Confronto tra chiusura dell’auricola sinistra e anticoagulanti orali diretti nei pazienti con fibrillazione atriale

Risultati a 4 anni del trial PRAGUE-17

Background

- Left atrial appendage closure (LAAC) is a nonpharmacologic option for preventing cardioembolic events in patients with atrial fibrillation (AF) at significant stroke risk.
- Long-term results are only available from 2 randomized studies comparing LAAC using the Watchman device with warfarin. In these reports, LAAC was associated with lower rates of non-procedure-related bleeding.
- Direct oral anticoagulants (DOACs) have largely replaced warfarin. Because treatment using DOACs is associated with less bleeding (including intracranial hemorrhage) than warfarin, 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.

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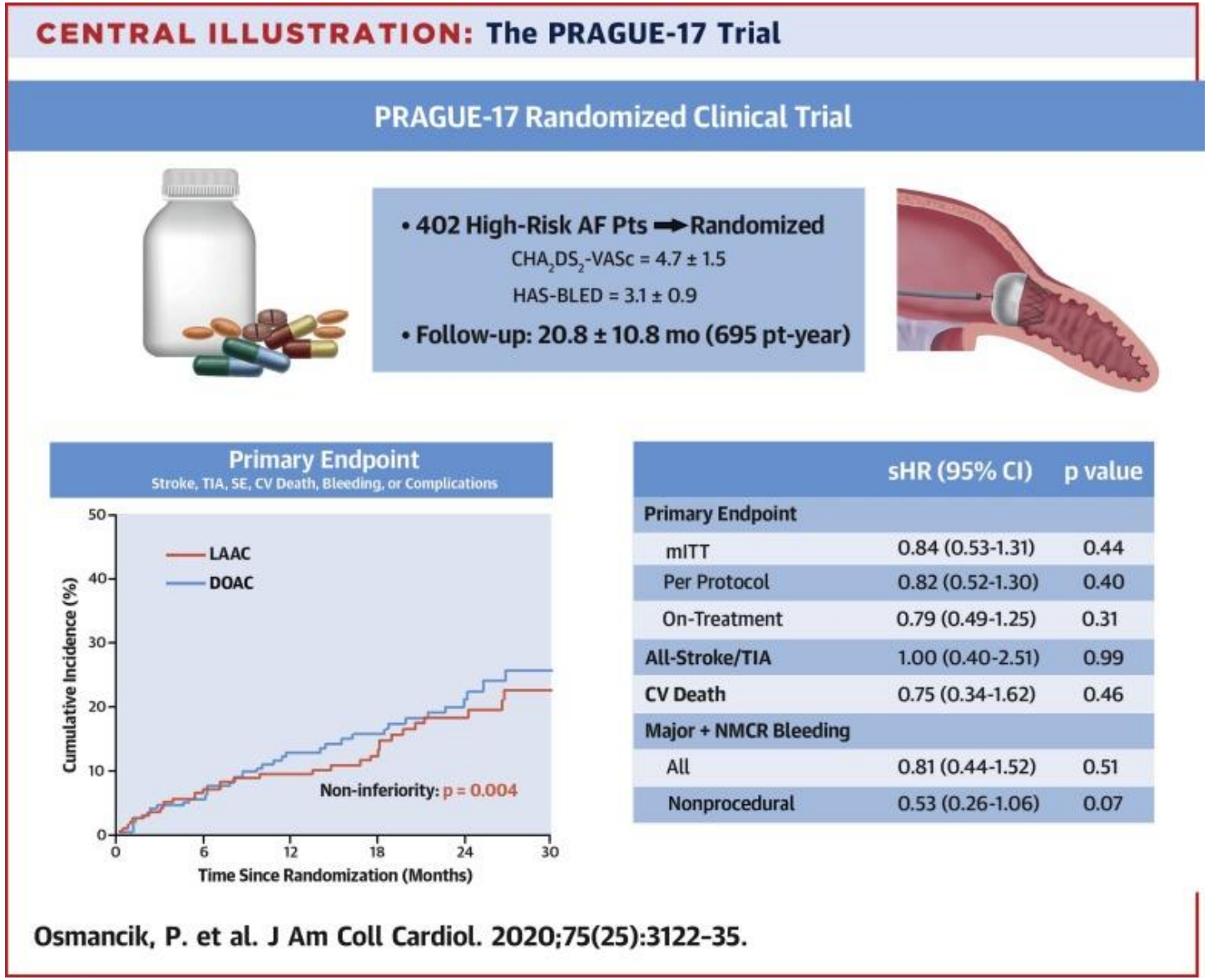
PRAGUE-17 trial

- In the primary analysis, at a median follow-up of 20 months, the incidence of the primary endpoint was similar between groups.
- The trial was not powered to identify differences in the individual components of the primary composite endpoint



Aim of the study

- As prespecified by protocol, patients in PRAGUE-17 continued to be followed up beyond the time point of the initial analysis.
- Results of clinical outcomes after 4 years of follow-up of the PRAGUE-17 trial population.

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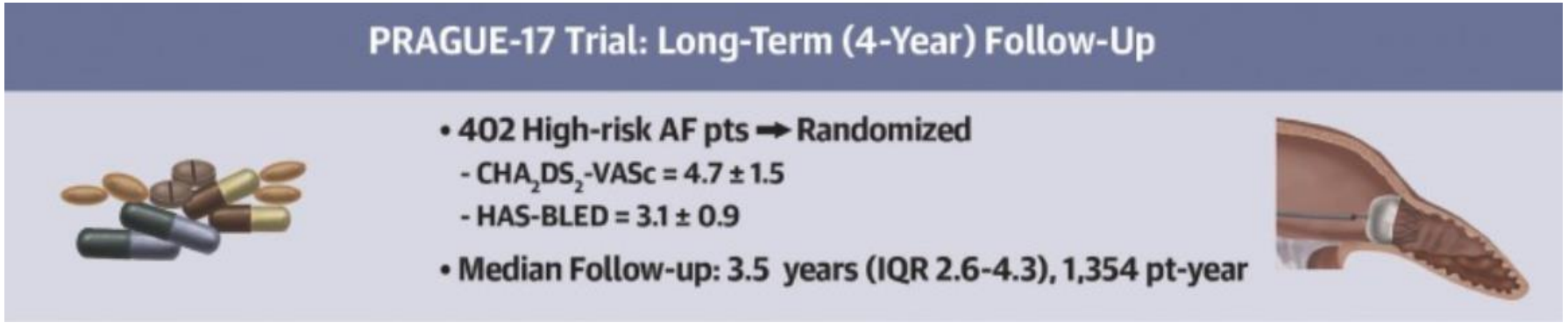
Methods

- PRAGUE-17 was a randomized non-inferiority 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 CHA2DS2-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.



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Antithrombotic therapy after LAAC

- 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.
- 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.
  - 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.

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Baseline characteristics

	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)

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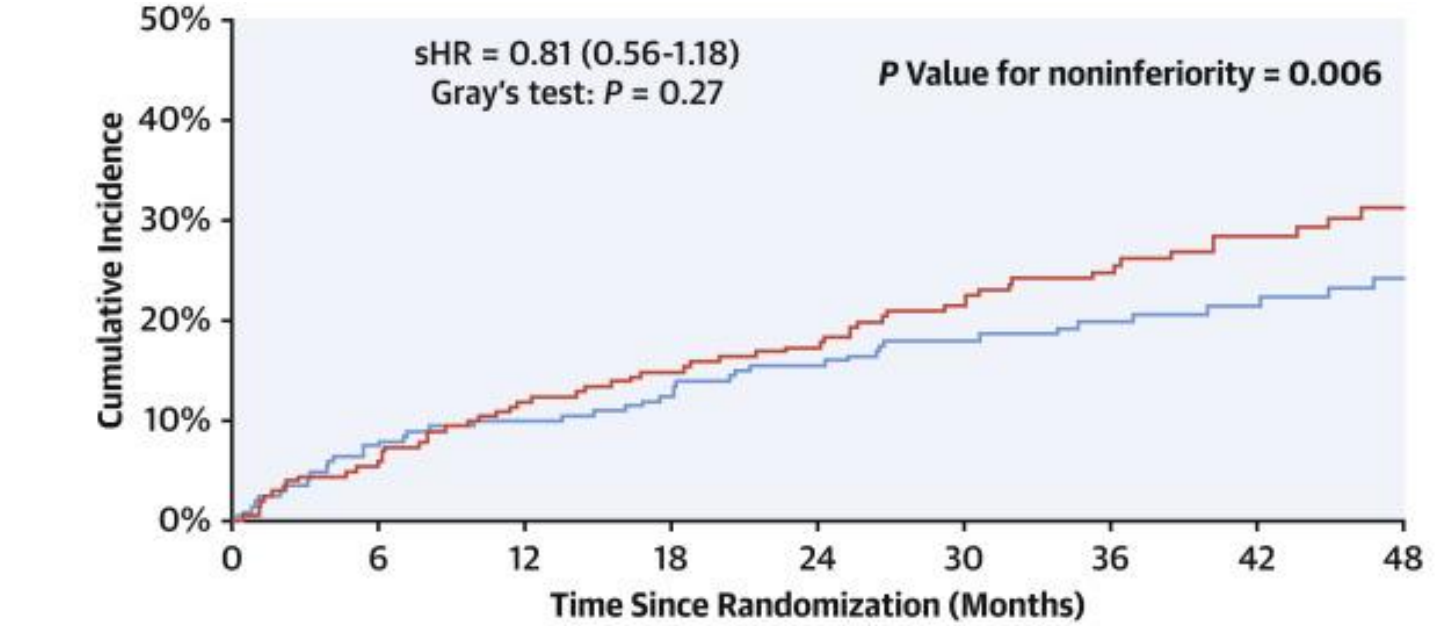
Primary Outcome in the mITT Analysis

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.



	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%)

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

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

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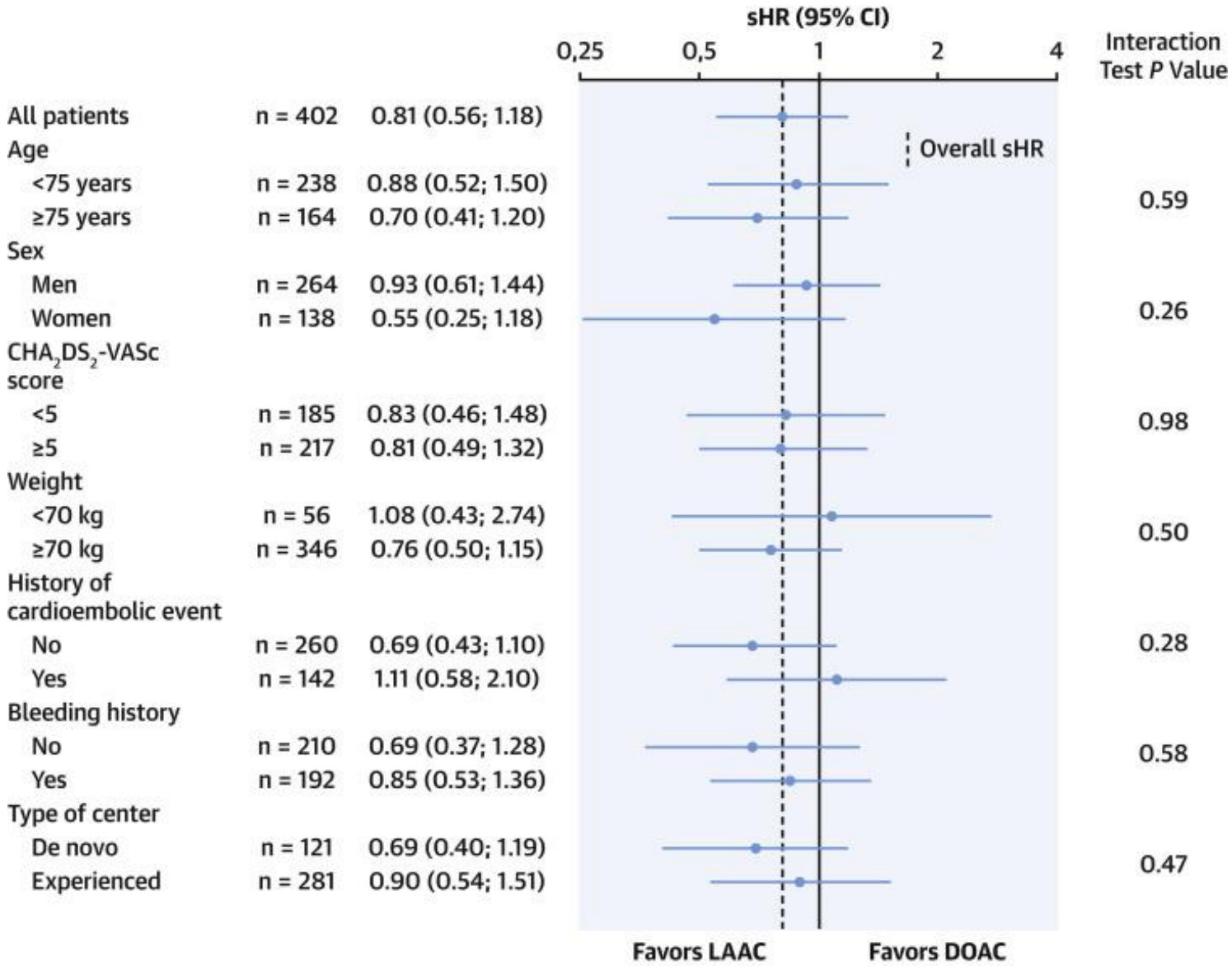
Subgroup Analysis



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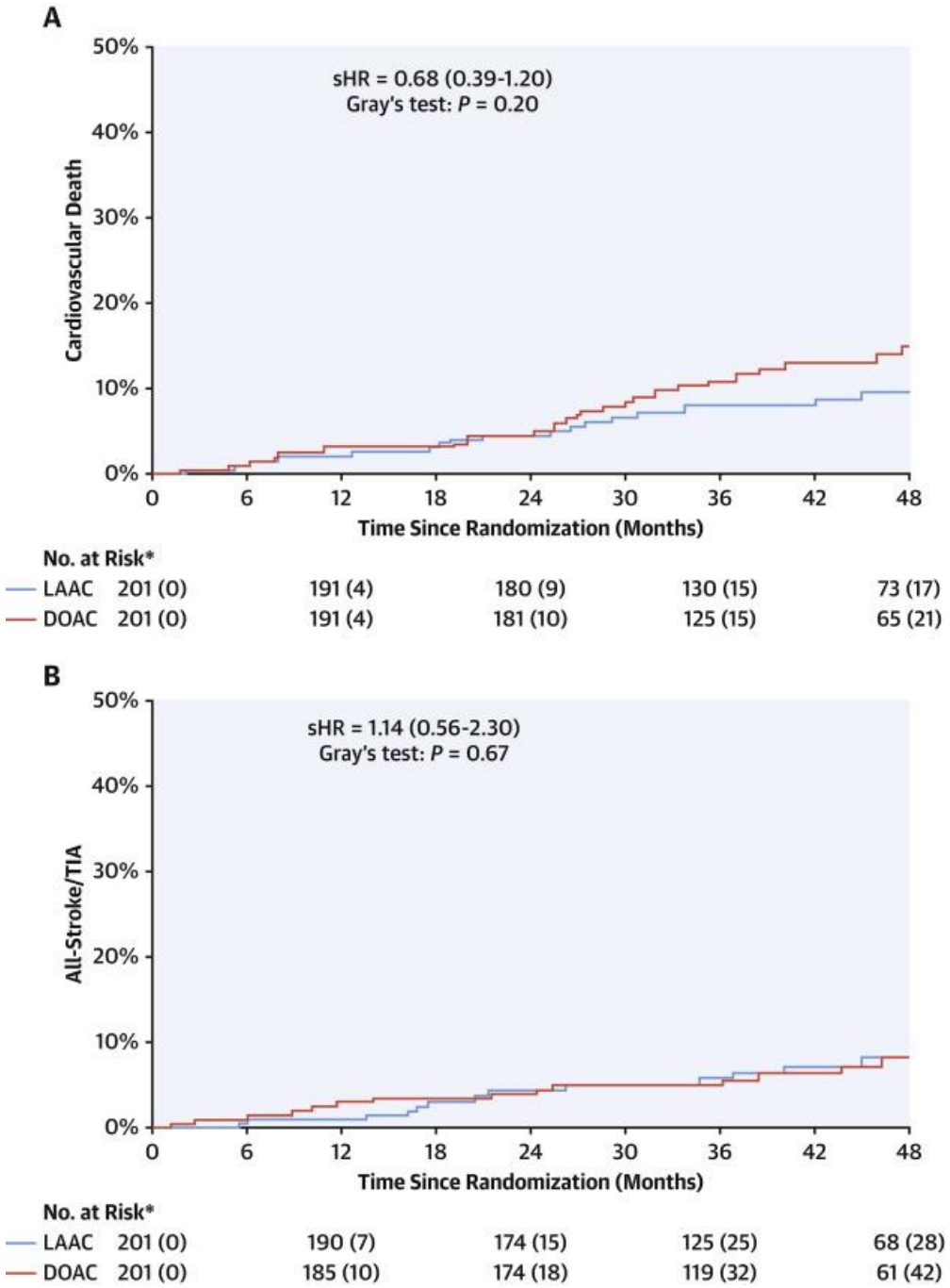
Secondary Outcomes in the mITT Analysis



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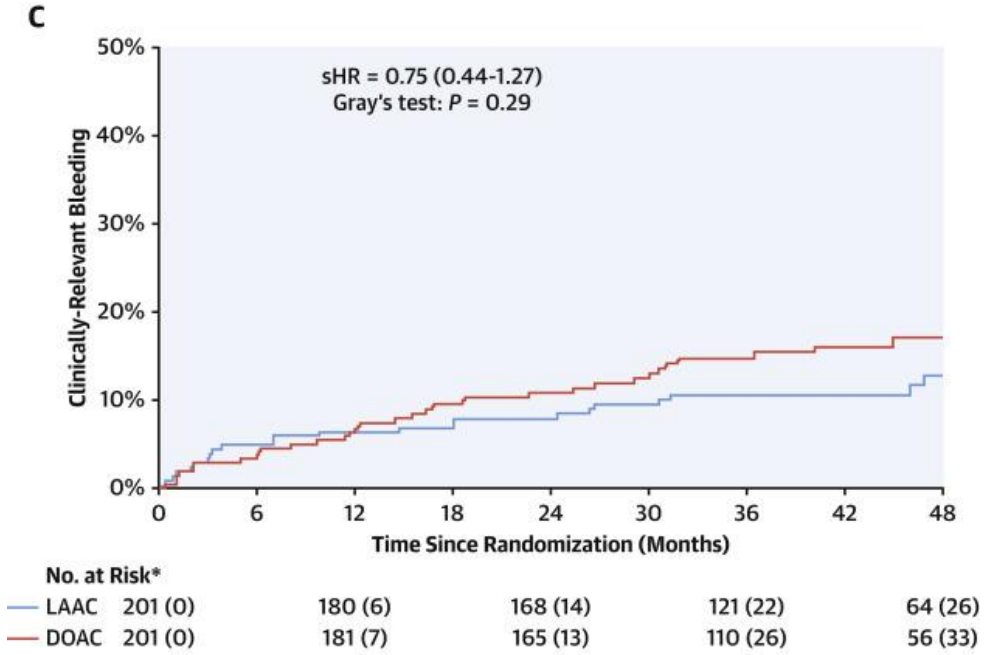
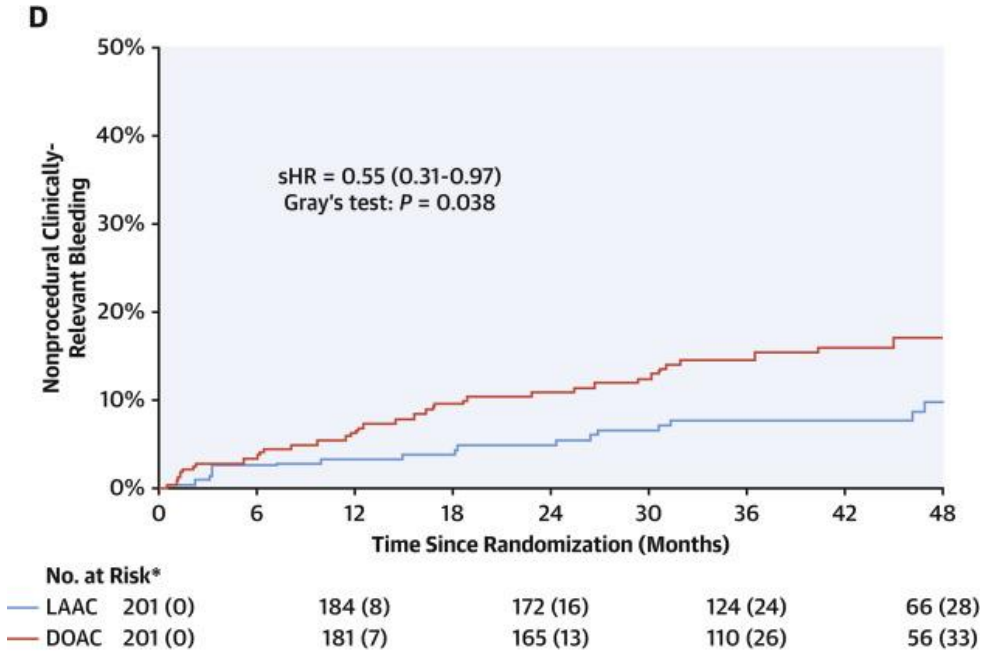
Secondary Outcomes in the mITT Analysis

Clinically relevant bleeding occurred in 24 patients with LAAC (29 events) and in 32 patients with DOACs (40 events). 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)





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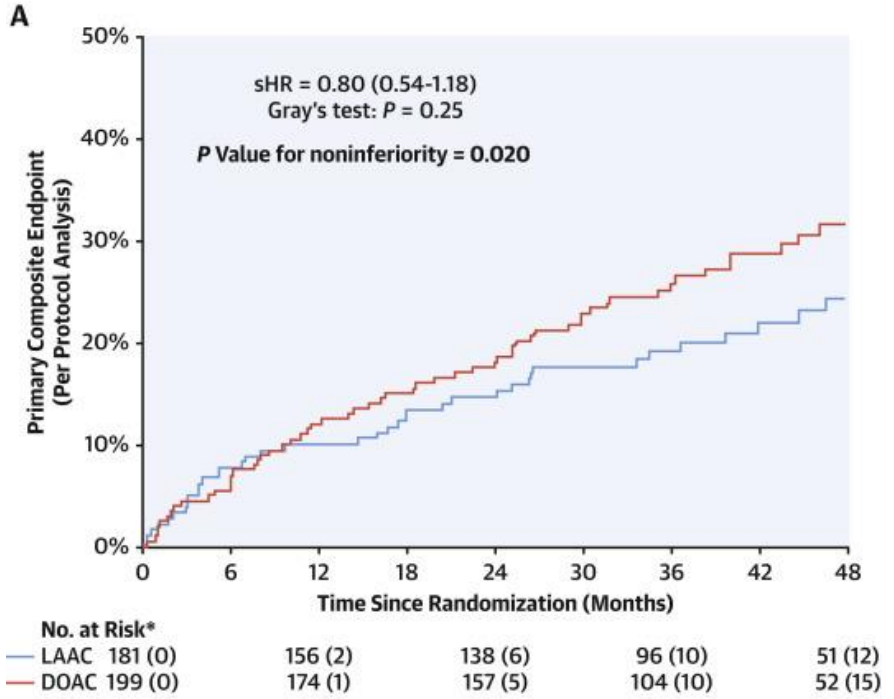
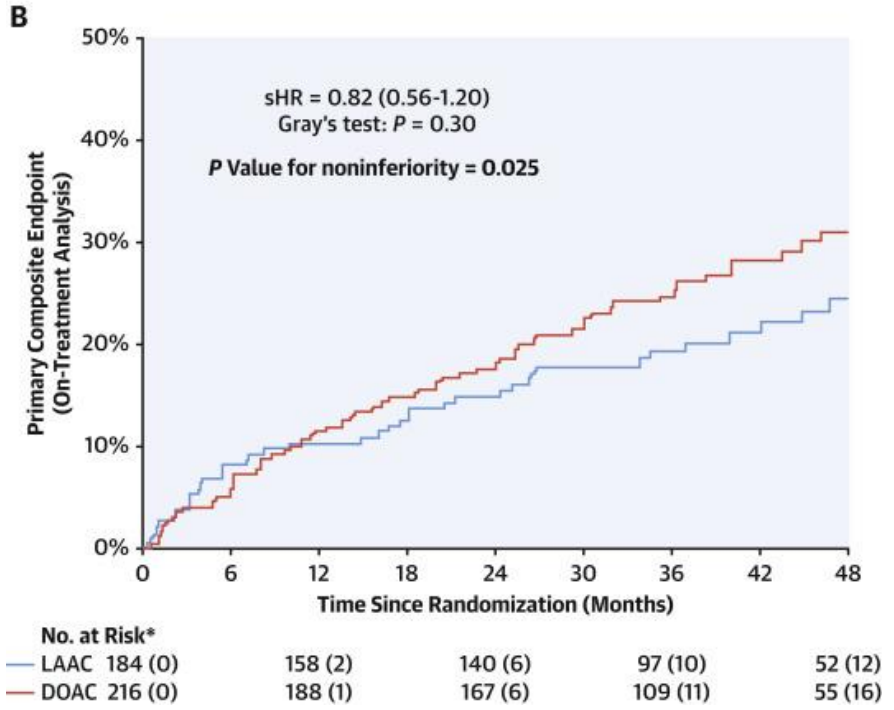
Primary Outcome in the Per-Protocol and On-Treatment Analyses





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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 CHA2DS2-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.

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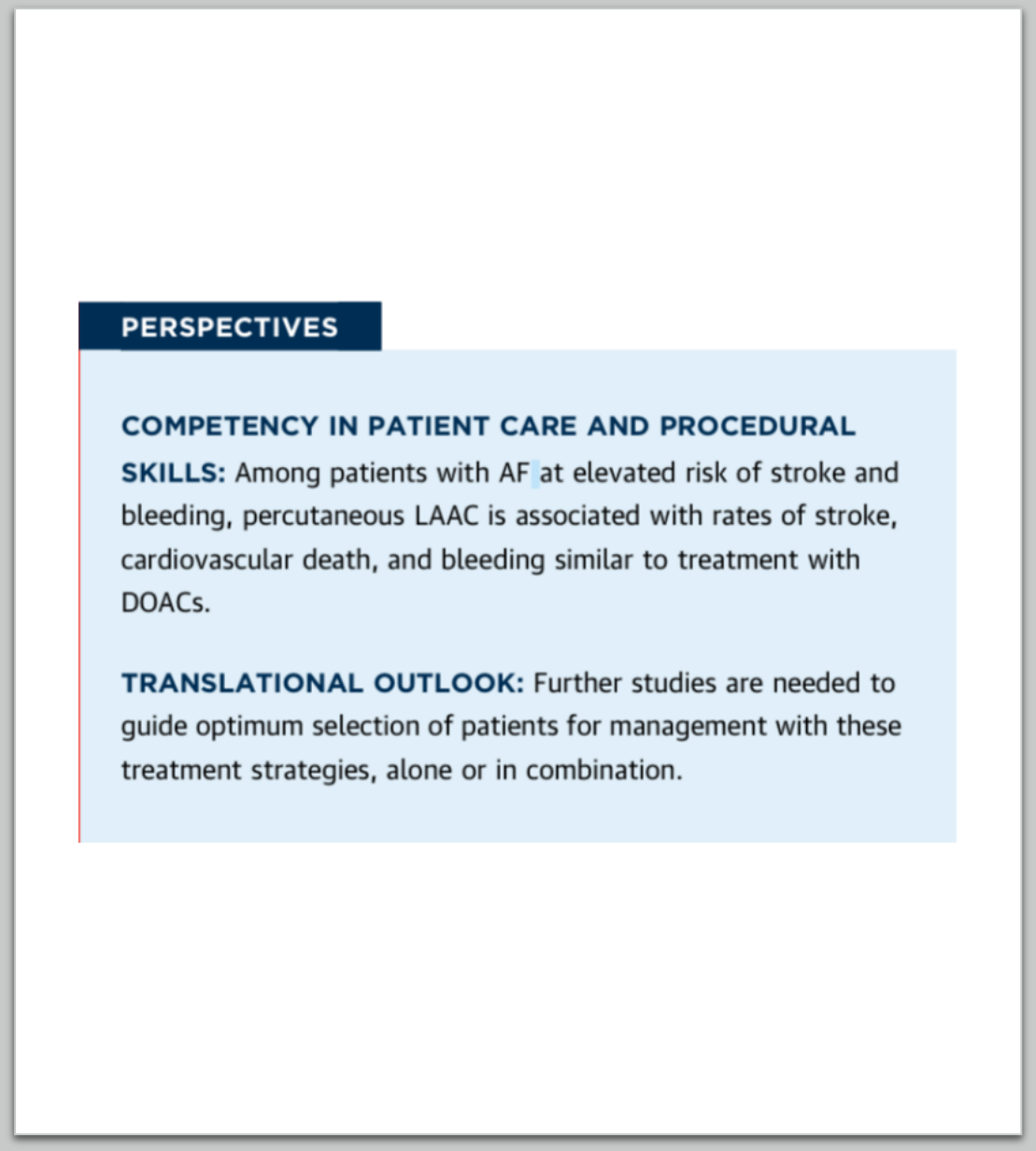
Conclusions

- 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.



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.

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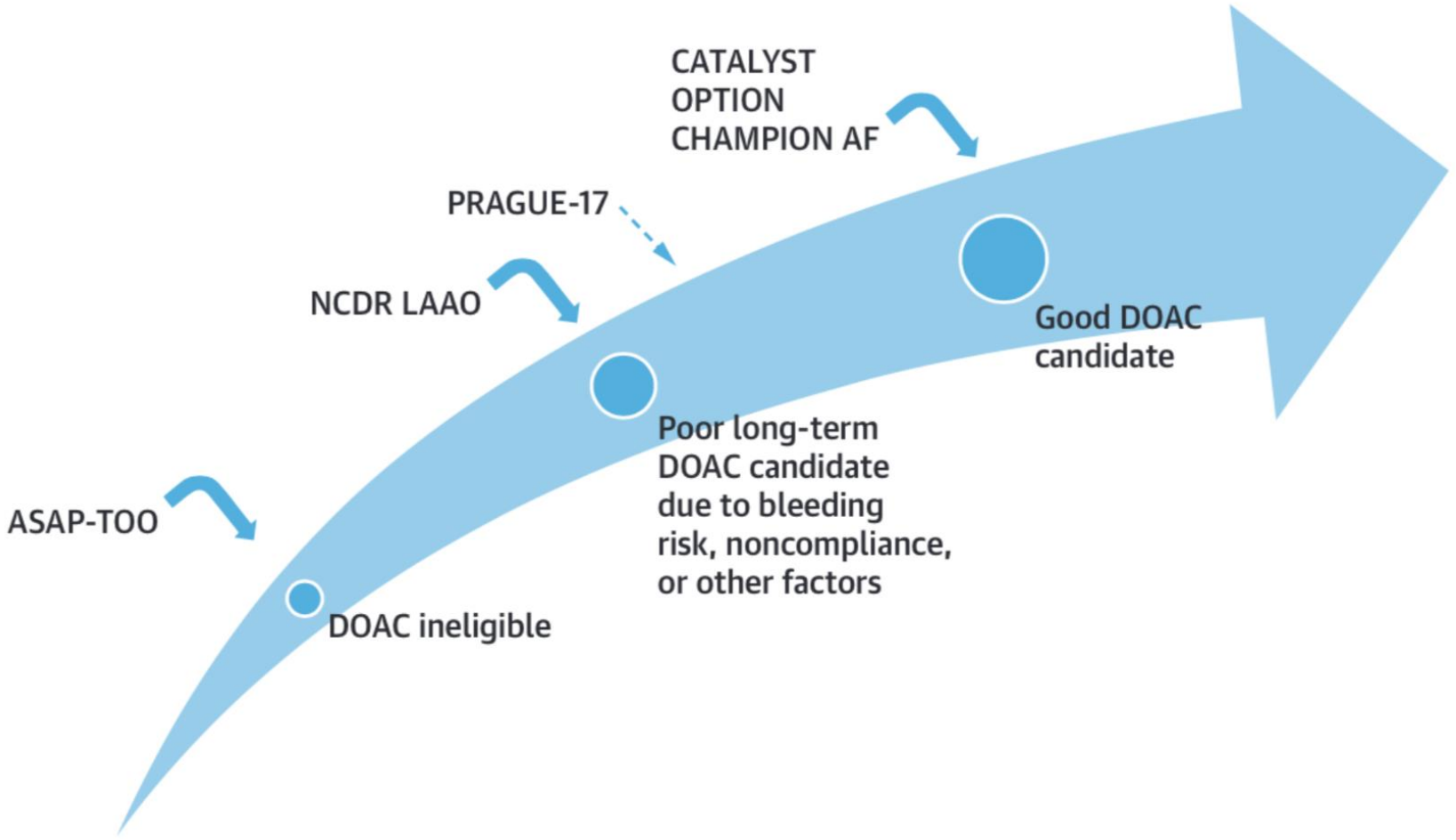
Ongoing trials



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