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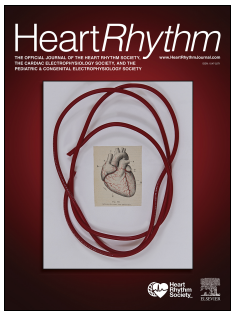

Outcomes of left atrial appendage closure versus oral anticoagulation after catheter ablation among patients with higher and lower stroke risk: A sub-analysis of the OPTION clinical trial.

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PII: S1547-5271(26)02462-8

DOI: https://doi.org/10.1016/j.hrthm.2026.05.057

Reference: HRTHM 12031

To appear in: *Heart Rhythm*

Received Date: 29 December 2025

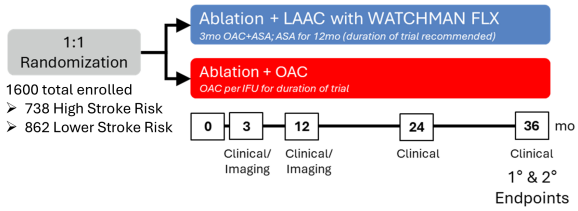
Revised Date: 19 May 2026

Accepted Date: 30 May 2026

Please cite this article as: Healey JS, Doshi R, Nair DG, Reddy VY, Piccini J, Das M, Chaudhry M, Mittal S, Gonzalez IC, Joyner C, Boveda S, Loureiro RE, Kim J, Reiss JA, Sanchez CE, Holshouser JW, Heaslop J, Mikealian B, Gopinathannair R, Gharib W, Schuler BT, Jaber W, Mansour M, Tondo C, Natale A, Phillips KP, Boersma L, Leger K, Sutton B, Stein K, Christen T, Wazni OM, Outcomes of left atrial appendage closure versus oral anticoagulation after catheter ablation among patients with higher and lower stroke risk: A sub-analysis of the OPTION clinical trial., *Heart Rhythm* (2026), doi: https://doi.org/10.1016/j.hrthm.2026.05.057.

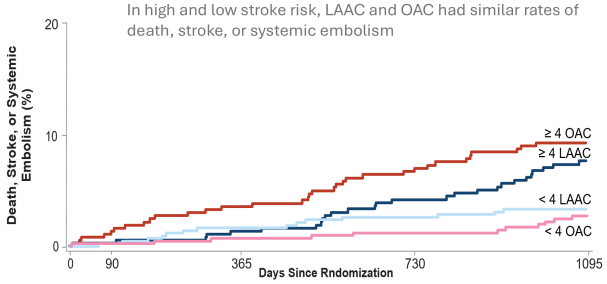
Stroke Risk Sub-analysis of the OPTION Trial

High Risk: CHA_2DS_2-VASc ≥ 4
Lower Risk: CHA_2DS_2-VASc ≤ 3

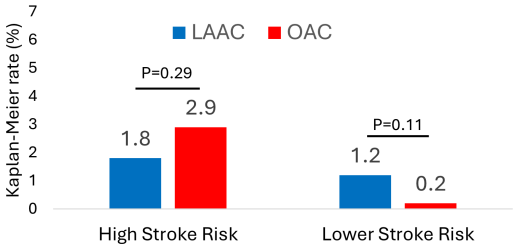


Primary Effectiveness Endpoint

In high and low stroke risk, LAAC and OAC had similar rates of death, stroke, or systemic embolism

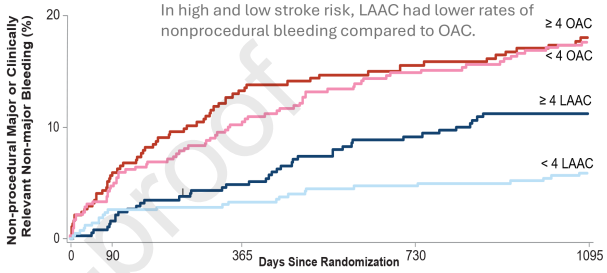


Rates of Ischemic Stroke or Systemic Embolism at 36 Months



Primary Safety Endpoint

In high and low stroke risk, LAAC had lower rates of nonprocedural bleeding compared to OAC.



Outcomes of left atrial appendage closure versus oral anticoagulation after catheter ablation among patients with higher and lower stroke risk: A sub-analysis of the OPTION clinical trial.

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Conflict of Interest Disclosures:

JSH reports research grants and speaking fees from Boston Scientific, Medtronic, and BMS/Pfizer. RD is a consultant to Boston Scientific. DGN has received research grants, consulting fees, or honoraria from Boston Scientific Corp, Medtronic Inc, Abbott Medical, J&J Medtech, Siemens, Volta, and Atraverse. JPP has received grants for clinical research from Abbott, the American Heart Association, iRhythm, and Philips; is a consultant to Abbott, Medtronic, Milestone Pharmaceuticals, Novartis, Philips, PhysCade, Sanofi, SymKardia, and Up-to-Date; and serves on data safety and monitoring boards for Kardium and Conformal. MD, GMC, CJ, JWH, and JH report no disclosures. VYR serves as an unpaid consultant to and grant recipient from Boston Scientific; and unrelated to this manuscript, he serves as a consultant for and has equity in Anumana, APN Health, Append Medical, Aquaheart, Atacor, Atraverse, Autonomix,

BioSig, CardiaCare, Cardiofocus, CardioNXT/AFTx, Circa Scientific, CoRISMA, Cortex-Boston Scientific, Corvia Medical, Dinova-Hangzhou DiNovA EP Technology, East End Medical, EP Frontiers, Field Medical, Focused Therapeutics, Heartbeam, HRT, Intershunt, Javelin, Kardium, Laminar-JNJ MedTech, LuxMed, Medlumics, Orchestra Biomed, PhysioMap, Pulse Biosciences, Restore Medical, Sirona Medical, SoundCath-Boston Scientific, Volta Medical; and unrelated to this work, he has served as a consultant for Abbott, Adagio Medical, AtriAN, BioTel Heart, Biotronik, BTL, Boston Scientific, Cairdac, Cardionomic, Conformal Medical, CoreMap, Fire1, Impulse Dynamics, JNJ MedTech, Medtronic, Novartis, Novo Nordisk, Philips, SmartValves; and unrelated to this work, he has equity in DRS Vascular, Manual Surgical Sciences, Newpace, Nyra Medical, Soundcath, Surecor, and Vizaramed. SM is a consultant to Boston Scientific. ICG is a proctor and consultant for Boston Scientific, Abbott, SMT, and IHT. SB is a consultant for Medtronic, Boston Scientific, Microport, and Zoll. REL is a consultant for Abbott Vascular, Edwards Lifesciences, Boston Scientific, Jenscare, Valgen, and Venus Medtech. CES is an advisory board member at Boston Scientific. BM is a consultant and advisor to Boston Scientific and a consultant to Johnson & Johnson. RG is a consultant for Boston Scientific, Abbott Medical, and J&J. WG has served as an advisory board member for Boston Scientific. BTS has served as an advisor board member, speaker, and consultant for Boston Scientific. WJ is a consultant for Boston Scientific and Pfizer. CT is a member of the Boston Scientific advisory board. MM has served as a consultant for Boston Scientific, Biosense Webster, Medtronic, and Abbot, and holds equity in NewPace Ltd. AN is a consultant for Abbott, Biosense Webster, Biotronik, Boston Scientific, Field Medical, Hemonetics, iRhythm, Medtronic, and Pulse Bioscience. KPP has received consultant/honoraria for presentations from Abbott and Boston Scientific. LB is a consultant and speaker for Boston Scientific, Medtronic, ZOLL, and Biosense Webster, and has received grants from Boston Scientific and Medtronic; all fees and funding go to the Cardiology Department and hospital. KL, BS, KS, and TC are employees and shareholders of Boston Scientific Corporation. OMW is a consultant for Boston Scientific.

Word count for text proper (excluding abstract, references, tables, and figure legends): 2253

Total word count: 5135

Keywords: atrial fibrillation, left atrial appendage closure, catheter ablation, oral anticoagulation, stroke risk

Abbreviations:

Abbreviation	Definition
AF	Atrial fibrillation
LAAC	Left atrial appendage closure
(N)OAC	(non-vitamin K antagonist) oral anticoagulation
ISTH	International Society on Thrombosis and Haemostasis
CEC	Clinical Events Committee
TIA	Transient ischemic attack

Abstract:

Background: The OPTION trial demonstrated that following atrial fibrillation (AF) ablation, left atrial appendage closure (LAAC) reduced non-procedural bleeding and was non-inferior to oral anticoagulation (OAC) with respect to death, stroke, or systemic embolism.

Objective: To evaluate event rates in relation to patients' baseline stroke risk.

Methods: The primary safety endpoint was non-procedural major or clinically relevant non-major bleeding, and primary efficacy endpoint was a composite of death, stroke, or systemic embolism, measured at 3 years. Patients were stratified based on CHA_2DS_2-VASc ≥4 versus ≤ 3.

Results: The trial enrolled 1600 patients aged 70±8 years, with 738 and 862 patients having a CHA_2DS_2-VASc score ≥4 and ≤3, respectively. The primary efficacy outcome was similar for the OAC and LAAC arms both among patients with CHA_2DS_2-VASc ≥4 (9.4% vs. 7.8% p=0.37) and those with CHA_2DS_2-VASc ≤3: (2.7% vs. 3.3%, p=0.59). Patients with CHA_2DS_2-VASc ≤3 had an annual risk of ischemic stroke of 0.3% with LAAC and 0.1% with OAC (p=0.19). Bleeding was more frequent with OAC for CHA_2DS_2-VASc score ≥4 (18.4% vs. 11.5%, p<0.01) and CHA_2DS_2-VASc ≤3 (17.9% v 6.0%, p<0.01).

Conclusion: Following ablation of AF, the rates of cardiovascular events are low among individuals with a CHA_2DS_2-VASc ≤ 3 who were treated with either LAAC or OAC, and their annual risk of ischemic stroke is ≤ 0.3% with either treatment. Bleeding risk with OAC is similar for patients with high and low CHA_2DS_2-VASc and significantly lower with LAAC for both groups.

Atrial fibrillation (AF) is increasing in prevalence and is a major cause of patient symptoms and cardiovascular events including stroke [1,2]. Over the last five years, randomized trials have demonstrated that therapies to maintain sinus rhythm, particularly catheter ablation, may reduce the risk of cardiovascular events [3-6]. Success rates with modern AF ablation procedures are high and AF burden can be reduced to very low levels [6], below which the risk of stroke for many patients is very low [7]. When the risk of stroke and systemic embolism falls below 1% per year, the risks of bleeding due to oral anticoagulation (OAC) may become greater than the reduction in stroke [8], calling into question the value of continuing OAC in such patients. For these lower-risk individuals, alternative methods of stroke prevention with lower rates of bleeding might still prevent stroke with a more favorable risk-benefit profile.

In patients with device-detected subclinical AF, the ARTESIA trial suggests that OAC does not substantially reduce the risk of stroke or systemic embolism among patients with a CHA_2DS_2-VASc score of ≤ 3 but is associated with a trend towards more major bleeding than aspirin [8]. Thus, continued OAC may not be desirable following AF ablation in patients at lower risk of stroke who have very low or no residual burden of AF. OAC discontinuation following successful AF ablation was recently evaluated in the OCEAN trial, which enrolled patients with a CHA_2DS_2-VASc of ≥ 1 [9]. For higher-risk individuals, alternative strategies that can prevent stroke with a lower risk of bleeding may be desirable. The OPTION trial randomized patients following AF ablation to left atrial appendage closure (LAAC) vs. OAC and demonstrated non-inferiority against a composite of death, stroke or systemic embolism, with a significant reduction in the risk of non-procedural bleeding with LAAC [10]. This sub-analysis of the OPTION trial will examine study outcomes based on the baseline stroke risk of patients, defined using the CHA_2DS_2-VASc score.

Methods

Study design and patients.

The OPTION trial was a multicenter, randomized clinical study that assessed whether LAAC using the WATCHMAN FLX device presents a reasonable alternative to OAC after percutaneous catheter ablation in moderate and high-risk patients with non-valvular AF [10]. The trial was registered on ClinicalTrials.gov (NCT03795298), and both the protocol and primary results have been previously published [10,11]. All trial activities adhered to the Declaration of Helsinki. The ethics or institutional review board at each participating site approved the study, and all participants provided written informed consent. Clinical events were adjudicated by a clinical events committee.

Endpoints and statistical methods.

The analyzed sub-group populations (higher stroke risk and lower stroke risk) were defined according to CHA_2DS_2-VASc score at baseline. Patients with scores 4 or higher were classified as higher stroke risk, and patients with scores 3 or below comprised the lower stroke risk group. Descriptive statistics are provided for baseline patient characteristics, procedure characteristics, and medication compliance. Endpoints for OAC versus LAAC were statistically compared within each sub-group.

The primary effectiveness endpoint for the OPTION trial was a composite rate of stroke (ischemic and/or hemorrhagic), death, or systemic embolism at 36 months tested for non-inferiority of LAAC compared to OAC [11]. The primary safety endpoint for the trial was non-procedural International Society on Thrombosis and Haemostasis (ISTH) major bleeding or clinically relevant non-major bleeding at 36 months tested for superiority. All primary and secondary endpoints and their individual components were defined as the Kaplan-Meier estimates of time to first event occurrence [11]. In the overall OPTION trial population, LAAC was non-inferior for the primary effectiveness and secondary safety endpoints and demonstrated superiority for the primary safety endpoint [10]. Subgroups were not statistically powered for primary and secondary endpoints, but subgroup analyses based on stroke risk assessed using the CHA_2DS_2-VASc score were prespecified in the statistical analysis plan [10,11].

Results

Study Population and Procedure Characteristics.

A total of 1600 patients were randomized at 106 investigational sites worldwide between November 2019 and June 2021. Seven hundred-thirty-eight patients (46.1% of total enrollment) had a CHA_2DS_2-VASc score of 4 or greater at baseline and were characterized as the higher stroke risk group (370 LAAC, 368 OAC). The remaining 862 patients had CHA_2DS_2-VASc scores of 3 or less and were characterized as the lower stroke risk group (433 LAAC, 429 OAC. Within each stroke risk group, baseline clinical characteristics were not statistically significant different between the LAAC and OAC arms (Table 1). The mean CHA2DS2-VASc score was 3.5±1.3 in both the LAAC and OAC study arms (Table 1). Patient flow through the study is shown in Figure 1. In both stroke risk groups, approximately 90% of patients who were alive at the time of last follow-up completed 36-month visits.

Among patients randomized to LAAC, the rates of successful device implant were 93.2% (345/370) for patients with CHA_2DS_2-VASc ≥ 4 and 94.2% (408/433) for patients with CHA_2DS_2-VASc ≤ 3. LAAC and catheter ablation were performed concomitantly for 37.0% (137/370) of patients with CHA_2DS_2-VASc ≥ 4 and 44.1% (191/433) of patients with CHA_2DS_2-VASc ≤ 3. From randomization through 36 months, 29.2% (108/370) of higher stroke-risk LAAC patients and 28.8% (106/368) of higher stroke-risk OAC patients underwent cardioversion or a repeat ablation, P=0.91. These rates were 27.5% (119/433) and 23.3% (100/429; P=0.16), respectively for the LAAC and OAC patients within the lower stroke risk group. The proportion of patients receiving OAC in both the OAC and LAAC arms of the trial was similar for higher and lower stroke risk groups at all points during follow-up (Table 2).

Efficacy and Safety Outcomes.

The 36-month primary efficacy composite endpoint of death, stroke, and systemic embolism (Figure 2) was not significantly different between the LAAC (7.8%) and OAC arms (9.4%) in patients with a CHA_2DS_2-VASc ≥ 4 (P=0.37), nor among those with a CHA_2DS_2-VASc ≤ 3 (3.3% vs. 2.7%, P=0.59). However, the primary event rate was 2-3-times higher for both treatment arms among patients with a

CHA_2DS_2-VASc ≥ 4 (Supplemental Table 1). In CHA_2DS_2-VASc ≥ 4 group, ischemic stroke or systemic embolism occurred with a similar frequency in the LAAC (1.8%) and OAC (2.9%) arms (p=0.29), while for patients with CHA_2DS_2-VASc ≤ 3, the corresponding rates were 1.2% with LAAC and 0.2% with OAC, p=0.11. Event rates for death, stroke, and systemic embolism within each CHA_2DS_2-VASc score are shown in Supplemental Table 1.

Ischemic stroke rates in both the higher and lower CHA_2DS_2-VASc-risk groups were markedly lower than expected rates among untreated patients at different stroke risk strata (Supplementary Figure 1)[12]. A Fine–Gray competing risk model was used to assess 36-month ischemic stroke rates accounting for competing risk of death. These adjusted rates were not different from Kaplan-Meier event rates, indicating stroke prevention efficacy with LAAC or OAC is a robust effect, even when the disparate mortality risks in the higher and lower stroke risk groups are considered.

Within the CHA_2DS_2-VASc ≥ 4 group, the primary safety composite endpoint of 36-month non-procedural ISTH major bleeding and clinically relevant non-major bleeding was significantly lower in the LAAC arm (11.5%) compared to OAC (18.4%), p=0.007 (Table 3, Figure2). This same pattern of results was also observed among patients with CHA_2DS_2-VASc ≤ 3, with bleeding rates of 6.0% with LAAC and 17.9%, p<0.0001 with OAC. In both stroke risk groups, the lower composite bleeding rates in LAAC versus OAC were driven by significant differences in clinically relevant non-major bleeding (Table 3). Analyses of the secondary safety endpoint (procedural and nonprocedural major bleeding) show no significant difference between LAAC and OAC within either stroke risk group (Table 3, Figure2). Rates of all major and non-major bleeding at each CHA_2DS_2-VASc score are show in Supplemental Table 2.

Event Rates Among Patients with Prior Stroke or Transient Ischemic Attack (TIA).

In the subgroup of patients with prior stroke or TIA (n=183), the primary efficacy endpoint occurred in 9.0% of LAAC and 14.7% OAC patients at 36 months, P=0.23. In these same patients, the 36-month stroke rates were 2.6% and 9.5% for LAAC and OAC, and ischemic stroke rates were 1.4% for

LAAC and 6.4% for OAC. In patients without a prior stroke or TIA, the primary efficacy endpoint rate was 4.9% in the LAAC and 4.6% in the OAC cohorts (P=0.76) with respective stroke rates 1.5% and 0.9% and ischemic stroke rates of 1.2% for LAAC and 0.6% for OAC. The primary safety endpoint occurred at a rate of 8.9% in LAAC and 20.1% in OAC-treated patients (P=0.04) with a prior stroke or TIA and were similar among patients without a prior stroke or TIA: 8.4% with LAAC and 17.8% with OAC, P<0.0001.

Discussion

This pre-specified subgroup analysis of the OPTION randomized trial demonstrates that following catheter ablation of AF, patients with a CHA_2DS_2-VASc ≤ 3 who were treated with LAAC or OAC had a very low risk of cardiovascular events. Their risk of stroke, systemic embolism, and death was around 1% per year, including a <0.5% per year risk of ischemic stroke or systemic embolism, which was similar with either LAAC or OAC. However, patients treated with LAAC had substantially less non-procedural bleeding, making LAAC preferable to OAC in this lower risk group of individuals following AF ablation in the OPTION trial.

Individuals in the OPTION trial had an average CHA_2DS_2-VASc score of 2.6, which overlaps substantially with that of patients in the OCEAN trial (mean score of 2.2 ± 1.1)[9], and the ALONE-AF[13] trial (mean score of 2.1 ± 1.0), which randomized patients to OAC discontinuation following at least one year of AF-free monitoring following AF ablation. These two studies demonstrated that patients randomized to discontinue OAC had a risk of stroke and embolism of well less than 1% per year and lower rates of bleeding than those continuing OAC. Together, these trials suggest that following successful AF ablation, patients with a CHA_2DS_2-VASc score ≤ 3 may not need any stroke prevention therapy, including OAC or LAAC[9,13]. However, in the first months following AF ablation, one cannot predict if a given patient will have long-term freedom from AF, as was seen in patients in the OCEAN and ALONE-AF trials. In OPTION, 47% of patients had recurrent AF within 3 years, which was driven by the 39% prevalence of persistent AF among enrolled individuals[14]. Thus, only half of OPTION

patients would not have been eligible for OAC discontinuation based on the results of OCEAN and ALONE-AF. Overall, the results from OPTION, OCEAN and ALONE-AF can be taken along with assessment of individuals' post-ablation AF burden and their preferences regarding stroke prevention[15] to inform the best approach for stroke prevention for individuals in this lower-risk population.

Patients with a CHA_2DS_2-VASc of ≥ 4 represented 46% of individuals in the OPTION trial. Despite catheter ablation of AF ablation, their risk of cardiovascular events remained around 3% per year with either LAAC or OAC, including a stroke risk of 3.7% risk at 3 years for patients assigned to OAC. This stroke risk in the OAC arm was observed despite an 86% adherence to OAC at 36 months, which is substantially better than what is observed in real-world registries [16, 17]. This observation is even more apparent among patients with a history of stroke or TIA, who had a stroke risk of over 3% per year in the OAC arm. Thus, for patients following AF ablation with a CHA_2DS_2-VASc of ≥ 4 or those with a history of stroke or TIA, it appears likely that some form of ongoing stroke prevention therapy is required despite ablation. Patients with CHA_2DS_2-VASc ≥ 4 represented only a very small proportion of individuals in the OCEAN and ALONE-AF trials [9,13], thus we have little trial data regarding the safety of OAC withdrawal following long-term freedom from AF recurrence in this higher-risk group. However, given the stroke rates observed in OPTION, OAC withdrawal would be expected to have an unacceptably high risk of stroke.

The risk of cardiovascular events in patients with CHA_2DS_2-VASc ≥ 4 was similar among patients randomized to LAAC compared to OAC. LAAC is also associated with substantially fewer non-procedural bleeding events. As bleeding is a frequent cause for OAC discontinuation in real world cohorts [18], the excess in bleeding observed in the OAC arm of OPTION could drive OAC discontinuation over longer-term follow-up in real-world practice and lead to a greater excess of stroke among OAC-treated patients. Thus, OPTION suggests that LAAC could be a reasonable alternative to OAC in the post-ablation setting, again depending on a patient's specific risks of stroke and bleeding [19], their residual AF burden and their preferences regarding stroke prevention [15]. Of course, the results of OPTION must be

considered in the context of the abundant trial evidence supporting the use of OAC to prevent stroke, particularly among patients at higher-risk [19]. The implications of OPTION will also evolve as we learn more about the impact of modern rhythm control on the reduction of AF burden and the associated cardiovascular risks [19-22].

Finally, OPTION demonstrated an important residual risk of cardiovascular events and stroke following AF ablation, despite OAC or LAAC, in patients with a CHA_2DS_2-VASc ≥ 4 and particularly in those with a history of prior stroke or TIA. This raises the possibility that LAAC and OAC could be used in combination for certain patients at very high stroke risk. While not in a post AF ablation population, this concept is currently under investigation in the LAAOS-4 trial (NCT05963698), which is enrolling patients with CHA_2DS_2-VASc ≥ 4 and persistent or permanent AF, or paroxysmal AF with a history of stroke or systemic embolism.

Study Limitations

This is a pre-specified secondary analysis of a randomized, non-inferiority trial. Thus, this analysis was not separately powered to have sufficient statistical power to make definitive conclusions for each of the sub-groups and outcomes evaluated.

Conclusions

Following ablation of AF, the rates of cardiovascular events are substantially lower among individuals with a CHA_2DS_2-VASc ≤ 3 treated with either LAAC or OAC, and their annual risk of ischemic stroke is $\leq 0.3\%$ with either treatment. Bleeding risk with OAC is similar for patients with high and low CHA_2DS_2-VASc and significantly lower with LAAC for both groups.

Acknowledgements:

The authors thank Scott Wehrenberg (Boston Scientific Corporation) for his support with statistical analyses and Elisabeth Gabin and Anne Cornaille (both Boston Scientific Corporation) for support with clinical trial management.

Funding:

The OPTION trial was funded by Boston Scientific Corporation.

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Tables and Figures

Table 1 – Patient Characteristics

Table 1. Patient Characteristics						
	High Stroke Risk – CHA2DS2-VASc ≥4 N=738			Lower Stroke Risk – CHA2DS2-VASc ≤ 3 N=862		
	LAAC Device N=370	OAC Control N=368	P-value	LAAC Device N=433	OAC Control N=429	P-value
Demographics						
Female	189 (51.1)	178 (48.4)	0.47	94 (21.7)	85 (19.8)	0.49
Age at time of consent (years)	72.8±6.3	72.1±6.8	0.12	67.0±7.2	67.2±8.1	0.69
Caucasian	318 (85.9)	314 (85.3)	0.81	355 (82.0)	372 (86.7)	0.06
Black, of African Heritage	5 (1.4)	6 (1.6)	0.75	9 (2.1)	5 (1.2)	0.29
American Indian or Alaska Native	0 (0.0)	1 (0.3)	0.50	2 (0.5)	0 (0.0)	0.50
Asian	1 (0.3)	1 (0.3)	1.00	3 (0.7)	0 (0.0)	0.25
Hispanic or Latino	3 (0.8)	6 (1.6)	0.34	10 (2.3)	6 (1.4)	0.32
Other	0 (0.0)	1 (0.3)	0.50	3 (0.7)	2 (0.5)	1.00
Race/ethnicity not disclosed	43 (11.6)	39 (10.6)	0.66	51 (11.8)	44 (10.3)	0.48
Medical History						
Atrial fibrillation						
Persistent	155 (41.9)	151 (41.0)	0.81	171 (39.5)	145 (33.8)	0.08
Paroxysmal	215 (58.1)	217 (59.0)	0.81	262 (60.5)	284 (66.2)	0.08
Greater than 1 year	258 (69.7)	259 (70.4)	0.85	288 (66.5)	287 (66.9)	0.90
History of major bleeding	18 (4.9)	22 (6.0)	0.50	12 (2.8)	14 (3.3)	0.67
Prior stroke or TIA	70 (18.9)	87 (23.6)	0.12	13 (3.0)	13 (3.0)	0.98
Congestive heart failure	145 (39.2)	147 (39.9)	0.40	71 (16.4)	64 (14.9)	0.55
Hypertension	348 (94.1)	343 (93.2)	0.83	373 (86.1)	358 (83.4)	0.27
Vascular disease	246 (66.5)	247 (67.1)	0.86	108 (24.9)	133 (31.0)	0.05
Diabetes	136 (36.8)	145 (39.4)	0.46	86 (19.9)	76 (17.7)	0.42
CHA2DS2-VASc score	4.7±0.9	4.7±0.8	0.75	2.6±0.5	2.6±0.5	0.98
HAS-BLED score	1.4±0.8	1.5±0.8	0.05	1.0±0.8	1.0±0.7	0.69
Data is presented as n (%) or mean ± standard deviation						

Table 2 – Patients on Any OAC Across Follow-up

Table 2. Patients on Any OAC Across Follow-up				
	High Stroke Risk – CHA2DS2-VASc ≥4 N=738		Lower Stroke Risk – CHA2DS2-VASc ≤ 3 N=862	
	LAAC Device N=370	OAC Control N=368	LAAC Device N=433	OAC Control N=429
On Any OAC				
3 Months	91.3% (324/355)	98.3% (342/348)	89.4% (373/417)	98.5% (400/406)
12 Months	13.7% (47/344)	92.7% (307/331)	8.8% (36/407)	92.4% (354/383)
24 Months	10.6% (35/329)	89.2% (281/315)	8.6% (35/408)	87.2% (334/383)
36 Months	10.9% (34/311)	86.3% (264/306)	9.4% (38/403)	83.6% (312/373)
Data is presented as % (n/N).				

Table 3 – 36-Month Kaplan-Meier Clinical Event Rates

Table 3. 36-Month Clinical Event Rates (Kaplan-Meier)							
	High Stroke Risk – CHA2DS2-VASc ≥4 N=738			Lower Stroke Risk – CHA2DS2-VASc ≤ 3 N=862			
	LAAC Device N=370	OAC Control N=368	P-value	LAAC Device N=433	OAC Control N=429	P-value	Interaction P-value
Composite Endpoints							
Primary Effectiveness	27 (7.8)	33 (9.4)	0.37	14 (3.3)	11 (2.7)	0.59	0.35
Primary Safety	40 (11.5)	64 (18.4)	0.007	25 (6.0)	73 (17.9)	<0.0001	0.05
Death	21 (6.0)	24 (6.9)	0.61	8 (1.9)	10 (2.5)	0.58	0.85
Cardiovascular	5 (1.5)	6 (1.7)	0.74	4 (1.0)	4 (1.0)	0.97	0.85
Non-cardiovascular	10 (2.9)	15 (4.4)	0.30	4 (1.0)	4 (1.0)	0.95	0.63
Unexplained	6 (1.8)	3 (0.9)	0.33	0 (0.0)	2 (0.5)	0.15	0.99
Stroke	6 (1.8)	13 (3.7)	0.09	6 (1.4)	2 (0.5)	0.16	0.05
Ischemic	5 (1.5)	9 (2.6)	0.26	4 (1.0)	1 (0.2)	0.19	0.11
Hemorrhagic	1 (0.3)	3 (0.9)	0.31	2 (0.5)	0 (0.0)	0.16	0.99
Undetermined	0 (0.0)	1 (0.3)	0.31	0 (0.0)	1 (0.2)	0.31	1.00
Systemic embolism	1 (0.3)	1 (0.3)	0.99	1 (0.2)	0 (0.0)	0.33	0.99
Major bleeding*	18 (5.1)	23 (6.6)	0.39	12 (2.9)	15 (3.7)	0.51	0.97
Procedural† major bleeding	4 (1.1)	NA	NA	1 (0.2)	NA	NA	NA
Clinically relevant non-major bleeding*	28 (8.0)	49 (14.2)	0.008	18 (4.3)	61 (14.9)	<0.0001	NA
Procedural† clinically relevant non-major bleeding	0 (0)	NA	NA	3 (0.7)	NA	NA	0.06
Pericardial effusion requiring intervention	2 (0.6)	1 (0.3)	0.57	0 (0.0)	4 (1.0)	0.04	NA
Data is presented as n (Kaplan-Meier event rate). All endpoints were CEC-adjudicated *Bleeding classified per International Society on Thrombosis and Haemostasis (ISTH) definitions. Includes procedural and non-procedural bleeding. †Procedural bleeding is defined as bleeding within 3 days post index procedure							

Figure 1 – Patient Disposition

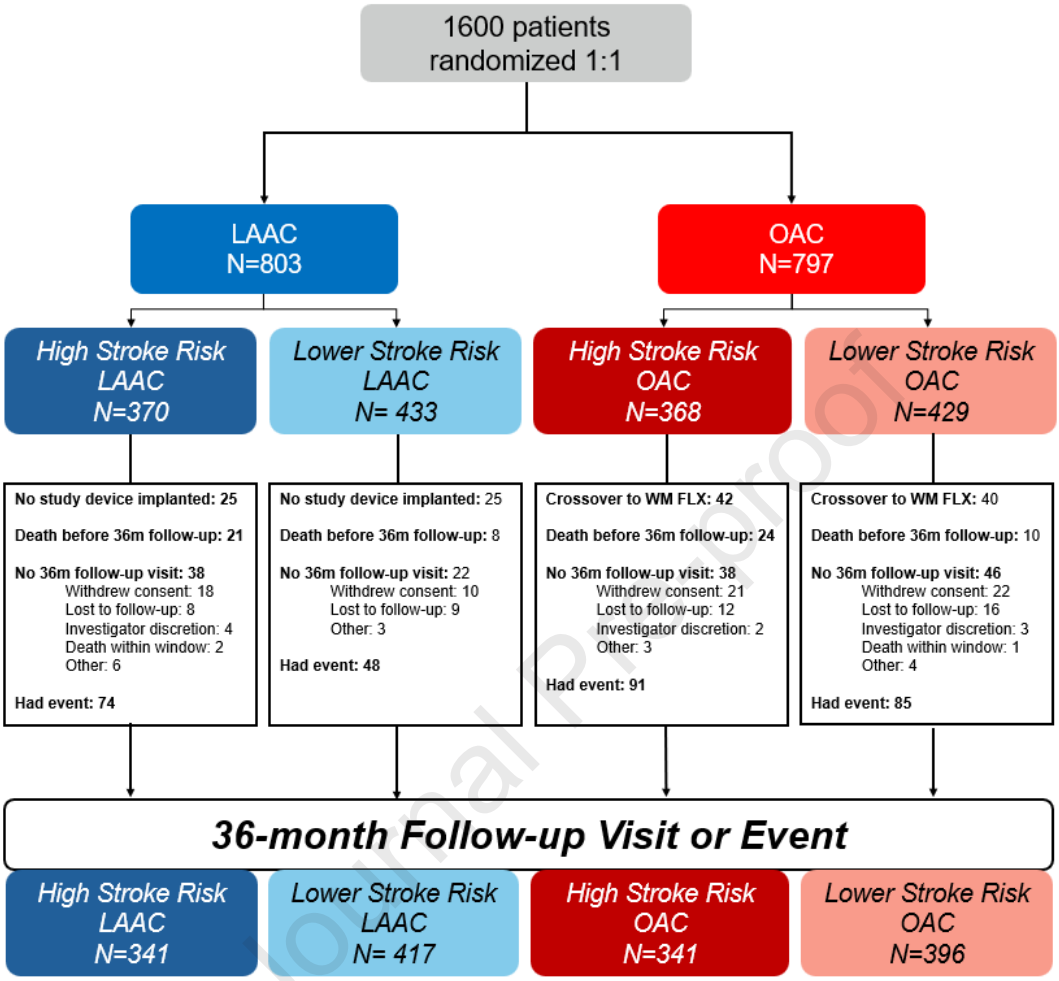
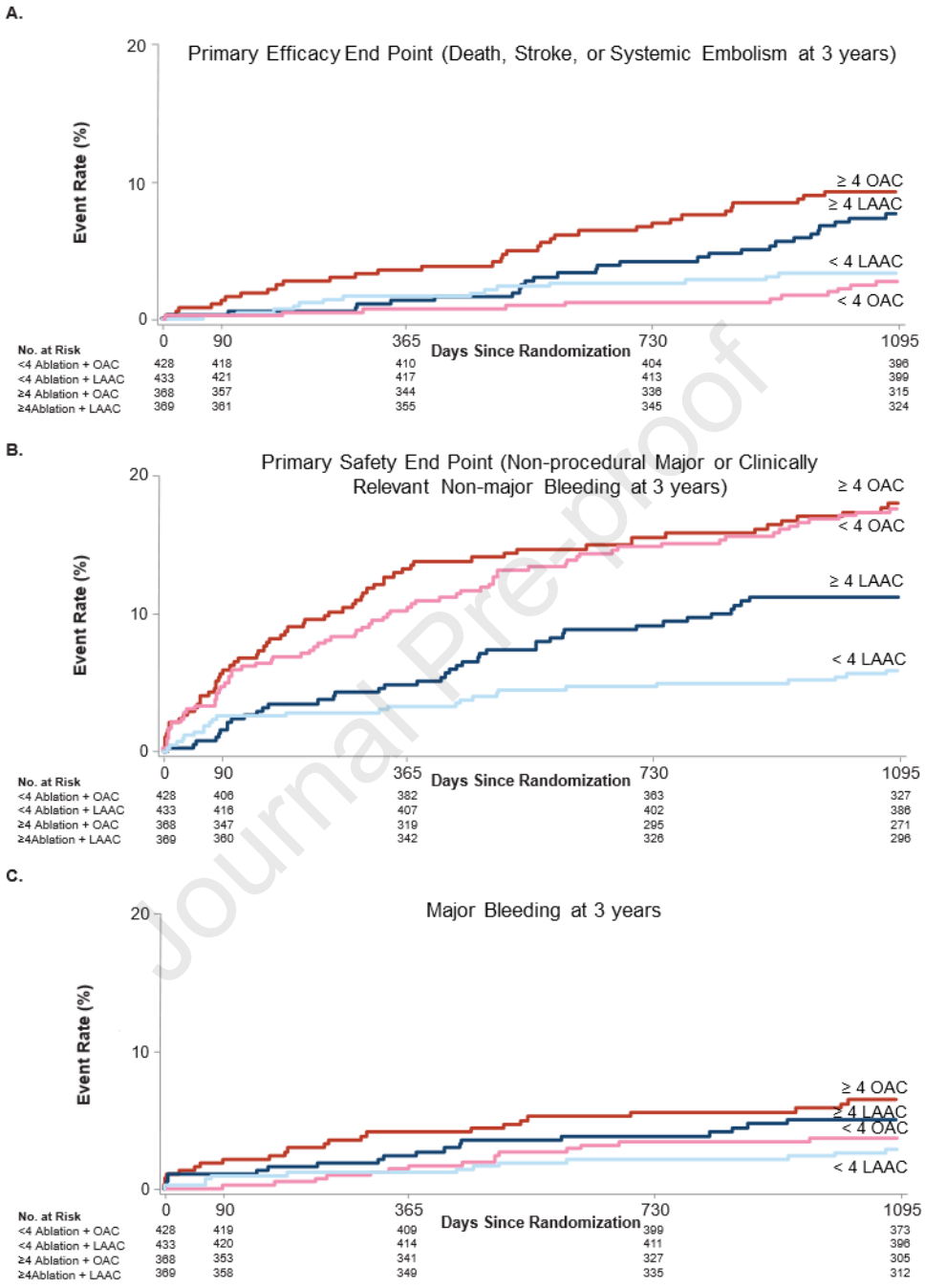
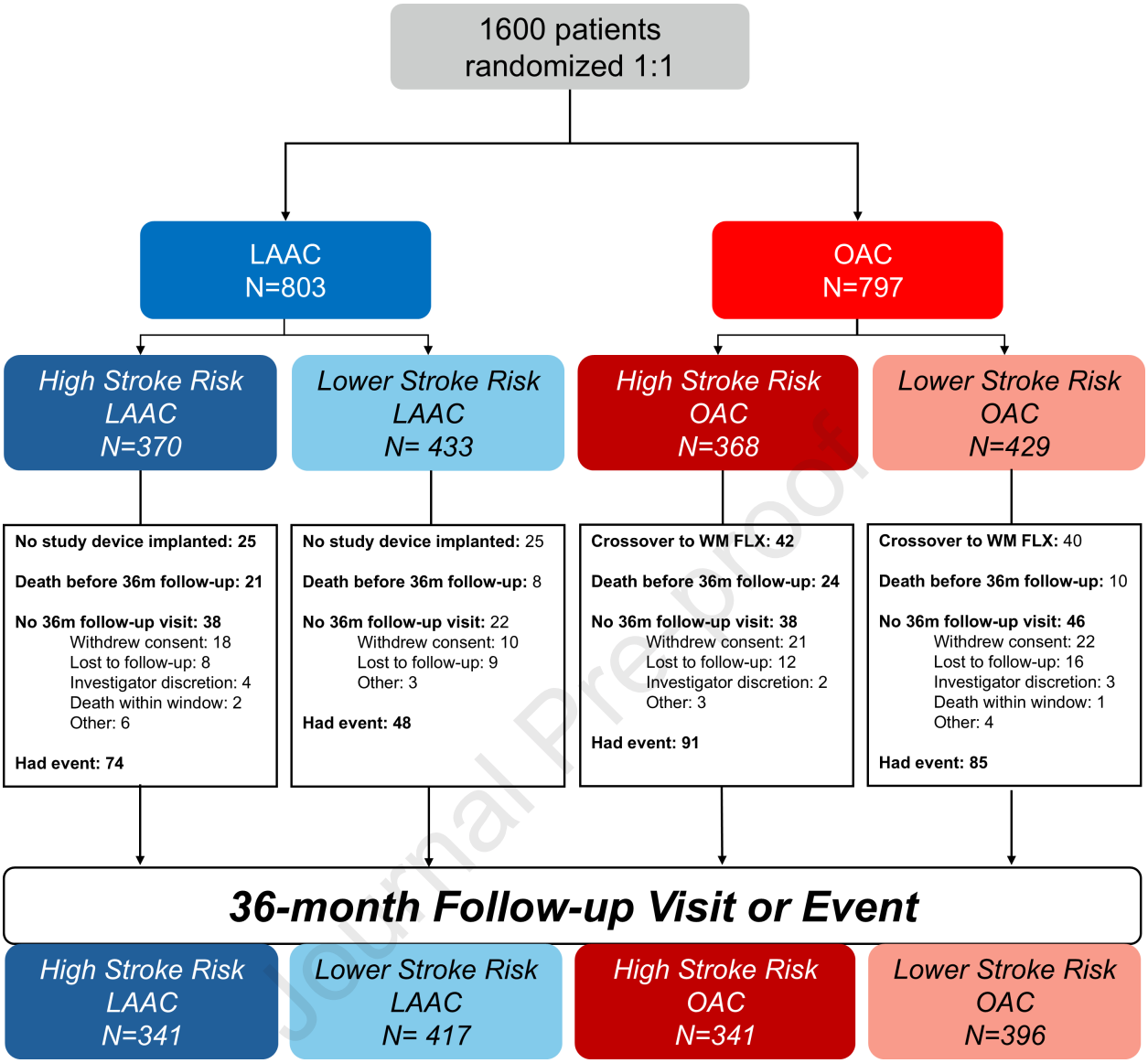
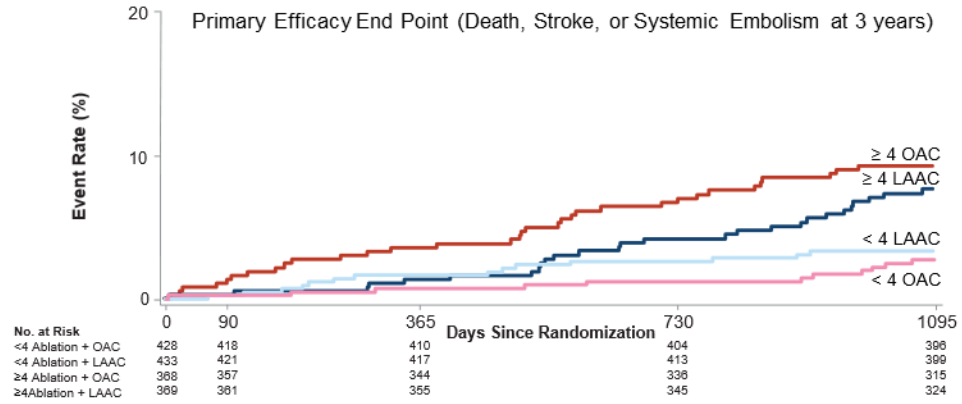


Figure 2 – Kaplan-Meier Plots for the Primary and Secondary Endpoints



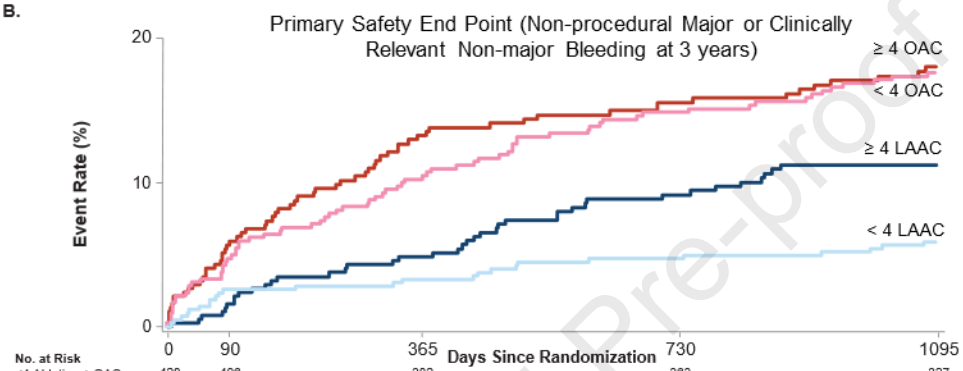


A.



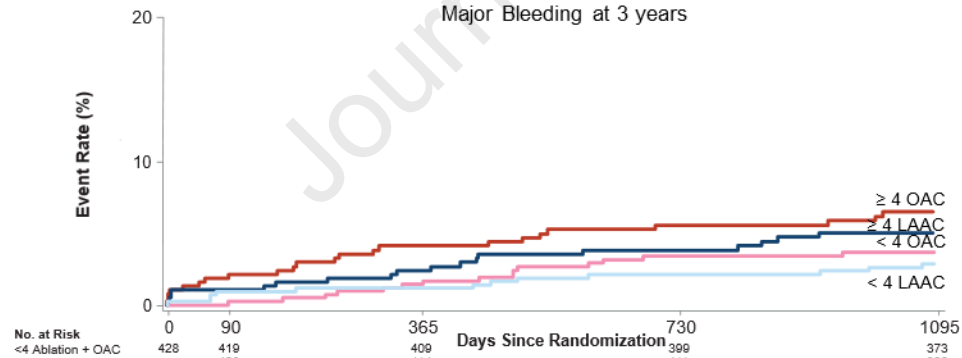
No. at Risk					
<4 Ablation + OAC	428	418	410	404	396
<4 Ablation + LAAC	433	421	417	413	399
≥4 Ablation + OAC	368	357	344	336	315
≥4Ablation + LAAC	369	361	355	345	324

B.



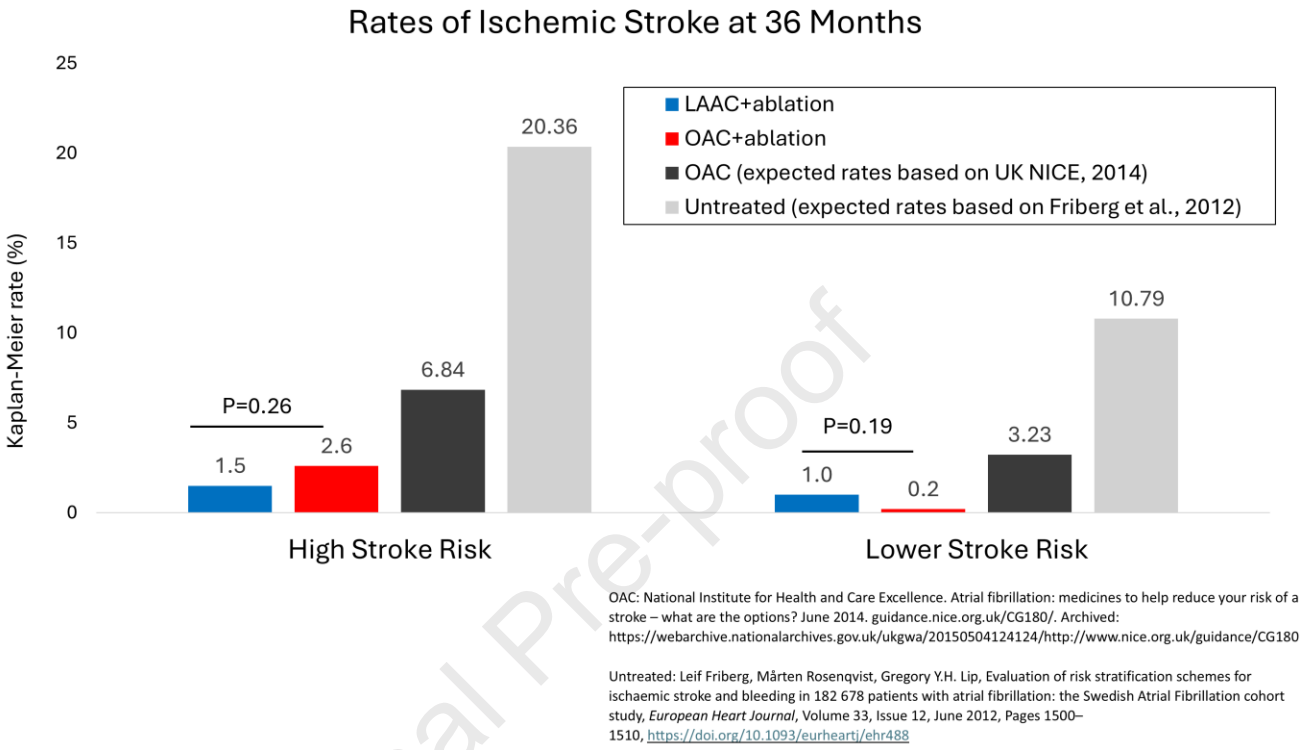
No. at Risk					
<4 Ablation + OAC	428	406	382	363	327
<4 Ablation + LAAC	433	416	407	402	386
≥4 Ablation + OAC	368	347	319	295	271
≥4Ablation + LAAC	369	360	342	326	296

C.



No. at Risk					
<4 Ablation + OAC	428	419	409	399	373
<4 Ablation + LAAC	433	420	414	411	396
≥4 Ablation + OAC	368	353	341	327	305
≥4Ablation + LAAC	369	358	349	335	312

Supplementary Figure 1



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Untreated: Leif Friberg, Mårten Rosenqvist, Gregory Y.H. Lip, Evaluation of risk stratification schemes for ischaemic stroke and bleeding in 182 678 patients with atrial fibrillation: the Swedish Atrial Fibrillation cohort study, *European Heart Journal*, Volume 33, Issue 12, June 2012, Pages 1500–1510, https://doi.org/10.1093/eurheartj/ehr488

Supplemental Table 1 – Kaplan-Meier Event Rates by High vs Low CHA_2DS_2-VASc Group

	I >> @»Absf b			L > @»@l kqpl i			
Bsbkq	@E > / AP / * S > P` »≥»1 K: 04-	@E > / AP / * S > P` »≤»0 K: 100	I l d*O^kh» MfS ^ir b	@E > / AP / * S > P` »≥» 1 K: 035	@E > / AP / * S > P` »≤»0 K: 1/ 6	I l d*O^kh» MfS ^ir b	Rkqbo^` qfl k» MfS ^ir b
Mofj ^ov»Bcob`qfsbkbpp	*/ 4»%4-5&*	14 (3.3)	0.0081	33 (9.4)	11 (2.7)	<.0001	0.3493
Mofj ^ov»P^obqv	*1- »%. -2&*	25 (6.0)	0.0075	64 (18.4)	73 (17.9)	0.7783	0.0454
>ii»Ab^qe	*/. »%3+&*	8 (1.9)	0.0032	24 (6.9)	10 (2.5)	0.0033	0.8547
@^oafl s^p`ri^o»Ab^qe	5 (1.5)	4 (1.0)	0.5436	6 (1.7)	4 (1.0)	0.3631	0.8479
Kl k@^oafl s^p`ri^o»Ab^qe*	10 (2.9)	4 (1.0)	0.0470	15 (4.4)	4 (1.0)	0.0034	0.6348
Rkbumi^fkba	6 (1.8)	0 (0.0)	0.0069	3 (0.9)	2 (0.5)	0.5122	0.9904
Pqpl hb	6 (1.8)	6 (1.4)	0.7511	13 (3.7)	2 (0.5)	0.0014	0.0485
Ep`ebj f`	5 (1.5)	4 (1.0)	0.5341	9 (2.6)	1 (0.2)	0.0049	0.1131
Ebj l ooe^df`	1 (0.3)	2 (0.5)	0.6622	3 (0.9)	0 (0.0)	0.0596	0.9923
Rkabqboj fkba	0 (0.0)	0 (0.0)	N/A	1 (0.3)	1 (0.2)	0.8984	1.0000
Pvpqbj f`»Bj _l ifpj	1 (0.3)	1 (0.2)	0.8951	1 (0.3)	0 (0.0)	0.2691	0.9945
Major bleeding*	18 (5.1)	12 (2.9)	0.1018	23 (6.6)	15 (3.7)	0.0605	0.9743

Procedural[c] major bleeding	4 (1.1)	1 (0.2)	0.1271	NA	NA	NA	NA
Clinically relevant non-major bleeding*	28 (8.0)	18 (4.3)	0.0372	49 (14.2)	61 (14.9)	0.7931	0.0605
Procedural[c] clinically relevant non-major bleeding	0 (0)	3 (0.7)	0.1093	NA	NA	NA	NA
Mbof^oaf^i»Bccrpfl k»Obnrfofkd» Fkqbosbkqfl k	2 (0.6)	0 (0.0)	0.1236	1 (0.3)	4 (1.0)	0.2497	0.9915

*A^q^yfp»mobpbkqba»^pk»Hl^mi^k*J bfbo»hsbkqo^qb&»>ii»bkamlfkqp»t bob»@B@*^agraf^qba*

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'?ibbafkd»i^ppfqfba»mbo»Fkqbok^qfl k^i»Pl `fbq»l k»Qeolj _lpfp»^ka»E^bj lpq^pfp»HPQE&abqfkfqflkp»Fk`irabp»mol `baro^i»^ka»klk*mol `baro^i»_ibbafkd+

çMol `baro^i»_ibbafkd»fp»abqfkba»^p»_ibbafkd»t fqefk»0»a^vp»mlpqfkabu»mol `barob

Supplementary Table 2

36-Month Kaplan-Meier Clinical Event Rates by CHA_2DS_2-VASc Score

CHA2DS2-VASc	≤2			3			4			5			≥6		
Outcomes Through 3 Year Post-Randomization	**Control (N=174)**	**Device (N=178)**	**P value**	**Control (N=255)**	**Device (N=255)**	**P value**	**Control (N=193)**	**Device (N=203)**	**P value**	**Control (N=114)**	**Device (N=107)**	**P value**	**Control (N=61)**	**Device (N=60)**	**P value**
All-cause Mortality	5 (3.0)	1 (0.6)	0.0914	5 (2.2)	7 (2.9)	0.5932	10 (5.3)	7 (3.6)	0.4218	8 (7.6)	8 (8.0)	0.9331	6 (10.7)	6 (10.9)	0.8838
Cardiovascular	3 (1.8)	1 (0.6)	0.3019	1 (0.4)	3 (1.2)	0.3261	1 (0.5)	2 (1.1)	0.5837	1 (1.0)	2 (2.1)	0.5441	4 (7.5)	1 (1.9)	0.1523
Unexplained	1 (0.6)	0 (0.0)	0.2998	1 (0.4)	0 (0.0)	0.3153	0 (0.0)	3 (1.6)	0.0896	3 (2.9)	2 (2.1)	0.6895	0 (0.0)	1 (2.0)	0.3375
Non-cardiovascular	1 (0.6)	0 (0.0)	0.3013	3 (1.3)	4 (1.6)	0.7364	9 (4.8)	2 (1.1)	0.0299	4 (3.9)	4 (4.1)	0.9497	2 (3.5)	4 (7.4)	0.4785
Stroke	2 (1.2)	2 (1.2)	0.973	0 (0.0)	4 (1.6)	0.0455	6 (3.2)	2 (1.1)	0.1359	5 (4.8)	2 (2.2)	0.2706	2 (3.5)	2 (3.6)	0.9843
Ischemic	1 (0.6)	2 (1.2)	0.5857	0 (0.0)	2 (0.8)	0.159	4 (2.1)	2 (1.1)	0.3807	4 (3.9)	2 (2.2)	0.4321	1 (1.7)	1 (1.9)	0.9779
Hemorrhagic	0 (0.0)	0 (0.0)	Undef	0 (0.0)	2 (0.8)	0.1573	1 (0.5)	0 (0.0)	0.3062	1 (1.0)	0 (0.0)	0.3243	1 (1.8)	1 (1.7)	0.9898
Undetermined	1 (0.6)	0 (0.0)	0.3117	0 (0.0)	0 (0.0)	Undef	1 (0.5)	0 (0.0)	0.3082	0 (0.0)	0 (0.0)	Undef	0 (0.0)	0 (0.0)	Undef
Systemic embolism	0 (0.0)	1 (0.6)	0.3333	0 (0.0)	0 (0.0)	Undef	0 (0.0)	0 (0.0)	Undef	1 (1.0)	1 (1.0)	0.9659	0 (0.0)	0 (0.0)	Undef
Major Bleeding*	3 (1.8)	3 (1.7)	0.9352	12 (5.0)	9 (3.7)	0.5023	11 (5.9)	11 (5.7)	0.9211	7 (6.6)	4 (4.0)	0.388	5 (9.2)	3 (5.5)	0.4455
Non-Major Bleeding*	23 (13.7)	6 (3.4)	0.0008	38 (15.8)	12 (4.9)	<.0001	29 (15.4)	16 (8.3)	0.0225	15 (14.5)	9 (9.0)	0.2534	5 (9.2)	3 (5.2)	0.4102
Pericardial Effusion resulting in an intervention	0 (0.0)	0 (0.0)	Undef	4 (1.7)	0 (0.0)	0.0425	0 (0.0)	0 (0.0)	Undef	0 (0.0)	2 (2.0)	0.1502	1 (1.6)	0 (0.0)	0.3213

Data is presented as n (Kaplan-Meier event rate). All endpoints were CEC-adjudicated
*Bleeding classified per International Society on Thrombosis and Haemostasis (ISTH) definitions