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Epicardial left atrial appendage AtriClip occlusion reduces the incidence of stroke in patients with atrial fibrillation undergoing cardiac surgery

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Aims Left atrial appendage (LAA) occlusion has emerged as an interesting alternative to oral anticoagulation (OAC) for stroke prevention in patients with atrial fibrillation (AF). We report the safety, efficacy, and durability of concomitant device-enabled epicardial LAA occlusion during open-heart surgery. In addition to long-term follow-up, we evaluate the impact on stroke risk in this selected population.

Methods and results A total of 291 AtriClip devices were deployed epicardially in patients (mean CHA_2DS_2-VASc-Score: 3.1 ± 1.5) undergoing open-heart surgery (including isolated coronary artery bypass grafting, valve, or combined procedures) comprising of forty patients from a first-in-man device trial (NCT00567515) and 251 patients from a consecutive institutional registry thereafter. In all patients ($n = 291$), the LAA was successfully excluded and overall mean follow-up (FU) was 36 ± 23months (range: 1–97 months). No device-related complications were detected throughout the FU period. Long-term imaging work-up (computed tomography) in selected patients ≥5years post-implant (range: 5.1–8.1 years) displayed complete LAA occlusion with no signs of residual reperfusion or significant LAA stumps. Subgroup analysis of patients with discontinued OAC during FU ($n = 166$) revealed a relative risk reduction of 87.5% with an observed ischaemic stroke-rate of 0.5/100 patient-years compared with what would have been expected in a group of patients with similar CHA_2DS_2-VASc scores (expected rate of 4.0/100 patient-years). No strokes occurred in the subgroup with OAC.

Conclusion The long-term results from our first-in-man prospective human trial plus our institutional registry of epicardial LAA occlusion with the AtriClip in patients with AF undergoing cardiac surgery demonstrate the safety and durability of the procedure. In addition, our data are suggestive for the potential efficacy of LAA occlusion in reducing the incidence of stroke. If validated in future large randomized trials, routine LAA occlusion in patients undergoing cardiac surgery (with contraindications to treatment with oral anticoagulants) may represent a reasonable adjunct procedure to reduce the risk of future stroke.

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Keywords Atrial fibrillation • Stroke • Oral anticoagulation • Left atrial appendage occlusion • Warfarin • Epicardial • Non-vitamin-K-dependent oral anticoagulant (NOAC) • Bleeding • CHA2DS2-VASc-Score • HAS-BLED • Alternatives to anticoagulation

Introduction

For decades, the gold standard of stroke prevention in patients with non-valvular atrial fibrillation (AF) has been oral anticoagulation (OAC) therapy with vitamin K antagonists (VKAs). In addition, newer non-vitamin K oral anticoagulants (NOACs) with improved safety and comparable efficacy profiles have been introduced and currently become the new standard-of-care for many patients.[1–4]

However, relative or absolute contraindications for OAC, poor patient compliance, the necessity for continuous monitoring and an inherent risk of serious bleeding complications limit their applicability to selected patients that, importantly has led to a relative underuse particularly in older patients who are often at the highest risk of stroke.[5]

As a potential alternative to circumvent the use of OAC, novel therapy strategies targeting the left atrial appendage (LAA) in patients with AF for stroke prevention have become a major focus in recent years and are currently under intensive investigation.[6–10]

Based on the seminal report of Madden more than 60 years ago suggesting exclusion of the LAA for stroke prevention, various surgical and interventional approaches have emerged for LAA occlusion.[11] While initial data on various surgical methods of LAA exclusion such running sutures, purse-string or external ligation failed to provide reproducible and durable LAA occlusion,[12] percutaneous approaches have provided the first clinical evidence that LAA occlusion is a valid alternative to OAC therapy in AF patients. Both, the randomized, controlled, multicentre PROTECT-AF and Prospective Randomized Evaluation of the WATCHMAN LAA Closure Device in Patients With Atrial Fibrillation Versus Long Term Warfarin Therapy (PREVAIL) trials demonstrated non-inferiority or superiority of an interventional LAA occlusion device (Watchman Device, Boston Scientific, Maple Grove, MN, USA) compared with OAC for stroke risk reduction.[13–15] Based primarily on these trials, the 2012 Focused Update on the Guidelines for the Management of Atrial Fibrillation the European Society of Cardiology listed for the first time a Class IIb recommendation for percutaneous LAA occlusion in patients who are at high stroke risk and who are not amendable to long-term OAC.[16]

However, these catheter-based approaches fail to provide a 100% solution due to inherent limitations. The need for further optimization and a tailored individual patient approach becomes apparent[7,17,18] and the AtriClip (AtriCure, Inc., West Chester, PA, USA) provides a valid alternative to previous surgical techniques.[19–21] We report the long-term safety, efficacy, and durability of concomitant epicardial AtriClip LAA occlusion during open-heart surgery. In addition to long-term clinical and imaging FU after AtriClip implantation, we particularly focus on its potential impact on stroke risk in this selected population.

Methods

Study aim

The primary aim of this study was to evaluate the safety, efficacy, and long-term durability [assessed by computed tomography (CT) imaging] of epicardial LAA occlusion using the AtriClip device and its subsequent impact on stroke-prevention in patients with AF undergoing cardiac surgery.

Study design

The present study includes a total of 291 patients and combines long-term outcomes of two cohorts (see Supplementary material online, *Figure S1*):

(1) Prospective trial cohort (n = 40; TC) with long-term data from our first-in-man prospective AtriClip device trial (NCT00567515) and 3-month and 3-year FU data reported previously.[20,21]
(2) Institutional registry cohort (n = 251; RC) of consecutive implants with the AtriClip device after inclusion of the first 40 patients for the above mentioned prospective first-in-man-trial.

Ethics approval

All long-term data collection was performed prospectively and approved by the local ethics committee (Ref. KEK-ZH-Nr. 2015-0402) including a waiver of informed consent (for patients treated before 1 January 2014) and a signed informed consent (for patients treated after 1 January 2014).

Inclusion and exclusion criteria

The primary inclusion criterion for the trial was elective cardiac surgery in adult patients with AF.[20,21] The exclusion criteria for the trial cohort were reoperation, known LAA-thrombus, patients from the intensive care unit, history of pericarditis, recent myocardial infarction, (<90 days) and a known allergy to the device components. The registry included all patients in whom the AtriClip was implanted in the absence of contraindications.

Device description and delivery

The device has been described previously.[19–22] The AtriClip is currently available in four sizes (35, 40, 45, and 50 mm) and four deployment versions (standard, flexible, long, and quick deploy feature) facilitating minimal-invasive (e.g. thoracoscopic) approaches (*Figure 1*). Concomitant AtriClip delivery was performed as previously described[20,21] and successful LAA occlusion (defined as a threshold of a remaining residual stump in the LAA <10mm) was controlled visually during the procedure and

Table 1 Baseline demographic characteristics and risk factors

Characteristics	
Age (years)	70.7 ± 9.8 (34.3,94.2)
Height (cm)	170.5 ± 9.4 (135.0,197.0)
Weight (kg)	79.5 ± 15.8 (41.0, 150.1)
BMI (kg/m^2)	27.3 ± 4.8 (17.2,46.8)
Female	93/291 (32.0%)
Male	198/291 (68.0%)
Stroke risk calculation	
CHA_2DS_2-VASc score (categorical)	
0	9/291 (3.1%)
1	25/291 (8.6%)
2	77/291 (26.5%)
3	79/291 (27.1%)
4	56/291 (19.2%)
5	25/291 (8.6%)
6	15/291 (5.2%)
7	3/291 (1.0%)
8	2/291 (0.7%)
CHA_2DS_2-VASc score (continuous)	3.1 ± 1.5 (0.0,8.0)
$CHADS_2$ score (categorical)	
0	32/291 (11.0%)
1	100/291 (34.4%)
2	88/291 (30.2%)
3	41/291 (14.1%)
4	24/291 (8.2%)
5	4/291 (1.4%)
6	2/291 (0.7%)
$CHADS_2$ score (continuous)	1.8 ± 1.2 (0.0,6.0)
CHF	75/291 (25.8%)
History of hypertension	223/291 (76.6%)
Age ≥75 years	111/291 (38.1%)
Diabetes	44/291 (15.1%)
Previous TIA/ischaemic stroke	36/291 (12.4%)
LVEF (%)	56.6 ± 12.5 (291)
Vascular disease	47/291 (16.2%)
Age 65–74	114/291 (39.2%)
Female	93/291 (32.0%)
AF type	
Paroxysmal (≥90% with multiple episodes)	174/291 (59.8%)
Persistent	84/291 (28.9%)
Permanent	26/291 (8.9%)
No AF	7/291 (2.4%)
Previous N/OAC use	196/291 (67.4%)
Rhythm on admission	
SR	149/291 (51.2%)
AF	142/291 (48.8%)

Values are mean ± SD (minimum, maximum) or *n*/*N* (%).
AF, atrial fibrillation; SR, sinus rhythm; CHA_2DS_2-VASc, congestive heart failure, hypertension, age >75 years, age 65–74 years, diabetes, previous stroke/transient ischaemic attack, vascular disease, age 65-74yrs, and female sex; $CHADS_2$, CHA_2DS_2-VASc variables without vascular disease, age 65–74 years, and female sex; CHF, congestive heart failure; LVEF, left ventricular ejection fraction; TIA, transient ischaemic attack; N/OAC, new non-vitamin-K-dependent/oral anticoagulation; HAS-BLED, hypertension, abnormal renal or liver function, stroke, bleeding history, labile INR, elderly, and drugs or alcohol.

confirmed with simultaneous intraoperative transesophageal echocardiography (TEE) and if necessary repositioned. By the systematic use of intraoperative TEE and despite this pre-defined threshold (residual stump <10 mm), care was taken to stay significantly below or at best, not to create a measurable stump at all.

Data collection/follow-up questionnaire

The patients from the prospective trial ($n = 40$) were followed-up 3 months after surgery and then annually up to 3 years with clinical status evaluations, laboratory examination, electrocardiogram, and computed tomography (CT).[20,21] Patient data including baseline characteristics, perioperative variables, and postoperative outcome were collected from our database and the medical records of referring cardiologists/general practitioners. For the long-term FU a questionnaire with the following items were completed: survival, cause of death (cardiovascular, non-cardiovascular, device-related, etc.), major adverse cardiac and cerebrovascular events including stroke and systemic embolism, device-related complications, current rhythm status/changes and changes in the antithrombotic/antiaggregation therapy and current antithrombotic/antiaggregation regimen. Data from the questionnaires were collected from our database, the medical records of referring cardiologists/general practitioners, and/or by contacting the patients and referring physicians. In addition, survivors with a FU of ≥5 years were identified in our database ($n = 32$) and clinical FU with CT was conducted to evaluate the long-term impact of LAA occlusion.

Oral anticoagulation management and regime for discontinuation

Based on an institutional consent, OAC was ceased initially after 3 months. As a response to the promising results of the initial trial, the anticoagulation/anti therapy evolved over time. In patients operated after 2010, OAC was discontinued immediately after surgery unless it was otherwise indicated. Routinely following surgery, we administered Aspirin 100 mg/day then replaced OAC if patients were in sinus rhythm (SR) or aspirin 300 mg/day if patients were in AF.

Endpoints

The primary efficacy endpoint for stroke reduction was defined as the occurrence of ischaemic or haemorrhagic neurological events during FU (stroke). The primary safety endpoint was any device-related event (perioperatively, in-hospital, FU). Secondary endpoints included overall mortality; in addition complete obliteration of the LAA was assessed by CT. A composite secondary endpoint included death for cardiac reason or of unknown cause, systemic embolism, and haemorrhagic or ischaemic stroke.

Cardiac computed tomography protocols and data analysis

See Supplementary material online for details.

Assessment of stroke reduction

To assess the efficacy after epicardial LAA occlusion, time-intervals for each patient on or off OAC or antiplatelet treatment were recorded. Individual risks for stroke (expected stroke risk) according to the recorded time-intervals and the CHA_2DS_2-VASc-Score were calculated based on the published rates from the validation study.[23]

Statistics

In tables with descriptive statistics, continuous variables are presented as mean± standard deviation (SD) as well as medians and ranges. Groups

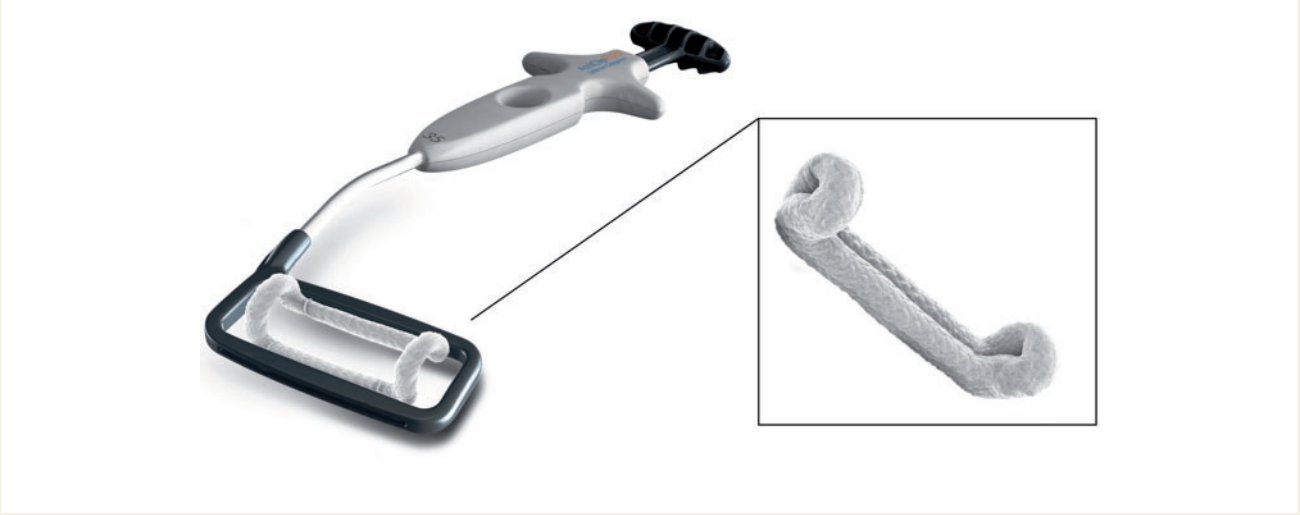

Figure 1 AtriClip device.

are compared using independent samples *t* tests and Mann–Whitney tests. Continuous variables were compared between first postoperative and last CT using the Wilcoxon signed ranks test. Categorical data are presented as frequencies with percentages and compared by Pearson χ^2 or Fisher's exact test as appropriate. Kaplan–Meier curves with 95% confidence interval (CI) were used to analyse freedom from stroke and compared graphically with expected survival at a constant hazard.

Standardized incidence ratios (SIR) were computed using indirect standardization and are reported with 95% Wilson CIs. Individual incidence rates of stroke in the reference population are reported with 95% CIs based on Poisson distribution.[24] Two-sided *P*-values less than 0.05 are considered statistically significant. Statistical analysis was performed using IBM SPSS Statistics, Version 22 (IBM Corp., Armonk, NY, USA) and R version 3.1.2.

Results

Study population and AtriClip implantation

A total of 291 patients (whole-cohort; WC) including forty patients from the initial first-in-man device trial ($n = 40$; TC) and 251 consecutive patients from our institutional registry ($n = 251$; RC) were included with a mean age of 70.7 ± 9.8years and a mean CHA_2DS_2-VASc-Score of 3.1 ± 1.5. All but seven patients had a clear documented history of AF (59.8% paroxysmal, 28.9% persistent, and 8.9% permanent). Of these, 51.2% of patients were in sinus-rhythm when admitted and 67.4% of patients were on treatment with oral anticoagulants preoperatively (*Table 1*). In five patients with risk factors for AF but unclear history of AF 'prophylactic' LAA occlusion was performed and in two patients with intra-operatively detected thrombus within the LAA therapeutic clipping of the LAA was performed. In addition to LAA occlusion, 195 patients (67%) underwent concomitant surgical ablation, while 96 patients (33.0%) did not (please see Supplementary material online and Supplementary material online, *Tables S1–S4* for further details). The types of surgical procedures performed concomitantly with LAA occlusion are summarized in *Table 2*. The mean and median follow-up (FU) for the whole cohort was 36.1 ± 23.1 months and 31.1 months (0.7–97.1 months).

Table 2 Type of primary surgery and concomitant surgical ablation

Isolated CABG	59/291 (20.3%)
Combined procedures (CABG and valve/s)	63/291 (21.7%)
Single or multiple valve procedures	122/291 (41.9%)
Other non-valvular procedures	42/291 (14.4%)
Surgical ablation	195/291 (67.0%)
Biatrial MAZE	40/291 (13.8%)
Left atrial MAZE	51/291 (17.5%)
PVI	104/291 (35.7%)
No surgical ablation	96/291 (33.0%)

Values are *n*/*N* (%).
CABG, coronary artery bypass grafting; AF, atrial fibrillation; PVI, pulmonary vein isolation.

The AtriClip device was implanted in all patients ($n = 291$) and no device-related perioperative complications occurred. Intraoperative TEE confirmed successful AtriClip delivery and complete LAA-closure without residual perfusion or substantial LAA stump (>1.0 cm) in all patients.

Clinical outcomes and follow-up

For the whole-cohort ($n = 291$), early in-hospital mortality was 5.5% ($n = 16$) with 3.8% ($n = 11$) due to cardiovascular-causes (*Table 3*). The long-term mortality in the remaining 275 survivors was 13.1% ($n = 36$) with 8.7% ($n = 24$) attributed to death from cardiovascular-causes or un-explained.

Follow-up was complete in 273 of 275 survivors (99.3%). The overall mortality in the whole-cohort during the entire study period

Table 3 In-hospital, follow-up, and overall clinical outcomes

	In-hospital events	Follow-up events	Overall events
Efficacy[a]	16/291 (5.5%)	26/291 (8.9%)	42/291 (14.4%)
Ischaemic stroke	3/291 (1.0%)	2/291 (1.7%)	5/291 (1.7%)
TIA	0/291 (0%)	4/291 (1.4%)	4/291 (1.4%)
Haemorrhagic stroke	2/291 (0.7%)	0/291 (0%)	2/291 (0.7%)
Cardiovascular death	11/291 (3.8%)	17/291 (5.8%)	28/291 (9.6%)
Non-cardiovascular death	5/291 (1.7%)	12/291 (4.1%)	17/291 (5.8%)
Unexplained death	0/291 (0%)	7/291 (2.4%)	7/291 (2.4%)
Safety end point	0/291 (0%)	0/291 (0%)	0/291 (0%)

[a]Defined as composite of death for cardiac/unknown reason, or haemorrhagic/ischaemic stroke.
Values are *n*/*N* (%).

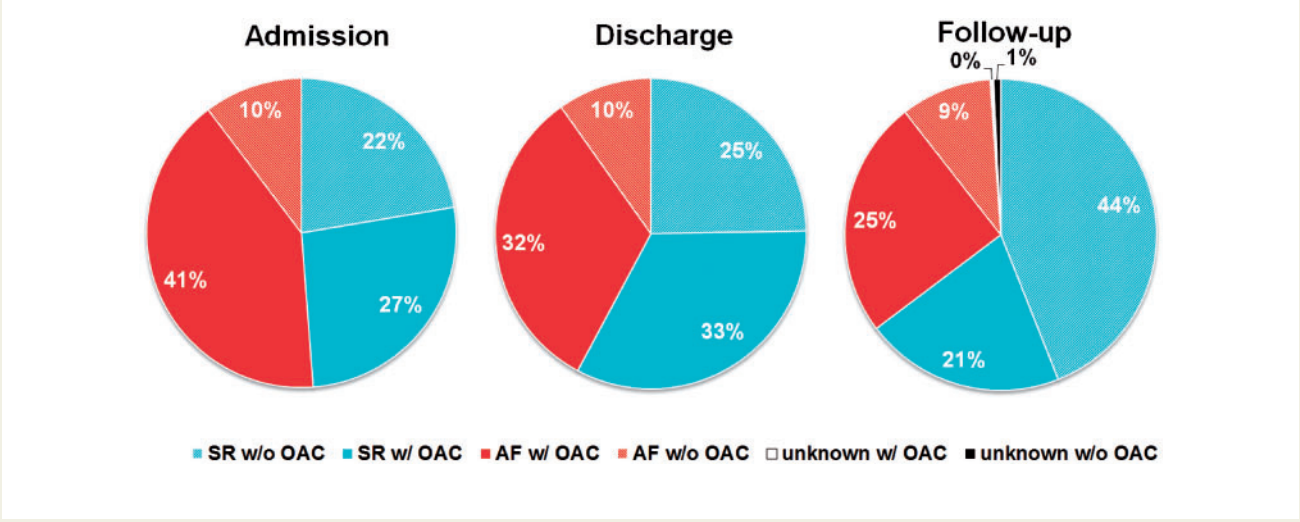

Figure 2 Rhythm and oral anticoagulation status at admission, discharge, and follow up.

was 17.9% (*n* = 52) with 9.6% (*n* = 28) from cardiovascular-causes or un-explained (2.4%, *n* = 7) deaths (please see Supplementary material online, *Table S5* for full list of deaths/events and its causes).

While 57.8% (159/275) of patients were in SR when discharged, 64.8% (177/273) of patients presented with SR at FU. 65.5% (180/275) of all patients were discharged on OAC and 45.8% (125/273) of patients were on OAC at FU (*Figure 2*, Supplementary material online, *Table S6*).

Safety

There were no peri-procedural device-related complications in any of the patients. Complete LAA occlusion was achieved in all patients. No device-related complications occurred during the follow-up period.

Durability

To further assess the long-term durability of LAA occlusion with the AtriClip device, thirty-two survivors (*n* = 20 trial-cohort, *n* = 12 registry-cohort), each with a FU ≥5years were identified in our database out of which long-term CT was available in 23/32 patients (71.9%; 5.1–8.1 years post-implant. The CT confirmed durable and complete LAA occlusion with no signs of a substantial residual stump or reperfusion. When compared with earlier serial CT scans of these patients, the AtriClip device appeared to maintain a stable position, showing no late migration or displacement due to material-fatigue (see Supplementary material online, *Table S7*, *Figures 3* and *4*).

Occurrence of stroke

Occurrence of perioperative stroke

Peri-operatively, five strokes were observed with three of ischaemic (embolism from a large left-atrial thrombus, intraoperative hypoxia during cardiopulmonary-bypass and intraoperative air-embolism) and two of haemorrhagic origin (under OAC and antiplatelet therapy with biventricular assist-device and secondary intracranial bleeding after preoperative ischaemic stroke due to septic emboli; for further details see Supplementary material online, *Table S3*). However, none of these were device-related or AF/LAA-related (*Table 3* and Supplementary material online, *Table S5*).

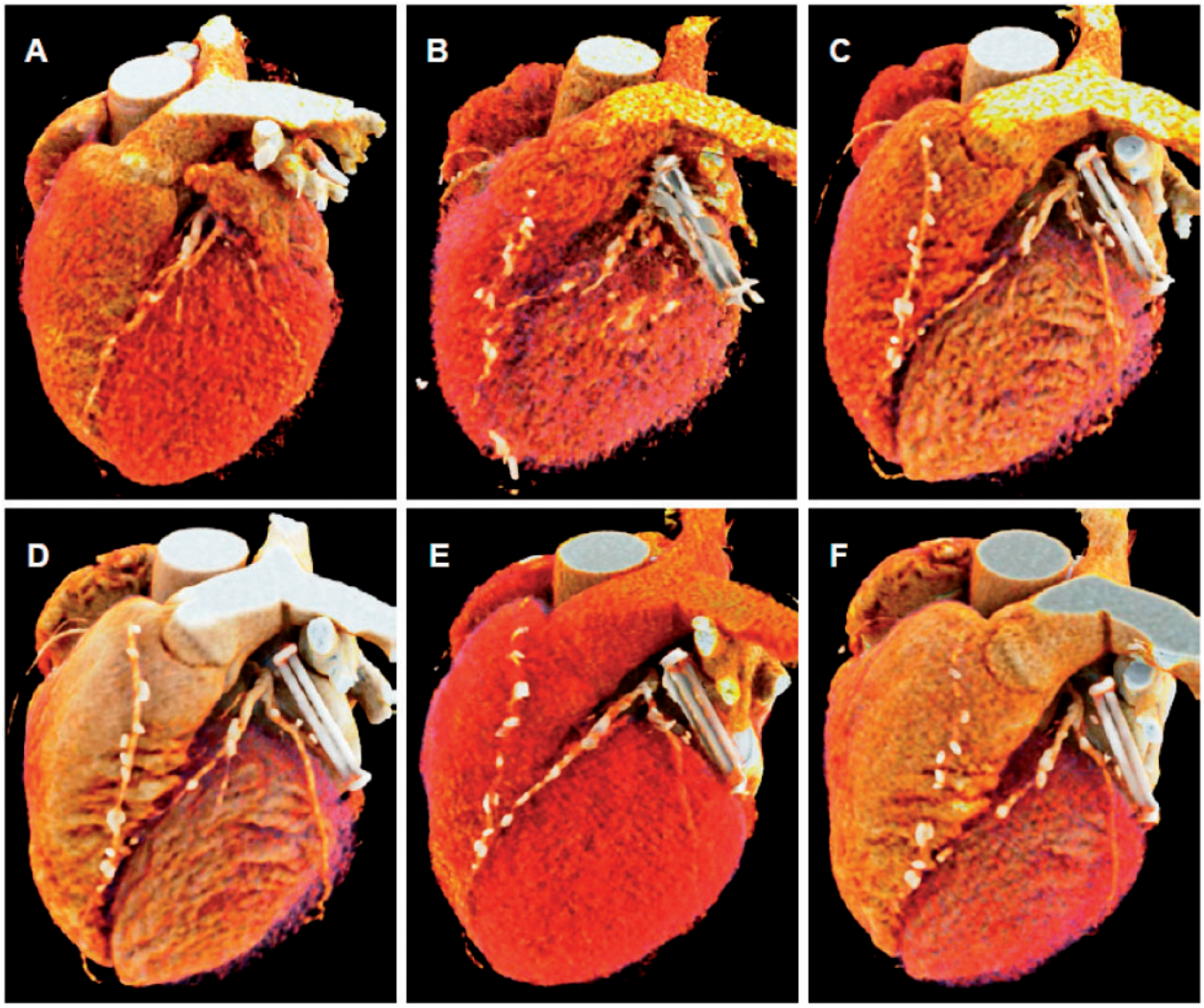

Figure 3 Three-dimensional CT images with cinematic rendering in a 76-year-old male patient before (*A*), immediately after surgery (*B*), after 3 months (*C*), 1 year (*D*), 3 years (*E*), and 7.5 years (*F*) of AtriClip implantation.

Strokes during follow-up

During FU, (survivors of the WC; $n = 275$) only two strokes occurred. One patient sustained a lethal ischaemic stroke most likely due to thromboembolism of cardiac-origin. This patient was on anti-platelet therapy throughout the follow-up period (25.8 months) and the last documented rhythm was SR. The second ischaemic stroke occurred in a patient with recurrent AF and could also have been of cardiac-origin. At the time of this event the patient was off OAC and was being treated with aspirin only.

Impact of AtriClip left atrial appendage occlusion on stroke prevention

Whole-cohort

Based on the individual CHA_2DS_2-VASc-Scores and FU times with or without OAC and/or antiplatelet therapy, the predicted ischaemic stroke rate was 2.9 events/100 patient-years in the whole-cohort (WC; $n = 275$), corresponding to an expected total of 24 ischaemic strokes. In contrast, only two events of ischaemic stroke were observed accounting for a rate of only 0.2/100 patient-years (95% CI 0.1–0.9). This represents a 14.5-fold (93.1%) relative risk reduction when compared with the expected stroke rate (*Tables 4* and *5*, *Figure 5*).

Patients without oral anticoagulation during follow-up

In the subgroup analysis of 166 patients without OAC (mean CHA_2DS_2-VASc score of 3.2) only two ischaemic strokes could be observed accounting for an observed rate of 0.5/100 patient-years (95% CI 0.1–1.7). According to the expected ischaemic stroke rate of 4.0/100 patient-years based on the individual CHA_2DS_2-VASc-Scores and time-intervals, the expected number of strokes was

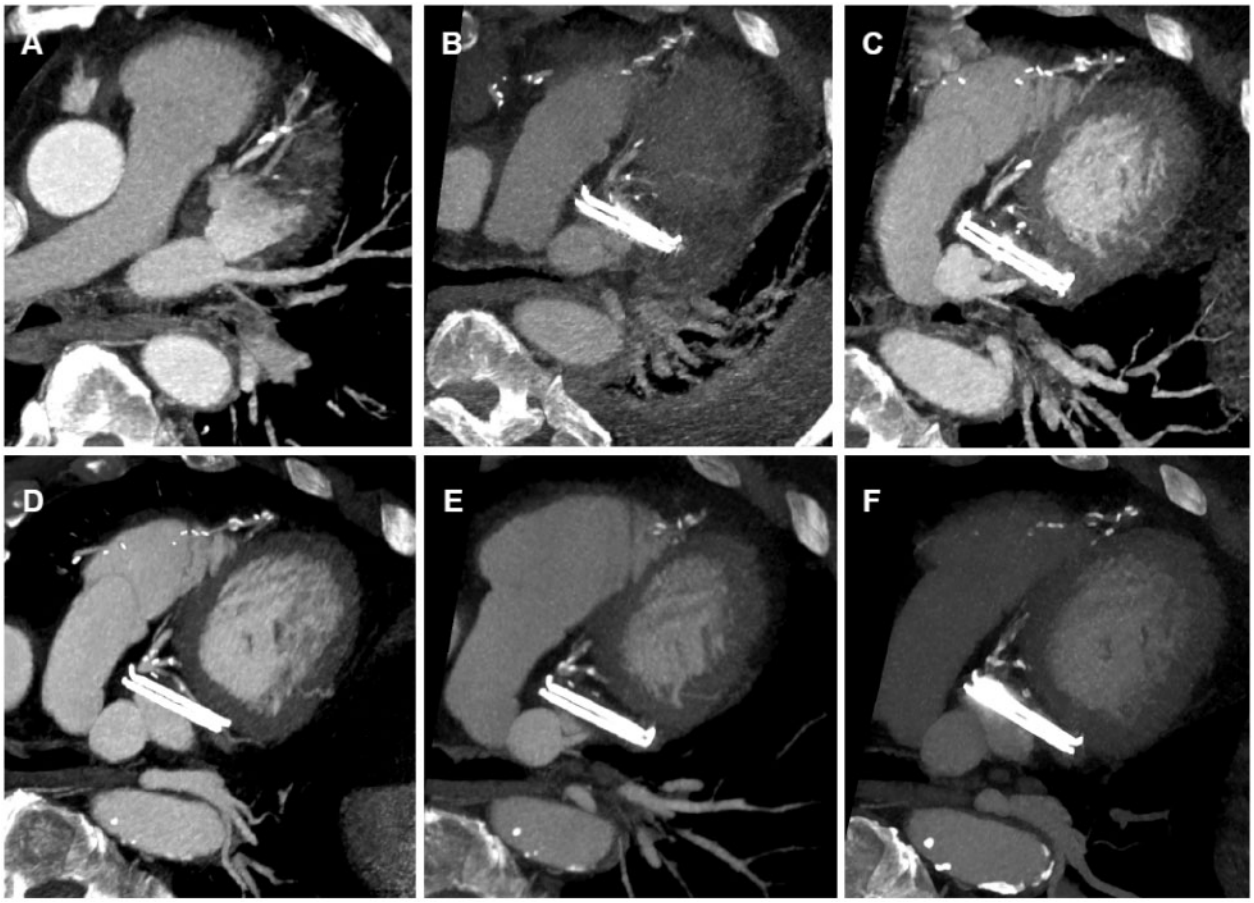

Figure 4 Oblique transverse thin maximum intensity projection in the same patient as in *Figure 3* before (*A*), immediately after surgery (*B*), after 3 months (*C*), 1 year (*D*), 3 years (E), and 7.5 years (*F*) of AtriClip implantation.

calculated to be 17.5 events. Thus, a relative risk reduction of 87.5% for ischaemic strokes was achieved by AtriClip enabled LAA occlusion (*Table 5*, *Figure 5*). Kaplan–Meier curves for freedom from stroke with a 95% CI are shown in *Figure 6* and compared with expected survival at a constant rate of 4.0/100 patient-years.

Patients with oral anticoagulation during follow-up

In the subgroup of patients with OAC (mean CHA_2DS_2-VASc score of 2.9) during FU, no ischaemic strokes occurred 0.0/100 patient-years; 95% CI, 0–1.2). According to the predicted ischaemic stroke rate of 1.7/100 patient-years, the expected number of strokes was calculated to be 6.5 events in this subgroup (*Table 5*).

Discussion

The LAA is the primary source for thromboembolic events in patients with AF.[25] Therefore, besides the standard-of-care with oral anticoagulation (OAC), novel treatment strategies targeting the LAA for stroke prevention have become a major interest of investigation.[6–10] Recent seminal reports from the interventional PROTECT-AF and PREVAIL trials utilizing the percutaneous Watchman LAA occlusion device were the first to confirm the importance of the role of the LAA as the source of stroke in selected AF patients.[13–15,26] When compared with OAC, in the PROTECT-AF trial, the Watchman device met criteria for both non-inferiority and superiority for preventing the combined outcome of stroke, systemic embolism, and cardiovascular death, and thus established the basis for targeting the LAA as an alternative strategy to OAC.[15]

Surgical LAA occlusion has failed to prove efficacy in stroke prevention,[10] and available studies primarily report safety- and feasibility data. Simple suture epicardial ligation, endo-or epicardial oversewing, and stapling devices for LAA occlusion provided rather low success rates with a high degree of incomplete occlusion or the creation of thrombogenic "pouches" at the base of the occluded appendage,[27] leading to a potentially even more dangerous situation, confirmed by multiple studies.[12,28]

The study provides the first data on the potential efficacy of epicardial LAA closure in regard to stroke-prevention in patients with AF undergoing cardiac surgery. Based on the expected risk for stroke,[23]

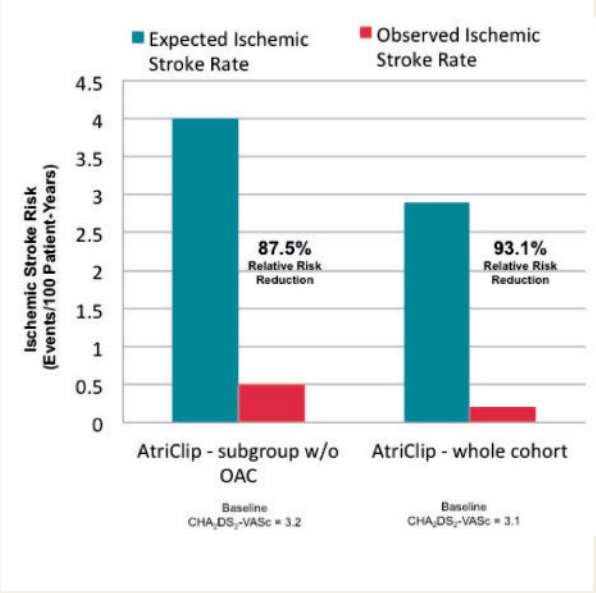

Figure 5 Relative Risk Reduction—AtriClip (subgroup w/o OAC) vs. AtriClip (whole cohort).

Table 4 Clinical outcomes during FU

	Events/Patient-years	Observed rate[a]
Efficacy[b]	26/826.8	3.2 (2.2–4.6)
Ischaemic stroke	2/826.8	0.2 (0.1–0.9)
TIA	4/826.8	0.5 (0.2–1.2)
Haemorrhagic stroke	0/826.8	0 (0–0.5)
Cardiovascular death	17/826.8	2.1 (1.3–3.3)
Non-cardiovascular death	12/826.8	1.5 (0.8–2.6)
Unexplained death	7/826.8	0.9 (0.4–1.8)
Safety	0/826.8	0 (0–0.5)

[a]Events per 100 patient-years (95% Wilson CI).
[b]Defined as composite of death for cardiac/unknown reason, or haemorrhagic/ischaemic stroke.

our data display a significant risk reduction. These findings may be of two-fold interest as they support the principal therapeutic concept of targeting the LAA (either interventionally or surgically) in AF patients to reduce stroke, but more importantly they also provide first encouraging data of surgical, device-enabled LAA occlusion to reduce the incidence of stroke associated with AF. This may warrant further evaluation in a prospective, randomized trial but may also pave the way for future direct comparison against interventional (e.g. Watchman) or pharmacological approaches (i.e. NOACs), especially since stand-alone, minimally-invasive AtriClip LAA occlusion in patients with non-valvular AF has already been established.[29,30]

Our institutional anticoagulation/antiaggregation regimen evolved over time,[20,21] In contrast to the interventional RCT's evaluating the Watchman device, in whom patients received OAC for only 6 weeks post device implantation per protocol,[13–15] more of our patients required at least short-term continuation of OAC and/or antiplatelet therapy for other surgical indications such as valve implantations or surgical ablations. In the absence of such indications, OAC was initially stopped at 3 months post LAA occlusion. However, after our first institutional results became available demonstrating the safety and efficacy of the AtriClip device, our practice was to discontinue OAC immediately postoperatively. It should be mentioned, however, that at the beginning of our study referring physicians did not always adhere to our recommendations due the lack of available supporting data or any guideline recommendations. The reluctance to discontinue OAC by the referring physicians improved substantially after the favorable outcomes and low complication rates of stroke following discontinuation of OAC in the Watchman trials.[14,31]

Current status of epicardial left atrial appendage AtriClip occlusion

Since its introduction in our first-in-man prospective device trial in 2007 (NCT00567515), the epicardial AtriClip LAA Exclusion System has proven to be a valid tool for safe and durable LAA occlusion in patients undergoing cardiac surgery.[21] Consistent with our findings, Ailawadi *et al.*[19] reported excellent short-term safety and durability outcomes in a prospective, but non-randomized multicentre study. Moreover, we recently provided 3-year FU data from our initial trial cohort that documented 100% durability and complete LAA occlusion by CT imaging.[20]

The present study confirms our previous findings regarding safety and durability of the surgical AtriClip and provides promising data on the potential efficacy for stroke prevention in patients in whom OAC was discontinued.

However, so far, available data remain scarce in the literature and therefore, were not included in any guidelines or consensus statements apparently as large prospective, randomized trials have not yet been performed.[32] To address this deficiency, the LAA Occlusion Study (LAAOS) III has recently been initiated. This is a large randomized trial with 4700 patients (NCT01561651), comparing concomitant surgical LAA occlusion (including AtriClip application) to no LAA occlusion in patients with AF who are undergoing routine cardiac surgery.[33] Furthermore, just recently, 'The Stroke Feasibility Study' (NCT01997905),[34] a prospective, multicentre study of stand-alone minimally-invasive AtriClip LAA occlusion for non-valvular AF patients, was initiated with a larger pivotal trial focusing on stroke prevention to follow.

Future implications

To date, recommendations on LAA closure (either percutaneous or surgical) for stroke-prevention are limited in the current guidelines due to lack of conclusive data. According to the most recent 2016 ESC Guidelines for the management of AF, interventional LAA occlusion may be considered in patients with high stroke risk and contraindications for long-term OAC (Class IIb)[35]; however, interestingly both criteria were not met in PROTECT-AF and thus evidence for this subgroup of patients is still lacking.[13–15] In contrast, the 2014 AHA/ACC/HRS Guideline does not make any statement for interventional LAA closure at all.[36] However, both guidelines state that surgical LAA excision may be considered in patients undergoing

Table 5 Subgroup analysis of observed ischaemic stroke rate vs. expected ischaemic stroke rate (based on CHA_2DS_2-VASc and $CHADS_2$ score) with and without OAC

	Ischaemic stroke		CHA_2DS_2-VASc				$CHADS_2$			
	Events/ Patient-years	Observed Rate[a]	Score	Expected events/ Patient-years	Expected rate[a]	Standardized incidence ratio (SIR)[b]	Score	Expected events/ Patient-years	Expected rate[a]	Standardized incidence ratio (SIR)[b]
Subgroup without oral anticoagulation	2/436.9	0.5 (0.1–1.7)	3.2	17.5/436.9	4.0	0.1 (0.3–0.4)	1.9	19.4/436.9	4.4	0.1 (0.03–0.4)
Subgroup with oral anticoagulation	0/382.9	0 (0–1.0)	2.9	6.5/382.9	1.7	0 (0–0.6)	1.7	7.5/382.9	2.0	0 (0–0.5)

[a]Events per 100 patient-years (95% Wilson CI).
[b]With 95% Wilson CI.

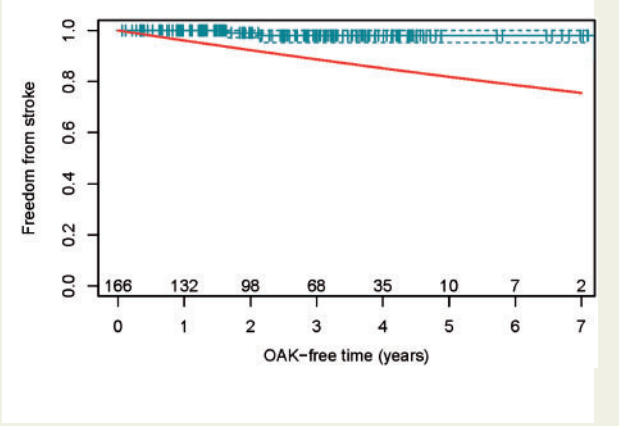

Figure 6 Freedom from stroke with 95% CI and expected survival at a constant hazard per patient year.

open-heart surgery (Class IIb; Evidence Level B).[35,36] This non-uniformity demonstrates the substantial lack of adequate clinical evidence indicating that further surgical, interventional, or combined trials are of high importance.

In this regard, it is to mention that our mixed surgical cohort also included patients with valvular AF. Although current guidelines still lack uniform definitions of the etiology of AF,[16,36,37] such valvular AF patients carry an even higher risk of stroke than the non-valvular AF patients like those in the WATCHMAN trials[6,13,15] because the incidence of stroke is underestimated by the CHA_2DS_2-VASc score alone.[25,38]

We strongly believe that only a Heart Team approach will generate the required clinical evidence for the role of LAA closure in AF.[17,39] As successfully highlighted in other interdisciplinary programs such as transcatheter aortic valve implantation or MitraClip,[40,41] it is important to establish an outcome-oriented collaboration between cardiologists and surgeons focusing on technique, device, and patient selection. Thus, prior to any type of procedure, patient-specific anatomical, and morphological considerations are mandatory to define a patient-tailored treatment strategy, and thereby ultimately ensuring a safe, complete, and durable LAA occlusion in all patients.

Conclusions

In our study, the AtriClip device demonstrated excellent safety, efficacy and long-term durability of LAA closure. Computed tomography scans in selected patients from our initial clinical trial cohort and from our subsequent RC revealed a 100% complete and durable LAA-occlusion after ≥5years. Additionally, none of our patients had any device-related complications reported. This is an important new observation because most of the previously reported surgical techniques often resulted in incomplete LAA closure[42,43] as well as procedural complications such as bleeding.[12,28] Moreover, the present study suggests its potential efficacy in reducing the future risk of stroke in patients with AF undergoing concomitant cardiac surgery. If validated in future prospective, randomized trials, routine LAA-closure in patients undergoing cardiac surgery may represent a reasonable adjunct strategy to reduce the future risk of stroke.

Study limitations

The study has several limitations: First, owing to its single-centre experience and non-randomized, observational design, all established disadvantages apply. Obviously, the follow-up of the consecutive RC was not as systematic and rigorous as in the initial prospective trial. However, on the other hand the available data on these 251 consecutive patients represent a real-world setting without any selection bias and therefore add clinical value. Next, data from large randomized controlled trials are needed to validate our findings and to evaluate the AtriClip device in regard to stroke-prevention compared with current pharmacological and interventional therapies. Finally, a possible confounding effect of concomitant surgical ablations on the favorable outcomes cannot be completely ruled out.

Supplementary material

Supplementary material is available at *Europace* online.

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References

1. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A *et al.* Dabigatran versus warfarin in patients with atrial fibrillation. *New Engl J Med* 2009;**361**:1139–51.
2. Giugliano RP, Ruff CT, Braunwald E, Murphy SA, Wiviott SD, Halperin JL *et al.* Edoxaban versus warfarin in patients with atrial fibrillation. *New Engl J Med* 2013;**369**:2093–104.
3. Granger CB, Alexander JH, McMurray JJV, Lopes RD, Hylek EM, Hanna M *et al.* Apixaban versus warfarin in patients with atrial fibrillation. *New Engl J Med* 2011;**365**:981–92.
4. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W *et al.* Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *New Engl J Med* 2011;**365**:883–91.
5. Gladstone DJ, Bui E, Fang J, Laupacis A, Lindsay MP, Tu JV *et al.* Potentially preventable strokes in high-risk patients with atrial fibrillation who are not adequately anticoagulated. *Stroke* 2009;**40**:235–40.
6. Holmes DR Jr, Schwartz RS. Left atrial appendage occlusion eliminates the need for warfarin. *Circulation* 2009;**120**:1919–26; discussion 26.
7. Masoudi FA, Calkins H, Kavinsky CJ, Drozda JP Jr, Gainsley P, Slotwiner DJ *et al.* 2015 ACC/HRS/SCAI left atrial appendage occlusion device societal overview. *J Am Coll Cardiol* 2015;**66**:1497–513.
8. Meier B, Blaauw Y, Khattab AA, Lewalter T, Sievert H, Tondo C *et al.* EHRA/EAPCI expert consensus statement on catheter-based left atrial appendage occlusion. *Europace* 2014;**16**:1397–416.
9. Whitlock RP, Healey JS, Connolly SJ. Left atrial appendage occlusion does not eliminate the need for warfarin. *Circulation* 2009;**120**:1927–32; discussion 32.
10. Whitlock RP, Healey JS, Holmes DR. Left atrial appendage occlusion debate revisited. *Circulation* 2015;**131**:756–61.
11. Madden JL. Resection of the left auricular appendix: a prophylaxis for recurrent arterial emboli. *J Am Med Assoc* 1949;**140**:769–72.
12. Kanderian AS, Gillinov AM, Pettersson GB, Blackstone E, Klein AL. Success of surgical left atrial appendage closure: assessment by transesophageal echocardiography. *J Am Coll Cardiol* 2008;**52**:924–9.
13. Holmes DR Jr, Kar S, Price MJ, Whisenant B, Sievert H, Doshi SK *et al.* Prospective randomized evaluation of the watchman left atrial appendage closure device in patients with atrial fibrillation versus long-term warfarin therapy: the PREVAIL trial. *J Am Coll Cardiol* 2014;**64**:1–12.
14. Holmes DR, Reddy VY, Turi ZG, Doshi SK, Sievert H, Buchbinder M *et al.* Percutaneous closure of the left atrial appendage versus warfarin therapy for prevention of stroke in patients with atrial fibrillation: a randomised non-inferiority trial. *Lancet* 2009;**374**:534–42.
15. Reddy VY, Sievert H, Halperin J, Doshi SK, Buchbinder M, Neuzil P *et al.* Percutaneous left atrial appendage closure vs warfarin for atrial fibrillation: a randomized clinical trial. *JAMA* 2014;**312**:1988–98.
16. Camm AJ, Lip GY, De Caterina R, Savelieva I, Atar D, Hohnloser SH *et al.* 2012 focused update of the ESC guidelines for the management of atrial fibrillation: an update of the 2010 ESC guidelines for the management of atrial fibrillation–developed with the special contribution of the European Heart Rhythm Association. *Europace* 2012;**14**:1385–413.
17. Salzberg SP, Grunenfelder J, Emmert MY. Left atrial appendage closure to prevent stroke in patients with atrial fibrillation: a call for the heart team approach. *EP Europace* 2015;**17**:1880–1881.
18. Emmert MY, Salzberg SP. Left atrial appendage occlusion device societal overview: the surgeon's comment. *J AmColl Cardiol* 2016;**67**:124.
19. Ailawadi G, Gerdisch MW, Harvey RL, Hooker RL, Damiano RJ Jr, Salamon T *et al.* Exclusion of the left atrial appendage with a novel device: early results of a multicenter trial. *J Thorac Cardiovasc Surg* 2011;**142**:1002–9, 1009.e1.
20. Emmert MY, Puippe G, Baumuller S, Alkadhi H, Landmesser U, Plass A *et al.* Safe, effective and durable epicardial left atrial appendage clip occlusion in patients with atrial fibrillation undergoing cardiac surgery: first long-term results from a prospective device trial. *Eur J Cardiothorac Surg* 2014;**45**:126–31.
21. Salzberg SP, Plass A, Emmert MY, Desbiolles L, Alkadhi H, Grunenfelder J *et al.* Left atrial appendage clip occlusion: early clinical results. *J Thorac Cardiovasc Surg* 2010;**139**:1269–74.
22. Salzberg SP, Gillinov AM, Anyanwu A, Castillo J, Filsoufi F, Adams DH. Surgical left atrial appendage occlusion: evaluation of a novel device with magnetic resonance imaging. *Eur J Cardiothorac Surg* 2008;**34**:766–70.
23. Olesen JB, Lip GY, Hansen ML, Hansen PR, Tolstrup JS, Lindhardsen J *et al.* Validation of risk stratification schemes for predicting stroke and thromboembolism in patients with atrial fibrillation: nationwide cohort study. *BMJ* 2011;**342**:d124.
24. Baum M, Sylvester R. Statistics with confidence: confidence intervals and statistical guidelines. Martin J. Gardner and Douglas G. Altman (eds), British medical journal, London, 1989. no. of pages: 140. *Stat Med* 1990;**9**:344–5.
25. Blackshear JL, Odell JA. Appendage obliteration to reduce stroke in cardiac surgical patients with atrial fibrillation. *Ann Thorac Surg* 1996;**61**:755–9.
26. Reddy VY, Doshi SK, Sievert H, Buchbinder M, Neuzil P, Huber K *et al.* Percutaneous left atrial appendage closure for stroke prophylaxis in patients with atrial fibrillation: 2.3-year follow-up of the PROTECT AF (Watchman Left Atrial Appendage System for Embolic Protection in Patients with Atrial Fibrillation) Trial. *Circulation* 2013;**127**:720–9.
27. Healey JS, Crystal E, Lamy A, Teoh K, Semelhago L, Hohnloser SH *et al.* Left Atrial Appendage Occlusion Study (LAAOS): results of a randomized controlled pilot study of left atrial appendage occlusion during coronary bypass surgery in patients at risk for stroke. *Am Heart J* 2005;**150**:288–93.
28. García-Fernández Mn, Pérez-David E, Quiles J, Peralta J, García-Rojas I, Bermejo J *et al.* Role of left atrial appendageobliteration in stroke reductionin patients with mitral valve prosthesis: a transesophageal echocardiographic study. *J Am Coll Cardiol* 2003;**42**:1253–8.
29. Moss J. Left atrial appendage exclusion for prevention of stroke in atrial fibrillation: review of minimally invasive approaches. *Curr Cardiol Rep* 2014;**16**:1–10.
30. Ohtsuka T, Ninomiya M, Nonaka T, Hisagi M, Ota T, Mizutani T. Thoracoscopic stand-alone left atrial appendectomy for thromboembolism prevention in nonvalvular atrial fibrillation. *J Am Coll Cardiol* 2013;**62**:103–7.
31. Reddy VY, Holmes D, Doshi SK, Neuzil P, Kar S. Safety of percutaneous left atrial appendage closure: results from the watchman left atrial appendage system for embolic protection in patients with AF (PROTECT AF) clinical trial and the continued access registry. *Circulation* 2011;**123**:417–24.
32. Tsai YC, Phan K, Munkholm-Larsen S, Tian DH, La Meir M, Yan TD. Surgical left atrial appendage occlusion during cardiac surgery for patients with atrial fibrillation: a meta-analysis. *Eur J Cardiothorac Surg* 2015;**47**:847–54.
33. Whitlock R, Healey J, Vincent J, Brady K, Teoh K, Royse A *et al.* Rationale and design of the left atrial appendage occlusion study (LAAOS) III. *Ann Cardiothorac Surg* 2014;**3**:45–54.
34. Ramlawi B, Abu Saleh WK, Edgerton J. The left atrial appendage: target for stroke reduction in atrial fibrillation. *Methodist DeBakey Cardiovasc J* 2015;**11**:100–3.
35. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B *et al.* 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Europace* 2016;**18**:1609–78.
36. January CT, Wann LS, Alpert JS, Calkins H, Cigarroa JE, Cleveland JC *et al.* 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. *Circulation* 2014;**130**:e199–267.
37. Molteni M, Polo Friz H, Primitz L, Marano G, Boracchi P, Cimminiello C. The definition of valvular and non-valvular atrial fibrillation: results of a physicians' survey. *Europace* 2014;**16**:1720–5.
38. Whitlock RP, Sun JC, Fremes SE, Rubens FD, Teoh KH; American College of Chest P. Antithrombotic and thrombolytic therapy for valvular disease: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2012;**141**:e576S–600S.
39. Holmes DR Jr, Rich JB, Zoghbi WA, Mack MJ. The heart team of cardiovascular care. *J Am Coll Cardiol* 2013;**61**:903–7.
40. Coylewright M, Mack MJ, Holmes DR Jr, O'Gara PT. A call for an evidence-based approach to the Heart Team for patients with severe aortic stenosis. *J Am Coll Cardiol* 2015;**65**:1472–80.
41. Holmes DR Jr, Mohr F, Hamm CW, Mack MJ. Venn diagrams in cardiovascular disease: the Heart Team concept. *Eur Heart J* 2014;**35**:66–8.
42. Aryana A, Singh SK, Singh SM, Gearoid O'Neill P, Bowers MR, Allen SL *et al.* Association between incomplete surgical ligation of left atrial appendage and stroke and systemic embolization. *Heart Rhythm* 2015;**12**:1431–7.
43. Schneider B, Stöllberger C, Sievers HH. Surgical closure of the left atrial appendage—a beneficial procedure? *Cardiology* 2005;**104**:127–32.