JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
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PUBLISHED BY ELSEVIER

ORIGINAL INVESTIGATIONS

4-Year Outcomes After Left Atrial Appendage Closure Versus Nonwarfarin Oral Anticoagulation for Atrial Fibrillation

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ABSTRACT

BACKGROUND The PRAGUE-17 (Left Atrial Appendage Closure vs Novel Anticoagulation Agents in Atrial Fibrillation) trial demonstrated that left atrial appendage closure (LAAC) was noninferior to nonwarfarin direct oral anticoagulants (DOACs) for preventing major neurological, cardiovascular, or bleeding events in patients with atrial fibrillation (AF) who were at high risk.

OBJECTIVES This study sought to assess the prespecified long-term (4-year) outcomes in PRAGUE-17.

METHODS PRAGUE-17 was a randomized noninferiority trial comparing percutaneous LAAC (Watchman or Amulet) with DOACs (95% apixaban) in patients with nonvalvular AF and with a history of cardioembolism, clinically-relevant bleeding, or both CHA_2DS_2-VASc ≥3 and HASBLED ≥2. The primary endpoint was a composite of cardioembolic events (stroke, transient ischemic attack, or systemic embolism), cardiovascular death, clinically relevant bleeding, or procedure-/device-related complications (LAAC group only). The primary analysis was modified intention-to-treat.

RESULTS This study randomized 402 patients with AF (201 per group, age 73.3 ± 7.0 years, 65.7% male, CHA_2DS_2-VASc 4.7 ±1.5, HASBLED 3.1 ± 0.9). After 3.5 years median follow-up (1,354 patient-years), LAAC was noninferior to DOACs for the primary endpoint by modified intention-to-treat (subdistribution HR [sHR]: 0.81; 95% CI: 0.56-1.18; $P = 0.27$; P for noninferiority = 0.006). For the components of the composite endpoint, the corresponding sHRs were 0.68 (95% CI: 0.39-1.20; $P = 0.19$) for cardiovascular death, 1.14 (95% CI: 0.56-2.30; $P = 0.72$) for all-stroke/transient ischemic attack, 0.75 (95% CI: 0.44-1.27; $P = 0.28$) for clinically relevant bleeding, and 0.55 (95% CI: 0.31-0.97; $P = 0.039$) for nonprocedural clinically relevant bleeding. The primary endpoint outcomes were similar in the per-protocol (sHR: 0.80; 95% CI: 0.54-1.18; $P = 0.25$) and on-treatment (sHR: 0.82; 95% CI: 0.56-1.20; $P = 0.30$) analyses.

CONCLUSIONS In long-term follow-up of PRAGUE-17, LAAC remains noninferior to DOACs for preventing major cardiovascular, neurological, or bleeding events. Furthermore, nonprocedural bleeding was significantly reduced with LAAC. (PRAGUE-17 [Left Atrial Appendage Closure vs Novel Anticoagulation Agents in Atrial Fibrillation]; NCT02426944)
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ISSN 0735-1097/$36.00 https://doi.org/10.1016/j.jacc.2021.10.023

ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation

CV = cardiovascular

DAPT = dual antiplatelet treatment

DOAC = direct oral anticoagulant

IQR = interquartile range

ITT = intention-to-treat

LA = left atrial

LAA = left atrial appendage

LAAC = left atrial appendage closure

mITT = modified intention-to-treat

OAC = oral anticoagulant

SE = systemic embolism

sHR = subdistribution HR

TEE = transesophageal echocardiography

TIA = transient ischemic attack

Left atrial appendage closure (LAAC) is a nonpharmacologic option for preventing cardioembolic events in patients with atrial fibrillation (AF) at significant stroke risk. However, long-term results from randomized clinical trials are sparse; indeed, long-term results are only available from 2 randomized studies comparing LAAC using the Watchman device with warfarin (1). In these reports, LAAC was associated with lower rates of nonprocedure-related bleeding. However, since their introduction into clinical practice, direct oral anticoagulants (DOACs) have largely replaced warfarin. Because treatment using DOACs is associated with less bleeding (including intracranial hemorrhage) than warfarin (2), the potential benefit of LAAC relative to DOACs is unclear, prompting the PRAGUE-17 (Left Atrial Appendage Closure vs Novel Anticoagulation Agents in Atrial Fibrillation; NCT02426944) trial.

In PRAGUE-17, we compared LAAC with DOAC treatment for the incidence of the composite primary endpoint of cardioembolism, cardiovascular (CV) death, clinically relevant bleeding, and procedure- or device-associated complications (3). In the primary analysis, at a median follow-up of 20 months, the incidence of the primary endpoint was similar between groups. Because the trial was not powered to identify differences in the individual components of the primary composite endpoint, there were no statistically-significant differences in their incidence, including the incidence of nonprocedural clinically relevant bleeding. However, the maximum benefit of LAAC, particularly in terms of bleeding, is expected to be long term, that is, after patients have ceased (D)OAC and/or dual antiplatelet treatment (DAPT). Accordingly, short-term results have the potential for a type II error—a potential to miss significant LAAC benefits on bleeding. Conversely, if there are late LAAC events, the relatively short follow-up in the trial also raises a potential for a type I error, that is, inappropriately concluding noninferiority for the primary composite endpoint. But as prespecified by protocol, patients in PRAGUE-17 continued to be followed up beyond the time point of the initial analysis. Herein, we report the clinical outcomes after 4 years of follow-up of the PRAGUE-17 trial population.

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METHODS

STUDY DESIGN. The protocol and results of the PRAGUE-17 trial have been described previously (3,4). In brief, the PRAGUE-17 trial was an investigator-initiated, multicenter, prospective, open-label, randomized, noninferiority trial conducted at 10 cardiac centers in the Czech Republic. Patient enrollment began in October 2015 and concluded in January 2019. The trial was approved by the multicenter ethics committee at University Hospital Kralovske Vinohrady (approval no. EK-VP/29/0/2014) and by the local ethics committees at participating centers.

CRITERIA FOR ELIGIBILITY. Patients with nonvalvular AF and at moderate or high risk for stroke or bleeding were eligible. Inclusion criteria were AF and one of the following: 1) history of bleeding requiring intervention or hospitalization; 2) history of cardioembolism while taking anticoagulation; or 3) a moderate to high risk profile, defined as CHA_2DS_2-VASc ≥3 plus HAS-BLED ≥2. Key exclusion criteria include mechanical valve prosthesis, mitral stenosis, comorbidities other than AF mandating anticoagulation, patent foramen ovale with large atrial septal aneurysm, mobile aortic plaque, symptomatic carotid arterial atherosclerosis, clinically significant bleeding within 30 days, cardioembolic event within 30 days, and creatinine clearance <30 mL/min. If

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Faisal Merchant, MD, served as Guest Associate Editor for this paper. Javed Butler, MD, MPH, MBA, served as Guest Editor-in-Chief for this paper.
The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

Manuscript received September 17, 2021; revised manuscript received October 5, 2021, accepted October 14, 2021.

randomized to LAAC, transesophageal echocardiography (TEE) was performed to exclude LA thrombi. Consistent with clinical practice, the protocol only mandated TEE in the LAAC group and not before DOAC initiation. The presence of a thrombus in the LAA or LA was a prespecified additional exclusion criterion. Patients were randomly assigned to LAAC or DOACs in a 1:1 ratio using a centralized computer system and stratified by center to ensure comparable CHA_2DS_2-VASc scores between groups.

TREATMENTS AND FOLLOW-UP. Patients randomized to DOAC therapy could receive rivaroxaban, apixaban, or dabigatran (the approved DOACs at the time of the trial) at the manufacturer-recommended dose. Investigators were instructed to reserve crossover from DOACs to LAAC for cases of bleeding while taking the prescribed DOACs. Patients randomized to LAAC underwent implantation using a commercially available Amulet (Abbott Inc) or Watchman/Watchman-FLX (Boston Scientific Inc) device. Device selection was at the discretion of the implanting center. After LAAC, the recommended antithrombotic regimen was aspirin 100 mg/d plus clopidogrel 75 mg/d for 3 months. If a TEE then demonstrated no device-related thrombus or leak ≥5 mm, clopidogrel was withdrawn, and aspirin was continued indefinitely. Based on patient characteristics and device type, this postimplantation antithrombotic regimen could be individualized and was ultimately left to the physician's discretion. In patients at high risk for bleeding, DAPT could be shortened to 6 weeks. Conversely, in patients with a very high thrombotic risk, alternative regimens included DOAC substitution for DAPT for up to 3 months, or DOACs for 6 weeks followed by DAPT for 6 weeks. For both groups, outpatient follow-up occurred at 6 weeks; 3, 6, 9, and 12 months; and every 6 months thereafter.

STUDY OUTCOMES. Because the risks associated with each treatment strategy are significantly different, the primary endpoint was a composite of safety and efficacy characteristics of both strategies: 1) stroke (ischemic or hemorrhagic) or transient ischemic attack (TIA); 2) systemic embolism (SE); 3) clinically significant bleeding; 4) CV death; or 5) a significant periprocedural or device-related complication. Clinically significant bleeding was a composite of major and nonmajor clinically relevant bleeding according to the International Society on Thrombosis and Hemostasis criteria. Major bleeding includes either a decrease in hemoglobin ≥2.0 g/dL over a 24-hour period, transfusion of ≥2 U of packed red cells, bleeding at a critical site (intracranial, intraspinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome, or retroperitoneal), or fatal bleeding. Nonmajor clinically relevant bleeding is defined as bleeding requiring hospitalization or an invasive procedure, but not meeting International Society on Thrombosis and Hemostasis major criteria.

STATISTICAL DESIGN AND ANALYSIS. The primary hypothesis was that LAAC would be noninferior to DOACs for the primary endpoint. The primary analysis was prespecified to be performed on a modified intention-to-treat (mITT) basis, including all randomized patients without an LAA thrombus by TEE. As previously described (3), 13% and 10% of the DOAC and LAAC cohorts, respectively, were estimated to experience the primary endpoint annually. A minimum of 396 study subjects provided 80% power at an α-level of 0.05, for a noninferiority margin of 5% (or HR: 1.47). This margin is concordant with the U.S. Food and Drug Administration guidance. The power analysis was computed using PASS software version 13 (NCSS). Because ITT outcomes can potentially bias noninferiority trials toward the null hypothesis, post hoc secondary per-protocol and on-treatment analyses were also performed. Cumulative incidence functions and Fine-Gray competing risk regression models were adopted for data visualization and description. As previously described, primary analyses were conducted after adjusting for the competing risk of mortality. For other data, standard descriptive statistical methods were used: absolute and relative frequencies for categorical data and the median with interquartile range (IQR) or mean ± SD for continuous data. The influence of patient characteristics on the occurrence of endpoints was calculated using the Fine-Gray regression models with the study group as a covariate and is displayed as subdistribution HR (sHR). The sHR for the primary endpoint was compared to the noninferiority margin of 5% evaluated for 4-year cumulative incidence using Wald statistic. Statistical analyses were performed using SPSS software version 25.0 (IBM Corporation) and cmprsk (2.2-10) package in R version 4.0.0 (R Foundation).

RESULTS

Between October 14, 2015, and January 18, 2019, 415 patients were enrolled at 10 centers (Supplemental Figure 1). Thirteen patients were excluded, 8 withdrew informed consent, and 5 had LAA thrombus on preprocedure TEE imaging. Ultimately, 201 patients were randomized per group and followed for a median

TABLE 1 Baseline Characteristics and Risk Factors of Participants

	DOACs (n = 201)	LAAC (n = 201)
Age, y	73.2 ± 7.2	73.4 ± 6.7
<75 y	122 (60.7)	116 (57.7)
>75 y	79 (39.3)	85 (42.3)
Male	130 (64.7)	134 (66.7)
Weight, kg	88.1 ± 16.2	86.9 ± 17.6
Clinical history		
AF type		
Paroxysmal	67 (33.3)	53 (26.4)
Persistent	46 (22.9)	47 (23.4)
LS persistent	16 (8.0)	18 (9.0)
Permanent	72 (35.8)	83 (41.3)
CHA_2DS_2-VASc	4.7 ± 1.5	4.7 ± 1.5
CHA_2DS_2-VASc ≤3	50 (24.9)	48 (23.9)
CHA_2DS_2-VASc = 4	40 (19.9)	47 (23.4)
CHA_2DS_2-VASc = 5	57 (28.4)	50 (24.9)
CHA_2DS_2-VASc ≥6	54 (26.9)	56 (27.9)
HAS-BLED	3.0 ± 0.9	3.1 ± 0.9
Heart failure	90 (44.8)	88 (43.8)
Hypertension	186 (92.5)	186 (92.5)
Diabetes mellitus	90 (44.8)	73 (36.3)
History of cardioembolic event	69 (34.3)	73 (36.3)
Of which is stroke	63 (91.3)	66 (90.4)
History of MI	39 (19.4)	30 (14.9)
Randomized at experienced centers	140 (69.7)	141 (70.1)
Prior antithrombotic treatment		
Warfarin	104 (51.7)	85 (42.3)
DOACs	55 (27.4)	66 (32.8)
If no OACs, new AF appearance	30 (71.4)	38 (76)
Aspirin	32 (15.9)	39 (19.4)
Clopidogrel	11 (5.5)	17 (8.5)
Dual antiplatelet treatment	6 (3.0)	7 (3.5)
Other (low dose LMWH, none)	19 (9.5)	24 (11.9)

Values are mean ± SD or n (%).

AF = atrial fibrillation; DOAC = direct oral anticoagulant; LAAC = left atrial appendage closure; LMWH = low molecular weight heparin; LS = long-standing; MI = myocardial infarction.

of 3.5 years (IQR: 2.6-4.3 years) in the LAAC group and 3.5 years (IQR: 2.6-4.2 years) in the DOAC group, for an aggregate of 1,354 patient-years. Baseline clinical characteristics are shown in **Table 1** and Supplemental Table 1. The mean age was 73.3 ± 7.0 years, 34.3% were women, mean CHA_2DS_2-VASc = 4.7 ± 1.5 (>25% being CHA_2DS_2-VASc >6), prior cardioembolism in 35.3%, and prior clinically relevant bleeding in 47.8% of patients.

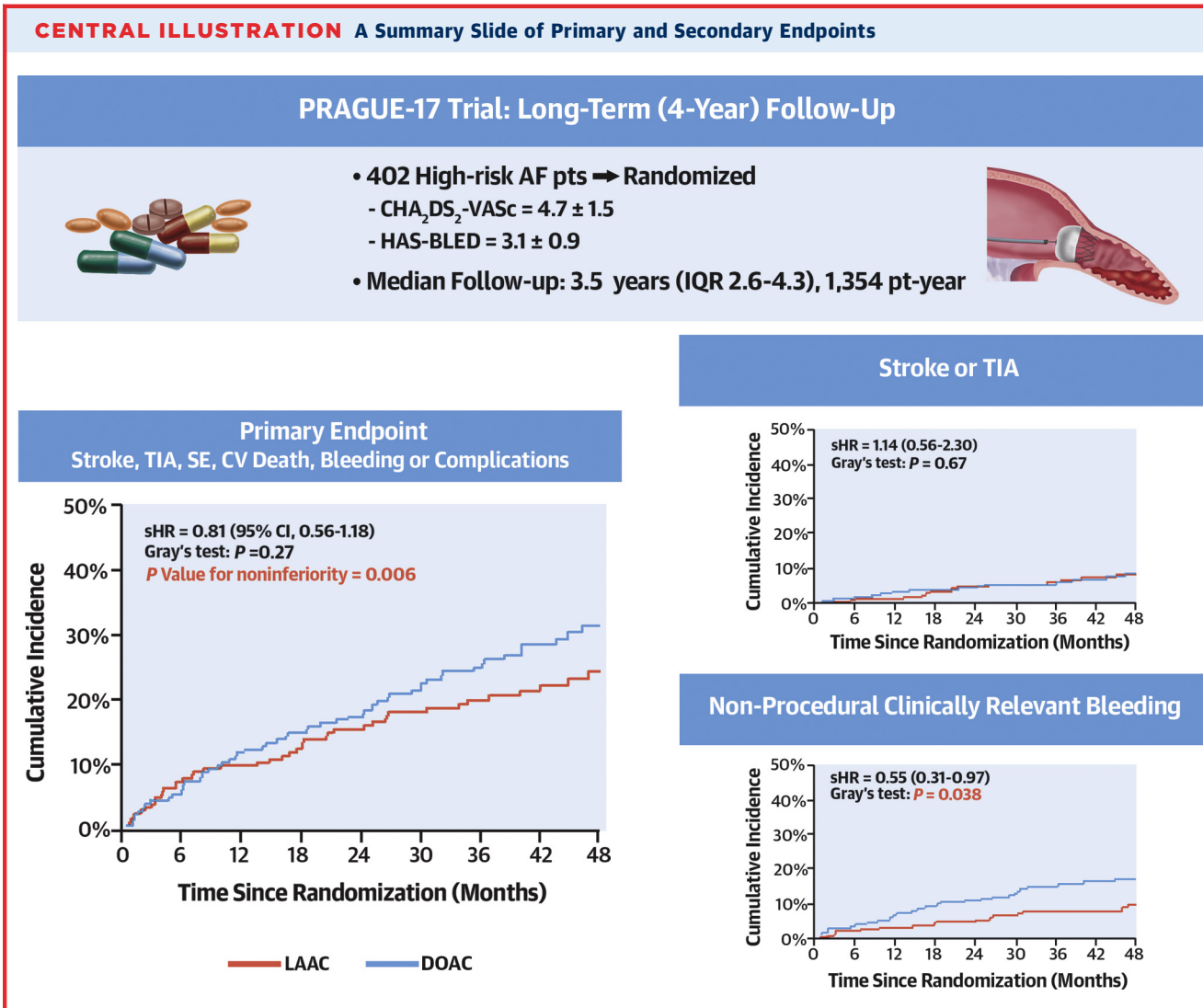
As previously published (3), 7.0% of patients (14 of 201) did not undergo the procedure because of either patient refusal (n = 9) or anatomical considerations. All 14 patients continued follow-up, and 12 crossed over to DOACs. Ultimately, 187 patients underwent LAAC, with the LAA being successfully occluded in 96.8% of procedure attempts (181 of 187). Significant complications occurred in 9 patients including 1 device embolization with a need for surgical extraction and surgical LAA closure. Five patients with unsuccessful closure (including the aforementioned patient) also crossed over to DOACs. The implanted devices were Amulet, Watchman, or Watchman-FLX in 61.3%, 35.9%, or 2.8%, respectively. Most patients (n = 148, 81.8%) received DAPT on discharge, 25 patients (13.8%) received apixaban for 3 months followed by aspirin, and 8 patients (4.4%) received apixaban for 6 weeks followed by DAPT for 6 weeks. In the DOAC group, the most frequently used anticoagulant was apixaban, in 192 patients (95.5%): 5 and 2.5 mg twice daily in 159 patients (79.1%) and 33 patients (16.4%), respectively. Dabigatran and rivaroxaban were used in 8 patients (4.0%) and 1 patient (0.5%), respectively. In 17 patients in the LAAC cohort, long-term DOACs were initiated at some point during the study period (in 5 patients because of ischemic stroke/TIA). Conversely, DOAC treatment was permanently stopped in 26 patients in the DOAC cohort during follow-up (in 15 because of clinically relevant bleeding) with (n = 13) or without subsequent crossover to the LAAC (for details see the Supplemental Appendix).

PRIMARY AND SECONDARY ENDPOINTS IN THE mITT ANALYSIS. The primary outcome occurred in 49 patients (a total of 58 events) with LAAC (8.6 events per 100 patient-years) compared with in 60 patients (81 events) with DOACs (11.9 events per 100 patient-years; sHR: 0.81; 95% CI: 0.56-1.18; P = 0.27) (**Central Illustration, Figure 1, Table 2**). Also in the present long-term analysis, LAAC remained noninferior to DOAC treatment (1-sided P value for noninferiority = 0.006). The result was consistent across all subgroups with no statistically significant interactions (**Figure 2**).

Death from CV reasons occurred in 20 patients in the LAAC arm (3.0 events per 100 patient-years) and 30 patients in the DOAC arm (4.4 events per 100 patient-years; sHR: 0.68; 95% CI: 0.39-1.20; P = 0.19) (**Figure 3, Table 2**). Non-CV mortality (sHR: 0.99; 95% CI: 0.55-1.77; P = 0.96) and all-cause mortality (HR = 0.81; 95% CI: 0.54-1.22; P = 0.31) were similar in both groups (Supplemental Figures 2 and 3).

All-stroke/TIA occurred in 16 patients with LAAC (16 events, 15 ischemic and 1 hemorrhagic events; 14 of them were strokes) and in 15 patients with DOACs (18 events, 16 ischemic and 2 hemorrhagic events; 12 strokes). The corresponding annualized rate of all-stroke/TIA was 2.4% with LAAC and 2.7% with DOACs (sHR: 1.14; 95% CI: 0.56-2.30; P = 0.72) (**Central Illustration, Figure 3, Table 2**). When TIAs were

CENTRAL ILLUSTRATION A Summary Slide of Primary and Secondary Endpoints



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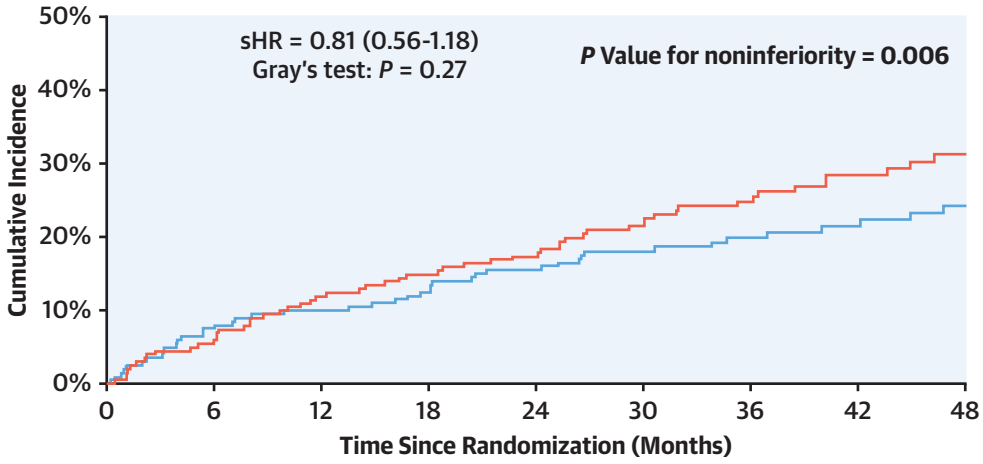
Shown are the patient characteristics, cumulative incidence function for primary endpoint, as well as for stroke/transient ischemic attack and nonprocedural clinically relevant bleeding in the modified intention-to-treat population. AF = atrial fibrillation; CV = cardiovascular; SE = systemic embolism; sHR = subdistribution HR; TIA = transient ischemic attack.

excluded, the annualized rate for stroke was 2.1% with LAAC, and 1.8% with DOACs (sHR: 1.38; 95% CI: 0.63-3.03; $P = 0.42$). SE occurred in only 1 patient, who was in the DOAC arm.

Clinically relevant bleeding occurred in 24 patients with LAAC (29 events) and in 32 patients with DOACs (40 events). The corresponding annualized rate of clinically relevant bleeding was 4.3% with LAAC and 5.9% with DOACs (sHR: 0.75; 95% CI: 0.44-1.27; $P = 0.28$) (Figure 3, Table 2). However, 6 bleeding events in the LAAC arm were procedure-related. Accordingly, the annualized incidence of nonprocedural clinically relevant bleeding was significantly different between the groups: 3.4% with LAAC and 5.9% with DOACs (sHR: 0.55; 95% CI: 0.31-0.97; $P = 0.039$) (Central Illustration, Figure 3, Table 2).

PER-PROTOCOL ANALYSIS. In the post hoc per-protocol analysis, 181 and 199 patients were included in the LAAC and DOAC groups, respectively (details of patient assignment and censoring are noted in the Supplemental Appendix). LAAC was noninferior to DOACs for the primary endpoint outcome (sHR: 0.80; 95% CI: 0.54-1.18; $P = 0.25$; 1-sided P value for noninferiority = 0.020) (Figure 4). There were also no

FIGURE 1 Primary Outcome in the mITT Analysis



No. at Risk*

LAAC	201 (0)	183 (1)	176 (3)	167 (6)	159 (8)	135 (11)	113 (12)	82 (13)	59 (14)
DOAC	201 (0)	190 (0)	176 (1)	169 (2)	160 (5)	138 (6)	106 (10)	83 (12)	53 (15)

	Primary Endpoint – CIF (95% CI)			
	1 Year	2 Years	3 Years	4 Years
LAAC	10.0% (5.8%; 14.1%)	15.5% (10.5%; 20.6%)	20.0% (14.3%; 25.6%)	24.4% (17.8%; 30.9%)
DOAC	11.9% (7.4%; 16.4%)	17.4% (12.2%; 22.7%)	24.9% (18.8%; 31.0%)	31.3% (24.2%; 38.3%)

Cumulative incidence function (CIF) for the primary composite outcome (cardiovascular death, all-stroke/transient ischemic attack, clinically relevant bleeding, and device-/procedure-related complications) in the presence of competing risk (noncardiovascular death) in the modified intention-to-treat (mITT) population. *Number of patients who are free of any event is supplemented (in parentheses) by number of patients with competing risk up to given time. DOAC = direct oral anticoagulant; LAAC = left atrial appendage closure; sHR = subdistributional HR.

significant differences between groups for all-stroke/TIA (sHR: 1.01; 95% CI: 0.48-2.11; $P = 0.99$), all-stroke (sHR: 1.30; 95% CI: 0.57-2.93; $P = 0.53$), or CV mortality (sHR: 0.70; 95% CI: 0.38-1.31; $P = 0.27$) (Supplemental Figure 4, Supplemental Table 2). The rate of clinically relevant bleeding was not significantly different between groups (sHR: 0.76; 95% CI: 0.44-1.31; $P = 0.32$); however, for non-procedural- and device-related events, LAAC was again associated with a significantly reduced rate of clinically relevant bleeding (sHR: 0.52; 95% CI: 0.29-0.97; $P = 0.039$).

ON-TREATMENT ANALYSIS. The post hoc on-treatment analysis ultimately included 184 and 216 patients in the LAAC and DOAC groups, respectively (details of patient assignment and censoring are noted in the Supplemental Appendix). Again, LAAC was noninferior to DOACs for the primary endpoint outcome (sHR: 0.82; 95% CI: 0.56-1.20; $P = 0.30$; 1-sided P value for noninferiority = 0.025) (**Figure 4**). There were also no significant differences between groups for all-stroke/TIA (sHR: 0.86; 95% CI: 0.42-1.75; $P = 0.68$), all-stroke (sHR: 1.12; 95% CI: 0.52-2.45; $P = 0.77$), or CV mortality (sHR: 0.70; 95% CI: 0.38-1.30; $P = 0.26$) (Supplemental Figure 5, Supplemental Table 3). Again, the rate of clinically relevant bleeding was similar between groups (sHR: 0.78; 95% CI: 0.45-1.35; $P = 0.38$), but nonprocedural clinically relevant bleeding was significantly reduced with LAAC (sHR: 0.54; 95% CI: 0.30-1.00; $P = 0.049$).

TABLE 2 Number of Events, Annualized Event Rate, and sHR for Primary and Secondary Outcomes in the mITT Analysis

	Total (N = 402)			DOAC (n = 201)			LAAC (n = 201)				
	No. of Patients With Events	No. of Events	Event Rate	No. of Patients With Events	No. of Events	Event Rate	No. of Patients With Events	No. of Events	Event Rate	sHR (95% CI)	*P* Value
Primary endpoint	109	139	10.27	60	81	11.92	49	58	8.60	0.81 (0.56- 1.18)	0.27
Cardiovascular death	50	50	3.69	30	30	4.42	20	20	2.96	0.68 (0.39-1.20)	0.19
All-stroke/TIA	31	34	2.51	15	18	2.65	16	16	2.37	1.14 (0.56-2.30)	0.72
All-stroke	25	26	1.92	11	12	1.77	14	14	2.08	1.38 (0.63-3.03)	0.42
Systemic embolism	1	1	0.07	1	1	0.15	0	0	0.00	–	–
Clinically relevant bleeding	56	69	5.10	32	40	5.89	24	29	4.30	0.75 (0.44-1.27)	0.28
Nonprocedural clinically relevant bleeding	50	63	4.65	32	40	5.89	18	23	3.41	0.55 (0.31-0.97)	0.039
Procedure- or device-related complication	9	9	0.66	0	0	0.00	9	9	1.33	–	–
Noncardiovascular death	45	45	3.32	23	23	3.39	22	22	3.26	0.99 (0.55-1.77)	0.96
All-cause death	95	95	7.02	53	53	7.80	42	42	6.23	0.81 (0.54-1.22)	0.31

Incidence of composite primary endpoint and its components in the presence of competing risk in the intention-to-treat populations. sHRs for the LAAC group in comparison to the DOAC group and corresponding *P* values were calculated using Fine-Gray regression models with the study group as a covariate. In case of multiple endpoints of the same type, sHR are based on the first event only. Event rate is defined as number of events per 100 patient-years. Dashes indicate nonanalyzable events.

mITT = modified intention-to-treat; sHR = subdistribution HR; TIA = transient ischemic attack; other abbreviations as in Table 1.

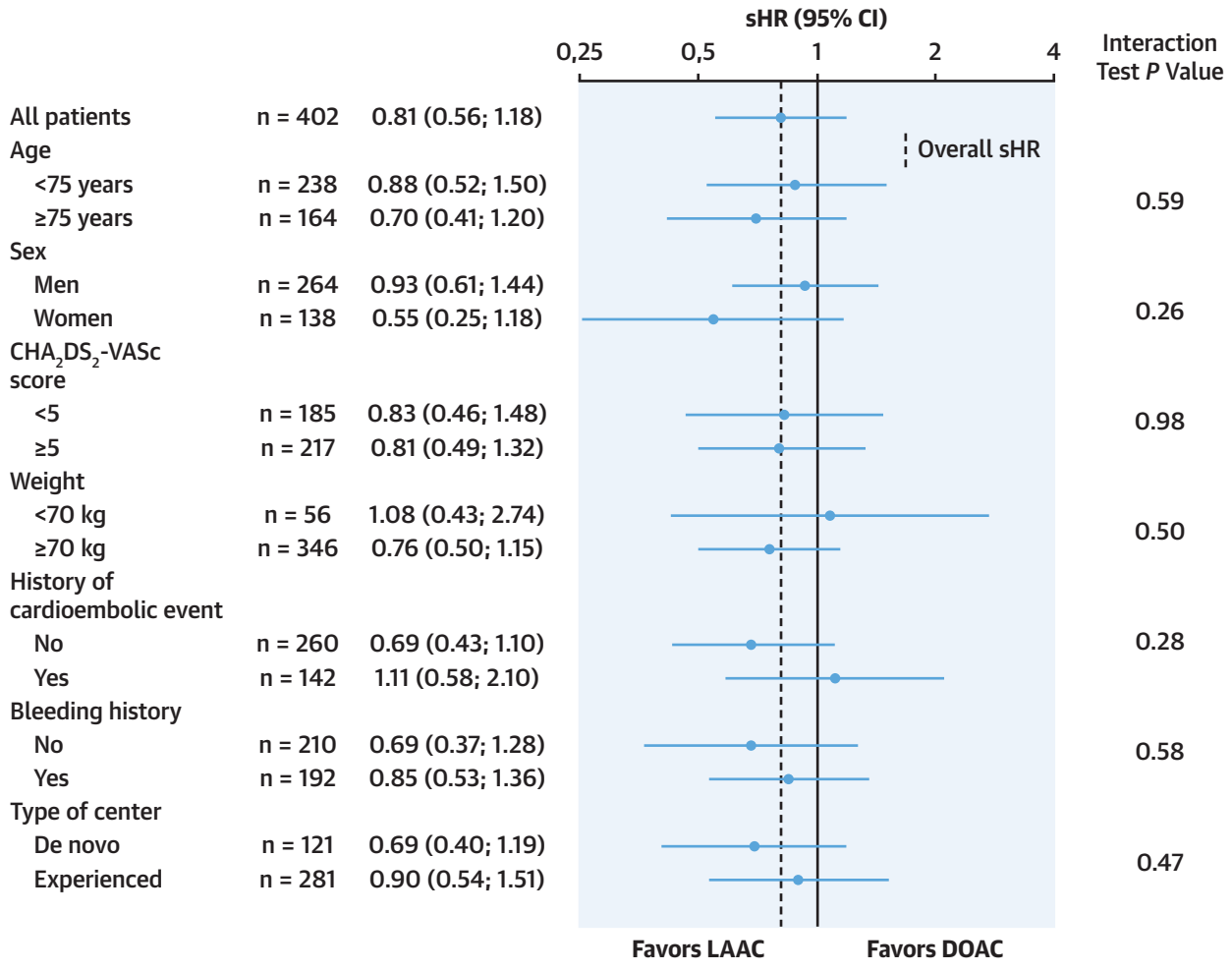
DISCUSSION

In this long-term analysis of the PRAGUE-17 trial, noninferiority of LAAC vs DOACs was maintained for the primary composite endpoint after ~4 years of follow-up. The results were similar in both the prespecified mITT analysis, and the post hoc per-protocol and on-treatment analyses. There were no significant differences in the rates of all-stroke/TIA or CV death between groups. On the other hand, in this extended follow-up, the incidence of nonprocedural clinically relevant bleeding was significantly reduced with LAAC in all presented analyses.

In our study, the benefit of LAAC on clinically relevant bleeding was derived from a reduction in late events. Events during the first year post-implantation are primarily driven by procedural complications and postimplantation antithrombotic medications, so the benefit of LAAC was best appreciated over longer periods of follow-up. These findings are in agreement with other randomized trials of LAAC in patients with AF. The 5-year outcomes of the PROTECT-AF (Percutaneous closure of the left atrial appendage versus warfarin therapy for prevention of stroke in patients with atrial fibrillation: a randomised non-inferiority trial) and PREVAIL (Evaluation of the Watchman Left Atrial Appendage [LAA] Closure Device in Patients With Atrial Fibrillation Versus Long Term Warfarin Therapy) trials showed that the composite of stroke, SE, and CV death occurred at similar frequencies in the LAAC and warfarin groups (HR: 0.82; 95% CI: 0.58-1.17); similarly, the rate of all-stroke or SE was also not different between groups (HR: 0.96; 95% CI: 0.60-1.54). However, patients who underwent LAAC experienced substantially fewer nonprocedural major bleeding events than patients on warfarin did (HR: 0.48; 95% CI: 0.32-0.71) (1).

After the initial publication of the PRAGUE-17 trial, several nonrandomized registries and studies with propensity score-matched control subjects have been published—all of which further corroborate the embolic role of the LAA in patients with AF. The largest of these propensity-matching studies compared the 2-year clinical follow-up of 1,088 patients after LAAC with a propensity score-matched cohort of 1,184 patients with AF who were treated using DOACs. The risk of ischemic stroke was similar between groups (HR: 1.11), whereas the risk of major bleeding (HR: 0.62; 95% CI: 0.49-0.79) and even all-cause mortality (HR: 0.53; 95% CI: 0.43-0.64) were significantly reduced with LAAC (5). In the APPLY (NCT02787525) study, 500 patients after LAAC were compared with 500 patients with medically treated AF (78.8% on OACs), also using propensity score-matching (6). After a mean follow-up of 2.7 years, the incidence of the primary composite endpoint of stroke and CV death were significantly lower in the LAAC group (HR: 0.7; 95% CI: 0.53-0.95). The primary safety endpoint, consisting of major bleeding and procedure-/device-related complications, was similar in both groups (HR: 0.80; 95% CI: 0.55-1.18). However, of the 48 safety events in the LAAC group, one-half were procedural adverse events, suggesting that

FIGURE 2 Subgroup Analysis



Summary forest plots for the primary composite outcome in the mITT analysis. Abbreviations as in Figure 1.

with continued follow-up, one could suspect further divergence between groups in favor of LAAC.

STROKE AND SYSTEMIC CARDIOEMBOLIC EVENTS. The annualized rates of all-stroke/TIA and ischemic stroke were 2.4% and 1.9% for LAAC and 2.7% and 1.5% for DOACs, respectively, in our high-risk patient cohort (CHA_2DS_2-VASc = 4.7 ± 1.5). Certainly, these data must be considered cautiously because the study was not powered to evaluate the differences in these components of the primary endpoint. However, the incidence of approximately 2% per year is in agreement with previously published data on annualized stroke rates in other randomized trials as well as nonrandomized registries of patients with AF who underwent LAAC vs those on DOACs. Hildick-Smith et al (7) reported an annualized ischemic stroke incidence of 2.2% in a group of 1,088 subjects (CHA_2DS_2-VASc = 4.2 ± 1.6) after LAAC using the Amulet device. Boersma et al (8) reported annualized rates of stroke or stroke/TIA/SE as 1.3% and 2.0% in the 2-year follow-up of 1,020 patients (CHA_2DS_2-VASc = 4.5 ± 1.6) after LAAC using the Watchman device.

With regard to DOAC therapy, in the ROCKET-AF (Rivaroxaban Once-Daily, Oral, Direct Factor Xa Inhibition Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation) trial (mean $CHADS_2$ = 3.5), stroke or SE occurred in 1.7% of patients per year. In the lower risk AVERROES (A Phase III Study of Apixaban in Patients

With Atrial Fibrillation) trial patient cohort (mean $CHADS_2 = 2.0$, prior stroke or TIA in only 14%), the annualized incidence of stroke (without TIA) was 1.6% in the apixaban arm and 3.7% in the aspirin arm (9). In older warfarin vs placebo trials, the incidence of stroke/TIA/SE in patients without antithrombotic treatment was significantly higher. For instance, in the AFASAK (Placebo-controlled, randomised trial of warfarin and aspirin for prevention of thromboembolic complications in chronic atrial fibrillation) trial, the annualized incidence of stroke/TIA/SE was 2.0% on warfarin and 5.5% on placebo (10), and the annual incidence of cardioembolic events in the placebo arms of other warfarin trials varied from 4.7% to 8.0% (11).

Further reductions in cardioembolic events may be difficult to achieve using OAC or LAAC strategies alone. Interestingly, the recently published LAAOS III (Left Atrial Appendage Occlusion Study III) trial demonstrated the superiority of a novel strategy that combines surgical LAA closure with OACs vs OACs alone: the composite of ischemic stroke/TIA/SE was significantly reduced in the surgical LAAC group (HR: 0.67) (12). However, this combination strategy has never been tested using transcatheter techniques and might present a challenge for a standalone LAAC procedure (unlike concomitant surgical LAA ligation).

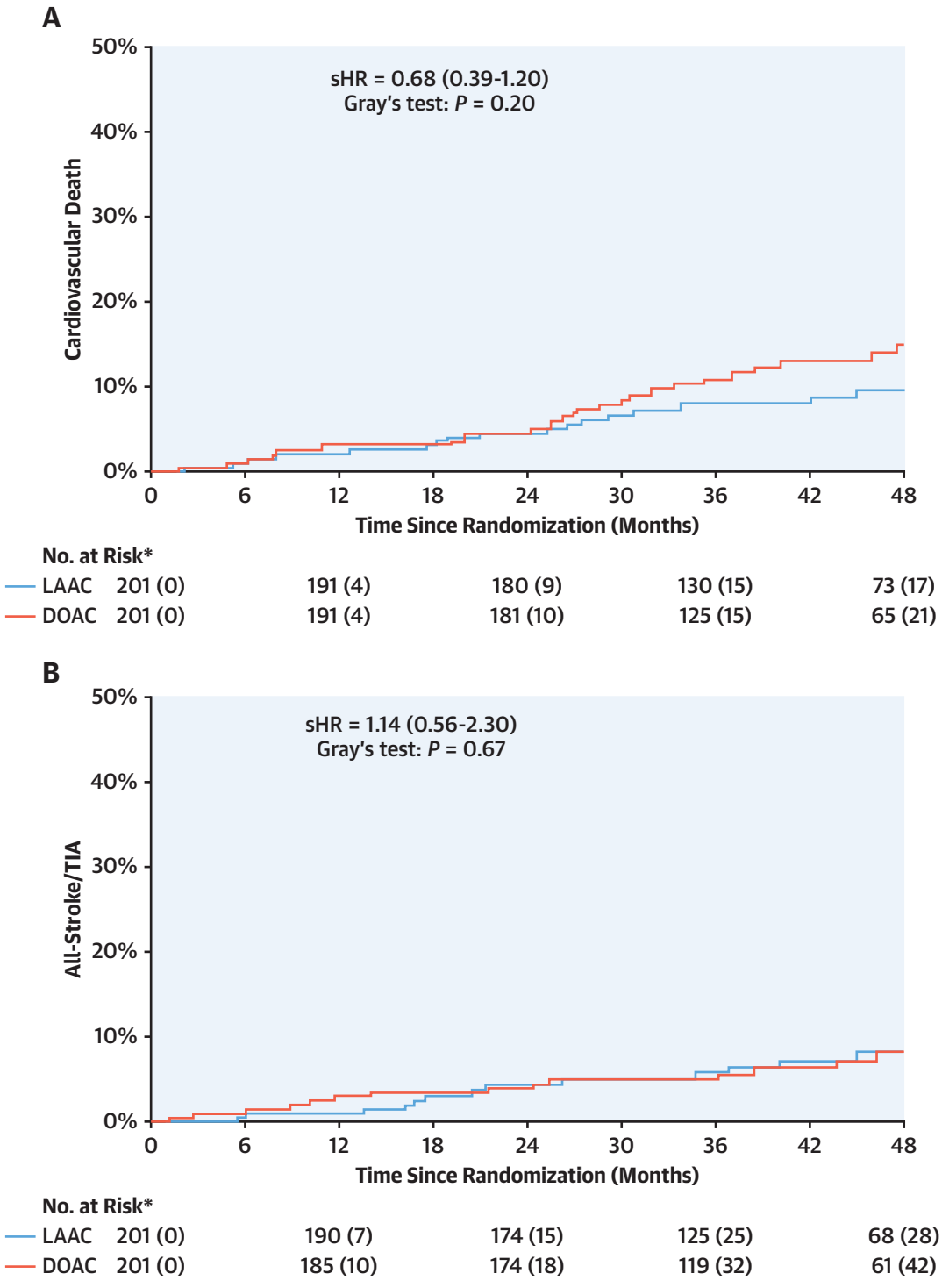
In our cohort, 26 patients (12.9%) stopped DOAC treatment during the study period. In previous publications, DOAC discontinuation was associated with an increased risk of subsequent cardioembolic events (13,14). This is particularly important because OAC discontinuation occurs relatively frequently in clinical practice and even in clinical trial settings. In a meta-analysis of DOAC trials in AF, the drug was discontinued in 21.7% of patients, and discontinuation of both warfarin and DOACs was associated with an increased risk for cardioembolism (15). The most common reasons for discontinuation were adverse events, especially bleeding. In the AVERROES trial, apixaban was discontinued in 21.7% of patients during 1.8 years of follow-up. In the propensity score-matched study of Amulet vs DOAC therapy, 20% of patients in the DOAC cohort permanently stopped DOAC treatment after 3 months (5). Discontinuation of DOACs increases the risk of cardioembolic events, and as such, could have contributed to similar results in the LAAC and DOAC arms relative to our trial. Indeed, drug discontinuation can happen with any medication, especially those that cause side effects.

BLEEDING. In the present follow-up of ~4 years, nonprocedural clinically relevant bleeding was significantly reduced with the LAAC strategy (sHR: 0.55; 95% CI: 0.31-0.97). The bleeding rate in patients who underwent LAAC (3.4% per year) was similar to that reported in other LAAC studies: in PROTECT-AF, the postimplantation (>7 days) bleeding rate was 3.5% per year (16,17). In the EWOLUTION (Registry on Watchman Outcomes in Real-Life Utilization) and Iberian registries, both of which included patients with OAC contraindications, the corresponding major bleeding rates were 2.7% per year and 3.9% per year, respectively (8,18).

In PRAGUE-17, a temporal analysis of bleeding events reveals progressive separation in favor of LAAC during follow-up starting at 6 months (**Central Illustration**). This again emphasizes that the benefits of LAAC become more evident as time progresses. The early postimplantation period is burdened by both: 1) procedure-/device-related complications that are typically bleeding events (6 of 9 complications in PRAGUE-17 were bleeding events); and 2) the temporarily more intense antithrombotic treatment, both of which increase early bleeding. A reduction in nonprocedural (>7 days) bleeding in favor of LAAC was also observed in the 5-year patient-level meta-analysis of the PROTECT-AF and PREVAIL trials, and even with a similar HR of 0.48 (95% CI: 0.32-0.71) (1).

Similar findings were also reported in nonrandomized studies and registries. In the Amulet observational study of 1,088 patients, there was a decrease in the annualized rate of major bleeding from 10.1% for the first year to 4.0% for the second year (7). In the aforementioned propensity-matched analysis, there were fewer major bleeding events after LAAC compared to a matched DOAC control cohort (HR: 0.62; 95% CI: 0.49-0.79); interestingly, the time-to-event curves started to separate at 3 months postimplantation, with progressive separation over time (5). In the APPLY propensity-matched analysis, the primary safety endpoint (major bleeding + procedure-/device-related complications) occurred in 3.6% per year with LAAC: 52% of events were procedural adverse events, and the remaining 48% were major bleeds during follow-up (6). In the 4.5-year analysis of the CAP (Continued Access to PROTECT-AF) and CAP2 (Continued Access to PREVAIL) registries, together including 1,144 patients undergoing Watchman implantation, primary safety events composed of major bleeding and procedure-related complications occurred in 3.1% per year. Roughly one-half of these events occurred within the first 6 months postimplantation (19). Again, a significant number of complications were bleeding events, further emphasizing the need to reduce procedure- and device-related complications. To this point, next-generation devices such as the Watchman-FLX

FIGURE 3 Secondary Outcomes in the mITT Analysis



Cumulative incidence functions for cardiovascular death **(A)**, all-stroke/transient ischemic attack (TIA) **(B)**, clinically relevant bleeding **(C)**, and nonprocedural clinically-relevant bleeding **(D)**, in the presence of competing risk (noncardiovascular death, cardiovascular death, and all-cause death for remaining end points) in the mITT population. *Number of patients who are free of any event is supplemented (in parentheses) by number of patients with competing risk up to given time. Abbreviations as in Figure 1.

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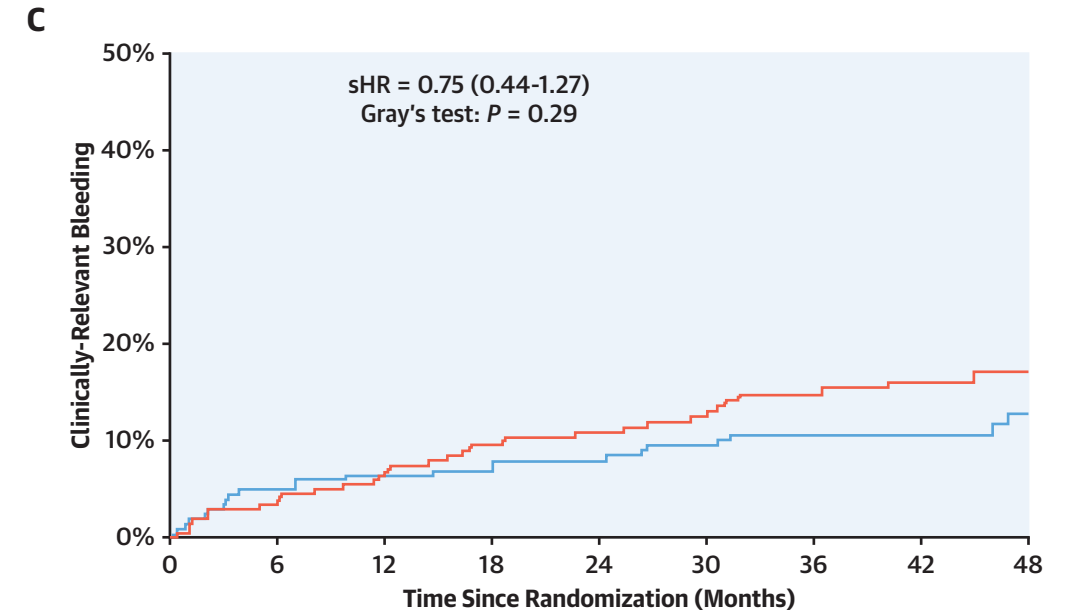
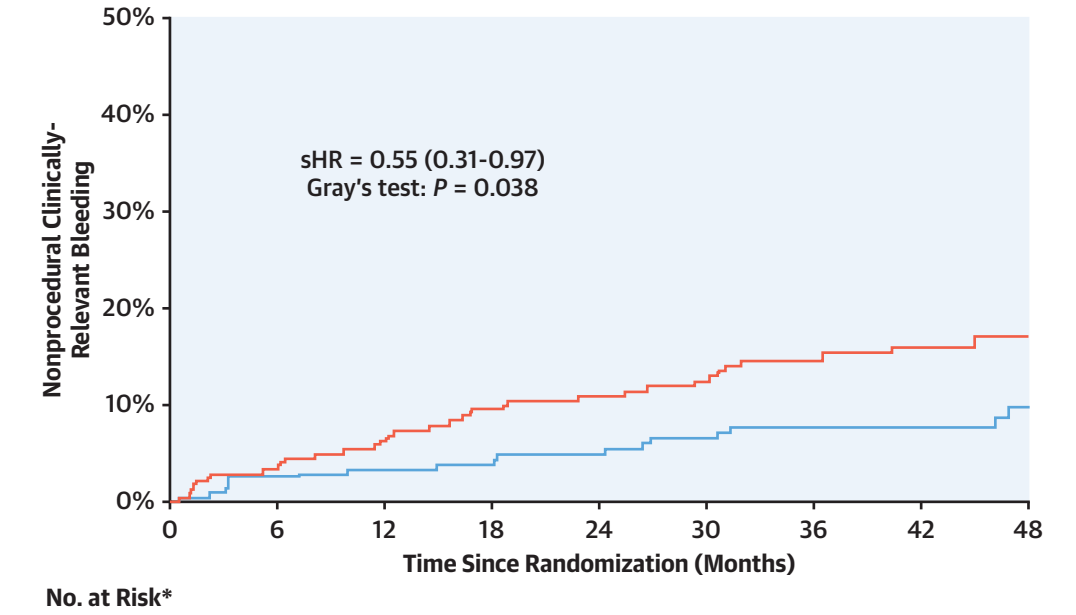
FIGURE 3 Continued

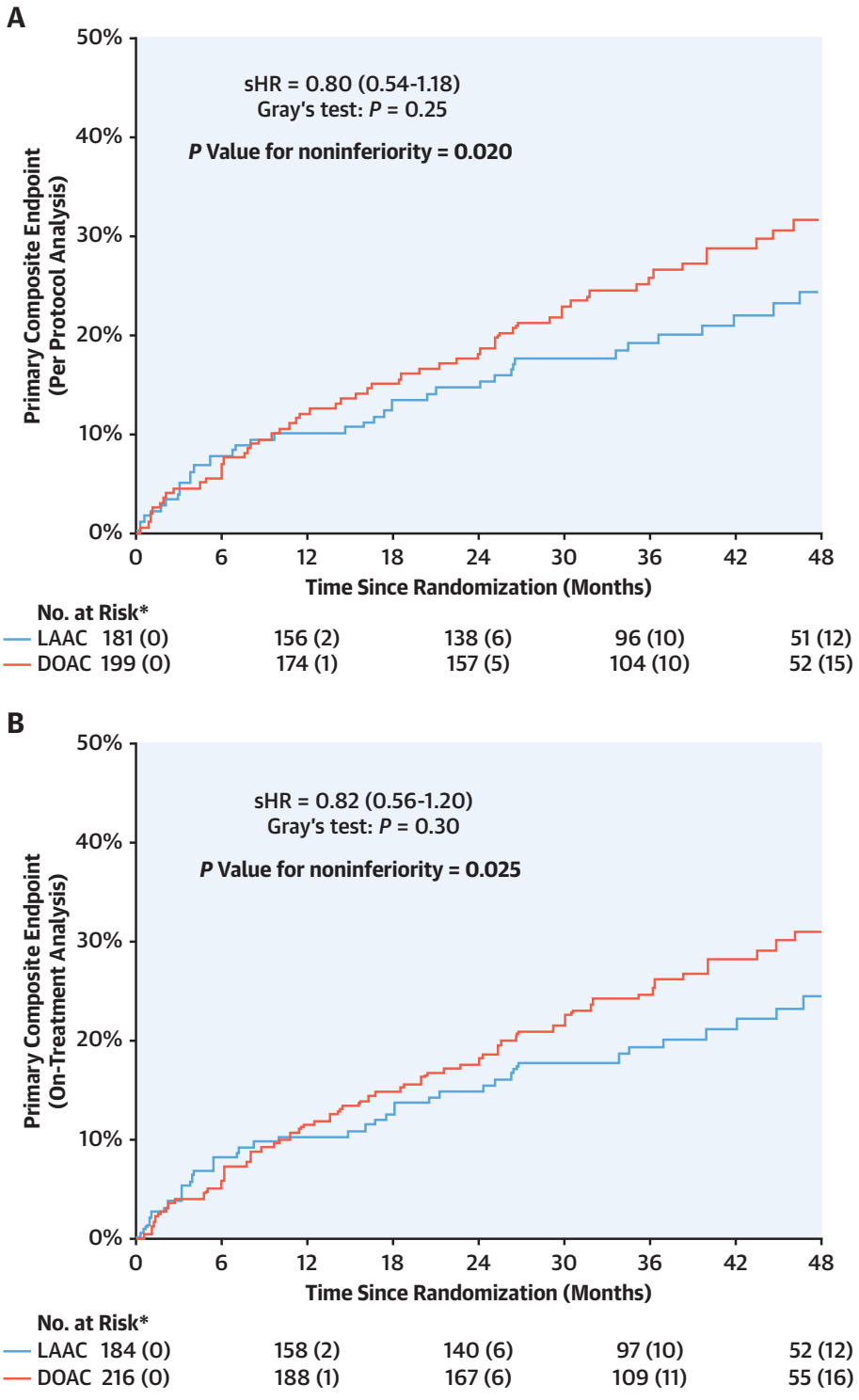


No. at Risk*					
LAAC	201 (0)	180 (6)	168 (14)	121 (22)	64 (26)
DOAC	201 (0)	181 (7)	165 (13)	110 (26)	56 (33)



No. at Risk*					
LAAC	201 (0)	184 (8)	172 (16)	124 (24)	66 (28)
DOAC	201 (0)	181 (7)	165 (13)	110 (26)	56 (33)

FIGURE 4 Primary Outcome in the Per-Protocol and On-Treatment Analyses



Cumulative incidence functions for the primary composite endpoint (cardiovascular death, all-stroke/transient ischemic attack, clinically relevant bleeding, and device-/procedure-related complications) in the per-protocol **(A)** and on-treatment **(B)** analyses. *Number of patients who are free of any event is supplemented (in parentheses) by number of patients with competing risk up to given time. Abbreviations as in Figure 1.

seem to be associated with a lower rate of procedural complications, as was recently demonstrated in the PINNACLE-FLX (Protection Against Embolism for Nonvalvular AF Patients: Investigational Device Evaluation of the Watchman FLX LAA Closure Technology) clinical trial (20).

STUDY LIMITATIONS. The composite endpoint itself contains both thromboembolism and bleeding components, potentially with competing directions of effect. The PRAGUE-17 trial was underpowered to evaluate the relative differences in individual components of the primary composite endpoint, so all analyses of individual components need to be weighed carefully. In the DOAC arm, no medication logs were kept. The results may not apply to all patients with AF because the study focused on patients who were high risk with high CHA_2DS_2-VASc scores. Crossovers from the LAAC to DOAC arm could theoretically bias toward the null hypothesis; however, the per-protocol analysis of only patients treated as randomized yielded similar results. Device-related thrombosis was not prospectively studied in all patients with LAAC because of the disruption caused by the COVID-19 pandemic; many of the planned TEEs had to be cancelled.

CONCLUSIONS

Among patients who are nonvalvular with AF and at high risk for stroke and bleeding, the noninferiority of LAAC to DOACs relative to the composite of cardioembolic events, CV death, significant procedure-/device-related complications, or clinically relevant bleeding was maintained during long-term follow-up. The rate of nonprocedural clinically relevant bleeding was significantly reduced with LAAC compared with DOAC therapy, but the study was underpowered to detect differences in stroke rate. The curves of clinically relevant bleeding appear to separate at ~6 months.

ACKNOWLEDGMENTS The authors are grateful to the members of Data Safety and Monitoring Board, and Clinical End point Committee, as well as the whole team of information technology specialists and statisticians who were responsible for the development of the randomization software and e-database and all statistical analyses.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

This work was supported by a research grant AZV 15-29565A from the Ministry of Health, Czech Republic. Dr Osmancik has received occasional speaking honoraria from Bayer and Abbott. Dr Taborsky has served on Advisory Boards for Bayer and Pfizer. Dr Kala has served on an Advisory Board and Speakers Bureau for Bayer; has served on an Advisory Board for Boston Scientific; and has received consulting fees from Boston Scientific. Dr Poloczek has received speaking honoraria from Abbott. Dr Haman has received speaking honoraria from Pfizer. Dr Zemanek has received speaking honoraria from Abbott and Bayer. Dr Peichl has received occasional speaking honoraria from Abbott; and has received consulting fees from Abbott, Biotronik, and Medtronic. Dr Havranek has received speaking honoraria from Boehringer Ingelheim; and has served on an Advisory Board for Boehringer Ingelheim. Dr Widimsky has received occasional honoraria from Bayer, Pfizer, and Boehringer Ingelheim. Dr Reddy has received consulting income and grant support from Abbott Inc and Boston Scientific Inc; unrelated to this manuscript, he has also served as a consultant for Ablacon, Acutus Medical, Affera, Apama Medical, APN Health, Aquaheart, Atacor, Autonomix, Axon Therapies, Backbeat, BioSig, Biosense Webster, BioTel Heart, Biotronik, Cardiac Implants, CardiaCare, Cardiofocus, Cardionomic, CardioNXT/AFTx, Circa Scientific, CoreMap, Corvia Medical, Dinova-Hangzhou DiNovA EP Technology, East End Medical, EBR, EPD, Epix Therapeutics, EpiEP, Eximo, Farapulse, Fire1, Gore and Associates, HRT, Impulse Dynamics, Intershunt, Javelin, Kardium, Keystone Heart, LuxMed, Medlumics, Medtronic, Middlepeak, Nuvera, Philips, Pulse Biosciences, Sirona Medical, and Valcare Vizaramed; and owns equity in Ablacon, Acutus Medical, Affera, Apama Medical, APN Health, Aquaheart, Atacor, Autonomix, Axon Therapies, Backbeat, BioSig, Cardiac Implants, CardiaCare, CardioNXT/AFTx, Circa Scientific, Corvia Medical, Dinova-Hangzhou DiNovA EP Technology, East End Medical, EPD, Epix Therapeutics, EpiEP, Eximo, Farapulse, Fire1, HRT, Intershunt, Javelin, Kardium, Keystone Heart, LuxMed, Manual Surgical Sciences, Medlumics, Middlepeak, Newpace, Nuvera, Pulse Biosciences, Sirona Medical, Surecor, Valcare, and Vizaramed. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: Among patients with AF at elevated risk of stroke and bleeding, percutaneous LAAC is associated with rates of stroke, cardiovascular death, and bleeding similar to treatment with DOACs.

TRANSLATIONAL OUTLOOK: Further studies are needed to guide optimum selection of patients for management with these treatment strategies, alone or in combination.

REFERENCES

1. Reddy VY, Doshi SK, Kar S, et al, PREVAIL and PROTECT AF Investigators. 5-Year outcomes after left atrial appendage closure: from the PREVAIL and PROTECT AF trials. *J Am Coll Cardiol*. 2017;70(24):2964–2975.

2. Ruff CT, Giugliano RP, Braunwald E, et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. *Lancet*. 2014;383(9921):955–962.

3. Osmancik P, Herman D, Neuzil P, et al, PRAGUE-17 Investigators. Left atrial appendage closure versus direct oral anticoagulants in high-risk patients with atrial fibrillation. *J Am Coll Cardiol*. 2020;75(25):3122–3135.

4. Osmancik P, Tousek P, Herman D, et al, PRAGUE-17 Investigators. Interventional left atrial appendage closure vs novel anticoagulation agents in patients with atrial fibrillation indicated for long-term anticoagulation (PRAGUE-17 study). *Am Heart J*. 2017;183:108–114.

5. Nielsen-Kudsk JE, Korsholm K, Damgaard D, et al. Clinical outcomes associated with left atrial appendage occlusion versus direct oral anticoagulation in atrial fibrillation. *J Am Coll Cardiol Intv*. 2021;14(1):69–78.

6. Gloekler S, Furholz M, de Marchi S, et al. Left atrial appendage closure versus medical therapy in patients with atrial fibrillation: the APPLY study. *EuroIntervention*. 2020;16(9):e767–e774.

7. Hildick-Smith D, Landmesser U, Camm AJ, et al. Left atrial appendage occlusion with the Amplatzer Amulet device: full results of the prospective global observational study. *Eur Heart J*. 2020;41(30):2894–2901.

8. Boersma LV, Ince H, Kische S, et al, EWOLUTION Investigators. Evaluating real-world clinical outcomes in atrial fibrillation patients receiving the WATCHMAN left atrial appendage closure technology: final 2-year outcome data of the EWOLUTION trial focusing on history of stroke and hemorrhage. *Circ Arrhythm Electrophysiol*. 2019;12(4):e006841.

9. Connolly SJ, Eikelboom J, Joyner C, et al, AVERROES Steering Committee and Investigators. Apixaban in patients with atrial fibrillation. *N Engl J Med*. 2011;364(9):806–817.

10. Petersen P, Boysen G, Godtfredsen J, et al. Placebo-controlled, randomised trial of warfarin and aspirin for prevention of thromboembolic complications in chronic atrial fibrillation: the Copenhagen AFASAK study. *Lancet*. 1989;1(8631):175–179.

11. Segal JB, McNamara RL, Miller MR, et al. Prevention of thromboembolism in atrial fibrillation: a meta-analysis of trials of anticoagulants and antiplatelet drugs. *J Gen Intern Med*. 2000;15(1):56–67.

12. Whitlock RP, Belley-Cote EP, Paparella D, et al, LAAOS III. Left atrial appendage occlusion during cardiac surgery to prevent stroke. *N Engl J Med*. 2021;384(22):2081–2091.

13. Park JH, Han SW, Lee KY, et al. Impact of non-vitamin K antagonist oral anticoagulant withdrawal on stroke outcomes. *Front Neurol*. 2018;9:1095.

14. Patel MR, Hellkamp AS, Lokhnygina Y, et al. Outcomes of discontinuing rivaroxaban compared with warfarin in patients with nonvalvular atrial fibrillation: analysis from the ROCKET AF trial (Rivaroxaban Once-Daily, Oral, Direct Factor Xa Inhibition Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation). *J Am Coll Cardiol*. 2013;61(6):651–658.

15. Chatterjee S, Sardar P, Giri JS, Ghosh J, Mukherjee D. Treatment discontinuations with new oral agents for long-term anticoagulation: insights from a meta-analysis of 18 randomized trials including 101,801 patients. *Mayo Clin Proc*. 2014;89(7):896–907.

16. Holmes DR, Reddy VY, Turi ZG, et al, PROTECT AF Investigators. Percutaneous closure of the left atrial appendage versus warfarin therapy for prevention of stroke in patients with atrial fibrillation: a randomised non-inferiority trial. *Lancet*. 2009;374(9689):534–542.

17. Reddy VY, Sievert H, Halperin J, et al, PROTECT AF Steering Committee and Investigators. Percutaneous left atrial appendage closure vs warfarin for atrial fibrillation: a randomized clinical trial. *JAMA*. 2014;312(19):1988–1998.

18. Lopez-Minguez JR, Nogales-Asensio JM, Infante De Oliveira E, et al. Long-term Event Reduction After Left Atrial Appendage Closure. Results of the Iberian Registry II. *Rev Esp Cardiol (Engl Ed)*. 2019;72(6):449–455.

19. Holmes DR Jr, Reddy VY, Gordon NT, et al. Long-term safety and efficacy in continued access left atrial appendage closure registries. *J Am Coll Cardiol*. 2019;74(23):2878–2889.

20. Kar S, Doshi SK, Sadhu A, et al, PINNACLE FLX Investigators. Primary outcome evaluation of a next-generation left atrial appendage closure device: results from the PINNACLE FLX trial. *Circulation*. 2021;143(18):1754–1762.

KEY WORDS atrial fibrillation, cardioembolism, dire oral anticoagulant, left atrial appendage closure, oral anticoagulation

APPENDIX For supplemental methods, results, figures, tables, and for lists of investigators, participating sites, and board and committee members, please see the online version of this paper.