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CLINICAL RESEARCH
Interventional cardiology

Left atrial appendage occlusion with the Amplatzer™ Amulet™ device: full results of the prospective global observational study

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Aims To evaluate the safety and efficacy of left atrial appendage occlusion (LAAO) with the Amplatzer™ Amulet™ occluder.

Methods and results Patients with atrial fibrillation eligible for LAAO were recruited to a prospective global study. Implant procedures were undertaken with echocardiographic guidance. Transoesophageal echocardiography (TOE) was undertaken 1–3 months post-LAAO. Implant and follow-up TOEs were evaluated by a CoreLab. The primary endpoint was a composite of ischaemic stroke and cardiovascular death at 2 years. Serious adverse events were adjudicated by an independent clinical events committee. A total of 1088 patients were enrolled, aged 75.2 ± 8.5 years; 64.5% were male. CHA_2DS_2-VASc and HAS-BLED scores were 4.2 ± 1.6 and 3.3 ± 1.1, respectively. A total of 71.7% had prior major bleeding, and 82.8% had contraindications to oral anticoagulants. Implant success was 99.1%. Major adverse events (≤7 days post-procedure) occurred in 4.0%, including death (0.3%), stroke (0.4%), major vascular (1.3%), and device embolization (0.2%). A total of 80.2% of patients were discharged on antiplatelet therapy alone. Peridevice flow was <3 mm in 98.4% at follow-up TOE. Device-related thrombus (DRT) was seen in 1.6% of cases. Cardiovascular death or ischaemic stroke occurred in 8.7% of patients at 2 years. The ischaemic stroke rate was 2.2%/year—a 67% reduction compared to the CHA2DS2-VASc predicted rate. Major bleeding (Bleeding Academic Research Consortium type ≥ 3) occurred at rates of 10.1%/year (year 1) and 4.0%/year (year 2).

Conclusion Following LAAO with the Amplatzer Amulet device, the ischaemic stroke rate was reduced by 67% compared to the predicted risk. Closure was complete in 98.4% of cases and DRT seen in only 1.6%.

Keywords Antithrombotic treatment • Bleeding • Death • LAA closure • Stroke

Introduction

Atrial fibrillation (AF) is a highly prevalent arrhythmia. There will be 13 million adults with AF in the European Union by 2030.[1] It is estimated that 10–40% of AF patients are hospitalized each year.[2] Atrial fibrillation increases the risk of ischaemic stroke by 3–5 times,[3] and these AF-related strokes are twice as likely to be fatal.[4]

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The use of oral anticoagulants (OAC) to prevent thromboembolism in patients with AF has a Class I recommendation in international guidelines,[2,5] with direct or novel OAC widely used in the prevention of AF-related stroke.[6] However, a portion of AF patients at high risk for stroke are not suitable for long-term OAC due to previous major bleeding, risk of major bleeding, poor compliance, or personal preference.

Percutaneous left atrial appendage occlusion (LAAO) is increasingly performed in AF patients contraindicated to OAC. The WATCHMAN™ left atrial appendage (LAA) closure device (Boston Scientific, Marlborough, MA, USA) was shown to be non-inferior to warfarin in randomized controlled trials,[7,8] and reduced the risk of thromboembolic events as compared to predicted rates in a registry of patients largely contraindicated to OAC.[9]

The 1st generation Amplatzer™ LAAO occluder, the Amplatzer™ Cardiac Plug™, was evaluated in a retrospective registry, with good safety and efficacy.[10] The Amulet Observational Study prospectively enrolled patients prior to implant attempt with the Amulet™ occluder—the 2nd generation Amplatzer™ LAAO device. Landmesser *et al.*[11,12] previously detailed the periprocedural and interim 1-year results. We now report the primary endpoint results of the Amulet Observational Study, according to pre-specified study objectives, in a large all-comer population of AF patients undergoing implant attempt in standard clinical practice.

Methods

Study objectives

The Amulet Observational Study specified four primary reporting objectives: the rate of ischaemic stroke, systemic embolism, and cardiovascular (CV) death at 2 years; the rate of major bleeding events at 2 years; the assessment of acute (0–7 days) serious adverse events; and the assessment of late (>7 days–2 years) serious adverse events. The study further specified three secondary reporting objectives: the rates of technical and procedural success (defined in the Supplementary material online, *Appendix*) and the rate of patients taking OAC and antiplatelet drugs through 2 years. Sites were encouraged to enrol patients consecutively in an all-comers manner.

Implant procedure

Left atrial appendage occlusion was performed following the manufacturer's instructions for use. Physicians were trained on the procedure through didactic and hands-on sessions prior to study implants. Baseline imaging was performed to exclude the presence of intracardiac thrombus and to assess LAA size and shape. Enrolment in the study was defined as introduction of the device delivery system to the vasculature following informed consent. Operators could use intracardiac echocardiography (ICE) instead of transoesophageal echocardiography (TOE) if they met pre-specified experience criteria.

Follow-up

Follow-up assessments occurred at discharge, 1–3 months, 6 months, 1 year, and 2 years (±3 months) post-procedure. A TOE was required per the protocol at the 1- to 3-month visit. Patients not implanted were followed for 7 days and then withdrawn per protocol. Antithrombotic medication and adverse event assessments were performed at each visit. The 1- to 3-month TOE was reviewed by a CoreLab (MedStar Health Research Institute, Washington, DC, USA).

Safety events

Safety reporting began when the device delivery system entered the vasculature and continued through study completion or patient withdrawal. Reporting of serious adverse events followed the ISO 141555 definition (Supplementary material online, *Appendix*). Sites were instructed to submit notification of adverse events to the Sponsor as they occurred, and monitor events until resolution. Serious adverse events were defined as acute if ≤7 days post-procedure and late if >7 days post-procedure. Major adverse events defining procedural success are provided in the Supplementary material online, *Appendix*. An independent clinical events committee (CEC) reviewed site-reported source documentation to adjudicate all serious adverse events, including relatedness to the procedure or device and mode of death. The CEC relied upon site interpretations of brain imaging. The CEC classified deaths as resulting from CV, non-CV, or unknown causes (defined in the Supplementary material online, *Appendix*).

Imaging

Cardiac computed tomography (CT) may have been utilized for procedural planning, but was not mandatory per the study protocol. The procedure was guided by echocardiography and fluoroscopy. A transthoracic echocardiogram was obtained before discharge to assess adverse events. Residual flow around the device was assessed by the CoreLab from the implant and follow-up TOEs and was defined as none, small (jet <3 mm), medium (3–5 mm jet), or large (jet >5 mm). Left atrial appendage occlusion was considered clinically good if residual flow was absent or <3 mm.

Statistical analysis

Baseline demographic and clinical characteristics were summarized using descriptive statistics. Categorical variables were summarized with percentages, and continuous variables summarized by mean ± standard deviation (SD). The Kaplan–Meier method was used to calculate event rates at 2 years post-procedure for mortality, the composite of ischaemic stroke, systemic embolism, and CV death, and device-related thrombus (DRT). The incidence rates of other clinical events are presented as annualized rates (events/patient-years of follow-up) unless otherwise noted.

The study complied with the Declaration of Helsinki and patients provided informed consent. The authors had access to the data and final authority over this publication. The study was entered on ClinicalTrials.gov (NCT02447081).

Results

A total of 1088 patients were enrolled between June 2015 and September 2016 and underwent an implant attempt. Cases were performed by 93 implanters at 61 centres in 17 countries. Forty implanters performed ≥10 cases in the study. *Figure 1* details subject follow-up. The follow-up rate at 2 years was 94.2%, with 864 of the 917 expected 2-year visits performed. The 40 patients who withdrew their consent were followed for an average of 167 ± 210 days, while the 15 patients lost to follow-up were followed for an average of 743 ± 227 days.

Patient characteristics

Patient demographics and clinical characteristics are shown in *Table 1*. Patients were aged 75.2 ± 8.5 years; 64.5% were male. The study population was at high risk for thromboembolic events, with a

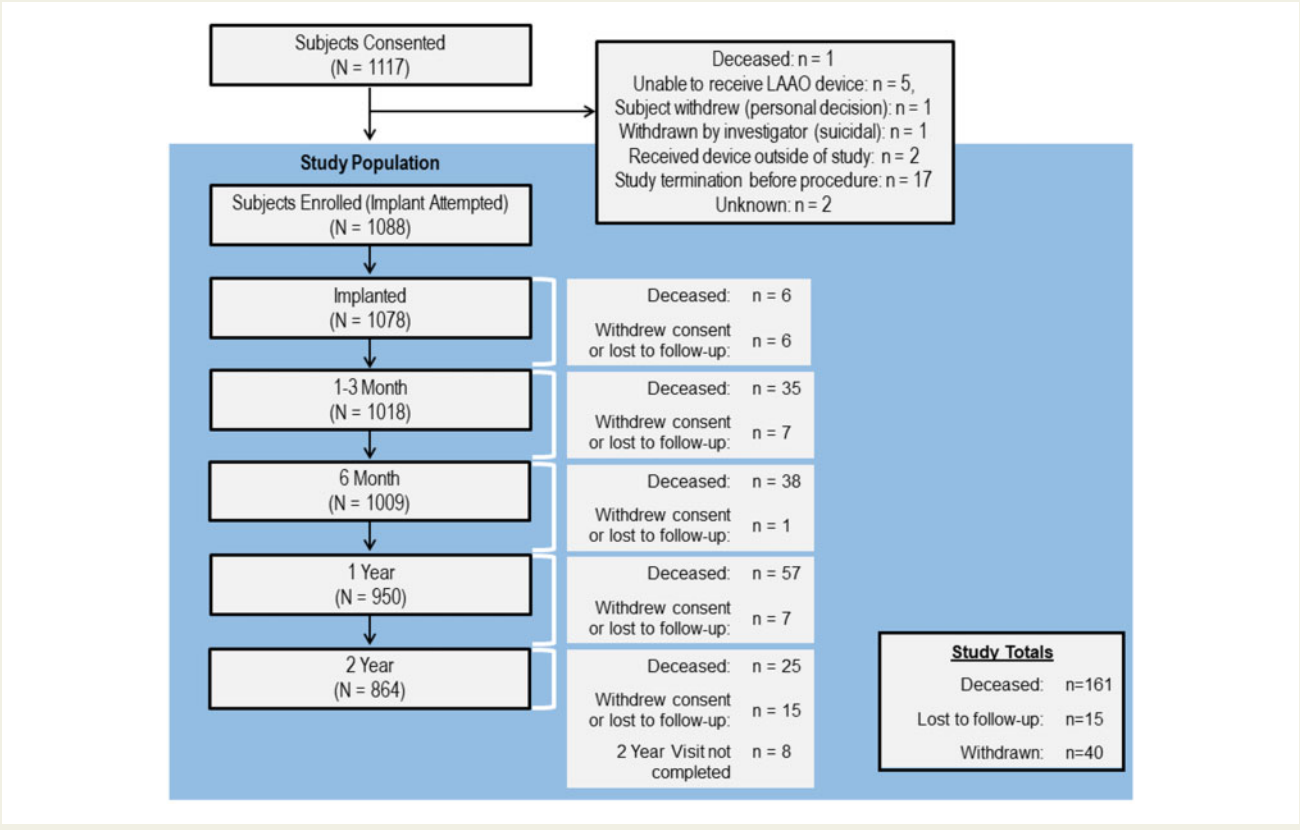


Figure 1 Flow chart of patient follow-up. Patients were considered enrolled when an Amulet occluder implant was attempted. The follow-up rate at 2 years was 94.2%.

CHA_2DS_2-VASc score of 4.2 ± 1.6 and a 27.5% incidence of prior stroke. Most patients were at high risk for major bleeding events, with a HAS-BLED score of 3.3 ± 1.1. A total of 71.7% of patients had prior major bleeding and 82.8% had contraindications to OAC. Contraindicated patients included 42.1% with known bleeding risk and 40.7% with classic clinical cautioning conditions for OAC, such as intracranial haemorrhage, major bleeding, oesophageal varices, liver disease, or severe renal impairment. The CHA_2DS_2-VASc and HAS-BLED scores corresponded to a predicted ischaemic stroke rate of 6.7%/year without anticoagulation, and a predicted 6.7%/year rate of major bleeding while on warfarin.[13,14]

Technical and procedural success

Technical implant success was achieved in 99.1% of patients (1078/1088). Of the 10 unsuccessful implant attempts, seven were due to LAA anatomy not accommodating an Amulet occluder. Procedural success was defined as technical success and the absence of a major adverse event during the index hospitalization. A total of 39 patients had a major adverse event prior to discharge, resulting in a procedural success rate of 95.5% (1039/1088).

Echocardiography

The procedure was guided by TOE in 955 patients (88%) of cases and by ICE in 130 patients (12%). It is unknown what proportion of procedures were preceded by cardiac CT. Good LAAO, as assessed by the CoreLab, was achieved in 99.3% of patients following implant. No residual flow was observed in 89.4% of patients, while minimal flow (<3 mm) was seen in 9.9%. Transoesophageal echocardiography was acquired in 797 of 1018 subjects completing a 1- to 3-month follow-up visit. A total of 763 TOEs were analysed by the CoreLab, with 98.4% of patients exhibiting clinically good occlusion (no flow or flow <3 mm).

Ischaemic stroke, systemic embolism, and cardiovascular death

Clinical events rates are shown in *Table 2*. The annualized rate of ischaemic stroke was 2.2%/year [95% confidence interval (CI) 1.6–2.9%] with 42 strokes in 39 patients—a 67% reduction (95% CI 57–76%) in the risk of ischaemic stroke compared to the predicted rate (*Take home figure*). Four ischaemic strokes occurred ≤7 days of the procedure and were adjudicated as procedure- or device-related. Two further late (days 71 and 161) ischaemic strokes were also adjudicated device-related in the context of DRT. The CEC adjudicated six deaths from stroke. No systemic embolisms were reported. Death due to CV causes occurred in 55 patients, a rate of 5.5% at 2 years. The rate of ischaemic stroke, systemic embolism, or CV death at 2 years was 8.7%.

Major bleeding events

The annualized rate of major bleeding was 7.2%/year, with 140 events observed in 110 patients. Thirty major bleeds occurred ≤7 days of

Table 1 Patient demographics and clinical characteristics

Characteristics	All enrolled (*N* = 1088)
Age (years)	75.2 ± 8.5 (40.1–94.0)
Male gender	702 (64.5)
AF at time of implant	647 (59.5)
Hypertension	913 (83.9)
Abnormal renal function[a]	156 (14.3)
Abnormal liver function[b]	56 (5.1)
Previous stroke	299 (27.5)
Previous TIA	115 (10.6)
Previous major bleed event	780 (71.7)
Previous PCI or CABG	277 (25.5)
CHA_2DS_2-VASc score	4.2 ± 1.6 (1.0–9.0)
HAS-BLED score	3.3 ± 1.1 (1.0–8.0)
Contraindicated to OAC	901 (82.8)

Data presented as mean ± SD (min–max) or count (%).
AF, atrial fibrillation; CABG, coronary artery bypass grafting; OAC, oral anticoagulation; PCI, percutaneous coronary intervention; TIA, transient ischaemic attack.
[a]Abnormal renal function defined as chronic dialysis, renal transplant, or serum creatinine ≥200 µmol/L.
[b]Abnormal liver function defined as chronic hepatic disease (e.g. cirrhosis) or biochemical evidence of significant hepatic derangement (e.g. bilirubin >2× upper limit of normal, in association with aspartate transaminase/alanine transaminase/alkaline phosphatase >3× upper limit normal).

Table 2 Pre-specified primary and secondary study objectives

Primary objectives	
Major adverse events ≤7 days	4.0% (3.0–5.4%)
Patients with pericardial effusion or tamponade	1.4% (1.0–2.3%)
Patients with a major vascular complication	1.3% (1.0–2.1%)
Late serious adverse events	
Patients with a procedure- or device-related event	2.4% (1.6–3.5%)
Device-related thrombus rate (at 2 years)	1.6% (1.0–2.6%)
Cardiovascular events	
Ischaemic stroke	2.2%/year (1.6–2.9%)
Systemic embolism	0.0%/year
Cardiovascular death (at 2 years)	5.5% (4.3–7.1%)
Major bleeding events	7.2%/year (6.1–8.5%)
Related to the procedure or device	1.7%/year (1.1–2.3%)
Secondary objectives	
Technical success	99.1% (98.3–99.6%)
Procedural success	95.5% (94.1–96.6%)
OAC usage	
Discharge	11.2% (9.4–13.2%)
1 year	5.9% (4.5–7.6%)
2 years	6.6% (5.0–8.5%)
Adequate LAA sealing (residual flow absent or <3 mm)	
Procedure	99.3% (98.2–99.8%)
1–3 m following implant	98.4% (97.2–99.2%)

Data presented as estimated rate (95% CI).

the procedure, with an additional 20 bleeds between days 8 and 30 post-procedure. The annualized rate (events/patient-years follow-up) of major bleeding decreased from 10.1%/year (103 events per 1016 patient-years) over the 1st year of follow-up to an annualized rate of 4.0%/year (37 events per 917 patient-years) over the 2nd year. The proportion of patients experiencing a major bleeding event followed a similar trend and decreased from 8.0% (87/1088 patients) over the 1st year to 3.2% (31/958 patients) over the 2nd year of follow-up (*Table 3*).

Most (77%) major bleeding events were adjudicated as unrelated to the procedure or the device. Sixteen major bleeds were due to pericardial effusions, with 12 resulting in tamponade. Four events required surgical repair, and one led to death. Ten haemorrhagic strokes were reported, an annualized rate of 0.5%/year. Gastrointestinal bleeds accounted for 47.9% (67/140) of major bleeding events, with most gastrointestinal bleeds ($n = 52$; 77.6%) occurring in patients with a history of gastrointestinal bleeding. The rate of major bleeding was greater in the 708 patients with a history of major bleeding than in the 308 patients without a history of major bleeding (8.7%/year vs. 3.5%/year). The antithrombotic medication regimen at the time of major bleeding was anticoagulation in 13.6%, dual antiplatelet therapy (APT) in 35.7%, single APT in 37.1%, and no medications in 13.6%. At the time of gastrointestinal bleeding the regimen was anticoagulation (oral or injectable) in 10.5%, dual APT in 41.8%, single APT in 34.3%, and no medications in 13.4%.

Acute serious adverse events

Major adverse events, consisting of death, stroke, embolism, major bleeds, device embolization, and major vascular complications occurred in 4.0% of patients ≤7 days of the procedure. All three deaths occurring ≤7 days of the procedure were adjudicated as CV deaths, and two as device- or procedure-related. One patient had recurrent episodes of post-procedural hypotension and bradycardia, temporarily controlled with inotropic agents. A TOE showed no pericardial effusion. A hypotensive episode resulted in cardiorespiratory arrest resistant to resuscitation. The 2nd patient suffered cardiogenic shock secondary to a 3 mm perforation at the LAA ostium—a surgical pericardial patch was placed but the patient died 2 days later. The 3rd patient collapsed and was found pulseless as an inpatient 2 days after implant. After over 90 min of resuscitation efforts were ended. An autopsy attributed death to acute myocardial infarction due to severe atherosclerosis of the main stem of the left coronary artery, unrelated to the procedure or the device.

Major bleeding was the most frequent major adverse event occurring during the 1st 7 days ($n = 30$ bleeds; 2.8% of patients). Procedure-related vascular complications ≤7 days were reported in 1.3% of patients, with haematomas, arteriovenous fistulas, and pseudoaneurysms the most common complications.

Device embolization occurred in two patients. In the 1st patient, a 25 mm device was implanted, but embolized to the aortic arch. The device was snared and removed via the right common femoral artery. The patient returned 3 months later, and a 22 mm device was

Table 3 Major bleeding events over year 1 and year 2 of follow-up

	All enrolled (*N* = 1088)	
	Bleeding rate (*N* patients with events/*N* patients at risk)	Annualized rate (*N* events/ patient-years)
Year 1	8.0 (87/1088)	10.1 (103/1016)
Year 2	3.2 (31/958)	4.0 (37/917)

implanted. In the 2nd patient, a 28 mm device was implanted, but embolized and entangled in the mitral valve. The device was surgically removed, a bioprosthetic valve implanted, and the LAA surgically excluded.

Late serious adverse events

One-hundred sixty-one (161) patients died over the course of study follow-up, a rate of 15.2% at 2 years. The number of deaths occurring over the 1st and 2nd years of follow-up was 91 and 70, respectively. Deaths were due to CV, non-CV, and unknown causes in 55, 71, and 35 patients, respectively.

A total of 19 DRT episodes occurred in 17 patients, a rate of 1.6% at 2 years. Patients with DRT were discharged on single APT in 11.8%, dual APT in 58.8%, and anticoagulants in 29.4% of cases, while patients without DRT were discharged on single APT in 22.7%, dual APT in 57.6%, and anticoagulants in 17.5%. Most (87%) of the DRTs were located at the superior edge of the disc, in the untrabeculated area of the LAA ostium between the pulmonary vein ridge and the upper edge of the disc.[15] Following DRT diagnosis, patients received anticoagulant treatment in 83% of cases (oftentimes longer than 3 months). No major bleeding events occurred in patients following DRT, despite anticoagulant use to resolve the DRT.

Twenty transient ischaemic attacks (TIAs) occurred in 16 patients, an annualized rate of 1.0%/year. All TIAs occurred ≥7 days of the procedure, with 9 over the 1st year of follow-up and 11 over the 2nd year of follow-up. Two of 16 patients with a TIA also suffered an ischaemic stroke during the study.

Antithrombotic medications

Most patients received antiplatelets alone following LAAO, as shown in *Figure 2* (detailed in the Supplementary material online, *Appendix*). Patients were usually discharged on dual (57.7%) or single (22.4%) APT, while 11.2% of patients received OAC and 6.6% injectable anticoagulants. The proportion of patients on single APT was 52.3%, 61.8%, 64.6%, and 62.8% at 3 months, 6 months, 1 year, and 2 years, respectively. A rise in the proportion of patients without antithrombotic medications was observed: 7.5%, 14.6%, 19.2%, and 21.5% at 3 months, 6 months, 1 year, and 2 years, respectively.

Discussion

The Amulet Observational Study prospectively evaluated safety and efficacy of the Amplatzer™ Amulet™ LAA occluder in an all-comer population of AF patients at high risk of cardioembolic events. In this large cohort of patients, the CEC-adjudicated ischaemic stroke rate was 67% lower than the rate for AF patients without OAC predicted by the baseline CHA_2DS_2-VASc score. Annual rates of TIA and systemic embolism were 1.0% and 0.0%, respectively. The high rate of Amulet implant technical success and high degree of LAA sealing as adjudicated by the independent CoreLab on procedural and 1- to 3-month follow-up TOEs are postulated to have reduced the risk for ischaemic stroke without the need for long-term OAC in this group.

Periprocedural outcomes of the Amulet Observational Study were previously detailed.[11] In this study, among a diverse group of implanters, ranging from 1 to 54 (median 8) enrolments per operator, a high degree of technical success (1078 of 1088 attempts; 99.1%) was observed. Major adverse events during the procedure and index hospitalization occurred in 3.6% of patients, a rate comparable to those reported in the registries of WATCHMAN (2.8%) and ACP (4.9%) devices.[9,10] In our population at high risk of bleeding, major bleeds accounted for most periprocedural adverse events.

Device-related thrombus was seen in 1.6% of patients. This is comparable to previous reports of Amplatzer LAAO devices. A total of 110 consecutive Amplatzer LAAO patients receiving aspirin monotherapy were prospectively followed for a median of 2.3 years, with a 1.9% DRT rate observed.[16] Similarly, a DRT rate of 1.8% was reported in the 218 Amplatzer occluder patients undergoing a 6-month TOE in the Italian LAAO registry.[17] Aminian *et al.*[15] recently detailed the incidence, characterization, and clinical impact of DRT observed within the 1st year post-implantation, noting that the left upper pulmonary vein ridge was not covered by the Amulet occluder disc in 82% of patients with a DRT, suggesting suboptimal implantation as a contributing factor to DRT development. While no peridevice leak of any size was observed in subjects with DRT, further investigations using more sensitive CT are warranted to evaluate this relationship. DRT was associated with an increased risk of ischaemic stroke or TIA (hazard ratio 5.27, 95% CI 1.58–17.55, $P < 0.01$).[15] A similar association between the presence of DRT and an increased rate of clinical events has been reported in patients implanted with the WATCHMAN device. Of 1739 WATCHMAN patients followed for 7159 patient-years, DRT was seen in 3.7% and was associated with a 3.2 times increased risk for ischaemic stroke or systemic embolism.[18] While DRT is an infrequent event post-LAAO, its presence is concerning and seems to have associated risks. Refinements in implant technique and device sizing may improve Amulet-LAA sealing, potentially reducing the risk of DRT formation.

The favourable clinical results seen in this study were achieved with only 11% of patients discharged on OAC. Nearly 60% of patients were on single APT or no antithrombotic medications at 1–3 months after implant, and this proportion increased to 84% at 2 years. In this population at high risk for bleeding, 83% of whom had contraindications to anticoagulants, our study suggests that LAAO is an attractive therapy to reduce the ongoing risk of ischaemic stroke.

Several factors limit comparison to the lower rates of ischaemic stroke reported in large registries of WATCHMAN[9] (1.1%/year) and ACP[10] (1.3%/year) devices. The WATCHMAN population had a lower risk of major bleeding events and utilized a more intense antithrombotic regimen following implant. Oral anticoagulants were prescribed in 27% of patients at discharge, with therapy continued up to 3 months post-implant. The average time to discontinuation of

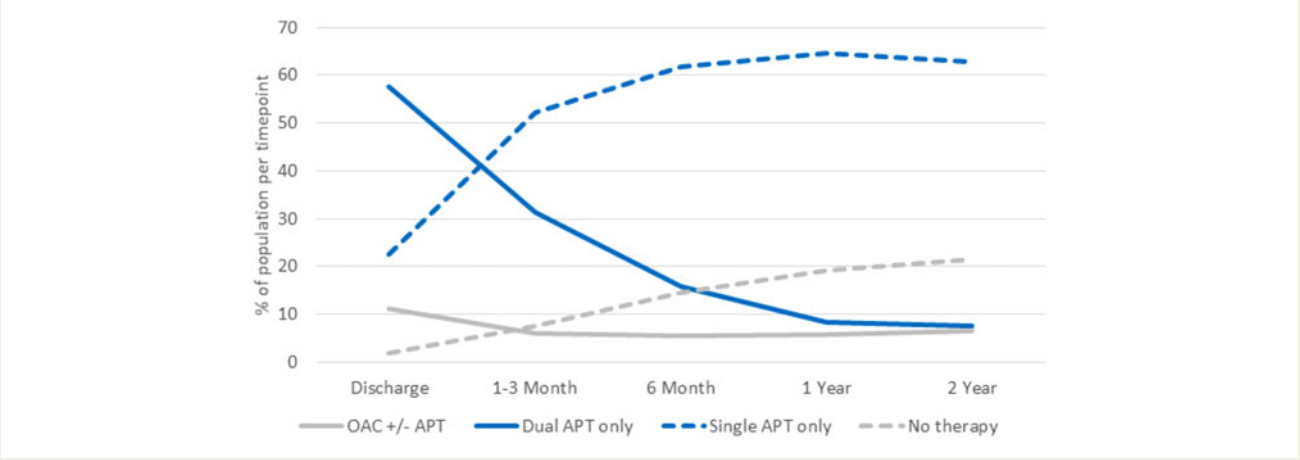
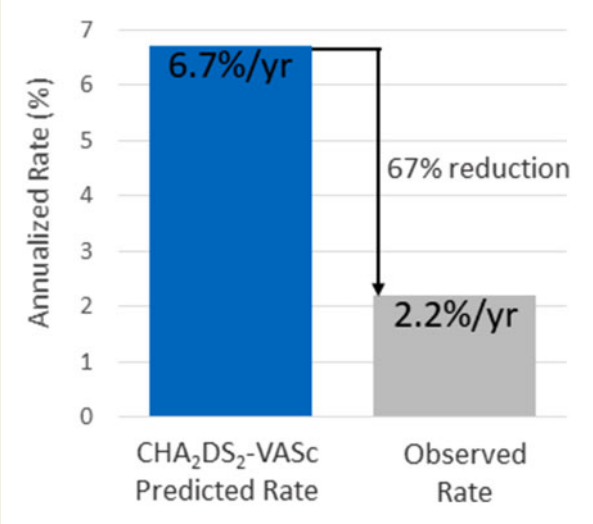


Figure 2 Utilization of antithrombotic therapy through 2 years. Patients were often discharged on dual (57.7%) or single (22.4%) antiplatelet therapy. Oral anticoagulation was prescribed in 11.2% of patients at discharge. Patients often received single antiplatelet therapy or no antithrombotic medications beginning 1–3 months post-implant and were maintained on this regimen over long-term follow-up.



Take home figure Patients were prospectively enrolled and followed for 2 years, with clinical events independently adjudicated by a clinical events committee. In a population of atrial fibrillation patients mostly on antiplatelet therapy alone, the observed ischaemic stroke rate of 2.2%/year (95% confidence interval 1.6–2.9%) was reduced 67% (95% confidence interval 57–76%) compared to the 6.7%/year predicted by baseline CHA_2DS_2-VASc score for atrial fibrillation patients without anticoagulants.

dual APT was 6 months. By comparison, in the current study, only 11% of patients were discharged on OAC, and dual APT was only taken by 31% and 16% of patients at the 1- to 3- and 6-month visits, respectively. While the ACP registry replied upon retrospective self-reporting of clinical events without independent adjudication, the current study prospectively followed patients with required visits to ascertain if clinical events had occurred, with events adjudicated by a CEC independent of the Sponsor.

The current Amulet study enrolled a population at higher risk for major bleeding events than prior registries of similar size. A history of major bleeding was present in 72% of Amulet patients compared to 47% and 31% of patients in the ACP and EWOLUTION registries. The average HAS-BLED score was elevated at 3.3 in this Amulet study, compared to 3.1 and 2.3, respectively. The EWOLUTION registry reports a major bleeding rate of 4.2%/year in subjects with HAS-BLED score ≥3 (40% of population). This rate is similar to the long-term rate (4.0%/year) in the current study, where 78% of patients had a HAS-BLED score ≥3. In patients at high risk for bleeding, events unrelated to the LAAO procedure or device are still prevalent and future investigations optimizing antithrombotic regimen post-LAAO are warranted.

Following patients for 2 years in the current study allowed for characterization of longer-term benefits. As with other interventional therapies, LAAO is associated with procedure- or device-related complications that must be outweighed by long-term clinical benefit. We observed reductions in both the rates of ischaemic stroke (2.9–1.4%/year) and major bleeding (10.1–4.0%/year) in the 2nd year of follow-up. Events within the 1st year post-implant are largely driven by procedural complications and post-implant antithrombotic medications, and the benefit of LAAO therapy is best appreciated over the longer-term. Unlike anticoagulants, where the non-compliance rate is ∼25% over a few years[19], LAAO provides long-term protection against cardioembolic events. In an elderly population with many comorbidities, the majority of patient deaths ($n = 71$) were attributed to non-CV causes.

A number of factors may have contributed to the increased bleeding rate over the 1st year of follow-up compared to the HAS-BLED predicted rate. First, in a population at high risk for major bleeding (71.7% with a history), intense antithrombotic medications of dual APT or anticoagulation were prescribed at discharge in 75.5% of subjects. The majority of 1st year bleeding events (77/103 events) occurred within 3 months of implant, prior to when most patients transitioned to aspirin monotherapy. Periprocedural major bleeding

events contributed 3.1% to the 1st year rate of 10.1%. Finally, more than one bleed occurred in some patients—the total proportion of patients who had a bleed in the 1st year was 8.0%.

In addition to most events occurring early in follow-up, we noticed other major bleeding trends. Many major bleeds, 67 of 140 (47.9%), were adjudicated as gastrointestinal in nature. Gastrointestinal bleeds occurred despite modest levels of antithrombotic medication, with 41.8% of bleeds on dual APT, 34.3% on single APT, and 10.4% while on anticoagulants. Similar results were reported during Iberian Registry II long-term follow-up of OAC contraindicated patients. In the 598 patients followed for an average of 22.9 months, the primary driver of the 3.9%/year major bleeding rate was a gastrointestinal bleeding rate of 3.2%/year.[20] A history of gastrointestinal bleeding was the main predictor of gastrointestinal bleeding following LAAO in the Iberian Registry (hazard ratio 4.27, 95% CI 1.87–9.73). In our study, patients with prior major bleeding had a higher risk of post-LAAO bleeding, with rates of 8.7% (previous bleeding) and 3.5% (no previous bleeding), respectively. Finally, it is worth noting that 12.9% of major bleeds in this study met the Bleeding Academic Research Consortium ≥3 definition due to pre-existing anaemia resulting in a haemoglobin decrease, despite no definitive site of bleeding being found. Anaemic events may have been less prevalent in prior studies of LAAO without independent adjudication.

Limitations

The current large observational study enrolled an all-comer population. It is unknown to what degree potential study patients were enrolled consecutively. There was no control group, and while the use of CHA_2DS_2-VASc and HAS-BLED scores to compare observed to predicted event rates is a common practice for standard clinical practice LAAO studies, the methodology is imperfect. The independent CEC relied upon study sites to identify clinical events; some events may have not been reported. The independent CoreLab did not evaluate LAA sealing in all patients, as some did not undergo follow-up imaging, while technical issues prevented transfer of some studies. Finally, the current study only evaluated a single LAAO device, and results may not be applicable to other devices, in other patient populations, or with other post-implant antithrombotic medication regimens.

Conclusions

This large study prospectively followed AF patients at high risk for both ischaemic stroke and major bleeding for 2 years after LAAO with the Amplatzer™ Amulet™ occluder, and utilized an independent CEC and echo CoreLab for data consistency and validity. The annual rates of ischaemic stroke, TIA, and systemic embolism were low at 2.2%, 1.0%, and 0.0%, respectively. The Amulet occluder allows for prevention of AF-related thromboembolic events without the need for long-term OAC.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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Conflict of interest: D.H.-S. has served as a proctor and consultant for Abbott. U.L. has served as an advisor to and received fees from Abbott, Biotronik, Rewa, and Bayer. A.J.C. has served on advisory boards and received speaker fees from Bayer, Boehringer Ingelheim, Daiichi Sankyo, Pfizer/BMS, Abbott, and Boston Scientific. H.-C.D., over the last 3 years, received honoraria for participation in clinical trials, contribution to advisory boards, or oral presentations from Abbott, Allergan, AstraZeneca, Bayer Vital, BMS, Boehringer Ingelheim, Daiichi Sankyo, Johnson & Johnson, MSD, Medtronic, Novartis, Pfizer, Portola, Sanofi-Aventis, Servier, St. Jude, and WebMD. Financial support for research projects was provided by Boehringer Ingelheim. The Department of Neurology at the University Duisburg-Essen received research grants from the German Research Council (DFG), German Ministry of Education and Research (BMBF), European Union, NIH, Bertelsmann Foundation and Heinz-Nixdorf Foundation. H.-C.D. has no ownership interest and does not own stocks of any pharmaceutical company. H.-C.D. served as editor of Aktuelle Neurologie, Arzneimitteltherapie, as co-editor of Cephalalgia, and on the editorial board of Lancet Neurology, Stroke, European Neurology, and Cerebrovascular Disorders. H.-C.D. chairs the Treatment Guidelines Committee of the German Society of Neurology and contributed to the EHRA and ESC guidelines for the treatment of AF. V.P. has served on an advisory board and received teaching fees from Medtronic and has served as a proctor for Abbott. B.S. has served on advisory boards and received speaker fees from Abbott and Boston Scientific. M.S. has served as a proctor and on advisory boards for Abbott, Medtronic, Boston Scientific, and W.L. Gore. E.T. and J.E.N.-K. have served as a proctor for Abbott. C.T. has served on an advisory board for Boston Scientific and received lecture and proctor fees from Abbott.

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