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Safety and effectiveness of left atrial appendage occlusion in patients with atrial fibrillation and high bleeding risk: a cardinality-matched comparison with direct oral anticoagulation on long-term stroke and bleeding rates

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Summary

STUDY AIMS: Left atrial appendage occlusion (LAAO) is an accepted alternative stroke prevention strategy for patients with atrial fibrillation (AF) and contraindications to oral anticoagulation despite the lack of randomised data in this population. This study aims to compare the outcomes of LAAO and direct oral anticoagulation (DOAC) therapy in patients with high bleeding risk.

METHODS: This cardinality-matched analysis comprised data from the Beat-AF and Swiss-AF cohorts (n = 3960; enrolment from 2010 to 2014 and from 2014 to 2017, respectively), along with the Zurich LAAO Registry (n = 535; patients included between 2010 and 2023). The primary endpoint was a composite of stroke, cardiovascular death or major bleeding. The individual components constituted the secondary endpoints. Time-dependent cumulative incidence curves were constructed and a competing risk analysis was included.

RESULTS: After matching, 478 patients with a DOAC score ≥8 and 159 patients with previous major bleeding were compared in a 1:1 and 1:2 ratio, respectively, regarding their stroke prevention strategy (DOAC versus LAAO). After a median follow-up time of 4.9 years (interquartile range [IQR]: 2.2–6.1) in all patients with a DOAC score ≥8 and 4.4 years (IQR: 2.0–6.0) in all patients with previous major bleeding, there were no significant differences in the primary endpoint (hazard ratio [HR]: 0.88, 95% confidence interval [CI]: 0.67–1.14, p = 0.33 and HR: 0.79, 95% CI: 0.50–1.27, p = 0.33) and in the rates of stroke (HR: 0.74, 95% CI: 0.39–1.42, p = 0.36 and HR: 1.09, 95% CI: 0.33–3.62, p = 0.89) and cardiovascular death (HR: 0.97, 95% CI: 0.68–1.38, p = 0.85 and HR: 0.91, 95% CI: 0.50–1.64, p = 0.74). The rate of major bleedings was significantly lower in the LAAO group of both cohorts (HR:

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0.55, 95% CI: 0.32–0.94, p = 0.029 and HR: 0.32, 95% CI: 0.13–0.79, p = 0.013).

CONCLUSION: In this high bleeding risk population, LAAO was associated with similar effectiveness in preventing atrial fibrillation-related stroke and cardiovascular death and significantly lower rates of major bleeding compared to DOAC therapy. This strengthens the value of LAAO as an alternative stroke prevention strategy for patients at high risk of bleeding.

Introduction

Atrial fibrillation (AF) remains a widespread and concerning cardiac arrhythmia, affecting millions of individuals worldwide. It is associated with a significantly increased risk of stroke, making it a major cause of morbidity and mortality [1, 2]. To mitigate this risk, oral anticoagulation therapy has been the standard of care for atrial fibrillation patients at high risk of stroke [2]. While oral anticoagulation therapy is generally effective in preventing stroke [3], it comes with a significant downside – the potential for severe or life-threatening bleeding complications, in particular intracranial haemorrhage. This inherent risk has led to a critical dilemma in the management of atrial fibrillation patients, who are at increased risk of thromboembolic events but also have comorbidities that heighten their likelihood of experiencing major bleeding events.

One viable solution to address this dilemma is left atrial appendage occlusion (LAAO). Two randomised controlled trials (RCTs) of LAAO versus warfarin published already ten years ago and a more recent trial of LAAO versus direct oral anticoagulation (DOAC) have demonstrated non-inferiority of LAAO in comparison to oral anticoagulation for preventing thromboembolic events in patients eligible for oral anticoagulation [4–7]. On top of that, the recently published OPTION trial also showed significantly fewer relevant bleeding events in all-comer patients after pulmonary vein isolation treated with LAAO as compared with DOAC [8]. LAAO even proved to have a mortality benefit for Watchman LAAO against vitamin K antagonists in the PROTECT-AF RCT [5] and for Amplatzer LAAO against DOACs in two large propensity score-matched studies [9, 10]. The mortality benefit emerges after a few years and continues to become more conspicuous with time, which is explainable by the accruing bleeding events in patients with oral anticoagulation. These events occur at an increasing rate as the patients get older and sicker. The protection against embolic events with oral anticoagulation suffers from the typically poor compliance [9]. It is therefore not really superior to that associated with LAAO, which represents a mechanical vaccination against embolic events and therefore has a 100% compliance rate [11]. All this, however, is not reflected in current guidelines. These guidelines suggest considering LAAO in atrial fibrillation patients with contraindications to oral anticoagulation [1, 2], with a IIb recommendation in the European and a IIa recommendation in the American guidelines. Interestingly, a contraindication to oral anticoagulation is an exclusion criterion in almost all RCTs on LAAO including the large ongoing Champion-AF and CATALYST trials, which are currently in the follow-up phase (ClinicalTrials.gov ID: NCT04394546 and NCT04226547, respectively). The ASAP-TOO study, which randomised patients with a contraindication to oral anticoagulation to treatment with LAAO or no treatment, was prematurely discontinued due to slow patient enrolment and it is unlikely that new randomised studies with adequate power will be available soon [12].

The hypothesis of this study was that atrial fibrillation patients at risk of thromboembolic events but concomitantly at high or very high risk of DOAC-related bleeding complications may benefit from LAAO with equally good stroke prevention compared to DOAC but with fewer bleeding complications due to less intense antithrombotic therapy. The study aim was to demonstrate both the effectiveness of thromboembolic protection, in terms of stroke and cardiovascular mortality, and its safety, in terms of bleeding rates, in a patient population at such high risk that – depending on the stroke prevention strategy – it is usually excluded from RCTs.

Methods

Study population

Swiss-AF and Beat-AF cohorts (n = 3960)

The Beat-AF (n = 1545) and Swiss-AF (n = 2415) studies constitute prospective, multicentre, observational cohort investigations conducted across 14 medical facilities in Switzerland, with enrolment spanning the years 2010 to 2014 and 2014 to 2017, respectively [13]. With the exception of individuals experiencing reversible forms of atrial fibrillation, those with acute illness within the preceding 4 weeks and those unable to provide informed consent, there were no significant exclusion criteria for participation in either study [13]. The start of participation in Beat-AF and Swiss-AF was determined as the initial contact between the patient and the study site. In both registries, atrial fibrillation patients received stroke prevention measures in accordance with prevailing guidelines [1]. Beyond this standard of care, no predefined interventions were implemented post-inclusion in the Beat-AF and Swiss-AF registries. For the present analysis, only patients treated with DOAC were included (n = 1230). Trained study personnel conducted yearly outpatient visits and annual telephone follow-ups, with systematic event adjudication.

Zurich Left Atrial Appendage Occlusion (LAAO) registry

The Zurich LAAO Registry is a combined prospective/retrospective, single-centre registry encompassing all atrial fibrillation patients undergoing LAAO at University Hospital Zurich. The procedural date aligned with the study entry in the LAAO group of this comparative study, where only patients with a suitably positioned LAA occluder at the conclusion of the procedure between June 2010 and October 2023 were considered in the current analysis. Standard methodologies from the literature were employed for LAAO procedures at University Hospital Zurich [14]. The procedures were performed either under general anaesthesia with transoesophageal echocardiography or under local anaesthesia and fluoroscopic guidance with or without intracardiac echocardiography, depending on the physician's preference [15]. Periprocedural adverse events were incorporated for examination. Unsuccessful procedures were excluded, along with those involving concomi-

tant transcatheter aortic valve implantation or transcatheter mitral valve edge-to-edge repair, owing to the elevated baseline risk associated with severe valvular heart disease. Follow-up involved periodic assessments during both inpatient and outpatient visits at University Hospital Zurich, extending to non-cardiology visits. For patients under the care of external physicians, family physicians were asked to complete a standardised follow-up questionnaire. In instances where family physicians lacked comprehensive follow-up data, direct contact with individual patients or their relatives was made via telephone. Documentation of the source of all adverse events was systematically compiled, and adjudication of adverse events was undertaken by two senior interventional cardiologists.

Study design

This study encompassed participants from all three registries, with the aim of constructing a cardinality-matched cohort to facilitate a comparative analysis of atrial fibrillation patients with a DOAC score of ≥8 [16] who were either treated with DOAC or underwent LAAO for primary or secondary stroke prevention, in a 1:1 ratio. In a second analysis, patients with a history of major bleeding either treated with LAAO or DOAC were cardinality-matched in a 1:2 ratio. Cardinality matching represents a refinement of propensity score matching that prioritises both balance (minimising differences in covariates between groups) and sample size (retaining the largest possible subset of units that satisfy a predefined level of balance). It explicitly sets constraints on differences in covariates, ensuring that matched groups are highly comparable. Instead of sequentially matching pairs, it solves an optimisation problem to find the best subset of treated and control units. By ensuring good balance across multiple covariates, it helps mitigate confounding and reduce selection bias, making comparisons more reliable.

Endpoints

The study specified a primary combined endpoint of stroke, cardiovascular death or major bleeding.

As secondary endpoints, the individual components of the primary combined endpoint were assessed. Major bleeding was defined according to the International Society of Thrombosis and Hemostasis criteria as either a fatal bleeding, a bleeding in a critical area or organ (e.g. intracranial haemorrhage of any origin) or a bleeding causing a fall of 2 g/dl in haemoglobin levels within 7 days or leading to transfusion of two or more units of whole blood or red blood cells [17]. The supplementary material includes the rate of clinically relevant bleeding events (major bleeding or clinically overt non-major bleeding that either led to hospital admission, required medical or surgical intervention or a change in antithrombotic therapy) in patients treated with DOAC or LAAO.

Ethics

This investigation adhered to the ethical principles laid down in the Declaration of Helsinki. The study protocols for all three cohorts received approval from and can be accessed at the pertinent local ethics committees (Ethikkommission Nordwest- und Zentralschweiz, PB_2016_00793, and Kantonale Ethikkommission Zuerich, 2022-01431) or can be provided by the authors upon request. In the Swiss-AF and Beat-AF cohorts, explicit written informed consent was obtained from every participant. Within the Zurich LAAO Registry, individuals retrospectively included since 2016 granted general consent, acknowledging their willingness for their data to be utilised in research. Notably, for patients enrolled in this registry prior to 2016, the ethics committee (Kantonale Ethikkommission Zuerich, 2022-01431) waived the requirement to obtain informed consent and approved the approach of contacting either the patients or their respective family physicians as part of the follow-up process.

Statistical analysis

The distribution of continuous variables was assessed using density plots. Continuous variables were indicated as median with interquartile range (IQR) and were tested for differences with the student's t-test or the Mann-Whitney U test, according to their distribution. Categorical variables were summarised as counts and percentages and analysed using Pearson's chi-squared test or Fisher's exact test. Long-term outcomes were assessed by constructing cumulative incidence curves. The proportional-hazards assumptions were verified with the use of Schoenfeld residuals. Considering the presence of competing risks that could be related to different risk profiles qualifying for a change in stroke prevention strategy in one group of patients, a Fine-Gray sub distribution hazards model was employed for the primary and secondary endpoints using the *cmprsk* package in R. A two-sided p-value <0.05 was considered statistically significant. R version 4.2 (R Foundation, Vienna, Austria) was used for the statistical analyses and the compilation of graphs.

To compare the various treatment strategies, cardinality matching was employed using the *MatchIt* package in R. The matching covariates for the main analysis examining patients with DOAC score ≥8 as well as for the analysis of patients with prior major bleeding were selected based on their clinical relevance and potential to confound the association of interest and included age, sex, hypertension, diabetes mellitus, dyslipidaemia, the presence of coronary artery disease (CAD), a history of heart failure, a history of stroke or transient ischaemic attack (TIA) as well as the individual CHA_2DS_2-VASc and DOAC scores. The balance of matching characteristics was assessed by estimating standardised mean differences (SMD) between groups. Operationally, the objective was to achieve a standardised mean difference of ≤0.20 to eliminate imbalance in a given variable between the groups. All patients in the included registries undergo annual follow-ups. If a patient was lost to follow-up, the last follow-up response was used only if clinical data were available for endpoint analyses.

Results

Between 2010 and 2017, a total of 3960 patients were included in Beat-AF and Swiss-AF, while between 2010 and 2023, 473 patients received successful LAAO at University Hospital Zurich.

Comparison of patients with direct oral anticoagulation (DOAC) score ≥8

After cardinality matching, 478 atrial fibrillation patients with DOAC score ≥8 were included in the primary analysis (figure 1); 239 atrial fibrillation patients treated with DOAC were compared with 239 atrial fibrillation patients who underwent successful LAAO. The median age of patients was 79.4 (74.9 to 83.0) years and 64% were male. After cardinality matching, baseline characteristics were comparable between groups. The median CHA_2DS_2-VASc score was 5 (4 to 6) in both groups (SMD: 0.0) and the median DOAC score was 9 (8.5 to 10) in the DOAC group and 10 (8 to 10) in the LAAO group (SMD: 0.12). LAAO patients had better left ventricular (LV) function (55% [48 to 60] in the DOAC groups and 58% [53 to 62] in the LAAO group; SMD: 0.424) and renal function, as measured by a clinically irrelevant but statistically significant difference in glomerular filtration rate (53.1 [39.1–60.5] ml/min in the DOAC group and 56.0 [40.0–71.5] ml/min in the LAAO group; SMD: 0.247). There were more patients with previous major bleeding in the LAAO group (15% in the DOAC group versus 75% in the LAAO group; SMD: 1.521). Detailed baseline characteristics in the cohort of patients with a DOAC score ≥8 are summarised in table 1.

Within the LAAO group, combined procedures were performed in 27% of patients (LAAO and concomitant diagnostic angiography in 22%, percutaneous coronary intervention [PCI] in 10%, patent foramen ovale [PFO] closure in 5% or atrial septal defect [ASD] closure in <1%) (table S1). Atrial fibrillation patients in the DOAC group were either started on DOAC or continued their previously prescribed DOAC after study entry. The majority of patients (76%) in the LAAO group received dual antiplatelet therapy for a median of 3 (1–6) months. Lifelong single antiplatelet therapy with either aspirin or clopidogrel monotherapy was chosen for 23% of patients after LAAO. Oral anticoagulation was prescribed in 1% of LAAO patients for various reasons for a median of 4 (2 to 19) months followed by single antiplatelet therapy lifelong.

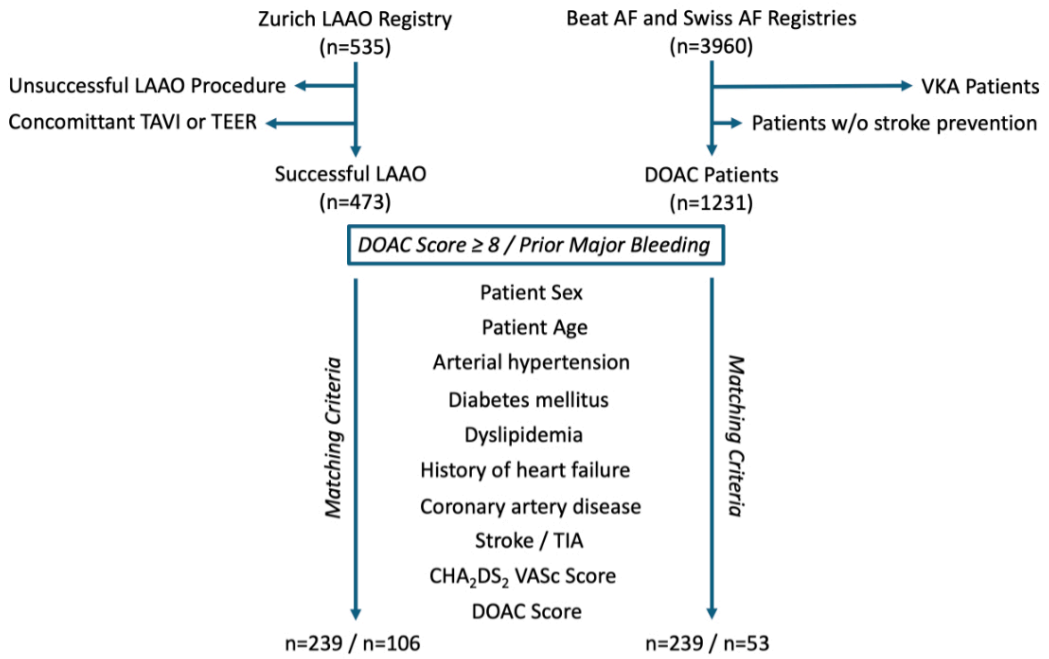
Outcome of patients with a direct oral anticoagulation (DOAC) score ≥8

After a median follow-up time of 4.9 (2.2 to 6.1) years for all patients (5.9 [4.1 to 6.3] years in the DOAC group and 2.9 [1.2 to 5.4] years in the LAAO group), there was no difference in the primary combined endpoint of stroke, cardiovascular death or major bleeding (118 events in the DOAC group and 88 events in the LAAO group; hazard ratio [HR]: 0.88, 95% confidence interval [CI]: 0.67–1.14, p = 0.33; figure 2A) between the matched cohorts of patients anticoagulated with a DOAC versus those who underwent LAAO. While there was no significant difference in the occurrence of stroke (20 in the DOAC group versus 11 in the LAAO group; HR: 0.74, 95% CI: 0.39–1.42, p = 0.36; figure 2B) or cardiovascular death (68 in the DOAC group versus 56 in the LAAO group; HR: 0.97, 95% CI: 0.68–1.38, p = 0.85; figure 2C), a significantly lower rate of major bleeding events (38 in the DOAC group versus 21 in the LAAO group; HR: 0.55, 95% CI: 0.32–0.94, p = 0.029; figure 2D) and a significantly lower rate of clinically relevant bleedings (79 in the DOAC group versus 50 in the LAAO group; HR: 0.70, 95% CI: 0.50–0.99, p = 0.048; supplementary material, figure S1) was demonstrated in the LAAO group.

Comparison of patients with previous major bleeding

Following the matching process using the same matching criteria as outlined in the "Methods" section, 53 atrial fibrillation patients with previous major bleeding managed

Figure 1: Flowchart on patient matching of the two groups (direct oral anticoagulation [DOAC] score ≥8 and Prior Major Bleeding) using the MatchIt package in R (R Foundation, Vienna, Austria). AF: atrial fibrillation; LAAO: left atrial appendage occlusion; TAVI: transcatheter aortic valve implantation; TEER: transcatheter edge-to-edge-repair; TIA: transient ischaemic attack; VKA: vitamin K antagonist.



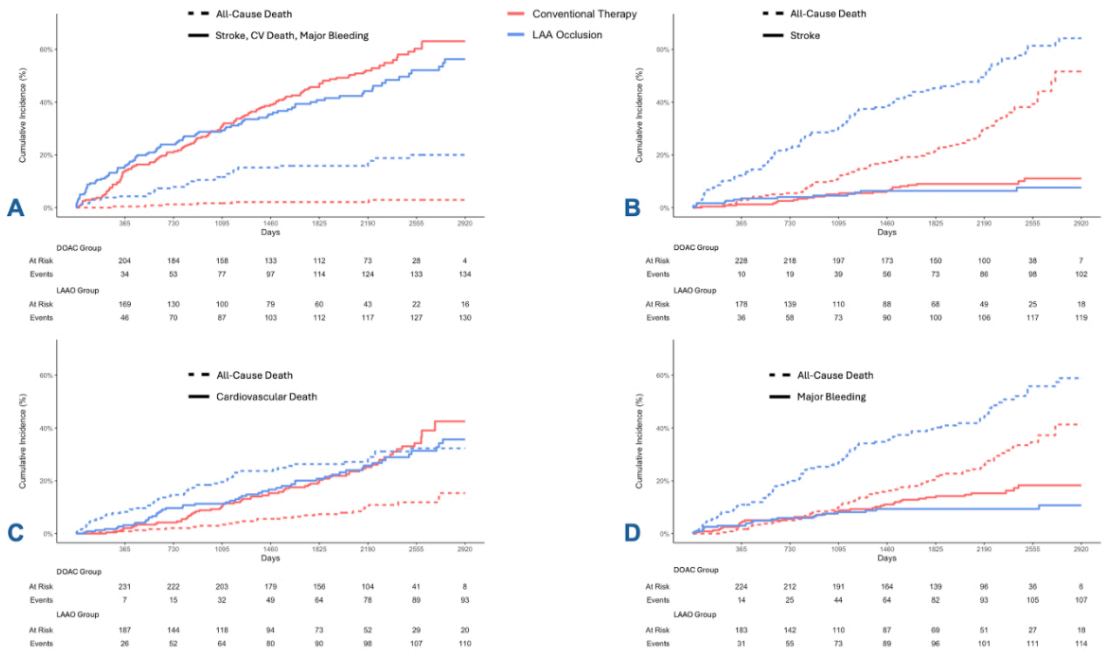
with conventional stroke prevention using DOAC were compared to 106 atrial fibrillation patients with previous major bleeding who underwent successful LAAO. The median age of patients was 74.0 (69.0 to 79.0) years and 63% were male. Baseline characteristics including stroke risk and estimated bleeding risk under DOAC were comparable in both groups. The median CHA_2DS_2-VASc score was 4 (2 to 5) in the DOAC group and 4 (3 to 5) in the LAAO group (SMD: 0.177) and the median DOAC score was 9 (7 to 10) in both groups (SMD: 0.047). Persistent or permanent atrial fibrillation was more commonly documented in patients in the DOAC group (59% in the DOAC group

Table 1:
Baseline characteristics of matched patients with a direct oral anticoagulation (DOAC) score of ≥8 who were either treated with DOAC or with left atrial appendage occlusion (LAAO). Values are reported in n (%) or median (IQR).

Characteristic	All (n = 478)	DOAC (n = 239)	LAAO (n = 239)	SMD
Age (years)	79.4 (74.9–83.0)	79.3 (74.8–82.8)	80.0 (75.5–83.0)	0.093
Male sex (%)	307 (64.2)	154 (64.4)	153 (64.0)	0.009
BMI (kg/m²)	26.3 (23.6–29.2)	26.8 (23.7–29.7)	26.1 (23.5–28.7)	0.152
Hypertension (%)	401 (83.9)	197 (82.4)	204 (85.4)	0.08
Diabetes mellitus (%)	135 (28.2)	63 (26.4)	72 (30.1)	0.084
Dyslipidaemia (%)	245 (51.3)	115 (48.1)	130 (54.4)	0.126
Coronary artery disease (%)	167 (34.9)	78 (32.6)	89 (37.2)	0.097
Previous myocardial infarction (%)	85 (17.8)	41 (17.2)	44 (18.4)	0.033
Previous percutaneous coronary intervention (%)	115 (24.1)	49 (20.5)	66 (27.6)	0.167
Previous coronary artery bypass grafting (%)	44 (9.2)	27 (11.3)	17 (7.1)	0.145
Congestive heart failure (%)	125 (26.2)	62 (25.9)	63 (26.4)	0.01
Previous stroke or transient ischaemic attack (%)	163 (34.1)	79 (33.1)	84 (35.1)	0.044
Previous systemic embolisation (%)	23 (4.8)	15 (6.3)	8 (3.3)	0.137
Paroxysmal atrial fibrillation (%)	259 (54.2)	124 (51.9)	135 (56.5)	0.092
Persistent or permanent atrial fibrillation (%)	219 (45.8)	115 (48.1)	104 (43.5)	0.092
Previous major bleeding (%)	216 (45.2)	36 (15.1)	180 (75.3)	1.521
CHA_2DS_2 VASc score	5 (4–6)	5 (4–6)	5 (4–6)	0.0
DOAC score	10 (8–10)	9 (8.5–10)	10 (8–10)	0.12
HAS BLED score	3 (2–4)	2 (2–3)	4 (3–4)	1.8
Creatinine (µmol/l)	104 (85.0–129.0)	108 (93.0–130.3)	97 (78.0–125.0)	0.332
GFR (ml/min)	54.7 (39.2–65.0)	53.1 (39.1–60.5)	56.0 (40.0–71.5)	0.247
LVEF (%)	58.0 (51.3–62.0)	55.0 (48.0–60.0)	58.0 (53.0–62.0)	0.424
Left atrium size (mm)	45.0 (40.0–50.0)	44.5 (40.0–50.0)	45.0 (40.0–51.0)	0.064

BMI: body mass index; GFR: glomerular filtration rate; LVEF: left ventricular ejection fraction; SMD: standardised mean difference.

Figure 2: Cumulative incidence curves on long-term outcome of patients with a direct oral anticoagulation (DOAC) score≥8 treated either with DOAC or with left atrial appendage occlusion (LAAO). While there was no significant difference in the combined endpoint of stroke, cardiovascular (CV) death and major bleeding ([A] HR: 0.88, 95% CI: 0.67–1.14, p = 0.33) and no significant difference in the stroke rate ([B] HR: 0.74, 95% CI: 0.39–1.42, p = 0.36) or in the rate of cardiovascular death ([C] HR: 0.97, 95% CI: 0.68–1.38, p = 0.85), patients with LAAO experienced significantly fewer major bleeding events during follow-up ([D] HR: 0.55, 95% CI: 0.32–0.94, p = 0.029). LAA: left atrial appendage.



versus 42% in the LAAO group; SMD: 0.364). Although coronary artery disease was equally distributed among both groups (SMD: 0.102), as was previous myocardial infarction (SMD: 0.119), there were more patients with previous percutaneous coronary intervention in the LAAO group (9% vs 21%; SMD: 0.32) and more patients with prior coronary artery bypass grafting (CABG) in the DOAC group (15% vs 3%; SMD: 0.44). LAAO patients had slightly worse left ventricular function (60% [56 to 65] in the DOAC group and 58% [52 to 62] in the LAAO group; SMD: 0.392). Renal function was slightly better in the LAAO group as measured by a glomerular filtration rate of 55.6 (44.7 to 64.6) ml/min in the DOAC group versus 65.0 (45.0 to 83.3) ml/min in the LAAO group (SMD: 0.419). Detailed baseline characteristics of patients with previous major bleeding are summarised in table 2. Within the LAAO group, 22% of patients underwent a combined procedure of LAAO and either concomitant diagnostic angiography (19%), percutaneous coronary intervention (7%) or patent foramen ovale closure (4%) (table S2).

Outcome of patients with previous major bleeding

When comparing the matched cohorts of patients with a history of major bleeding, after a median follow-up time of 4.4 (2.0 to 6.0) years for all patients (5.9 [4.3 to 6.0] years in the DOAC group and 3.2 [1.5 to 6.0] years in the LAAO group), there was no significant difference regarding the primary composite endpoint of stroke, cardiovascular death or major bleeding (31 events in 53 DOAC patients versus 29 events in 106 LAAO patients; HR: 0.79, 95% CI: 0.50–1.27, p = 0.33; figure 3A). There were no significant differences between the two groups in the occurrence of stroke (2 strokes in 53 DOAC patients and 6 strokes in 106 LAAO patients; HR: 1.09, 95% CI: 0.33–3.62, p = 0.89; figure 3B) or cardiovascular death (17 cardiovascular deaths in 53 DOAC patients and 15 cardiovascular deaths in 106 LAAO patients; HR: 0.91, 95% CI: 0.50–1.64, p = 0.74; figure 3C). However, the LAAO group had a significantly lower rate of major bleeding events (12 in 53 DOAC patients versus 8 in 106 LAAO patients; HR: 0.32, 95% CI: 0.13–0.79, p = 0.013; figure 3D) and a significantly lower rate of clinically relevant bleedings (21 in 53 DOAC patients versus 21 in 106 LAAO patients; HR: 0.45, 95% CI: 0.24–0.83, p = 0.01; supplementary material, figure S2).

Discussion

This study demonstrates that atrial fibrillation patients with an indication for stroke prevention and a high or very high bleeding risk according to a direct oral anticoagulation (DOAC) score of ≥8 or a history of major bleeding have lower rates of major bleeding events and similar rates of cardiovascular death and stroke at long-term follow-up when treated with left atrial appendage occlusion (LAAO) as compared to a DOAC.

Current guidelines recommend to only treat patients with LAAO if they have absolute contraindications to oral anticoagulation [1, 18]. While the European Society of Cardiology limits the indication for LAAO to patients with a history of major bleeding events with an irreversible cause (ESC Class IIb recommendation) [2], the American guidelines add recurrent falls as another potential contraindication to oral anticoagulation (ACC/AHA/ACCP/HRS Class IIa recommendation) [18]. Generally, the definition of contraindication to oral anticoagulation in the literature remains blurry. The ASAP-TOO study required a shared de-

Table 2:
Baseline characteristics of matched patients with prior major bleeding who were either treated with direct oral anticoagulation (DOAC) or with left atrial appendage occlusion (LAAO). Values are reported in n (%) or median (IQR).

Characteristic	All (n = 159)	DOAC (n = 53)	LAAO (n = 106)	SMD
Age (years)	74.0 (69.0–79.0)	75.0 (69.5–78.3)	74.0 (69.0–79.0)	0.038
Male sex (%)	100 (62.9)	32 (60.4)	68 (64.2)	0.078
BMI (kg/m²)	26.5 (23.5–30.1)	27.2 (23.9–30.1)	26.4 (23.5–30.1)	0.084
Hypertension (%)	126 (79.2)	41 (77.4)	85 (80.2)	0.069
Diabetes mellitus (%)	40 (25.2)	12 (22.6)	28 (26.4)	0.088
Dyslipidaemia (%)	78 (49.1)	27 (51.0)	52 (49.1)	0.038
Coronary artery disease (%)	50 (31.4)	15 (28.3)	35 (33.0)	0.102
Previous myocardial infarction (%)	17 (10.7)	7 (13.2)	10 (9.4)	0.119
Previous percutaneous coronary intervention (%)	27 (17.0)	5 (9.4)	22 (20.8)	0.32
Previous coronary artery bypass grafting (%)	11 (6.9)	8 (15.1)	3 (2.8)	0.44
Congestive heart failure (%)	45 (28.3)	14 (26.4)	31 (29.2)	0.063
Previous stroke or transient ischaemic attack (%)	25 (15.7)	7 (13.2)	18 (17.0)	0.106
Previous systemic embolisation (%)	5 (3.1)	3 (5.7)	2 (1.9)	0.199
Paroxysmal atrial fibrillation (%)	85 (53.5)	22 (41.5)	63 (59.4)	0.364
Persistent or permanent atrial fibrillation (%)	74 (46.5)	31 (58.5)	43 (40.6)	0.364
Previous major bleeding (%)	159 (100.0)	53 (100.0)	106 (100.0)	NA
CHA_2DS_2 VASc score	4.0 (3.0–5.0)	4.0 (2.0–5.0)	4.0 (3.0–5.0)	0.177
DOAC score	9.0 (7.0–10.0)	9.0 (7.0–10.0)	9.0 (7.3–10.0)	0.047
HAS BLED score	3.0 (3.0–4.0)	3.0 (2.0–3.0)	3.0 (3.0–4.0)	0.9
Creatinine (µmol/l)	93 (78.0–119.0)	104 (84.5–125.5)	90.5 (75.3–115.0)	0.37
GFR (ml/min)	60.8 (45.0–79.0)	55.6 (44.7–64.6)	65.0 (45.0–83.3)	0.419
LVEF (%)	58.5 (51.8–62.0)	60.0 (55.5–65.0)	58.0 (52.0–62.0)	0.392
Left atrium size (mm)	44.0 (40.0–49.0)	43.0 (40.0–46.0)	45.0 (40.5–49.5)	0.353

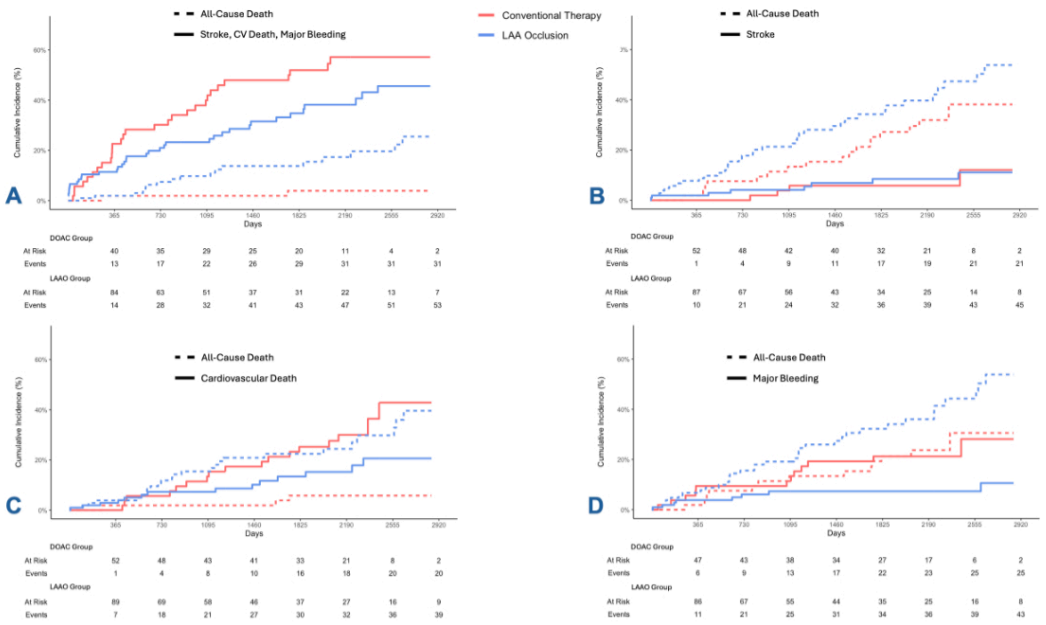
BMI: body mass index; GFR: glomerular filtration rate; LVEF: left ventricular ejection fraction; SMD: standardised mean difference.

cision by two physicians that a patient was deemed unsuitable for oral anticoagulation based on a history of bleeding, blood dyscrasia and falls or other reasons to be defined as contraindicated [12]. Similarly, consensus papers written by LAAO experts but also by non-interventional cardiologists recommend a more liberal indication for LAAO including atrial fibrillation patients with recurrent bleeding events on oral anticoagulation, patients with severely reduced renal function, patients with haemophilia, very frail patients with an elevated risk of falls or a history of recurrent falls, and also taking into consideration a patient's wish to avoid oral anticoagulation [14, 19].

Bleeding risk scores have been established to predict a patient's risk of major bleeding events. Comparing them to the risk of thromboembolism in atrial fibrillation patients is the challenge for the treating physician balancing both risks and deciding on the optimal stroke prevention strategy. As DOACs have replaced vitamin K antagonists during the last ten years owing to their lower risk of major bleeding [20–23], the DOAC score was recently established for more accurate bleeding prediction in the current era [16]. A score of 8 or 9 is assigned a high bleeding risk (5–9.99% per year) and a maximum score of 10 a very high bleeding risk (≥10% per year). A history of major bleeding on oral anticoagulation represents an important criterion in all available bleeding risk scores and is the most common indication for LAAO in current practice [16, 24].

As LAAO is already accepted as a valid stroke prevention strategy, at least in patients with contraindications to oral anticoagulation despite a lack of randomised data on that topic [1, 2], new randomised controlled trials (RCTs) involving such patients are hard to perform. After premature termination of ASAP-TOO, it is unlikely that there will be an RCT enrolling patients with contraindications to oral anticoagulation in the near future. The only published RCT comparing LAAO to DOAC therapy showed that stroke prevention with LAAO resulted in similar stroke rates but significantly fewer bleeding complications after four years of follow-up [7]. While in the respective study by Osmancik et al., patients with high bleeding risk or patients with prior clinically relevant bleeding were included, only half of patients had a history of previous bleeding requiring intervention or hospitalisation. The number of patients with previous major bleeding according to the ISTH criteria is unknown in that study but expected to be low [17]. Furthermore, an important part of the inclusion criteria of that study was the HAS BLED score, which based its prognostic value for the estimation of major bleeding events on patients treated with a vitamin K antagonist [25]. Therefore, the degree of (estimated) bleeding risk of patients included in the study by Osmancik et al. remains somewhat speculative [7]. As matched comparisons represent the second-highest grade of evidence after randomised controlled data, the current study provides important and reassuring evidence on stroke prevention using LAAO in atrial fibrillation patients with high or very high bleeding risk. While stroke reduction by LAAO was not significantly better than that by DOACs in both cohorts (DOAC score ≥8 and history of major bleeds), there was a numerically smaller stroke rate after LAAO by almost 50% and 30%, respectively. Hence, closing the left atrial appendage for stroke prevention in atrial fibrillation may not be a must compared to DOACs but it certainly looks attractive and should be elevated at least to the level of DOACs in the guidelines, because of the significantly reduced bleeding risk.

Figure 3: Cumulative incidence curves on long-term outcome of patients with previous major bleedingtreated either with direct oral anticoagulation (DOAC) or with left atrial appendage occlusion (LAAO). While there was no significant difference in the combined endpoint of stroke, cardiovascular (CV) death and major bleeding ([A] HR: 0.79, 95% CI: 0.50–1.27, p = 0.33) and no significant difference in the stroke rate ([B] HR: 1.09, 95% CI: 0.33–3.62, p = 0.89) or in the rate of cardiovascular death ([C] HR: 0.91, 95% CI: 0.50–1.64, p = 0.74), patients with LAAO experienced significantly fewer major bleeding events during follow-up ([D] HR: 0.32, 95% CI: 0.13–0.79, p = 0.013). LAA: left atrial appendage.



Previous propensity score-matched studies by Gloekler et al., Nielsen-Kudsk et al., Elsheikh et al. and our group also showed favourable results of LAAO in comparison to oral anticoagulation [9, 10, 26, 27]. However, both vitamin K antagonists and DOAC were used in the control group of the study by Gloekler et al. and all four studies focused primarily on patients with high stroke risk but not specifically on patients at highest risk of bleeding [9, 10, 26, 27]. Our first comparison between atrial fibrillation patients treated either conventionally or with LAAO also included patients from the Zurich LAAO Registry as well as from the Beat-AF and Swiss-AF cohort studies [27]. Only 50% of patients in the control group received DOAC therapy, 42% were treated with a vitamin K antagonist and 8% did not receive any stroke prevention [27]. While the first paper focused on secondary stroke prevention and a patient population with highest stroke risk in general, the present paper focused on a population with highest bleeding risk requiring different matching criteria and only patients treated with DOACs, the current standard of oral anticoagulation for most patients, were included in the control group for analysis.

Besides the obvious benefits of LAAO compared to oral anticoagulation in atrial fibrillation-related stroke prevention representing a one-time procedure obviating the risk associated with medication malcompliance, critical factors contributing to the relatively limited adoption of LAAO are its potential periprocedural risks, device-related complications and the challenge associated with antithrombotic therapy post-LAAO [28]. The optimal regimen for antiaggregation, the duration and individualised protocols have not been well established, leading to uncertainty and hesitancy among clinicians. This underscores the need for further research in this area to define recommendations for post-LAAO antithrombotic therapy. Based on the curves in figures 2D and 3D, the present study did not show any significant rise in bleeding events during the first three months following LAAO, the time when the vast majority of LAAO patients was on dual antiplatelet therapy. This adds to the encouraging literature about dual antiplatelet therapy being safe in patients with previous bleeding events under oral anticoagulation [29]. Alternative antithrombotic medication protocols like half-dose DOAC have been tested with promising results [30]. Single antiplatelet therapy following LAAO has been used in a few cases in our registry and also worldwide. Data on the routine implementation of single antiplatelet therapy, however, are lacking, although from a pathophysiological perspective single antiplatelet therapy could have its justification and could potentially minimise bleeding rates even more. An RCT comparing the different protocols will be needed to clarify the optimal antithrombotic strategy post-LAAO.

Medication-based alternatives to DOAC and LAAO for atrial fibrillation patients with elevated bleeding risk, namely factor XI inhibitors, are being studied but despite their promising theoretical pharmacological effects, the OCEANIC-AF study (NCT05643573), the first RCT comparing this novel anticoagulation agent to DOAC, was prematurely terminated due to inferior efficacy with regards to thromboembolic protection [31].

Limitations and strengths

This is a non-randomised comparison. Despite matching, there is residual confounding probably due to a selection bias, reflected by the significantly higher all-cause mortality rates in the LAAO group compared to the DOAC group (represented by the dotted lines in figures 2 and 3). This shows that patients currently referred for LAAO may represent an extremely high-risk group, often due to comorbidities that also increase their risk of bleeding events which could be supported by the observation of many more cancer-related deaths and more deaths from infection or sepsis in the LAAO group (list of non-cardiovascular mortality causes in supplementary material). Risk scores like the CHA_2DS_2 VASc and the DOAC scores are imperfect matching parameters [16, 32]. Although they help in estimating the likelihood of a certain event, they do not represent measurable characteristics. To compensate for this, a large number of measurable baseline characteristics was chosen for the matching process. However, despite adequate matching, the real bleeding risk, at least in the analysis of patients with a high DOAC score, is likely to be higher in the LAAO group as it included many more patients with a history of major bleeding. Although outdated in the current DOAC era and therefore not a matching criterion, the HAS BLED score, a more traditional risk score estimating the risk of major bleeding events in atrial fibrillation patients when treated with a vitamin K antagonist, is significantly higher in both LAAO groups [25]. This, however, highlights the potential of LAAO in such high-risk populations as the bleeding rates at follow-up are still significantly lower among the patients treated with LAAO in both analyses. Although a success rate of LAAO of around 98% is reported in the current literature [33], which corresponds to results in the Zurich LAAO Registry [15], only successful LAAO procedures were included in the current study which represents another limitation.

Strengths of the study include the observational design allowing a broader and more inclusive patient population, thus offering valuable insights into the real-world utilisation of LAAO, and the long-term follow-up. Nevertheless, based on the nature of this study it needs to be highlighted that retrospective studies can only provide hypothesis-generating results and are not intended to provide definitive evidence.

Conclusion

In patients with atrial fibrillation and a high bleeding risk and in patients with a history of major bleeding, percutaneous LAAO may provide similar stroke prevention and a reduced risk of bleeding on long-term follow-up compared to DOAC therapy. Acknowledging the still-lacking RCTs to confirm these hypotheses-generating data, to LAAO as first-line stroke protection in patients with atrial fibrillation, at least in patients with a life expectancy of 5 years or more.

Data sharing statement

As this study contains large raw patient data of three different cohorts including multiple parameters not relevant to this manuscript, the authors were granted access to the requested information necessary for the production of the

current analysis from the responsible study board. Access to the deidentified patient data from all three cohorts used for matching can be granted by the corresponding author upon request.

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Appendix

Supplementary Tables:

Table S1: List of combined procedures included in the LAAO group of patients with DOAC score of ≥ 8.

Procedure N (%)	**LAAO** (N=239)
All Combined LAAO Procedures	65 (27.2)
Combined LAAO + Coro	52 (21.8)
Combined LAAO + PCI	23 (9.6)
Combined LAAO + PFO-Closure	12 (5.0)
Combined LAAO + ASD-Closure	1 (0.4)

LAAO = left atrial appendage occlusion; Coro = coronary angiography; PCI = percutaneous coronary intervention; PFO = patent foramen ovale; ASD = atrial septal defect.

Table S2: List of combined procedures included in the LAAO group of patients with prior major bleeding.

Procedure N (%)	**LAAO** (N=106)
All Combined LAAO Procedures	24 (22.6)
Combined LAAO + Coro	20 (18.9)
Combined LAAO + PCI	7 (6.6)
Combined LAAO + PFO-Closure	4 (3.8)

LAAO = left atrial appendage occlusion; Coro = coronary angiography; PCI = percutaneous coronary intervention; PFO = patent foramen ovale.

Supplementary Figures:

Figure S1: Rate of clinically relevant bleeding events in patients with DOAC score of ≥ 8 treated either with DOAC or with LAAO. Patients treated with LAAO experienced significantly fewer clinically relevant bleeding events during follow-up (HR 0.70, CI 95%: 0.50 to 0.99, p=0.048).

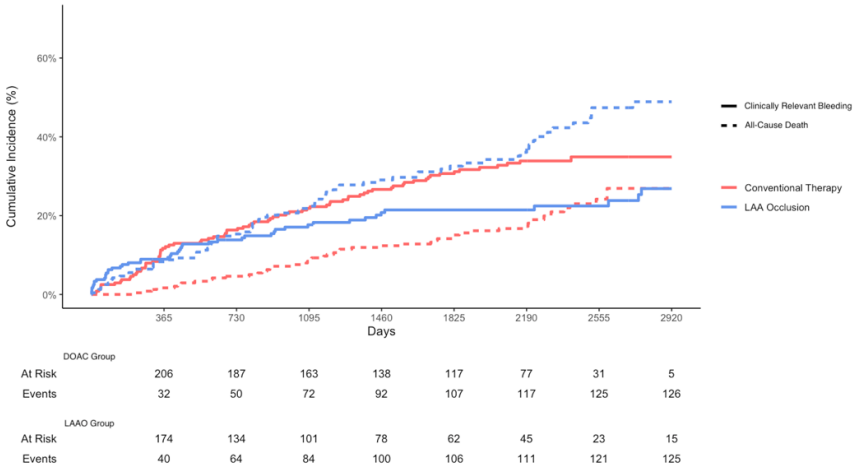
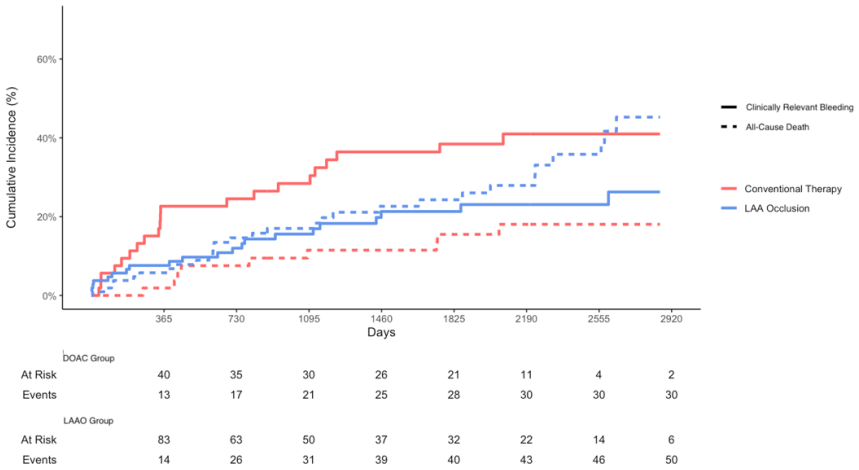


Figure S2: Rate of clinically relevant bleeding events in patients with previous major bleeding treated either with DOAC or with LAAO. Patients treated with LAAO experienced significantly fewer clinically relevant bleeding events during follow-up (HR 0.45, CI 95%: 0.24 to 0.83, p=0.01).



Lists of non-CV mortality causes:

Non-CV mortality causes in patients with DOAC score of ≥ 8:

	DOAC (n=25)	LAAO (n=58)
Cancer (n)	8	13
Infection/sepsis (n)	6	16
Renal failure (n)	1	3
Respiratory failure (n)	4	3
Accident or trauma (n)	1	5
COVID (n)	1	3
Fatal bleeding (n)	0	7
Suicide (n)	0	1
Other (n)	4	6

Non-CV mortality causes in patients with previous major bleeding:

	DOAC (n=3)	LAAO (n=25)
Cancer (n)	1	7
Infection/sepsis (n)	1	7
Renal failure (n)	1	1
Respiratory failure (n)	0	1
Accident or trauma (n)	0	1
COVID (n)	0	4
Fatal bleeding (n)	0	1
Other (n)	0	3