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A real-world multicenter study on left atrial appendage occlusion: The Italian multi-device experience

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ABSTRACT

Background: Transcatheter left atrial appendage occlusion (LAAO) has emerged as an alternative treatment for stroke prevention in patients with atrial fibrillation (AF) at high risk of thromboembolism, who cannot tolerate long-term oral anticoagulation (OAC). Questions persist regarding effectiveness and safety of this treatment and the optimal post-interventional antithrombotic regimen after LAAO.

Methods: We retrospectively gathered data from 428 patients who underwent percutaneous LAAO in 6 Italian high-volume centres, aimed at describing the real-world utilization, safety, and effectiveness of LAAO procedures, also assessing the clinical outcomes associated with different antithrombotic strategies.

Results: Among the entire population, 20 (4.7 %) patients experienced a combination of pericardial effusion and periprocedural major bleeding: 8 (1.9 %) pericardial effusion, 1 (0.3 %) fatal bleeding, and 3 (0.7 %) non-fatal procedural major bleeding. Patients were discharged with different antithrombotic regimens: dual (DAPT) (27 %) or single (SAPT) (26 %) antiplatelet therapy, OAC (27 %), other antithrombotic regimens (14 %). Very few patients were not prescribed with antithrombotic drugs (6 %). At a medium 523 ± 58 days follow-up, 14 patients (3.3 %) experienced all-cause death, 6 patients (1.4 %) cardiovascular death, 3 patients (0.7 %) major bleeding, 10 patients (2.6 %) clinically relevant non-major bleeding, and 3 patients (0.7 %) ischemic stroke. At survival analysis, with DAPT as the reference group, OAC therapy was associated with better outcomes.

Conclusions: Our findings confirm that LAAO is a safe procedure. Different individualized post-discharge antithrombotic regimens are now adopted, likely driven by the perceived thrombotic and hemorrhagic risk. The incidence of both ischemic and bleeding events tends to be low.

1. Introduction

In current medical practice, the estimated prevalence of atrial fibrillation (AF) in adults falls between 2 % and 4 %, and this figure is expected to rise significantly due to the increasing longevity of the general population [1]. This arrhythmia accounts for more than 20 % of all strokes and leads to more disabling symptoms, lower survival and higher health care costs compared to other causes of stroke [2]. The

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incidence of stroke associated with AF has declined in the past years in parallel with an increased use of oral anticoagulation (OAC). Both vitamin K antagonists (VKAs) and direct oral anticoagulants (DOACs) have been shown to reduce the risk of stroke and mortality [3,4], but some conditions – e.g. relevant bleeding, bleeding-prone co-morbidities, severe thrombocytopenia or anaemia or a recent high-risk bleeding event, such as intracranial hemorrhage (ICH) – are considered absolute contraindications to OAC. In light of these challenges, transcatheter left atrial appendage occlusion (LAAO) has emerged as an alternative for patients at high risk of AF-related thromboembolism who are unable to tolerate long-term OAC. To date, only 3 randomised controlled trials (RCTs) comparing LAAO to anticoagulation have been published [5–7]. The multicenter PROTECT AF study enrolled 707 patients with AF, no contraindication to OAC and $CHADS_2$ score $\geq$1, who were randomised to receive warfarin or the Watchman device. After a mean follow-up of 18 months, the primary efficacy composite endpoint, including stroke, systemic embolism, and cardiac death, resulted non-inferior in the device group [5]. The subsequent PREVAIL trial [6] did not confirm the non-inferiority of the LAAO procedure, maybe due to a lower than expected event rate in the control arm, but showed a decreasing incidence of peri-procedural complications in the intervention arm. The most recent patient-level meta-analysis of these trials with 5-year follow-up confirmed that the primary efficacy endpoint occurred with a similar frequency in both groups (hazard ratio [arms (HR]: 0.82; 95 % CI: 0.58–1.17; P = 0.27), with additional reductions in major bleeding, particularly haemorrhagic stroke, in patients receiving LAAO [8]. Notably, the rate of ischemic stroke remained numerically higher in the Watchman arm. Nevertheless, the relevance of these results to current practice, where warfarin has been largely replaced by DOACs, remains an area of ongoing debate. In this view, particularly informative is the message of the PRAGUE-17 randomized trial, showing the non-inferiority of LAAO compared with DOAC treatment at 4-year follow-up [9].

Although available data are reassuring, concerns regarding the effectiveness of LAAO remain. To date, no randomised study has specifically addressed the category of patients with absolute contraindications to DOAC because of a high bleeding risk, and data regarding this setting are derived only from registries [10–12]. Moreover, available data suggest that ischemic events may be more frequent with device implantation, raising questions about whether LAAO is effective in completely eliminating the risk of embolic events or whether its primary benefit lies in reducing bleeding and avoiding long-term anticoagulation. The relatively low rate of ischemic events observed in the aforementioned randomized trials has prompted concerns about the strength of their conclusions.

The optimal post-interventional antithrombotic regimen, as well as antithrombotic treatment duration after LAAO, remain a controversial issue [13]. Device-related thrombosis (DRT) has been described in approximately 4 % of cases <12 months post-implantation, with a higher risk in the early phase and subsequent decline after complete device endothelization, generally within 30–90 days [14]. In landmark trials, patients undergoing LAAO generally received a sequence of dual antithrombotic therapy (DAT), dual antiplatelet therapy (DAPT), and then lifelong aspirin alone. According to the latest consensus of the European Association for Percutaneous Cardiovascular Interventions (EAPCI), in patients with contraindication to OAC, a regimen of 3–6 month DAPT is recommended, regardless of the type of device [15]. Moreover, in this context, a trans-oesophageal echocardiogram (TOE) during follow-up is frequently used to exclude DRT and guide DAPT de-escalation to single antiplatelet therapy.

We designed a registry to give a real-world picture of current indications, safety and efficacy of LAAO in high-volume Italian centers, focusing also on post-procedural antithrombotic strategies employed looking for potential disparities in clinical outcomes.

2. Methods

2.1. Study design

We retrospectively collected data on 428 patients who underwent percutaneous LAAO in 6 Italian centers from January 2014 to March 2023. No exclusion criteria regarding patients' risk profile, type of implanted device, and post-implantation antithrombotic approach were specified. Involved centers were: "SS. Annunziata Hospital", Chieti; "Santo Spirito" Hospital, Pescara; Azienda Ospedaliero-Universitaria delle Marche, Ancona; A.O.R.N. "Sant'Anna e San Sebastiano", Caserta; Maggiore della Carità Hospital, Novara; Monzino Cardiac Center, IRCCS, Milan. Interventions were performed according to local standard practice. One investigator at each center collected information related to in-hospital stay from medical records and to follow-up data from office visits, scheduled according to the usual center's practice. All data regarding demographics, clinical history, comorbidities, laboratory investigations, medications, procedural aspects and endpoint events were anonymised, entered in an electronic database, and centrally collected. The study protocol was conducted in accordance with the principles of the Declaration of Helsinki.

2.2. Study endpoints

Safety outcomes were defined as in-hospital and peri-procedural pericardial effusion necessitating drainage, and major bleeding, as per the criteria outlined by the International Society on Thrombosis and Haemostasis (ISTH): clinically overt bleeding which was fatal or associated with any of the following: (a) a fall in hemoglobin level of 2 g/dL or more or documented transfusion of at least 2 units of packed red blood cells, (b) involvement of a critical anatomical site (intracranial, spinal, ocular, pericardial, articular, intramuscular with compartment syndrome, retroperitoneal) [16]. Secondary safety indicators were DRT and peri-device leaks. Net clinical benefit (NCB) of the intervention throughout the entire follow-up was assessed through the combined occurrence of all-cause mortality, ischemic stroke, systemic embolism, major bleeding, and clinically-relevant non-major bleeding (CRNMB, i.e. any sign or symptom of hemorrhage that does not fit the criteria for the ISTH definition of major bleeding but does meet at least one of the following criteria: requiring medical intervention by a healthcare professional, leading to hospitalization or increased level of care, prompting a face to face (i.e., not just a telephone or electronic communication) evaluation [16]. Individual components of this composite endpoint were also reported. All the outcome data were verified using source documentation.

2.3. Statistical analysis

Baseline categorical variables were summarised as frequencies and percentages and contingency was investigated by Fisher's test. Continuous variables were reported as either mean and standard deviation (SD) or median and interquartile range (IQR), according to their distribution. Time-to-event curves were generated through Kaplan-Meier analysis to compare distinct post-discharge antithrombotic therapy cohorts, with dual antiplatelet therapy (DAPT) utilized as the reference. Additionally, in assessing the influence of diverse antithrombotic strategies on outcomes following hospitalization, a survival analysis employing the Cox method was performed to estimate hazard ratios (HRs) along with corresponding 95 % confidence intervals (CIs).

All statistical analyses were performed using the Statistical Package for the Social Sciences (IBM SPSS Statistics for Windows, IBM Corp., Version 26.0, Armonk, NY).

3. Results

3.1. Study population

Baseline characteristics of the study population are shown in Table 1. Mean age was 73 ± 9 years; 36 % of patients were female. Mean CHA_2DS_2-VASc score was 3.0 ± 1.3, mostly driven by hypertension and heart failure. Mean HAS-BLED score was 3.1 ± 1.2. Indications for LAAO consisted mainly of previous bleeding events in vital organs (e.g., ICH in the vast majority of cases), recurrent bleeding on OAC requiring blood transfusions, and elevated bleeding risk for solid organs (e.g., tumours) or hematologic diseases (e.g., myelodysplastic syndrome) (Table 1).

The implanted devices were Watchman in 173 patients (40.4 %), Amplatzer Cardiac Plug (ACP) in 125 (29.2 %), Amulet in 76 (17.8 %), Cardia in 23 (5.4 %), LAmbre in 18 (4.2 %) and WaveCrest in 13 (3.0 %). Devices' distribution by enrolling centers is reported in Fig. 1.

3.2. Periprocedural outcomes

During hospitalization, 20 patients (4.7 %) experienced a combination of periprocedural pericardial effusions and major bleeding. 8 cases (1.9 %) of pericardial effusions were reported, of which only 3 (0.7 %) necessitating drainage. Additionally, there was 1 fatal bleeding (0.3 %), along with 3 cases (0.7 %) of non-fatal procedural major bleeding. 13 patients (3.1 %) exhibited in-hospital hemoglobin drop ≥ 2 g/dL, with only 3 requiring blood transfusion. During the early follow-up phase, transoesophageal echocardiography revealed 3 DRTs (0.7 %) and 16 cases (3.7 %) of *peri*-device leaks exceeding 5 mm size.

Table 1
Baseline characteristics of the population.

Baseline characteristics	Overall (n = 428)
Age (years), mean ± SD	73.2 ± 9.2
Age ≥ 75 - n. (%)	208 (49)
Female sex - n. (%)	155 (36)
BMI (kg/m2) - mean ± SD	25.9 ± 4.5
Baseline Hb level (mg/dl) - mean ± SD	12.4 ± 2.0
Hb nadir (mg/dl) - mean ± SD	11.4 ± 2.0
Baseline creatinine level (mg/dl) - mean ± SD	1.3 ± 1.3
Type of AF	
• Paroxysmal - n. (%)	222 (52)
• Permanent - n. (%)	96 (22)
• Persistent - n. (%)	94 (22)
Diabetes mellitus - n. (%)	56 (13)
Previous ischemic stroke - n. (%)	97 (23)
Previous hemorrhagic stroke - n. (%)	56 (13)
Hypertension - n. (%)	297 (69)
Previous MI - n. (%)	66 (15)
Peripheral arterial disease - n. (%)	29 (7)
LVEF (%) - mean ± SD	55 ± 10
LVEF (%) <40 % - n. (%)	32 (7)
Heart failure - n. (%)	67 (16)
CHA_2DS_2-VASc score - mean ± SD	3.0 ± 1.3
CHA_2DS_2-VASc score >2 - n. (%)	271 (63)
HAS-BLED score - mean ± SD	3.1 ± 1.2
Dialysis - n. (%)	18 (4)
Liver cirrhosis - n. (%)	14 (3)
Portal hypertension - n. (%)	8 (2)
Active cancer - n. (%)	14 (3)
Previous ICH - n. (%)	90 (21)
Previous GI bleeding - n. (%)	130 (30)
Anatomical bleeding diathesis - n. (%)	108 (25)
Hematologic disease - n. (%)	40 (9)
Recurrent bleeding - n. (%)	119 (28)

AF = atrial fibrillation; BMI = body mass index; GI = gastrointestinal; Hb = hemoglobin; ICH = intracranial hemorrhage; LVEF = left ventricular ejection fraction.

3.3. Antithrombotic therapy before and after LAAO

Antithrombotic treatment regimens before and after the procedure are detailed in Table 2 and Fig. 2. Upon discharge, the distribution of patients among therapy groups was as follows: 27 % received dual antiplatelet therapy (DAPT), consisting of aspirin and clopidogrel (3 % of patients were treated with DAPT before the procedure); 27 % were prescribed oral anticoagulants (OAC) (30 % before the procedure), with 7 % on Vitamin K antagonists (VKAs) and 20 % on direct oral anticoagulants (DOACs); 26 % were administered single antiplatelet therapy (SAPT, aspirin or clopidogrel) (18 % before the procedure); and 14 % received other antithrombotic regimens, including dual antithrombotic therapy (DAT) or mainly low-molecular weight heparin (LMWH), this latter for a minimum of two months after the LAAO procedure (15 % of patients were treated with these other antithrombotic regimens before the procedure; please refer to Table 2 for more information). Within the group receiving DAPT, 37 % of patients discontinued one antiplatelet drug within one month following the procedure, 33 % continued DAPT for up to three months post-intervention, 10 % remained on both drugs for six months, and 20 % were still on DAPT at the conclusion of the follow-up period. A small portion of patients (6 %) were discharged without any antithrombotic therapy (patients not treated were 34 % before the procedure).

Baseline characteristics varied among different antithrombotic strategy groups, especially regarding CHA_2DS_2VASC and HAS-BLED score (ANOVA $p < 0.001$ for both) and their respective single components. Of note, CHA_2DS_2VASC was higher in SAPT (3.3 ± 0.2) and DAPT (3.30 ± 0.2) groups as compared to OAC group (2.6 ± 0.2). The same applies to HAS-BLED score, that was higher in SAPT (3.6 ± 0.2) and DAPT (3.3 ± 0.2) groups as compared to OAC group (2.9 ± 0.2).

3.4. Clinical outcomes during follow-up

Over a mean follow-up duration of 523 ± 58 days, a total of 33 patients (7.7 %) experienced the NCB composite outcome. When examining individual outcomes, 14 patients (3.3 %) suffered from all-cause death, 6 patients (1.4 %) experienced cardiovascular death, 3 patients (0.7 %) major bleeding, 10 patients (2.6 %) CRNMB, and 3 patients (0.7 %) ischemic stroke. Bleeding sites were: 3 intracranial, 5 gastrointestinal, 1 urinary tract, 1 nasopharyngeal tract, and 4 unknowns.

At survival analysis, with DAPT as the reference group, there was evidence of a protective effect of OAC therapy in reducing the occurrence of the composite outcome (Hazard Ratio [HR]: 0.12; 95 % Confidence Interval [CI]: 0.03–0.53; P = 0.005) as illustrated in Fig. 3.

4. Discussion

Our study, conducted in six experienced Italian centers, validates the safety of LAAO. It also highlights the discrepancy in antithrombotic approaches between global guidelines and practical implementation in clinical settings.

In contrast to earlier studies, our research reported a significantly lower mean CHA_2DS_2-VASc score when compared to the extensive dataset of previous observational data (3.0 as compared to the average of 4.2) [17,18]. However, even when accounting for the limitations of the HAS-BLED score's predictive abilities in a population with limited VKA usage, our study cohort consistently mirrored previous research (HAS-BLED 3.1 compared to 3.04) [17]. To date, the first and the largest multicenter registry with an all-comers design, including all commercially available devices is the LAARGE registry [19]: in this investigation, the computed CHA_2DS_2-VASc and HAS-BLED scores were 4.5 ± 1.6 and 3.9 ± 1.1, respectively.

During follow-up we observed a reduced incidence of thromboembolic events (0.7/100 patients-years) compared with the anticipated rate based on the CHA_2DS_2-VASc score (3.9/100 patients-years) [20,21], resulting in a remarkable relative risk reduction (RRR) of 82

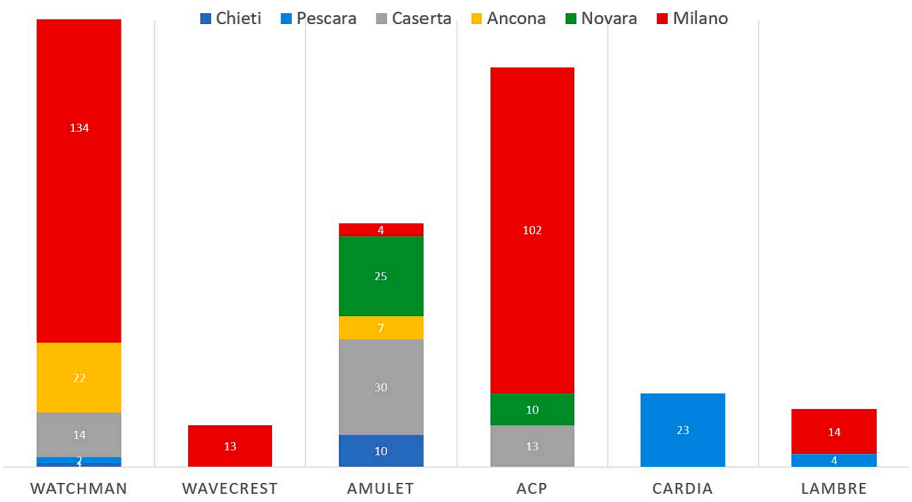

Fig. 1. Devices' distribution by enrolling centers.

Table 2
Antithrombotic strategies before the LAAO procedure and after the discharge.

Antithrombotic strategy	Overall (n = 428)
Antithrombotic strategy before LAAO	
No antithrombotic strategy – n. (%)	144 (34)
DOAC – n. (%)	99 (23)
VKA – n. (%)	31 (7)
DAPT – n. (%)	14 (3)
SAPT – n. (%)	76 (18)
DAT (SAPT + VKA) – n. (%)	4 (1)
DAT (SAPT + LMWH) – n. (%)	7 (2)
DAT (SAPT + DOAC) – n. (%)	3 (1)
TAT (DAPT + LMWH) – n. (%)	6 (1)
LMWH – n. (%)	44 (10)
Antithrombotic strategy at discharge	
No antithrombotic strategy – n. (%)	25 (6)
SAPT – n. (%)	110 (26)
DAPT – n. (%)	117 (27)
DOAC – n. (%)	87 (20)
VKA – n. (%)	29 (7)
DAT* – n. (%)	10 (2)
LMWH – n. (%)	50 (12)
DAPT de-escalation	
<1 month – n. (%)	43 (37)
1–3 months – n. (%)	38 (32)
Other – n. (%)	13 (11)
Long-term	23 (20)

DAPT = dual antiplatelet therapy; DAT = dual antithrombotic therapy; DOAC = direct oral anticoagulant; LMWH = low-molecular weight heparin; SAPT = single antiplatelet therapy (aspirin or clopidogrel); TAT = triple antithrombotic therapy; VKA = vitamin-K antagonist.

* DAT = DOAC + SAPT or VKA + SAPT.

%. Similarly, despite the elevated frequency of potent post-discharge antithrombotic therapy, we noted a decreased rate of major bleeding (0.7/100 patients-years) in comparison to the rate predicted by the HAS-BLED score (3.7/100 patients-years [22]). In keeping with our results, almost all previous studies confirmed this trend, reporting significantly lower major bleeding rates and pooled RRR compared with what was expected based on the HAS-BLED score resulted 55.0 % (95 % CI, 44.2 % to 65.9 %) [17]. Furthermore, in the comparison of our findings with the data from the LAARGE registry, which shares a similar study design and encompasses a larger population, the rates of ischemic events and bleeding incidents exhibited remarkable similarity (0.8 % for non-fatal strokes and 0.6 % for severe bleeding) [19].

Numerous insights can be derived from our analysis. As per the National Cardiovascular Data Registry (NCDR) LAAO Registry, which has included over 38,000 patients implanted with the Watchman device, major in-hospital adverse events were observed in 2.2 % of patients [12]. In the LAARGE registry the cumulative occurrence of MACCE (death, stroke, and myocardial infarction) and other severe in-hospital complications was 4.5 % [19].

Even though it is challenging to directly compare the overall rate of serious procedural complications with data from previous studies, the occurrence of specific adverse events, such as pericardial effusions necessitating interventions and severe or fatal bleeding, demonstrated either similar or lower incidence rates than those reported in these large registries.

In terms of the effectiveness and safety outcomes at the maximum follow-up period, we noted a low occurrence of both ischemic and bleeding events. However, interpreting these results presents several challenges. Firstly, the sample size is insufficient to comprehensively explore these outcomes. Secondly, subclinical events were not thoroughly investigated and may be underreported. Finally, all statistical analyses are only exploratory and despite the emergence of a significant protective effect for oral anticoagulants among different antithrombotic regimens, the lack of statistical adjustments hinders the formation of robust conclusions.

Nonetheless, even when considering these limitations, we can confirm that the risk of ischemic events following the procedure does not outweigh the propensity for bleeding. In light of this, considering that observational data has demonstrated that the use of SAPT instead of DAPT is associated with a reduction in bleeding complications, with no significant increase in the risk of thrombotic events [23], and that in patients with early de-escalation of DAPT (within 105 days), the same effect has been demonstrated, adopting a strategy of transitioning to a SAPT regimen at discharge or early during follow-up appears to strike a reasonable balance between safety and effectiveness [10]. Several ongoing trials, including ARMYDA AMULET (NCT02879448) and ASPIRIN-LAAO (NCT03821883), are investigating these approaches.

In our registry, we did not observe a definitive trend of antithrombotic therapy de-escalation following LAAO. Instead, a significant number of patients who were not initially prescribed antithrombotic medications received some kind of therapy after the procedure. Furthermore, a substantial portion of patients adopts OAC strategy following LAAO. This finding may seem perplexing, considering that many of these patients might have contraindications to OAC. However, when taking into account the recognized prothrombotic condition linked to atrial cardiomyopathy in AF patients, extending beyond left atrial appendage exclusion, our observations concerning the potential

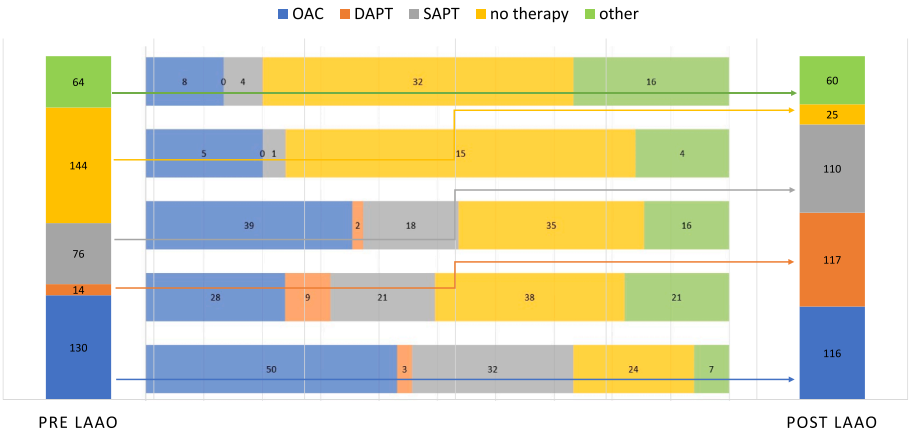

Fig. 2. Antithrombotic strategies pre- and post-LAAO. The horizontal bars represent the baseline treatments of patients prescribed with different regimens at discharge. Other = DAT (including VKA + SAPT, DOAC + SAPT, LMWH + SAPT) or LMWH or TAT. OAC = VKA or DOAC. DAPT = dual antiplatelet therapy; DAT = dual antithrombotic therapy; DOAC = direct oral anticoagulant; LMWH = low-molecular weight heparin; OAC = oral anticoagulant; SAPT = single antiplatelet therapy (aspirin or clopidogrel); TAT = triple antithrombotic therapy; VKA = vitamin-K antagonist.

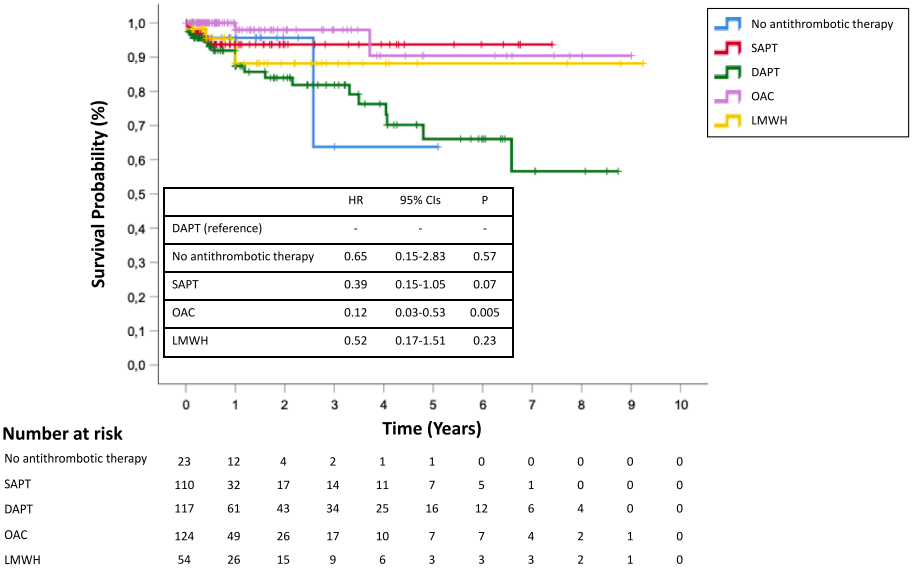

Fig. 3. Event free survival curves. Kaplan-Meier curves plotting the occurrence of the composite endpoint for the different antithrombotic strategies over the follow-up period, with dual antiplatelet therapy (DAPT) used as the reference. Plus symbols indicate censored.

advantages of OAC may serve as a basis for generating hypotheses. Furthermore, these results are consistent with those of a recent network meta-analysis comparing initial antithrombotic therapies after LAAO in forty-one studies comprising 12,451 patients and showing that mono-therapy with DOAC had the highest likelihood of lower thromboembolic events and major bleeding compared with other antithrombotic strategies [24].

However, it is important to note that a multivariate Cox analysis for adjustment of potential confounding factors was not conducted due to the low event rate. At this regard, we found that baseline differences exist across the antithrombotic strategies, as for example documented in patients treated with SAPT or DAPT having higher CHA_2DS_2VASC and HAS-BLED score than those treated with OAC, confirming that clinical choice of antithrombotic regimens is driven by the perceived thrombotic and hemorrhagic risk. Given this perspective, ongoing trials may provide a clearer understanding of the advantages of anticoagulation in addressing the remaining risk [13].

5. Conclusions

Our findings confirm that LAAO is a safe procedure when executed at high volume centers. Different individualized post-discharge antithrombotic regimens are now adopted, likely driven by the perceived thrombotic and hemorrhagic risk. The incidence of both ischemic and bleeding events at mid-term follow-up tends to be low.

CRediT authorship contribution statement

Antonio Procopio: Writing – original draft, Software, Methodology, Formal analysis, Data curation. **Francesco Radico:** Writing – original draft, Software, Methodology, Formal analysis, Data curation. **Felice Gragnano:** Writing – review & editing, Validation, Investigation, Data curation. **Chiara Ghiglieno:** Validation, Investigation, Data curation. **Gaetano Fassini:** Writing – review & editing, Methodology, Investigation, Data curation. **Annalisa Filtz:** Validation, Methodology, Data curation. **Alessandro Barbarossa:** Validation, Methodology, Investigation, Data curation. **Daniele Sacchetta:** Validation, Investigation. **Massimiliano Faustino:** Validation, Investigation. **Fabrizio Ricci:**

Supervision, Methodology, Data curation. **Antonio Dello Russo:** Writing – original draft, Software, Methodology, Formal analysis, Data curation. **Paolo Calabrò:** Writing – review & editing, Project administration, Methodology, Investigation. **Giuseppe Patti:** Writing – review & editing, Project administration, Methodology, Investigation, Data curation. **Sabina Gallina:** Writing – review & editing, Supervision. **Giulia Renda:** Writing – review & editing, Validation, Supervision, Project administration, Methodology, Data curation, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: **Daniele Sacchetta**: payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Medtronic. **Fabrizio Ricci**: support for attending meetings and/or travel from Bayer. **Antonio Dello Russo**: consultant for Abbott and Medtronic. **Giuseppe Patti**: grant or contract from Abbott, Chiesi, Biotronic, Boston; consulting fees from Amgen, Sanofi, Novartis, Daichi Sankyo, Amarin, Aurora BioPharma, Malesci, PIAM, Boheringer Ingheleim, Bayer, Pfizer/BMS, Astra Zeneca, Biotronik, Terumo, Medtronic, Abbott, Edwards, Amicus, Novo Nordisk, Chiesi; payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Amgen, Sanofi, Novartis, Daichi Sankyo, Amarin, Aurora BioPharma, Malesci, PIAM, Boheringer Ingheleim, Bayer, Pfizer/BMS, Astra Zeneca, Biotronik, Terumo, Medtronic, Abbott, Edwards, Amicus, Novo Nordisk, Chiesi; participation on a Data Safety Monitoring Board or Advisory Board for Amgen, Daichi Sankyo, Amarin, Aurora Bayer, Pfizer/BMS, MSD. **Giulia Renda**: grant or contract to my Institution from Bayer and Janssen/Bristol-Myers Squibb (not related to the manuscript); speaker/consultant/advisory board fees from Bayer, Boehringer Ingelheim, Menarini; support for attending meetings from Bayer and Daiichi Sankyo.

References

[1] E.J. Benjamin, P. Muntner, A. Alonso, M.S. Bittencourt, C.W. Callaway, A. P. Carson, et al., Heart disease and stroke statistics-2019 update: a report from the American Heart Association, Circulation 139 (2019) e56–e528.

[2] M. Alkhouli, F. Alqahtani, S. Aljohani, M. Alvi, D.R. Holmes, Burden of atrial fibrillation-associated ischemic stroke in the United States, JACC Clin. Electrophysiol. 4 (2018) 618–625.

[3] R.G. Hart, L.A. Pearce, M.I. Aguilar, Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation, Ann. Intern. Med. 146 (2007) 857–867.

[4] C.T. Ruff, R.P. Giugliano, E. Braunwald, E.B. Hoffman, N. Deenadayalu, M. D. Ezekowitz, et al., Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials, Lancet (London, England) 383 (2014) 955–962.

[5] D.R. Holmes, V.Y. Reddy, Z.G. Turi, S.K. Doshi, H. Sievert, M. Buchbinder, et al., Percutaneous closure of the left atrial appendage versus warfarin therapy for prevention of stroke in patients with atrial fibrillation: a randomised non-inferiority trial, Lancet (London, England) 374 (2009) 534–542.

[6] D.R. Holmes Jr., S. Kar, M.J. Price, B. Whisenant, H. Sievert, S.K. Doshi, et al., Prospective randomized evaluation of the watchman left atrial appendage closure device in patients with atrial fibrillation versus long-term warfarin therapy: the PREVAIL trial, J. Am. Coll. Cardiol. 64 (2014) 1–12.

[7] P. Osmancik, D. Herman, P. Neuzil, P. Hala, M. Taborsky, P. Kala, et al., Left atrial appendage closure versus direct oral anticoagulants in high-risk patients with atrial fibrillation, J. Am. Coll. Cardiol. 75 (2020) 3122–3135.

[8] V.Y. Reddy, S.K. Doshi, S. Kar, D.N. Gibson, M.J. Price, K. Huber, et al., 5-year outcomes after left atrial appendage closure: from the PREVAIL and PROTECT AF trials, J. Am. Coll. Cardiol. 70 (2017) 2964–2975.

[9] P. Osmancik, D. Herman, P. Neuzil, P. Hala, M. Taborsky, P. Kala, et al., 4-year outcomes after left atrial appendage closure versus nonwarfarin oral anticoagulation for atrial fibrillation, J. Am. Coll. Cardiol. 79 (2022) 1–14.

[10] L.V. Boersma, H. Ince, S. Kische, E. Pokushalov, T. Schmitz, B. Schmidt, et al., Evaluating real-world clinical outcomes in atrial fibrillation patients receiving the WATCHMAN left atrial appendage closure technology: final 2-year outcome data of the EWOLUTION trial focusing on history of stroke and hemorrhage, Circ. Arrhythm. Electrophysiol. 12 (2019) e006841.

[11] L. Asmarats, J.-B. Masson, P.A. Pagnotta, S. Cook, M. Foresti, R. Ibrahim, et al., Percutaneous left atrial appendage closure with the ultraseal device: insights from the initial multicenter experience, J. Am. Coll. Cardiol. Intv. 11 (2018) 1932–1941.

[12] J.V. Freeman, P. Varosy, M.J. Price, D. Slotwiner, F.M. Kusumoto, C. Rammohan, et al., The NCDR left atrial appendage occlusion registry, J. Am. Coll. Cardiol. 75 (2020) 1503–1518.

[13] G. Patti, C. Ghiglieno, Indications, evidence, and controversy in the closure of the left atrial appendage, Eur. Heart J. Suppl. 25 (2023) B126–B130.

[14] P. Calabro, F. Gragnano, G. Niccoli, R. Marcucci, M. Zimarino, C. Spaccarotella, et al., Antithrombotic therapy in patients undergoing transcatheter interventions for structural heart disease, Circulation 144 (2021) 1323–1343.

[15] M. Glikson, R. Wolff, G. Hindricks, J. Mandrola, A.J. Camm, G.Y.H. Lip, et al., EHRA/EAPCI expert consensus statement on catheter-based left atrial appendage occlusion - an update, EuroIntervention 15 (2020) 1133–1180.

[16] S. Kaatz, D. Ahmad, A.C. Spyropoulos, S. Schulman, Subcommittee on Control of A, Definition of clinically relevant non-major bleeding in studies of anticoagulants in atrial fibrillation and venous thromboembolic disease in non-surgical patients: communication from the SSC of the ISTH, J Thrombosis Haemostasis: JTH 13 (2015) 2119–2126.

[17] T. Busu, S.U. Khan, M. Alhajji, F. Alqahtani, D.R. Holmes, M. Alkhouli, Observed versus expected ischemic and bleeding events following left atrial appendage occlusion, Am. J. Cardiol. 125 (2020) 1644–1650.

[18] P. Kirchhof, S. Benussi, D. Kotecha, A. Ahlsson, D. Atar, B. Casadei, et al., 2016 ESC guidelines for the management of atrial fibrillation developed in collaboration with EACTS, Eur J Cardio-Thoracic Surg.: Off. J. Eur. Assoc. Cardio-Thoracic Surgery 50 (2016) e1–e88.

[19] J. Brachmann, T. Lewalter, Interventional occlusion of left atrial appendage in patients with atrial fibrillation, Acute and Long-Term Outcome of Occluder Implantation in the LAARGE Registry 58 (2020) 273–280.

[20] G.Y. Lip, R. Nieuwlaat, R. Pisters, D.A. Lane, H.J. Crijns, Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation, Chest 137 (2010) 263–272.

[21] C.T. January, L.S. Wann, J.S. Alpert, H. Calkins, J.E. Cigarroa, J.C. Cleveland, et al., 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: executive summary, Circulation 130 (2014) 2071–2104.

[22] R. Pisters, D.A. Lane, R. Nieuwlaat, C.B. de Vos, H.J. Crijns, G.Y. Lip, A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey, Chest 138 (2010) 1093–1100.

[23] G. Patti, A. Sticchi, G. Verolino, V. Pasceri, V. Vizzi, E. Brscic, et al., Safety and efficacy of single versus dual antiplatelet therapy after left atrial appendage occlusion, Am. J. Cardiol. 134 (2020) 83–90.

[24] P.E.P. Carvalho, D.M. Gewehr, I.A. Miyawaki, A. Nogueira, N. Felix, P. Garot, et al., Network meta-analysis of initial antithrombotic regimens after left atrial appendage occlusion, J. Am. Coll. Cardiol. 82 (2023) 1765–1773.