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Nonprocedural bleeding after left atrial appendage closure versus direct oral anticoagulants: A subanalysis of the randomized PRAGUE-17 trial

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Abstract

Introduction: Observational studies have shown low bleeding rates in patients with atrial fibrillation (AF) treated by left atrial appendage closure (LAAC); however, data from randomized studies are lacking. This study compared bleeding events among patients with AF treated by LAAC and nonvitamin K anticoagulants (NOAC).

Methods: The *Prague-17* trial was a prospective, multicenter, randomized trial that compared LAAC to NOAC in high-risk AF patients. The primary endpoint was a composite of a cardioembolic event, cardiovascular death, and major and clinically relevant nonmajor bleeding (CRNMB) defined according to the International Society on Thrombosis and Hemostasis (ISTH).

Results: The trial enrolled 402 patients (201 per arm), and the median follow-up was 3.5 (IQR 2.6–4.2) years. Bleeding occurred in 24 patients (29 events) and 32 patients (40 events) in the LAAC and NOAC groups, respectively. Six of the LAAC bleeding events were procedure/device-related. In the primary intention-to-treat analysis, LAAC was associated with similar rates of ISTH major or CRNMB (sHR 0.75, 95% CI 0.44–1.27, $p = 0.28$), but with a reduction in *nonprocedural* major or CRNMB (sHR 0.55, 95% CI 0.31–0.97, $p = 0.039$). This reduction for nonprocedural bleeding with LAAC was mainly driven by a reduced rate of CRNMB (sHR for major bleeding 0.69, 95% CI 0.34–1.39, $p = .30$; sHR for CRNMB 0.43, 95% CI 0.18–1.03, $p = 0.059$). History of bleeding was a predictor of bleeding during follow-up. Gastrointestinal bleeding was the most common bleeding site in both groups.

Conclusion: During the 4-year follow-up, LAAC was associated with less *nonprocedural* bleeding. The reduction is mainly driven by a decrease in CRNMB.

KEYWORDS
atrial fibrillation, bleeding, gastrointestinal bleeding, left atrial appendage closure, major bleeding, nonvitamin K anticoagulants

1 | INTRODUCTION

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia associated with a 5-fold increase in the risk of stroke. Several randomized trials have found that warfarin reduces the risk of cardioembolic events in AF patients by ~62% but increases the risk of bleeding.[1] Over the last 10 years, nonvitamin K anticoagulants (NOAC) have largely replaced warfarin. In head-to-head comparisons, the rate of major bleeding and intracranial bleeding was significantly reduced with NOAC compared to warfarin.[2]

Since the left atrial appendage (LAA) is the most common location of thrombus formation in a fibrillating atrium, closure of the LAA was a logical step in the development of a nonpharmacological AF treatment that protects against cardioembolic events. Two randomized trials and the associated long-term follow-up demonstrated that LAAC was noninferior to warfarin in terms of the incidence of all-cause stroke, and was superior in terms of reducing major bleeding, especially intracranial hemorrhage.[3]

However, whether LAAC is also associated with reduced bleeding risk, compared to the significantly safer NOACs, remains unknown. Recently, the *PRAGUE-17* trial, a prospective, randomized trial comparing NOAC treatment to LAAC in a high-risk AF cohort, found that LAAC was non-inferior to NOAC relative to the composite endpoint of all-stroke/transient ischemic attack (TIA), clinically significant bleeding, and cardiovascular death; wherein clinically significant bleeding included both major bleeding and clinically relevant nonmajor bleeding (CRNMB).[4,5] The current analysis assessed the relative risk of major and nonmajor bleeding events in the *PRAGUE-17* population between patients assigned to LAAC or NOAC treatment.

2 | METHODS

2.1 | Trial design

The left atrial appendage closure versus novel anticoagulation agents in patients with atrial fibrillation indicated for long-term anticoagulation

trial (*PRAGUE-17*; NCT02426944) was an investigator-initiated, multicenter, prospective, open-label, randomized noninferiority trial conducted at 10 cardiac centers in the Czech Republic.[4] Briefly, patients were randomly assigned to LAAC or NOAC in a 1:1 ratio. Randomization was designed to ensure comparable CHA_2DS_2-VASc scores between groups. The ethics committees at the participating centers approved the protocol. All patients provided written informed consent. Events were adjudicated by an independent clinical endpoint committee (CEC).

2.2 | Study participants

We recruited NOAC-eligible patients with nonvalvular AF and either: (i) a history of bleeding requiring intervention or hospitalization, (ii) a history of a cardioembolic event while on anticoagulation, or (iii) a moderate or high-risk profile defined as CHA_2DS_2-VASc ≥3 and HAS-BLED ≥ 2. CHA_2DS_2-VASc risk factors included congestive heart failure, hypertension, age ≥65 or ≥75 (two points), diabetes, a prior cardioembolic event, female or vascular disease; HAS-BLED factors included uncontrolled hypertension (i.e., systolic blood pressure >160 mmHg despite antihypertensive treatment), a prior bleeding, age >75, a prior cardioembolic event, abnormal liver or renal function, and a labile international normalized ratio (INR).[6] Key exclusion criteria included mechanical valve prosthesis, clear indication (other than AF), or contraindication for NOAC or LAAC; for details, see the original publications.[4,5]

2.3 | Study treatment

Patients randomized to the NOAC group received either rivaroxaban, apixaban, or dabigatran at the manufacturer-recommended dose. The participating centers agreed that apixaban was preferred, although all available NOACs were permitted. Medication compliance was monitored by querying patients about regular medication use during each visit.

Patients randomized to LAAC underwent appendage closure using a commercially available Amulet (Abbott Inc) or Watchman/Watchman FLX device (Boston Scientific Inc). After LAAC, the recommended antithrombotic regimen was aspirin 100 mg/day plus clopidogrel 75 mg/day for 3 months. After 3 months, transesophageal echocardiography (TEE) was performed, and clopidogrel was withdrawn (in the absence of device-related thrombus or leak ≥5 mm). Aspirin was continued indefinitely. Based on patient characteristics and device type, this postimplant antithrombotic regimen could be individualized. For example, dual antiplatelet treatment (DAPT) could be shortened to 6 weeks in patients with high-bleeding risk.[4,5] Regardless of group, outpatient follow-up occurred at 6 weeks, and 3, 6, 9, and 12 months, and every 6 months thereafter.

2.4 | Study outcomes

The primary endpoint of the trial was the occurrence of any of the following events following randomization: (i) stroke or TIA, (ii) systemic embolism, (iii) clinically significant bleeding, (iv) cardiovascular death, or (v) a significant procedure-related or device-related complication. Clinically significant bleeding was a composite of major bleeding and CRNMB, based on the International Society on Thrombosis and Hemostasis (ISTH) criteria.[7] ISTH-major bleeding includes (i) decrease in hemoglobin ≥20.0 g/L over 24 h, (ii) transfusion of ≥2 units of packed red cells, (iii) bleeding at a critical site (i.e., intracranial, intraspinal, intraocular, pericardial, intramuscular with compartment syndrome, or retroperitoneal), or (iv) fatal bleeding. CRNMB was defined as bleeding requiring hospitalization or an invasive procedure but not meeting ISTH major criteria, irrespective of whether antithrombotic treatment was later re-initiated or permanently withdrawn. Procedure- or device-related complications were defined as all complications that occurred as a consequence of the procedure or were related to the device. For the purpose of the present post hoc analysis, bleeding events not associated with the procedure or device in the LAAC group (nonprocedural) were analyzed separately.

2.5 | Statistical analysis

The primary hypothesis was that LAAC would be noninferior to NOAC for the primary endpoint. The primary analysis was prespecified to be performed on a modified intention-to-treat basis.[5] In addition, post hoc secondary per-protocol and on-treatment analyses were performed; for details, see the original publication.[4,5]

For the current analysis, the following standard descriptive statistical methods were used to describe the data: absolute and relative frequencies for categorical data and the median with interquartile range (IQR) or mean with standard deviation for continuous data. For categorical variables, statistical analysis was done using Fisher's exact test, and for continuous variables, the Mann–Whitney *U* test was used. Cumulative incidence functions (CIFs) and Fine-Gray competing risk regression models were used for data visualization and description, and the incidence of all described bleeding endpoints was adjusted for *all-cause* mortality. Statistical analyses were performed using SPSS v. 28.0.1.1 software (IBM Corporation, 2021).

3 | RESULTS

3.1 | Patients and follow-up

Between October 2015 and January 2019, from 860 patients screened at 10 centers, 415 patients were enrolled in the study. Of these, 13 patients were excluded, 8 for informed consent withdrawal and 5 for the presence of LAA thrombus on TEE before the procedure. Ultimately, 402 patients were randomized (201 to each group) with a median of 3.5 years (IQR: 2.6–4.3) in the LAAC group and 3.5 years (IQR: 2.6–4.2) in the NOAC group, producing an aggregate of 1354 patients-years. One patient was lost to follow-up after the 6-month visit.

The groups were well-balanced in clinical characteristics (Table 1). The mean age was 73.3 years, and 34.3% were women, the mean CHA_2DS_2-VASc was 4.7 ± 1.5, the HAS-BLED score was 3.0, 35.3% had a prior cardioembolism, and 47.8% had a prior bleeding event. Most patients had previously received anticoagulants, either vitamin-K antagonists (VKAs) (47.0%) or NOACs (30.1%); of the remaining patients, most (74%) had presented with de novo AF.

3.1.1 | Treatment characteristics

Of the patients randomized to LAAC, 7.0% (14 of 201) did not undergo the procedure because of either patient refusal ($n = 9$) or due to anatomical consideration ($n = 5$). All 14 patients agreed to continued follow-up, and 12 crossed over to the NOAC group. Ultimately, 187 patients underwent LAAC, and the LAA was successfully occluded in 181 (96.8%). Amulet, Watchman, or Watchman FLX devices were implanted in 61.3%, 35.9%, and 2.8% of patients, respectively. Most LAA occluded patients (148, 81.8%) received DAPT upon discharge (8 of whom received it for 6 weeks only), 25 patients (13.8%) received apixaban for 3 months (23 pts. 5 mg and 2 pts. 2.5 mg twice daily) followed by aspirin. Eight patients (4.4%) received apixaban (all 5 mg twice daily) for 6 weeks, followed by DAPT for 6 weeks. In the NOAC group, the most frequently used anticoagulant was apixaban, which was used in 192 patients (95.5%). Apixaban was dosed at 5 or 2.5 mg twice daily in 159 (79.1%) and 33 (16.4%) patients, respectively. Dabigatran was used in eight patients at a dose of 150 mg twice daily in seven patients (3.5%) or 110 mg twice daily in one patient (0.5%). Rivaroxaban, 20 mg daily, was used in one (0.5%) patient.

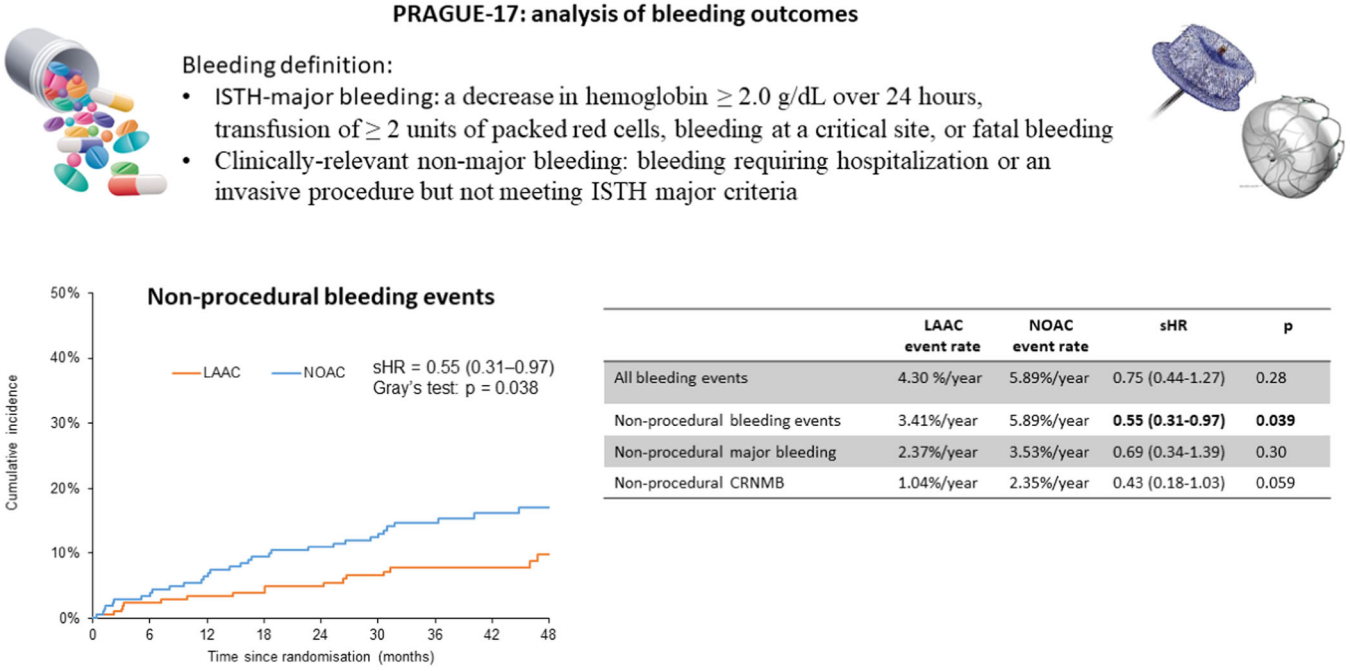
3.1.2 | Bleeding events in the modified intention-to-treat (mITT) analysis

In total, there were 69 bleeding events in 56 patients. Based on mITT criteria, there were 40 bleeding events in 32 patients in the NOAC group (5.89 per 100 patient-years) compared to 29 bleeding events in 24 patients in the LAAC group (4.30 per 100 patient-years). The difference between groups was not statistically significant (sHR 0.75, 95% CI 0.44–1.27, $p = .28$) (Central Illustration 1, Figure 1 and Table 2). In the NOAC group, due to a bleeding event, NOAC treatment was permanently stopped in 15 patients (47% of NOAC patients with bleeding events), and 13 were subsequently crossed-over to the LAAC treatment. Six bleeding events in the LAAC group were procedure/device-related (three pericardial effusions and three vascular access bleeds). As such, if only nonprocedural bleeding events (all ISTH-major + CRNMB) were calculated, there were 23 bleeding events in 18 patients in the LAAC group (3.41 per 100 patients-year) which was significantly lower compared to the NOAC group (sHR 0.55, 95% CI 0.31–0.97, $p = 0.039$) (Central Illustration 1, Figure 1 and Table 2) There were 16 nonprocedural major bleeding events in 13 patients in the LAAC group (2.37 per 100 patients-year) and 24 nonprocedural major bleeding events in 19 patients in the

TABLE 1 Baseline characteristics and risk factors of study participants.

	NOAC ($n = 201$)	LAAC ($n = 201$)	p Value
Demographics			
Age (years)	73.2 ± 7.2	73.4 ± 6.7	0.68
Male gender (%)	130 (64.7%)	134 (66.7%)	0.67
Weight (kg)	88.1 ± 16.2	86.9 ± 17.6	0.49
Clinical history			
CHA_2DS_2-VASc	4.7 ± 1.5	4.7 ± 1.5	0.93
HAS-BLED	3.0 ± 0.9	3.1 ± 0.9	0.17
Heart failure (%)	90 (44.8%)	88 (43.8%)	0.84
Hypertension (%)	186 (92.5%)	186 (92.5%)	1.0
Uncontrolled hypertension	62 (30.8%)	56 (27.9%)	0.51
Diabetes mellitus (%)	90 (44.8%)	73 (36.3%)	0.08
History of cardioembolic event (%)	69 (34.3%)	73 (36.3%)	0.68
Of which stroke (%)	63 (91.3%)	66 (90.4%)	
History of MI (%)	39 (19.4%)	30 (14.9%)	0.23
History of bleeding predisposition (%)	95 (47.3%)	109 (54.2%)	0.16
Bleeding history (%)	91 (45.3%)	102 (50.7%)	0.27
Abnormal renal/liver function (%)	47 (23.4%)	44 (21.9%)	0.72
Labile INR (%)	88 (43.8%)	109 (54.2%)	0.04
Alcohol abuse (%)	8 (4%)	7 (3.5%)	0.79
Drugs increasing bleeding risk (%)	29 (14.4%)	28 (13.9%)	0.89
Prior antithrombotic treatment			
Warfarin	104 (51.7%)	85 (42.3%)	0.06
NOACs	55 (27.4%)	66 (32.8%)	0.23
If no OAC, new AF appearance	30 (71.4%)	38 (76%)	0.28
Aspirin	32 (15.9%)	39 (19.4%)	0.36
Clopidogrel	11 (5.5%)	17 (8.5%)	0.24
Dual antiplatelet treatment	6 (3.0%)	7 (3.5%)	0.78
Other (low dose LMWH, none)	19 (9.5%)	24 (11.9%)	0.42
Other medication			
ACEI	114 (56.7%)	127 (63.2%)	0.19
Beta-blocker	157 (78.1%)	155 (77.1%)	0.81
Diuretics	129 (64.2%)	133 (66.2%)	0.68
NSAID	17 (8.5%)	14 (7.0%)	0.57
Oral corticosteroids	8 (4%)	6 (3%)	0.59

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; INR, international normalized ratio; NOAC, nonvitamin K anticoagulants; NSAID, nonsteroidal anti-inflammatory drug.



	LAAC event rate	NOAC event rate	sHR	p
All bleeding events	4.30 %/year	5.89%/year	0.75 (0.44-1.27)	0.28
Non-procedural bleeding events	3.41%/year	5.89%/year	**0.55 (0.31-0.97)**	**0.039**
Non-procedural major bleeding	2.37%/year	3.53%/year	0.69 (0.34-1.39)	0.30
Non-procedural CRNMB	1.04%/year	2.35%/year	0.43 (0.18-1.03)	0.059

CENTRAL ILLUSTRATIONSTRATION 1 A reduction in nonprocedural bleeding rates following LAAC compared to NOAC treatment. LAAC, left atrial appendage closure.

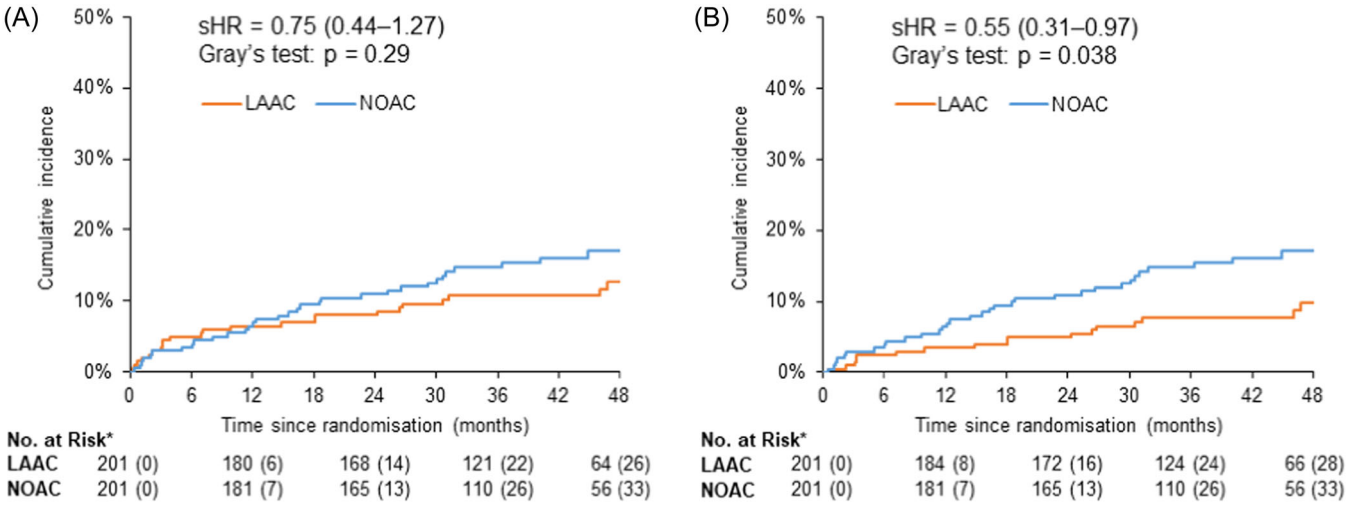


FIGURE 1 Cumulative incidence function for ISTH-major or CRNMB (A, left), and nonprocedural ISTH-major, or CRNMB (B, right), in mITT populations. CRNMB, clinically relevant nonmajor bleeding.

NOAC (3.53 per 100 patient-years); the difference was not statistically significant (sHR 0.69, 95% CI 0.34–1.39, $p = 0.30$) (Figure 2, Table 2). There were seven nonprocedural CRNMB events in seven patients in the LAAC group (1.04 per 100 patient-years), compared to 16 CRNMB events in 16 patients in the NOAC group (2.35 per 100 patient-years); this difference narrowly missed statistical significance (sHR 0.43, 95% CI 0.18–1.03, $p = 0.059$) (Figure 2, Table 2).

3.1.3 | Antithrombotic treatment at the time of bleeding events

There were 40 bleeding events in the NOAC group; all 40 patients were on NOAC at the time of the bleeding event. There were 29 bleeding events in the LAAC group; the antithrombotic medication at the time of the event was single antiplatelet treatment in 12 (41.4%), dual antiplatelet in 7 (24.1%), no antithrombotic treatment in 3

TABLE 2 Incidence of bleeding events in the modified intention-to-treat populations.

	NOAC (*N* = 201) No. of pts with event	No. of events	Event rate	LAAC (*N* = 201) No. of pts with event	No. of events	Event rate	sHR (95% CI)	*p* Value
All major/nonmajor ISTH bleeds	32	40	5.89	24	29	4.30	0.75 (0.44; 1.27)	0.28
ISTH major bleeds only	19	24	3.53	16	19	2.82	0.86 (0.44; 1.66)	0.65
ISTH nonmajor bleeds only	16	16	2.35	10	10	1.48	0.62 (0.28; 1.36)	0.23
ISTH major/nonmajor bleeding, not device-related	32	40	5.89	18	23	3.41	0.55 (0.31; 0.97)	0.039
ISTH major bleeds, not device-related	19	24	3.53	13	16	2.37	0.69 (0.34; 1.39)	0.30
ISTH nonmajor bleeds not device-related	16	16	2.35	7	7	1.04	0.43 (0.18; 1.03)	0.059

Note: Subdistribution hazard ratios (sHR) for the LAAC group in comparison to the NOAC group and corresponding *p* Values were calculated using Fine-Gray regression models with the study group as a covariate. In case of primary endpoint and bleeding, sHR are based on the first event only. Event rate is defined as no. of events per 100 patient-years.

Abbreviations: ISTH, International Society on Thrombosis and Hemostasis; LAAC, left atrial appendage closure; NOAC, nonvitamin K anticoagulation.

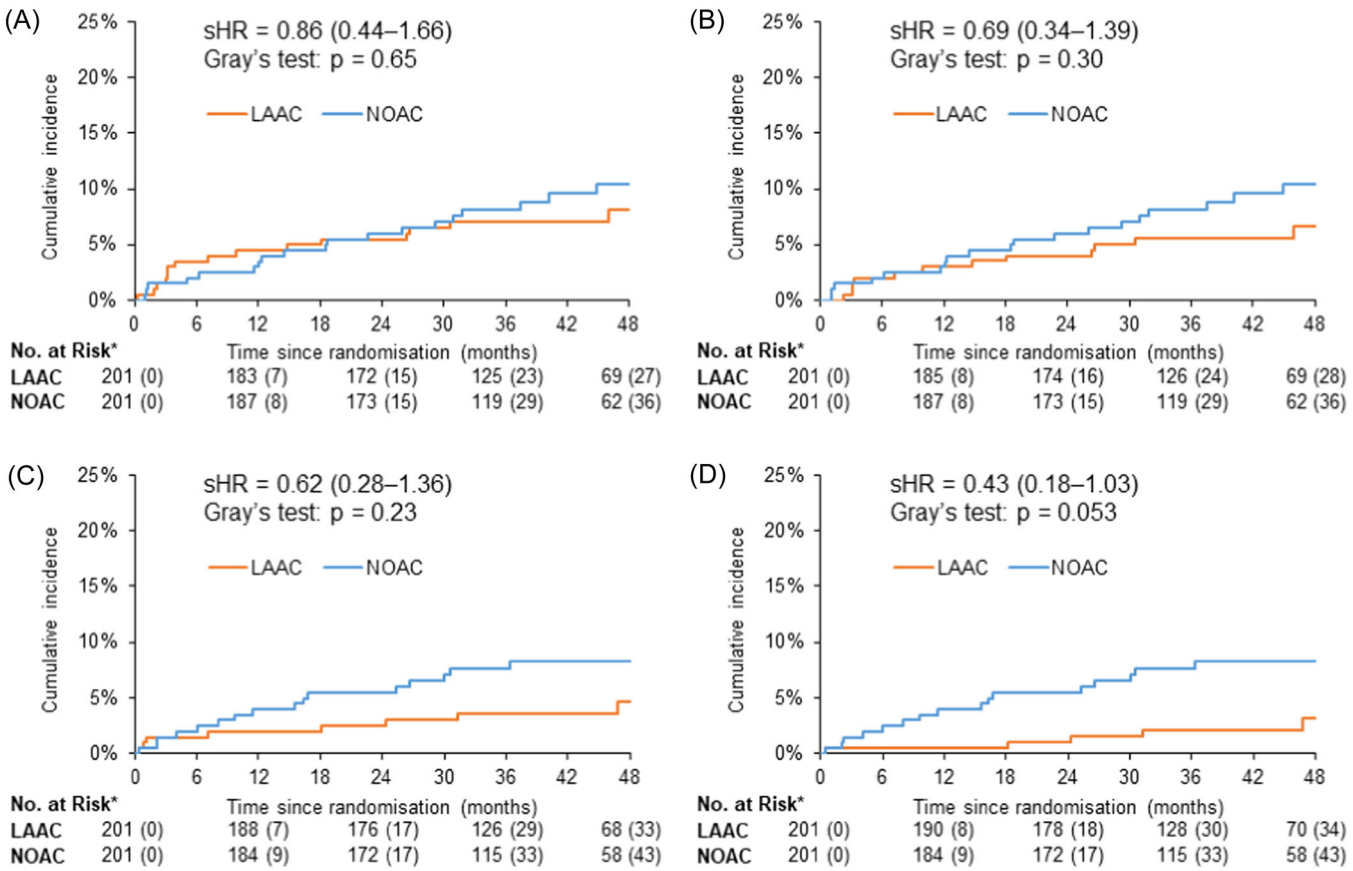


FIGURE 2 Cumulative incidence function for ISTH-major (A), nonprocedural ISTH-major (B), CRNMB (C), and nonprocedural CRNMB (D) in mITT populations. CRNMB, clinically relevant nonmajor bleeding.

(10.3%), and oral anticoagulation in 7 (24.1%) patients. Regarding the presence of oral anticoagulation in the LAAC group at the time of the bleeding events: three patients were in the early period after the implant (within 3 months), and in four patients, NOAC was initiated for stroke or venous thrombosis (i.e., all cases were for clinical reasons, and none were due to device-related thrombosis or peri-device leakage).

3.1.4 | Per-protocol and on-treatment analyses

In the *per-protocol analysis*, 181 patients were analyzed in the LAAC group (i.e., only those with a successfully occluded LAA) and 199 patients in the NOAC group (i.e., only those in whom NOAC treatment had been actually administered). The incidence of all bleeding events (ISTH-major and CRNMB) was not different between groups (4.34% per year with LAAC vs. 6.04% per year with NOACs, sHR 0.76, 95% CI 0.44–1.31, $p = 0.32$). However, the incidence of nonprocedural ISTH-major and CRNMB was lower in the LAAC group compared to the NOAC group (3.30% per year with LAAC vs. 6.04% per year with NOACs, sHR 0.52, 95% CI 0.29–0.97, $p = 0.039$). The *On-Treatment* analysis included 184 and 216 patients in the LAAC and NOAC groups, respectively. In the On-treatment analysis, the incidence of all bleeding events (i.e., ISTH-major and CRNMB) was also similar between both groups (4.29% per year with LAAC vs. 5.85% per year with NOACs, sHR = 0.78, 95% CI 0.44–1.35, $p = 0.38$). However, if procedure-related bleeding events were excluded, the incidence of ISTH-major and CRNMB was lower with LAAC compared to NOAC treatment (3.26% per year with LAAC vs. 5.85% per year with NOACs, sHR = 0.54, 95% CI 0.30–1.00, $p = 0.049$). Hence, both per-protocol and On-treatment analyses yielded results similar to the mITT analysis; LAAC was associated with a significantly lower risk of nonprocedural bleeding. Similarly with mITT analysis, the reduction in bleeding events was driven by the reduced rate of nonprocedural CRNMB (sHR for CRNMB 0.35, 95% CI 0.13–0.94, $p = 0.037$ in the per-protocol analysis, and 0.34, 95% CI 0.13–0.95, $p = 0.035$ in the On-treatment analysis).

3.2 | Bleeding events in relation to patient history

A history of bleeding at the time of randomization was present in 91 NOAC and 102 LAAC patients (48% of the entire cohort). The annualized event rate for major/CRNMB was 8.0%/year in NOAC and 5.75%/year in LAAC patients with prior bleeding, resulting in similar sHR (0.72 (95% CI 0.38–1.37), $p = 0.32$), which was seen in the entire cohort. History of bleeding at randomization was associated with a significantly higher risk of major/CRNMB during the study follow-up in both groups: LAAC (2.47, 95% CI 1.03–5.94, $p = 0.043$) and NOAC (sHR 2.42, 95% CI 1.18–4.98, $p = 0.016$). The risk of bleeding in patients with a bleeding history was mainly driven by a higher risk of CRNMB in both groups: LAAC, sHR for major bleeding 1.66 (95% CI 0.61–4.56), $p = 0.32$, sHR for CRNMB 3.89 (95% CI 0.83–18.21), $p = 0.085$; NOAC, sHR for major bleeding 1.32 (95% CI 0.54–3.22), $p = 0.54$, sHR for CRNMB 3.72 (95% CI 1.20–11.50), $p = 0.022$.

3.3 | Bleeding types in both groups

The most common bleeding site in both groups was the gastrointestinal tract (GIT), which was the source of 52.5% of bleeding events in the NOAC group and 56.5% of bleeding events in the LAAC group, followed by urological bleeding (Figure 3).

3.4 | Blood count and biochemistry results

Samples for blood counts and basic biochemistry (creatinine, urea nitrogen, liver enzymes) were drawn at baseline and the last patient follow-up visit of the initial study design. Both samples (baseline and follow-up) were obtained in 254 (63.2%) patients (Table 3), and the mean time between the admission and the last follow-up visit with laboratory values available was 20.7 ± 11.1 months. There were no differences in the baseline blood count and biochemistry results between groups. Compared with the baseline values, there were no significant changes in the last follow-up results of blood count in both groups. There was only a small, similar, and nonsignificant decrease in

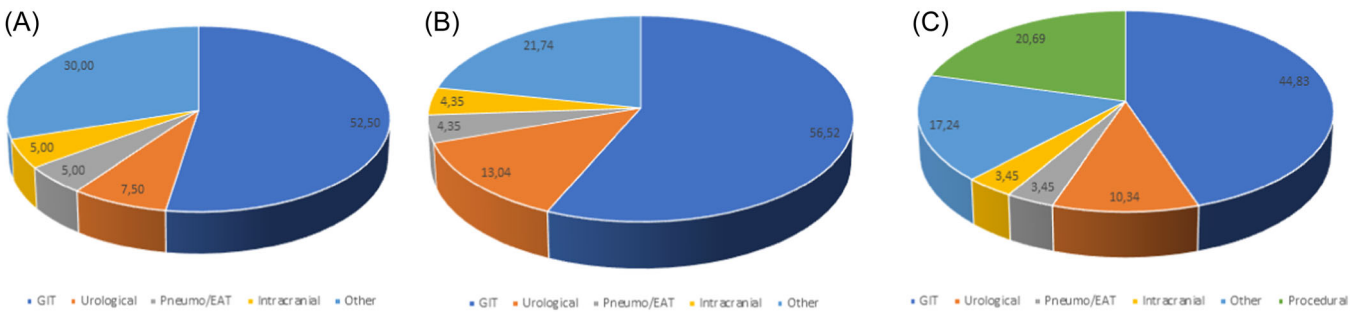


FIGURE 3 Location of bleeding events (A) NOAC group, (B) LAAC, non-procedural bleeding events, (C) LAAC, all bleeding events.

TABLE 3 Baseline, last follow-up visit, and change in laboratory values between the admission and the last follow-up visit in the intention-to-treat populations.

	NOAC (*n* = 138)			LAAC (*n* = 116)			*p* Value (comparison of delta)
		Last visit	Delta	Baseline	Last visit	Delta	
	Baseline mean (± SD)	Mean (± SD)	Mean (± SD)	Mean (± SD)	Mean (± SD)	Mean (± SD)	
Hemoglobin [g/L]	139 (± 15)	136 (± 18)	−3 (± 16)	140 (± 17)	137 (± 20)	−3 (± 16)	0.712
White blood cells [10^9/L]	7.8 (± 2.1)	7.8 (± 2.2)	0.0 (± 2.0)	7.5 (± 2.0)	7.7 (± 2.2)	0.2 (± 1.9)	0.605
Platelets [10^9/L]	217 (± 58)	220 (± 69)	3 (± 50)	206 (± 60)	204 (± 60)	−2 (± 40)	0.708
Hematocrit [%]	41.3 (± 4.1)	40.9 (± 5.0)	−0.4 (± 4.5)	41.5 (± 4.9)	41.2 (± 5.6)	−0.3 (± 4.7)	0.941
Creatinine [μmol/L]	101 (± 33)	107 (± 38)	6 (± 29)	106 (± 42)	112 (± 53)	5 (± 29)	0.597
Urea [mmol/L]	7.0 (± 4.1)	7.4 (± 3.6)	0.4 (± 3.9)	7.1 (± 3.6)	7.9 (± 4.4)	0.8 (± 3.5)	0.404
ALT [μkat/L]	0.50 (± 0.36)	0.41 (± 0.25)	−0.09 (± 0.29)	0.48 (± 0.28)	0.42 (± 0.21)	−0.07 (± 0.28)	0.401
AST [μkat/L]	0.50 (± 0.28)	0.46 (± 0.26)	−0.04 (± 0.20)	0.45 (± 0.20)	0.41 (± 0.17)	−0.03 (± 0.18)	0.973
CRP [mg/dL]	7.3 (± 16.5)	7.6 (± 12.2)	0.3 (± 18.9)	6.1 (± 10.5)	7.8 (± 12.5)	1.8 (± 13.7)	0.389

Note: *p* Value of Mann–Whitney *U* test is reported to compare change in laboratory values in patients from NOAC and LAAC groups; Bonferroni correction was applied.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CRP, C-reactive protein; LAAC, left atrial appendage closure; NOAC, nonvitamin K anticoagulation.

hemoglobin (−3 g/L) in both groups. Regarding biochemistry, there was a small nonsignificant increase in serum creatinine in both groups (+6 μmol/L with NOAC and +5 μmol/L with LAAC, resp.) The changes in blood count as well as in biochemistry were not statistically different between groups (Table 3).

4 | DISCUSSION

In the *PRAGUE-17* population of high thrombotic and bleeding risk, assignment to the LAAC was associated with reduced nonprocedural bleeding events. This difference was mainly driven by a reduction in clinically relevant nonmajor bleeding. Bleeding sites were similar between both groups, with GIT bleeding being the most often common. A history of bleeding before randomization was associated with a higher risk for bleeding during follow-up.

4.1 | LAAC versus warfarin in previous randomized control trials

In a pooled analysis of the 3-year follow-up of the *PROTECT-AF* and *PREVAIL* trials, bleeding event rates from randomization to the end of follow-up were similar between patients assigned to LAAC and warfarin (3.5 events vs. 3.6 events per year, RR 0.96).[8] Approximately half the bleeds (48%) in the LAAC group occurred within the first 7 days after randomization: many of these were complications of the procedure and likely a consequence of more intensive antithrombotic treatment in the days just after the procedure (warfarin for 6 weeks, and DAPT for 6 months). On the other hand, during long-term follow-up (i.e., after 7 days post-randomization), the LAAC group had a significantly reduced rate of major bleeding compared with long-term warfarin (1.8 events vs. 3.6 events per 100 patient-years, RR = 0.49, $p = 0.001$). This difference became even more pronounced in Landmark analyses commencing later in follow-up (1.3 vs. 3.6 events per 100 patient-years beyond 45 days, RR 0.37, $p < 0.001$; and 1.0 vs. 3.5 events per 100 patient-years beyond 6 months, RR 0.28, $p < 0.001$).[8]

In the initial report of the *PRAGUE-17* trial with 20 months of follow-up, the difference in the number of nonprocedural bleeding events did not reach statistical significance (sHR 0.53, 95% CI 0.26–1.06).[4] In the present analysis of 3.5 years of follow-up, the rate of nonprocedural bleeding events was significantly reduced with LAAC compared to NOAC (sHR 0.55, 95% 0.31–0.97), which is in agreement with previous results and emphasizes the importance of the length of follow-up in studies on LAAC. In the Amulet observation registry of 1088 patients, the annualized rate of major bleeding was 7.2%/year for the whole study period. However, it decreased from 10.1%/year over the first year to an annualized rate of 4%/year over the second year.[9] The immediate LAAC postprocedure period was associated with procedural complications (most of them were bleeding events) or the need for more intensive anti-thrombotic treatment (either DAPT, warfarin, or NOAC). Although several studies have tried to optimize antithrombotic treatment post-LAAC to minimize bleeding risk and achieve a low risk of device-related thrombosis, the immediate antithrombotic treatment needs to be more intense than that used later in the follow-up. Therefore, the profit of LAAC should be expected later on, as was the case in our study, that is, the bleeding curves started to diverge ~6 months after the

procedure (Central Illustration 1). Although bleeding was more often in patients with a history of bleeding than without, the relative profit (according to the sHR) was similar in both patient cohorts.

Directly comparing annual bleeding rates between the *PRAGUE-17* versus *PROTECT-AF* and *PREVAIL* trials is difficult due to significant differences between the studies. In the PROTECT and PREVAIL trials, major bleeding was defined as an adverse event assigned one of several bleeding codes and adjudicated by the CEC as significant (i.e., life-threatening or resulting in hospitalization, prolongation of hospitalization, or death), ISTH criteria were not used. In the *PRAGUE-17* trial, major bleeding was defined according to the ISTH criteria, and bleeding events requiring hospitalization or an invasive procedure but not meeting ISTH major criteria were adjudicated as clinically relevant nonmajor events. Thus, some nonmajor bleeds in *PRAGUE-17* (e.g., requiring hospitalization) may have been adjudicated as major bleeds in *PROTECT-AF* or *PREVAIL*. Additionally, the *PRAGUE-17* cohort, with HAS-BLED scores of 3.0, was at higher risk compared to *PROTECT-AF* and *PREVAIL* (modified HAS-BLED 1.9).

In contrast to the Watchman randomized trials, in which LAAC reduced major bleeding events, this post hoc analysis of *PRAGUE-17* found that the reduction of nonprocedural bleeding was driven by clinically relevant nonmajor bleeding. The explanation might be the better safety profile of NOAC compared to warfarin, documented in large trials comparing NOAC with warfarin. On the other hand, the definition of major bleeding according to the ISTH is very stringent, and many bleeding events that are not evaluated as "major" are, in fact, clinically significant. In clinical studies, any event requiring hospitalization should be adjudicated as a severe adverse event since any hospitalization can lead to consequent hospitalization-related events (e.g., pneumonia or other infections, pulmonary embolism, etc.), especially in elderly patients. Furthermore, in clinical practice with antithrombotic medication, bleeding is the most common reason for drug discontinuation (which leaves AF patients unprotected). Therefore, the term "clinically-relevant bleeding" as a common term for major and nonmajor bleeding could be better suited to its clinical importance.

4.2 | Bleeding in previous large apixaban trials

Definitions of bleeding used in the *PRAGUE-17* trial were similar to the ones used in the major NOAC (apixaban) trials. The *AVERROES* trial compared apixaban versus aspirin in AF patients. The annual rates of ISTH-major bleeding events in *AVERROES* were 1.34% on aspirin and 1.56% on apixaban in patients with CHA_2DS_2VASc scores of 3–5, 4.06% on aspirin, and 4.7% on apixaban in patients with CHA_2DS_2VASc scores of 6–8.[10] In the current analysis of the *PRAGUE-17*, the corresponding rates of major bleeding were 3.53% on NOAC and 2.37% (or 2.82%, including procedure-related events) with LAAC. The higher bleeding rates observed in our study were probably related to the higher-risk population enrolled (history of bleeding was present in only 3% of *AVERROES* patients vs. 47.3% of *PRAGUE-17* patients). It is also in agreement with a published subanalysis of high-risk bleeding patients in the *ARISTOTLE* trial, in which the rate of major bleeding in patients on apixaban was 3.46% per 100 patient-years in patients with HAS-BLED scores >3.0.[11]

Bleeding is the most common adverse event for all available NOACs. In *AVERROES*, the incidence of any bleeding was present in 20.2% of patients per year.[11] Bleeding is also the most common cause of NOAC discontinuation. In a NOACs trial in AF patients, NOACs were discontinued due to all causes in 21.7% of patients, including temporary discontinuations, and permanently due to adverse events (mainly bleeding) in 7.19% of patients.[12] Persistence of anticoagulation in nonrandomized registries was worse than in randomized clinical trials. In one of the largest observational cohort studies with over 40 000 AF patients on oral anticoagulation, the 1-year persistence for warfarin was only 70%.[13]

4.3 | Bleeding locations

The most common bleeding site in the *PRAGUE-17* trial was GIT (52.5% with NOAC vs. 56.5% with LAAC), followed by genito-urinary bleeding. It is similar to that reported in both arms of *AVERROES* and other NOAC trials, in which GIT bleeding was also the dominant one.[14] GIT bleeding often occurs despite low or modest level of antithrombotic treatment and are, therefore, difficult to reduce. However, despite the increased safety of NOACs compared to warfarin with regard to intracranial hemorrhage, the incidence of GIT bleeding remains high even with NOACs.[2,14] Three patients had an intracranial hemorrhage in the *PRAGUE-17* trial (two with NOACs and one on aspirin in the LAAC arm). Finally, hemoglobin or hematocrit levels were similar during follow-up, so there was no evidence of a difference in small, inapparent bleedings between groups.

4.4 | The importance of bleeding in the persistence of treatment

Bleeding events, such as tamponade after LAAC, can present the most dangerous part of this treatment strategy and can be life-threatening. Of note, the risk of peri-procedural pericardial effusion was lower with the new generation of Watchman FLX compared to the Amulet device in the recent Amulet IDE trial[15]; no pericardial effusions were associated with the Watchman FLX implantation in our study. Although all peri-procedural bleeding events in a high-risk cohort represent a serious risk and can be life-threatening, fortunately, the vast majority of postprocedural bleedings had good clinical outcomes and, as such, had no impact on the antithrombotic treatment after discharge or in the long-term. In contrast, bleeding associated with NOAC treatment is different in nature. It is usually spontaneous bleeding occurring later during follow-up and is often a reason for NOAC withdrawal. In the large NOAC trials, NOAC

treatment was discontinued in ~20% of patients during the long term (and in >7% permanently), and the most often reason for NOAC discontinuation was bleeding. Not only clinically relevant bleeding but also minor bleeding can play a role in the persistence of patients on OAC. Considering patient preference regarding the type of medication and treatment is therefore of great importance. In a recent survey assessing oral anticoagulation preference in AF patients, the attribute of anticoagulation treatment ranked most important was stroke prevention, followed by a reduction in bleeding risk.[16] Also, in a recent systematic meta-analysis that assessed the preferences of AF patients with regard to long-term anticoagulation, stroke risk reduction and risk of medication-associated bleeding are the most important attributes for an AF patient when deciding whether they are "for" or "against" oral anticoagulation.[17] Variations in patient preference, and differences in bleeding outcomes between pharmacological and nonpharmacological treatment, should be considered in the decision-making process when determining the optimal treatment for each particular patient. Both treatment strategies, LAAC and NOAC, seem to offer similar protection from cardioembolic events and CV death.[18] As such, the reduced risk of bleeding associated with LAAC could represent a significant benefit for AF patients.

On the other hand, a combination of surgical LAAC and oral anticoagulation in the LAAOS III trial was associated with a reduction in cardioembolic events.[19] These results were achieved using surgical and not percutaneous LAAC. However, this concept has to pay attention, and percutaneous LAAC with OAC should be tested as a treatment alternative for AF patients with high thrombotic risk.

5 | LIMITATIONS

The present analyses are post hoc sensitivity analyses underpowered for analysis of any part of the composite endpoint; the study was designed and powered to compare the primary composite outcome.

6 | CONCLUSION

During the 4-year follow-up, LAAC was associated with fewer cases of *nonprocedural* bleeding. The reduction is mainly driven by a decrease in CRNMB.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request. The data that support the findings of this study are available on request from the corresponding author, dr. Pavel Osmancik.

ETHICS STATEMENT

The study was approved by the Ethics Committeee of the University Hospital Kralovske Vinohrady, and all local Ethics Committtee of all participating centers. All patients signed the informed content before the enrollment in the study

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