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CLINICAL RESEARCH

Percutaneous left atrial appendage closure following catheter ablation therapy of atrial fibrillation: outcomes stratified by bleeding risk – a sub-analysis of the OPTION study

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Aims Concerns have been raised over the safety and necessity of continuing oral anticoagulation (OAC) in patients following catheter ablation for atrial fibrillation (AF). OPTION demonstrated the safety and efficacy of left atrial appendage closure (LAAC) in a post-ablation population. We sought to analyse the impact of baseline bleeding risk, per HAS-BLED scores, on the outcomes for patients in a pre-specified sub-analysis.

Methods and results Patients with AF and high stroke risk undergoing catheter ablation were randomly assigned to LAAC vs. OAC in OPTION and were stratified by HAS-BLED score: 0, 1, 2, ≥3. OPTION enrolled 1600 patients (CHA_2DS_2-VASc score: 3.5 ± 1.3; HAS-BLED score: 1.2 ± 0.8); randomized 1:1 to ablation/LAAC or ablation/OAC. Primary effectiveness (all-cause death/stroke/systemic embolism) and safety (bleeding composite) endpoints were directionally similar in HAS-BLED subgroups; both thromboembolic and bleeding event rates were higher in patients with increasing HAS-BLED score. A significant reduction in primary safety bleeding events was noted in favour of LAAC across HAS-BLED subgroups, with more striking reductions noted for lower HAS-BLED scores of 0 (n = 265; hazard ratio: 0.25; 95% confidence interval: 0.20, 0.50) and 1 (n = 890; hazard ratio: 0.41, 95% confidence interval: 0.27–0.61).

Conclusion Regardless of bleeding risk, LAAC is comparable to OAC in stroke protection while demonstrating greater freedom from bleeding in a post-ablation AF population, even in patients with low HAS-BLED scores. The OPTION study highlights an opportunity to mitigate future bleeding risk with a strategy of LAAC after ablation in patients deemed at high risk of stroke according to clinical guidelines.

Trial registration number NCT03795298

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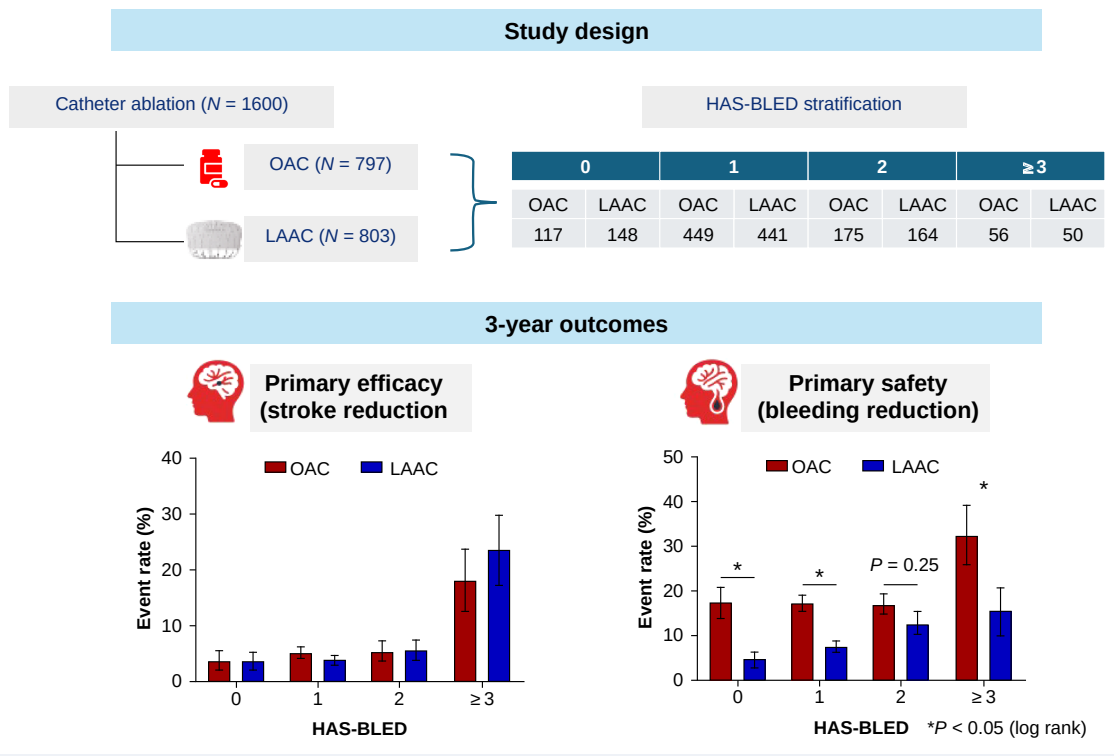
Graphical Abstract

Key question
How does bleeding risk impact outcomes of left atrial appendage closure (LAAC) versus oral anticoagulation (OAC) after ablation for atrial fibrillation?

Key finding
Across risk strata, three-year bleeding rates were lower with LAAC compared to OAC while stroke prevention efficacy was comparable between therapies.

Take home message
This sub-analysis of the OPTION trial highlights an opportunity to mitigate future bleeding risk with a strategy of LAAC after ablation in patients deemed at high risk of stroke according to clinical guidelines.



Keywords Left atrial appendage closure • Atrial fibrillation • Anticoagulation • Bleeding

What's new?

- This sub-study of the OPTION Trial stratified by HAS-BLED scores has highlighted the significant rates of clinically relevant bleeding events that occur in post-ablation patients recommended to take long-term anticoagulation, even in patients with perceived low bleeding risk.
- The data show a dramatic reduction in bleeding events across all HAS-BLED scores for post-ablation patients who received Watchman FLX LAA device closure instead of remaining on anticoagulation.

Background and aims

The need for continued anticoagulation following catheter ablation treatment in patients with a history of atrial fibrillation (AF) at high risk of stroke remains contentious.[1,2] The current clinical guidelines recommend continuation of oral anticoagulation treatment in moderate-high risk patients regardless of the perceived ablation outcome.[3] The risk of AF/atrial tachycardia arrhythmia recurrences in long-term studies is acknowledged.[3] Several studies have highlighted the detrimental effect of continuing anticoagulation in a population that appears to have a lowered risk of stroke after ablation therapy.[4–6] Of note, patients with a higher baseline bleeding risk (HAS-BLED scores of 2 or greater) may have a low risk-benefit ratio.[6]

Several of the studies have raised the enthusiasm for discontinuing anticoagulation post-ablation by analysing the respective stroke/transient ischaemic attack and bleeding event rates in patients with 'successful catheter ablation outcomes' which has generally been defined as being free of detectable AF for the first 12 months following ablation therapy.[6,7] This approach is contrary to the 'set and forget' strategy of the guidelines for stroke prevention and creates a requirement for stringent monitoring and prompt notification of patients to restart anticoagulation when recurrent AF or atrial arrhythmia is detected. The

OPTION study evaluated a strategy of left atrial appendage device occlusion (LAAC) for stroke prevention, performed alongside catheter ablation therapy as an alternative to continuing long-term anticoagulation in such patients at moderate- high risk of stroke.[8] Given a key safety concern for continuing anticoagulation in a post-ablation population relates to bleeding complications, we sought to analyse the impact of baseline bleeding risk as captured by HAS-BLED scores on the outcomes for patients in the OPTION study.

Methods

Study design

The OPTION trial was a multicentre, randomized clinical trial designed to determine if LAAC with the WATCHMAN FLX device is a reasonable alternative to oral anticoagulation following percutaneous catheter ablation for high-risk patients with non-valvular atrial fibrillation. The aim of this sub-analysis is to assess outcomes of LAAC vs. OAC within different bleeding risk strata. The trial was registered on ClinicalTrials.gov (NCT03795298), and the protocol and primary results have been published previously.[8,9] Trial activities were conducted in accordance with the Declaration of Helsinki. The ethics or institutional review board at each participating site approved the trial, and all patients provided written consent to participate. A clinical events committee (CEC) adjudicated all clinical outcome events, and an independent core laboratory assessed images.

Patients were eligible for randomization if they had a CHA_2DS_2-VASc score of at least 2 for men or at least 3 for women and had a catheter ablation performed 90 to 180 days prior to randomization (sequential) or were scheduled to be performed within 10 days after randomization (concomitant). Full inclusion and exclusion criteria are detailed in prior publications.[8,9] In all cases, cardiac ablation was required to be performed before LAAC. Patients were randomized in equal proportion to undergo LAAC with the WATCHMAN FLX device (Device group) or receive oral anticoagulation (Control group). Randomization was stratified by site and ablation procedure timing.

Clinical follow-up occurred at 3, 12, 24, and 36 months, with LAA imaging at 3 and 12 months in the LAAC group. After implantation, LAAC subjects were prescribed a market-approved OAC and aspirin until the 3-month visit, followed by aspirin alone until at least the 12-month visit, with a recommendation to continue aspirin for the duration of trial (36 months).

For the present sub-analysis, patients were grouped according to their HAS-BLED score at baseline assessment: 0, 1, 2, and ≥3. HAS-BLED is a validated scoring system to assess baseline bleeding risk in patients with atrial fibrillation receiving anticoagulants[10,11] and assigns one point for each of the following risk factors: Hypertension (uncontrolled systolic blood pressure >160 mm Hg), Abnormal renal and/or liver function, Stroke history, Bleeding history or predisposition, Labile international normalized ratio (INR), Elderly age (≥65 years), and Drugs and/or alcohol use. The total score ranges from 0 to 9, with higher scores indicating greater bleeding risk. A score ≥3 is considered high risk.

Endpoints and statistical methods

Outcomes between OAC vs. LAAC were statistically compared within each bleeding risk strata. The primary and secondary endpoint analyses were not statistically powered for the bleeding risk subgroups, but subgroup analyses based on the HAS-BLED score were prespecified in the study protocol. The present analysis deviates slightly from the specifications in the protocol, such that HAS-BLED scores of 1 and 2 were examined separately rather than collapsed into a single category. This was done to more precisely assess outcomes as bleeding risk increases.

The primary effectiveness endpoint for the OPTION trial was a composite rate of stroke (ischaemic and/or haemorrhagic), death, or systemic embolism at 36 months, tested for non-inferiority of LAAC compared to OAC. 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 of LAAC vs. OAC. The secondary safety endpoint was ISTH major bleeding (including procedural bleeding) at 36 months, tested for non-inferiority of LAAC compared to OAC. All endpoints were defined as the Kaplan–Meier estimates of time to first event occurrence. In the overall OPTION trial population, tested against OAC therapy, LAAC with the WATCHMAN FLX device was non-inferior for the primary effectiveness and secondary safety endpoints and demonstrated superiority for the primary safety endpoint.[8]

Individual components of the trial's primary and secondary endpoints were reviewed by the independent CEC and analysed. Device implant success and core laboratory-assessed imaging findings were also analysed. Descriptive statistics are provided for baseline patient characteristics, procedure characteristics, medication compliance, and quality of life (EQ-5D-5L[12] and SF-12[13] questionnaires).

Results

Patient characteristics

A total of 1600 patients were randomized at 106 investigational sites worldwide between November 2019 and June 2021. A total of 797 patients were randomized to OAC, and 803 patients were randomized to LAAC. In the OAC treatment arm, stratification by the HAS-BLED score yielded the following distribution: 0 (n = 117), 1 (n = 449), 2 (n = 175), and ≥3 (n = 56). In the LAAC treatment arm, stratification by HAS-BLED score yielded the following distribution: 0 (n = 148), 1 (n = 441), 2 (n = 164), and ≥3 (n = 50). Among patients randomized to the LAAC arm that had an attempted procedure, rates of successful device implantation were high across bleeding risk strata: 0 (98.5%, 131 of 133), 1 (98.8% 418 of 423), 2 (98.7% (156 of 158), ≥3 (100.0%, 48 of 48). Completion of clinical follow-up at 36 months was not markedly different between both OAC and LAAC arms by HAS-BLED score: 0 (OAC 86.7%, LAAC 88.9%), 1 (OAC 90.7%, LAAC 93.1%), 2 (OAC 88.2%, LAAC 94.9%), and ≥3 (OAC 81.6%, LAAC 85.0%).

Overall, within each HAS-BLED risk group, patient characteristics and medical history were not significantly different between OAC vs. LAAC treatment arms (*Table 1*). A few differences were observed between OAC vs. LAAC for HAS-BLED risk group of 0, for age (58.8 ± 6.3 vs. 60.4 ± 4.8 years, P = 0.02), Caucasian (87.2% vs. 75.7%, P = 0.02), paroxysmal AF (72.6% vs. 58.8%, P = 0.02), and persistent AF (27.4% vs. 41.2%, P = 0.02).

Rates of death, stroke, and systemic embolism

Kaplan–Meier event rates for the composite primary efficacy endpoint (death, stroke, or systemic embolism at 36 months) for OAC vs. LAAC within each HAS-BLED category are illustrated in *Figure 1*, and rates for individual components of the endpoint are shown in *Table 2*. Event rates were higher as HAS-BLED score advanced, but there were no significant differences between OAC and LAAC in any bleeding risk strata (*Figure 1*) and the interaction between treatment arm and bleeding risk strata was not significant (P = 0.73). In all bleeding risk groups, death was the most common primary efficacy event and occurred in OAC and LAAC at similar rates (*Table 2*). Importantly, in all HAS-BLED strata, rates of stroke and systemic embolism did not significantly differ between OAC and LAAC

Table 1 Patient characteristics

HAS-BLED Score	0			1			2			≥3		
	OAC	LAAC	*P-value*	OAC	LAAC	*P-value*	OAC	LAAC	*P-value*	OAC	LAAC	*P-value*
# of Patients (*n*)	117	148		449	441		175	164		56	50	
Age at time of consent (years)	58.8 ± 6.3	60.4 ± 4.8	0.02	71.0 ± 6.9	71.4 ± 6.6	0.40	71.5 ± 5.9	72.5 ± 5.1	0.12	72.8 ± 5.4	72.9 ± 5.2	0.98
Female (% *n*)	28.2%	24.3%	0.48	33.6%	37.9%	0.19	36.6%	37.2%	0.62	26.8%	38.0%	0.98
Ethnicity and Race												
American Indian or Alaska Native	0.0%	0.7%	1.00	0.2%	0.0%	1.00	0.0%	0.6%	0.48	0.0%	0.0%	Undef
Asian	0.0%	2.7%	0.13	0.0%	0.0%	Undef	0.0%	0.0%	Undef	1.8%	0.0%	1.00
Black, or African heritage	2.6%	2.7%	1.00	0.7%	1.4%	0.34	2.3%	2.4%	1.00	1.8%	0.0%	1.00
Caucasian	87.2%	75.7%	0.02	87.3%	85.0%	0.33	84.6%	86.6%	0.60	78.6%	88.0%	0.20
Hispanic or Latino	2.6%	5.4%	0.36	1.3%	0.9%	0.75	1.7%	0.0%	0.25	0.0%	2.0%	0.47
Native Hawaiian or other Pacific Islander	0.0%	0.0%	Undef	0.0%	0.0%	Undef	0.0%	0.0%	Undef	0.0%	0.0%	Undef
Other	0.0%	1.4%	0.51	0.4%	0.2%	1.00	0.6%	0.0%	1.00	0.0%	0.0%	Undef
Not disclosed	7.7%	11.5%	0.30	10.0%	12.5%	0.25	10.9%	10.4%	0.88	17.9%	10.0%	0.25
Medical History												
Persistent AF	27.4%	41.2%	0.02	39.2%	38.8%	0.90	38.3%	45.7%	0.16	37.5%	38.0%	0.96
Paroxysmal AF	72.6%	58.8%	0.02	60.8%	61.2%	0.90	61.7%	54.3%	0.16	62.5%	62.0%	0.96
CHA_2DS_2-VASc score	2.7 ± 0.9	2.8 ± 0.9	0.59	3.5 ± 1.1	3.5 ± 1.1	0.62	4.0 ± 1.4	3.9 ± 1.4	0.71	4.5 ± 1.2	4.6 ± 1.5	0.50
HAS-BLED score components												
Uncontrolled hypertension (>160 mm Hg systolic)	0.0%	0.0%	Undef	0.9%	1.4%	0.54	10.9%	7.9%	0.36	5.4%	12.0%	0.30
Abnormal renal function	0.0%	0.0%	Undef	1.6%	1.6%	0.97	21.7%	25.0%	0.47	48.2%	48.0%	0.98
Abnormal liver function	0.0%	0.0%	Undef	0.4%	0.0%	0.50	2.9%	1.8%	0.72	5.4%	8.0%	0.70
History of stroke	0.0%	0.0%	Undef	2.9%	1.8%	0.29	12.0%	12.2%	0.96	26.8%	32.0%	0.56
History of major bleeding or predisposition to bleeding	0.0%	0.0%	Undef	1.3%	0.9%	0.75	16.6%	15.9%	0.86	32.1%	36.0%	0.68
History of labile INR	0.0%	0.0%	Undef	0.0%	0.7%	0.12	7.4%	1.8%	0.015	17.9%	16.0%	0.79
Age >65 years	0.0%	0.0%	Undef	89.3%	90.9%	0.42	91.4%	96.3%	0.061	94.6%	96.0%	1.00
Medication usage predisposing to bleeding	0.0%	0.0%	Undef	2.2%	2.0%	0.85	22.9%	22.0%	0.84	48.2%	50.0%	0.85
Alcohol usage (>8 drinks/week)	0.0%	0.0%	Undef	1.3%	0.7%	0.51	14.3%	17.1%	0.48	32.1%	20.0%	0.16

Categorical variables presented as % and continuous variables presented as mean ± SD.

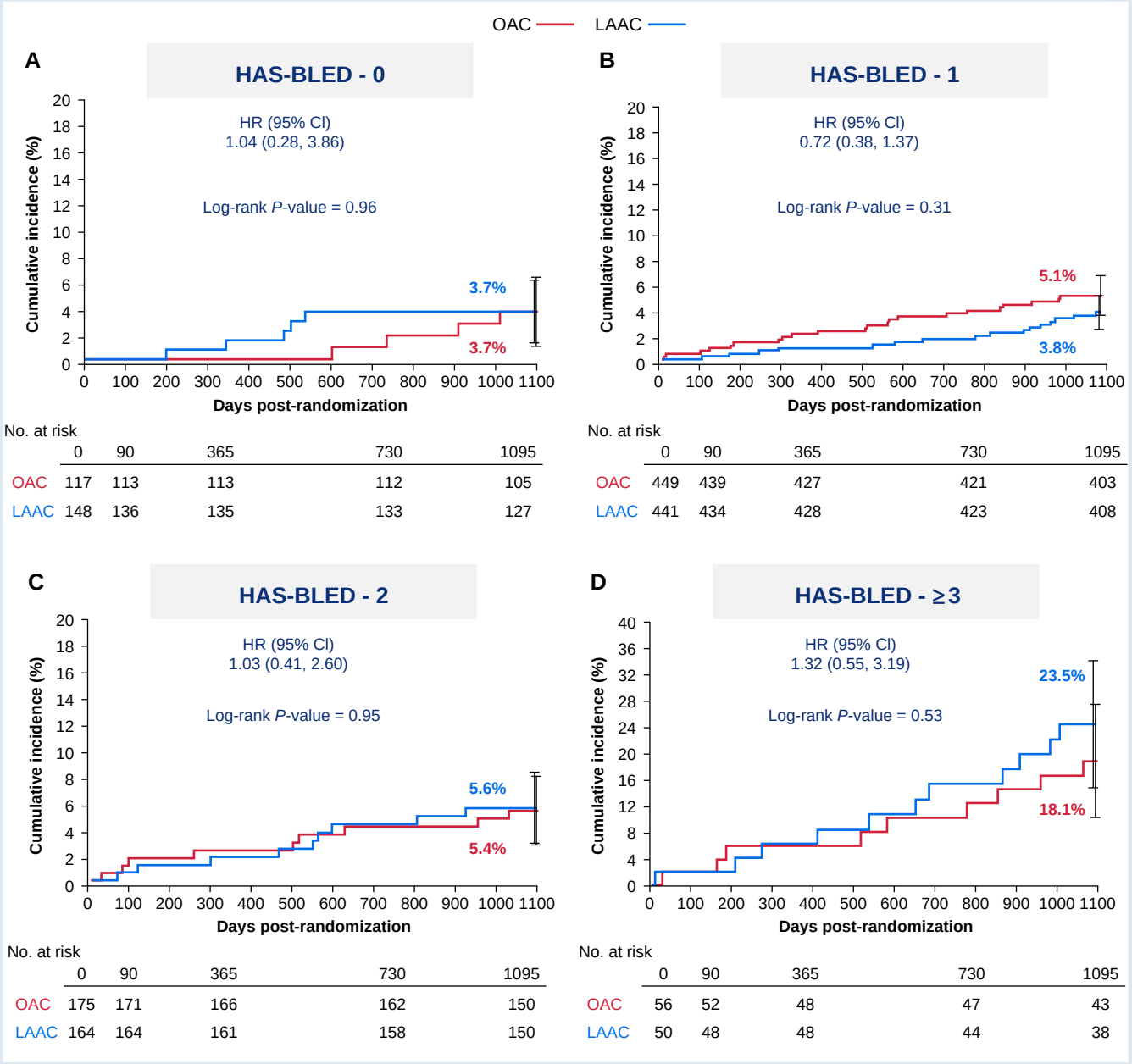


Figure 1 Primary efficacy endpoint by HAS-BLED score. Kaplan–Meier curves demonstrating cumulative incidence of all-cause mortality, stroke, or systemic embolism at 36 months in patients treated with LAAC vs. OAC post-ablation across all HAS-BLED strata (*A*–*D*). Differences between groups were assessed using the log-rank test.

even when accounting for the competing risk of death (all Gray's Test *P*-values >0.30).

Rates of bleeding events

In the HAS-BLED 0, 1, and ≥3 groups, the 36-month Kaplan–Meier event rate for all non-procedural bleeding (primary safety endpoint) was clinically and statistically significantly lower for LAAC compared to OAC (*Figure 2*), driven primarily by higher rates of clinically relevant non-major bleeding in OAC patients (*Table 2*). The interaction between treatment arm and HAS-BLED score was not significant for the primary safety endpoint ($P = 0.22$). In the HAS-BLED 0, 1, and ≥3 groups, a significant difference between treatment arms was still observed when accounting for the competing risk of death (all Gray's Test *P*-values <0.05). The advantage of LAAC vs. OAC was also observed in the HAS-BLED 0, 1, and ≥3 groups when procedural bleeding events were counted (*Table 2*). Among patients with intermediate risk (HAS-BLED 2), bleeding event rates (counting and not counting procedural bleeding) were numerically lower with LAAC vs. OAC, especially for clinically relevant non-major bleeding, but this comparison did not reach statistical significance unlike the other HAS-BLED score categories. Statistical significance for the primary safety endpoint (all non-procedural bleeding) was also not reached when accounting for the competing risk of death (Gray's Test *P*-value = 0.26).

Table 2 36-month clinical event rates (Kaplan–Meier)

HAS-BLED score	0			1			2			≥3		
	OAC	LAAC	*Hazard ratio [95% CI]*	OAC	LAAC	*Hazard ratio [95% CI]*	OAC	LAAC	*Hazard ratio [95% CI]*	OAC	LAAC	*Hazard ratio [95% CI]*
# of Patients (*n*)	117	148		449	441		175	164		56	50	
Death	3.7% (4)	3.0% (4)	0.83 [0.21, 3.30]	4.0% (17)	2.1% (9)	0.52 [0.23, 1.17]	3.7% (6)	3.8% (6)	1.03 [0.33, 3.20]	14.0% (7)	21.4% (10)	1.54 [0.59, 4.05]
Cardiovascular/ Unexplained	1.9% (2)	1.5% (2)	0.83 [0.12, 5.88]	1.6% (7)	1.2% (5)	0.71 [0.22, 2.23]	1.8% (3)	2.5% (4)	1.38 [0.31, 6.18]	6.2% (3)	9.2% (4)	1.40 [0.31, 6.27]
Non-cardiovascular	1.9% (2)	1.5% (2)	0.82 [0.12, 5.85]	2.4% (10)	1.0% (4)	0.39 [0.12, 1.26]	1.9% (3)	1.3% (2)	0.68 [0.11, 4.10]	8.3% (4)	13.5% (6)	1.64 [0.46, 5.83]
Ischaemic stroke or systemic embolism	0.0% (0)	0.0% (0)	NA	1.4% (6)	1.7% (7)	1.15 [0.39, 3.44]	1.2% (2)	1.9% (3)	1.54 [0.26, 9.23]	6.2% (3)	2.4% (1)	0.36 [0.04, 3.44]
Stroke	0.0% (0)	0.8% (1)	NA	1.6% (7)	1.4% (6)	0.85 [0.28, 2.52]	2.4% (4)	1.9% (3)	0.78 [0.17, 3.47]	7.9% (4)	4.4% (2)	0.53 [0.10, 2.91]
Ischaemic	0.0% (0)	0.0% (0)	NA	1.4% (6)	1.4% (6)	0.99 [0.32, 3.06]	1.2% (2)	1.2% (2)	1.03 [0.15, 7.33]	4.0% (2)	2.4% (1)	0.53 [0.05, 5.87]
Haemorrhagic	0.0% (0)	0.8% (1)	NA	0.0% (0)	0.0% (0)	NA	0.6% (1)	0.6% (1)	1.04 [0.07, 16.62]	4.1% (2)	2.0% (1)	0.52 [0.05, 5.77]
Undetermined	0.0% (0)	0.0% (0)	NA	0.2% (1)	0.0% (0)	NA	0.6% (1)	0.0% (0)	NA	0.0% (0)	0.0% (0)	NA
Systemic embolism	0.0% (0)	0.0% (0)	NA	0.0% (0)	0.2% (1)	NA	0.0% (0)	0.7% (1)	NA	2.2% (1)	0.0% (0)	NA
ISTH Bleeding	17.2% (19)	6.5% (9)	0.38* [0.17, 0.85]	17.2% (74)	8.4% (36)	0.46** [0.31, 0.69]	16.8% (28)	12.5% (20)	0.72 [0.41, 1.28]	32.3% (16)	17.4% (8)	0.47 [0.20, 1.10]
Major Bleeding	3.6% (4)	1.4% (2)	0.41 [0.08, 2.26]	3.9% (17)	3.5% (15)	0.88 [0.44, 1.75]	6.2% (10)	4.3% (7)	0.73 [0.28, 1.91]	13.8% (7)	13.0% (6)	0.89 [0.30, 2.64]
Procedural		0.7% (1)			0.7% (3)			0.0% (0)			2.0% (1)	
Non-procedural		0.8% (1)			2.8% (12)			4.3% (7)			11.0% (5)	
Clinically relevant non-major Bleeding	13.6% (15)	5.1% (7)	0.38* [0.15, 0.93]	14.0% (60)	5.1% (22)	0.35** [0.21, 0.57]	13.8% (23)	8.1% (13)	0.56 [0.28, 1.11]	25.3% (12)	8.7% (4)	0.31* [0.10, 0.96]
Procedural		1.4% (2)			0.2% (1)			0.0% (0)			0.0% (0)	
Non-procedural		3.7% (5)			4.9% (21)			8.1% (13)			8.7% (4)	
Pericardial Effusion resulting in an intervention	0.9% (1)	0.0% (0)	NA	0.5% (2)	0.2% (1)	0.50 [0.05, 5.51]	1.3% (2)	0.0% (0)	NA	0.0% (0)	2.3% (1)	NA

Values are presented at Kaplan–Meier rate % (*n*) with the exception of procedural major bleeding and procedural clinically relevant non-major bleeding which are presented as binary rate % (*n*) as these endpoints only include events that occurred on or within 3 days post procedure. All events were adjudicated by a clinical events committee.
CI = confidence interval; NA = not applicable.
P-value for OAC vs. LAAC: * < 0.05; ** < 0.001.

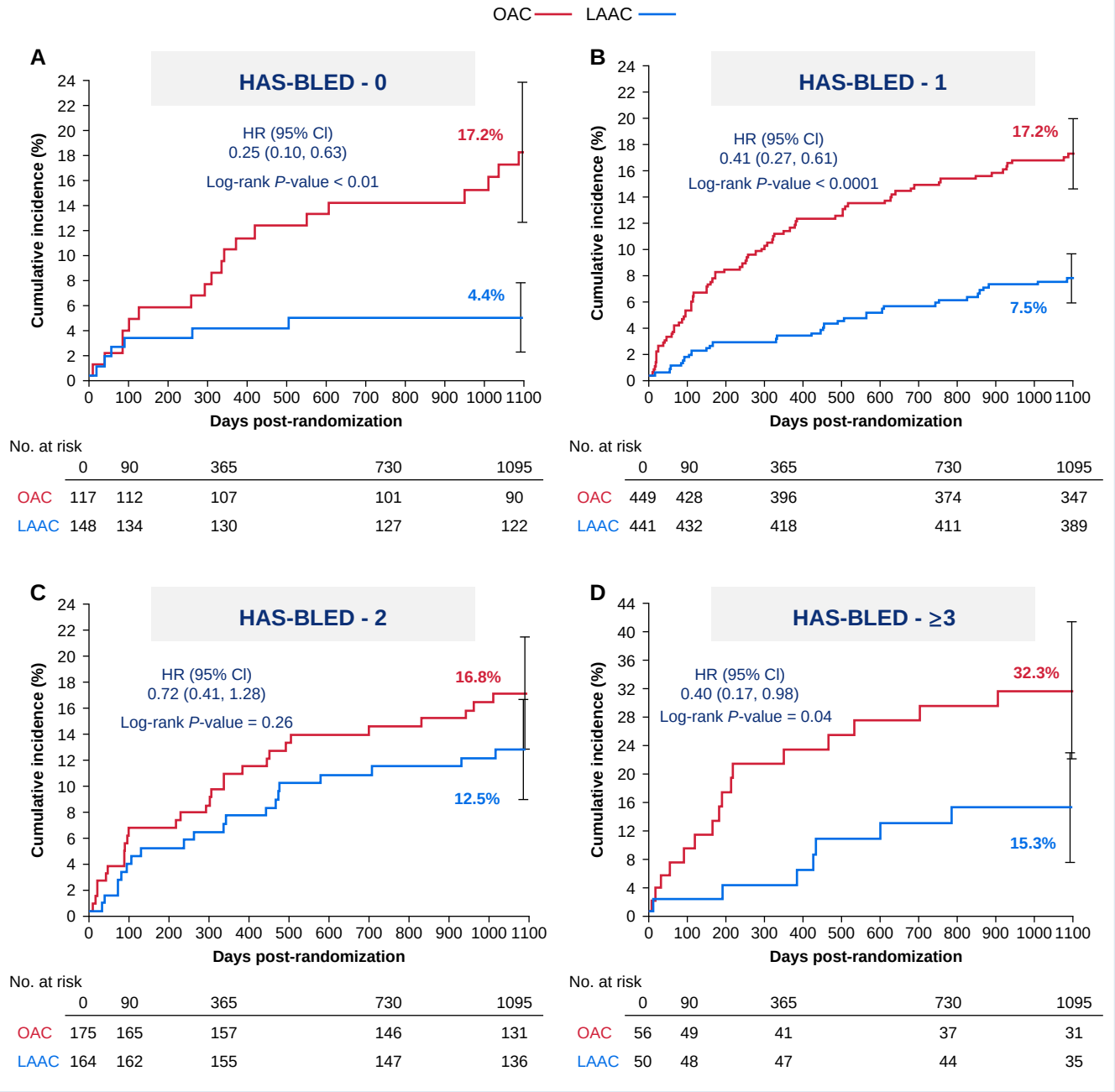


Figure 2 Primary safety endpoint by HAS-BLED score. Kaplan–Meier curves demonstrating cumulative incidence of ISTH non-procedural, major bleeding or clinically-relevant, non-major bleeding at 36 months in patients treated with LAAC vs. OAC post-ablation across all HAS-BLED strata (*A*–*D*). Differences between groups were assessed using the log-rank test.

A total of four fatal bleeding events occurred: one LAAC patient with HAS-BLED 1, two OAC patients with HAS-BLED 2, and one OAC patient with HAS-BLED ≥3. Event rates for all bleeding events (procedural and non-procedural, major and clinically relevant non-major) are shown in *Table 2*, and Kaplan–Meier plots for the primary and secondary safety endpoint are shown in *Figure 2* and *Figure 3*. Of note, the secondary safety endpoint of procedural and non-procedural related major bleeding events showed non-inferiority but did not reach superiority for LAAC vs. OAC in the overall OPTION study.[8] Unsurprisingly, no significant difference emerged across the substudy analysis (*Figure 3*), and the non-significant results were consistent when accounting for the competing risk of death (all Gray's Test *P*-values >0.28). The interaction between treatment arm and HAS-BLED score was not significant for the secondary safety endpoint ($P = 0.87$).

Anticoagulation usage

Rates for OAC usage across follow-up are shown in *Table 3*. In all bleeding risk strata, a high proportion of patients in the OAC arm were still on OACs at 36-month follow-up, ranging from 82.5%

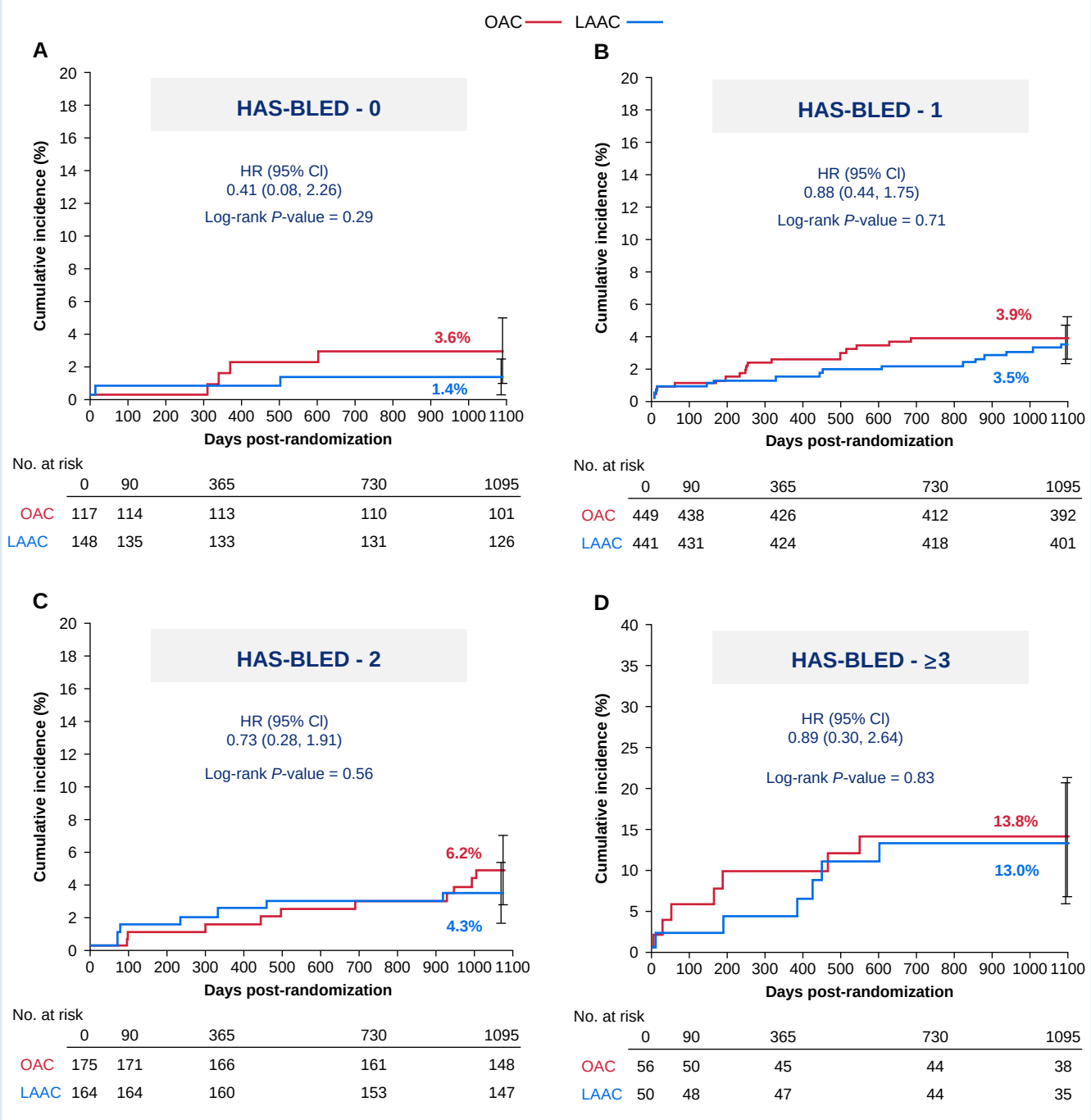


Figure 3 Secondary safety endpoint by HAS-BLED. Kaplan–Meier curves demonstrating cumulative incidence of major bleeding (procedural and non-procedure-related) at 36 months in patients treated with LAAC vs. OAC post-ablation across all HAS-BLED strata (*A*–*D*). Differences between groups were assessed using the log-rank test.

in HAS-BLED ≥3 to 85.7% in HAS-BLED 0. For LAAC patients, 36-month OAC usage varied notably across bleeding risk levels, with HAS-BLED 2 having the highest rate (13.3%) and HAS-BLED ≥3 having the lowest rate (2.9%). Single anti-platelet therapy (SAPT) use was comparable for LAAC patients at 36 months across HAS-BLED scores: 0 (76.6%), 1 (77.9%), 2 (76.7%), and ≥3 (79.4%). Across bleeding risk strata, cardioversion or repeat ablation was the most commonly cited reason for resumption of OAC.

Quality of life

Overall, changes in quality of life as measured by the EQ-5D and SF-12 questionnaires from baseline to 36 months did not

Table 3 Patients on any OAC across follow-up

HAS-BLED	0		1		2		≥3	
	OAC	LAAC	OAC	LAAC	OAC	LAAC	OAC	LAAC
3 months	99.1% (109/110)	90.3% (121/134)	98.4% (422/429)	90.1% (384/426)	99.4% (165/166)	90.2% (147/163)	93.9% (46/49)	91.8% (45/49)
1 year	93.1% (94/101)	8.5% (11/130)	92.7% (379/409)	10.0% (42/418)	93.7% (149/159)	17.7% (28/158)	86.7% (39/45)	4.4% (2/45)
2 years	87.6% (92/105)	9.2% (12/131)	87.9% (348/396)	8.0% (33/411)	88.8% (135/152)	14.9% (23/154)	88.9% (40/45)	4.9% (2/41)
3 years	85.7% (84/98)	7.8% (10/128)	85.7% (336/392)	10.2% (41/402)	82.6% (123/149)	13.3% (20/150)	82.5% (33/40)	2.9% (1/34)

Values are presented as % (n/n). Numerator represents patients on any OAC at the specified follow-up visit. Denominator represents patients with evaluable data.

significantly differ between OAC and LAAC in any bleeding risk group, except for HAS-BLED ≥3 (*Table 4*). To assess the impact of bleeding on quality of life, OAC and LAAC treatment arms were stratified by subgroups that experienced a bleeding event vs. no-bleeding event. No significant interaction was observed between treatment arm and occurrence of bleeding on quality of life from baseline to long-term follow-up (*Table 5*).

Discussion

The somewhat unexpected finding from this sub-analysis was that the most striking reduction in bleeding events occurred in patients with low bleeding scores HAS-BLED 0 and 1 who received LAAC. This finding deserves discussion as this is one of the few studies directly comparing bleeding rates in anticoagulated vs. predominantly non-anticoagulated patients in a randomized controlled design. The results demonstrate the propensity for anticoagulation to increase bleeding events and the magnitude of this effect even in patients at low risk for bleeding. While major anticoagulation trials and the HAS-BLED validation study have reported only major bleeding as endpoints,[10,14,15] the OPTION study also included clinically relevant non-major bleeding.[8] The relevance of the latter to clinical practice and to patients cannot be overstated as these are bleeding events that lead to healthcare resource utilization and cause morbidity and anxiety for patients. These events are also a known contributor to anticoagulant non-compliance and cessation.[16,17] While concern has been predominantly focused in guidelines on balancing risks of anticoagulation for patients with higher baseline bleeding risk, this sub-analysis shows with certainty that bleeding events occur at significant rates in all patients subjected to anticoagulation, regardless of perceived bleeding risk. The latest ESC clinical guidelines[18,19] have moved away from a simplistic bleeding risk evaluation based solely on HAS-BLED score to recommend dynamic re-evaluation of patients prescribed oral anticoagulation for potential interaction of baseline risk scores with modifiable bleeding risk factors. The implications of LAAC are therefore not only a reduction in long-term bleeding event rates[20] but also reduced health care utilization for patients who would otherwise require more frequent review of bleeding risk factors.

The recently published OCEAN trial[21] which examined the need for ongoing anticoagulation in a 'successful' post-ablation cohort who had demonstrated freedom from AF for over 12 months also used clinically relevant non-major bleeding as an endpoint. The bleeding rates on OAC were lower as compared with the OPTION study; however, the study design deliberately used a sub-therapeutic dose of rivaroxaban to limit bleeding risk. Further, the lower mean CHA_2DS_2-VASc score of 2.2 ± 1.1 in OCEAN as compared with 3.5 ± 1.3 in OPTION limits the generalizability of the results in a post-ablation population.

Bleeding event rates in this study were observed to rise in magnitude according to the HAS-BLED score. This remained true even for patients in the LAAC arm. While patients in the LAAC arm still had short periods of anticoagulation during the study, it can be concluded that even with discontinuation of anticoagulation, a higher baseline bleeding risk is still associated with spontaneous bleeding events. Indeed, this was demonstrated in the HAS-BLED validation studies that the score accurately predicted bleeding events even for patients on aspirin or no anti-thrombotic therapy.[10] This sub-analysis therefore highlights that all patients subjected to anticoagulation are at increased risk of bleeding events, and while there is greatest concern for a narrow therapeutic margin in patients with high

Table 4 Quality of life—change from baseline across follow-up

HAS-BLED score	0			1			2			≥3		
Change from baseline	OAC	LAAC	*P-value*	OAC	LAAC	*P-value*	OAC	LAAC	*P-value*	OAC	LAAC	*P-value*
1 Year												
SF-12 Physical Summary Score	−0.3 ± 10.8	1.5 ± 8.6	0.17	0.0 ± 9.1	1.0 ± 8.8	0.10	−0.9 ± 9.6	0.3 ± 9.2	0.24	0.7 ± 10.4	−0.7 ± 9.9	0.51
SF-12 Mental Health Summary Score	−1.1 ± 8.5	0.8 ± 9.3	0.12	0.5 ± 8.6	−0.2 ± 8.8	0.25	0.2 ± 9.8	−1.4 ± 8.9	0.11	−0.7 ± 9.2	−0.5 ± 7.6	0.93
EQ-5D Index Values	−0.03 ± 0.21	0.02 ± 0.18	0.33	−0.01 ± 0.16	0.01 ± 0.16	0.14	−0.01 ± 0.15	0.00 ± 0.20	0.42	−0.01 ± 0.22	0.00 ± 0.12	0.87
EQ Visual Analogue Scale	4.65 ± 20.93	2.22 ± 15.13	0.31	−0.41 ± 15.74	1.17 ± 15.16	0.14	−0.23 ± 15.78	0.94 ± 16.11	0.52	−0.02 ± 0.20	0.03 ± 0.14	0.21
3 Years												
SF-12 Physical Summary Score	2.5 ± 10.5	2.4 ± 9.0	0.95	−0.7 ± 10.5	0.4 ± 10.0	0.12	−0.7 ± 10.3	−0.5 ± 10.6	0.88	−0.5 ± 10.3	1.9 ± 9.6	0.31
SF-12 Mental Health Summary Score	−0.4 ± 10.1	0.9 ± 9.9	0.33	0.9 ± 10.1	0.2 ± 9.3	0.32	0.5 ± 9.8	−0.5 ± 9.5	0.41	−1.3 ± 10.1	2.2 ± 9.9	0.14
EQ-5D Index Values	−0.01 ± 0.21	0.02 ± 0.18	0.33	−0.03 ± 0.17	0.00 ± 0.17	0.04	−0.04 ± 0.22	−0.02 ± 0.20	0.45	−0.02 ± 0.20	0.03 ± 0.14	0.21
EQ Visual Analogue Scale	4.65 ± 20.93	2.22 ± 15.13	0.31	−0.97 ± 15.92	−1.07 ± 16.48	0.93	−1.74 ± 18.80	−2.05 ± 17.58	0.88	−4.68 ± 14.13	8.38 ± 21.94	0.003

Values are presented as mean ± SD.

Table 5 Quality of life—change from baseline to follow-up (bleeding vs. Non-Bleeding)

Visit	Change from baseline	OAC	LAAC	*P*-Value	Interaction *P*-Value
1 Year Follow-up	SF-12 Physical Summary Score	−0.2 ± 9.5 (700)	0.9 ± 8.9 (739)	0.0299	0.1899
	Did not have bleeding since previous visit	−0.3 ± 9.6 (618)	0.7 ± 8.9 (701)	0.0587	
	Had bleeding since previous visit	0.2 ± 9.3 (82)	3.7 ± 9.8 (38)	0.0739	
	SF-12 Mental Health Summary Score	0.2 ± 8.9 (700)	−0.3 ± 8.8 (739)	0.3258	0.8547
	Did not have bleeding since previous visit	0.3 ± 9.0 (618)	−0.2 ± 8.9 (701)	0.3138	
	Had bleeding since previous visit	−0.6 ± 7.7 (82)	−1.4 ± 8.5 (38)	0.6103	
	EQ-5D Index Values	−0.01 ± 0.17 (701)	0.01 ± 0.17 (746)	0.0316	0.1735
	Did not have bleeding since previous visit	−0.01 ± 0.17 (619)	0.01 ± 0.17 (708)	0.1013	
	Had bleeding since previous visit	−0.03 ± 0.19 (82)	0.03 ± 0.17 (38)	0.0728	
	EQ Visual Analogue Scale	−0.49 ± 15.83 (702)	1.76 ± 15.86 (746)	0.0068	0.8605
	Did not have bleeding since previous visit	−0.32 ± 16.09 (620)	1.81 ± 15.95 (708)	0.0158	
	Had bleeding since previous visit	−1.83 ± 13.72 (82)	0.87 ± 14.41 (38)	0.3363	
3 Year Follow-up	SF-12 Physical Summary Score	−0.2 ± 10.5 (659)	0.7 ± 10.0 (699)	0.1095	0.9717
	Did not have bleeding since previous visit	−0.0 ± 10.3 (552)	0.8 ± 9.8 (636)	0.1773	
	Had bleeding since previous visit	−1.3 ± 11.1 (107)	−0.5 ± 11.8 (63)	0.6417	
	SF-12 Mental Health Summary Score	0.5 ± 10.0 (659)	0.3 ± 9.5 (699)	0.7317	0.1815
	Did not have bleeding since previous visit	0.5 ± 9.8 (552)	0.5 ± 9.3 (636)	0.9903	
	Had bleeding since previous visit	0.4 ± 11.0 (107)	−1.8 ± 10.8 (63)	0.2071	
	EQ-5D Index Values	−0.03 ± 0.19 (664)	−0.00 ± 0.18 (701)	0.0114	0.4903
	Did not have bleeding since previous visit	−0.02 ± 0.19 (557)	−0.00 ± 0.18 (638)	0.0403	
	Had bleeding since previous visit	−0.05 ± 0.20 (107)	−0.00 ± 0.21 (63)	0.1937	
	EQ Visual Analogue Scale	−0.54 ± 17.41 (665)	−0.23 ± 16.92 (701)	0.7412	0.9178
	Did not have bleeding since previous visit	0.06 ± 17.19 (558)	0.13 ± 16.69 (638)	0.9427	
	Had bleeding since previous visit	−3.64 ± 18.28 (107)	−3.87 ± 18.87 (63)	0.9387	

Values are presented as mean ± SD.

bleeding risk scores, more attention should be paid to the 'price paid' and trade-off for lower bleeding risk patients maintained on anticoagulation.

Conjecture has been raised surrounding the recent negative LAAC trial results from CLOSURE-AF[22] which failed to show non-inferiority over standard care OAC for a combined stroke/mortality/bleeding endpoint in a high- bleeding risk AF population. The trial only used major bleeding and did not include all clinically relevant bleeding events. Fortunately, major bleeding events are rare and OAC may not have as much impact on their occurrence in the era of direct-acting OAC agents as we might expect.[23] Further, there was a significant difference in the rates of procedural major bleeding in CLOSURE-AF of 4.3% as compared with 0.6% in the overall OPTION study LAAC arm or 2.0% in the comparable high HAS-BLED score ≥ 3 subgroup in the current analysis. This might be explained by the use of the Amplatzer Amulet device in the CLOSURE-AF study, which was assocaited with higher procedural complications and rates of pericardial effusion as compared with the Watchman device in the Amulet IDE trial.[24]

The OPTION study showed that a strategy of LAAC was non-inferior to oral anticoagulation for the primary efficacy endpoint of all-cause mortality, stroke and systemic embolism. Similar benefit was maintained for LAAC across all HAS-BLED subgroups. An increasing HAS-BLED score is correlated with the CHA_2DS_2-VASc score due to several risk factors in common. Abnormal renal function is also a recognized stroke risk factor in other AF risk scoring schemes.[25] The data support a similar protective benefit of LAAC over OAC at each stroke and bleeding risk score, with no signal that LAAC may under-protect or evade detection in a low stroke event rate environment.

Indications for catheter ablation treatment for AF have mostly included symptomatic indications in previous guidelines; therefore, quality of life outcomes are important endpoints. The potential for incremental quality of life benefit from the added LAAC strategy was also explored. It is expected that the main driver of improved quality of life, however, would be a reduction in AF symptoms from catheter ablation treatment, which was common to both arms. Directionally, there was a trend for patients receiving LAAC to experience greater improvements in quality-of-life scores; however, none of the subgroup analyses were statistically significant except for the highest HAS-BLED score of 3 and above. Improved quality of life scores were shown in a sub-study of the original PROTECT-AF trial favouring Watchman LAAC; however, the comparator was warfarin anticoagulation, and the study cohorts had different demographics than a post-ablation population.[26] The occurrence of bleeding or no bleeding did not influence the impact of OAC or LAAC treatment on quality of life from baseline. Although bleeding events impact quality of life, it is possible that this study design cannot capture this effect due to low sample size and timing of QoL assessments relative to bleeding events.

Therefore, more targeted studies are required to assess the relative impact of bleeding on quality of life in AF patients treated with either OAC or LAAC.

Study limitations

The effect of LAAC on reducing bleeding events in the post-ablation population may have been underestimated as aspirin use was mandated by the FDA according to the instructions for use with the Watchman FLX device. The implications for this included a requirement for dual anticoagulant and concomitant aspirin use for the first 3 months, followed by continued aspirin therapy for the first 12 months in patients receiving LAAC. The implications for increased bleeding in the LAAC arm are clear, and potential simplification of post-implant antithrombotic therapy and earlier discontinuation of aspirin would serve to reduce therapy-related bleeding rates further.

A further impact on bleeding rates in the LAAC arm included significant periods of resumption of anticoagulation during the study for rhythm control interventions—predominantly DC cardioversion, but also small numbers of repeat catheter ablation. Currently, there is insufficient data to recommend that LAAC patients can undergo DC cardioversion without the usual recommended peri-procedural anticoagulation according to guidelines. These additional periods of anticoagulation contribute to increased bleeding risk. Future recommendations for DC cardioversion may include patient selection criteria that do not require peri-procedural anticoagulation or allow for shortened duration in patients with LAAC. Further, the impact of resumption and use of anticoagulation across LAAC subgroups may have contributed to the inability to show a statistically significant difference in bleeding events for patients with HAS-BLED Score 2 (*Figure 2*). Anticoagulation usage in LAAC patients with HAS-BLED Score of 2 was consistently higher at all time points compared with other score categories (*Table 1*),

Although the overall study was powered to detect differences in efficacy and safety endpoints, subgroup analyses struggle with small sample sizes, which limits the likelihood of finding statistically significant differences. Clinical and statistically significant reductions in clinically relevant non-major bleeding were found in favour of LAAC for 3 of the 4 HAS-BLED subgroup analyses however several factors, including statistical power and variation in anticoagulation resumption/usage across the subgroups, limit the study conclusions. Major bleeding events occur at lower rates in a generally younger and less comorbid population of post-ablation patients as compared with the cohorts included in major anticoagulation or LAAC randomized trials. While conclusions can be confidently drawn about overall bleeding rates, this is mainly driven by the contribution of clinically relevant non-major bleeding. Larger sample sizes of this lower event rate population would be required to demonstrate statistically significant differences in major bleeding rates. Analysis of quality-of-life changes in both OAC and LAAC arms was also limited by low sample size, varying duration of time between bleeding events and quality of life assessment, and a potential confounding impact of AF ablation timing (sequential vs. concomitant) on quality of life.

Conclusion

This sub-analysis of the OPTION study has shown that LAAC offers reduced bleeding compared to OAC in patients with both low and high baseline bleeding risk, further supporting LAAC as a safe and effective non-pharmacological approach for protection against stroke in post-ablation AF patients. The subgroup analysis highlights the direct impact of long-term anticoagulation on bleeding complications and patient morbidity in a post-ablation population. The OPTION study highlights an opportunity to mitigate future bleeding risk with a strategy of Watchman FLX LAAC after ablation in patients deemed at high risk of stroke according to clinical guidelines.

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Data availability

The data underlying this article will be shared on reasonable request to Boston Scientific in accordance with its Data Sharing Policy (https://www.bostonscientific.com/en-US/data-sharing-requests.html).

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