attempting to improve the modest predictive accuracy of these scores (47, 48).

The relative clinical benefit of LAAO and OACs in patients with AF depends on the patients' baseline risks for stroke and bleeding. The LAAO strategy was preferred in those with the highest risk for bleeding. However, the benefit became less certain with increasing risk for ischemic stroke and decreasing bleeding risk. This description of LAAO benefit has the potential to improve shared decision making when selecting patients for LAAO.

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