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Left Atrial Appendage Closure Versus Direct Oral Anticoagulants in High-Risk Patients With Atrial Fibrillation

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ABSTRACT

BACKGROUND Percutaneous left atrial appendage closure (LAAC) is noninferior to vitamin K antagonists (VKAs) for preventing atrial fibrillation (AF)–related stroke. However, direct oral anticoagulants (DOACs) have an improved safety profile over VKAs, and their effect on cardiovascular and neurological outcomes relative to LAAC is unknown.

OBJECTIVES This study sought to compare DOACs with LAAC in high-risk patients with AF.

METHODS Left Atrial Appendage Closure vs. Novel Anticoagulation Agents in Atrial Fibrillation (PRAGUE-17) was a multicenter, randomized, noninferiority trial comparing LAAC with DOACs. Patients were eligible to be enrolled if they had nonvalvular AF; were indicated for oral anticoagulation (OAC); and had a history of bleeding requiring intervention or hospitalization, a history of a cardioembolic event while taking an OAC, and/or a CHA_2DS_2-VASc of ≥3 and HAS-BLED of >2. Patients were randomized to receive LAAC or DOAC. The primary composite outcome was stroke, transient ischemic attack, systemic embolism, cardiovascular death, major or nonmajor clinically relevant bleeding, or procedure-/device-related complications. The primary analysis was by modified intention to treat.

RESULTS A high-risk patient cohort (CHA_2DS_2-VASc: 4.7 ± 1.5) was randomized to receive LAAC (n = 201) or DOAC (n = 201). LAAC was successful in 181 of 201 (90.0%) patients. In the DOAC group, apixaban was most frequently used (192 of 201; 95.5%). At a median 19.9 months of follow-up, the annual rates of the primary outcome were 10.99% with LAAC and 13.42% with DOAC (subdistribution hazard ratio [sHR]: 0.84; 95% confidence interval [CI]: 0.53 to 1.31; p = 0.44; p = 0.004 for noninferiority). There were no differences between groups for the components of the composite endpoint: all-stroke/TIA (sHR: 1.00; 95% CI: 0.40 to 2.51), clinically significant bleeding (sHR: 0.81; 95% CI: 0.44 to 1.52), and cardiovascular death (sHR: 0.75; 95% CI: 0.34 to 1.62). Major LAAC-related complications occurred in 9 (4.5%) patients.

CONCLUSIONS Among patients at high risk for stroke and increased risk of bleeding, LAAC was noninferior to DOAC in preventing major AF-related cardiovascular, neurological, and bleeding events. (Left Atrial Appendage Closure vs. Novel Anticoagulation Agents in Atrial Fibrillation [PRAGUE-17]; NCT02426944) (J Am Coll Cardiol 2020;75:3122-35)

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Vitamin K antagonists (VKAs) such as warfarin had long served as the therapeutic mainstay for preventing stroke in atrial fibrillation (AF). However, VKAs are limited by a narrow therapeutic profile, numerous diet-drug interactions, and requisite blood level monitoring. Accordingly, a novel site-specific therapeutic alternative, mechanical left atrial appendage closure (LAAC), entered clinical practice (1). In 2 randomized trials, LAAC was noninferior to VKAs for all stroke or systemic embolism and was associated with 78% and 52% reductions in hemorrhagic stroke and cardiovascular mortality, respectively (2).

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Coincident with these LAAC trials, the pharmacological options for stroke prevention expanded significantly with the advent of 4 direct oral anticoagulants (DOACs) that inhibit either factor IIa (dabigatran) or factor Xa (rivaroxaban, apixaban, and edoxaban) (3–6). In total, DOACs were associated with 19%, 51%, and 10% reductions in stroke or systemic embolism, hemorrhagic stroke, and mortality, respectively (7). Similar to the benefit of LAAC over VKAs, the benefit of DOACs over VKAs was related to a decrease in intracranial hemorrhage. Not surprisingly, DOACs have largely replaced VKAs as first-line therapy for AF stroke prevention.

The efficacy and safety of LAAC compared to oral anticoagulation in this era of more effective and safer anticoagulants is unknown, because, to our knowledge, there has never been a direct comparison of LAAC with DOACs. Accordingly, in patients with nonvalvular AF, we compared DOACs with LAAC using commercially available closure devices for the prevention of stroke, transient ischemic attack (TIA), systemic embolism, cardiovascular death, clinically significant bleeding, or procedure-/device-related complications.

METHODS

TRIAL DESIGN. The PRAGUE-17 (Left Atrial Appendage Closure vs. Novel Anticoagulation Agents in Atrial Fibrillation; NCT02426944) trial was an investigator-initiated, multicenter, prospective, open-label, randomized, noninferiority trial conducted at 10 cardiac centers in the Czech Republic (8). The trial was coordinated at Charles University and University Hospital Kralovske Vinohrady, Prague. Database management and primary analyses were performed at the Institute for Biostatistics and Analyses, Masaryk University, Brno. The multicenter ethics committee at University Hospital Kralovske Vinohrady and the ethics committees at participating centers approved the protocol. All patients provided written informed consent. Patient enrollment began in October 2015 and concluded in January 2019, with follow-up of the last enrolled patient occurring at least 6 months post-randomization.

PARTICIPANTS. Moderate- or high-risk patients with nonvalvular AF were eligible if indicated for anticoagulation and had: 1) history of bleeding requiring intervention or hospitalization; 2) history of a cardioembolic event while taking anticoagulation agents; or 3) a moderate to high risk profile, defined as CHA_2DS_2-VASc (congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke, transient ischemic attack, or thromboembolism, vascular disease, age 65-74 years, sex category [female]) of ≥3 plus HAS-BLED (uncontrolled hypertension, abnormal renal or liver function, stroke, bleeding, labile international normalized ratio, elderly, drugs or alcohol) of ≥2. These CHA_2DS_2-VASc and HAS-BLED scores have been previously defined (9). 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,

ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation
CEC = clinical endpoint committee
CI = confidence interval
DAPT = dual antiplatelet treatment
DOAC = direct oral anticoagulant
DSMB = Data Safety and Monitoring Board
HR = hazard ratio
IQR = interquartile range
LAA = left atrial appendage
LAAC = left atrial appendage closure
mITT = modified intention-to-treat
NMCRB = nonmajor clinically relevant bleeding
OAC = oral anticoagulant
sHR = subdistribution hazard ratio
TEE = transesophageal echocardiography
TIA = transient ischemic attack
VKA = vitamin K antagonists

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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 *JACC* author instructions page.

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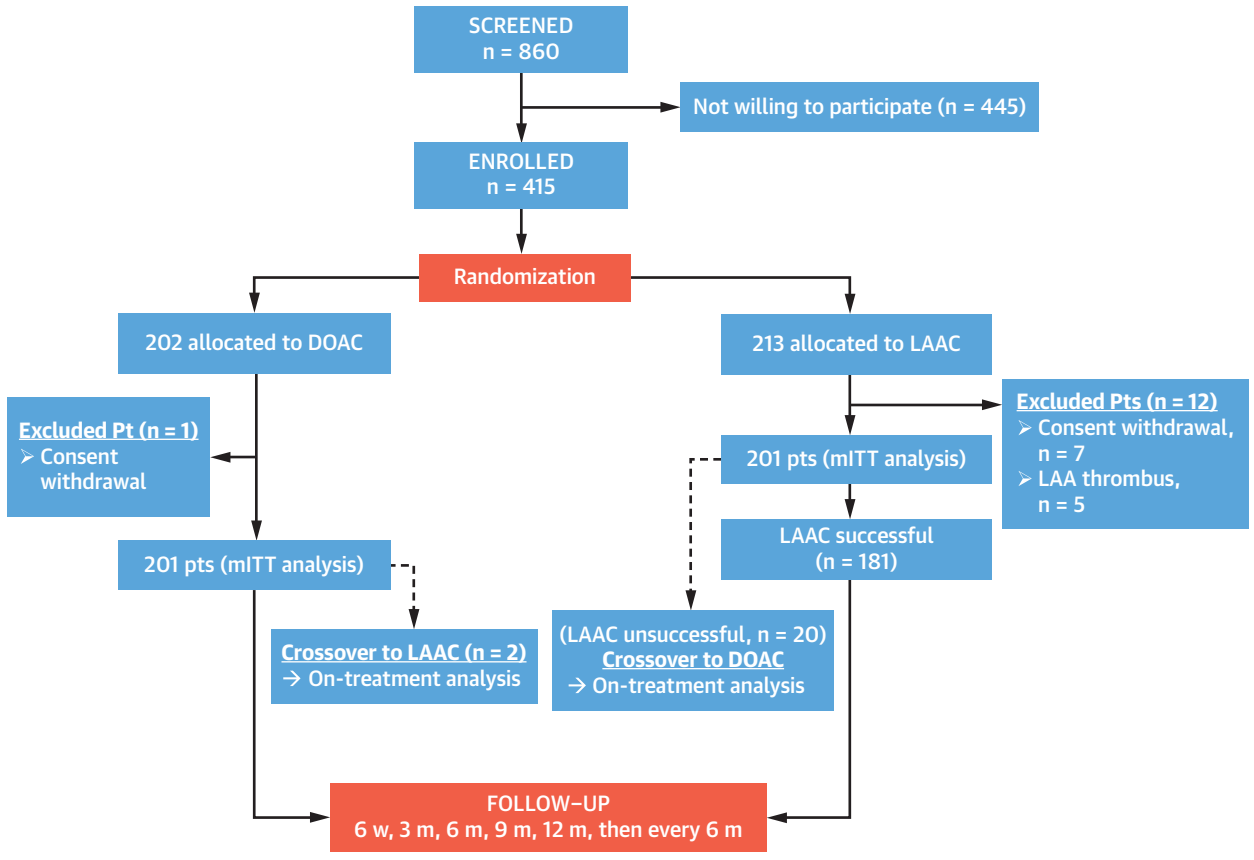
FIGURE 1 Patient CONSORT Diagram



Flow diagram of the progress through the study (enrollment, allocation, exclusion or withdrawal, and follow-up). CONSORT = Consolidated Standards of Reporting Trials; DOAC = direct oral anticoagulant; LAAC = left atrial appendage closure; m = months; mITT = modified intention-to-treat; Pt = patient; Pts = patients; w = weeks.

cardioembolic event within 30 days, and creatinine clearance of <30 ml/min. If randomized to LAAC, transesophageal echocardiography (TEE) was performed to exclude left atrial thrombi. Consistent with clinical necessity, the protocol mandated only TEE in the LAAC group, and not before DOAC initiation. The presence of a thrombus in the left atrial appendage (LAA) or left atrium was a pre-specified additional exclusion criterion (8).

RANDOMIZATION AND MASKING. With a centralized computer system, patients were randomly assigned to LAAC or DOAC in a 1:1 ratio, with block sizes of 18 to 22 patients (this variance prevented sites from deducing treatment assignment near the end of a block) and stratified by center to ensure comparable CHA_2DS_2-VASc scores between groups. Patient data were uploaded into a database by using a secure web interface. Treatment allocation was not blinded to participants and local investigators; however, as best as possible, members of the clinical endpoint committee were blinded to patient allocation.

STUDY TREATMENT AND PROCEDURES. Patients randomized to the DOAC group could receive either rivaroxaban, apixaban, or dabigatran at the manufacturer-recommended dose. Investigators were instructed to reserve crossover from DOAC to LAAC for patients with bleeding while taking the prescribed DOAC and not simply based on patient preference. Medication compliance was monitored by querying patients about regular medication use during each visit.

Patients randomized to LAAC underwent implantation with a commercially available Amulet (Abbott Inc., St. Paul, Minnesota) or Watchman/Watchman-FLX (Boston Scientific Inc., St. Paul, Minnesota) device. Device selection was at the discretion of

the implanting center. Centers without previous LAAC experience were mandated to perform procedures before study initiation and to perform the first 5 study procedures with active proctoring by an experienced operator (10). Under conscious sedation or general anesthesia, after femoral venous access and transseptal puncture, the LAAC device was placed at the appendage ostium by using a combination of fluoroscopy and either TEE or intracardiac echocardiography at centers experienced with this technology.

After LAAC, the recommended antithrombotic regimen was aspirin 100 mg/day plus clopidogrel 75 mg/day for 3 months. If a TEE then showed no device-related thrombus or leak of ≥5 mm, clopidogrel was withdrawn; aspirin was continued indefinitely. Based on patient characteristics and device type, this post-implant antithrombotic regimen could be individualized and was ultimately left to physician discretion. In patients at high risk for bleeding, dual antiplatelet treatment (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 (10).

For both groups, outpatient follow-up occurred at 6 weeks and 3, 6, 9, and 12 months and every 6 months thereafter. The minimum follow-up for the last enrolled patient was the 6-month visit. During each visit, patients were asked about the endpoint occurrence, all other changes in clinical status, hospitalization or other health care utilization, and medication changes.

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 TIA; 2) systemic embolism; 3) clinically significant bleeding; 4) cardiovascular death; or 5) a significant peri-procedural or device-related complications. Clinically significant bleeding was a composite of major and nonmajor clinically relevant bleeding (NMCRB), according to the International Society on Thrombosis and Hemostasis (ISTH) criteria. Major bleeding includes either a decrease in hemoglobin of ≥2.0 g/dl during a 24-h period, transfusion of ≥2 units of packed red cells, bleeding at a critical site (intracranial, intraspinal, intraocular, pericardial, intramuscular with compartment syndrome, or retroperitoneal), or fatal bleeding. NMCRB is defined as bleeding requiring hospitalization or an invasive procedure but not meeting ISTH major criteria (11). Complications included pericardial effusion requiring drainage/pericardiocentesis or surgery, cardioembolism, peri-procedural bleeding requiring surgical revision or transfusion, device embolization, device-related thrombus with cardioembolism, or others as assessed by the operator and clinical endpoint committee (CEC). Secondary endpoints included the individual components of the primary endpoint. Detailed endpoint definitions are provided in the Supplemental Appendix.

An independent CEC adjudicated events, and an independent data safety and monitoring board (DSMB) monitored adverse events associated with the LAAC procedure. The DSMB was immediately informed of any procedural adverse events. In addition to the sum of adverse events, the DSMB also

TABLE 1 Baseline Characteristics and Risk Factors of Participants

	DOAC (n = 201)	LAAC (n = 201)	Missing Values
Demographics			
Age, yrs	73.2 ± 7.2	73.4 ± 6.7	–
<75	122 (60.7)	116 (57.7)	–
>75	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)	
Long-standing 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 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 OAC, 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; CHA_2DS_2-VASc = congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke, transient ischemic attack, or thromboembolism, vascular disease, age 65-74 years, sex category (female); HAS-BLED = uncontrolled hypertension, abnormal renal or liver function, stroke, bleeding, labile international normalized ratio, elderly, drugs or alcohol; LAAC = left atrial appendage closure; LMWH = low-molecular-weight heparin; MI = myocardial infarction; DOAC = direct oral anticoagulant; OAC = oral anticoagulant.

TABLE 2 Procedural Characteristics of the LAAC Group (N = 181)

Procedure duration, min	60 (45-85)
Fluoroscopy, min	11 (6-16)
Device type	
Amulet	111 (61.3)
Watchman	65 (35.9)
Watchman-FLX	5 (2.8)
Procedures requiring >1 device	17 (9.4)
Size of the final device	
Amulet	25.5 ± 4.1
Watchman	27.3 ± 3.8
Watchman-FLX	26.4 ± 1.3
Leak on the device by TEE or ICE imaging	7 (3.9)
Qualitative assessment of device position*	
Optimal	172 (95.0)
Suboptimal	7 (3.9)
Poor	2 (1.1)
Temporary thrombus during procedure†	2 (1.1)
Ultrasound navigation	
TEE	92 (50.8)
ICE	74 (40.9)
TEE + ICE	15 (8.3)
Sedation	
General anesthesia	55 (30.4)
Deep analgosedation	28 (15.5)
Mild analgosedation	98 (54.1)
Mild pericardial effusion (post-procedural)‡	4 (2.2)
Antithrombotic treatment at discharge	
Aspirin	149 (82.3)
Clopidogrel	149 (82.3)
DOAC	20 (11.1)
Warfarin	9 (5.0)
LMWH	9 (5.0)

Values are median (interquartile range), n (%), or mean ± SD. *Procedures continued and were successfully performed without complications. †These effusions did not require intervention. ‡This was a qualitative assessment by the operator.

ICE = intracardiac echocardiography; TEE = transesophageal echocardiography; other abbreviations as in Table 1.

received aggregated outcome data from all study participants (patient recruitment, baseline characteristics, and aggregate rate of endpoints) on an annual basis and was responsible for comparing the actual to expected event rates. This was necessary to potentially stop the study if the recruitment was insufficient or if the endpoints occurred with significantly less frequency than expected. No between-group statistical comparisons were planned or performed during these interim DSMB analyses.

STATISTICAL 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. Based on previous randomized DOAC trials and randomized and observational LAAC trials, we estimated that 13% and 10% of the DOAC and LAAC cohorts, respectively, would experience the primary endpoint annually (1,3-6,12-16). We determined that a minimum of 396 study participants would provide 80% power at a 2-sided alpha level of 0.05 for a noninferiority margin of 5% (or 1.469, expressed as a hazard ratio [HR]). Estimating the noninferiority margin is complicated by the absence of any trial comparing DOACs with placebo; therefore, one must estimate the minimum treatment effect of DOACs over placebo in high-risk patients with AF. Importantly, this margin is concordant with (and, indeed, somewhat stricter than) the U.S. Food and Drug Administration guidance: for active control event rates below 20%, a 1.67 margin for the odds ratio should be used. Also, the 1.469 margin is similar to that used in the prior DOAC trials (3-5).

Because ITT outcomes can potentially bias noninferiority trials toward the null hypothesis, post hoc secondary on-treatment and per protocol analyses were performed. The Supplemental Appendix contains details regarding patients censored in these secondary analyses.

The primary endpoint power analysis was computed for the differences in proportions of the 1-year endpoint occurrence; the Barnard-Rohmel-Kieser test was used for testing the noninferiority hypothesis. The power analysis was computed with PASS 13 software (NCSS, LLC, Kaysville, Utah). Cumulative incidence functions and Fine-Gray competing risk regression models were adopted for data visualization and description. The trial statistical plan included Kaplan-Meier curves and Cox proportional hazard models for data description (see Supplemental Appendix) and did not pre-specify any adjustment for the competing risk of mortality. However, at trial conclusion, consistent with the prevailing change in convention of statistical methodology, all primary analyses were conducted after adjusting for the competing risk for mortality. Accordingly, for the primary composite and cardiovascular mortality endpoints, calculations adjusted for noncardiovascular mortality. Similarly, other (nonmortality) endpoints were adjusted for all-cause mortality.

For other data, standard descriptive statistical methods were used: absolute and relative frequencies for categorical data and the median (interquartile range [IQR]) or mean ± standard deviation 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 reported as subdistribution hazard ratios (sHRs). Statistical analyses were done using SPSS, version 25.0, software (IBM Corporation, Armonk, New York).

RESULTS

PATIENTS AND FOLLOW-UP. Between October 2015 and January 2019, of 860 patients screened at 10 centers, 415 patients were enrolled in the study. Thirteen patients were excluded, 8 for informed consent withdrawal and 5 for the presence of LAA thrombus on TEE before the procedure (Figure 1). The baseline characteristics of these 13 excluded patients were not different from those of the remaining LAAC cohort (Supplemental Table 1). Regarding the 5 patients excluded for LAA thrombus, there were no strokes during follow-up; rather, there were 2 late ISTH major bleeds in patients taking VKAs (at 498 and 1,159 days post-randomization) and 1 noncardiovascular death. Patients withdrawing informed consent refused study follow-up; ultimately, 402 patients were randomized (201 to each group). History of bleeding was present in 192 patients and history of a cardioembolic event in 142 patients; 112 patients were entered only on the basis of the CHA_2DS_2-VASc and HAS-BLED scores. The median follow-up was 21.1 months (IQR: 11.8 to 28.9 months) in the DOAC group and 19.3 months (IQR: 12.4 to 28.3 months) in the LAAC group, for an aggregate of 695.9 patient-years. One patient in the LAAC group was lost to follow-up after the 6-month visit because of migration.

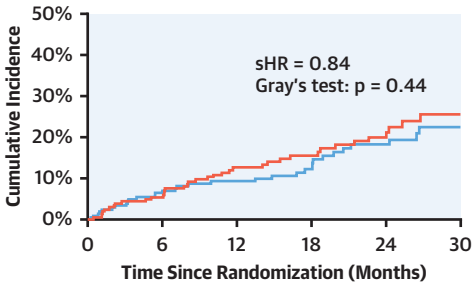
The groups were well-balanced for clinical characteristics (Table 1 and Supplemental Table 2). The mean age was 73.3 years, and 34.3% were women. The cohort was high risk, with a mean CHA_2DS_2-VASc of 4.7 ± 1.5 and >25% with a CHA_2DS_2-VASc of >6, prior cardioembolism in 35.3%, and prior bleeding in 47.8%. Most patients had previously received anticoagulants, either VKAs (47.0%) or DOACs (30.1%). In most of the remaining patients (74%), AF was recently diagnosed.

TREATMENT CHARACTERISTICS. Of patients randomized to LAAC, 7.0% (14 of 201) did not undergo the procedure because of either patient refusal (n = 9) or anatomic considerations: overly large LAA in 3 patients, pre-existing pericardial effusion in 1 patient, and suspicion for infective endocarditis on TEE in 1 patient. All 14 patients agreed to continued follow-up, and 12 crossed over to the DOAC group (Figure 1). Ultimately, 187 patients underwent LAAC, and the LAA was successfully occluded in 96.8% (181 of 187) of procedure attempts, or in 90% (181 of 201) of patients assigned to LAAC. The implanted devices were either Amulet, Watchman, or Watchman-FLX in 61.3%, 35.9%, or 2.8%, respectively. Four of the 10 enrolling centers were de novo centers (Supplemental Table 3). Most patients (148; 81.8%) received DAPT upon discharge (8 for 6 weeks only), 25 (13.8%) patients received apixaban for 3 months followed by aspirin, and 8 (4.4%) patients received apixaban for 6 weeks followed by DAPT for 6 weeks. Procedure details are shown in Table 2.

TEE imaging was performed at 3 months in 178 LAAC patients. Device-related thrombi were observed in 6 (3.4%) patients, 5 of which resolved with 4 weeks of low-molecular-weight heparin treatment, whereas the last patient underwent surgical extraction. Regarding peri-device leak into the LAA past the device, a >5-mm leak was seen in 4 (2.2%) patients, 1- to 5-mm leaks in 20 (11.2%), and no leak in 154 (86.5%).

In the DOAC group, the most frequently used anticoagulant was apixaban, in 192 patients (95.5%): 5 mg and 2.5 mg twice daily in 159 (79.1%) and 33 (16.4%) patients, respectively. Among patients with reduced dose, the criteria for dose reduction recommended by the manufacturer were not met in 16 (48.5%) of them. These patients had similar CHA_2DS_2-VASc scores as the remaining patients (4.68 ± 1.19 vs. 4.70 ± 1.5) but had higher HAS-BLED scores (3.4 ± 0.8

FIGURE 2 Primary Endpoint



No. at Risk*

LAAC	201 (0)	178 (1)	144 (3)	107 (6)	74 (6)	41 (7)
DOAC	201 (0)	181 (0)	136 (1)	102 (2)	67 (4)	32 (4)

Primary Endpoint – CIF (95% CI)

	6M	12M	18M	24M	30M
LAAC	7.0% (3.5% to 10.6%)	9.4% (5.2% to 13.5%)	12.3% (7.4% to 17.2%)	18.4% (12.0% to 24.7%)	22.5% (14.9% to 30.2%)
DOAC	5.5% (2.3% to 8.6%)	12.7% (7.9% to 17.5%)	15.6% (10.2% to 21.0%)	20.1% (13.7% to 26.5%)	25.6% (17.6% to 33.6%)

Cumulative incidence function for the primary endpoint in the presence of competing risk (noncardiovascular death) in the mITT population. *Number of patients who are free of an event is supplemented (in parentheses) by number of patients with competing risk up to given time. CI = confidence interval; CIF = cumulative incidence function; sHR = subdistribution hazard ratio; other abbreviations as in Figure 1.

TABLE 3 Incidence of Composite Primary Endpoint and its Components in the Presence of Competing Risk (Noncardiovascular Death for Primary Endpoint and Cardiovascular Death, All-Cause Death for Other Endpoints) in the Intention-to-Treat Populations

	DOAC (n = 201)			LAAC (n = 201)					
	No. of Patients With Event	No. Events	Event Rate/Yr	No. of Patients With Event	No. Events	Event Rate/Yr	Subdistribution Hazard Ratio (95% CI)	p Value	p Value for Noninferiority
Primary endpoint	41	47	13.42	35	38	10.99	0.84 (0.53–1.31)	0.44	0.004
Cardiovascular death	15	15	4.28	11	11	3.18	0.75 (0.34–1.62)		
All stroke/TIA	9	9	2.57	9	9	2.60	1.00 (0.40–2.51)		
Ischemic stroke/TIA	8	8	2.28	9	9	2.60	1.13 (0.44–2.93)		
Systemic embolism	1	1	0.29	0	0	0.00	–		
Procedure/device related complications	–	–	–	9	9	2.60	–		
ISTH major/nonmajor bleeding	22	26	7.42	18	19	5.50	0.81 (0.44–1.52)		
ISTH major/nonmajor bleeding not related to device	22	26	7.42	12	13	3.76	0.53 (0.26–1.06)		

CI = confidence interval; ISTH = International Society on Thrombosis and Hemostasis; TIA = transient ischemic attack; other abbreviations as in Table 1.

vs. 2.95 ± 0.89). No cardioembolic events and 1 major bleeding event occurred during follow-up in these patients. Dabigatran was used in 8 patients: 150 mg and 110 mg twice daily in 7 (3.5%) and 1 (0.5%) patients, respectively. Rivaroxaban 20 mg daily was used in 1 (0.5%) patient.

PRIMARY ENDPOINT. By mITT, the primary outcome occurred in 35 patients with LAAC (10.99% per 100 patient-years) compared to 41 patients with DOACs (13.42% per 100 patient-years; sHR: 0.84; 95% confidence interval [CI]: 0.53 to 1.31; p = 0.44) (**Figure 2, Table 3**). The upper bound of the 95% CI in the LAAC group was 16.1%, which was substantially less than the event rate in the DOAC group plus noninferiority margin (18.42%); therefore, the study met the criteria for noninferiority of LAAC relative to DOACs (p = 0.004 for noninferiority) (**Central Illustration**). The Kaplan-Meier estimate yielded similar outcomes (Supplemental Figure 1). This result was consistent across all subgroups with no statistically significant interactions (**Figure 3**). Similarly, no significant between-center differences were found: the overall sHR for all centers was within the CI of the individual sHRs (Supplemental Figure 2).

SECONDARY ENDPOINTS IN THE INTENTION-TO-TREAT ANALYSIS. The annual rate of all stroke/TIA was 2.60% with LAAC compared to 2.57% with DOACs (sHR: 1.00; 95% CI: 0.40 to 2.51) (**Figure 4A, Table 3**). There were 8 and 7 strokes and 1 and 2 TIAs in the LAAC and DOAC groups, respectively. Mean stroke severity as assessed by modified Rankin score at discharge was 2.38 ± 1.5 in the LAAC group and 2.29 ± 0.76 in the DOAC group. There was 1 intracranial hemorrhage with DOACs and none with LAAC; all other strokes were ischemic in origin, as confirmed by computed tomography. No intraprocedural stroke or TIA occurred during LAAC.

The annual rate of cardiovascular mortality was 3.18% with LAAC compared to 4.28% with DOACs (sHR: 0.75; 95% CI: 0.34 to 1.62) (**Figure 4B, Table 3**). Two deaths in the LAAC group were classified as being procedure or device related. The rates of noncardiovascular and all-cause mortality were also similar between groups (sHR: 1.16; 95% CI: 0.42 to 3.18; and HR: 0.88; 95% CI: 0.48 to 1.63, respectively) (Supplemental Figures 3 and 4).

The bleeding rate was similar between the LAAC and DOAC groups (**Figure 4C, Table 3**). The annual rate of ISTH major/NMCRB was 5.50% with LAAC compared with 7.42% with DOAC (sHR: 0.81; 95% CI: 0.44 to 1.52). The distribution between ISTH major and NMCRB was 13 and 6 with LAAC and 14 and 12 with DOACs, respectively. Six (31.6%) of the LAAC bleeding events were procedure/device related. After excluding these procedural/device bleeding events, the annual rate of ISTH major/NMCRB was 3.76% with LAAC (sHR: 0.53; 95% CI: 0.26 to 1.06) (**Figure 4D, Table 3**).

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 DOAC for the primary endpoint outcome (sHR: 0.82; 95% CI: 0.52 to 1.30; p = 0.40; p = 0.003 for noninferiority) (**Figure 5A**). There were also no significant differences between groups for the embolic events: all stroke/TIA (2.20% with LAAC vs. 2.68% with DOACs; sHR: 0.81; 95% CI: 0.30 to 2.15) and ischemic stroke/TIA (2.20% with LAAC vs. 2.38% with DOACs; sHR: 0.91; 95% CI: 0.33 to 2.48). Similar rates were also seen for ISTH major/NMCRB (sHR: 0.89; 95% CI: 0.48 to 1.65) and cardiovascular death (sHR: 0.74; 95% CI: 0.33 to 1.67) (Supplemental Figure 5).

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.) LAAC was again noninferior to DOAC for the primary endpoint outcome ($p = 0.013$), and again, there were no significant differences between groups for either the primary endpoint (sHR: 0.79; 95% CI: 0.49 to 1.25; $p = 0.31$) (**Figure 5B**) or its individual components: all stroke/TIA (sHR: 0.70; 95% CI: 0.28 to 1.78), ISTH major/NMCRB (sHR: 0.91; 95% CI: 0.48 to 1.72), and cardiovascular death (sHR: 0.68; 95% CI: 0.30 to 1.54) (Supplemental Figure 6).

LAAC DEVICE OR PROCEDURE-RELATED COMPLICATIONS. As shown in **Table 4** and Supplemental Table 4, significant complications occurred in 9 patients (4.5%, or 4.8% of procedural attempts), including 4 (2.1%) within 7 days of the procedure and 5 (2.7%) occurring 104 ± 57 days post-procedure. (Characteristics of patients with complications are shown in Supplemental Table 4.) Among these was a procedure-related death in a patient with a groin bleed requiring vascular surgery complicated by a large myocardial infarction that culminated in death; an autopsy revealed previously unrecognized severe 3-vessel coronary artery disease. Also, a device-related death occurred approximately 6 weeks post-procedures as a result of a late pericardial tamponade (details in the Supplemental Appendix).

TABLE 4 LAAC Device- or Procedure-Related Complications

	Early (≤7 Days) Occurrence	Late (>7 Days) Occurrence	Total
Pericardial effusion	0	2*	2
Device embolization	1†	0	1
Device-related death	0	1‡	1
Procedure-related death	1‡	0	1
Vascular complications	2§	0	2
Other complications	0	2‖	2
Total	4	5	9

*Late pericardial effusions occurred at 89 and 194 days after implantation with the Amulet device. One was treated with pericardiocentesis and the other conservatively; both patients had good outcomes. †Acute device embolization during the procedure, requiring surgical removal. ‡See details in the Supplemental Appendix. §Includes 1 femoral pseudoaneurysm and 1 large groin hematoma, both treated with vascular surgery. ‖One device malposition at the left inferior pulmonary vein, with successful removal and reimplantation. One large device-related thrombus was diagnosed by TEE imaging 113 days after implantation. The thrombus was considered potentially malignant (although no embolic event had occurred), so surgical removal was successfully performed.

LAAC = left atrial appendage closure.

DISCUSSION

To our knowledge, among patients with nonvalvular AF at high risk for stroke, PRAGUE-17 is the first randomized trial comparing percutaneous LAAC with DOACs, primarily apixaban, for the prevention of all-cause stroke, systemic embolism, cardiovascular death, clinically significant bleeding, or procedure-/device-related complications. LAAC was noninferior to DOACs for this composite endpoint, in both the pre-specified mITT primary analysis and the post hoc on-treatment and per protocol analyses (**Central Illustration**). Furthermore, there were no significant differences in any particular component of the primary endpoint.

Evidence for LAAC first came from 2 trials, PROTECT-AF (Watchman Left Atrial Appendage System for Embolic Protection in Patients With Atrial Fibrillation) and PREVAIL (Prospective Randomized Evaluation of the Watchman Left Atrial Appendage Closure Device in Patients With Atrial Fibrillation Versus Long-Term Warfarin Therapy), in which VKA-eligible patients were randomized to either the Watchman device or VKAs (1,13). LAAC proved noninferior to VKAs for the composite primary endpoint of all-cause stroke, systemic embolism, or cardiovascular death. An approximately 80% reduction in intracranial hemorrhage significantly contributed to the positive effect of LAAC, including an approximately 50% cardiovascular mortality benefit. However, as with all procedures, LAAC is susceptible to complications. Furthermore, there was a contemporaneous introduction into clinical practice of new non-VKA anticoagulants with more favorable risk-benefit profiles. DOACs also resulted in an approximately 50% reduction in hemorrhagic stroke and an approximately 10% mortality benefit (7). Because decreased intracranial hemorrhage with LAAC contributed significantly to the positive outcomes in PROTECT-AF and PREVAIL, and because DOACs are also associated with a reduced rate of intracranial hemorrhage, a randomized study comparing these 2 treatment options was warranted.

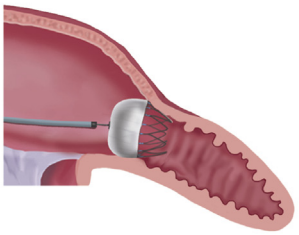
In contrast to OAC-versus-OAC comparisons, the risks and benefits of the treatment strategies in PRAGUE-17 differ significantly. Long-term OAC use increases hemorrhagic risk, whereas LAAC is associated with procedural complications. Therefore, a composite clinical endpoint was selected to encapsulate both efficacy, such as stroke and critical outcomes like mortality, and the completely disparate risks plausibly associated with each treatment modality.

STROKE AND TIA. In our high-risk cohort, the annual incidence of both all-stroke/TIA and ischemic stroke/TIA was similar between groups whether analyzed by mITT (sHRs: 1.00 and 1.13, respectively), per protocol

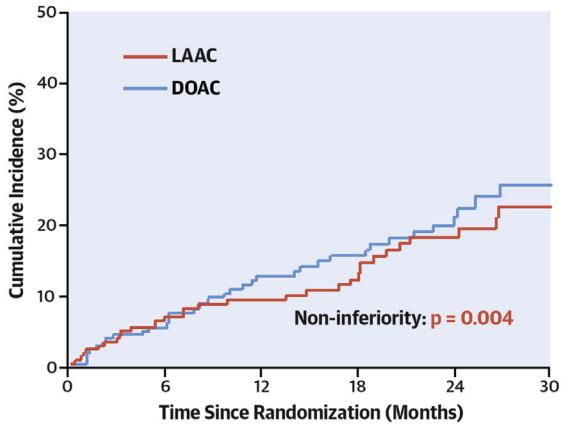
CENTRAL ILLUSTRATION The PRAGUE-17 Trial

PRAGUE-17 Randomized Clinical Trial

- 402 High-Risk AF Pts ➡ Randomized
  - CHA_2DS_2-VASc = 4.7 ± 1.5
  - HAS-BLED = 3.1 ± 0.9
- Follow-up: 20.8 ± 10.8 mo (695 pt-year)



Primary Endpoint
Stroke, TIA, SE, CV Death, Bleeding, or Complications



	sHR (95% CI)	p value
Primary Endpoint		
mITT	0.84 (0.53-1.31)	0.44
Per Protocol	0.82 (0.52-1.30)	0.40
On-Treatment	0.79 (0.49-1.25)	0.31
All-Stroke/TIA	1.00 (0.40-2.51)	0.99
CV Death	0.75 (0.34-1.62)	0.46
Major + NMCR Bleeding		
All	0.81 (0.44-1.52)	0.51
Nonprocedural	0.53 (0.26-1.06)	0.07

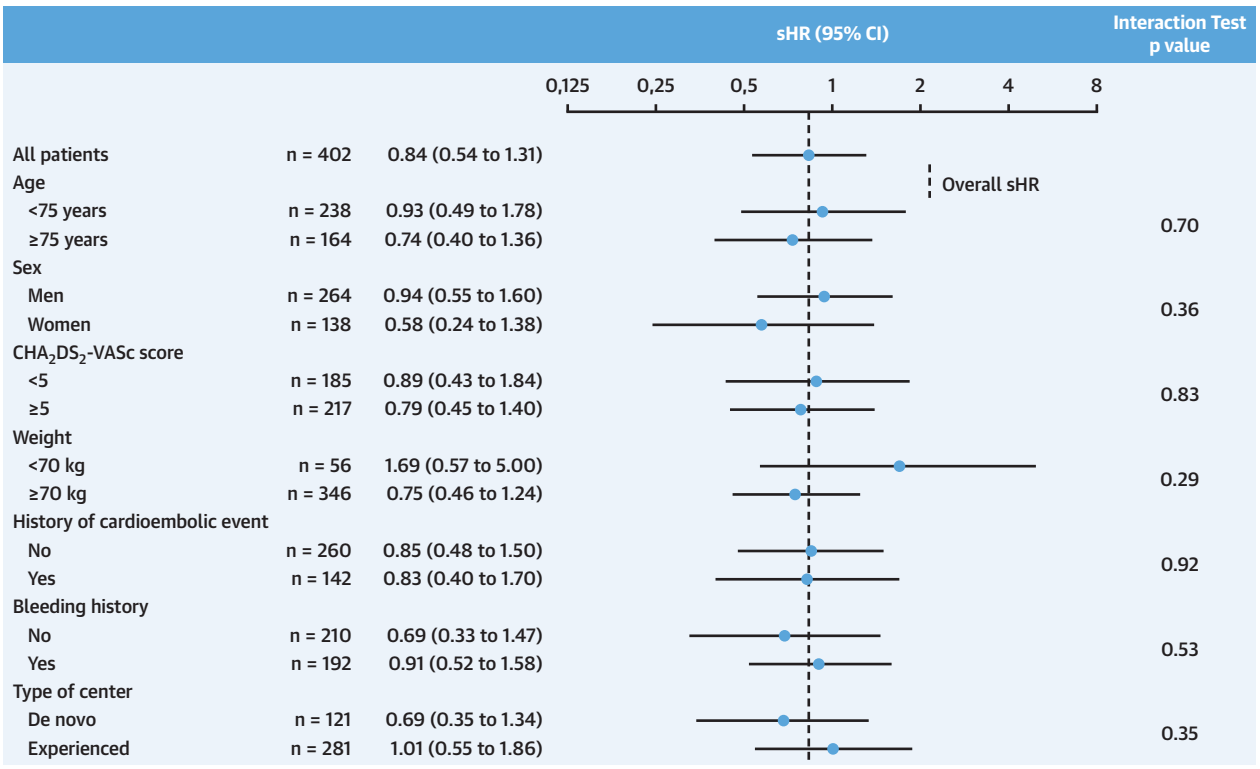
Osmancik, P. et al. J Am Coll Cardiol. 2020;75(25):3122-35.

Shown are the patient characteristics, cumulative incidence function for the primary endpoint in the modified intention-to-treat population, and the subdistribution hazard ratios of the various secondary endpoints. AF = atrial fibrillation; CHA_2DS_2-VASc = congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke, transient ischemic attack, or thromboembolism, vascular disease, age 65–74 years, sex category (female); CI = confidence interval; CV = cardiovascular; DOAC = direct oral anticoagulant; HAS-BLED = hypertension, abnormal renal or liver function, stroke, bleeding, labile international normalized ratio, elderly, drugs or alcohol; LAAC = left atrial appendage closure; mITT = modified intention-to-treat; NMCR = nonmajor and major clinically relevant; PRAGUE-17 = Left Atrial Appendage Closure vs. Novel Anticoagulation Agents in Atrial Fibrillation; Pt = patient; SE = systemic embolism; sHR = subdistribution hazard ratio; TIA = transient ischemic attack.

(sHRs: 0.81 and 0.91, respectively), or on treatment (sHRs: 0.70 and 0.77, respectively) and was substantially lower if compared to the expected rate of ischemic stroke according to the CHA_2DS_2-VASc score (7.57% per year). The corresponding annualized ischemic stroke/TIA/systemic embolism rates were recently reported from 2 large observational LAAC registries with similarly high-risk AF cohorts: 2.3% in the Amplatzer Cardiac Plug registry of 1,047 patients (CHA_2DS_2-VASc: 4.5 ± 1.6; stroke/TIA history in 39%) and 2.0% in the Watchman EWOLUTION (Evaluate Real-World Clinical Outcomes in Patients With AF and High Stroke Risk-Treated With the WATCHMAN Left Atrial Appendage Closure Technology) registry of 1,020 patients (CHA_2DS_2-VASc: 4.5 ± 1.6; stroke/TIA history in 30.5%) (14,15). Although our study was not powered to compare the rates of cardioembolic events alone, together, all these data bolster support for the role of the LAA in stroke pathogenesis and reinforce the hypothesis that site-specific therapy with LAAC can serve as an OAC alternative.

Aspirin, the background long-term antithrombotic therapy after LAAC, reduces the risk of stroke by about a fifth compared with placebo. In an analysis of the secondary prevention patients of the AVERROES (Apixaban in Patients With Atrial Fibrillation) trial

FIGURE 3 Subgroup Analysis

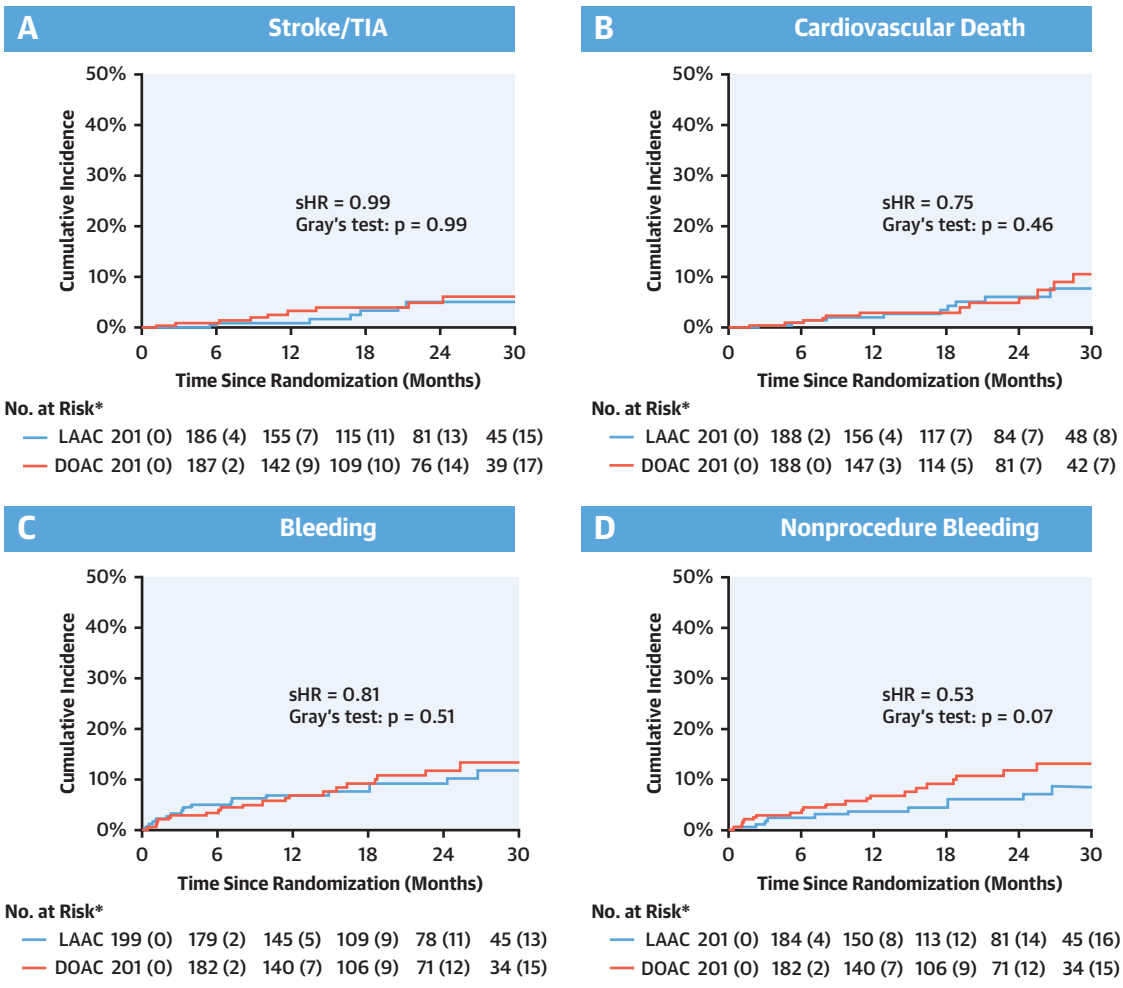


Incidence of the primary endpoint in the mITT population by subgroups in the presence of competing risk (noncardiovascular death). CHA_2DS_2-VASc = congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke, transient ischemic attack, or thromboembolism, vascular disease, age 65–74 years, sex category (female); other abbreviations as in Figures 1 and 2.

(i.e., patients with a history of stroke/TIA), the annualized incidence of stroke or systemic embolism was 9.16% with aspirin versus 2.39% with apixaban (17). Furthermore, the annualized ischemic stroke rates in the aspirin arm of AVERROES were 3.49% and 8.75% in the CHA_2DS_2-VASc 3 to 5 and 6 to 8 cohorts, respectively; the corresponding apixaban rates were 1.29% and 4.19% (HRs: 0.37 and 0.47) (18). Thus, the similar incidence of stroke in the 2 arms of PRAGUE-17 cannot be explained by any beneficial effect of aspirin in the LAAC group. Again, however, as highlighted by the wide 95% confidence bounds of the sHR point estimate (95% CI: 0.40 to 2.51), the limited number of patients in PRAGUE-17 precludes definitive conclusions about this endpoint. However, approximately 7,000 patients would be required for a noninferiority study of LAAC versus DOAC with a composite primary endpoint including only all stroke, TIA, or systemic embolism (details in the Supplemental Appendix).

BLEEDING. Despite their significant reduction in hemorrhagic stroke, DOACs are associated with an increase of other bleeding, such as gastrointestinal bleeding (7). In our trial, ISTH major/NMCRB occurred in 7.42% of patients annually in the DOAC arm. In 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), ISTH major/NMCRB with rivaroxaban was 14.9% annually (3). However, the most commonly used DOAC in our study was apixaban, which in ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation) and AVERROES exhibited ISTH major/NMCRB rates of 4.07% and 4.5%, respectively (5,12). The ARISTOTLE and AVERROES populations were at lower risk ($CHADS_2$ [congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke or transient ischemic attack]: 2.1 and 2.0, respectively), however, and had an infrequent bleeding history (16.7% and 3%, respectively). In comparison, the PRAGUE-17 DOAC patients were higher risk (CHA_2DS_2-VASc: 4.7 ± 1.5; 47.3% bleeding history)—likely the explanation for the disparate bleeding rates.

FIGURE 4 Secondary Endpoints

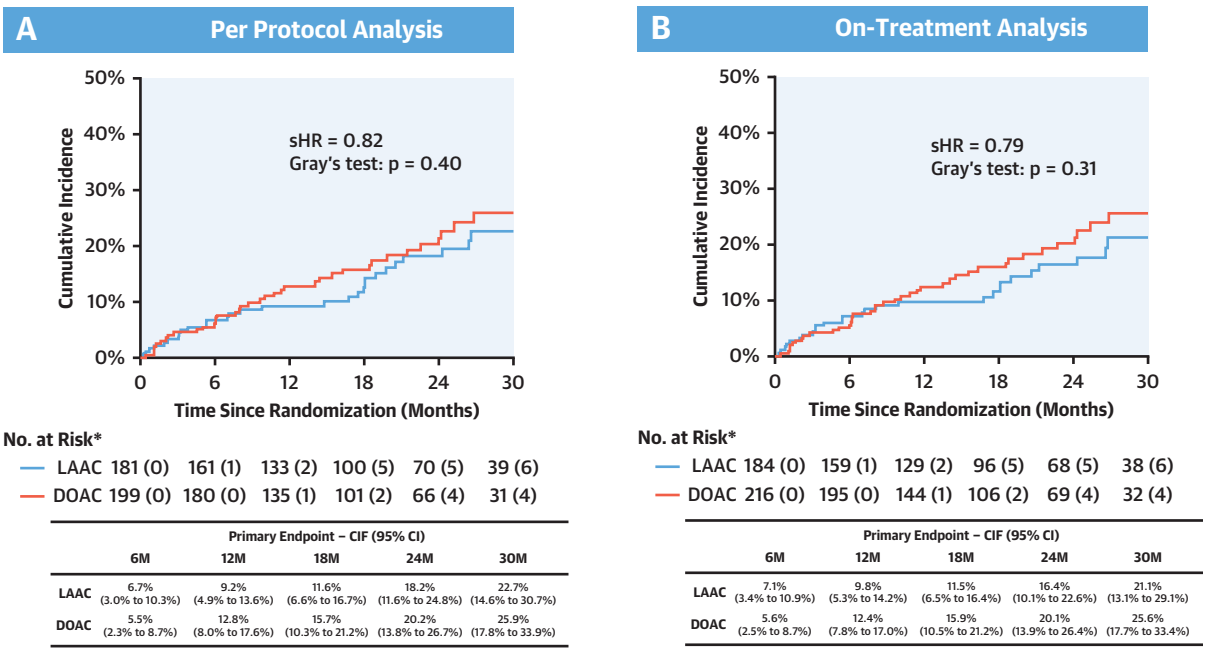


Cumulative incidence function for **(A)** all-stroke/TIA, **(B)** cardiovascular death, **(C)** clinically relevant bleeding, and **(D)** nonprocedure clinically relevant bleeding in the presence of competing risk (noncardiovascular death for cardiovascular death and all-cause death for the remaining endpoints) in the mITT population. *Number of patients who are free of an event is supplemented (in parentheses) by number of patients with competing risk up to given time. TIA = transient ischemic attack; other abbreviations as in Figures 1 and 2.

Similarly, in the LAAC arm of our study, ISTH major/NMCRB occurred in 5.50% annually, which was higher than observed with aspirin in AVERROES (3.9%). In the analysis of AVERROES by CHA_2DS_2-VASc, major bleeding occurred in 1.34% of patients per year in the CHA_2DS_2-VASc 3 to 5 population taking aspirin but in only 0.53% patients per year with a CHA_2DS_2-VASc of 2 in the aspirin arm (18). These data further support the explanation of higher bleeding rates in our study compared to AVERROES being due to the higher risk profile of our cohort.

There were similar rates of ISTH major/NMCRB between groups (SHR: 0.81). This ostensibly unexpected outcome is explained, first, by the fact that 6 of 9 complications were bleeds. Indeed, if one excludes these device/procedure bleeding events, thereby comparing spontaneous ISTH major/NMCRB events between aspirin (the background antithrombotic after LAAC) with DOACs (mainly apixaban), LAAC had numerically fewer bleeds (SHR: 0.53; p = 0.07). This is consistent with the on-treatment analysis of AVERROES: major bleeding was more frequent with apixaban than aspirin (HR: 1.54; 95% CI: 0.96 to 2.45; p = 0.07) (12). Statistical significance was not reached because of insufficient statistical power for this particular endpoint in both studies. Indeed, longer follow-up may demonstrate differences of bleeding. Moreover, use of a truncated

FIGURE 5 Secondary Analyses



Primary Endpoint – CIF (95% CI)

	6M	12M	18M	24M	30M
LAAC	6.7% (3.0% to 10.3%)	9.2% (4.9% to 13.6%)	11.6% (6.6% to 16.7%)	18.2% (11.6% to 24.8%)	22.7% (14.6% to 30.7%)
DOAC	5.5% (2.3% to 8.7%)	12.8% (8.0% to 17.6%)	15.7% (10.3% to 21.2%)	20.2% (13.8% to 26.7%)	25.9% (17.8% to 33.9%)

Primary Endpoint – CIF (95% CI)

	6M	12M	18M	24M	30M
LAAC	7.1% (3.4% to 10.9%)	9.8% (5.3% to 14.2%)	11.5% (6.5% to 16.4%)	16.4% (10.1% to 22.6%)	21.1% (13.1% to 29.1%)
DOAC	5.6% (2.5% to 8.7%)	12.4% (7.8% to 17.0%)	15.9% (10.5% to 21.2%)	20.1% (13.9% to 26.4%)	25.6% (17.7% to 33.4%)

Cumulative incidence functions for the primary endpoint in the presence of competing risk (noncardiovascular death) in the **(A)** per protocol and **(B)** on-treatment populations. *Number of patients who are free of an event is supplemented (in parentheses) by number of patients with competing risk up to given time. Abbreviations as in Figures 1 and 2.

post-LAAC antithrombotic regimen that minimizes bleeding while still preventing device-related thrombosis may further enhance LAAC outcomes.

These data also highlight the relatively low rate of bleeding with apixaban, with the absolute reduction relative to VKAs being in the highest-risk cohorts. In ARISTOTLE, annualized major bleeding was reduced from 3.55% to 2.60% in patients with CHA_2DS_2-VASc of ≥3 and from 4.7% to 3.46% in patients with HAS-BLED ≥3 (19). Thirty-three (16.4%) DOAC patients received low-dose apixaban, appropriately in 16 (48.5%). Dose reduction is relatively common in clinical practice, especially with apixaban (20). In a population-based study of >10,000 patients with AF, 21.6% received inappropriate apixaban underdosing. Compared to appropriately dosed patients, underdosed patients had higher HAS-BLED scores (2.0 vs. 1.6), suggesting that underdosing may be related to the clinical fear of bleeding.

COMPLICATIONS. Various randomized and observational LAAC studies have documented a steady decline in complication rates. Complications occurred in 8.7% in PROTECT-AF, including a 4.3% rate of pericardial tamponade, but then decreased in the Amplatzer Cardiac Plug and EWOLUTION registries to overall complication and tamponade rates of 4.97% and 2.7%, and 1.2% and 0.3%, respectively (1,14,15,21). In PRAGUE-17, the short-term (up to 7 days or discharge) complication rate was 2.1%, consistent with this improving trend. However, the 2.7% late complication rate, including 3 late pericardial effusions, with 1 resulting in death, is suboptimal. Given the overall similar rate of primary events in the arms of the study, the safety of the LAAC is paramount and requires further improvement.

On the other hand, a strength of PRAGUE-17 was its real-world implications: 4 of the 10 implanting centers were truly de novo, initiating their LAAC experience in this trial itself. For the remaining 6 centers, in the year preceding trial commencement, only 18.7 ± 11.8 LAAC procedures had been performed per center (range 8 to 40) (Supplemental Table 3).

STUDY LIMITATIONS. PRAGUE-17 is underpowered to evaluate the relative differences in the individual components of the primary endpoint. Regarding the primary endpoint, stroke reduction may be more important than bleeding reduction. The composite endpoint was chosen to cover the risks and benefits of

2 very different treatment modalities. On the other hand, this trial enrolled one of the highest-risk AF populations ever studied in an AF stroke prevention trial. The consequent high event rate allowed sufficient power to assess the primary endpoint. Although the mean follow-up is substantial (20.8 ± 10.8 months), additional follow-up is needed to determine the relative long-term differences between groups. In the DOAC group, no medication logs were kept; however, the observed ischemic stroke rate suggests reasonable DOAC compliance.

The results may not apply to all with AF who are indicated for a DOAC (e.g., those at low bleeding risk). Five LAAC patients with LAA thrombi on pre-procedural TEE were excluded. However, a post hoc pure intention-to-treat analysis including these patients yielded similar results (sHR: 0.85; 95% CI: 0.55 to 1.32; p = 0.48; p = 0.003 for noninferiority) (Supplemental Figure 7). Furthermore, imputation of these 5 patients has minimal effect on the per protocol and on-treatment analyses, because these patients received VKA. The crossover of 14 LAAC patients to DOACs would bias toward the null hypothesis; however, the per-protocol and on-treatment analyses yielded similar results.

CONCLUSIONS

Among patients with nonvalvular AF at high risk for stroke and increased risk of bleeding, mechanical LAAC was noninferior to DOACs for the composite of cardioembolic events, cardiovascular death, clinically significant bleeding, or procedure-/device-related complications. However, safety issues remain with LAAC, warranting further refinements in both operator technique and device technology.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: Among selected patients with AF at risk for stroke and bleeding, LAAC provides protection against stroke, systemic embolism, and bleeding comparable to DOACs.

TRANSLATIONAL OUTLOOK: Although enhancements in LAAC technology improve the safety of the device-based strategy, longer-term follow-up of larger numbers of patients will be needed to establish relative risks and benefits and inform selection of these alternative treatments.

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KEY WORDS atrial fibrillation, cardioembolic event, direct oral anticoagulant, left atrial appendage, stroke

APPENDIX For a list of investigators, expanded Methods and Results sections as well as supplemental tables and figures, please see the online version of this paper.