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Clinical outcomes of left atrial appendage occlusion versus direct oral anticoagulation in patients with atrial fibrillation and prior ischemic stroke: A propensity-score matched study

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ABSTRACT

Background: This propensity-score matched study investigated clinical outcomes associated with left atrial appendage occlusion (LAAO) versus direct oral anticoagulation (DOAC) in patients with AF and prior ischemic stroke.

Methods: AF patients enrolled in the Amulet Observational Study with a history of ischemic stroke and successful LAAO ($n = 299$) were compared with a propensity-score matched cohort of incident AF patients with prior ischemic stroke and treated by DOAC ($n = 301$). The control cohort was identified through the Danish National Patient Registries. Propensity score matching was based on covariates of the CHA_2DS_2-VASc and HAS-BLED scores, with a 1:2 ratio and using Greedy 5:1 digit matching with replacement. The analysis included 2-years follow-up, with a primary composite outcome of ischemic stroke, major bleeding (BARC $\geq$ 3) or all-cause mortality.

Results: Mean (SD) CHA_2DS_2-VASc scores were 5.26 (1.42) and 5.40 (1.31) and HAS-BLED scores were 3.95 (0.91) and 4.03 (0.96), for the LAAO and DOAC group, respectively.

Total number of primary composite outcome events were 61 (12.4 events/100 patient-years) and 117 (26.9 events/100 patient-years) in the LAAO and DOAC group, respectively. Risk of the primary composite outcome was significantly lower in the LAAO group, hazard rate ratio [HR] 0.48 (95% CI: 0.35–0.65).

Ischemic stroke risk was comparable, HR 0.71 (95% CI: 0.34–1.45), while risk of major bleeding, HR 0.41 (95% CI: 0.25–0.67), and all-cause mortality, HR 0.48 (95% CI: 0.32–0.71), were significantly lower with LAAO. Cardiovascular mortality did not differ statistically between the LAAO and DOAC group, HR 0.75 (95% CI: 0.39–1.42). Results were consistent across sensitivity analyses.

Conclusion: This study indicated significantly lower risk of the composite outcome of stroke, major bleeding and all-cause mortality with LAAO therapy compared to DOAC, in patients with AF and prior stroke. The stroke prevention effectiveness appeared similar, with a significantly lower risk of major bleeding events with LAAO. The suggested clinical benefit of LAAO over DOAC require confirmation in the ongoing randomized OCCLUSION-AF trial.

Abbreviations: AF, Atrial fibrillation; DOAC, Direct-oral anticoagulation; LAA, Left atrial appendage; LAAO, Left atrial appendage occlusion.

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1. Introduction

Stroke is one of the leading causes of morbidity and mortality in atrial fibrillation (AF) [1]. Overall, AF increases the risk of stroke 5-fold, and up to 25% of all ischemic strokes are related to AF [1]. Prior ischemic stroke is the strongest predictor for stroke recurrence [2]. Additionally, patients with prior stroke carry a significantly higher risk of major adverse bleeding events and intracranial bleeding compared to patients without prior stroke [3–6]. Bleeding during anticoagulation is associated with a higher risk of death in AF [7,8].

The causative role of the left atrial appendage (LAA) in AF-related stroke was recently emphasized by the LAAOS III trial, demonstrating superiority of surgical LAA ligation combined with anticoagulation over anticoagulation alone in AF-patients undergoing heart surgery [9]. Surgical LAA occlusion (LAAO) resulted in a 33% relative risk reduction for the endpoint of stroke or systemic embolism, with an absolute risk reduction of 2.2% [9]. Although not designed to investigate patients with prior stroke, a percutaneous approach or subsequent termination of anticoagulation, LAAOS III confirmed that the LAA plays a significant role in thromboembolic stroke.

Percutaneous LAAO with the Watchman device (Boston Scientific, Marlborough, Massachusetts) has demonstrated non-inferiority compared to warfarin in prevention of stroke, systemic embolism, and cardiovascular death [10]. The Amplatzer™ Amulet™ device has shown similar results [11], but comparative data on safety and efficacy of LAAO compared to direct oral anticoagulation (DOAC) are sparse [12,13], particularly in secondary prevention of AF-patients with prior ischemic stroke. These patients could potentially have a particular high net-clinical benefit from LAAO due to their markedly higher risk of both ischemic and hemorrhagic events. This study was designed to investigate the clinical outcomes associated with LAAO versus DOAC in patients with AF and a prior ischemic stroke, based on a propensity-score matched analysis including data from the Amulet Observational Study [14] and a matched control cohort from the Danish National Patient Registries.

2. Methods

2.1. Study design

A cohort study of AF patients enrolled in the Amulet Observational Study (n = 1088) having a history of ischemic stroke and technically successful treatment by LAAO (n = 299). Clinical outcomes were compared with a propensity score-matched control cohort of patients with incident AF, history of ischemic stroke and treated by DOAC.

All patients provided informed consent prior to enrolment in the Amulet Observational Study, which was approved by local ethics committees. No informed written consent or permission from ethics committee are required for register-based studies in Denmark.

2.1.1. Study population

The LAAO cohort consisted of patients with paroxysmal, persistent, or permanent AF enrolled in the global Amulet Observational Study between 2015 and 2016 (n = 1088) and treated with technically successful LAAO by use of the Amplatzer Amulet device (n = 1078). Technical success was defined as successful implantation of the Amulet device in the LAA [14,15]. Patients with evidence of intracardiac thrombus on preprocedural imaging, active infection or endocarditis, and LAA anatomy not accommodating a device according to sizing guidelines were excluded from the Amulet Observational Study. The present study was restricted to patients with a history of ischemic stroke (n = 299).

The DOAC control cohort was identified through the Danish National Patient Registry and the Danish National Prescription Registry comprising nationwide patient-level information on all hospital admissions and outpatient visits since 1977, along with filled and reimbursed prescriptions. The control cohort was sampled from incident AF cases diagnosed between 2013 and 2015 (n = 26,725), with a history of ischemic stroke and initiating treatment with any DOAC after diagnosis (n = 3518).

After propensity-score matching based on each of the individual covariates in the CHA_2DS_2-VASc *(congestive heart failure, hypertension, age, diabetes mellitus, ischemic stroke or transient ischemic attack, vascular disease, sex)* and HAS-BLED score *(hypertension, abnormal renal or liver function, ischemic or hemorrhagic stroke, bleeding, labile international normalized ratio, elderly, drugs or alcohol)* the LAAO cohort comprised of 286 patients and the DOAC cohort of 301 patients for the primary outcome analysis (Fig. 1).

2.1.2. Study follow-up

The LAAO cohort was followed from time of LAAO with study visits at 3-, 6-, 12- and 24-months.

Patients in the DOAC cohort were followed from first redeemed prescription after AF diagnosis, with follow-up through the Danish National Patient Registry [16,17] (stroke, bleeding), the Civil Registration System [18] (mortality) and the National Causes of Death Registry [19].

For the primary analysis, patients were censored at time of first event or at end of follow-up 2-years after either LAAO or initiation of DOAC therapy. In case of an event, patients continued follow-up up to 2-years after inclusion to account for potential subsequent events in the secondary outcome analyses of individual endpoints.

2.1.3. Clinical outcomes

The primary outcome was a composite of ischemic stroke, systemic embolism, major bleeding (Bleeding Academic Research Consortium $\geq$ 3) [20], or all-cause mortality. Secondary outcomes included each of the individual endpoints of the primary composite outcome, along with cardiovascular death, hemorrhagic stroke, and adherence to DOAC. Endpoints were defined according to the Munich consensus document on definitions, endpoints, and data collection requirements for LAAO studies [15]. For the DOAC cohort, major bleeding was defined as an acute hospital admission with a bleeding diagnosis. Definitions of outcomes are provided in Supplemental Table 1.

DOAC discontinuation was defined as >60 days without drug estimated by calculating the cumulative daily defined dosages (DDD) as well as the gaps between the date of expected last available DDD and the date of the next reimbursed prescription if any. The beginning of first gap plus 60 days was set as time of discontinuation.

2.2. Statistics

Propensity score matching of patients was done in a 1:2 ratio using Greedy 5:1 digit matching with replacement. The propensity score was calculated for each patient based on the CHA_2DS_2-VASc score, HAS-BLED score, and each of the separate covariates of the scores. Each patient in the DOAC group was assigned a weight according to the number of matches and to ensure sum of weights equal to number of patients. Balance was assessed by visual inspection of weighted centiles of the propensity scores and the weighted distributions of applied confounders. Distribution of propensity scores before and after matching are illustrated in Supplemental fig. 1.

Cox proportional hazard regression was used to compare the primary outcome between LAAO and DOAC with administrative censoring after 2-years follow-up. The cumulative incidence was estimated by the Kaplan-Meier estimator as well as the number of events and annualized event rates. Hazard rate ratios (HRs) were calculated from Cox regression. Cumulative incidence of secondary outcomes was analyzed by the Aalen-Johansen estimator. For ischemic stroke and major bleeding, all-cause death was considered a competing event, while for cardiovascular death, other causes of death were treated as competing events. Throughout analyses, subjects were weighted according to the matching procedure. Event rates, cumulative incidences, and HRs were presented

with 95% confidence intervals (CIs). Time to discontinuation of DOAC analysis was conducted for the DOAC population using the Aalen-Johansen estimator, with death, LAAO, and major bleeding as competing events. Data analysis was performed using STATA 16 (StataCorp, College Station, Texas).

2.2.1. Sensitivity analyses

Sensitivity analyses were performed to assess the robustness of the primary analyses. The risk of bleeding and adverse events is most pronounced in the early months after diagnosis and treatment initiation [21]. Therefore, a sensitivity analysis with additional propensity-score matching was restricted to patients who adhered to DOAC for a minimum of 60 days following first prescription, and without bleeding in this period. Furthermore, ischemic stroke while on oral anticoagulation treatment carry a substantially higher risk of stroke recurrence [22] which was adjusted for in a sensitivity analysis matching for whether the baseline stroke occurred on oral anticoagulation. Furthermore, an additional sensitivity analysis was done by excluding all patients in the DOAC cohort with a history of cancer at baseline, as it may influence prognosis. Finally, time from stroke until LAAO or DOAC treatment was adjusted for in a sensitivity analysis. All sensitivity analyses assessed the same primary outcome.

3. Results

The mean age was 76 years, with comparable CHA_2DS_2-VASc (5.26 vs 5.40) and HAS-BLED score (3.95 vs 4.03) for the LAAO and DOAC cohort. Further patient characteristics after matching are summarized in Table 1. Comorbidity appeared well-balanced after propensity score matching, however, stroke while on oral anticoagulation and prior coronary revascularization was more prevalent in the LAAO cohort, whereas chronic obstructive pulmonary disease was more prevalent in the DOAC cohort. In the LAAO cohort, patients were discharged after the procedure on single antiplatelet therapy in 116 (39%), dual antiplatelet therapy in 150 (50%), oral anticoagulation in 20 (7%) and other regimens in 13 (4%). At 3 months, single antiplatelet therapy was used by 174 (58%), dual antiplatelet therapy by 67 (22%) and oral anticoagulation in 28 (9.4%). After 6 months, 193 (65%) were on single antiplatelet therapy, 54 (17%) on dual antiplatelet therapy and 28 (9.4%) on anticoagulation therapy.

Table 1
Baseline characteristics

	LAAO cohort	DOAC cohort
	N = 286	*N* = 301
Age in years, median (IQR)	76.0 (71–81)	76.4 (69–82)
Male gender	189 (66.4%)	202 (67.2%)
Hypertension	232 (81.5%)	261 (86.8%)
Congestive heart failure	40 (13.9%)	41 (13.7%)
Diabetes mellitus	75 (26.2%)	93 (31%)
Vascular disease	96 (33.6%)	104 (34.7%)
Abnormal renal function	27 (9.4%)	33 (10.9%)
Abnormal liver function	7 (2.4%)	10 (3.2%)
Prior bleeding	222 (77.6%)	238 (79.1%)
Antiplatelet/NSAID use	85 (29.7%)	101 (33.7%)
Alcohol use	14 (4.9%)	15 (4.9%)
Prior myocardial infarction	43 (15.0%)	80 (26.7%)
Known CAD	77 (26.9%)	84 (28.2%)
Prior CABG/PCI	67 (23.1%)	33 (11.1%)
Peripheral vascular disease	45 (15.7%)	53 (17.6%)
Prior carotid artery intervention	10 (3.5%)	9 (3.1%)
COPD	22 (7.7%)	65 (21.5%)
Ischemic stroke on OAC	116 (40.9%)	53 (17.6%)
Years between stroke and LAAO/NOAC, median (IQR)	0.63 (0.24–2.4)	0.13 (0.01–3.9)
CHA2DS2-VASc score, mean (SD)	5.26 (1.4)	5.40 (1.3)
HAS-BLED score, mean (SD)	3.95 (0.9)	4.03 (0.9)

Data are presented as median (interquartile range), mean (SD) or frequency (%). NSAID: Non-steroid anti-inflammatory drugs, CAD: coronary artery disease, CABG: Coronary artery bypass-grafting, PCI: percutaneous coronary intervention, COPD: Chronic obstructive pulmonary disease, OAC: oral anticoagulation.

3.1. Primary outcome analysis

The primary outcome of ischemic stroke, systemic embolism, major bleeding or all-cause mortality occurred with 61 events in the LAAO cohort, and 117.8 events in the DOAC cohort, translating into annualized rates of 12.4 (95% CI: 9.66–16.18) for the LAAO cohort and 26.9 (95% CI: 20.58–35.31) for the DOAC cohort. The HR was 0.48 (95% CI: 0.35–0.65), indicating a significant lower risk of the composite outcome for the LAAO cohort. The Kaplan-Meier curve is illustrated in Fig. 2 and results are summarized in Table 2.

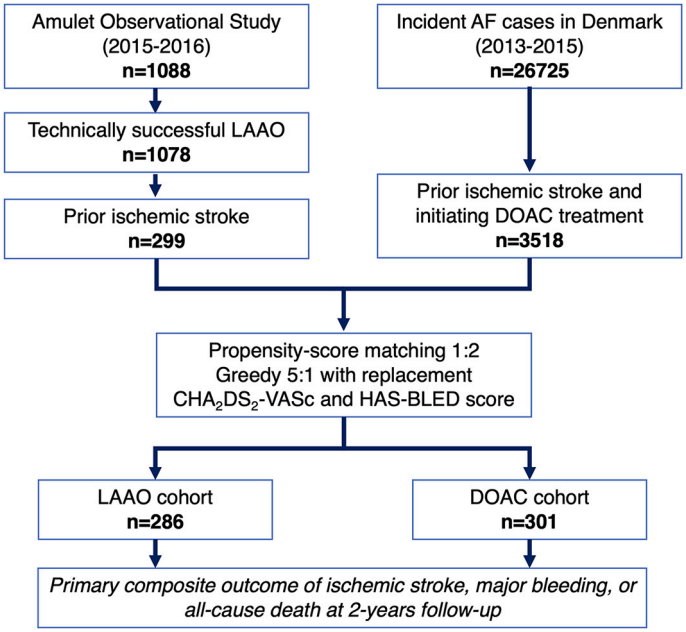

Fig. 1. Consort diagram. LAAO: Left atrial appendage occlusion, DOAC: Direct-oral anticoagulation

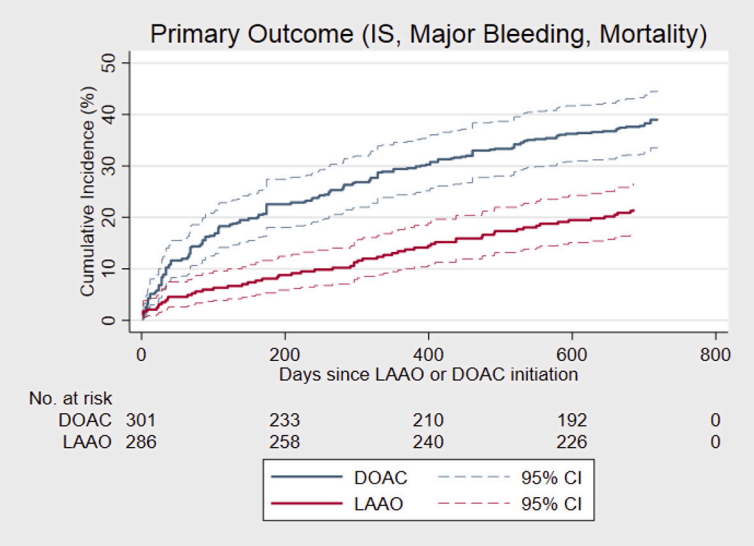

Fig. 2. Primary outcome analysis.
Kaplan-Meier curve for the primary composite outcome of ischemic stroke, major bleeding or all-cause mortality. CI: Confidence interval IS: Ischemic stroke, DOAC: Direct oral anticoagulation, LAAO: Left atrial appendage occlusion.

Table 2
Primary outcome analysis.

Analysis	No. of events		Event-rates (events/100 pt. yrs)		Hazard rate ratios (95% CI)	*p*-value
	LAAO	DOAC	LAAO	DOAC		
Primary composite outcome	61	118	12.42	26.87	0.48 (0.35–0.65)	<0.001
Ischemic stroke	13	18	2.54	3.67	0.71 (0.35–1.44)	0.34
Hemorrhagic stroke	7	3	1.33	0.60	2.20 (0.57–8.40)	0.25
Major bleeding	22	52	4.35	11.26	0.41 (0.25–0.67)	<0.001
All-cause mortality	36	74	6.83	14.43	0.58 (0.32–0.71)	<0.001
CV mortality	17	23	3.23	4.31	0.75 (0.39–1.42)	0.38

Primary composite outcome of ischemic stroke, major bleeding, and all-cause mortality. Weighted outcomes are displayed CV: Cardiovascular, DOAC: Direct oral anticoagulation, LAAO: Left atrial appendage occlusion. CI: Confidence interval.

3.2. Secondary outcome analyses

The ischemic stroke rate did not significantly differ between groups with annualized rates of 2.5 events/100 patient-years for the LAAO cohort, and 3.6 events/100 patient-years for the DOAC cohort, HR 0.71 (95% CI: 0.35–1.45). Hemorrhagic stroke was very rare in both cohorts with low annualized rates of 1.3 events/100 patient-years for LAAO, and 0.60 events/100 patient-years for DOAC, HR 2.2 (95% CI: 0.57–8.4). Major bleeding was lower with LAAO therapy, HR 0.40 (95% CI: 0.25–0.67), with annualized rates of 4.35 events/100 patient-years in LAAO cohort, and 11.26 events/100 patient-years in DOAC treated patients. All-cause death was also markedly lower, HR 0.48 (95% CI: 0.32–0.71), while cardiovascular death was not significantly lower, HR 0.75 (95% CI: 0.40–1.42). Secondary outcome analyses are summarized in Table 2, with corresponding cumulative incidence curves illustrated in Fig. 3.

Any peri-procedural complication occurred in 5% during the first 7 days post-procedure, which was comparable with the 4% periprocedural complication risk in the general Amulet Observational Study cohort [14].

The adherence to DOAC therapy was modest in overall patients with prior ischemic stroke ($n = 3518$), with nearly 50% discontinuation at 2-years follow-up (Fig. 4).

3.3. Sensitivity analyses

Results of the sensitivity analyses are summarized in Table 3 with baseline characteristics of the sensitivity analyses cohorts displayed in Supplemental table 3. First analysis restricted the DOAC cohort to patients who were adherent to DOAC the first 60 days without bleeding events in this period. Here, the annualized rate of the composite outcome was 12.69 events/100 patients-years in the LAAO cohort, and 18.12 events/100 patient-years in the DOAC cohort, with a HR 0.71 (95% CI: 0.51–0.97). The individual endpoints of ischemic stroke, major bleeding, all-cause and cardiovascular mortality did not significantly differ (Table 3).

When adjusting for stroke while on prior treatment with an anticoagulant, the primary composite outcome occurred with an annualized rate of 12.55 events/100 patient-years for LAAO and 31.13 events/100 patient-years for DOAC, HR 0.42 (95% CI: 0.31–0.57). The risk of all individual endpoints was significantly lower in the LAAO cohort, including cardiovascular mortality.

After exclusion of patients with a history of cancer in the DOAC cohort, the risk of the composite outcome was still lower in the LAAO cohort, with annualized rates of 12.68 events/100 patient-years for LAAO and 27.97 events/100 patient-years for DOAC, HR 0.47 (95% CI: 0.34–0.64). The ischemic stroke risk was comparable, with significantly lower risk of major bleeding, all-cause and cardiovascular mortality in the LAAO cohort.

Final sensitivity analysis adjusted for time from stroke to LAAO or DOAC therapy. Here, the composite outcome was significantly reduced, HR 0.44 (0.32–0.61), driven by a significant reduction in risk of major bleeding and all-cause mortality in the LAAO cohort. Ischemic stroke and cardiovascular mortality were comparable.

Each of the above sensitivity analyses were repeated with restriction to DOAC-patients who were adherent to DOAC therapy for the first 60 days without events in this period (Supplemental table 4). Here, the risk of the composite outcome was lower with LAAO therapy across analyses, but mainly driven by a lower all-cause mortality. The individual

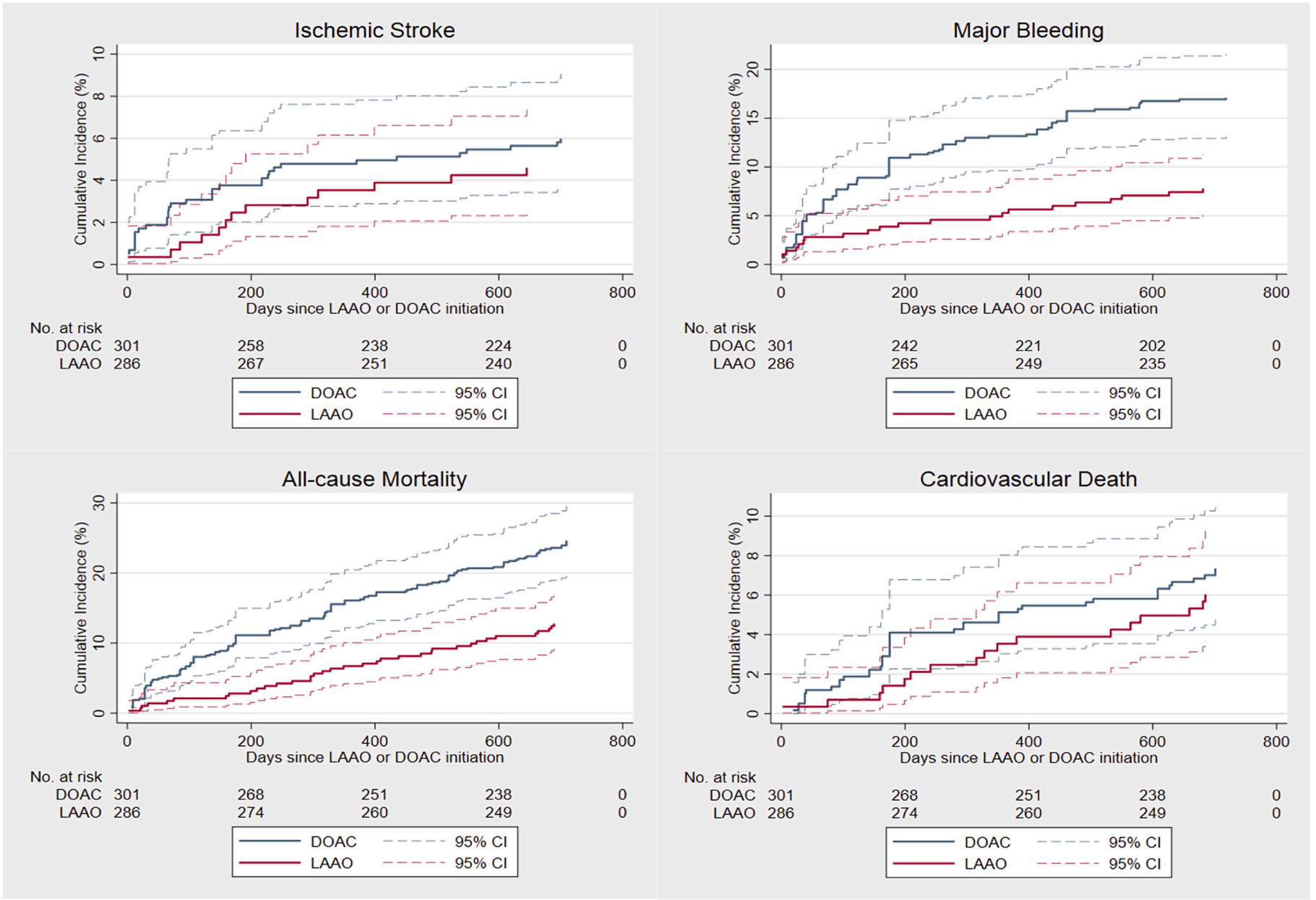

Fig. 3. Secondary outcome analyses.
Cumulative incidence of ischemic stroke, major bleeding, all-cause mortality, and cardiovascular mortality based on Aalen-Johansen estimates with death as competing risk for ischemic stroke and major bleeding analyses, and death of other causes treated as competing risk for cardiovascular death analysis. CI: Confidence interval, DOAC: Direct oral anticoagulation, LAAO: Left atrial appendage occlusion.

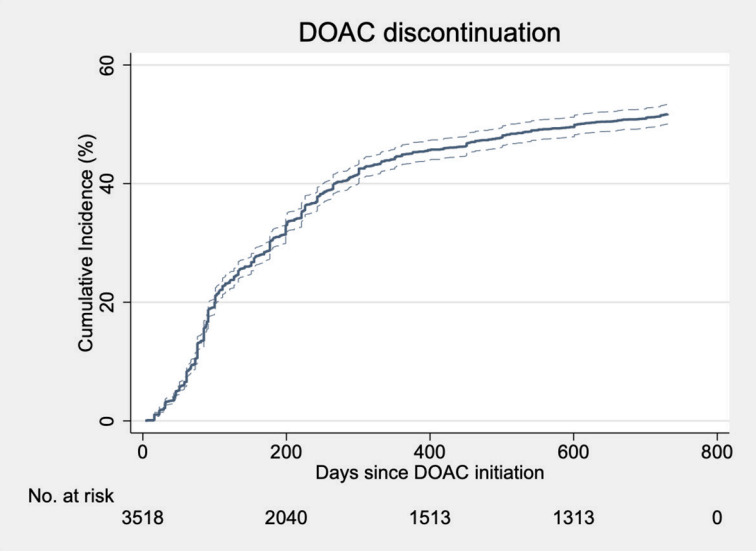

Fig. 4. DOAC discontinuation for the overall patient cohort with AF and prior stroke.
Adherence to direct oral anticoagulation over time. Discontinuation was defined as >60 days without coverage estimated by cumulative daily defined dosages from redeemed prescriptions.

endpoints were comparable across analyses, with a trend towards lower risk of major bleeding and cardiovascular mortality in the analysis adjusting for stroke on treatment while restricting to DOAC-adherent patients (Supplemental table 2).

4. Discussion

The main findings of the present study were a significantly lower risk of the composite outcome of ischemic stroke, major bleeding and all-cause mortality in AF-patients treated by LAAO and enrolled in the Amulet Observational Study, as compared to a propensity-score matched cohort treated by DOAC. The rate of ischemic stroke was comparable between cohorts, while the risk of major bleeding and all-cause mortality was markedly lower in the LAAO cohort. These results appeared consistent across sensitivity analyses, although, the lower risk of major bleeding diminished when restricting the control cohort to patients who were adherent to DOAC therapy for the first 60 days without events. Interestingly, when adjusting for prior stroke on anticoagulation therapy a significantly lower risk in the LAAO group was observed for all individual endpoints, including cardiovascular mortality.

Patients with AF and a prior ischemic stroke are at particularly high risk of stroke recurrence. The risk appears twofold increased when stroke occurs during anticoagulation treatment [22]. The evidence supporting secondary stroke prevention by anticoagulation in AF is strong. A causal association between the LAA and cardioembolic stroke in AF seems evident from the recent LAAOS III trial [9]. Both the primary analysis and sensitivity analyses of this current investigation suggested a comparable ischemic stroke rate in LAAO and DOAC treated patients, with point estimates favoring LAAO. Still, the relatively restricted sample size is reflected in the confidence interval width, and we acknowledge the associated uncertainty of point estimates. The annualized stroke rate in our LAAO cohort was 2.5 events/100 patient-years in the main analysis and ranged between 2.5 and 2.99 events/100 patient-years across sensitivity analyses. A similar low stroke recurrence rate has been reported in the Amplatzer Cardiac Plug [23] and EWOLUTION [24] registries. In the prior ischemic stroke subgroup of the DOAC trials, the ischemic stroke recurrence rate ranged between 1.8 and 2.3 events/100 patient-years [3–6]. These event rates cannot, however, be directly compared to the current analysis as patients in the DOAC trials were at lower risk, most evidently exemplified by a lower age which is a known strong predictor of stroke [2]. The randomized PRAGUE-17 trial reported a similar ischemic stroke rate between LAAO and DOAC treatment in AF-patients at high risk of both ischemic and hemorrhagic events, although not specifically investigating secondary stroke prevention (~30% with prior stroke) [12]. Around 40% of our LAAO cohort had a prior stroke while on anticoagulation treatment, placing them at a particularly high risk of recurrence and yet the ischemic stroke rate was similar, although numerically less, in the LAAO group in our study. Studies report annualized ischemic stroke rates around 8.2–8.8 events/100 patient-years in these patients despite continued anticoagulation therapy [22]. Interestingly, our sensitivity analysis adjusting for stroke on anticoagulation yielded a significantly lower risk of all individual endpoints in the LAAO cohort.

The reduced risk of major bleeding observed with LAAO treatment is intuitively a result of the less pronounced antithrombotic regimen after LAAO, with the majority treated by single antiplatelet therapy after 3 months [14]. The PROTECT-AF trial found a lower risk of intracranial hemorrhage with LAAO compared to warfarin [10]. In the present study, intracranial hemorrhage was a rare event in both cohorts and without significant difference. This finding may be either explained by the documented lower risk of intracranial hemorrhage with DOAC treatment compared to warfarin [3–5] or the low event rate of intracranial hemorrhage in our study. The risk of extracranial hemorrhage was, however, increased with DOAC therapy in the randomized trials comparing it to warfarin [3–5]. The AVERROES trial indicated similar major bleeding rates with aspirin and apixaban, however, on-treatment analysis indicated lower risk with aspirin [25] and it appears evident that higher aspirin doses are associated with a higher bleeding risk [26,27]. Most LAAO-centers use a low-dose of aspirin 75–81 mg/daily after LAAO and may explain the lower observed bleeding risk. Furthermore, the AVERROES trial data cannot be extrapolated to patients with prior stroke, as only 13% had a prior stroke or transient ischemic attack and most patients were low-risk with CHA_2DS_2-VASc score 0–1 [25]. The concept of LAAO is to mitigate the cardioembolic stroke risk associated with AF without anticoagulation, however, long-term secondary stroke prevention with either aspirin or clopidogrel should still be considered as the risk of concomitant small-vessel or large-artery atherosclerosis is high in these comorbid patients [26]. The effects of continued anticoagulation therapy (full or reduced dose) after LAAO in anticoagulation eligible patients are still questionable but should be investigated in future trials.

Table 3
Sensitivity analyses.

	No. of events		Event-rates (events/100 pt. yrs)		Hazard rate ratios (95% CI)	p-value
	LAAO	DOAC	LAAO	DOAC		
Sensitivity analysis #1: DOAC cohort is restricted to patients adherence to DOAC first 60 days without bleeding prior to propensity matching. LAAO; n = 299, DOAC; *n* = 305						
Composite outcome	65	91	12.69	18.12	0.71 (0.51–0.97)	0.03
Ischemic stroke	16	18	2.99	3.32	0.91 (0.46–1.78)	0.78
Major bleeding	22	34	4.15	6.50	0.65 (0.38–1.11)	0.12
All-cause mortality	37	56	6.71	10.00	0.67 (0.44–1.01)	0.06
CV mortality	18	21	3.26	3.76	0.87 (0.46–1.63)	0.65
Sensitivity analysis #2: Analysis including adjustment for prior stroke occurring despite oral anticoagulation. LAAO; *n* = 297, DOAC; *n* = 298						
Composite outcome	64	131	12.55	31.13	0.41 (0.31–0.57)	<0.001
Ischemic stroke	15	26	2.82	5.69	0.51 (0.27–0.96)	0.04
Major bleeding	22	43	4.18	9.65	0.45 (0.27–0.76)	0.003
All-cause mortality	37	88	6.75	18.19	0.38 (0.26–0.56)	<0.001
CV mortality	18	36	3.29	7.48	0.44 (0.25–0.78)	0.005
Sensitivity analysis #3: Patients with a prior cancer diagnosis is excluded from the DOAC cohort prior to propensity matching. LAAO; *n* = 281, DOAC; n = 297						
Composite outcome	61	121	12.68	27.97	0.47 (0.34–0.63)	<0.001
Ischemic stroke	13	18	2.59	3.81	0.69 (0.34–1.41)	0.31
Major bleeding	22	53	4.44	11.83	0.39 (0.24–0.64)	<0.001
All-cause mortality	36	73	6.96	14.46	0.49 (0.33–0.73)	<0.001
CV mortality	17	32	3.29	6.42	0.51 (0.29–0.93)	0.03
Sensitivity analysis #4: Analysis including adjusting for time from prior ischemic stroke to LAAO or DOAC treatment. LAAO; *n* = 254, DOAC; *n* = 291						
Composite outcome	53	121	12.11	28.81	0.44 (0.32–0.61)	<0.001
Ischemic stroke	12	18	2.63	3.75	0.72 (0.35–1.50)	0.38
Major bleeding	20	48	4.44	11.03	0.42 (0.25–0.71)	0.001
All-cause mortality	30	73	6.39	14.90	0.44 (0.28–0.67)	<0.001
CV mortality	17	27	3.62	5.43	0.67 (0.37–1.23)	0.19

CV: Cardiovascular, DOAC: Direct oral anticoagulation, LAAO: Left atrial appendage occlusion. CI: Confidence interval. Baseline characteristics for the sensitivity analyses cohorts are displayed in Supplemental table 3. All sensitivity analyses included propensity matching based on CHA_2DS_2-VASc and HAS-BLED scores including each covariate herein, as for the primary outcome analysis.

The all-cause mortality difference between the LAAO cohort and DOAC cohort cannot be directly explained. A similar finding was present in the randomized PROTECT-AF and PREVAIL studies but was also apparent in the cardiovascular mortality analysis [10]. Theoretically, bleeding may be a contributor to the mortality difference. It can be difficult to evaluate cause-specific mortality from the Danish Causes of Death Registry [19], hence, all-cause mortality was chosen as outcome to minimize bias. The sensitivity analyses attempted to reduce confounding from prognostic risk factors like cancer, yet, all-cause mortality and even cardiovascular mortality was lower with LAAO in this comparison. A selection bias cannot be ruled out given the early separation of mortality curves. However, the GARFIELD AF-registry reported that the risk of early mortality in newly diagnosed AF patients is high, and here the causes were cardiovascular in the majority [21]. Independent predictors of early mortality were age, heart failure, prior stroke, cirrhosis, vascular disease, moderate-severe chronic kidney disease, and diabetes [21]. All these risk factors were balanced in our cohorts, as they were part of the matching algorithm. The time from stroke to prescription of NOAC was, however, shorter than the time to LAAO and could represent a confounder, yet, the sensitivity analysis attempted to adjust for this imbalance and yielded similar outcome results. Nevertheless, we acknowledge the uncertainty of the observed mortality benefit with LAAO which warrants further scrutiny in the upcoming randomized Occlusion-AF trial [28].

5. Limitations

The study was limited by the observational nature with inherent limitations regarding confounding and bias. The Amulet Observational Study enrolled patients globally, with trial-like follow-up and independent centralized endpoint adjudication. However, there is a risk for selection bias for LAAO therapy and enrollment in the Amulet Study. The Danish registries collect information on all citizens, hospital admission and treatments, with validated and reliable outcome data in a universal tax-funded health care system. Nonetheless, the study may be limited by comparison of cohorts sampled from two different sources with potential geographical differences in health care access or risk profiles, involving different outcome assessment and potential unmeasured confounders. The LAAO cohort was a prevalent AF-cohort, while the DOAC cohort was incident, which may confound the outcome analysis. We attempted to account for this through sensitivity analyses, however, risk of residual confounding should be acknowledged when interpreting results. We acknowledge that the present study should be regarded as hypothesis-generating, and the results must be confirmed in a randomized clinical trial like the ongoing Occlusion-AF trial initiated by the authors (Clinicaltrials.gov NCT03642509) [28].

6. Conclusion

This propensity-score matched study based on the Amulet Observational Study and the Danish Patient Registries, indicated a significantly lower risk of the composite outcome of ischemic stroke, major bleeding, and all-cause mortality with LAAO therapy as compared to DOAC in AF-patients with prior ischemic stroke. The stroke prevention effectiveness was similar, while risk of major bleeding was significantly lower with LAAO, supporting the hypothesis of a net-clinical benefit of LAAO in these patients. This awaits further testing in the ongoing randomized Occlusion-AF trial.

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Appendix A. Supplementary data

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