Received: 18 October 2022 | Revised: 7 February 2023 | Accepted: 21 February 2023

DOI: 10.1002/joa3.12838

Journal of Arrhythmia Open Access WILEY

ORIGINAL ARTICLE

Left atrial appendage occlusion after thromboembolic events or left atrial appendage sludge during anticoagulation therapy: Is two better than one? Real-world experience from a tertiary care hospital

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Abstract

Background: The role of left atrial appendage occlusion (LAAO) for atrial fibrillation patients that during oral anticoagulant therapy (OAC) suffer from ischemic events or present LAA sludge, and the best postinterventional anticoagulant regimen, need to be defined. We present our experience with a hybrid approach of LAAO+ lifelong OAC therapy in this cohort of patients.

Methods: Out of 425 patients treated with LAAO, 102 underwent LAAO because, despite OAC, suffered from ischemic events or presented with LAA sludge. Patients without high bleeding risk were discharged with the aim of maintaining lifelong OAC. This cohort was then matched to a population who underwent LAAO in primary ischemic events prevention. The primary endpoint was the composite of all-cause death and major adverse cardiovascular events consisting of ischemic stroke, systemic embolism (SE), and major bleeding.

Results: Procedural success was 98%, and 70% of patients were discharged with anticoagulant therapy. After a median follow-up of 47.2 months, the primary endpoint occurred in 27 patients (26%). At multivariate analyses, coronary artery disease (OR 5.1, CI 1.89–14.27, $p = .003$) and OAC at discharge (OR 0.29, CI 0.11–0.80, $p = .017$) were associated with the primary endpoint. After propensity score matching, no significant difference was found in the survival free from the primary endpoint according to the indication for LAAO ($p = .19$).

Conclusions: In this high-ischemic risk cohort, LAAO + OAC seem a long-term safe and effective therapeutical approach, with no difference in the survival free from the primary endpoint according to the indication for LAAO in a matched cohort.

KEYWORDS
antithrombotic therapy, ischemic embolic events, left atrial appendage, left atrial appendage sludge

1 | INTRODUCTION

Solid data have recently emerged supporting the feasibility and safety of left atrial appendage occlusion (LAAO) for ischemic stroke prevention.[1–4] LAAO is most commonly indicated in cases of high bleeding risk or contraindication to oral anticoagulant (OAC) therapy, where it was demonstrated to be noninferior to vitamin K antagonist (VKA) for ischemic stroke prevention but presented a significant reduction in the risk of major bleeding or hemorrhagic stroke in atrial fibrillation (AF) patients.[5,6] Following these results, the increasing use of LAAO devices has led to a class IIb indication in the latest European Society of Cardiology guidelines for stroke prevention in patients with AF and contraindications for long-term anticoagulant treatment, even in case of concomitant need of cardiac surgery.[7] However, to date, uncertainty remains as for the optimal antithrombotic therapy after LAAO and for the most appropriate indications of LAAO versus OAC therapy in different common clinical scenario.[7,8] Particularly, the best management of patients suffering from ischemic events during anticoagulant treatment or in the presence of LAA sludge, whose predictive role in clinical embolic events has been demonstrated,[9] still needs to be defined.[7,8] In fact, intensification of OAC is usually the most used strategy to achieve thrombus resolution/effective secondary prevention, but this strategy is associated with a suboptimal result and a concomitant higher risk of bleeding.[10,11] Whether the addition of LAAO to prolonged OAC increases the efficacy of preventing embolism in patients who develop embolism or have LAA sludge despite appropriate anticoagulation therapy is a matter of debate not yet clarified.[12,13] Therefore, in this study, we want to present our real-world experience of a hybrid approach consisting of LAAO + OAC maintenance in a cohort of AF patients suffering from ischemic events, or documented to have LAA sludge, despite ongoing OAC therapy.

2 | METHODS

2.1 | Study design

This is a single-center retrospective study carried out at the San Raffaele Hospital, Milan, Italy. We searched our clinical databases for AF patients who underwent percutaneous LAAO at our center from January 2013 to June 2022. Patients were considered eligible if, during this period, LAAO was performed because, despite an ongoing OAC therapy with either VKA or direct oral anticoagulant (DOAC), a thromboembolic event had occurred or sludge in the LAA was visualized at transesophageal echocardiography (TEE) performed pre-procedure at our hospital. As for the thromboembolic events, ischemic stroke was defined as a sudden onset of a focal or global neurological deficit, lasting >24 h or <24 h but with imaging-documented new or presumed new ischemic lesion[14]; transient ischemic attack (TIA) was defined as a neurological dysfunction lasting <24 h and without any new alteration identified on imaging studies.[14] Systemic embolism (SE) was defined as an abrupt vascular insufficiency associated with clinical or radiological evidence of arterial occlusion in the absence of another likely mechanism.[15] LAA sludge was reported in the preprocedural TEE in case of an intracavitary echodensity consisting of a prethrombotic state with very pronounced spontaneous echocontrast but without being a thrombus formed, seen through the cardiac cycle.[9,16] Data were recorded in a dedicated database in compliance with the ethic committee of our center. All patients provided informed consent before the procedure.

2.2 | Patient population management

Baseline clinical characteristics and therapy were recorded for all the patients. TEE was routinely performed preprocedure by a senior echocardiographist using a Vivid E95 (GE Healthcare) with a 6VT-D probe. LAAO procedure was performed as previously described,[17,18] directly by or under the supervision of the same operator (P.M.). The devices used were the Amplatzer Amulet (Abbot Medical) and the Watchman (Boston Scientific), with different generations of occluders related to the year of the procedure. To minimize the risk of complications, intra-procedural TEE monitoring was always conducted, and cerebral protection devices were used according to the operator's discretion. Before the release of the device, its position, anchoring and sizing were evaluated, and procedure success was defined, after device release, in the absence of all the following: pericardial effusion causing hemodynamic instability, device embolization, procedure-related stroke or significant paradevice leak (PDL, ≥5 mm at a Nyquist limit of 20–30 cm/s[19]).

2.3 | Follow-up

Patients were discharged from the hospital with the aim of maintaining lifelong anticoagulant therapy to prevent the recurrence of ischemic events with a hybrid strategy consisting of LAAO+ anticoagulant therapy, as they were judged to be a population at particularly high ischemic risk. Only in case of a concomitant high bleeding risk (HAS-BLED ≥3[20]), OAC was immediately stopped after LAAO and patients were discharged with antiplatelet therapy. Therefore, at discharge, two antithrombotic regimens were planned: if possible, 1–6 months of anticoagulant plus a single antiplatelet regimen, followed by a lifelong anticoagulant therapy. Otherwise, 1–6 months (variability according to bleeding risk) of double antiplatelet (DAPT) regimen followed by a lifelong single antiplatelet therapy (SAPT).

Clinical follow-up was performed with routine visits according to our internal protocol and via phone contact: we recorded data concerning medical therapy and adverse events during follow-up, in particular death (cardiovascular and all-cause), ischemic events (ischemic stroke, TIA, and SE) and major bleeding, defined as type III or V of the Bleeding Academic Research Consortium classification.[21] Moreover, when possible, a TEE examination was performed to rule

out major complications such as device-related thrombosis (DRT), device embolization, or significant PDL.

The primary endpoint was the composite of all-cause death (ACD) and major adverse cardiovascular events (MACE) consisting of ischemic stroke, SE, and major bleeding.

2.4 | Statistical analyses

Categorical variables were expressed as count (percentage) and compared with the χ^2 or Fisher exact test. Continuous variables were expressed as mean (standard deviation) or median [interquartile range (IQR)] and Student's *t*-test and ANOVA test were used as appropriate.

The predictors of events were identified by performing a univariate Cox proportional hazards analysis. The odds ratio (OR) and 95% confidence interval (CI) were defined. To confirm the independent predictive value, only covariates that were significantly associated with the endpoint at univariate analysis ($p < .05$) were tested in a multivariate model. Survival and event-free survival were estimated by the Kaplan–Meier method and compared by log-rank test. Analysis was performed by censoring follow-up at the time of the last follow-up or at the time of event occurred. The convention of limiting the number of independent variables to 1 for every 10 events was followed. A two-tailed $p \leq .05$ was considered statistically significant.

To confirm the feasibility and efficacy of LAAO in this particular population, this group was matched 1:1 to patients who underwent LAAO in our center to prevent ischemic events and without sludge at preprocedural TEE. To reduce the potential for imbalance in baseline characteristics among the two groups, a propensity score matching with the use of a 1:1 nearest-neighbor strategy was used. The baseline characteristics matched among the two groups are the following: age, gender, hypertension, diabetes mellitus, CHA2DS2-VASc score, prior bleeding or bleeding diathesis, and chronic kidney disease (CKD, defined as eGFR <30 mL/min/m^2). After matching, *p* values ≤.05 were considered statistically significant. Statistical analysis was performed in the R environment (R Foundation for Statistical Computing, Vienna, Austria).

3 | RESULTS

Out of 425 patients treated with LAAO in the designated period, 102 (24%) met the inclusion criteria and were included in the study. Among them, despite OAC therapy, 79 (78%) presented LAA sludge on the preprocedural TEE, 7 (7%) suffered from ischemic stroke, and 16 (15%) from TIA. Baseline characteristics are presented in Table 1.

OAC therapy was well balanced between VKA (57%) and DOAC (43%); only 6% of patients in VKA had a history of suboptimal time in the therapeutic range of INR, and the majority of patients in DOAC were in full-dose regimen according to current guidelines.[7]

TABLE 1 Baseline clinical characteristics (102 pts).

Variable	
Age	69 ± 8
Gender (female, %)	39 (38%)
BMI (kg/m^2)	26.1 ± 3
Smoking (either former or current)	40 (39%)
Comorbidities	
Dislipidemia	61 (60%)
Hypertension	64 (63%)
Diabetes mellitus	11 (10%)
Peripheral artery disease	15 (14%)
Carotid vasculopathy	13 (12%)
LVSD	39 (38%)
CAD	22 (22%)
Previous MI	14 (13%)
Previous CABG	4 (3%)
Mechanical valve replacement	10 (9%)
CKD	20 (19%)
AF	102 (100%)
Paroxysmal	22 (22%)
Persistent	31 (30%)
Permanent	49 (48%)
Previous AF ablation	25 (24%)
PM	20 (19%)
ICD/CRT	13 (12%)
NSAIDs use	33 (32%)
Risk scores	
CHA2DS2-VASc median ± IQR	3 ± 2
HAS-BLED, median ± IQR	2 ± 2
Anticoagulant treatment (pre LAAO)	
DOAC	44 (43%)
At standard dose	35 (79%)
At reduced dose according to guidelines[7]	9 (21%)
VKA	58 (57%)
History of labile INR control	4 (6%)
Echocardiographic parameters	
LVEF (%)	46 ± 12
LAVi (mL/m^2)	54 ± 26
≥ moderate MV stenosis	2 (1%)
≥ moderate MV regurgitation	40 (39%)
≥ moderate AV stenosis	5 (4%)
≥ moderate AV regurgitation	18 (17%)

Note: Values are mean ± SD or *n* (%), unless otherwise specified.

Abbreviations: AF, atrial fibrillation; AV, aortic valve; BMI, body mass index; CABG, coronary artery bypass graft; CAD, coronary artery disease; CKD, chronic kidney disease; CRT, cardiac resynchronization therapy; CV, cardiovascular; DOAC, direct oral anticoagulant; ICD, implantable cardioverter defibrillator; LAAO, left atrial appendage occlusion; LAVi, left atrial volume indexed; LVEF, left ventricular ejection fraction; LVSD, left ventricular systolic dysfunction (EF <50%); MI, myocardial infarction; MV, mitral valve; NSAID, nonsteroidal antiinflammatory drugs; PM, pacemaker; TIA, transient ischemic attack; VKA, vitamin-k antagonist.

Noteworthy, 12 patients (11%) suffered from valvular AF, as 10 presented a history of mechanical valve replacement and 2 (1%) had at least moderate MV stenosis.

3.1 | Procedure outcome

The devices utilized for LAAO were the Watchman 2.5 (22 patients, 21%), the Watchman FLX in (18 patients, 17%), the Amplatzer Amulet (61 patients, 60%), and the Amplatzer Cardiac Plug (1 patient, 1%). Procedural success was achieved in 100 patients (98%): two patients suffered from intra-procedural pericardial effusion resulting in cardiac tamponade. None had device embolization, significant PDL, or ischemic stroke; one patient was diagnosed with TIA after the procedure, with complete resolution of neurological symptoms the following day. Four patients presented vascular periprocedural access site complications (3 arteriovenous fistula and 1 pseudoaneurysm).

After careful balancing ischemic and bleeding risk, 71 patients (70%) were discharged with the aim of maintaining lifelong anticoagulant therapy, while 31 (30%) were discharged only with dual antiplatelet therapy (see Figure 1).

3.2 | Follow-up and clinical events

After a median follow-up of 47.2 months, 18 patients (17%) died; among these, cardiovascular death occurred in 8 patients (7%).

During follow-up, two patients suffered from ischemic stroke (1.9%), with a mean time from LAAO to ischemic stroke of 27 months. Both patients were not discharged with OAC after LAAO.

Four patients were diagnosed with TIA (3%), with a mean time from LAAO to TIA of 15 months. Two of them were discharged with VKA, and two were in antiplatelet therapy. SE occurred in three patients (2%) with a mean time from LAAO to SE of 78 months. All these three patients were discharged with dual antiplatelet therapy. As the mean CHA2DS2-VASc score of the population, 3, implied an expected 47 months risk of ischemic stroke of 12.5% and an expected composite risk of ischemic stroke/TIA/SE of 18%,[22,23] the observed long-term reduction of these events after LAAO was particularly significant for patients discharged with OAC, compared to the general study population ($p = .002$, $p = .003$, and $p = .042$, respectively; see Figure 2).

Major bleeding occurred in 6 patients (5%) with a mean time from LAAO to the event of 35 months. None of these was fatal nor intracranial hemorrhage. Three of these patients were discharged under the DOAC regimen, one in VKA, and two in antiplatelet therapy.

Among the 84 patients still alive at follow-up, 32 (38%) were still treated with DOAC, 25 (30%) with VKA, 23 (27%) with SAPT and 4 (5%) were still with DAPT (see Figure 1).

During follow-up, the primary composite endpoint of ACD+ MACE occurred in 27 patients (26%). Patients affected during follow-up by the primary composite outcome presented at baseline with more history of CAD, diabetes mellitus, and left ventricular systolic dysfunction (LVSD) and were more often discharged without anticoagulant therapy, compared to those who did not (see Table 2).

Kaplan–Meyer curves showed that there was a constant trend toward a longer survival free from the primary composite endpoint for patients discharged in anticoagulant therapy compared to those without, but not reaching statistical significance ($p = .41$, see Figure 3).

After univariate analyses, age, a history of CAD, and anticoagulant therapy at discharge resulted in predictors of the primary composite endpoint; after multivariate analyses, a history of CAD (OR 5.1, CI 1.89–14.27, $p = .003$) and anticoagulant therapy at discharge as a protective factor (OR 0.29, CI 0.11–0.80, $p = .017$) remained independent predictors of the outcome (see Table 3).

Interestingly, there was no difference in the occurrence of the primary outcome at follow-up according to LAAO indication (21 events out of 79 patients with preprocedural sludge and 8 events out of 23 patients with ischemic events on OAC, $p = .54$), while the occurrence of ischemic stroke/TIA/SE at follow-up was significantly more frequent in the subgroup of patients with a history of ischemic events on OAC (4 vs. 5 events respectively, $p = .018$). Finally, as for the 79 patients with preprocedural sludge, at follow-up after LAAO, both the primary endpoint as well as the occurrence of ischemic stroke/TIA/SE were significantly less common in the 56 patients discharged with OAC compared to the 23 patients discharged with antiplatelet therapy (11 vs. 10 events, $p = .029$ and 1 vs. 3 events, $p = .038$, respectively).

3.3 | Echocardiographic follow-up

TEE follow-up study was performed in 73 patients (72%). None presented device embolization. DRT was discovered in two patients

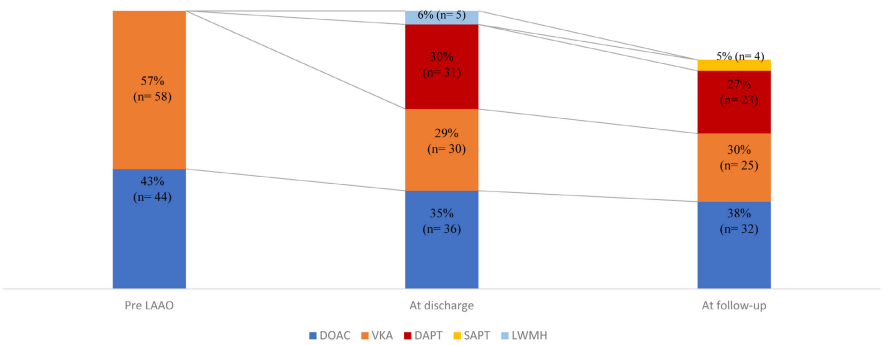

FIGURE 1 Prevalence of different antithrombotic regimens before LAAO, at discharge, and at the last follow-up.

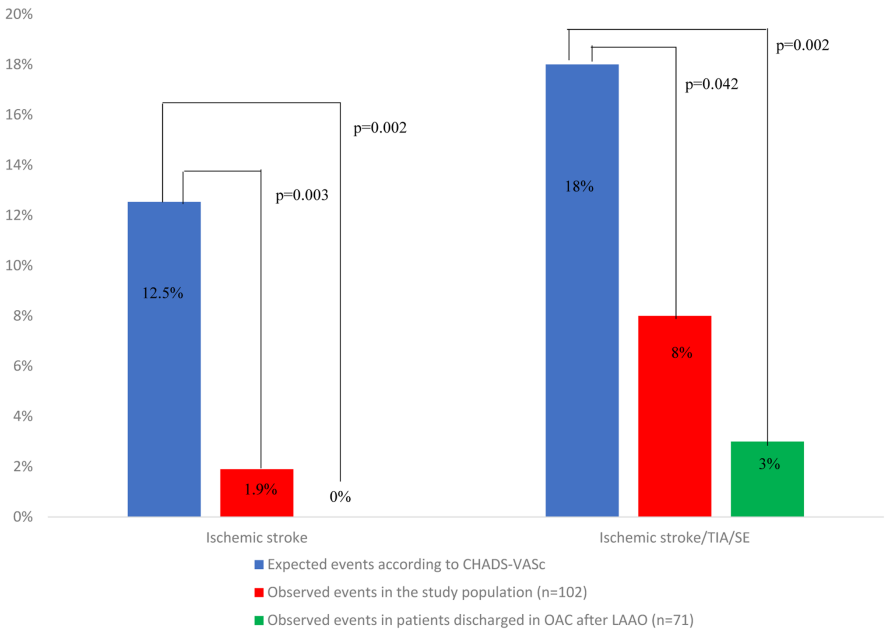

FIGURE 2 Prevalence of expected, according to baseline CHA2DS2-VASc score, and observed ischemic events during follow-up in the general population and in those discharged with OAC therapy.

TABLE 2 Baseline characteristics of patients who suffered from the primary composite EP of ACD + MACE at follow-up compared to those who did not.

	Primary composite EP (27 patients)	No primary composite EP (75 patients)	*p*-value
Age (years)	70 ± 9	68 ± 9	ns
Weight (kg)	70 ± 13	75 ± 13	ns
Gender (female)	10 (37%)	29 (38%)	ns
Hypertension	19 (70%)	45 (60%)	ns
Diabetes mellitus	7 (26%)	4 (5%)	**0.003**
CAD	12 (44%)	10 (13%)	**<0.001**
Mechanical valve replacement	1 (3%)	9 (12%)	ns
Permanent AF	16 (59%)	33 (44%)	ns
LVSD	17 (62%)	22 (29%)	**0.004**
Anticoagulant therapy at discharge	13 (48%)	58 (77%)	**0.005**

Note: Bold indicates statistical signficance.

(3%), both discharged in dual antiplatelet therapy after LAAO. Both patients were subsequently switched to VKA treatment, showing complete resolution of DRT at TEE follow-up. Finally, PDL was noticed in five patients (7%): vena contracta of the leak was >5 mm in two patients, =5 mm in one patient, and 3–5 mm in two patients.

3.4 | Matched cohort

Propensity score matching matched 204 patients 1:1 between LAAO with sludge or history of ischemic events despite OAC therapy (n = 102) and LAA closure to prevent ischemic events without sludge (n = 102) based on similar propensity scores. Baseline characteristics of propensity-matched pairs stratified by the indication to LAAO were almost identical (see Table 4). A significant difference remains only for the variable age: however, the absolute standardized difference was <10%, indicating an acceptable balance.

At baseline, 67 patients (66%) in the matched cohort were treated with VKA and 35 (34%) with DOAC (no difference between the two populations, p = .150) After propensity score matching, Kaplan–Meyer curves showed that there were no significant differences in the long-term survival free from the primary composite EP (p = .19, see Figure 4) or free from ischemic events (p = .107, see Figure 5), according to the indication for LAAO.

4 | DISCUSSION

The main results of our study are as follows:

- This real-world experience of a high-volume center shows that percutaneous LAAO+ prolonged OAC seems to be a long-term safe and effective therapeutical hybrid approach, even in a high-ischemic risk AF population without a typical indication for this intervention.
- Multivariate analyses support the idea of lifelong OAC maintenance despite LAAO is provided in this high-risk group for embolism.
- The long-term survival free from ACD + MACE does not seem to differ between our group and a matched population of patients who underwent LAAO with a typical guidelines-supported indication.

The primary aim of this study was to present our experience on the management and on long-term outcomes of AF patients

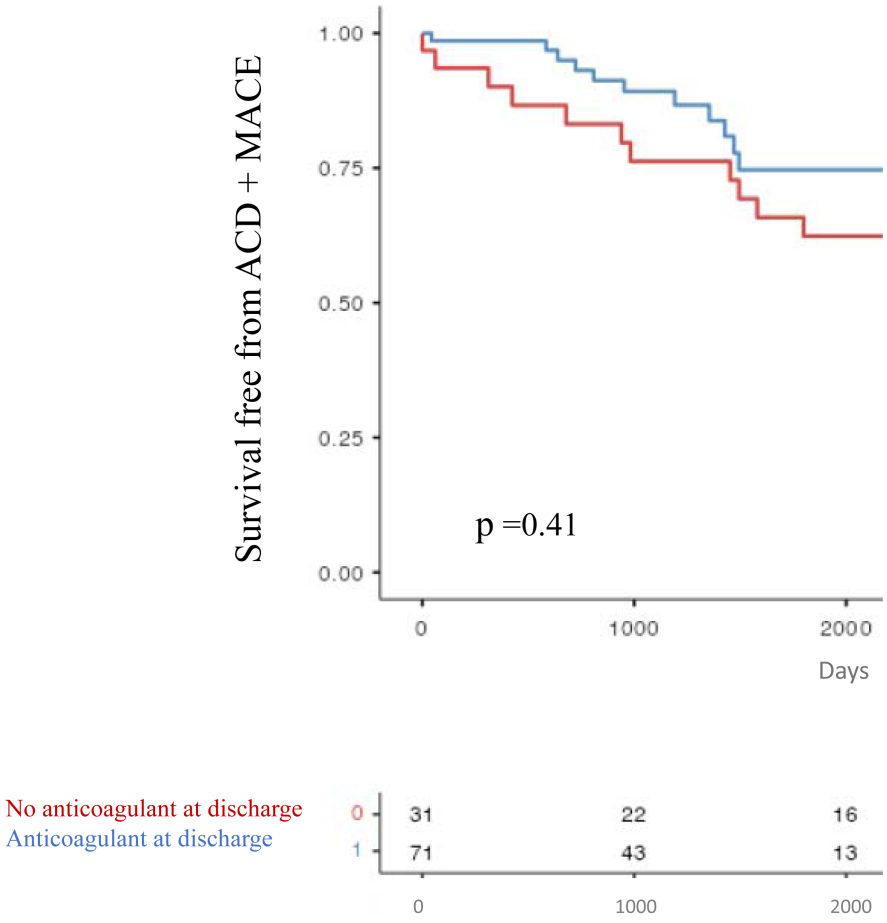

FIGURE 3 Kaplan–Meyer curves showing the survival free from the primary composite EP according to anticoagulant therapy at discharge.

Parameter	Univariate OR (95% CI)	*p*-value	Multivariate OR (95% CI)	*p*-value
Age	1.05 (1.00–1.15)	**0.05**	1.03 (0.9–1.09)	0.23
CAD	5.2 (1.77–15.1)	**0.001**	5.1 (1.89–14.27)	**0.003**
Permanent AF	1.37 (0.55–3.39)	0.49		
Anticoagulant therapy at discharge	0.22 (0.08–0.87)	**0.002**	0.29 (0.11–0.80)	**0.017**

TABLE 3 Univariate and multivariate analysis showing predictors of the primary composite endpoint.

Note: Bold values are those reaching statistical significance. Abbreviations as explained in Table 1.

TABLE 4 Two groups comparison after propensity score matching.

	LAAO without prior ischemic event/LAA sludge (*n* = 102)	LAAO for prior ischemic event/LAA sludge despite OAC therapy (*n* = 102)	*p*-value
Age (years)	72 ± 10	69 ± 8	**0.009**
Gender (female)	38 (37%)	39 (38%)	0.067
Hypertension	62 (61%)	64 (63%)	0.311
Diabetes mellitus	18 (18%)	11 (10%)	0.115
CKD	30 (29%)	20 (19%)	0.205
Prior bleeding or bleeding diathesis	20 (19%)	17 (16%)	0.586
CHA2DS2-VASc	3 ± 3	3 ± 2	0.861

Note: Bold values are those reaching statistical significance. Abbreviations as explained in Table 1.

treated with percutaneous LAAO in the presence of ischemic clinical events or LAA sludge despite ongoing OAC therapy. In this high-ischemic risk cohort, our standardized approach relies on LAAO as an adjuvant to OAC therapy, in the absence of a concomitant high-bleeding risk which halts us from maintaining the anticoagulant regimen. The long-term clinical outcomes were

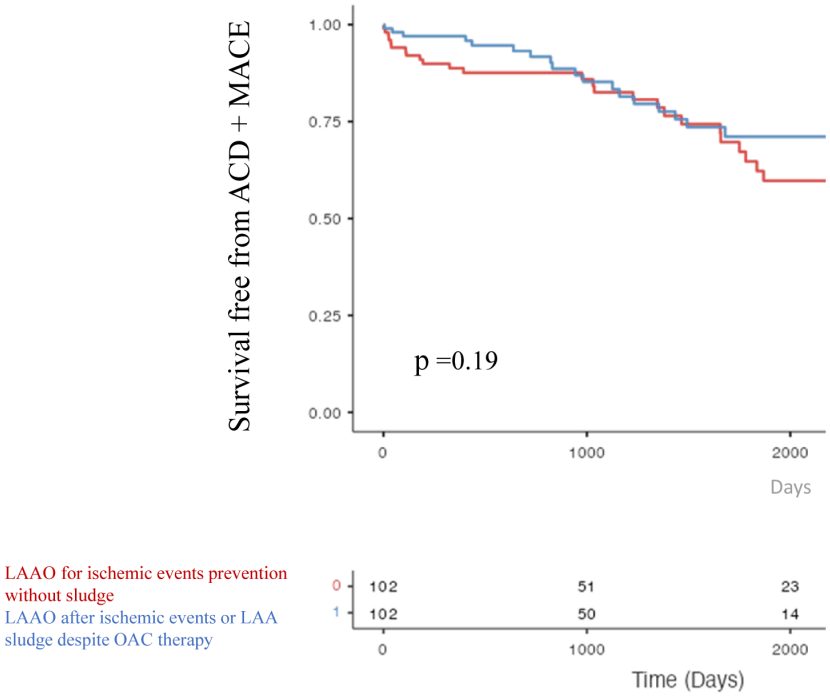

FIGURE 4 Kaplan–Meyer curves showing, after propensity score matching, the difference in the survival free from the primary composite EP according to anticoagulant therapy at discharge.

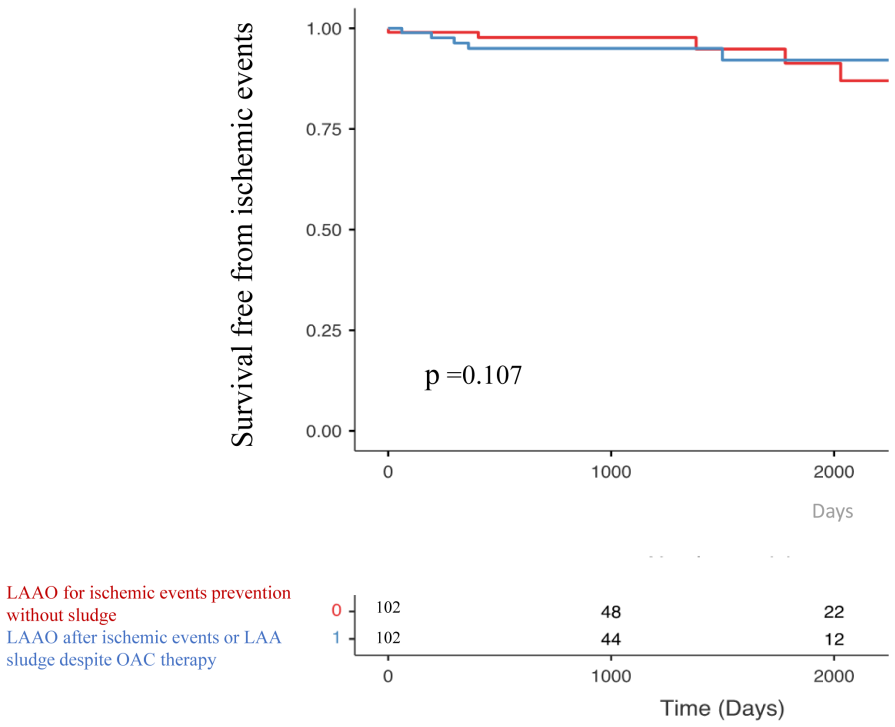

FIGURE 5 Kaplan–Meyer curves showing, after propensity score matching, the difference in the survival free from ischemic events according to anticoagulant therapy at discharge.

not altered by the indication of percutaneous LAAO, enforcing our proposal of this hybrid approach in a cohort with an atypical indication for LAAO: in fact, in our propensity score matching there was no difference in the long-term survival free from the primary composite EP between the population study and a matched cohort who underwent LAAO with a "canonical" indication, that is, primary prevention of ischemic events and without LAA sludge.

Antithrombotic therapy after LAAO is required to prevent thrombus formation on the atrial side of the device. However, the postprocedural antithrombotic regimen is still a hot topic, with many unanswered questions, particularly in patients suffering from ischemic events during OAC therapy or in those with preprocedural evidence of LAA sludge or thrombus.[6,12] Our hybrid therapeutical approach in this context relies not only on the feasibility of percutaneous LAAO (our intra-procedural success rate was 98%, without

device embolism or significant PVL) but even on the experience of the main limitations of long-term anticoagulant therapy alone. First, thrombosis, particularly in the LAA, has long been reported even despite appropriate anticoagulant therapy.[12] Thromboembolic events in AF patients on anticoagulation have a reported rate of 1.1–2.8 per 100 patients year, the differences are mainly related to the type of anticoagulation and the frequencies of typical risk factors.[24–28] This is a clinical problem often leading to a switch or to an intensification in the anticoagulant regimen or perhaps to the addition of an antiplatelet agent. These approaches are not based on published data, present limited efficacy[11] and eventually increase the bleeding risk.[6,7] Moreover, the problem with OAC therapy discontinuation is still an actual one, even in the post-DOAC-era. Discontinuation frequency has been reported from 26% to 81%.[24,29,30] Most common reasons for this choice are the permanent restoration of sinus rhythm and the concern for bleeding,[7] particularly in older patients, where each increasing decade has been previously associated with a 14% decrease in warfarin utilization.[31] Again, although the hazard is perceived to outweigh the benefit, there is no evidence supporting these approaches. Therefore, in our institution, we have decided to approach this high-risk ischemic cohort of patients with the synergistic use of LAAO+ long-term OAC therapy, when the bleeding risk does not force the user to choose a regimen of LAAO+ antiplatelet therapy. The additive beneficial effect of LAAO beyond OAC therapy has recently been demonstrated in the LAAOS trial,[32] in which AF patients who had undergone cardiac surgery, most of whom continued to be treated with antithrombotic therapy, the risk of ischemic stroke or SE was significantly lower with concomitant LAAO performed during the surgery than without it. The results here presented seem to be supporting our therapeutical strategy. During a long-term follow-up, none of the patients discharged with OAC suffered from ischemic stroke, SE, or DRT. The global incidence of DRT, which has been demonstrated to be an independent predictor of ischemic events,[33] was 3% (the range from previous studies varying between 1.5% and 14%[8,11,13]) and the two events of DRT were both solved after switching from antiplatelet to OAC therapy. The few episodes of major bleeding were well-balanced across the two regimens of treatment. At the last follow-up, of the 84 patients still alive, the percentage of those still on anticoagulant (68%) was almost identical to that at discharge (70%): this might reflect the appropriate patient's education and perception of their very high risk of cardioembolic events.

As we identified baseline characteristics associated with the occurrence of the primary composite EP, we could speculate that this subset of AF patients (those with DM, history of CAD, or LVSD) could particularly benefit from the association of LAAO + lifelong OAC, maybe even in case of concomitant high bleeding risk.

Notably, even after multivariate analyses, discharge with OAC was an independent protective factor from the primary composite endpoint, enforcing the protective role of our strategy, when feasible. The comparison between the two regimens of antithrombotic therapy at discharge showed that patients discharged with OAC suffered from fewer ischemic events at follow-up (only two cases of TIA) compared to those on antiplatelet therapy. Kaplan–Meyer curves depicted an early and sustained difference of the survival free from the primary composite EP in favor of the group on OAC therapy, although nonstatistically significant: it is conceivable that the small sample of our population limited the statistical power of this analysis.

4.1 | Study limitations

This is an observational, single-center and retrospective study: therefore, it has the inherent limits of the study design, and our results must be confirmed in a larger sample size. The choice to use a hybrid strategy of LAAO+OAC therapy for a high-ischemic risk cohort of patients represents an approach based on real-world practice. In particular, 78% of our patients presented LAA sludge despite OAC, but we did not find any significant evidence to support LAAO in properly anticoagulated AF patients without prior ischemic events but with evidence of LAA sludge. However, our main aim was to present and discuss the results of our personal strategy in a therapeutical context considering a gap in the evidence. By focusing on this hybrid approach, we were not able to verify whether LAAO itself is beneficial in this group of patients with a history of stroke or LAA sludge.

At follow-up, not all patients underwent the TEE study and, therefore, we could not rule out DRT or significant PVL for the entire population. Because of the low incidence of procedural complications, independent predictors of these complications could not be searched.

Moreover, we focused on a non-Asian cohort of patients: considering that the bleeding risk is even higher in Asian patients, this may limit the reproducibility of our results. We did not perform screening with neuroimaging examinations, therefore we cannot rule out silent cerebral ischemia despite LAAO+OAC. Finally, there were no data available to compare our hybrid approach to an approach of anticoagulant intensification/switch treatment without LAAO: this comparison would indeed be of great importance to evaluate and, eventually, support the role of our strategy. However, in this paper, we aimed to propose to the scientific community our real-world experience in the management of this cohort of patients with atypical LAAO indications, for whom there is a gap in the evidence that needs to be addressed.

5 | CONCLUSIONS

In our study cohort with ischemic events or LAA sludge despite OAC, there was no significant long-term difference in the survival free from ACD and MACE, consisting of ischemic stroke, SE, and major bleeding, compared to a matched population patients who underwent LAAO to prevent ischemic events and without sludge. In the absence of high bleeding risk, the discharge with OAC therapy after LAAO was an independent protective factor from the primary

composite endpoint of ACD and MACE. These findings may suggest considering this hybrid therapeutical approach for AF patients in secondary ischemic prevention and the adjunctive role of OAC prosecution after LAAO in this high-risk group for embolism.

FUNDING INFORMATION

This study received no external fundings.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

PATIENTS CONSENT STATEMENT AND ETHICS APPROVAL STATEMENT

Data were recorded in a dedicated database in compliance with the ethics committee of our center (Institutional Ethics Committee of San Raffaele Hospital, LAAO projects). The study was conducted according to institutional guidelines and legal requirements and complied with the Declaration of Helsinki. All patients provided written informed consent for the anonymous collection of their clinical data.

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How to cite this article: Margonato D, Preda A, Ingallina G, Rizza V, Fierro N, Radinovic A, et al. Left atrial appendage occlusion after thromboembolic events or left atrial appendage sludge during anticoagulation therapy: Is two better than one? Real-world experience from a tertiary care hospital. J Arrhythmia. 2023;39:395–404. https://doi.org/10.1002/joa3.12838