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Left atrial appendage closure versus medical therapy in patients with atrial fibrillation: the APPLY study

Steffen Gloekler[1,2]*, MD; Monika Fürholz[1], MD; Stefano de Marchi[1], MD; Caroline Kleinecke[3], MD; Samuel R. Streit[1], MD; Eric Buffle[1], MD; Mátè Fankhauser[1], MD; Jonas Häner[1], MD; Fabian Nietlispach[4], MD, PhD; Roberto Galea[1], MD; Stephan Windecker[1], MD; Bernhard Meier[1], MD

1. Cardiology, Cardiovascular Department, University Hospital of Bern, Bern, Switzerland; 2. Cardiology, Klinikum Hochrhein, Waldshut-Tiengen, Germany; 3. Cardiology, Helmut-G.-Walther-Klinikum, Lichtenfels, Germany; 4. Department of Cardiology, University Hospital of Zurich, Zurich, and Cardiovascular Center Zurich, Hirslanden Klinik im Park, Zurich, Switzerland

S. Gloekler, M. Fürholz and S. de Marchi contributed equally to this article.

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KEYWORDS

- anticoagulant therapy
- atrial fibrillation
- bleeding risk
- death
- ischaemic stroke
- LAA closure

Abstract

Aims: Left atrial appendage closure (LAAC) with AMPLATZER occluders is used for stroke prevention in atrial fibrillation (AF). Net clinical benefit compared to medical therapy has not been tested. The aim of this study was to test whether long-term clinical outcome after LAAC with AMPLATZER occluders may be similar to medical therapy.

Methods and results: Five hundred consecutive patients who underwent LAAC with AMPLATZER occluders were compared to 500 patients with medical therapy by propensity score matching. The primary efficacy endpoint was a composite of stroke, systemic embolism and cardiovascular/unexplained death. The primary safety endpoint consisted of major procedural adverse events and major bleedings. For assessment of net clinical benefit, all of the above-mentioned hazards were combined. After 2,645 patient-years at a mean follow-up of 2.7±1.5 years, the primary efficacy endpoint was reached by 75/1,342, 5.6% in the LAAC group versus 102/1,303, 7.8% per 100 patient-years (hazard ratio [HR] 0.70, 95% confidence interval [CI]: 0.53-0.95, p=0.026). The primary safety endpoint occurred in 48/1,342, 3.6% versus 60/1,303, 4.6% per 100 patient-years (HR 0.80, 95% CI: 0.55-1.18, p=0.21), and the combined hazard endpoint in 109/1,342, 8.1% versus 142/1,303, 10.9% per 100 patient-years (HR 0.76, 95% CI: 0.60-0.97, p=0.018). Patients receiving LAAC demonstrated lower rates of both all-cause and cardiovascular mortality (111/1,342, 8.3% vs 151/1,303, 11.6% per 100 patient-years [HR 0.72, 95% CI: 0.56-0.92, p=0.005] and 54/1,342, 4.0% vs 84/1,303, 6.5% per 100 patient-years [HR 0.64, 95% CI: 0.46-0.89, p=0.007]).

Conclusions: LAAC with AMPLATZER devices showed a net clinical benefit over medical therapy by superior efficacy, similar safety and a benefit in all-cause and cardiovascular mortality.

**Corresponding author: Department of Cardiology, Bern University Hospital, CH-3010 Bern, Switzerland. E-mail: steffengloekler@gmail.com*

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Abbreviations

ACP	AMPLATZER Cardiac Plug
AF	atrial fibrillation
ASD	atrial septal defect
BARC	Bleeding Academic Research Consortium
CI	confidence interval
HR	hazard ratio
INR	international normalised ratio
LAAC	left atrial appendage closure
NOAC	non-vitamin K antagonist
PFO	patent foramen ovale
PSM	propensity score matching
VARC	Valve Academic Research Consortium
VKA	vitamin K antagonist

Introduction

Non-valvular atrial fibrillation (AF) is the most common arrhythmia with a prevalence of 1%-2% in the general population, increasing with age and affecting approximately 7% of individuals aged >65 years and 15%-20% of octogenarians[1,2]. In comparison to non-cardioembolic strokes, a larger amount of cerebral tissue is affected by the larger cardiac emboli, resulting in larger areas of ischaemia with considerable disability and high mortality rates[3-5]. Therefore, medical therapy with oral anticoagulation (OAC) by vitamin K antagonists (VKA) or non-vitamin K antagonists (NOAC) is the mainstay for cardioembolic stroke prevention. The left atrial appendage (LAA) is the main source of thrombus formation in patients with AF who have suffered a stroke. Given the limitations of antithrombotic medical therapy, percutaneous left atrial appendage closure (LAAC) has evolved as an alternative option[6]. Based on superior efficacy, non-inferior safety and superior all-cause and cardiovascular mortality in comparison to warfarin from two randomised trials, the WATCHMAN™ occluder (Boston Scientific, Marlborough, MA, USA) was approved by the US Food and Drug Administration in March 2015 for patients with AF who are eligible for OAC[7-9]. Besides the WATCHMAN, the AMPLATZER™ occluders (Abbott Vascular, Santa Clara, CA, USA) are widely used for LAAC, typically in patients not amenable to OAC[6,10-12]. So far, only registry data of LAAC with AMPLATZER systems with a long-term follow-up have been published[13]; there have been no randomised trials. Therefore, the objective of the present propensity score-matched study was to test whether long-term clinical outcome after LAAC with AMPLATZER occluders may be similar to medical therapy.

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Methods

STUDY DESIGN

APPLY (ClinicalTrials.gov: NCT02787525) was a dual-centre observational retrospective study with a logistic 1:1 nearest neighbour propensity score matching (PSM). It was conducted between 2016 and 2018 in accordance with the Declaration of Helsinki, the International Conference on Harmonization Good Clinical Practice guidelines, and the Swiss regulations on clinical research. The protocol was approved by the independent ethics committees at the two centres. All patients provided written informed consent prior to enrolment.

STUDY POPULATION

LAAC GROUP

The first 500 consecutive patients who underwent LAAC with dedicated AMPLATZER occluders between January 2009 and June 2015 at the Bern and Zurich university hospitals were entered into this prospective observational registry in line with current recommendations[2,6,14,15]. Exclusion criteria were overt infection, endocarditis, pregnancy, intracardiac thrombus, and reasons for OAC other than AF.

CONTROL GROUP

During the same time frame, 500 patients with AF and need for OAC served as the control group. These patients were recruited from the cardiology department at Bern University Hospital, where they were hospitalised during the years 2009 to 2015. Patients with known malignant conditions were excluded.

TREATMENT

LAAC GROUP

Device characteristics and procedural aspects have been described in detail previously[10,14,16,17]. LAAC was performed exclusively with AMPLATZER occluders: 403 patients (81%) received the first-generation AMPLATZER™ Cardiac Plug (ACP) and 97 (19%) the second-generation AMPLATZER™ Amulet™ (both Abbott Vascular). The left atrium was accessed by transseptal puncture in most patients or through a patent foramen ovale (PFO) or atrial septal defect (ASD) if present[18]. Antiplatelet treatment following LAAC consisted of dual antiplatelet therapy for one to six months, and thereafter single or no antiplatelet therapy, tailored to each patient's bleeding risk.

CONTROL GROUP

Antithrombotic treatment usually consisted of OAC with VKA or NOAC. Since a substantial proportion of patients suffered from coronary artery disease in both groups, platelet inhibitors were frequently given continuously, in addition to OAC, in the medical group.

STUDY ENDPOINTS

In the LAAC group, demographic, clinical and procedural characteristics were prospectively collected in a dedicated database according to the current recommendations of the European Association of Percutaneous Cardiovascular Interventions[6,14] and the Munich Consensus Document (MCD) on definitions, endpoints and data collection requirements[14,15]. The MCD criteria were established on the basis of the Valve Academic Research Consortium-2 (VARC-2) criteria and the Bleeding Academic Research Consortium (BARC) criteria[19,20]. For the control group, the same characteristics were captured retrospectively. All study endpoints were predefined and adopted from the PROTECT-AF trial[7].

The primary safety endpoint was a composite of LAAC-related death, ischaemic stroke, cardiac tamponade, major access vessel complication, major device embolisation, severe kidney injury, need for cardiopulmonary resuscitation, need for urgent surgery (e.g., due to embolisation of the device, repair of procedure-related injury, or due to bleeding) and major or life-threatening bleeding according to VARC and BARC type 3a, 3b, 3c, or 5. The primary efficacy endpoint was a composite of stroke (non-disabling, disabling, ischaemic, haemorrhagic), systemic embolism, and cardiovascular or unexplained death.

For comparison of the net clinical benefit, the combined hazard endpoint was used. It is a composite of all hazards arising from the need for stroke protection by LAAC or anticoagulation, i.e., the above-mentioned LAAC-related complications, cardiovascular or unexplained death, any stroke, systemic embolism, pulmonary embolism, myocardial infarction and major or life-threatening bleeding. All event rates were calculated as the number of events per 100 patient-years of follow-up. Classification of death types was adjudicated according to the 2017 ACC/AHA 2017 Cardiovascular and Stroke Endpoint Definitions for Clinical Trials[21].

Data collection, PSM and statistical analysis are provided in **Supplementary Appendix 1**.

Table 1. Baseline characteristics.

Variable	LAAC (n=500)	Medical therapy (n=500)	*p*-value
Demographics, risk factors and clinical features			
Age*, years	73.9±10.1	74.1±10.3	0.47
Body mass index*, kg/m²	27.2±5.0	27.5±5.9	0.74
Female gender*, n (%)	155 (31)	155 (31)	1.00
Left ventricular ejection fraction*, %	55.0±11.5	55.3±13.5	0.64
Renal function, mean eGFR, ml/min	70.3±33.7	69.5±33.4	0.70
Haemoglobin level*, g/L	125.6±20.1	125.5±20.1	0.92
Stroke and bleeding risk			
CHA_2DS_2-VASc score, mean/median	4.3±1.7/4	4.3±1.8/4	0.97
HAS-BLED score*, mean/median	3.0±1.1/3	2.9±0.4/3	0.23
HAS-BLED score ≥3, n (%)	339 (67.8)	316 (63.2)	0.14

Categorical variables are expressed as frequencies (n) and percentages (%). Continuous data are reported as mean and standard deviation. * matching criteria. AF: atrial fibrillation; CABG: coronary artery bypass grafting; eGFR: estimated glomerular filtration rate; LAAC: left atrial appendage closure; PCI: percutaneous coronary intervention

Results

PATIENT POPULATION

Of the 1,000 AF patients enrolled in APPLY, 500 underwent LAAC with AMPLATZER devices, and 500 with standard medical therapy served as the matched control group **(Table 1, Supplementary Table 1)**. PSM resulted in excellent bias reduction in all categories with absolute standardised differences <0.1 **(Figure 1)**. Stroke risk and bleeding risk were high in both groups with HAS-BLED scores ≥3 in the majority of patients.

In the LAAC group, device success was 98%, i.e., in 10 of 500 patients no occluder could be placed for different reasons. Since the present study follows the intention-to-treat principle, these remained in their respective group.

LONG-TERM CLINICAL OUTCOME

After a mean follow-up of 2.7±1.5 versus 2.6±1.5 years and a total of 2,645 patient-years (1,342 vs 1,303), clinical information was available for all 1,000 patients **(Table 2, Supplementary Table 2, Supplementary Table 3)**. In the LAAC group, 7 of the 10 patients without an occluder were alive at follow-up: 4 of them underwent surgical LAAC, 1 was anticoagulated and 2 remained without any medical or device-based stroke protection. Thirty-nine of the 389 (10.0%) patients of the LAAC group received OAC apart from AF. In the control group, 275 of 349 (78.8%) were on VKA (53.6%) or NOAC (25.2%) **(Supplementary Figure 1A)**. In 95 of 125 (76.0%) patients, international normalised ratio (INR) measurements were

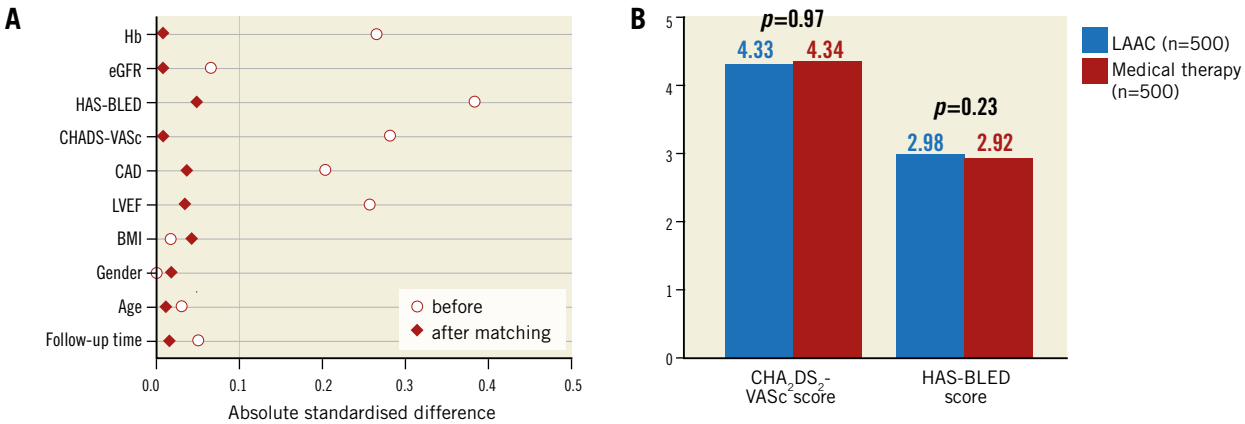

Figure 1. *Results before and after matching. Good comparability by excellent bias reduction (A) in all categories with equalisation in baseline risk for stroke and bleeding (B).*

Table 2. Long-term clinical outcome.

Variable	LAAC (n=500; 1,342 patient-years)		Medical therapy (n=500; 1,303 patient-years)		*p*-value
Follow-up					
Age at follow-up, years	77.1±9.8		77.1±9.9		0.98
Time from study inclusion to follow-up in years, mean	2.7±1.5		2.6±1.5		0.43
Patients alive	389 (77.8)		349 (69.8)		0.02
Any medical, surgical or device-based protection from stroke	387/389 (99.5)		275/349 (78.8)		<0.0001
Primary endpoints	**Events/ patient-years**	**Observed rate**	**Events/ patient-years**	**Observed rate***	***p*-value**
Primary efficacy endpoint	75/1,342	5.6 (4.4-7.0)	102/1,303	7.8 (6.4-9.4)	0.026
Primary safety endpoint	48/1,342	3.6 (2.7-4.7)	60/1,303	4.6 (3.5-5.8)	0.216
Combined hazard endpoint (net clinical benefit)	109/1,342	8.1 (6.7-9.7)	142/1,303	10.9 (9.3-12.7)	0.018

* Events per 100 patient-years (95% credible interval). LAAC: left atrial appendage closure; TIA: transient ischaemic attack

available; one or more measurements were out of therapeutic range (INR <2 or INR >3.5). Patients in the LAAC group had lower numbers of hospital stays (47.6% vs 69.8%, p<0.0001, mean number per patient 2.6±2.2 vs 3.0±2.4, p=0.016) and self-reported functional status was better in the LAAC group **(Table 2, Supplementary Table 2, Supplementary Figure 1B)**.

PRIMARY EFFICACY ENDPOINT

There were 75 primary efficacy events among the 500 LAAC patients during 1,342 patient-years, i.e., 5.6%, versus 102 events among the 500 patients of the control group during 1,303 patient-years, i.e., 7.8% per 100 patient-years (hazard ratio [HR] 0.70, 95% confidence interval [CI]: 0.53-0.95, p=0.026) **(Figure 2A,**

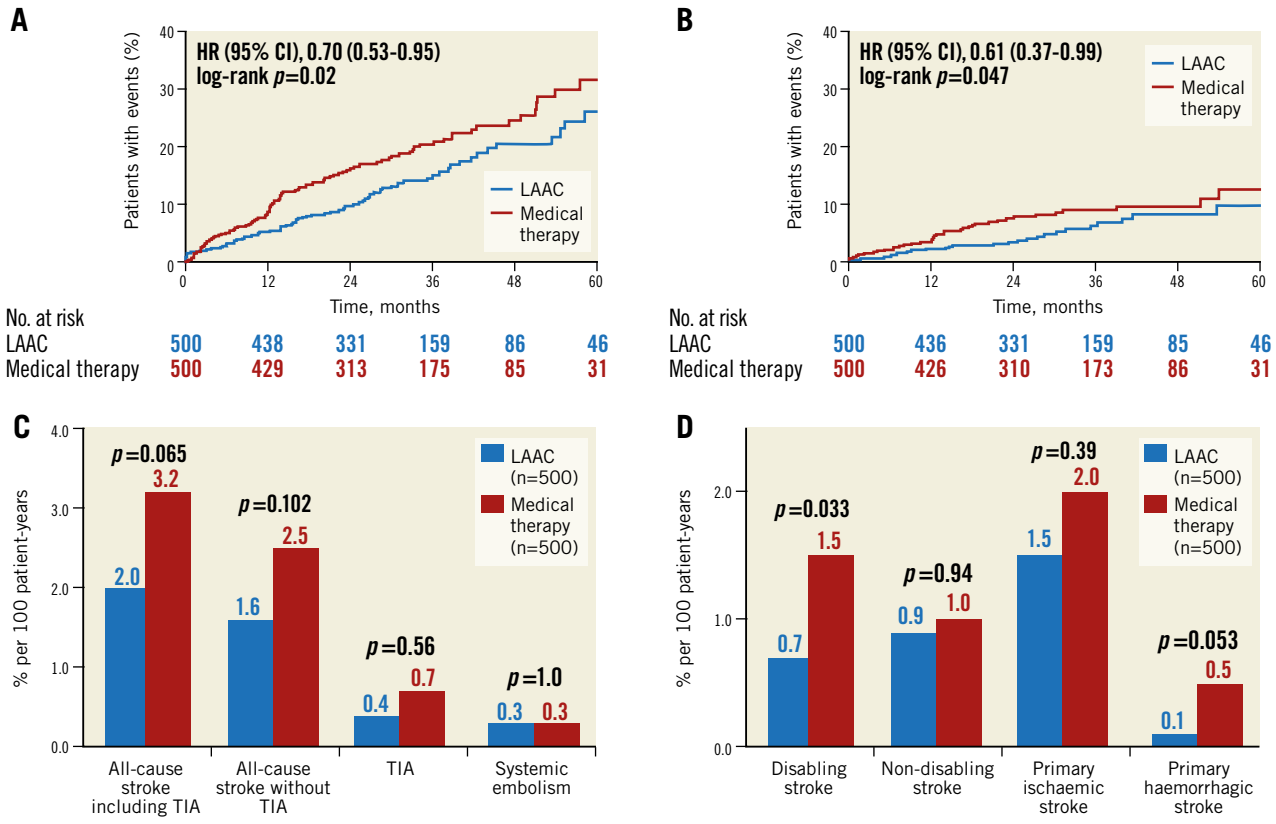

Figure 2. *Kaplan-Meier curves of the primary efficacy endpoint (A), all-cause stroke and TIA (B), and cumulative incidence of ischaemic events (C) and stroke types (D). Event rates per 100 patient-years.*

Table 2). In the LAAC group, the incidence of stroke and transient ischaemic attack (TIA) tended to be lower (27/1,342, 2.0% vs 41/1,303, 3.2%, p=0.065) and, according to Cox regression analysis, the difference reached statistical significance (p=0.047) **(Figure 2B, Figure 2C)**. Also, the rates of disabling and haemorrhagic strokes were lower in the LAAC group (9/1,342, 0.7% vs 20/1,303, 1.5%, p=0.033 and 1/1,342, 0.1% vs 6/1,303, 0.5%, p=0.053, respectively) **(Figure 2D)**.

PRIMARY SAFETY ENDPOINT

Safety events occurred in 48 of the 500 LAAC patients during 1,342 patient-years, i.e., 3.6%, versus in 60 of the 500 control group patients during 1,303 patient-years, i.e., 4.6% per 100 patient-years (HR 0.80, 95% CI: 0.55-1.18, p=0.21). Of the 48 safety events in the LAAC group, 25 (52.1%) were caused by severe procedural adverse events and 23 (47.9%) by major, life-threatening or fatal bleedings during follow-up **(Table 2, Figure 3)**.

COMBINED HAZARD ENDPOINT (NET CLINICAL BENEFIT)

The combination of efficacy and safety events occurred in 109 LAAC patients during 1,342 patient-years, i.e., 8.1%, versus in 142 control group patients during 1,303 patient-years, i.e., 10.9% per 100 patient-years (HR 0.76, 95% CI: 0.60-0.97, p=0.018) **(Table 2, Figure 4)**.

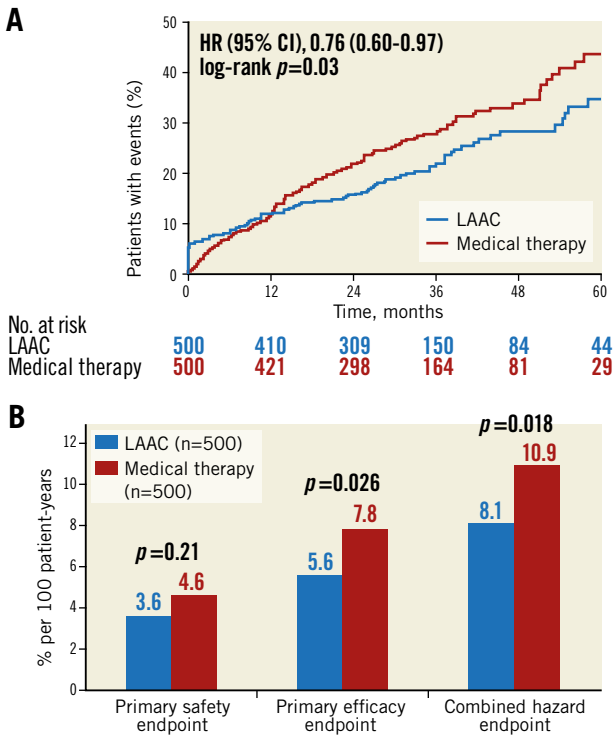

Figure 4. *Kaplan-Meier curves of the net clinical benefit (A) and cumulative incidence of event rates per 100 patient-years of the predefined endpoints (B).*

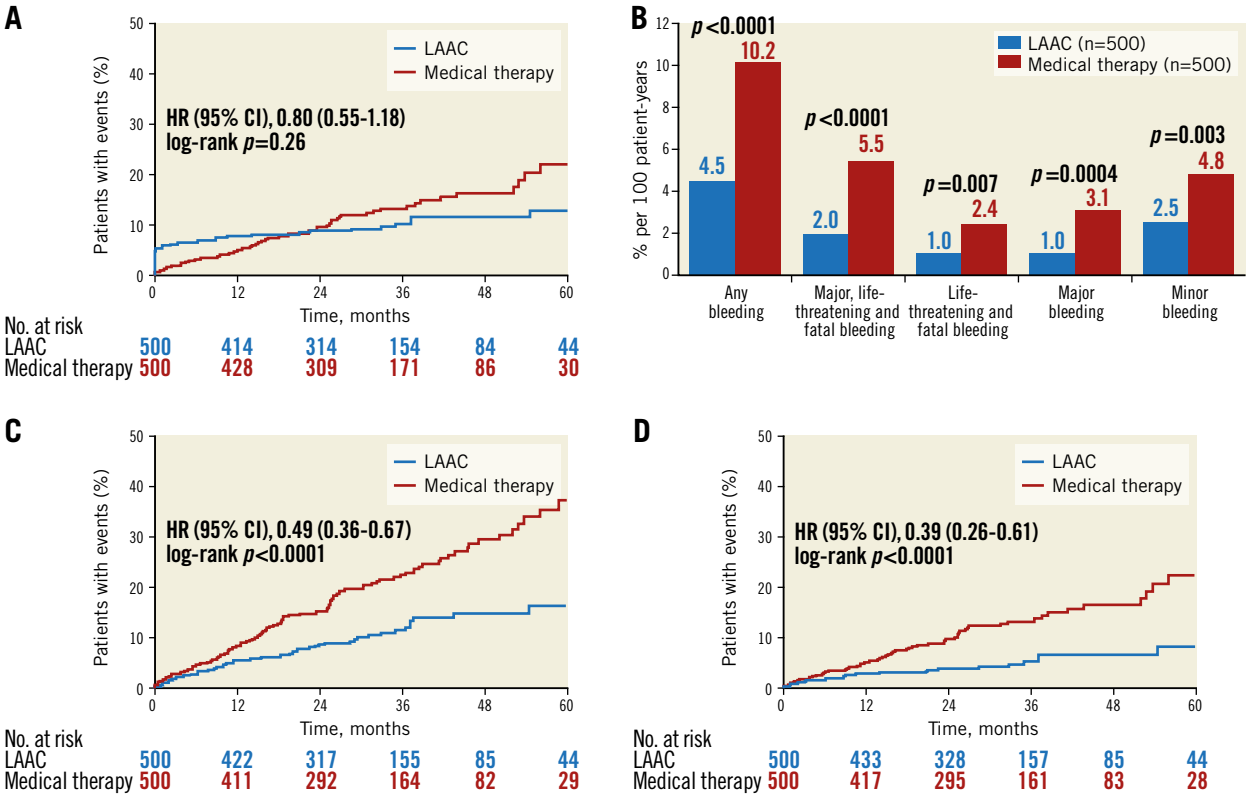

Figure 3. *Kaplan-Meier curves of the primary safety endpoint (A) and cumulative incidence of the different types of bleeding (B). Kaplan-Meier curves of any bleeding (C) and major and life-threatening bleedings only (D). Event rates per 100 patient-years.*

MORTALITY

All-cause mortality was lower in the LAAC group (111/1,342, 8.3% vs 151/1,303, 11.6% per 100 patient-years, HR 0.72, 95% CI: 0.56-0.92, p=0.005). It was driven mainly by a lower rate of cardiovascular and unexplained deaths (54/1,342, 4.0% vs 84/1,303, 6.5% per 100 patient-years, HR 0.64, 95% CI: 0.46-0.89, p=0.007), whereas non-cardiovascular mortality was similar between the groups (57/1,342, 4.3% vs 67/1,303, 5.1%, p=0.32) **(Supplementary Table 3, Supplementary Figure 2)**. The causes of death are listed in **Supplementary Table 3**.

Discussion

In this propensity-matched dual-centre study of 1,000 patients with AF, LAAC with AMPLATZER occluders was compared to medical therapy. After 2,645 patient-years and at a mean follow-up of 2.7±1.5 years, the principal findings were:

1) LAAC with AMPLATZER occluders showed superior efficacy over medical therapy, driven evenly by a lower incidence of cardiovascular mortality and strokes.
2) The composite safety endpoint in the LAAC group was similar to medical therapy and was driven mainly by procedural complications. With regard to non-procedure-related bleedings, LAAC was superior to medical therapy.
3) LAAC with AMPLATZER occluders showed a significant net clinical benefit over medical therapy.

In contrast to LAAC with the WATCHMAN occluder, no randomised controlled data against medical therapy with AMPLATZER occluders have been available so far[7,9]. Therefore, until definite results of ongoing randomised trials become available[22], we performed the APPLY study with a sizeable cohort of 1,000 patients. By PSM, good overall comparability between our all-comer high-risk LAAC cohort and a corresponding high-risk cohort of patients managed with standard medical therapy was shown. In spite of or because of dealing with higher-risk patients, APPLY resembles the results of the WATCHMAN trials, supporting the basic concept of LAAC for prevention not only of stroke but also of death and bleedings, irrespective of the device[6,7,9]. Consistent with the PROTECT-AF trial, death rates after LAAC were also lower in APPLY, despite the above-mentioned differences in four subcategories of the risk scores, where three of four, i.e., heart failure, prior stroke, and bleedings, were more frequent in the LAAC group. While non-cardiovascular death was similar in both groups, overall mortality was lower in the LAAC group. This was due to the lower rates of cardiovascular and unknown causes of death, which in turn was the result of lower rates of stroke and TIA, a lower rate of disabling strokes, fewer heart failure-related deaths (despite the higher baseline rate in the LAAC group), and presumably fewer clinically occult bleedings **(Figure 2, Figure 3, Supplementary Figure 2, Supplementary Table 3)**.

Given the fact that 99.5% of the patients in the LAAC group of APPLY had some kind of surgical, device-based or, in case of platelet inhibition only, incomplete medical stroke protection, the lower rate of stroke and TIA, as well as the lower rate of disabling strokes and the strong trend towards lower rates of stroke and systemic embolism, is compelling **(Figure 2B-Figure 2D)**. Our rate of 1.9% is comparable to the rate of the five-year outcomes after LAAC with the WATCHMAN of the PREVAIL and PROTECT-AF trials (1.7%) and lower than in the AMPLATZER Amulet global observational registry, where the stroke rate was 2.9% in a very elderly and high-risk cohort of 1,088 patients[11]. In contrast, only 78.8% of patients in the control group of APPLY were provided with an adequate stroke prophylaxis, reflecting the real-world issues of medically managed high-risk AF patients. Therefore, with time, the gap between the two groups in both efficacy and safety will probably spread further. In contrast to the above-mentioned WATCHMAN trials, not only the overall stroke rate, but also ischaemic stroke rates were lower in APPLY despite a higher stroke risk at baseline (1.5% vs 2.0% in APPLY vs 1.6% and 0.95% in the five-year patient-level meta-analysis of PROTECT-AF and PREVAIL)[9]. These figures are consistent with current AMPLATZER registries and support the assumption that, due to device-specific reasons, AMPLATZER occluders may be less thrombogenic than the WATCHMAN.

With regard to bleedings, the rates of both groups in APPLY are higher than in the WATCHMAN trials, reflecting our higher-risk cohorts. Due to immediate cessation of anticoagulation directly after LAAC in the vast majority of patients, and in contrast to the WATCHMAN trials, all categories of bleedings were drastically reduced in this group **(Table 2, Figure 3)**. The relatively high rate of patients in the control group who were taking OAC in addition to a single (7.6%) or dual (2.2%) antiplatelet therapy may also explain the higher bleeding rate in this group. On the other hand, 24% of the patients did not take any anticoagulation, which counterbalances this issue. Ischaemia protection suffers from relatively poor compliance with OAC. Compliance is not an issue after LAAC which blunts the assumed inferior protection against ischaemia of LAAC compared to optimal OAC. When added to the fact that bleedings are constantly and independently linked to an increased risk of mortality, the higher rate of cardiovascular/unknown deaths in APPLY in the control group becomes plausible[20]. This is also consistent with the lower rate of hospital stays due to fewer bleedings and a better self-reported functional status in the LAAC group of APPLY **(Supplementary Table 2, Supplementary Figure 1B)**.

Limitations

A major limitation of APPLY is its retrospective design and the bias that, despite the PSM, the rates for prior bleedings and strokes, heart failure and diabetes mellitus (DM) (the first three in disfavour of the LAAC group, the latter in disfavour of the control group) were different between the groups. On the one hand, the higher DM rate in the control group may have contributed to the higher cardiovascular mortality in this group. On the other hand, this effect is likely to be counteracted by the fact that three strongly prognostically relevant characteristics, namely congestive heart failure and prior stroke and bleeding rates were

more prevalent in the LAAC group, where the rates of death due to congestive heart failure and stroke were similar rather than higher **(Supplementary Table 3)**. The fact that already at study inclusion only 76% of patients of the control group left hospital with OAC may be regarded as a limitation, but it reflects the real-world character of APPLY and the well-known problems of any OAC in high-risk patients. A selection of 500 patients suitable for OAC and comparable with our high-risk LAAC cohort probably does not exist. This is a general problem of LAAC in patients receiving AMPLATZER occluders and different from randomised WATCHMAN studies, in which patients had to be eligible for OAC. Finally, and again due to the observational nature of APPLY, drug types in patients who were anticoagulated were heterogeneous, since one third received NOAC at the time of follow-up. Therefore, our results cannot be interpreted specifically for patients receiving either VKA only or NOAC only. The results of the prospective randomised and controlled PRAGUE-17 trial comparing LAAC with AMPLATZER or WATCHMAN occluders with NOAC, mainly with apixaban, are less contrasting, i.e., a significant superiority in non-procedure-related bleedings could not be shown[23-25]. This may be due to a lack of power to determine differences in the single components of the primary endpoint (which was a combined endpoint of stroke, death and bleeding) and by the comparison of LAAC to the predominantly used apixaban with relatively favourable bleeding rates. In a recently published propensity score-matched retrospective study, no differences in efficacy and safety were found between LAAC with WATCHMAN and AMPLATZER occluders (n=96) and various NOAC (n=96)[26].

Conclusions

Results from APPLY suggest that left atrial appendage closure with AMPLATZER devices offers a significant net clinical benefit over medical therapy by way of superior efficacy, similar safety and lower all-cause and cardiovascular mortality.

Impact on daily practice

Prevention of thromboembolic events in patients with AF remains a frequent and often challenging problem, especially in patients with a contraindication to OAC, the most frequently used therapeutic option. In this dual-centre, real-world propensity score-matched study comparing LAAC to medical therapy with OAC, LAAC showed a net clinical benefit compared to OAC, driven by superior efficacy. Thus, LAAC is a valuable treatment option in patients with AF.

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Conflict of interest statement

S. Windecker has received grants to the institution from Abbott, Biotronik, Boston Scientific, Medtronic and Edwards Lifesciences. B. Meier has received speaker and proctor fees from Abbott, Bayer and Sanofi. F. Nietlispach is a consultant to Abbott, Edwards Lifesciences and Medtronic. S. Gloekler has received grants to the institution from Abbott and the Swiss Heart Foundation. The other authors have no conflicts of interest to declare.

References

1. Kirchhof P. The future of atrial fibrillation management: integrated care and stratified therapy. *Lancet.* 2017;390:1873-87.

2. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, Castella M, Diener HC, Heidbuchel H, Hendriks J, Hindricks G, Manolis AS, Oldgren J, Popescu BA, Schotten U, Van Putte B, Vardas P; ESC Scientific Document Group. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Eur Heart J.* 2016;37:2893-962.

3. Freeman WD, Aguilar MI. Stroke prevention in atrial fibrillation and other major cardiac sources of embolism. *Neurol Clin.* 2008;26:1129-60.

4. Freeman WD, Aguilar MI. Prevention of cardioembolic stroke. *Neurotherapeutics.* 2011;8:488-502.

5. Gloekler S, Saw J, Koskinas KC, Kleinecke C, Jung W, Nietlispach F, Meier B. Left atrial appendage closure for prevention of death, stroke, and bleeding in patients with nonvalvular atrial fibrillation. *Int J Cardiol.* 2017;249:234-46.

6. Glikson M, Wolff R, Hindricks G, Mandrola J, Camm AJ, Lip GYH, Fauchier L, Betts TR, Lewalter T, Saw J, Tzikas A, Sternik L, Nietlispach F, Berti S, Sievert H, Bertog S, Meier B. EHRA/EAPCI expert consensus statement on catheter-based left atrial appendage occlusion - an update. *EuroIntervention.* 2020;15:1133-80.

7. Reddy VY, Sievert H, Halperin J, Doshi SK, Buchbinder M, Neuzil P, Huber K, Whisenant B, Kar S, Swarup V, Gordon N, Holmes D; PROTECT AF Steering Committee and Investigators. Percutaneous left atrial appendage closure vs warfarin for atrial fibrillation: a randomized clinical trial. *JAMA.* 2014;312:1988-98.

8. Reddy VY, Gibson DN, Kar S, O'Neill W, Doshi SK, Horton RP, Buchbinder M, Gordon NT, Holmes DR. Post-Approval U.S. Experience With Left Atrial Appendage Closure for Stroke Prevention in Atrial Fibrillation. *J Am Coll Cardiol.* 2017;69:253-61.

9. Reddy VY, Doshi SK, Kar S, Gibson DN, Price MJ, Huber K, Horton RP, Buchbinder M, Neuzil P, Gordon NT, Holmes DR Jr; PREVAIL and PROTECT AF Investigators. 5-Year Outcomes After Left Atrial Appendage Closure: From the PREVAIL and PROTECT AF Trials. *J Am Coll Cardiol.* 2017;70:2964-75.

10. Koskinas KC, Shakir S, Fankhauser M, Nietlispach F, Attinger-Toller A, Moschovitis A, Wenaweser P, Pilgrim T, Stortecky S, Praz F, Räber L, Windecker S, Meier B, Gloekler S. Predictors of Early (1-Week) Outcomes Following Left Atrial Appendage Closure With Amplatzer Devices. *JACC Cardiovasc Interv.* 2016;9:1374-83.

11. Landmesser U, Tondo C, Camm J, Diener HC, Paul V, Schmidt B, Settergren M, Teiger E, Nielsen-Kudsk JE, Hildick-Smith D. Left atrial appendage occlusion with the AMPLATZER Amulet device: one-year follow-up from the prospective global Amulet observational registry. *EuroIntervention.* 2018;14:e590-7.

12. Meier B, Stegink W, Tzikas A. History of Percutaneous Left Atrial Appendage Occlusion with AMPLATZER Devices. *Interv Cardiol Clin.* 2018;7:151-8.

13. Hildick-Smith D, Landmesser U, Camm AJ, Diener HC, Paul V, Schmidt B, Settergren M, Teiger E, Nielsen-Kudsk JE, Tondo C. Left atrial appendage occlusion with the Amplatzer™ Amulet™ device: full results of the prospective global observational study. *Eur Heart J.* 2020;41:2894-901.

14. Meier B, Blaauw Y, Khattab AA, Lewalter T, Sievert H, Tondo C, Glikson M; Document Reviewers. EHRA/EAPCI expert consensus statement on catheter-based left atrial appendage occlusion. *Europace.* 2014;16:1397-416.

15. Tzikas A, Holmes DR Jr, Gafoor S, Ruiz CE, Blomström-Lundqvist C, Diener HC, Cappato R, Kar S, Lee RJ, Byrne RA, Ibrahim R, Lakkireddy D, Soliman OI, Näbauer M, Schneider S, Brachman J, Saver JL, Tiemann K, Sievert H, Camm AJ, Lewalter T. Percutaneous left atrial appendage occlusion: the Munich consensus document on definitions, endpoints and data collection requirements for clinical studies. *EuroIntervention.* 2016;12:103-11.

16. Freixa X, Chan JL, Tzikas A, Garceau P, Basmadjian A, Ibrahim R. The Amplatzer™ Cardiac Plug 2 for left atrial appendage occlusion: novel features and first-in-man experience. *EuroIntervention.* 2013;8:1094-8.

17. Tzikas A, Gafoor S, Meerkin D, Freixa X, Cruz-Gonzalez I, Lewalter T, Saw J, Berti S, Nielsen-Kudsk JE, Ibrahim R, Lakkireddy D, Paul V, Arzamendi D, Nietlispach F, Worthley SG, Hildick-Smith D, Thambo JB, Tondo C, Aminian A, Kalarus Z, Schmidt B, Sondergaard L, Kefer J, Meier B, Park JW, Sievert H, Omran H. Left atrial appendage occlusion with the AMPLATZER Amulet device: an expert consensus step-by-step approach. *EuroIntervention.* 2016;11:1512-21.

18. Kleinecke C, Fuerholz M, Buffle E, de Marchi S, Schnupp S, Brachmann J, Nietlispach F, Fankhauser M, Streit SR, Windecker S, Meier B, Gloekler S. Transseptal puncture versus patent foramen ovale or atrial septal defect access for left atrial appendage closure. *EuroIntervention.* 2020;16:e173-80.

19. Kappetein AP, Head SJ, Généreux P, Piazza N, van Mieghem NM, Blackstone EH, Brott TG, Cohen DJ, Cutlip DE, van Es GA, Hahn RT, Kirtane AJ, Krucoff MW, Kodali S, Mack MJ, Mehran R, Rodés-Cabau J, Vranckx P, Webb JG, Windecker S, Serruys PW, Leon MB. Updated standardized endpoint definitions for transcatheter aortic valve implantation: the Valve Academic Research Consortium-2 consensus document. *Eur Heart J.* 2012;33:2403-18.

20. Mehran R, Rao SV, Bhatt DL, Gibson CM, Caixeta A, Eikelboom J, Kaul S, Wiviott SD, Menon V, Nikolsky E, Serebruany V, Valgimigli M, Vranckx P, Taggart D, Sabik JF, Cutlip DE, Krucoff MW, Ohman EM, Steg PG, White H. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. *Circulation.* 2011;123:2736-47.

21. Hicks KA, Mahaffey KW, Mehran R, Nissen SE, Wiviott SD, Dunn B, Solomon SD, Marler JR, Teerlink JR, Farb A, Morrow DA, Targum SL, Sila CA, Thanh Hai MT, Jaff MR, Joffe HV, Cutlip DE, Desai AS, Lewis EF, Gibson CM, Landray MJ, Lincoff AM, White CJ, Brooks SS, Rosenfield K, Domanski MJ, Lansky AJ, McMurray JJV, Tcheng JE, Steinhubl SR, Burton P, Mauri L, O'Connor CM, Pfeffer MA, Hung HMJ, Stockbridge NL, Chaitman BR, Temple RJ; Standardized Data Collection for Cardiovascular Trials Initiative (SCTI). 2017 Cardiovascular and Stroke Endpoint Definitions for Clinical Trials. *J Am Coll Cardiol.* 2018;71:1021-34.

22. Landmesser U. Left Atrial Appendage CLOSURE in Patients With Atrial Fibrillation Compared to Medical Therapy (CLOSURE-AF). https://clinicaltrials.gov/ct2/show/NCT03463317

23. Osmancik P, Tousek P, Herman D, Neuzil P, Hala P, Stasek J, Haman L, Kala P, Poloczek M, Branny M, Chovancik J, Cervinka P, Holy J, Vancura V, Rokyta R, Taborsky M, Kovarnik T, Zemanek D, Peichl P, Haskova S, Jarkovsky J, Widimsky P; PRAGUE-17 Investigators. Interventional left atrial appendage closure vs novel anticoagulation agents in patients with atrial fibrillation indicated for long-term anticoagulation (PRAGUE-17 study). *Am Heart J.* 2017;183:108-14.

24. Osmancik P. Left Atrial Appendage Closure vs. Novel Anticoagulation Agents in Atrial Fibrillation (PRAGUE-17). https://clinicaltrials.gov/ct2/show/NCT02426944?term=NCT02426944&draw=2&rank=1

25. Granger CB, Alexander JH, McMurray JJ, Lopes RD, Hylek EM, Hanna M, Al-Khalidi HR, Ansell J, Atar D, Avezum A, Bahit MC, Diaz R, Easton JD, Ezekowitz JA, Flaker G, Garcia D, Geraldes M, Gersh BJ, Golitsyn S, Goto S, Hermosillo AG, Hohnloser SH, Horowitz J, Mohan P, Jansky P, Lewis BS, Lopez-Sendon JL, Pais P, Parkhomenko A, Verheugt FW, Zhu J, Wallentin L; ARISTOTLE Committees and Investigators. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med.* 2011;365:981-92.

26. Godino C, Melillo F, Bellini B, Mazzucca M, Pivato CA, Rubino F, Figini F, Mazzone P, Della Bella P, Margonato A, Colombo A, Montorfano M. Percutaneous left atrial appendage closure compared to non-vitamin K oral anticoagulants in patients with non-valvular atrial fibrillation and high bleeding risk. *EuroIntervention.* 2020;15:1548-54.

27. Austin PC. An Introduction to Propensity Score Methods for Reducing the Effects of Confounding in Observational Studies. *Multivariate Behav Res.* 2011;46:399-424.

28. Ho DE, Imai K, King G, Stuart EA. MatchIt: Nonparametric Preprocessing for Parametric Causal Inference. *Journal of Statistical Software.* 2011;42:1-28. http://www.jstatsoft.org/v42/i08/

29. R Development Core Team. R: A language and environment for statistical computing. 2008. http://www.R-project.org

Supplementary data

Supplementary Appendix 1. Data collection, propensity score matching and statistical analysis.

Supplementary Figure 1. Antithrombotic therapy at follow-up and self-reported functional status.

Supplementary Figure 2. Kaplan-Meier curves of all-cause and cardiovascular mortality and the cumulative incidence of all-cause cardiovascular and non-cardiovascular deaths.

Supplementary Table 1. Antithrombotic medical therapy at study inclusion.

Supplementary Table 2. Long-term clinical outcome.

Supplementary Table 3. Causes of death.

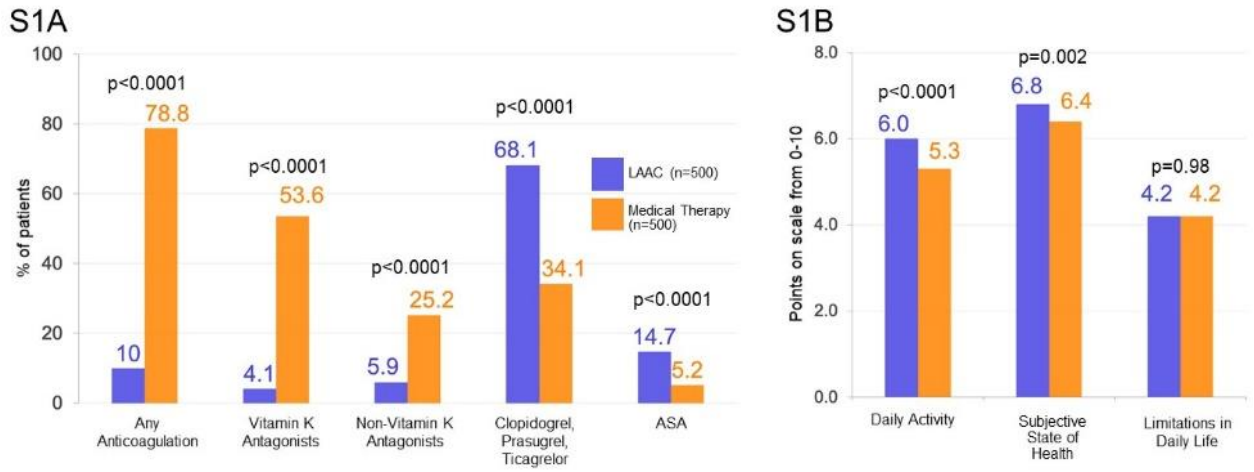
The supplementary data are published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-20-00201

Supplementary data

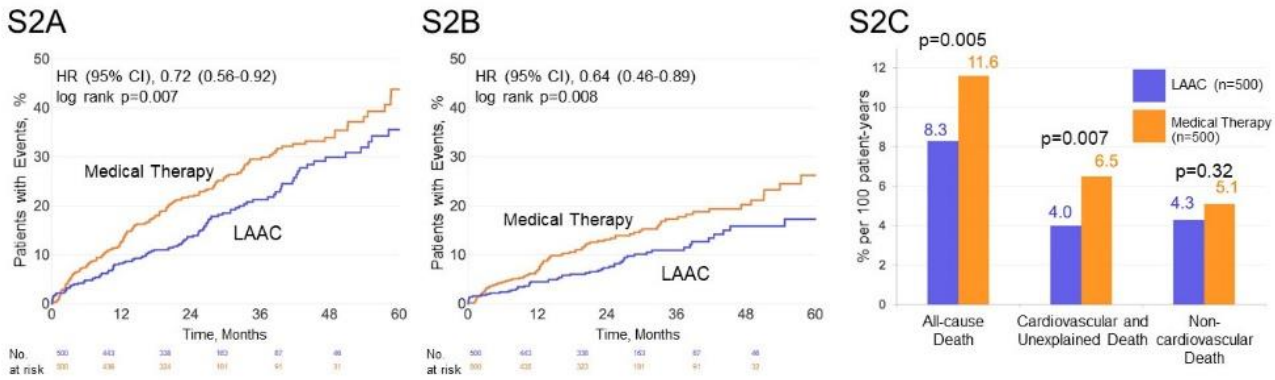
Supplementary Appendix 1. Data collection, propensity score matching and statistical analysis

By sweep follow-up from September 2016 to December 2018, all clinical adverse events were captured by dedicated paper forms and entered in a web-hosted database (REDCap). As a first step, a standardised questionnaire was sent to all patients. Non-responders were contacted directly by telephone calls and the follow-up form was completed. Information concerning all non-accessible patients or from those who had died was obtained from relatives, hospitals and treating physicians rather than from commonly incomplete sources of information such as death certificates. In case of clinical adverse events, the source documents were obtained from hospitals, general practitioners or cardiologists. According to the above-mentioned criteria, they were classified and adjudicated by an independent clinical events committee consisting of two cardiologists and, in case of disagreement, by a third cardiologist.

By a first logistic 4:1 nearest neighbour propensity score matching (PSM), 500 of 2,000 AF patients under medical therapy for AF were identified. A sufficient bias reduction between the two groups was considered to be a standard difference <0.1 [27]. PSM was conducted using the MatchIt package (Version: 2.4-21) for R software [28,29]. For optimal comparability to the LAAC group, follow-up time, gender, age, body mass index, stroke and bleeding risk (as determined by the CHA_2DS_2-VASc and HAS-BLED scores), as well as conditions with an impact on prognosis, such as coronary artery disease, left ventricular systolic and renal function, as well as haemoglobin levels, were matched. Thereafter, a 1:1 nearest neighbour matching with a calliper distance of 0.2 was run and statistical analysis was performed with Statistical Package for Social Sciences (SPSS), Version 16.0.0 for Windows (SPSS Inc., Chicago, IL, USA). Comparisons between the two groups were performed according to the intention-to-treat principle. Categorical variables are presented as numbers and percentages and compared with Fisher's exact test. Continuous variables are summarised as mean±SD and compared using the Mann-Whitney test. The Kaplan-Meier method was used for graphical assessment of time-dependent events and, for comparison of event curves, the log-rank (Mantel-Cox) test was used. For determination of hazard ratio, the Mantel-Haenszel method was applied. Findings were considered statistically significant at the 0.05 level.



Supplementary Figure 1. Antithrombotic therapy at follow-up (S1A) and self-reported functional status (S1B).



Supplementary Figure 2. Kaplan-Meier curves of all-cause (S2A) and cardiovascular mortality (S2B) and the cumulative incidence of all-cause cardiovascular and non-cardiovascular deaths (S2C).

Event rates per 100 patient-years.

Supplementary Table 1. Antithrombotic medical therapy at study inclusion.

Variable	LAAC	Medical therapy	*p*-value
ANTITHROMBOTIC MEDICAL THERAPY AT STUDY INCLUSION			
Any oral anticoagulation, n (%)	27 (5.4)	380 (76.0)	<0.0001
Vitamin K antagonists, n (%)	27 (5.4)	309 (61.8)	<0.0001
Non-vitamin K antagonists, n (%)	0 (0)	71 (14.2)	<0.0001
Acetylsalicylic acid, n (%)	452 (90.4)	269 (53.8)	<0.0001
Platelet inhibitors other than acetylsalicylic acid, n (%)	455 (91.0)	83 (16.6)	<0.0001
Dual antiplatelet therapy, n (%)	426 (85.2)	38 (7.6)	<0.0001
Triple antiplatelet therapy, n (%)	0 (0)	11 (2.2)	<0.0001

Supplementary Table 2. Long-term clinical outcome.

Variable	**LAAC**		**Medical therapy**		***p*-value**
	n=500		n=500		
	1,342 patient-years		1,303 patient-years		
LONG-TERM CLINICAL FOLLOW-UP					
Age at follow-up, years	77.1±9.8		77.1±9.9		0.98
Time from study inclusion to follow-up in years, mean	2.7±1.5		2.6±1.5		0.43
Patients alive	389 (77.8)		349 (69.8)		0.02
Any medical, surgical or device-based protection from stroke	387/389 (99.5)		275/349 (78.8)		<0.0001
DEATH					
	Events/PY	Observed rate	Events/PY	Observed rate	*p*-value
All-cause death	111/1,342	8.3 (6.8-9.9)	151/1,303	11.6 (9.9-13.5)	0.005
Cardiovascular/unexplained death	54/1,342	4.0 (3.0-5.2)	84/1,303	6.5 (5.2-7.9)	0.007
Non-cardiovascular death	57/1,342	4.3 (3.2-5.5)	67/1,303	5.1 (4.0-6.5)	0.319
STROKE					
Stroke and TIA (any)	27/1,342	2.0 (1.3-2.9)	41/1,303	3.2 (2.3-4.3)	0.065
Stroke without TIA (any)	21/1,342	1.6 (0.9-2.4)	32/1,303	2.5 (1.7-3.5)	0.102
Disabling stroke	9/1,342	0.7 (0.3-1.3)	20/1,303	1.5 (0.9-2.4)	0.033
Non-disabling stroke	12/1,342	0.9 (0.5-1.6)	13/1,303	1.0 (0.5-1.7)	0.941
Ischaemic stroke	20/1,342	1.5 (0.9-2.3)	26/1,303	2.0 (1.3-2.9)	0.398
Haemorrhagic stroke	1/1,342	0.1 (0.01-0.4)	6/1,303	0.5 (0.2-1.0)	0.053
TIA	6/1,342	0.5 (0.2-1.0)	9/1,303	0.7 (0.3-1.3)	0.565
Systemic embolism	4/1,342	0.3 (0.08-0.8)	4/1,303	0.3 (0.1-0.8)	1.000
BLEEDINGS					
Any bleeding	61/1,342	4.5 (3.5-5.8)	133/1,303	10.2 (8.6-12.0)	<0.0001
Fatal, life-threatening, major and clinically relevant non-major	50/1,342	3.7 (2.8-4.8)	129/1,303	9.9 (8.3-11.7)	<0.0001
Fatal, life-threatening and major bleedings	27/1,342	2.0 (1.3-2.9)	71/1,303	5.5 (4.3-6.8)	<0.0001
Fatal and life-threatening	13/1,342	1.0 (0.5-1.7)	31/1,303	2.4 (1.6-3.4)	0.0073
Major	14/1,342	1.0 (0.6-1.7)	40/1,303	3.1 (2.2-4.2)	0.0004
Minor	34/1,342	2.5 (1.8-3.5)	62/1,303	4.8 (3.7-6.1)	0.0031
LAAC procedure-related relevant adverse events	25/1,342	1.9 (1.2-2.7)	0/1,303	0 (0.0-0.3)	<0.0001

HOSPITAL STAYS					
Absolute number	639/1,342	47.6 (44.9-50.3)	910/1,303	69.8 (67.3-72.3)	<0.0001
Mean number per patient	2.6±2.2		3.0±2.4		0.016
ANTITHROMBOTICS					
Any oral anticoagulation	39/389 (10.0)		275/349 (78.8)		<0.0001
Vitamin K antagonists, n (%)	16 (4.1)		187 (53.6)		<0.0001
Non-vitamin K antagonists, n (%)	23 (5.9)		88 (25.2)		<0.0001
Acetylsalicylic acid, n (%)	265 (68.1)		119 (34.1)		<0.0001
Platelet inhibitors other than acetylsalicylic acid, n (%)	57 (14.7)		18 (5.2)		<0.0001
FUNCTIONAL STATUS AND QUALITY OF LIFE					
Activities in daily life (1-10)	6.0±2.1		5.3±2.2		<0.0001
Health status (1-10)	6.8±1.9		6.4±1.9		0.002
Limitation in daily life (1-10)	4.2±2.4		4.2±2.4		0.977

Events per 100 patient-years (95% credible interval).

LAAC: left atrial appendage closure; PY: patient years; TIA: transient ischaemic attack

Supplementary Table 3. Causes of death.

Variable	LAAC		Medical therapy		*p*-value
	n=500		n=500		
ALL-CAUSE DEATH	Events/PY	Observed rate	Events/PY	Observed rate	*p*-value
Death of any cause, n (%)	111	8.3%	151	11.6%	0.005
CARDIOVASCULAR & UNEXPLAINED DEATH					
Cardiovascular and unknown cause of death, n (%)	54	4.0%	84	6.5%	0.007
Procedural death	3	0.2%	0	0.0%	0.23
Sudden cardiac death	15	1.1%	7	0.5%	0.26
Congestive heart failure	11	0.8%	28	2.1%	0.02
Acute myocardial infarction	5	0.4%	6	0.5%	0.92
Stroke	6	0.4%	11	0.8%	0.40
Cardiovascular haemorrhage	2	0.1%	3	0.2%	0.87
Cardiovascular: other	0	0.0%	3	0.2%	0.20
Unexplained	12	0.9%	26	2.0%	0.06
NON-CARDIOVASCULAR DEATH					
Non-cardiovascular death, n (%)	57	4.3%	67	5.1%	0.32
Infection	26	1.9%	35	2.7%	0.36
Malignancy	16	1.2%	13	1.0%	0.93
Pulmonary	4	0.3%	3	0.2%	0.96
Renal	3	0.2%	7	0.5%	0.39
Hepatobiliary	1	0.1%	0	0.0%	0.63
Neurologic	0	0.0%	1	0.1%	0.59
Suicide	3	0.2%	0	0.0%	0.25
Trauma	2	0.1%	1	0.1%	0.87
Haemorrhage	0	0.0%	5	0.4%	0.07
Other non-cardiovascular	2	0.1%	2	0.2%	1.00

LAAC: left atrial appendage closure; PY: patient-years