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ORIGINAL RESEARCH

Left Atrial Appendage Occlusion in Patients With Anticoagulation Failure vs Anticoagulation Contraindication

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ABSTRACT

BACKGROUND Left atrial appendage occlusion (LAAO) provides mechanical cardioembolic protection for atrial fibrillation (AF) patients who cannot use oral anticoagulation therapy (OAT). Patients with a thrombotic event despite OAT are at high risk for recurrence and may also benefit from LAAO.

OBJECTIVES This study sought to investigate the efficacy of LAAO in AF patients with a thrombotic event on OAT compared to: 1) LAAO in AF patients with a contraindication for OAT; and 2) historical data.

METHODS The international LAAO after stroke despite oral anticoagulation (STR-OAC LAAO) collaboration included patients who underwent LAAO because of thrombotic events on OAT. This cohort underwent propensity score matching and was compared to the EWOLUTION (Evaluating Real-Life Clinical Outcomes in Atrial Fibrillation Patients Receiving the WATCHMAN Left Atrial Appendage Closure Technology) registry, which represents patients who underwent LAAO because of OAT contraindications. The primary outcome was ischemic stroke. Event rates were compared between cohorts and with historical data without OAT, yielding relative risk reductions based on risk scores.

RESULTS Analysis of 438 matched pairs revealed no significant difference in the ischemic stroke rate between the STR-OAC LAAO and EWOLUTION cohorts (2.5% vs 1.9%; HR: 1.37; 95% CI: 0.72-2.61). STR-OAC LAAO patients exhibited a higher thromboembolic risk (HR: 1.71; 95% CI: 1.04-2.83) but lower bleeding risk (HR: 0.39; 95% CI: 0.18-0.88) compared to EWOLUTION patients. The mortality rate was slightly higher in EWOLUTION (4.3% vs 6.9%; log-rank $P = 0.028$). Relative risk reductions for ischemic stroke were 70% and 78% in STR-OAC LAAO and EWOLUTION, respectively, compared to historical data without OAT.

CONCLUSIONS LAAO in patients with a thrombotic event on OAT demonstrated comparable stroke rates to the OAT contraindicated population in EWOLUTION. The thromboembolic event rate was higher and the bleeding rate lower, reflecting the intrinsically different risk profile of both populations. Until randomized trials are available, LAAO may be considered in patients with an ischemic event on OAT. (J Am Coll Cardiol Intv 2024;■:■–■) © 2024 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

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ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation

DOAC = direct oral anticoagulant

LAA = left atrial appendage

LAAO = left atrial appendage occlusion

OAT = oral anticoagulation therapy

PSM = propensity score matching

RRR = relative risk reduction

TIA = transient ischemic attack

Patients with atrial fibrillation (AF) are at increased risk for ischemic stroke, and the incidence of stroke is expected to increase over the following decades.[1] Although vitamin K antagonists and direct oral anticoagulants (DOACs) have proven effective in preventing strokes among AF patients, they do not offer full protection against thromboembolism for all individuals. In the pivotal DOAC trials,[2-6] annualized stroke or systemic embolism rates of 1.1% to 1.7% and 1.5% to 2.2% were observed for patients on adequate-dose DOACs and warfarin, respectively. The recurrence rate in the population that develops stroke on oral anticoagulation therapy (OAT) is high; 5% to 7% of patients have another ischemic stroke in the first year after their index event.[7-9] Moreover, switching OAT strategy after ischemic stroke does not appear to reduce the recurrence risk.[10] Therefore, there is an urgent need for a better thromboembolic prevention strategy for patients in whom OAT has proven ineffective.

Left atrial appendage occlusion (LAAO) provides mechanical protection against thromboembolism from the left atrial appendage. Currently, LAAO is only indicated in AF patients with a long-term contraindication for long-term OAT.[11] In this population, LAAO has developed into an accepted treatment option and has been given a Class 2a recommendation in the most recent U.S. AF guideline.[12]

In addition to AF patients with contraindications for long-term OAT, those in whom anticoagulation therapy has failed to prevent thrombotic events may also benefit from LAAO. Importantly, an effect of LAAO for secondary prevention may only be expected when the primary thrombotic event can be attributed to AF- or left atrial appendage (LAA)-related mechanisms rather than alternative ischemic mechanisms such as carotid artery atherosclerosis. The LAAOS III (Left Atrial Appendage Occlusion Study III) trial showed the effectiveness of concomitant surgical left atrial appendage exclusion and OAT, establishing the protective effect of LAAO on top of OAT.[13] Such a strategy may especially be beneficial in a population in which OAT alone proved insufficient. However, no guideline-recommended indication for LAAO in patients suffering from a thrombotic event on OAT currently exists.

The main objective of the current study is to evaluate the efficacy of LAAO in patients with a thrombotic event on OAT in comparison to patients who underwent LAAO because of a long-term contraindication for OAT.

METHODS

STUDY POPULATION AND DATA COLLECTION. The LAAO after stroke despite oral anticoagulation (STR-OAC LAAO) is an international, investigator-initiated, retrospective analysis of prospectively

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collected individual patient data from 21 implanting centers. Patients who successfully underwent percutaneous LAAO after a thrombotic event despite being on OAT were included (n = 439). Indications for LAAO consisted of ischemic stroke, systemic embolism, transient ischemic attack (TIA), or LAA thrombus while on OAT. Investigators from all participating centers filled in an identical data collection sheet for uniform data collection. Data were coded and non-traceable to individual patients. Patients from the STR-OAC LAAO cohort were compared to patients from the previously published international EWOLUTION (Evaluating Real-Life Clinical Outcomes in Atrial Fibrillation Patients Receiving the WATCHMAN Left Atrial Appendage Closure Technology) registry,[14] which enrolled 1,020 patients from 47 centers, all indicated for percutaneous LAAO because of a contraindication for long-term OAT. Only successful implantations (N = 1,005) were included in the current analysis. The local ethical committees of each hospital approved the study, and all patients provided informed consent either for 1 of the merged local registries constituting STR-OAC LAAO or for the EWOLUTION registry. All implanted LAA occluders have CE or Food and Drug Administration approval.

ENDPOINTS. Primary effectiveness endpoints comprised the time to the first ischemic stroke and the event rate of ischemic strokes per 100 patient-years. As secondary endpoints, time-to-event data and the event rate were collected for the composite of ischemic stroke, TIA and systemic embolism, major bleeding (defined as Bleeding Academic Research Consortium >2), and all-cause death. Clinical event definitions were prespecified (Supplemental Table 1).

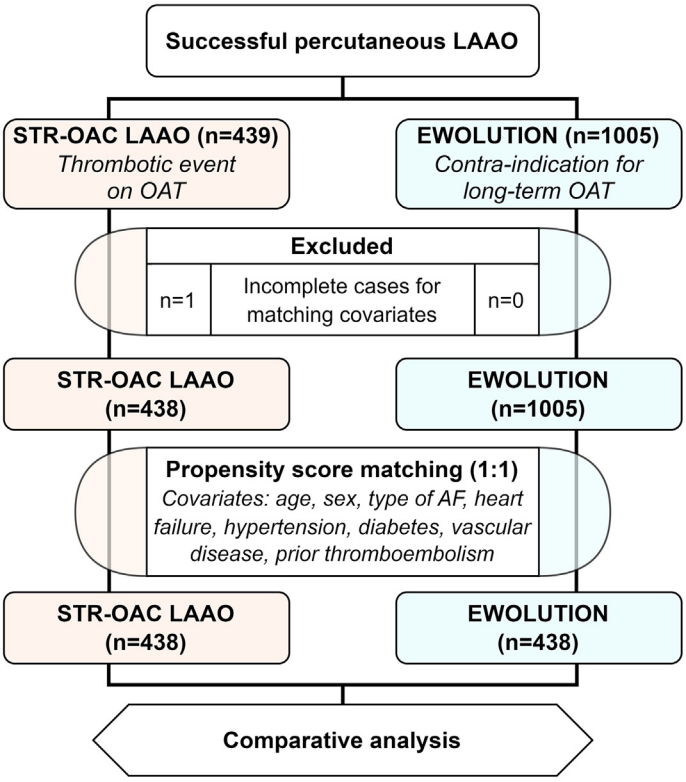
STATISTICAL ANALYSIS. To balance the baseline differences between groups, propensity score matching (PSM) was performed. Logistic regression was used for calculating propensity scores. We used an optimal matching algorithm with 1:1 matching without replacements and without caliper limitation. Possible predictors of stroke were selected as covariates within the PSM algorithm, including age, sex, heart failure, hypertension, diabetes mellitus, vascular disease, prior thromboembolism, and type of AF (paroxysmal, persistent, permanent, or unknown). To improve the comparability of both cohorts, all follow-up time was truncated at 854 days because this was considered as the end of the follow-up window in the EWOLUTION registry. Expected annualized event rates were extrapolated from historical event rates based on individual patient risk scores (ie, CHA_2DS_2-VASc score and HAS-BLED score), as was described in earlier EWOLUTION publications.[14] Relative risk reductions (RRRs) were calculated by comparing the expected annualized event rates to the observed event rates. Time-to-event data were plotted in Kaplan-Meier curves, and between-group comparisons were performed by Cox regression analysis. The proportional hazards assumption was assessed by the Schoenfeld test and visual inspection of plotted residuals against time. PSM was taken into account by clustering based on matched pairs within the Cox model, reporting HRs with 95% CIs based on the robust SE. To account for the competing risk of all-cause death, a Fine-Gray subdistribution hazard model was used for evaluating the primary endpoint, reporting the subdistribution HR.[15] A P value <0.05 was considered statistically significant. No correction for multiplicity was performed.

RESULTS

PATIENT CHARACTERISTICS. A total of 1,444 patients successfully received LAAO and were included in the analysis, 439 in the STR-OAC LAAO cohort and 1,005 in the EWOLUTION cohort (**Figure 1**). **Table 1** reports on the main clinical and procedural features per group. In the majority of STR-OAC LAAO patients (405/439 [92%]), their index event occurred while on adequate OAT. Index events mainly consisted of ischemic stroke (267/439 [61%]) followed by TIA (77/439 [18%]), LAA thrombus (79/439 [18%]), or systemic embolism (16/439 [4%]). Before matching, patients in the STR-OAC LAAO cohort by design more frequently had a history of thromboembolism, were in permanent AF, and were more frequently discharged with OAT after LAAO, whereas EWOLUTION patients were more often discharged with antiplatelet therapy. In 144 of 437 (33%) STR-OAC LAAO patients, a hybrid strategy involving both LAAO and chronic OAT was applied. Both the CHA_2DS_2-VASc score (5.0 ± 1.6) and the HAS-BLED score (2.8 ± 1.3) were higher in the STR-OAC LAAO cohort compared to the unmatched EWOLUTION cohort.

For the matched analysis, 438 STR-OAC LAAO patients could be compared to 438 EWOLUTION patients based on complete data for the matching covariates. Our cohorts were well balanced, with standardized mean differences <0.2 for all matching covariates and a variance <1 for age as a continuous covariate (**Table 1**). After matching, a priori risk for thromboembolic events equalized, with a mean CHA_2DS_2-VASc score of 5.2 ± 1.6 for the matched

FIGURE 1 Flowchart of Study Design



Only patients who underwent successful percutaneous left atrial appendage occlusion (LAAO) were selected. Consequently, patients with missing data for the matching covariates were excluded. This resulted in 438 STR-OAC LAAO patients and 1,005 EWOLUTION patients to form matches with; in total, 438 patients in both cohorts were matched and included in the comparative analysis. AF = atrial fibrillation; OAT = oral anticoagulation therapy.

EWOLUTION cohort. No matching for the HAS-BLED score was performed, and although scores were more similar after matching, a higher HAS-BLED score remained in the STR-OAC LAAO cohort.

CLINICAL OUTCOMES. The proportional hazards assumption was not violated for any of the clinical outcomes. Over nearly 1,500 patient-years of follow-up (after truncation and matching), 31 ischemic strokes occurred: 16 in the STR-OAC LAAO cohort and 15 in the matched EWOLUTION cohort. No statistically significant difference in the ischemic stroke rate was found for STR-OAC LAAO patients compared to EWOLUTION patients (2.5% vs 1.9%; HR: 1.37; 95% CI: 0.72-2.61) (**Table 2**; **Central Illustration**). STR-OAC LAAO patients more often suffered from a composite thrombotic endpoint after LAAO (HR: 1.71; 95% CI: 1.04-2.83). Major bleeding occurred less frequently in the STR-OAC LAAO cohort (HR: 0.39; 95% CI: 0.18-0.88). **Figure 2** shows Kaplan-Meier curves for ischemic stroke; the composite of stroke, TIA, and systemic embolism; and major bleeding. The all-cause mortality rate was high in both STR-OAC LAAO and EWOLUTION (4.3% and 6.9%). Significantly more patients died in the latter cohort (28/438 vs 55/438; log-rank $P = 0.028$).

A subdistribution hazard model was used to compare the ischemic stroke rate between groups accounting for the competing risk of all-cause death. This analysis demonstrated a subdistribution HR of 1.41 (95% CI: 0.70-2.83), which is consistent with the primary analysis (Supplemental Figure 1).

STR-OAC LAAO patients had a high thrombotic risk based on historically expected event rates (**Figure 3A**). LAAO in these patients was associated with an RRR of 70% for ischemic stroke, 53% for stroke/TIA/systemic embolism, and 79% major bleeding. After the matching process, the cohorts became more comparable in terms of a priori thromboembolic risk, resulting in increased similarity in expected event rates. Consequently, the RRRs were alike, with values of 70% and 78% for ischemic stroke within the STR-OAC LAAO and EWOLUTION cohorts, respectively (**Figure 3**).

EXPLORATORY ANALYSES. The indication for LAAO in the STR-OAC LAAO cohort included any thrombotic event on OAT. In an exploratory analysis including only patients indicated for LAAO because of ischemic stroke on OAT, the RRR for ischemic stroke was 66% compared to the historically expected ischemic stroke rate, with a recurrence rate of 3.1 per 100 patient-years. No statistically significant difference in stroke risk within this subgroup compared to the EWOLUTION cohort was observed (HR: 1.67; 95% CI: 0.82-3.39), which is consistent with the main analysis. The first-year cumulative incidence of recurrent ischemic stroke in this subset was 3.9% (95% CI: 1.2%-6.5%). Furthermore, when excluding patients with LAA thrombus but without a thromboembolic event from STR-OAC LAAO (ie, 79/438 [18%]), the ischemic stroke rate during follow-up remained not significantly different from EWOLUTION (HR: 1.71; 95% CI: 0.89-3.27).

One-third of the patients within STR-OAC LAAO (144/437) continued long-term OAT post-LAAO. These patients demonstrated an ischemic stroke rate similar to EWOLUTION patients who were mainly not using OAT (**Figure 4**). No statistically significant difference with STR-OAC LAAO patients who discontinued OAT in the period after LAAO was observed (hybrid vs nonhybrid strategy HR: 0.53; 95% CI: 0.15-1.81), although the annualized stroke rate was

TABLE 1 Patient Characteristics

	Unmatched			Matched		
	STR-OAC LAAO (n = 439)	EWOLUTION (n = 1,005)	*P* Value	STR-OAC LAAO (n = 438)	EWOLUTION (n = 438)	SMD
Age, y	72 ± 9	73 ± 9	0.004	72 ± 9	72 ± 9	0.05
Male	265 (60.4)	601 (59.8)	0.89	265 (60.5)	273 (62.3)	0.04
Type of AF			<0.001			
Paroxysmal	168 (38.3)	447 (44.5)		167 (38.1)	176 (40.2)	0.04
Persistent	76 (17.3)	221 (22.0)		76 (17.4)	84 (19.2)	0.04
Permanent	183 (41.7)	328 (32.6)		183 (41.8)	174 (39.7)	−0.04
Unknown	12 (2.7)	9 (0.9)		12 (2.7)	4 (0.9)	−0.19
CHA_2DS_2-VASc score	5.0 ± 1.6	4.5 ± 1.6	<0.001	5.0 ± 1.6	5.2 ± 1.6	
Congestive heart failure	105 (23.9)	348 (34.6)	<0.001	104 (23.7)	122 (27.9)	0.09
Hypertension	337 (76.8)	875 (87.1)	<0.001	336 (76.7)	364 (83.1)	0.19
Diabetes mellitus	109 (24.8)	299 (29.8)	0.06	108 (24.7)	117 (26.7)	0.04
History of thromboembolism	381 (86.8)	395 (39.3)	<0.001	380 (86.8)	380 (86.8)	0.00
Vascular disease	174 (39.7)	426 (42.4)	0.38	174 (39.7)	176 (40.2)	0.01
HAS-BLED score	2.8 ± 1.3	2.3 ± 1.2	<0.001	2.8 ± 1.3	2.4 ± 1.2	
Uncontrolled hypertension	NA	47 (4.7)	NA	NA	27 (6.2)	
Renal disease	40 (9.2)	162 (16.1)	<0.001	40 (9.2)	56 (12.8)	
Liver disease	4 (0.9)	44 (4.4)	0.002	4 (0.9)	19 (4.3)	
Hemorrhagic stroke history	42 (9.6)	148 (14.7)	0.01	42 (9.6)	146 (33.3)	
Ischemic stroke history	300 (68.3)	194 (19.3)	<0.001	299 (68.3)	188 (42.9)	
Prior major bleeding or predisposition	102 (23.6)	390 (38.8)	<0.001	101 (23.4)	140 (32.0)	
History of labile INR	74 (17.5)	169 (16.8)	0.81	74 (17.5)	63 (14.4)	
Alcohol use	16 (3.7)	44 (4.4)	0.66	16 (3.7)	24 (5.5)	
Index event on OAT						
Ischemic stroke	267 (60.8)			267 (61.0)		
Transient ischemic attack	77 (17.5)			76 (17.4)		
Systemic embolism	16 (3.6)			16 (3.7)		
LAA thrombus	79 (18.0)			79 (18.0)		
LAAO device						
Watchman (2.5/FLX; Boston Scientific)	235 (53.5)	1,005 (100.0)				
Amplatzer (ACP/AMULET; Abbott)	190 (43.3)	0 (0.0)				
Other	14 (3.2)	0 (0.0)				
Discharge medication			<0.001			
None	2 (0.5)	61 (6.1)		2 (0.5)	37 (8.4)	
SAPT	40 (9.2)	72 (7.2)		40 (9.1)	32 (7.3)	
DAPT	148 (33.9)	600 (60.1)		148 (33.8)	240 (54.8)	
VKA	107 (24.5)	156 (15.6)		107 (24.4)	71 (16.2)	
DOAC	132 (30.2)	109 (10.9)		131 (29.9)	54 (12.3)	
Other	8 (1.8)	0 (0.0)		8 (1.8)	0 (0.0)	

Values are mean ± SD or n (%). SMD is provided for propensity score matching covariates. All EWOLUTION patients received a Watchman 2.5 device.

ACP = Amplatzer Cardiac Plug; AF = atrial fibrillation; DAPT = dual antiplatelet therapy; DOAC = direct oral anticoagulant; INR INDENT= international normalized ratio; LAAO = left atrial appendage occlusion; NA = not available; OAT = oral anticoagulation therapy; SAPT = single antiplatelet therapy; SMD = standardized mean difference; VKA = vitamin K antagonist.

numerically higher in patients who discontinued OAT (2.8% vs 1.9%). Baseline characteristics for STR-OAC LAAO patients on a hybrid and nonhybrid strategy are shown in Supplemental Table 2.

To make cohorts more similar in terms of follow-up duration, follow-up was truncated in the STR-OAC LAAO cohort. When not applying truncation to the STR-OAC LAAO cohort, the total follow-up duration comprised 1,084 instead of 654 patient-years for this cohort. Over the total follow-up duration, RRRs compared to historically expected event rates within STR-OAC LAAO were 77%, 61%, and 81% for stroke, stroke/TIA/systemic embolism, and major bleeding, respectively, showing a more pronounced benefit of LAAO when following patients over a longer period of time.

DISCUSSION

Our study demonstrated no increased ischemic stroke risk in patients undergoing LAAO because of a thrombotic event on OAT compared to a guideline-indicated

TABLE 2 Clinical Outcomes

	Events			
	No. of Events (Events/100 Patient-Years)			
	STR-OAC LAAO (n = 438)	EWOLUTION (n = 438)	HR (95% CI)	Log-Rank *P* Value
Ischemic stroke	16 (2.5)	15 (1.9)	1.37 (0.72-2.61)	0.38
TIA	13 (2.0)	13 (1.7)	1.15 (0.52-2.51)	0.73
Systemic embolism	5 (0.8)	1 (0.1)	5.14 (0.55-48.22)	0.09
Ischemic stroke/TIA/SE	34 (5.5)	24 (3.1)	1.71 (1.04-2.83)	0.043
Major bleeding	8 (1.2)	23 (3.0)	0.39 (0.18-0.88)	0.016
All-cause mortality	28 (4.3)	55 (6.9)	0.60 (0.38-0.95)	0.028

SE = systemic embolism; TIA = transient ischemic attack.

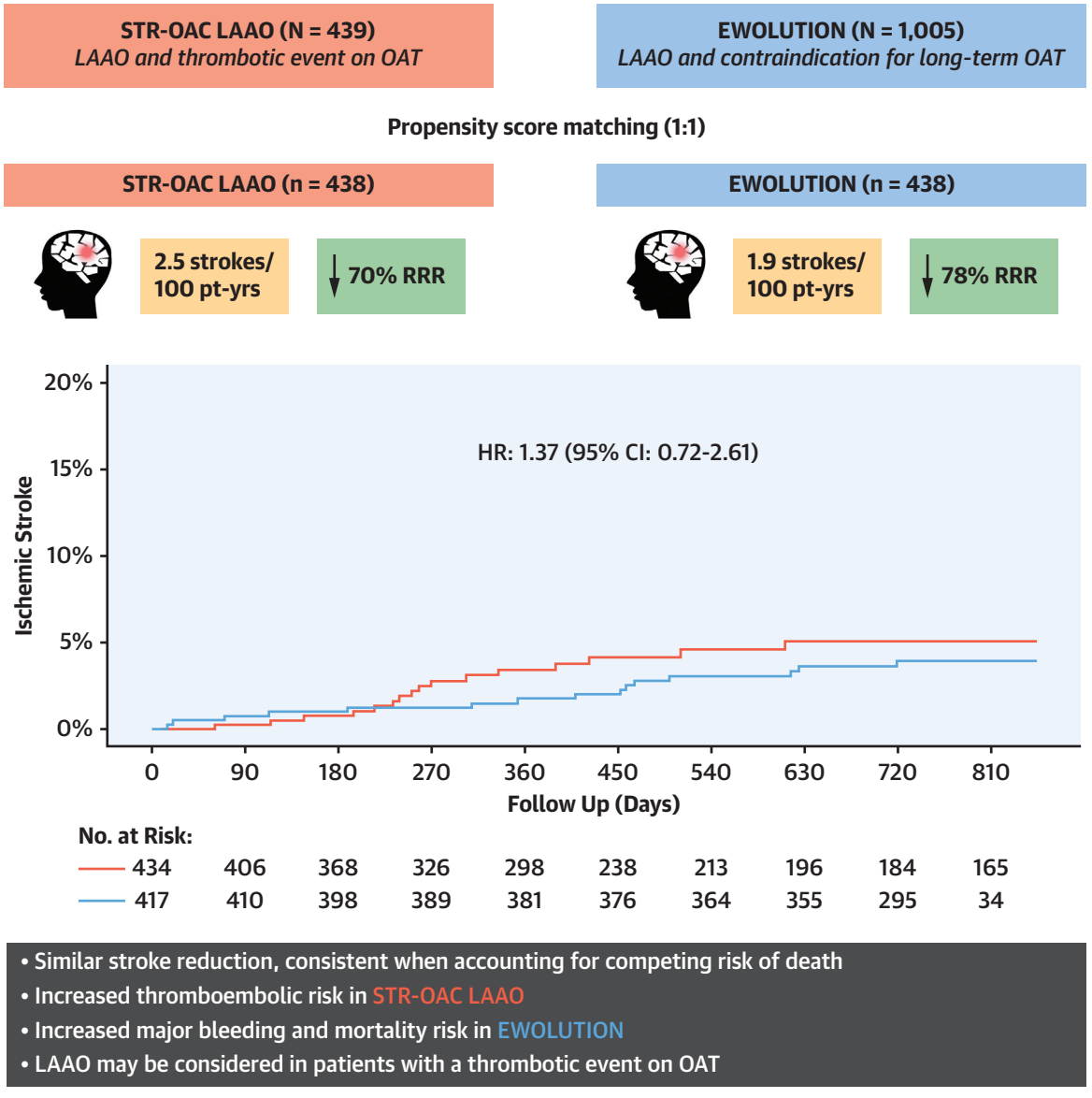
LAAO population with a long-term contraindication for OAT. STR-OAC LAAO patients had an increased composite thromboembolic risk and a reduced bleeding risk after LAAO compared to the OAT-contraindicated patients in EWOLUTION. The primary analysis on ischemic stroke remained valid after the adjustment for competing events. A clinically relevant 70% RRR in ischemic stroke was observed for the STR-OAC LAAO cohort compared to risk score-based historical data. These findings give an estimate of the efficacy of LAAO in patients who suffered from a thrombotic event on OAT compared to the current guideline-recommended population.

Within the STR-OAC LAAO cohort, the composite thrombotic endpoint occurred more frequently. This higher rate was primarily driven by an increased incidence of systemic embolism. Of 5 patients suffering from systemic embolism after LAAO within this cohort, 3 patients were already indicated for LAAO because of prior systemic embolism on OAT (of 16 patients with prior systemic embolism on OAT in total). It is unclear whether AF and LAA thrombus played a part in the mechanism leading to the index event for these 3 patients. Moreover, because the composite endpoint includes TIA, an endpoint that is very difficult to objectively score in a retrospective analysis, no strong conclusions should be drawn from this observation. Ischemic stroke is a much more objective endpoint that was narrowly defined within our cohorts. After correction for a priori stroke risk by matching both cohorts, no increased risk for ischemic stroke after LAAO was observed in the STR-OAC LAAO cohort compared to the EWOLUTION cohort. However, a reduction in statistical power because of the matching process cannot be excluded as a reason for the lack of statistical significance. Some of the index strokes on OAT may be attributed to mechanisms not related to AF or the LAA, such as large artery atherosclerosis or small vessel disease. This proportion may be up to 24%.[16] No data on the presence of LAA thrombus during the index event was available for STR-OAC LAAO. The trend toward a lower ischemic stroke rate in the hybrid approach group could indicate the presence of competing stroke mechanisms. There is a signal for a higher thromboembolic event rate after LAAO after OAT failure, and it is therefore vital to assess stroke etiology before considering LAAO in this population. Nonetheless, uncertainty about the mechanism of thromboembolic events during follow-up applies to both STR-OAC LAAO and EWOLUTION patients.

In line with our findings, Praćoń et al[17] observed a less pronounced RRR for stroke/TIA/systemic embolism and a more pronounced RRR for major bleeding in patients with a prior thrombotic event on OAT compared to patients receiving LAAO because of high bleeding risk, albeit in a smaller cohort of patients. Similarly, a subanalysis from the Amplatzer Cardiac Plug registry showed a 65% RRR for thromboembolic events in patients receiving LAAO after stroke on OAT (vs 78% RRR in patients without stroke on OAT).[18] Importantly, the CHA_2DS_2-VASc score was higher in the stroke on OAT cohort. In general, the subpopulation of patients who developed ischemic stroke on OAT has a very high recurrence risk. In an individual patient data meta-analysis of 5 pivotal DOAC trials, the recurrence rate of ischemic stroke was 7% within the first year after stroke on OAT.[7] In our sensitivity analysis including only patients with ischemic stroke on OAT, the recurrence rate was 3.9% in the first year after LAAO. Of note, the CHA_2DS_2-VASc score in our cohort (median = 5; Q1-Q3: 4-6) was not lower than in the meta-analysis (median = 4; Q1-Q3: 3-6). This suggests a benefit of LAAO in this high-risk population.

The higher incidence of major bleeding in EWOLUTION patients is not surprising because these patients have a contraindication for (long-term) OAT by indication and thus form a selected population that is prone to bleeding. More surprising is the difference in mortality between cohorts. This may be partly explained by the implantation period. EWOLUTION procedures were conducted between 2013 and 2015. During this period, LAAO was still a rather new treatment option preserved for patients as a last resort. This may have led to the selection of patients with a more severe comorbidity profile, as is demonstrated by the higher prevalence of renal and liver disease in EWOLUTION. STR-OAC LAAO procedures were performed from 2010 to 2021, with the median procedure date in 2018. The increasing

CENTRAL ILLUSTRATION **Left Atrial Appendage Occlusion in Patients With Anticoagulation Failure vs Anticoagulation Contraindication**



- Similar stroke reduction, consistent when accounting for competing risk of death
- Increased thromboembolic risk in STR-OAC LAAO
- Increased major bleeding and mortality risk in EWOLUTION
- LAAO may be considered in patients with a thrombotic event on OAT

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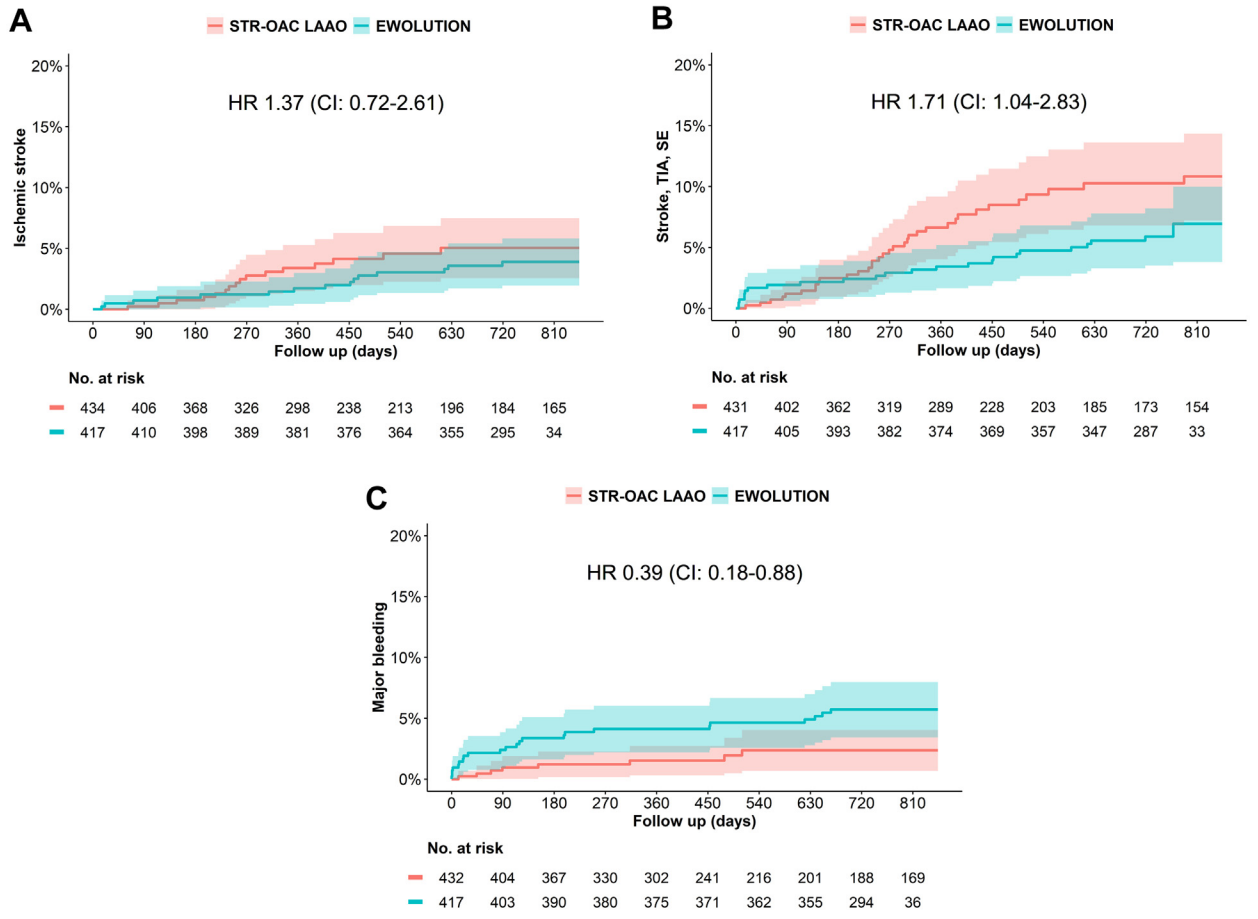
LAAO = left atrial appendage occlusion; OAT = oral anticoagulation therapy; pt-yrs = patient years; RRR = relative risk reduction.

adoption of LAAO and the growing safety of this intervention have led to the treatment of lower-risk patients during more recent years, thus possibly leading to a population with less comorbidities within STR-OAC LAAO. We could not match for unknown comorbidities such as cancer, pulmonary disease, or tobacco use, but these factors could have influenced the mortality rate.

In the STR-OAC LAAO cohort, one-third of the patients were planned for a hybrid strategy combining LAAO with long-term OAT. This proportion seems low because this population typically has a problem with

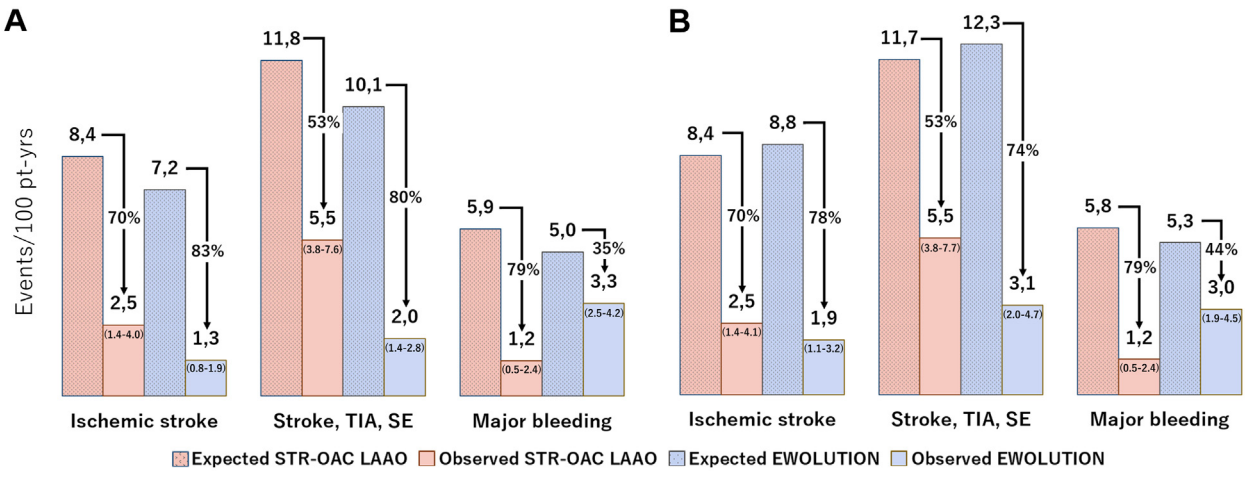
FIGURE 2 Kaplan-Meier Curves of Clinical Outcomes



Kaplan-Meier curves for (A) ischemic stroke; (B) the composite of stroke, transient ischemic attack (TIA), and systemic embolism (SE); and (C) major bleeding. Transparent bandwidths represent 95% CIs.

OAT efficacy and not safety. The presence of nonpermanent AF and a history of major bleeding may in part explain the high rate of OAT cessation in the nonhybrid group, as is shown in Supplemental Table 2. A hybrid strategy seemed favorable for ischemic stroke protection in our cohort, but this observation lacked statistical significance, possibly because of the low number of patients in the hybrid cohort. Such a strategy may nonetheless be the way forward in the specific subpopulation with exceptionally high thrombotic risk. The randomized LAAOS III trial showed a 33% lower incidence of stroke and systemic embolism when OAT was combined with surgical LAAO compared to OAT alone. This trial was conducted in a population with CHA_2DS_2-VASc ≥2, without the necessity of a prior thrombotic event for inclusion. The benefit of the hybrid strategy in our population with high thrombotic risk could be even greater, although surgical and percutaneous LAAO cannot be compared one-to-one. A subsequent randomized controlled trial, LAAOS-4 (The Fourth Left Atrial Appendage Occlusion Study) (NCT05963698), will hopefully shed more light on the value of percutaneous LAAO combined with OAT in patients with increased thrombotic risk, defined in this trial as a CHA_2DS_2-VASc score ≥4 with either permanent/persistent AF or paroxysmal AF with prior ischemic stroke or systemic embolism. In Occlusion-AF (Left Atrial Appendage Occlusion Versus Novel Oral Anticoagulation for Stroke Prevention in Atrial Fibrillation) (NCT03642509), patients are randomized to either LAAO or DOAC after ischemic stroke in the past half year irrespective of OAT use during the index stroke. Lastly, the randomized ELAPSE (Early Closure

FIGURE 3 Relative Risk Reductions



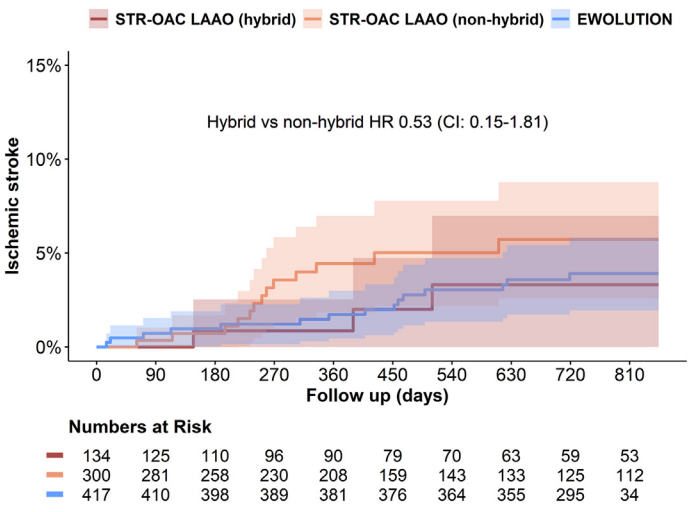
(A) Historically expected event rates, observed event rates, and relative risk reductions within unmatched cohorts. (B) Historically expected event rates, observed event rates, and relative risk reductions within matched cohorts. The numbers between parentheses represent 95% CIs for the observed event rates. Abbreviations as in Figure 2.

of Left Atrial Appendage for Patients With Atrial Fibrillation and Ischemic StrokE Despite Anticoagulation Therapy) trial (NCT05976685) will evaluate a hybrid strategy of LAAO + OAT vs OAT alone in patients who suffered from suspected cardioembolic stroke on OAT. All 3 trials are currently ongoing, and the first results are expected at the end of 2028, making a propensity score-matched analysis the best we have for now. Importantly, there seems to be a rationale for continuing OAT after LAAO in patients with OAT failure in the absence of an increased bleeding risk.

In our data, slight differences are noticeable with regard to event rates and RRRs compared to the original EWOLUTION publication.[14] These are attributable to 2 factors. First, we included only successful procedures (n = 1,005), instead of all of the procedures (N = 1,020). Second, we included all major bleedings (n = 56) instead of only nonprocedural major bleedings (n = 47). Minor differences in the expected and observed event rates can be attributed to these factors.

STUDY LIMITATIONS. A difference in both cohorts exists because of their indication for LAAO. We performed PSM to correct for the most important patient characteristics and thereby limit the risk of bias. However, some variables of interest derive from the indication for LAAO, such as the type of postprocedural antithrombotic medication prescribed (mostly OAT in the STR-OAC LAAO cohort and no long-term OAT in the EWOLUTION cohort). Any influence of the difference in postprocedural antithrombotic medication on outcome cannot be ruled out,

FIGURE 4 Kaplan-Meier Curves of Ischemic Stroke for Hybrid Therapy, Nonhybrid Therapy, and EWOLUTION Patients



Kaplan-Meier curves of ischemic stroke for 3 subgroups: STR-OAC LAAO patients planned for lifelong oral anticoagulation therapy (OAT) (hybrid), STR-OAC LAAO patients stopping OAT over time (nonhybrid), and EWOLUTION patients. Transparent bandwidths represent 95% CIs.

although this may be limited because EWOLUTION patients were more prone to bleeding. Nonetheless, the performed comparison by PSM is the best we have for comparing outcomes by LAAO indication because a randomized approach is impossible because of the comparator (indication for LAAO) not being random. PSM can only be performed for known covariates, and differences between cohorts for nonmatched variables may exist. However, the goal of matching was not to create a uniform indication for LAAO but rather to evaluate outcomes in similar cohorts with different OAT issues (ie, safety concerns in EWOLUTION and efficacy concerns in STR-OAC LAAO). Furthermore, in line with earlier EWOLUTION publications, RRRs were calculated based on risk score-based historical outcomes. This method has several limitations, and the predictive ability of the CHA_2DS_2-VASC score for our primary endpoint of ischemic stroke may only be modest.[19] Additionally, the difference in the implantation period between STR-OAC LAAO (2010-2021) and EWOLUTION (2013-2015) may have influenced the outcomes. Lastly, the EWOLUTION data consist of a real-world cohort, and although thrombotic event history was registered, it is not known if these events occurred on OAT. Thus, some overlap in the indication for LAAO may be present.

CONCLUSIONS

LAAO in patients who suffered from a thrombotic event on OAT may effectively prevent ischemic stroke. No difference in the ischemic stroke rate after LAAO was observed in this cohort of patients compared to a matched cohort of patients contraindicated for long-term OAT, as is the only current guideline-recommended indication for LAAO. Thrombotic risk was higher in patients with OAT failure, whereas bleeding risk was lower. Data from randomized controlled trials should further establish the position of LAAO in patients with a thrombotic event on OAT, either as an alternative to OAT or as adjunctive therapy.

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PERSPECTIVES

WHAT IS KNOWN? LAAO is an alternative to OAT for ischemic stroke prevention in patients with a long-term contraindication for OAT.

WHAT IS NEW? Patients with a thrombotic event on OAT could also benefit from LAAO to reduce their high risk of recurrence.

WHAT IS NEXT? A randomized controlled trial comparing LAAO to the continuation of OAT after a thrombotic event on OAT is warranted.

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KEY WORDS anticoagulation failure, atrial fibrillation, ischemic stroke, left atrial appendage occlusion

APPENDIX For supplemental tables and figures, please see the online version of this paper.