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Percutaneous left atrial appendage closure compared to non-vitamin K oral anticoagulants in patients with non-valvular atrial fibrillation and high bleeding risk (HAS-BLED ≥3).

NOACs versus LAAO indication in NVAF patients at HBR (HAS-BLED ≥3).

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Key Words: atrial fibrillation; bleeding risk; LAA closure; anticoagulant therapy

ABSTRACT

Aims: A relevant amount of patients with non-valvular atrial fibrillation (NVAF) are ineligible for non-vitamin K oral anticoagulants (NOACs) due to previous major bleeding or because at high bleeding risk (HBR). In this setting the indication for percutaneous left atrial appendage closure (LAAO) is a valuable alternative.

We evaluated the efficacy and safety of NOACs versus LAAO indication in NVAF patients at HBR (HAS-BLED ≥3).

Methods and results: All consecutive patients who underwent successful LAAO (n=193) and those treated with NOACs (n=189) (dabigatran, apixaban or rivaroxaban) were included. A 1:1 propensity-score-matching (PSM) was used to match LAAO and NOACs patients. At baseline, patients in the LAAO group had higher HAS-BLED (4.2% vs 3.3%, p<0.001) and lower CHADS-VASc (4.3% vs. 4.7%, p=0.005). After 1:1 PSM, 192 patients were enrolled in the final analysis (LAAO n=96; NOACs n=96). At 2-year follow-up, no significant difference in thromboembolic (7.3% vs. 6.3%, p=0.966) and ISTH-major bleeding events rate (6.7% vs. 4.8% p=0.503) were found between the two unmatched groups. All-cause death was significantly higher in the LAAO group (18.7% vs. 10.6%; p=0.049). After PSM, all-cause death, thromboembolic and ISTH-major bleeding event rates were similar between groups. Significant independent predictors of all-cause death were dialysis (HR 5.65, 2.16-14.85, p<0.001) and age (HR 1.08, 95% CI 1.05-1.13, p<0.001).

Conclusion: In NVAF patients at HBR, LAAO and NOACs performed similarly in terms of thromboembolic and major bleeding events up to 2-year follow-up. Our findings warrant further investigations in randomized trials and therefore can be considered as hypothesis generating.

CONDENSED ABSTRACT

We evaluated the efficacy and safety of non-vitamin K oral anticoagulants (NOACs) versus left atrial appendage closure (LAAO) indication in 382 NVAF patients (193 LAAO group, 189 NOACS group) at high bleeding risk (HAS-BLED ≥3). Patients in the LAAO group had higher HAS-BLED and lower CHADS-VASc. At 2-year follow-up, no significant difference in thromboembolic and ISTH-major bleeding events rate were found. All-cause death was significantly higher in the LAAO group, but did not differ after propensity score matching. Significant independent predictors of all-cause death were dialysis and age.

ABBREVIATIONS

NVAF=non-valvular atrial fibrillation
NOAC= non-vitamin K oral anticoagulants
LAAO=left atrial appendage occlusion
HBR=high bleeding risk
PSM=propensity score matching
CKD=chronic kidney disease
TIA=transient ischemic attack
SE=systemic embolism

IMPACT ON DAILY PRACTICE

Prevention of thromboembolic events in patients with NVAF at high bleeding risk is challenging. This single centre real-world 1:1 propensity-matched study showed that LAAO was as effective as NOACs in preventing ischemic events. On the other hand, NOACs were extremely safe with no excess of major bleeding. Thus, both treatments can be considered valuable in this high risk setting of patients.

INTRODUCTION

Non-vitamin K oral anticoagulants (NOACs), are the mainstay of the stroke prevention in patients with non-valvular atrial fibrillation (NVAF), showing at least the same efficacy as warfarin but less intracranial bleeding.(1) Nonetheless, there is still relevant amount of patients who do not receive the indication to anticoagulation (up to 40%) despite eligible to it(2) or who cannot benefit from this therapy because ineligible due to previous major bleeding (especially intracranial hemorrhage)(3)(4) or high bleeding risk (HBR).

In this setting, current AF Guidelines suggest considering percutaneous left atrial appendage occlusion (LAAO)(5). Antiplatelet therapy indeed cannot be recommended, being inferior to warfarin for stroke prevention(6) and similarly increasing bleeding risk.(7) Albeit thrombi from the LAA account for 90% of ischemic strokes(8), there are other sources of thrombi (i.e. left atrium, left ventricular apex, aorta and carotid arteries) that may be treated better with anticoagulant therapy (due to its systemic effects), which are not prevented by LAAO.

Head-to-head comparison between the indication for NOACs and LAAO are still lacking. A recent network meta-analysis of randomized controlled trials and observational studies(9) compared the efficacy and safety of LAAO and NOACs and showed that LAAO performed better than NOACs in avoiding major bleeding event but were less effective for ischemic stroke prevention. Considering this pathophysiological background, we sought to evaluate the efficacy and safety of the indication for NOACs and LAAO in a tertiary care real-world setting of NVAF patients at HBR.

MATERIALS AND METHODS

Study population.

This is a single-center, observational prospective study conducted at San Raffaele Hospital between July 2009 and December 2016. In the LAAO group were included all consecutive patients with NVAF who underwent successful percutaneous LAAO in the Arrhythmia and Electrophysiology Unit, and at the Interventional Cardiovascular Unit. A successful LAAO procedure was defined as an effective device implantation in LAA in absence of serious adverse events (such as cardiac perforation and pericardial effusion causing cardiac tamponade, procedure-related stroke, other major bleeding and cardiac death).

In the NOACs group, were included all consecutive patients with NVAF (either anticoagulation naive or switched from a vitamin K antagonist) that started a NOAC (dabigatran, apixaban or rivaroxaban). Patients with valvular AF (moderate-to severe mitral stenosis and mechanical prosthetic valves) were excluded. All patients were prospectively followed, and a minimum of 1-year follow-up was required to be included in the final analysis. Patients treated with edoxaban (introduced in September 2016) were not included in the present analysis due to a short time of follow-up. LAAO patients who shifted towards anticoagulant therapy before 1-year and those in NOACs group who underwent percutaneous left atrial appendage closure before 1-year after drug initiation were excluded. **Figure 1**.

All NOACs were used at reduced doses approved for stroke prevention in NVAF in elderly people and in patients with chronic kidney disease (CKD), when indicated(10). A patient was defined as having a HBR profile if the HAS-BLED score was ≥3. To achieve an equal distribution of baseline clinical characteristics, a 1:1 matched analysis (between NOAC vs LAAO groups) without replacement, was performed using propensity-score matching (PSM).

The study was approved by the Hospital Ethics Committee and each patient provided written informed consent for the procedure, data collection and subsequent analysis. No external source of funding supported this study.

Endpoint definition

The **primary safety endpoint** was major bleeding defined according to ISTH (International Society of Thrombosis and Haemostasis) classification: decrease in the hemoglobin level of at least 2 g/dL, transfusion of at least 2 units of packed red cells, occurring at a critical site or resulting in death. The **primary efficacy endpoint** included thromboembolic events: ischemic stroke, transient ischemic attack (TIA), systemic embolism (SE), acute myocardial infarction (AMI). The **combined efficacy and safety endpoint** was a composite endpoint of thromboembolic events (ischemic stroke, TIA, AMI, SE) and ISTH-major bleeding. The individual categories of efficacy endpoint, as well as all bleedings, intracranial bleedings, gastrointestinal bleedings, overall death and cardiac death were analyzed as **secondary endpoints**.

Data collection (see supplementary data)

Statistical analysis

Continuous variables were reported as mean±standard deviation(SD). Categorical variables were compared with $\chi 2$ or the Fisher exact test as appropriate. Clinical outcomes and adverse events were prospectively monitored by direct visit, phone interview or contact with referring physician, and specific hospital files were requested when needed. Event-free survival was evaluated according to the unadjusted Kaplan-Meier method and survivals among groups were compared using log-rank test (Cox-Mantel test). Finally, multivariable Cox-regression analysis was performed to analyze the influence of relevant variables (diabetes, prior myocardial infarction, prior intra-cerebral hemorrhage, dialysis and age) on mortality. To avoid multi-collinearity, a "low-noise model", in which each predictor variable correlate at most only minimally with the other, has been researched. Only covariates that were significantly associated with the risk of death at univariate analysis ($p<0.10$) were included, and convention of limiting the number of independent variables to 1 for every 10 events was followed. A propensity score-based sensitivity analysis method for uncontrolled confounding between groups was performed and obtained by fitting a logistic regression model with the type of treatment (NOAC vs LAAO) as binary outcome and other predictor variables for the primary endpoint.(11) Patients of the two groups were matched 1:1 through a greedy algorithm based on a caliper defined to have a maximum width of 0.2

standard deviation (SD) of the logit of the estimated propensity-score. The final caliper was 0.061.(12) Finally, success of PSM was judged by analysing the baseline clinical characteristics in propensity-matched groups, and absence of difference in all variables related to the endpoint (p-value>0.05) supports the assumption of a balance between matched groups.(13) Hosmer and Lemeshow (H-L) and c-statistic tests were used to assess the goodness of fit for logistic regression models and the predictive model discriminatory power, respectively. Data for patients lost to follow-up were censored at the time of the last contact. Two-side p-values<0.05 were considered statistically significant. The statistical analyses were performed using SPSS 23 (SPSS Inc., Chicago, USA).

RESULTS

Baseline clinical data

During the index period, from a total cohort of 940 patients with NVAF, 382 patients presented an HAS-BLED risk score ≥3 and were included in the present study. Of these, 193 patients (193/940, 20.5%) underwent successful LAAO (LAAO group) and 189 patients (189/940, 20.1%) were treated with NOACs (NOACs group), **Figure 1**. In the LAAO group, the Watchman device was used in 65 cases (33.7%), the Amplatzer Cardiac Plug in 43 cases (22.3%), while in the remaining 85 cases (44%) the Amulet device was used. After the procedure, 40 patients (20%) were discharged with an indication for only anticoagulation therapy up to 2-month, 141 patients (64%) with an indication for dual antiplatelet therapy up to 6-month and 12 patients (6%) in single antiplatelet therapy up to 2-month. In the NOACs group, 78 patients were treated with dabigatran (41%), 77 with apixaban (41%) and 34 with rivaroxaban (18%). Baseline clinical characteristics of the two groups (unmatched population) are reported in **Table 1**. Patients who underwent percutaneous LAAO had more comorbidities such as diabetes and lower creatinine clearance, more previous bleeding and intracranial bleeding, reflected in a higher HAS-BLED score (4.2 LAAO versus 3.3 NOACs, p<0.001). 14 LAAO patients (7%) were on dialysis, while, as expected, no one in the NOACs group. NOACs patients were older and at higher ischemic risk as estimated by CHA2DS2-VASc score (4.8 versus 4.3, p=0.005). After 1:1 PSM, 192 patients (96

NOAC group and 96 LAAO group) were adjusted for variables included in the CHADs-VASC and HAS-BLED scores). Finally, the two groups were homogeneous in terms of age (73.8±7.1 vs 75.3±6.8 years, p=0.15), ischemic and bleeding risk (CHADs-VASC 4.3±1.5 vs 4.3±1.5 p=0.88 and HAS-BLED 3.5±0.7 vs 3.5±0.6, p=0.83) as reported in **Supplementary Table 1.**

Clinical outcomes

Clinical outcomes of the two unmatched groups are reported in **Table 2**.

At 2-year follow-up (median/IQR 2.4/2.1-2.9 years), no significant difference in the primary efficacy endpoint (thromboembolic events) were observed between LAAO and NOACs groups (7.3% vs. 6.3%, p=0.966). Similarly, the ischemic stroke (3.1% vs 3.2%), TIA (2.1% vs. 1.1%), the SE (0% vs. 1.1%) and AMI rates (1.6% vs. 1.6%) were comparable between the two unmatched groups. Regarding the primary safety endpoint (ISTH-major bleeding events), this occurred in 13 LAAO patients and in 9 NOACs patients, with no statistical difference (6.7% vs. 4.8% p=0.503, respectively). Among LAAO patients, the ISTH-major bleeding event occurred in 2/13 (15.3%) and 6/13 (46.1%) patients during the first three and six months, respectively. Also gastrointestinal bleeding rate did not differ between NOACs and LAAO groups (8.5% vs. 5.2%, p=0.203). In terms of overall bleedings, more patients on NOACs experienced an event (20.6% vs. 11.9%; p=0.021). Unmatched Kaplan-Meyer curves for the primary efficacy, primary safety endpoints and for the combined endpoint are shown in **Figure 2**. The combined efficacy and safety endpoint occurred in 27 patients (14%) in the LAAO group and in 21 patients (11%) in the NOACs group (p=0.881). Compared to NOACs group, all-cause death rate was significantly higher in the LAAO group (18.7% vs. 10.6%; p=0.049). When considering cardiac death alone, any difference was evident. The incidences of minor procedural complications, leaks, device-associated thrombus and stroke at follow-up were low and similar between the three different occluder devices used for LAAO procedures, supplementary Table 2.

After PSM, no difference in all-cause death was evident between the two matched groups (10.4% vs. 15.6%, p=0.284, NOAC vs LAAO) and the rate of thromboembolic and ISTH-major bleeding events were still comparable (7.3% vs 6.3%,

p=0.77 and 6.3% vs 6.3%, p=1, respectively). Matched Kaplan-Meyer curves for the matched analysis are shown in **Supplementary Figure 1.**

According to the multivariate analysis, significant independent predictors of all-cause death (**Table 3**) were dialysis (HR 5.65, 95% CI 2.16-14.85, p<0.001) and age (HR 1.08, 95% CI 1.05-1.13, p<0.001), c-statistic value (0.72), Hosmer-Lemeshow (0.830).

DISCUSSION

This study is one of the first comparison between percutaneous left atrial appendage occlusion and use of direct oral anticoagulants for thromboembolic events prevention in HBR patients with non-valvular atrial fibrillation. The main findings of our study are the followings:

1. in this tertiary care real-world series of NVAF patients, one third of patients were at HBR (HAS-BLED ≥3) and were equally treated with NOACs or LAAO;
2. at 2-year follow-up, the primary efficacy and safety endpoints were equals for the two groups of indication (thromboembolic events: 7.3% in LAAO group vs. 6.3% in NOACs group and ISTH-major bleeding: 6.7% vs. 4.8%, respectively);
3. at the unmatched analysis, the LAAO group showed ~~a~~an higher rate of all-cause death, reflecting the real-world high-risk profile of patients undergoing this indication.
4. After 1:1 PSM, both NOACs and LAAO groups confirmed comparable outcomes for primary endpoints and also for all-cause death.

Large randomized clinical trials and real-world evidence(1)(14)(15)(16) have shown NOACs to be at least as effective as warfarin in the prevention of stroke in patients with NVAF, with less intracranial hemorrhages. This has led current ESC AF Guidelines to recommend NOACs over warfarin for stroke prevention in NVAF patients.(5)

However, although NOACs have a better safety profile than warfarin, use of anticoagulant therapy carries a not negligible risk of serious bleedings. This is a major concern especially for patients with high HAS-BLED or for patients who experienced previous major bleedings (especially ICH) due to the apprehension of possible recurrence of bleeding related to anticoagulation. At the same time, the ischemic risk might even overweight the bleeding risk, as described in some patients with previous ICH.(17)

In this setting, as suggested by current ESC Guidelines,(5) LAAO might be an option (grade IIb, level B). In the Protect-AF trial, the LAAO with Watchman device met criteria for both non-inferiority and superiority, compared to warfarin at one(18) and four-year(19) of follow-up, in terms of prevention of the combined outcome of stroke, systemic embolism, and cardiovascular death. Nonetheless, the Prevail Trial(20), failed to achieve the prespecified criteria for non-inferiority, raising some concerns about the efficacy of this procedure, at least in patients eligible to OAC therapy. Although randomized clinical trials evaluated LAAO in patients who were still eligible to anticoagulation, in the real-world practice there was a shift toward LAAO in higher risk patients with contraindication to anticoagulation or deemed at prohibitive risk of bleeding.(21)

Thromboembolic events prevention in these patients is challenging but necessary: the main objective of our research was to evaluate if, in a setting of patients with HBR or contraindication to oral anticoagulant therapy, LAAO represented a valuable alternative to standard care with NOACs, especially regarding effectiveness.

A network meta-analysis of both randomized clinical trials and observation studies(9) evaluated the safety and efficacy of LAAO and NOACs in anticoagulation-eligible patients and showed that LAAO performed better than NOACs in avoiding major bleeding events but was less effective for ischemic stroke prevention (randomized trials analysis). In the present study, at the unmatched analysis, patients with indication for LAAO experienced both comparable rates of thromboembolic and ISTH major bleeding events compared to patients with indication for NOACs. Although we expected a better efficacy profile with NOACs, our findings can be partially explained by taking into account 1) the increased ischemic risk of patients with indication for NOACs, as estimated by CHADs-VASC (4.8 vs 4.3, p=0.005), 2) the relative not long follow-up time (mean 2-year) and 3) the fact that two thirds of patients with indication for LAAO (64%) continue the antithrombotic treatment up to six months after the procedure. On the contrary, the finding of comparable safety (major bleeding events) between groups, albeit the increased bleeding risk of patients with indication for LAAO, highlights the safety profile of NOACs and encourages their use in a setting of HBR patients, if no clear contraindications exist. Notably, LAAO group showed an increased all-cause death, but this finding should be evaluated considering the baseline differences in

clinical profile and possible unmeasured confounders between groups. Indeed, this difference was lost after the matched analysis, adjusting for variables included in the CHADs-VASC and HAS-BLED scores. The matched groups, with similar comorbidities and ischemic and bleeding risks, showed comparable all-cause death rates as well as thromboembolic, ISTH-major bleeding events and combined end-point rates. Thus, both indications (NOAC and LAAO) seem to be valuable strategies for thromboembolic event prevention in patients at HBR.

Finally, we aimed to identify predictors of all-cause death in this cohort of NVAF patients at HBR: dialysis was the stronger predictor of all-cause death, further confirming that the reduced survival after LAAO could reflect the high-risk profile of patients who undergo this kind of procedure in the real-world.

Recently, in a propensity match study in patients with prior ICH treated with oral anticoagulants (one third with NOACs) or LAAO (one third receiving no antithrombotic treatment during follow-up), the primary composite endpoint (all-cause mortality, ischemic stroke and major bleeding) was lower in the LAAO group.(22) The estimated risk of the included population was similar to our study, but rates of ischemic stroke (8.7%/year in OAC group and 2.6%/year in LAAO group) were higher compared to our findings, while major bleeding (4.1%/year in OAC group and 2.5%/year in LAAO group) were similar. The increased stroke risk in that study may be partially explained by the time gap between starting of observation and initial of anticoagulation (within 180 days after their index ICH). In another study on LAAO with Amplatzer Plug in patients with previous major bleeding and estimated bleeding risk profile similar to our patients, the major bleeding rate was higher (6%/year), while the stroke rate was similar (2.1%/year).(23) The recent 2-year follow-up of EVOLUTION trial (Watchman device) reported similar incidence of major-bleeding (2.7%/year) and stroke (1.3%) events.(24) Conversely, both major-bleeding and stroke rates were higher in the 1-year follow-up of the prospective Amplatzer Amulet registry (10.3%/year and 2.9%/year, respectively); the high proportion of patients with previous major bleeding may probably account for the particularly high major-bleeding rate in this registry(25).

The ongoing PRAGUE-17(26), prospective, multicenter, randomized noninferiority trial will determine if LAAO is non-inferior to treatment with NOAC in moderate- to high-risk AF patients and the ongoing OPTION (NCT03795298) trial will determine if

LAAO with the WATCHMAN-FLX device is a reasonable alternative to oral anticoagulation in patients after AF ablation.

In conclusion, although the high ischemic risk of the present population, NOAC and LAAO showed comparable and reassuring efficacy in thromboembolic events prevention. Indeed, our initial hypothesis to find more cerebral ischemic events in LAAO group (because of the procedure's ineffectiveness on the other sources of thromboembolism other than left atrial appendage) was not confirmed.

On the other hand, NOACs did not show an increase in ISTH-major bleeding events as compared to LAAO group, highlighting the good safety profile of these drugs in this challenging setting. Thromboembolic event prevention should always be pursued in patients with AF, even if the bleeding risk is high. Our results contribute to the evidence about the encouraging safety of DAOCs and effectiveness of LAAO for this pursuit. Nevertheless, our findings warrant further investigations in larger randomized trials and therefore can be considered only as exploratory and hypothesis generating.

Study limitations

The principal limit of this study is represented by its observational nature. On the other hand, it represents a snapshot of a high-volume tertiary care center practice in this challenging setting. The PSM analysis, with the ability of balancing groups, contributed to a more precise estimation of treatments response. The relative small size of the population studied might have led to a possible underestimation of the events during follow-up. In order to fully evaluate the event rate a longer follow-up would have been useful. Moreover, the discharge antithrombotic regimen used was not standardized, but different according to the clinical characteristics of the patient and the device used.

CONCLUSIONS

This tertiary care single-center observational study showed good safety and efficacy outcome after LAAO and DAOCs indication in NVAF patients at HBR (HAS-BLED ≥3), with no differences in thromboembolic events or in major bleeding between groups even after propensity score matching analysis. The inherent limitations of the observational study design require these results to be confirmed in a randomized clinical trial.

DISCLOSURES

None

FUNDING

No funding was utilized for this study.

FIGURES LEGEND

Figure 1. Study flow chart

Figure 2. Unmatched Kaplan-Mayer analysis of thromboembolic events (panel A), ISTH major bleeding events (panel B) and combined thromboembolic and ISTH-major bleeding events (panel C) *[log-rank (Mantel Cox) test]*.

Table 1. Baseline clinical characteristics of LAAO and NOACs group

	LAAO n=193	**NOACs n=189**	**p value**
Age (years), mean±SD	74.2±7.7	77.7±6.9	<0.001
BMI	25.8±3.6	26.0±3.2	0.57
Female gender, n (%)	63 (32.6)	58 (30.7)	0.68
CHA_2DS_2-VASc score, mean±SD	4.3±1.5	4.8±1.5	0.005
HAS-BLED score, mean±SD	4.2±1.0	3.3±0.5	<0.001
Existing co-morbidities, n (%)			
Hypertension	169 (87.6)	180 (95.2)	0.080
Dyslipidemia	103 (53.4)	98 (51.9)	0.76
Diabetes mellitus	69 (35.8)	43 (22.8)	0.005
Insulin therapy	13 (6.7)	8 (4.2)	0.28
CKD	83 (43.0)	90 (47.6)	0.32
CrCl (ml/min), mean±SD	56.9±27.1	68.0±26.7	0.015
Dialysis	14 (7.3)	0 (0)	<0.001
Previous AMI	37.0 (19.2)	52 (27.5)	0.054
Liver disease	11 (5.7)	5 (2.6)	0.13
Previous ischemic stroke	56 (29)	55 (29.1)	0.98
Previous TIA	15 (7.8)	20 (10.6)	0.34
Previous bleeding	133 (68.9)	66 (34.9)	<0.001
Previous intra-cranial hemorrage	47 (24.4)	3 (1.6)	<0.001
LVEF, mean±SD	51.7±10.8	52.9±11.2	0.32

Table 2. 2-year clinical outcomes of LAAO and NOACs groups, unmatched population (*Mantel Cox test*)

	LAAO n=193	NOACs n=189	p value
Thromboembolic events, n (%)	14 (7.3)	12 (6.3)	0.96
Major bleeding (ISTH), n (%)	13 (6.7)	9 (4.8)	0.50
Combined efficacy and safety endpoint, n (%)	27 (14)	21 (11.1)	0.88
Secondary endpoints, n (%)			
Ischemic stroke	6 (3.1)	6 (3.2)	0.97
TIA	4 (2.1)	2 (1.1)	0.42
AMI	3 (1.6)	3 (1.6)	0.97
SE	0 (0)	2 (1.1)	0.15
All Bleeding	23 (11.9)	39 (20.6)	0.021
Intracranial bleeding	4(2.1)	2 (1.1)	0.42
Gastrointestinal bleeding	10 (5.2)	16 (8.5)	0.20
All-cause death	36 (18.7)	20 (10.6)	0.049
Cardiac death	15 (7.8)	6 (3.2)	0.064

Table 3. Predictors of all-cause death at 2-year follow-up, unmatched population (*Multivariate Cox regression analysis*)

Variable	Hazard Ratio	95% CI	P value
Diabetes	1.60	0.92-2.79	0.097
Prior AMI	1.62	0.89-2.92	0.11
Prior ICH	1.02	0.42-2.45	0.96
Dialysis	5.65	2.16-14.85	<0.001
Age	1.08	1.05-1.13	<0.001

AMI=acute myocardial infarction, ICH=intracranial bleeding

Figure 1.

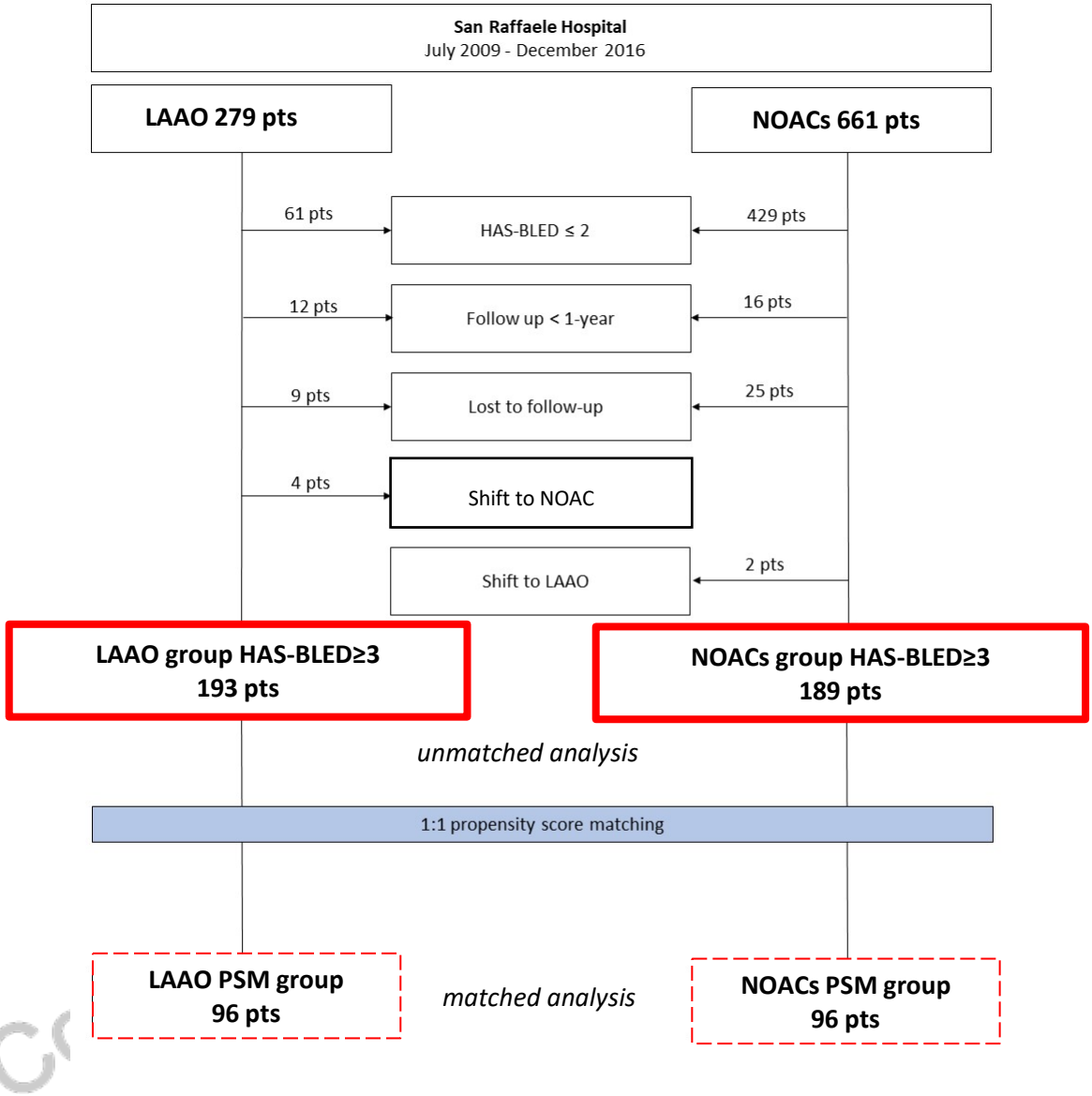
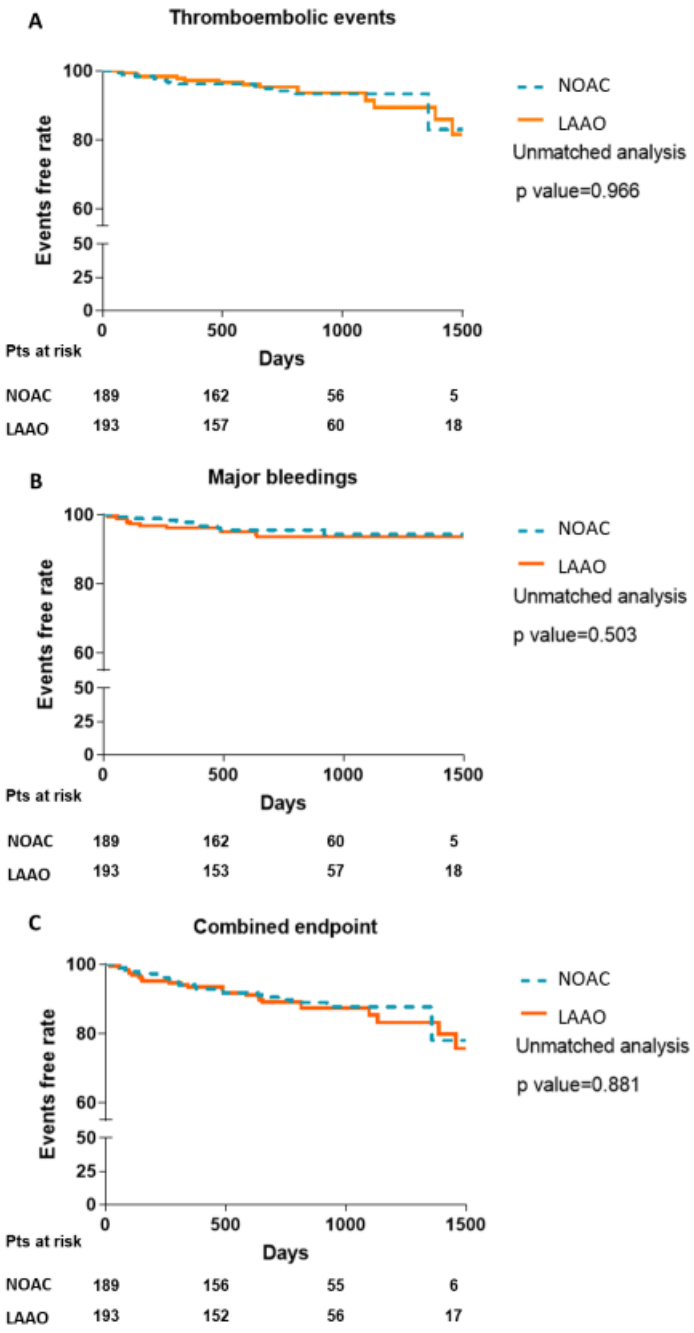


Figure 2.



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Supplementary material

2.3 Data collection

The clinical data, including age, gender, body mass index, date of treatment initiation or date of the procedure, prior events (bleeding, ischemic stroke, TIA, intra-cranial hemorrhage, AMI), ejection fraction, comorbidities (hypertension, diabetes, liver disease, CKD) were collected at baseline. Creatinine clearance (CrCl) was calculated using the Cockcroft-Gault formula, which has been used in all phase III DOAC trials. CKD was defined by CrCl<60 ml/min. All events and single components of both primary and secondary endpoints were evaluated and adjudicated independently by at least two physicians.

Supplementary Table 1. Baseline clinical characteristics of LAAO and NOACs groups after 1:1 propensity score matching.

	LAAO group N=96	**NOACs group N=96**	**p value**
Age (years), mean ± SD	73.8±7.1	75.3±6.8	0.15
BMI	25.7±3.6	26.4±4.3	0.23
Female gender, n (%)	42 (43.8)	18 (18.8)	0.002
CHA_2DS_2-VASc score, mean ± SD	4.3±1.5	4.3 ± 1.5	0.88
HAS-BLED score, mean ± SD	3.5±0.7	3.5±0.6	0.83
Existing co-morbidities, n (%)			
Hypertension	80 (83.3)	90 (93.8)	0.023
Dyslipidemia	37 (38.5)	50 (52.1)	0.059
Diabetes mellitus	24 (25)	23 (24)	0.86
Insulin therapy	5 (5.2)	4 (4.2)	0.73
CKD	36 (46.8)	34 (35.4)	0.13
CrCl (ml/min), mean ± SD	63.8±24.0	71.2±29.2	0.073
Dialysis	0 (0)	0 (0)	Na
Prior AMI	11 (11.5)	23 (24.5)	0.023
Liver disease	4 (4.2)	4 (4.2)	1
Previous ischemic stroke	34 (35.4)	28 (29.2)	0.35
Previous TIA	7 (7.3)	9 (9.4)	0.60
Previous bleeding	63 (65.6)	47 (49)	0.020
Previous ICH	25 (26)	1 (1)	<0.001
LVEF, mean ± SD	51.3±10.8	52.1±11.7	0.58

Supplementary Table 2. Procedural and device-related complications

	Watchman N=65	Amplatzer Cardiac Plug N=43	Amplatzer Amulet N=85
Procedural complications	1	1	2
Leak (>5 mm)*	0	1	0
Device thrombus	1	0	1
Stroke	2	1	3

*Leaks assessed by peri-procedural transesophageal echocardiogram;

Supplementary Figure 1. Matched Kaplan-Mayer analysis of thromboembolic events (panel A), ISTH-major bleeding events (panel B) and combined thromboembolic and ISTH-major bleeding events (panel C) [p-values generated by log-rank (Mantel Cox) test].