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The hybrid strategy of left atrial appendage closure on top of anticoagulation in patients with prior anticoagulation failure: a multicenter study

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Abstract

Introduction: The hybrid strategy, defined as left atrial appendage closure (LAAC) followed by long-term anticoagulation, may be considered in patients with thromboembolic events or left atrial appendage thrombus despite anticoagulation (anticoagulation failure).

Objectives: To report the adoption and outcomes of the hybrid strategy.

Patients and methods: High-volume Polish centers reported outcomes of LAAC after anticoagulation failure between 2014 and 2024. The hybrid strategy was compared with other pharmacotherapy regimens (non-hybrid) with respect to thromboembolic events, device-related thrombus (DRT), and major bleeding.

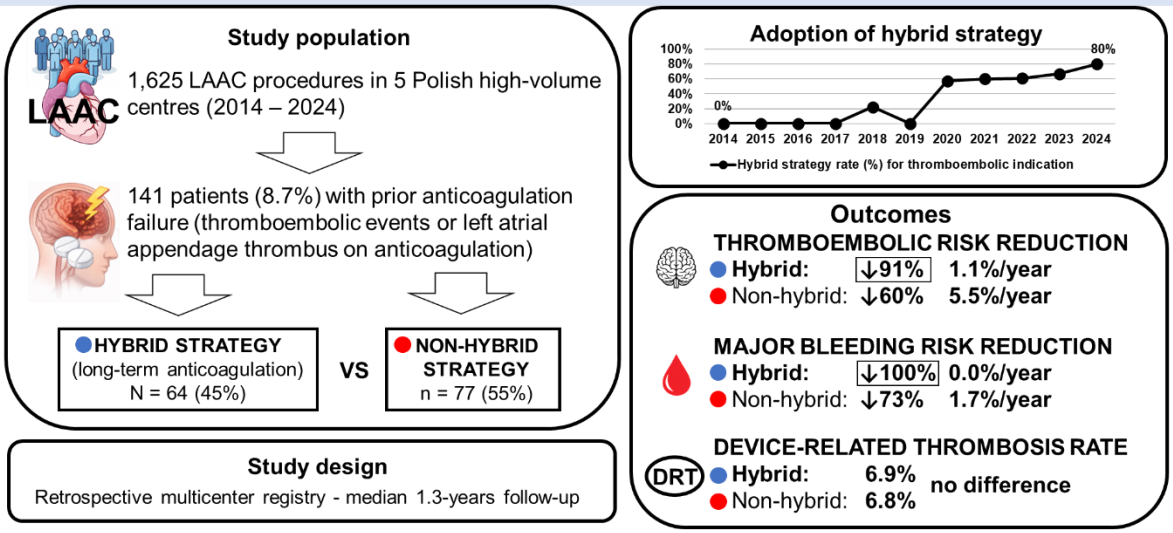
Results: Out of 1,625 LAAC procedures across 5 centers, 141 patients (8.7%) had a history of anticoagulation failure. The hybrid strategy was applied in n=64 (45%) and increased from none in 2014 to 80% of patients in 2024. Compared with the non-hybrid group, hybrid strategy patients received newer-generation occluders (98.4% vs 68.8%, P<0.001), had less prior bleeding (12.5% vs 35.1%, P=0.003), lower HAS-BLED scores [3 (2-3) vs 3 (2-4), P=0.008], more often had prior appendage thrombus (23.4% vs 10.4%, P=0.042) and LVEF<40% (18.8% vs 6.5%, P=0.037). During a median 1.3-year follow-up, the hybrid strategy showed greater thromboembolic risk reduction relative to CHA_2DS_2-VASc-predicted (91% vs 60%; annualized event rates of 1.1% vs 5.5%), and greater major bleeding risk reduction relative to HAS-BLED-predicted (100% vs 73%; annualized rates of 0.0% vs 1.7%), with similar DRT rates (6.9% vs 6.8%, P=1.000).

Conclusions: The hybrid strategy after LAAC for anticoagulation failure is increasingly adopted and was associated with greater thromboembolic risk reduction compared with the standard non-hybrid strategy, without compromising the bleeding profile.

Key words

atrial fibrillation, left atrial appendage closure, stroke, thromboembolism

GRAPHICAL ABSTRACT
The hybrid strategy of left atrial appendage closure (LAAC) followed by long-term anticoagulation in patients with history of anticoagulation failure became the predominant approach in Poland and was associated with greater thromboembolic risk reduction and an excellent bleeding safety profile compared with the standard strategy.



Introduction

Among patients with atrial fibrillation (AF) treated with oral anticoagulants, the residual annual risk of ischemic stroke or systemic embolism is approximately 1.3% [1], with a 7% yearly recurrence rate following an index thromboembolic event [2]. Percutaneous left atrial appendage closure (LAAC) is currently used mainly as an alternative stroke prevention method in patients with AF and contraindications to long-term anticoagulation [3]. A recent expert consensus recognized LAAC as a treatment option for thromboembolic events or left atrial appendage (LAA) thrombus occurring in anticoagulated patients (anticoagulation failure), albeit without specific recommendations due to limited and inconsistent evidence [4]. Prior studies suggested increased risk of thromboembolic events following LAAC in patients with a history of anticoagulation (AC) failure [5-8], which emphasizes the importance of optimizing post-procedural treatment strategies in this group of patients. Indeed, several studies have reported promising results with LAAC followed by long-term anticoagulation (the hybrid strategy), rather than antiplatelet therapy; however, the available evidence remains scarce and inconclusive, with only a trend toward improved outcomes [6, 9-14]. Thus, further data on

outcomes with the hybrid strategy in this high-risk population after LAAC are warranted. This study aimed to assess the adoption and outcomes of the hybrid strategy, as compared with the standard antiplatelet therapy, in patients undergoing LAAC for anticoagulation failure in high-volume centers across Poland.

Patients and methods

Study Population and Treatment Strategies

This is a retrospective, multicenter registry of patients with nonvalvular AF who underwent LAAC with an Amplatzer (Abbott, Plymouth, MN, USA) or WATCHMAN (Boston Scientific, Marlborough, MA, USA) device between 2014 and 2024 in 5 high-volume implanting centers in Poland. Consecutive patients who underwent LAAC with a history of stroke, transient ischemic attack (TIA), peripheral embolism (PE), or left atrial appendage (LAA) thrombus despite AC (AC failure) were identified and constituted the study population. For the purpose of this analysis, patients were classified into two groups according to post-LAAC antithrombotic strategy: (1) a hybrid strategy, defined as long-term anticoagulation after LAAC, and (2) a non-hybrid (standard) strategy, defined as antiplatelet therapy with or without short-term anticoagulation (discontinued within 6 months after LAAC following follow-up imaging). The registry was approved by the institutional review board.

Study Outcomes Definitions

The efficacy outcomes included: 1) a composite of ischemic stroke, TIA, or PE, and 2) device-related thrombus (DRT). The safety outcome was defined as major bleeding episodes. Ischemic stroke/TIA/PE were defined according to the Munich consensus document [15]. Major bleeding was defined as fatal or clinically overt bleeding associated with either transfusion of ≥2 units of blood or ≥2 g/dl decrease in hemoglobin or bleeding involving a critical anatomic site (intracranial, intraspinal, intraocular, pericardial, intramuscular with compartment syndrome,

or retroperitoneal) [16-18]. Bleeding requiring hospitalization or an invasive procedure but not meeting the above criteria was classified as non-major clinically relevant bleeding [16-18]. All patients were scheduled for a standard post-procedural imaging follow-up visit with transesophageal echocardiography (TEE) or computed tomography (CT). As the number of reported imaging examinations during follow-up varied across centers, which could influence the observed rates of device-related complications, only the first scheduled follow-up imaging study was analyzed. DRT was defined as a density on the left atrial aspect of the device not explained by imaging artifact, inconsistent with normal healing or device incorporation, visible in multiple TEE/CT planes, and in contact with the device [7].

Statistical methods

Continuous variables were presented as mean (standard deviation, SD) or as median with interquartile range (IQR), as appropriate. Normality was assessed using the Shapiro–Wilk test. If the assumption of normal distribution was met, comparisons were performed using the independent samples t-test with Levene's test for equality of variances. If the normality assumption was rejected, the Mann–Whitney U test was used. Categorical variables were presented as frequencies and percentages and compared using Fisher's exact test. Time-to-event variables were compared between groups using the log-rank test. The effectiveness of LAAC in preventing stroke/TIA/PE was tested by comparing the actual annual rate with the annual rate predicted by the CHA_2DS_2-VASc score [19]. Similarly, the bleeding reduction was assessed by comparing the actual annual major bleeding rate to the annual rate predicted by the HAS-BLED score [18]. To account for treatment crossovers, patients who permanently (for ≥ 3 months) transitioned between hybrid and non-hybrid regimens were censored at the time of the treatment change in the main analysis (per-protocol). Additional sensitivity analyses were conducted according to the intention-to-treat principle, with patients analyzed based on their initial treatment assignment, regardless of subsequent treatment modifications. A P value of less

than 0.050 was considered statistically significant. All statistical analyses were performed using SPSS software, version 25 (SPSS, Inc., Chicago, IL, USA).

Results

Baseline characteristics of the study cohort

A total of 1,625 LAAC procedures were reported by the 5 participating centers between 2014 and 2024. Out of this cohort, 141 (8.7%) patients had a history of AC failure, defined as thromboembolic events or LAA thrombus occurring despite AC, and comprised the final study population (Figure 1). The types of AC failure included ischemic stroke (n = 96; 68.1%), TIA (n = 8; 5.7%), PE (n = 5; 3.5%), LAA thrombus (n = 17; 12.1%), or a combination of complications (n = 15, 10.6%), most commonly a combination including ischemic stroke (13 of 15 cases). The proportion of patients treated with the hybrid strategy following LAAC due to AC failure increased from none in 2014 to 80% (20 patients) in 2024; overall, 64 patients (45.4%) received the hybrid strategy.

Baseline characteristics of patients in the hybrid and non-hybrid strategy groups are summarized in Table 1. Detailed thromboembolic and bleeding history is provided in the Supplementary Material (Table S1). Most thromboembolic events preceding LAAC occurred during direct oral anticoagulant (DOAC) therapy (n = 87; 61.7%), with a higher prevalence of prior DOAC vs vitamin K antagonist use in the hybrid group (P = 0.013, Table 1). Compared with the non-hybrid group, patients in the hybrid strategy group less often had a history of bleeding episodes (12.5% vs 35.1%, $P = 0.003$), had lower HAS-BLED scores [3 (2-3) vs 3 (2-4), $P = 0.008$], and more often had prior LAA thrombus (23.4% vs 10.4%, $P = 0.042$) and LVEF < 40% (18.8% vs 6.5%, $P = 0.037$).

Periprocedural data

Overall, 58.9% of procedures used WATCHMAN devices, with a similar frequency between the hybrid and non-hybrid group (65.6% vs 53.2%, respectively; P = 0.170). Newer-generation occluders (WATCHMAN FLX or Amulet) were used in 82.3% of procedures and were significantly more frequent in the hybrid group (98.4% vs 68.8%, P < 0.001). There were no periprocedural deaths or thromboembolic complications. Clinically significant periprocedural bleeding was reported in 4 (6.3%) patients in the hybrid group and 2 (2.6%) in the non-hybrid group (P = 0.285), including vascular access site bleeding in 5 patients and cardiac tamponade in 1 patient.

Post-LAAC pharmacological treatment regimens

Post-LAAC pharmacological treatment regimens are presented in Table 2. In the hybrid strategy group, the majority of patients (n = 39, 61%) received DOAC combined with short-term antiplatelet therapy [median duration of antiplatelet therapy 89 (IQR: 40-93) days], whereas n = 20 (31%) were managed with DOAC monotherapy. The DOAC used was apixaban in n = 37 (62.7%) patients, dabigatran in n = 15 (25.4%), and rivaroxaban in n = 7 (11.9%); a reduced dose of DOAC was used in 8 patients (13.3%) in this group.

In the non-hybrid strategy group n = 70 (91%) patients received transient post-procedural dual antiplatelet therapy [median duration of 90 (IQR: 50-180) days], followed by aspirin monotherapy in n = 58 (83%), whereas n = 5 (6%) patients received short-term post-procedural anticoagulation on top of antiplatelet therapy [median duration of 55 (IQR: 44-87) days].

During follow-up, treatment crossovers, defined as discontinuation of AC in the hybrid group or initiation of AC in the non-hybrid group, occurred in both groups. The reasons and timing of the crossovers are summarized in Supplementary material, Table S2.

Long-term efficacy and safety of LAAC

Patients were followed up for a median of 457 days (IQR 357–923) [401 days (310–742) in the hybrid group vs 555 days (365–1263) in the non-hybrid group; P = 0.035].

There were 10 deaths (3.7 per 100 patient-years) observed in the study cohort; 4 deaths (1.5 per 100 patient-years) had cardiovascular causes. There was no difference in overall mortality (n = 5, 5.4 per 100 patient-years vs n = 5, 2.8 per 100 patient-years, log-rank P value = 0.299) or cardiovascular mortality (n = 2, 2.2 per 100 patient-years vs n = 2, 1.1 per 100 patient-years, log-rank P value = 0.236) between the hybrid and non-hybrid strategy groups, respectively (Table 3). In two cases, the cause of death was unknown.

There were 10 strokes (3.7 per 100 patient-years) in 9 patients, 1 TIA (0.4 per 100 patient-years), and no reported PE in the studied cohort. There was 1 stroke (1.1 per 100 patient-years), occurring during warfarin therapy, and no TIA or PE in the hybrid strategy group, compared with 9 strokes and 1 TIA (5.5 per 100 patient-years), all occurring during aspirin monotherapy, in the non-hybrid group (log-rank P value = 0.095) (Table 3). Thromboembolic risk was reduced by 91% vs 60% relative to CHA_2DS_2-VASc predicted in the hybrid and non-hybrid groups, respectively (Figure 2). All cases of stroke/TIA/PE occurred in patients who received newer-generation occluders (FLX/Amulet). All events occurred in patients with prior stroke despite anticoagulation, except for one stroke that occurred in a patient with a history of TIA despite anticoagulation.

There were 3 major bleeding events (overall 1.1 per 100 patient-years) reported in the studied cohort, occurring exclusively in the non-hybrid group (1.7 per 100 patient-years) (log-rank P value = 0.271 for comparison of hybrid vs non-hybrid group, Table 3). Two events occurred during aspirin monotherapy and one during a transient crossover to warfarin. Major bleeding risk was reduced by 100% vs 73% relative to HAS-BLED predictions in the hybrid and non-hybrid groups, respectively (Figure 2). Non-major clinically relevant bleeding

occurred in 3 patients (3.2 per 100 patient-years) in the hybrid group, all on DOAC therapy, and in 2 patients (1.1 per 100 patient-years) in the non-hybrid group, both on aspirin, with no significant difference between the two groups (P = 0.386).

Among patients who underwent imaging follow-up (n = 132, 93.6%), the median time from LAAC to the first imaging follow-up visit was 55 days (IQR 38–90), with 63 days (IQR 44–95) in the hybrid group and 53 days (IQR 37–83) in the non-hybrid group (P = 0.073). TEE was performed in 111 patients (84.1%), n = 42 (72.4%) in the hybrid and n = 69 (93.2%) in the non-hybrid group (P = 0.002); the remaining patients underwent CT follow-up. DRT at the first imaging follow-up visit occurred in 9 patients (6.8%) with similar rates between the groups (n = 4, 6.9% in hybrid vs n = 5, 6.8% in non-hybrid group, P = 1.000). The incidence of DRT was 5.4% in patients assessed with TEE (6/111) and 14.3% in those assessed with CT (3/21) (*P* = 0.154). In the hybrid group, DRT was managed by adding an antiplatelet agent in n = 2 (50%) patients, switching to transient low-molecular-weight heparin in 1 (25%), and continuing DOAC in the remaining 1 (25%) patient. In the non-hybrid group, n = 4 (80%) patients received transient anticoagulation therapy, whereas 1 patient (20%) continued antiplatelet therapy. Significant peri-device leak (≥3mm) was observed in 6 patients (4.5%) with comparable rates between the groups (n = 2, 3.4% in hybrid vs n = 4, 5.4% in non-hybrid group, P = 0.694). All 2 patients with significant PDL in the hybrid group continued long-term anticoagulation. One patient with significant PDL in the non-hybrid group underwent transcatheter PDL closure, whereas the remaining 3 patients continued antiplatelet therapy. Nine patients (6.4%) did not undergo imaging follow-up (n = 6, 9.4% in the hybrid group and n = 3, 3.9% in the non-hybrid group; P = 0.162) due to death (n = 1), recent implantation (n = 2), unsuccessful TEE probe insertion (n = 1), and loss to imaging follow-up (n = 5).

Sensitivity analysis

To account for permanent treatment crossovers (≥3 months), follow-up was censored at the time

of crossover in the main analysis (per-protocol), whereas the intention-to-treat analysis was conducted irrespective of treatment changes. All events reported after the permanent crossover occurred in the non-hybrid group. Comparison of long-term outcomes is presented in Supplementary material, Table S3.

Discussion

To the best of our knowledge, this is the first analysis specifically comparing post-LAAC pharmacological regimens in patients undergoing LAAC for AC failure. The study found that: 1) the use of long-term anticoagulation after LAAC for AC failure (the hybrid strategy) increased across Polish centers from none in 2014 to 80% in 2024; 2) the hybrid strategy was associated with a greater reduction in the CHA_2DS_2-VASc predicted stroke/TIA/PE rates compared to the standard antiplatelet therapy (RRR 91% vs. 60%) and 3) the hybrid strategy showed an excellent bleeding risk profile in this cohort of patients.

Given the aging AF population and the growing recognition of AF-related morbidity and mortality among elderly patients, optimizing of secondary prevention strategies is increasingly relevant [20, 21]. Patients with nonvalvular AF who experience ischemic stroke despite AC are at particularly high risk of recurrence, with an estimated annual rate of 7.2% [2]. However, the optimal secondary prevention strategy in this population remains unknown, and recent randomized trials have further expanded the evidence base for LAAC in patients with AF [22, 23]. In this context, LAAC has emerged as a promising secondary prevention option. In our study, out of 1,625 LAAC procedures performed across five centers in Poland, 141 patients (8.7%) had a history of AC failure. Most published reports studying LAAC for AC failure so far included only stroke occurring despite oral anticoagulation as the indication for LAAC [5, 9, 24], with reported proportion of such indication among all LAAC procedures ranging from 5% to 24% [5, 9, 10]. Only a few reports, including this study, have also

considered other thromboembolic indications for LAAC, such as left atrial thrombosis and TIA, reflecting a broader clinical spectrum in which LAAC may be appropriate [6, 10].

Current guidelines recommend post-LAAC pharmacotherapy based on that used in LAAC randomized trials and large registries [3]. The recommendations include transient post-procedural dual antiplatelet therapy or short-term warfarin followed by long-term aspirin, but also allow short-term DOAC therapy as an alternative to warfarin or single antiplatelet therapy alone in patients at extremely high bleeding risk [4]. However, these varying strategies have not been directly compared in any randomized trials [25-26]. Unlike patients with high bleeding risk indications, post-LAAC pharmacotherapy in patients with AC failure is primarily aimed at recurrent stroke prevention, thus extended anticoagulation may potentially provide additional thromboembolic protection [3]. In our real-life cohort, we observed substantial heterogeneity and frequent off-label pharmacotherapy use, consistent with other LAAC registry data [27-28]. The strength of our study is the availability of precise longitudinal data on the type of pharmacotherapy applied, in contrast to prior publications on LAAC following AC failure that often defined subgroups irrespective of subsequent treatment modifications during follow-up [5, 6, 9-10, 24]. The hybrid strategy, emerging as the predominant approach in our registry, was applied in 45% of patients overall, increasing from none in 2014 to 80% in 2024. This trend was further reflected by permanent treatment crossover in 24.7% of patients who were initially managed with a non-hybrid strategy, where nearly half of these treatment modifications were driven by physician-judged high stroke risk, not clinical events or device-related complications (Supplementary material, Table S2). On the other hand, across other studies, the estimation of use of a hybrid strategy after AC failure is limited by inconsistent definitions and pharmacotherapy is reported at different time points during follow-up, resulting in heterogeneous estimates, with between 54% and 98% of patients discharged on anticoagulation after LAAC, and 33%-79% estimated to be kept on long-term AC as part of the hybrid regimen

[5, 6, 9-10, 24]. Our findings reflect a shift in stroke prevention: from LAAC as an alternative to anticoagulation toward an adjunctive approach aimed at augmenting thromboembolic protection in high-risk patients. This evolution is consistent with the concept demonstrated in the randomized LAAOS III trial, where surgical appendage occlusion added to anticoagulation reduced ischemic stroke risk [29]. Ongoing trials such as LAAOS IV will further clarify the benefit of this strategy (NCT05963698). Additionally, in our hybrid cohort, 63% of patients received a short-term (1–6 months), post-procedural antiplatelet therapy on top of DOAC, reflecting the concept of early device endothelialization, during which more intensive therapy may potentially reduce the risk of device-related thrombus [30]. Nevertheless, the necessity of combining antiplatelet therapy with AC, given its inherent bleeding risk, remains uncertain and warrants further investigation [31].

In our cohort, the overall recurrent stroke rate was 3.7 per 100 patient-years, irrespective of post-procedural therapy. This is significantly lower than the 7.2% annual recurrence reported in patients with AF who experience ischemic stroke despite anticoagulation [2]. While cross-study comparisons should be interpreted cautiously, this observation is consistent with the concept that LAAC may provide additional thromboembolic protection in this particularly high-risk population. The hybrid strategy was associated with a greater reduction in stroke/TIA/PE rates compared with that predicted by the CHA2DS2-VASc score, with a trend toward lower thromboembolic event rates in the hybrid population. This finding is supported by results of other registries describing the hybrid approach as a promising treatment option, which similarly reported numerically lower thromboembolic risk with the hybrid strategy [6, 9-10]. The rationale for this approach is that in patients with a high probability of cardioembolic mechanism of stroke, anticoagulant therapy may provide superior efficacy, regardless of whether the embolic source is the left atrial appendage [7]. Anticoagulation may also partially mitigate procedural limitations such as deep device implantation, which may result in residual

appendage and device-related thrombus, as well as residual peridevice leak, all of which are associated with an increased thromboembolic risk [32-33]. In our study, LAAC appeared highly effective among patients with a prior LAA thrombus despite anticoagulation, as no stroke, TIA, or PE events occurred during follow-up in this population. These patients demonstrated a strong prothrombotic tendency, reflected by two cases of lead thrombosis during follow-up, both of which prompted initiation of anticoagulation therapy (Supplementary material, Table S2). Importantly, the more favorable outcomes observed with the hybrid strategy are unlikely to be explained by a higher proportion of newer-generation devices in this group, as all stroke/TIA/PE events occurred in patients implanted with newer-generation occluders. Treatment crossovers are also unlikely to have significantly influenced the results, as permanent crossovers were excluded from the analysis, and sensitivity analysis showed consistent findings, whereas transient crossovers were infrequent (5.7%) and short in duration (median 39 days, IQR 9–64) (Supplementary material, Table S2).

The hybrid strategy demonstrated an excellent bleeding risk profile, with no major bleeding events reported during follow-up. It remains unclear whether short-term antiplatelet therapy is safer than anticoagulation with respect to bleeding risk in this population of patients. Interestingly, there are meta-analyses comparing anticoagulation with antiplatelet therapy after LAAC, which have suggested either no significant differences or even a more favorable safety profile with anticoagulation compared to antiplatelet therapy [31, 34-36]. Gastrointestinal bleeding is a frequent source of major bleeding after LAAC, which may partly explain the poorer outcomes observed with dual antiplatelet therapy [36].

The observed rates of DRT at the standard post-procedural imaging follow-up visit were similar (6.8% vs. 6.9%). Consequently, this study does not provide additional confirmation of prior reports suggesting a lower DRT risk with AC after LAAC [31]. Differences in follow-up modality and the shift from TEE to CT in the hybrid group primarily reflect the historical nature

of the non-hybrid cohort, as CT has become increasingly available and widely accepted as a reliable post-LAAC imaging modality. Importantly, a recent meta-analysis showed comparable detection rates of DRT and large (>5 mm) peridevice leaks with CT and TEE, indicating that this shift is unlikely to have significantly affected the results of our analysis [37].

Study limitations

This nonrandomized, retrospective observational study is subject to confounding due to baseline differences between the compared populations, and the limited sample size and number of clinical events precluded multivariable adjustment to mitigate this limitation. Time-to-event analyses were applied to account for differences in follow-up duration. Due to the retrospective design, adherence to prescribed therapy during follow-up could not be assessed. In addition, because of the retrospective multicenter design, some variables, including selected comorbidities, concomitant pharmacotherapy, and detailed echocardiographic parameters, were not systematically collected across centers and were therefore unavailable for analysis. To address treatment crossovers, follow-up was censored at the time of permanent crossover, and a sensitivity analysis based on the intention-to-treat principle was performed. Follow-up imaging protocols varied across centers; therefore, only the first scheduled post-procedural imaging examination was analyzed, precluding assessment of late DRT occurrence.

Conclusions

The hybrid strategy of long-term anticoagulation following LAAC for AC failure has become the predominant treatment approach and was associated with greater ischemic risk reduction compared to the standard non-hybrid strategy based on antiplatelet therapy, with a favorable bleeding profile.

Article information

Contribution statement KZ and RP contributed to the conception and design of the study, data acquisition, analysis and interpretation of data, and drafting of the manuscript. KK, MG,

PK, AS, JG, KS, JP, MM, AW, and MD contributed to data acquisition and critically revised the manuscript for important intellectual content. All authors approved the final version of the manuscript to be submitted.

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Table 1. Comparison of baseline characteristics between hybrid and non-hybrid therapy cohorts with thromboembolic indications.

Variable	Hybrid strategy (n = 64)	Non-hybrid strategy (n = 77)	p-Value
Demographics			
Female gender	31 (48.4)	37 (48.1)	1.000
Age; years	69 (65-73)	73 (64-77)	0.071
Comorbidities			
Hypertension	**52 (81.3)**	**72 (93.5)**	**0.037**
Diabetes mellitus	22 (34.4)	32 (41.6)	0.392
Smoking history	12 (21.4)	14 (20.3)	1.000
Coronary artery disease	15 (23.4)	28 (36.4)	0.103
Carotid artery disease	10 (15.6)	10 (13.0)	0.809
Peripheral artery disease	6 (9.4)	7 (9.1)	1.000
Pacemaker/ICD implanted	9 (14.1)	20 (26.0)	0.096
Permanent atrial fibrillation	24 (37.5)	40 (51.9)	0.093
Cancer history (active or prior)	10 (15.9)	8 (10.4)	0.448
DVT or pulmonary embolism history	2 (3.1)	3 (3.9)	1.000
Heart failure	29 (45.3)	28 (36.4)	0.305
LVEF < 40%	12 (18.8)	5 (6.5)	0.037
Cardiomyopathy (DCM + HCM)	10 (15.6)	5 (6.5)	0.091
Moderate-to-severe MR	11 (17.2)	11 (14.3)	0.649
Bioprosthetic valve	0 (0.0)	3 (3.9)	0.251

eGFR < 60 mL/min/1.73 m²	21 (32.8)	30 (39.0)	0.485
Thromboembolic risk			
CHA_2DS_2-VASc score	5 (4-6)	6 (5-7)	0.052
Predicted annual thromboembolic risk; %	11.7 (7.8-15.9)	15.9 (11.7-17.9)	0.055
Ischemic stroke on AC history	50 (78.1)	59 (76.6)	1.000
TIA on AC history	7 (10.9)	12 (15.6)	0.467
PE on AC history	2 (3.1)	4 (5.2)	0.689
LAA thrombus on AC history	15 (23.4)	8 (10.4)	0.042
Bleeding risk			
HAS-BLED score	3 (2-3)	3 (2-4)	0.008
Predicted annual bleeding risk; %	5.8 (4.1-5.8)	5.8 (4.1-8.9)	0.008
Clinically significant bleeding history	6 (9.4)	24 (31.2)	0.002

Values are n (%) or median (IQR). **Abbreviations**: AC, anticoagulation; DCM, dilated cardiomyopathy; DVT, deep vein thrombosis; eGFR, estimated glomerular filtration rate; HCM, hypertrophic cardiomyopathy; ICD, implantable cardioverter-defibrillator; IQR, interquartile range; LAA, left atrial appendage; LVEF, left ventricular ejection fraction; TIA, transient ischemic attack.

Table 2. Comparison of post-LAAC discharge pharmacological treatment regimens in hybrid vs. non-hybrid therapy groups

Hybrid strategy (n = 64)		**Non-hybrid strategy (n = 77)**	
Type of treatment	N (%)	**Type of treatment**	N (%)
DOAC + APT (1-6 m)	39 (61)	**ASA + CLO**	70 (91)
DOAC + ASA (1-6 m)	22 (34)	ASA + CLO (1-6 m)	52 (68)
DOAC + CLO (1-6 m)	15 (23)	ASA (1-6 m) + CLO (1-6 m)	12 (16)
DOAC + DAPT (1-6 m)	2 (3)	ASA + CLO (7-12 m)	6 (8)
DOAC monotherapy	20 (31)	**ASA + DOAC/VKA (1-6m)* ± CLO**	5 (6)
Other: DOAC/VKA/LMWH + APT (1-6 m)	5 (8)	**CLO (6 m or long-term)**	2 (3)

*Median duration of anticoagulation treatment of 55 (44-87) days.

Abbreviations: APT, antiplatelet therapy; ASA, acetylsalicylic acid; CLO, clopidogrel; DAPT, dual antiplatelet therapy; DOAC, direct oral anticoagulant; LMWH, low-molecular-weight heparin; VKA, vitamin K antagonist.

Table 3. Comparison of long-term outcomes between hybrid and non-hybrid strategy cohorts with thromboembolic indications

Events	**No. of Events (Events/100 Patient-Years)**		**Log-Rank P Value**
	Hybrid strategy (n = 64)	**Non-hybrid strategy (n = 77)**	
Ischemic stroke/TIA/PE	1 (1.1)	10 (5.5) [a]	0.095
Ischemic stroke	1 (1.1)	9 (5.0) [a]	0.148
TIA	0 (0.0)	1 (0.6)	0.384
PE	0 (0.0)	0 (0.0)	-
Any bleeding	3 (3.2)	5 (2.8)	0.870
mCRB	0 (0.0)	3 (1.7)	0.271
nmCRB	3 (3.2)	2 (1.1)	0.386
All-cause mortality	5 (5.4)	5 (2.8)	0.299

Abbreviations: LAAC, left atrial appendage closure; mCRB, major clinically relevant bleeding; nmCRB, non-major clinically relevant bleeding; PE, peripheral embolism; TIA, transient ischemic attack.

[a] One patient had two strokes during follow-up.

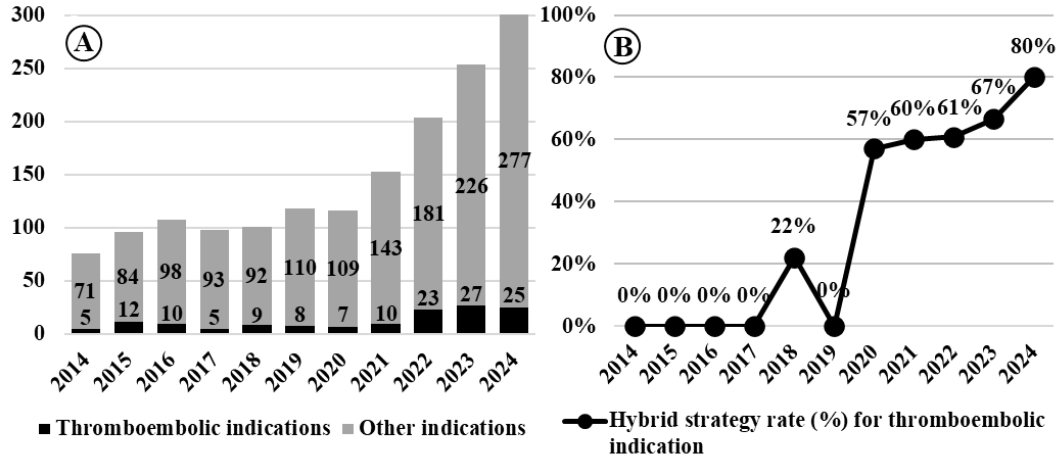

Figure 1. Total number of LAAC procedures and LAAC performed for thromboembolic indications reported by the five participating centers from 2014 to 2024 (panel A), along with the proportion of hybrid strategy use among patients with thromboembolic indications (panel B).

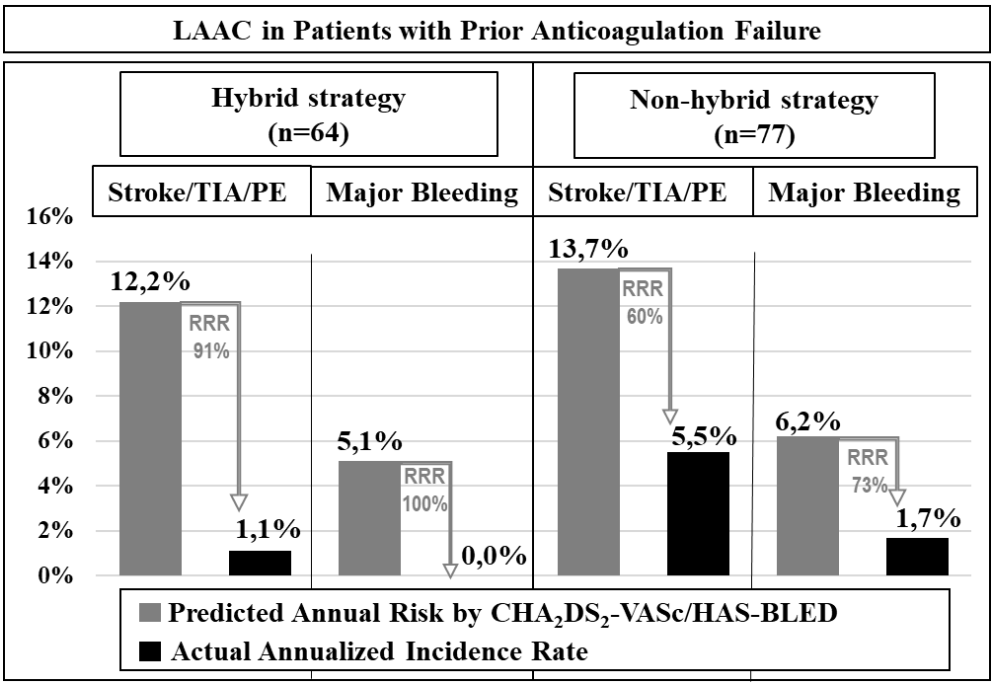

Figure 2. Effectiveness of LAAC in reducing stroke/TIA/PE and non-procedure-related major bleeding rates compared with that predicted by the CHA2DS2-VASc and HAS-BLED scores in the hybrid and non-hybrid strategy groups. PE = peripheral embolism; RRR = relative risk reduction; TIA = transient ischemic attack.

Short title: Appendage Closure for Resistant Thromboembolic Events