Structural Interventions Amplatzer™ Cardiac Plug & Amulet™ Device

CLINICAL INSIGHTS:

PERCUTANEOUS LEFT ATRIAL APPENDAGE OCCLUSION FOR STROKE PREVENTION IN PATIENTS WITH ATRIAL FIBRILLATION: PROCEDURAL EXPERIENCE AND CLINICAL FOLLOW-UP WITH THE AMPLATZER™ CARDIAC PLUG AND AMPLATZER™ AMULET™ DEVICE

Abbott

Clinical Insights

A PUBLICATION DELIVERING CONCISE CLINICAL DATA

AMPLATZER™ CARDIAC PLUG AND AMULET™ DEVICE

PERCUTANEOUS LEFT ATRIAL APPENDAGE OCCLUSION FOR STROKE PREVENTION IN PATIENTS WITH ATRIAL FIBRILLATION: PROCEDURAL EXPERIENCE AND CLINICAL FOLLOW-UP WITH THE AMPLATZER™ CARDIAC PLUG AND AMPLATZER™ AMULET™ DEVICE

New in this Version:

Two-year outcomes of the Global Amplatzer Amulet LAA Occlusion Observational Study.

Study Summary:

- The study generated 1933 patient-Years of follow-up from 1088 enrolled subjects.
- The ischemic stroke rate was 2.2%/year. LAAO with the Amulet device achieved a 67% reduction in the annual rate of ischemic stroke compared to the expected ischemic stroke rate according to the CHA_2DS_2-VASc score.
- The annual rate of major bleeding was 7.2%, similar to the HAS-BLED-predicted rate for a population at high risk of annual major bleeding.
- The major bleeding rate was reduced in year 2 of follow-up (4.0% vs 10.2%). Major bleeding over the first year was higher due to procedure-related bleeds and use of DAPT post implant. Most patients were on single antiplatelet therapy or no antithrombotic medications in the 2nd year.
- Device-related thrombus was an infrequent event in this population primarily discharged without OAC, as the rate at 2-years was 1.63%. Importantly, 82% of DRT patients did not experience any ischemic neurologic events 165.
- **Conclusion:** The data from the Amulet Observational Study suggests that Left Atrial Appendage Occlusion is a safe and effective treatment to reduce long-term stroke risk in AF patients at increased risk for ischemic stroke and often contraindicated to OAC, with a 67% relative risk reduction in ischemic stroke.

OBSERVATIONAL STUDY: AGE GROUP ANALYSIS

Despite the increased risk for ischemic stroke with increasing age in AF patients, LAAO with the Amplatzer Amulet Occluder reduced the risk for ischemic stroke compared to the predicted rate across all age groups without differences in major adverse events & without the need for long-term anticoagulation. [166]

Age groups	AMULET Ischemic Stroke Risk Reduction vs. predicted rate
<70 yrs	62% lower
≥70 & <80 yrs	57% lower
≥80 yrs	85% lower

OBSERVATIONAL STUDY: PRIOR GASTROINTESTINAL BLEEDING

Major bleeding, particularly recurrent Gastrointestinal bleeds, occurred at a high rate in patients with a history of Gastrointestinal bleed prior to LAAO. Reduced risk of stroke & relatively low device related thrombus rate following LAAO with Amulet support a restrained antithrombotic regimen. [167]

Prior GI bleeding	AMULET Ischemic Stroke Risk Reduction vs. predicted rate
Yes	70% lower
No	66% lower

OBSERVATIONAL STUDY: IMPACT OF CHA_2DS_2-VASC AND HAS-BLED SCORES ON CLINICAL OUTCOMES

LAAO with Amulet reduced the risk of ischemic stroke in patients at low, intermediate, and high risk for ischemic stroke, without increasing bleeding risk following discharge. [168]

CHA_2DS_2-VASc Score	AMULET Ischemic Stroke Risk Reduction vs. predicted rate	HAS-BLED Score	AMULET Major Bleeding After Discharge vs. predicted rate
<3	56% lower	≤3	11% lower
3-5	69% lower	>3	9% lower
≥6	68% lower		

ABSTRACT

Patients with atrial fibrillation (AF) are at increased risk for ischemic stroke. Although oral anticoagulation (OAC) is an established therapy to prevent AF-related stroke, it may be less suited for patients with a high risk of bleeding. In addition, some patients suffer a stroke despite OAC. Percutaneous occlusion of the left atrial appendage (LAA) has emerged as a feasible nonpharmacological option for stroke prevention in these patients. This paper discusses the clinical context of this therapy and reviews the current experience with the Amplatzer™ devices dedicated for percutaneous LAA occlusion (LAAO).

STROKE AND AF

Incidence and consequences of AF-related stroke

Atrial fibrillation independently increases the stroke risk approximately 5-fold throughout all ages[1]. As a result, AF is responsible for approximately 15% of the almost 2 million strokes occurring each year in Europe and the US[2]. The percentage of

strokes attributable to AF increases from 1.5% at 50 to 59 years of age to 23.5% in octogenarians[2]. The vast majority of all strokes and especially AF-related strokes are ischemic. AF-related stroke is associated with a high mortality and serious consequences for stroke survivors[3,4]. The three months mortality after a first-in-lifetime stroke in AF patients was found to be more than 30%, compared to almost 20% in patients without AF [4]. In Europe, stroke is responsible for 10% and 15% of all deaths among men and women, respectively [5]. Furthermore, AF-related stroke may result in severe, long-term disability and functional impairment.

Cost of stroke

For the US, in 2011/2012, the total annual costs and direct medical costs of stroke were $33 billion and $17.2 billion, respectively (2011/2012 data) [6]. The mean lifetime cost of all-cause ischemic stroke were estimated at $140,000 per patient[2]. In 2005 the total cost related to stroke in Europe was estimated at almost €22 billion, which is about one quarter of all costs related to neurological diseases and about 6% of the total budget spent on all brain disorders [7,8]. Other estimations of the cost of stroke in the 27 EU countries include a total annual cost of €27 billion, with €18.5 billion (68.5%) for direct and €8.5 billion (31.5%) for indirect costs [9]. In addition, €11.1 billion is spent on informal care[5]. AF-related strokes are significantly more costly than non-AF strokes. In a 2013 study among stroke patients in the US, the costs of hospitalization for AF-related ischemic and hemorrhagic stroke were increased compared with non-AF strokes by US$3,520 and US$2,799, respectively[10]. Compared with stroke patients without AF, the total health care costs over the first year after an AF-related stroke were US$4,726 and US$ 7,824 higher for ischemic and hemorrhagic stroke, respectively[10].

Risk factors for stroke

Overall, AF is associated with a fivefold increase in stroke risk[1]. The AF-related stroke risk increases with age and with coexisting cardiovascular diseases. The $CHADS_2$ risk assessment scheme [11,12] estimates the risk for stroke in patients with AF based on well-established risk factors, including cardiac failure, hypertension, age over 75 years and diabetes (contributing one point to the risk score) and previous stroke or transient ischemic attack (TIA) (contributing 2 points). The more recently developed CHA_2DS_2-VASc risk assessment scheme [13] assigns two points to age ≥ 75 years and previous stroke, TIA or thromboembolism and one point each to congestive heart failure or left ventricular dysfunction, hypertension, diabetes, vascular disease, age between 65 and 74 years and sex category (i.e., female sex). A recent validation [14] of these risk schemes in more than 90,000 patients without OAC but on aspirin showed annual ischemic stroke rates ranging between 0.6% (CHA_2DS_2-VASc = 1) to 4.8% (CHA_2DS_2-VASc = 4) to more than 12% (maximum CHA_2DS_2-VASc score of 9).

AF is responsible for a five-fold increase in stroke risk and approximately 15% of all strokes. Its effect on stroke risk increases markedly with age. AF-related stroke is associated with more severe consequences, higher mortality and increased costs, compared to non-AF strokes. The risk for stroke in AF patients based on known risk factors is estimated by the $CHADS_2$ risk assessment scheme or by the more recent CHA_2DS_2-VASc scheme. Recent data from a large cohort of AF patients show annual stroke rates between 0.6% and > 12% (CHA_2DS_2-VASc scores between 1 and 9).

1. Throughout this document the abbreviation OAC refers to oral anticoagulation in general, i.e. using VKA or NOAC agents. Specific therapies are referred to by VKA (most commonly warfarin) or NOAC (dabigatran, rivaroxaban, apixaban, edoxaban).

TABLE 1: RANDOMIZED CONTROLLED STUDIES ON NON-VKA ORAL ANTICOAGULANTS

Drug / Study	Baseline characteristics/ Endpoints	Randomization arms	Event rates [%/yr]		Overall outcome
			Effectiveness	Safety	
Dabigatran RE-LY[30]	*Baseline characteristics:* 18113 pts, 71 yrs, $CHADS_2$: 2.1 *Effectiveness:* Stroke and systemic embolism *Safety:* Major hemorrhage	110 mg dabigatran twice daily	1.53	2.71	Compared to warfarin: 110 mg dabigatran: non-inferior stroke prevention and significantly less bleeding. 150 mg dabigatran: superior stroke prevention and similar bleeding risk. 110 mg dose: similar risk for GI bleeding. 150 mg dose: significantly higher risk for GI bleeding.
		150 mg dabigatran twice daily	1.11	3.11	
		Adjusted dose warfarin	1.69	3.36	
Rivaroxaban ROCKET-AF[31]	*Baseline characteristics:* 14264 pts, 73 yrs, $CHADS_2$: 3.47 *Effectiveness:* All-case stroke and non-CNS systemic embolism *Safety:* Major and clinically relevant non-major bleeding	20 mg rivaroxaban daily	2.12 (ITT)	3.60	Rivaroxaban is noninferior to warfarin in prevention of stroke and non-CNS systemic embolism. Major bleeding rates of rivaroxaban and warfarin are similar.
		Adjusted dose warfarin	2.42 (ITT)	3.45	
Apixaban AVERROES[32]	*Baseline characteristics:* 5600 pts, 73 yrs, $CHADS_2$: 2.1 *Effectiveness:* Stroke and systemic embolism *Safety:* Major bleeding	5 mg apixaban twice daily	1.6	1.4	Compared to aspirin, apixaban provides superior prevention for stroke and systemic embolism and has similar bleeding risks.
		81 – 324 mg aspirin daily	3.7	1.2	
Apixaban ARISTOTLE[33]	*Baseline characteristics:* 18201 pts, 70 yrs, $CHADS_2$: 2.1 *Effectiveness:* Ischemic or hemorrhagic stroke or systemic embolism *Safety:* Major bleeding	5 mg apixaban twice daily	1.27	2.13	Prevention for stroke and systemic embolism by apixaban is non-inferior / superior to warfarin. Apixaban is associated with significantly lower major bleeding rate compared to warfarin.
		Adjusted dose warfarin	1.60	3.09	
Edoxaban ENGAGE AF- TIMI[34]	*Baseline characteristics:* 21,105 pts, 72 yrs, $CHADS_2$: 2.8 *Effectiveness:* Stroke (ischemic or hemorrhagic) *Safety:* Major bleeding	60 mg edoxaban daily	1.18	2.75	Compared to warfarin: Stroke prevention: 30 mg and 60 mg doses are non-inferior. Favorable trend for 60 mg and unfavorable trend for 30 mg. Bleeding: significantly less for both doses.
		30 mg edoxaban daily	1.61	1.61	
		Dose adjusted warfarin	1.50	3.43	

NOTE: Results from clinical trials are not directly comparable. Information provided for educational purposes only.

ANTITHROMBOTIC THERAPY IN AF PATIENTS

OAC using a vitamin K antagonist (VKA) or a non-vitamin K antagonist oral anticoagulant (NOAC) is the therapy of choice for prevention of ischemic stroke in AF patients. The current European Society of Cardiology (ESC) guidelines for management of AF [16] recommend OAC for prevention of thromboembolic stroke in male and female AF patients with a CHA_2DS_2-VASc score ≥2 and ≥3, respectively. In addition, OAC should be considered in male and female AF patients with a CHA_2DS_2-VASc score ≥1 and ≥2, respectively. Antiplatelet monotherapy is not recommended, regardless of stroke risk.

Vitamin K antagonists

Warfarin, the most commonly used VKA, reduces the risk for ischemic stroke in AF patients by approximately 65% [17 18 19 20 21] and is more effective than antiplatelet therapy in the prevention of ischemic stroke [22]. Management of warfarin therapy is complicated due to the perceived bleeding risk, the need for regular INR monitoring and dose adjustments, food and drug interactions and patient noncompliance. As a result, warfarin is severely under-prescribed [23 24 25 26 27 28]. Patients taking warfarin often have an INR outside the therapeutic window [29]. As a result, warfarin only achieves a fraction of its clinical potential in the prevention of AF-related stroke.

Non-VKA oral anticoagulants

In order to overcome the drawbacks of warfarin, NOACs have been developed with less dietary and pharmacological interactions and less stringent requirements for frequent INR monitoring. Results from recent trials on NOACs are summarized in Table 1. Dabigatran, rivaroxaban, apixaban and edoxaban are at least non-inferior to warfarin in the prevention of stroke and systemic embolism. Based on their improved net clinical benefit (less all-cause stroke and thrombo-embolic events), the focused update of the ESC guidelines for management of AF recommends NOAC rather than dose-adjusted VKA therapy [16]. However, especially in patients with severe chronic kidney disease, VKA therapy is considered a better alternative. Product labeling of several NOACs recommends that the agents are to be used with caution in patients with moderate renal or hepatic impairment and contraindicates their use in case of severe renal insufficiency. As with warfarin, therapy discontinuation may be a clinically relevant issue. In randomized controlled trials to demonstrate the effectiveness of NOAC, the use of the study drug was discontinued in 20 to 25% of the patients [30 31 33].

Overall, despite obvious improvements, NOACs are still associated with clinically relevant major bleeding and intracranial hemorrhage (see Table 1) and have similar or significantly higher rates of gastrointestinal (GI) bleeding compared with warfarin [30 31 33 34]. A recent study has shown that NOACs appear to replace non-NOAC alternatives (such as low-molecular weight heparin and to a lesser degree warfarin), rather than to increase the proportion of AF patients on anticoagulation for stroke prevention [35]. As a result there are still many eligible patients who are being left untreated.

OAC and bleeding

The most severe complications of OAC are hemorrhagic stroke and major extracranial bleeding. Typical annual rates for major bleeding and intracranial hemorrhage in AF patients receiving OAC are reported to be 1.2% and 0.5%, respectively [36 37]. Relatively high incidences of OAC-related GI bleeding have been reported, especially when OAC is used in combination with aspirin [38 39]. Specific GI bleeding risks were also underlined by the use of dabigatran (RE-LY trial) [30], rivaroxaban (ROCKET-AF trial) [31] and edoxaban (ENGAGE AF-TIMI trial) [34]. A recent study using data from 43,299 patients, recorded in Danish nationwide registries [40], concluded that NOACs (dabigatran, rivaroxaban and apixaban) were not associated with a lower risk of stroke or thromboembolic events, compared with VKA. However, the intracranial bleeding risk was significantly lower with dabigatran and apixaban. Absolute risks of intracranial bleeding at 1 year after therapy initiation were 0.60% and 0.47% for VKA and rivaroxaban, respectively, versus 0.40% and 0.26% for apixaban and dabigatran. Data from 118,891 Medicare patients [41] showed a higher bleeding risk for rivaroxaban compared with dabigatran (annual rate of intracranial hemorrhage: 0.58% vs. 0.37%; GI bleeding: 3.25% vs. 2.33%) with no significant benefit regarding stroke prevention (annual rate of thromboembolic stroke: 0.77% and 0.97% for rivaroxaban and dabigatran, respectively). Overall, NOACs may be associated with fewer bleeding events compared with VKA, but bleeding is still clinically significant, especially considering the risks for intracranial and GI bleeding.

While novel anticoagulants were introduced without specific reversal agents, such agents are currently under development and close to regulatory approval [42].

In order to quantify the risk for OAC-related bleeding, risk factors have been identified and incorporated in the HAS-BLED risk assessment scheme [43]. Risk factors accounted for by this scheme are hypertension, previous stroke, previous bleeding, labile INRs, and age > 65 years, all adding one point to the risk score, and abnormal renal and/or liver function and concomitant drugs and/or alcohol abuse, both adding 1 or 2 points to the HAS-BLED score. In a cohort of more than 48,000 patients on OAC, annual rates of intracranial and major bleeding were reported at 0.2% and 0.7%, respectively, for patients with a HAS-BLED score of 1 [14]. These rates sharply increase at higher risk scores, for instance to 1.2% and 3.4%, respectively, at a HAS-BLED score of 4. A HAS-BLED score of ≥ 3 is usually considered to indicate a high bleeding risk [44]. Guidelines state that a high bleeding risk should generally not result in withholding OAC, but that bleeding risk factors should be identified and treatable factors be corrected in the first place [17].

The costs of major bleeding complications may essentially compromise the savings of prevented ischemic strokes by OAC, as indicated by an analysis of Medicare claims for stroke and major hemorrhage [45]. Within the first year after the AF index (the first AF-related claim) the risk-adjusted incremental costs for patients with hemorrhage claims only was $26,168, which was similar to those for patients with ischemic stroke claims only ($26,776, both compared with patients without stroke or hemorrhage claims).

OAC is the therapy of choice for stroke prevention in AF patients. Warfarin is difficult to manage, carries the risk for hemorrhagic complications, and is often used at a subtherapeutic level or not prescribed although indicated. Non-VKA oral anticoagulants provide similar or better stroke prevention than warfarin but are still associated with bleeding complications, especially with GI bleeding.
The HAS-BLED risk assessment scheme estimates the bleeding risk based on a number of established risk factors. Some of these risk factors also increase the stroke risk in AF patients, underlining the complex risk-benefit analysis with respect to initiation and management of OAC therapy.

PERCUTANEOUS LAA OCCLUSION

Stroke and the LAA

The left atrial appendage appears to be the predominant location of atrial thrombus formation in patients with non-rheumatic AF [46 47].

Based on its role in cardioembolic events, surgical exclusion of the LAA emerged as a therapy to prevent AF-related stroke [46 47 48 49]. Currently, surgical resection of the LAA is recommended for patients undergoing mitral valve surgery [50].

Percutaneous occlusion of the LAA

Sievert et al.[51] were the first to report on occlusion of the LAA by means of a catheter-based technique. The procedure involves puncture of the femoral vein, introduction of a catheter mounted with the collapsed occlusion device into the right atrium, transseptal entry of the left atrium (LA) and deployment and fixation of the device in the LAA orifice.

Following the first clinical application, a number of devices for percutaneous LAA occlusion have been developed: the PLAATO™ system (eV3 Inc., Plymouth, MN, USA, no longer available), the WATCHMAN™‡ LAA closure device (Boston Scientific, Natick, MA, USA) and the Amplatzer™ Cardiac Plug and Amplatzer™ Amulet™ device (Abbott, St. Jude Medical, Plymouth, MN, USA). Patient cohorts implanted with these devices showed a lower stroke rate than expected based on their risk profile [52 53 54 55 56 57 58 59 60], demonstrating the proof of the concept. Results of the randomized controlled PROTECT-AF study [61] showed that percutaneous LAA occlusion with the WATCHMAN™ device and subsequent discontinuation of OAC at 45 days post-implant was non-inferior to warfarin therapy in the prevention of the primary composed endpoint of stroke, cardiac death and systemic embolism. Overall, there were more safety events in the device arm compared to the warfarin arm, and most of them were related to periprocedural complications. Meanwhile, long-term follow-up of the PROTECT-AF study has been reported [62]. At a mean follow-up of 3.8 years (2,621 patient years) LAA occlusion was superior to warfarin with regard to the primary endpoint (2.3% vs. 3.8% per year), as well as in the prevention of hemorrhagic stroke (0.2% vs. 1.1% per year)[63]. Cardiovascular as well as all-cause mortality were significantly lower in the device group compared with warfarin (1.0% vs. 2.4% per year, *P*=0.005 and 3.2% vs. 4.8% per year, *P*=0.04, respectively). A second randomized controlled study with the WATCHMAN™ device (PREVAIL) [64] demonstrated a higher procedural success rate relative to PROTECT-AF (95.1% vs. 90.9%) and a decrease in the incidence of all 7-day procedure-related complications from 8.7% to 4.2%. The study failed to show non-inferiority for the overall efficacy of the WATCHMAN™ device relative to warfarin. However, the ischemic stroke rate of patients receiving the WATCHMAN™ device was still considerably reduced relative to the untreated AF population [65]. Data from the PROTECT-AF and PREVAIL trials and the continued access studies (CAP, CAP2) of these trials (1739 patients, 7159 patient-years), was pooled to characterize the incidence, predictors, and outcomes of device-related thrombus occurring after implantation of the WATCHMAN device [66]. Device-related thrombus was observed in 3.7% of the patients. Independent predictors for device-related thrombus included prior stroke/TIA, permanent AF and vascular disease. The likelihood of device-related thrombus also increased with decreasing left ventricular ejection fraction and increasing LAA diameter. The analysis indicated that patients with device-related thrombus had a higher risk of ischemic stroke or systemic embolism than those without (annual rates: 6.28% and 1.65%, hazard ratio: 3.22, 95% confidence interval: 1.90 – 5.45, *P*<0.001, adjusted for the patients' CHA_2DS_2-VASc and HAS-BLED scores).

In addition to these randomized data, the international multicenter EWOLUTION registry was initiated to compile real-word clinical outcome for LAA occlusion with the WATCHMAN™ device [67]. Meanwhile, peri-procedural results [68] and 1-year outcomes [69] of this registry have been published from a total of 1025 enrolled patients. Among the enrolled patients, 45.4% had a history of TIA, ischemic stroke or hemorrhagic stroke, and 62% of the patients were considered not suitable for OAC therapy. Successful device deployment was achieved in 98.5% of the patients with no or minimal residual flow in 99.3% of the patients with a successful device implantation. The publication of short-term results [68] reported a total of 34 device- and/or procedure-related serious adverse events, with major bleeding requiring transfusion being the most frequent event (n = 8). Significantly fewer serious adverse events occurred in patients considered to be ineligible for OAC therapy, compared to those eligible for OAC therapy (6.5% vs. 10.2%, *P*=0.042). Overall 30-day mortality was 0.7%. Based on 1-year follow-up data, the annual ischemic stroke rate was 1.1%, representing an 84% reduction compared with the rate expected for a cohort with similar CHA_2DS_2-VASc score and without use of anticoagulation. Major bleeding was reduced by 48%, compared with the anticipated bleeding rate based on the patients' HAS-BLED score (2.9% vs. 5.0% for actual and expected rate, respectively). All-cause mortality at 1 year was 9.8%, reflecting the advanced age and comorbidities in this cohort. Final 2-year outcomes of the EWOLUTION study were presented during the EHRA 2018 congress [70]. An 83% reduction of ischemic stroke, as compared to the expected rate with no therapy was reported (observed vs. expected annual rate: 1.3% vs 7.2%). Major bleeding was reduced by 46%, relative to the expected rate in similar patients treated with warfarin (observed vs. expected annual rate: 2.7% vs. 5.0%) (source: www.watchman.com).

(Detailed clinical experience with the Amplatzer™ devices is described in a separate section of this document).

Cost-effectiveness of LAA occlusion

The majority of the costs related to LAA occlusion are associated with the implantation procedure and immediate follow-up, whereas the costs of OAC continue to accrue year after year. With the observed ischemic stroke and hemorrhage rates, this results in LAA occlusion becoming a cost-effective alternative to OAC at longer time horizons. A Canadian study [71] showed that, although overall lifetime costs of LAA occlusion were higher than for dabigatran, the costs per ICER (incremental cost-effectiveness ratio) were lower for LAA occlusion (Can$41,565 vs. Can$46,560, incremental costs compared with warfarin). In another study [72] both LAA occlusion and NOACs showed to be cost-effective stroke prevention strategies compared with warfarin. Relative to warfarin, LAA occlusion was cost-effective at 7 years. Moreover, it was dominant (more effective and less costly) over NOACs by 5 years and over warfarin by 10 years. In cost-effectiveness modelling for patients with absolute contraindications to warfarin [73], LAA occlusion was cost-effective to stroke prevention with aspirin or apixaban at 5 and 7 years, respectively. It was dominant over both therapies at 8 years and remained so over a 20-year time horizon. These results were consistent with another cost-effectiveness study [74] on stroke prevention in patients contraindicated to anticoagulation, showing that LAA occlusion was more effective while associated with lower lifetime cost compared with aspirin. Results from a budget impact model [75] suggested that LAA occlusion provides long-term economic benefit, with LAA occlusion being less expensive than dabigatran at 8 years after device implantation (total clinical costs: €15,061 vs. €16,184). At 10 years LAA occlusion was only 10% more expensive than warfarin, a less costly OAC drug (€16,763 vs. €15,168). The model inputs, derived from the PROTECT-AF and RE-LY study data, assumed markedly lower hemorrhagic complication rates for LAA occlusion compared to dabigatran, as well as a lower percentage of strokes that were disabling or fatal.

The importance of longer follow-up with regard to cost-effectiveness of LAAO was underlined by results reported by Freeman et al. [76]. Using data from the PROTECT-AF trial, including a relatively large cohort and long-term follow-up, LAAO was cost-effective (ICER: US$20,486 and US$23,422 per QALY compared with warfarin and dabigatran, respectively). However, using the data from shorter follow-up of the PREVAIL study, LAAO with the WATCHMAN device was no longer cost-effective. Using pooled data from the PROTECT-AF and PREVAIL trials [77], LAAO showed to be cost-effective compared with several antithrombotic therapies, including antiplatelets, VKA and NOAC. LAAO was dominant (less costly and more effective) over dabigatran, rivaroxaban and apixaban. Additional evidence for cost-effectiveness of LAAO was obtained from a real-word cohort of 110 patients implanted with the WATCHMAN device, showing lower stroke and major bleeding rates than in the randomized controlled PROTECT-AF study [78]. However, in both settings LAAO achieved cost parity in a relatively short period of time (4.9 – 8.4 years for the real-world cohort against all comparator treatments, 5.9 – 8.4 years for the PROTECT-AF cohort against all comparator treatments except warfarin). Comparator treatments included no therapy, antiplatelets, VKA and NOACs. A Markov model with a 20-year horizon was populated with 10,000 patients. LAAO outcomes were from pooled PROTECT-AF and PREVAIL 5-year follow-up, while warfarin and NOAC outcomes were derived from meta-analyses. LAAO proved not only cost-effective, but cost-saving relative to warfarin and NOACs. [164]

Clinical consensus and guidelines

The 2016 ESC guidelines for the management of AF [15] includes a class IIb recommendation to consider LAA occlusion for AF patients who are contraindicated to long-term OAC. The level B evidence for this recommendation was primarily obtained from randomized trials with the WATCHMAN device and their associated registries and from OAC-intolerant patients enrolled in registry studies with the WATCHMAN and Amplatzer devices. The guidelines call for additional evidence from patients who are truly unsuitable for OAC or who had a stroke while on OAC therapy. Furthermore, randomized comparisons of LAA occluders with NOAC therapy and assessment of the minimal antiplatelet therapy acceptable after LAA occlusion are required. Of note, the randomized controlled PRAGUE-17 trial recently reported results showing non-inferiority of LAAO compared to NOACs in the prevention of major cardiovascular and neurological events [79]. The UK National Institute for Health and Clinical Excellence (NICE) considers LAA occlusion an option for stroke prevention if anticoagulation is contraindicated or not tolerated [80]. NICE also issued an interventional procedure guidance, providing recommendations for patient selection and procedural aspects [81]. A 2011 EHRA position paper [82] considers percutaneous LAA occlusion an option for AF patients contraindicated to OAC due to a high bleeding risk. Stroke prevention without a long-term therapy-related bleeding risk is particularly desired for patients with a history of intracranial bleeding.

In a review paper [83] reflecting the opinion of a number of clinical experts on percutaneous LAA occlusion, patients with the following conditions were identified as potential candidates for this therapy:

- Recurrent ischemic stroke despite well-controlled OAC
- Previous intracranial hemorrhage
- Recurrent GI bleeding
- Comorbidities, such as uncontrolled hypertension, cerebral microbleeds and cerebral amyloid angiopathy
- Coagulapathies
- Intolerance to new OAC drugs

Similar indications were identified in a 2015 review on the incorporation of LAAO into clinical practice by Alli et al. [84]

Indications for LAAO were also addressed by a stroke prevention algorithm included in a 2014 EHRA/EAPCI consensus statement [85]. In brief, OAC is considered the therapy of choice for patients suitable for OAC and with an acceptable bleeding risk. Nevertheless, these patients should be informed about LAAO as a nonpharmacological option for stroke prevention. LAAO should be considered as the primary therapy for patients with an unacceptably high bleeding risk, patients refusing (N)OAC, or with contraindications for systemic anticoagulation.

Anticoagulation is usually suspended after an intracranial hemorrhage. Re-initiation of the therapy may be difficult if the cause of bleeding and bleeding-associated risk factors cannot be treated. In such a situation, the EHRA Practical Guide on the use of NOACs in AF patients [42] refers to LAA occlusion as a possible option to provide the necessary protection against thromboembolic stroke.

AF patients at risk for ischemic stroke undergoing percutaneous coronary intervention may have indications for the combined use of antiplatelets and OAC. However, this combined therapy potentially increases the bleeding risk. According to the 2014 ESC/EACTS guidelines on myocardial revascularization [86] LAAO in combination with antiplatelet therapy may be considered in such patients if they are contraindicated for the combination of OAC and antiplatelets.

A survey among 33 centers within the EHRA electrophysiology research network [87] indicated that the clinical practice with regard to indications for LAAO is highly consistent with current guidelines and expert consensus. Indications for LAAO in high-risk patients (CHA_2DS_2-VASc ≥ 2) included either a history or a high risk of bleeding, thrombo-embolic events despite adequate anticoagulation, end-stage renal dysfunction and the need for prolonged triple anticoagulant and antiplatelet therapy due to severe coronary artery disease treated with stents. Some centers indicated that LAAO was also considered for patients who preferred to discontinue OAC after their AF was treated by pulmonary vein isolation.

A survey [88] conducted by the European Association of Percutaneous Coronary Interventions (EAPCI) indicated a high level of confidence in percutaneous LAA occlusion among the 724 responding physicians (54.3% European respondents). Exclusive use of the Amulet™ (34.4%) and WATCHMAN™ (30.3%) devices was similar among the responding physicians, although the Amulet™ device was more frequently used in Europe. Compared to OAC therapy, 59.3% of the respondents considered LAA occlusion equally effective but safer in the prevention of ischemic stroke. Major concerns with regard to the therapy included peri-procedural complications (40.3% of respondents) and cost (28.8%). While NOACs are available to overcome some of the disadvantages of OAC therapy, most physicians (67%) did not expect this to impact the application of LAA occlusion. In the opinion of the respondents,

the lack of randomized data on the Amulet™ device or comparative effectiveness data versus NOAC therapy does not seem to undermine the value of LAA occlusion in clinical practice.

To encourage a more consistent reporting from studies on LAA occlusion, experts in this field reached a consensus on definitions and endpoints for clinical studies on LAA occlusion. These were published in a consensus document[89], endorsed by EAPCI, EHRA, ECAS, AFNET and IHF.

The 2019 AHA/ACC/HRS guidelines for the management of AF[15] includes a class IIb recommendation to consider LAA occlusion for AF patients at risk for stroke who have contraindications to long-term anticoagulation. Similarly, the 2016 ESC AF guidelines also include a recommendation to consider LAA occlusion for AF patients who are contraindicated to long-term OAC. Both guidelines are level of evidence B, and this recommendation was primarily obtained from randomized trials.

THE AMPLATZER™ LEFT ATRIAL APPENDAGE OCCLUDERS

The Amplatzer Cardiac Plug (ACP) (see Figure 1) consists of a lobe and a disc, connected by a flexible waist and is constructed from a nitinol mesh and a polyester patch[91]. While the lobe is retained within the neck of the LAA and stabilized by retention wires, the disc seals the LAA orifice. The device is available in several sizes to adapt to the dimensions of the LAA.

The second-generation Amplatzer Amulet™ device (see Figures 1 and 2) was released in Europe in 2013[92,93]. Compared to the ACP, the Amulet™ device has a larger disc diameter, a longer lobe and waist and more retention wires. Larger device sizes are available to treat a wider range of anatomical variations, and the Amulet™ device is provided pre-loaded within the delivery system.

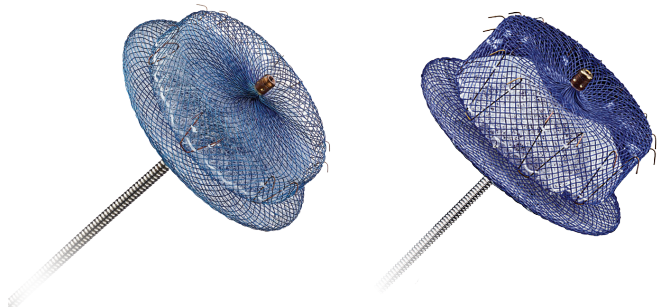


FIGURE 1: THE AMPLATZER™ CARDIAC PLUG (LEFT) AND THE SECOND-GENERATION AMPLATZER™ AMULET™ DEVICE (RIGHT).

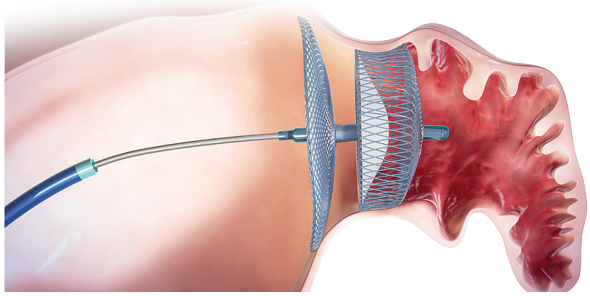


FIGURE 2: THE AMPLATZER™ AMULET™, POSITIONED IN THE LAA BY THE DEDICATED DELIVERY SYSTEM.

Clinical experience with the Amplatzer™ Left Atrial Appendage Occluders

The most comprehensive clinical data from the ACP device was published by Tzikas et al.[94] from a study involving 22 European and Canadian centers. Results of this study, reflecting the initial and advanced experience of operators covering 1047 patients considered for implantation of the ACP device, are summarized in Table 2. Overall, these data show that implantation of the ACP device is feasible and safe and that effective LAA closure is achieved in almost all patients. Effective stroke prevention is indicated by a reduced incidence of stroke compared to the expected stroke rate based on the patients' mean CHA_2DS_2-VASc score. Moreover, the observed bleeding rate is markedly reduced compared to OAC-related bleeding as predicted by the HAS-BLED score.

An analysis on the clinical impact of device-related thrombus and peri-device leak observed within this multicenter cohort did not reveal any association of these findings with an increased risk for cardiovascular events[95]. Evaluation of 339 TEE assessments obtained at a median of 134 days after implantation showed device-related thrombus in 3.2% and moderate (3-5 mm jet) or severe (>5 mm) peri-device leaks in 1.2% of the patients.

TABLE 2: TZIKAS ET AL.[94]: MULTICENTER STUDY INCLUDING 1047 PATIENTS CONSIDERED FOR IMPLANTATION WITH THE AMPLATZER™ CARDIAC PLUG

Demographics:	
Age:	75 ± 8 years
CHA_2DS_2-VASc:	4.5 ± 1.6
HAS-BLED:	3.1 ± 1.2
Procedural results:	
Attempted implantations:	1047
Device implanted:	1019 (97.3%)
Complications:	
Death:	8 (0.76%)
Pericardial tamponade:	13 (1.24%)
• Major bleeding:	13 (1.24%)
• Stroke:	9 (0.86%)
• Device embolization requiring surgery:	1 (0.10%)
• Device embolization (snared):	7 (0.67%)
• Myocardial infarction:	1 (0.10%)
Total:	**45 (4.30%)**
Follow-up:	
Patients included in follow-up:	1001
Patient years of follow-up:	1349 years
TEE at follow-up in 632 patients:	
• LAA closure rate:	98.1%
• Device-related thrombus:	4.4%
Observed annual stroke rate:	2.30%
Expected annual stroke rate:	5.62%
Reduction in stroke rate:	59%
Observed annual bleeding rate:	2.08%
Expected annual bleeding rate:	5.34%
Reduction in bleeding rate:	61%

NOTE: Results from clinical trials are not directly comparable. Information provided for educational purposes only.

Several authors have reported on smaller series of patients implanted with the ACP device. An overview of these studies, as far as implantation and follow-up was performed according to current clinical consensus and recommendations of the manufacturer, is provided in an appendix to this paper. In summary, patients included in these studies had a history of AF, were at medium to high risk for stroke and the majority were contraindicated for OAC. Contraindications were usually due to gastrointestinal bleeding, intracranial bleeding, patient noncompliance and frequent falls. The implant procedures were performed under fluoroscopy and usually under transesophageal echocardiography (TEE). In the majority of procedures, access to the left atrium was achieved by transseptal puncture. In the remaining procedures, the left atrium was reached by means of a patent or reopened foramen ovale or through an atrial septal defect. The reasons reported for not attempting LAA occlusion were the inability to reach the atrial septum due to cardiovascular anomalies, the presence of thrombus in the left atrium (LA) or the LAA, or conditions related to the LA or LAA anatomy.

Reported rates of successful device implantation range between 95% and 100% and in relatively large cohorts experienced operators achieve a procedure-related complication rate between 3% and 4%. Major periprocedural complications typically include stroke, myocardial infarction due to air embolism, device embolization and pericardial perforation and/or significant effusion, requiring pericardiocentesis. Minor complications include insignificant pericardial effusion not requiring intervention, thrombus formation on the device, transient coronary embolism or myocardial ischemia and hematoma at the venous access site.

In a comparative study between the Amplatzer™ Cardiac Plug and WATCHMAN™ devices (40 patients each), Chun et al.[96] found the devices to perform similarly. The rate of successful implantation achieved with the ACP device appeared to be non-significantly better than that of the WATCHMAN™ device (100% vs. 95%). TEE at follow-up revealed a significantly higher incidence of residual peri-device flow (jet < 5 mm) for the WATCHMAN™ device compared to the ACP device, although this was not associated with an increased incidence of thromboembolic events. This finding is consistent with other reports[97,98]. To date, this observation has not been associated with an increased rate of thromboembolic events, although the size of the studied cohorts may have been too small to detect such a relationship.

In the prospective multicenter German LAARGE registry[99], Amplatzer (ACP: n=88, Amulet: n=75) and WATCHMAN (n=95) devices were implanted and outcomes were compared between various LAA morphologies, including chicken wing, cauliflower, windsock, cactus and atypical morphology. While the choice of the device was left to the operator's discretion, the Amplatzer devices were more frequently used for the chicken wing, cauliflower and cactus morphologies, while a more frequent use of WATCHMAN devices was reported for atypical LAA morphologies. Implantation success ranged from 98.8% for cauliflower and windsock morphologies to 100% for cactus morphology and was not significantly different between the four typical morphologies. However, atypical morphologies were associated with a lower success rate (94.0%). Safety events were not significantly different between any of the four typical and atypical LAA morphologies and ranged between 2.4% and 5.8% for the various morphologies.

LAAO versus NOACs

The PRAGUE-17 study was the first randomized controlled trial comparing LAAO with NOACs in AF patients at high risk of ischemic stroke and bleeding. The study was conducted in 10 Czech centers and was powered to demonstrate non-inferiority of LAAO compared to NOACs with regard to prevention of primary endpoint events. These were composed of stroke or TIA, systemic embolism, clinically significant bleeding, cardiovascular death and significant peri-procedural or device-related complications. The most important study data and outcomes are summarized in Table 3.

First results of the study were presented at the ESC 2019 congress[100]. The PRAGUE-17 outcomes demonstrated that LAAO is non-inferior to NOACs in preventing major cardiovascular and neurological events in high-risk AF patients. Procedure/device-related complications warrant incremental improvements in operator techniques and device technology. Nevertheless, similar overall outcomes may be expected from each of the strategies, and LAAO may be considered for high-risk AF patients when supported by an adequate rationale for a non-pharmacological approach.

TABLE 3: PRAGUE-17 STUDY

	NOAC	LAAO
Patients	201 patients in ITT analysis	201 patients in ITT analysis
Mean CHA_2DS_2-VASc **Mean HAS-BLED**	4.7 ± 1.5 3.0 ± 0.9	4.7 ± 1.5 3.1 ± 0.9
Treatment	apixaban (95.5%) dabigatran (4.0%) rivaroxaban (0.5%)	Abbott AMPLATZER Amulet (61.3%) Boston Scientific WATCHMAN (38.7%) 12 patients crossed over to NOAC Implant success: 96.8% of attempts Complications: 4.8% (including 2 procedure/device-related deaths) Post-implant: DAPT in 82%
Follow-up	20.8 ± 10.8 months	
Outcomes	ITT analysis: LAAO is non-inferior to NOAC in the prevention of primary endpoint events (p-value for non-inferiority: 0.004). Results consistent with ITT analysis were obtained from on-treatment analysis (p=0.013) and per-protocol analysis (p=0.003).	

Results of a retrospective analysis, comparing Amplatzer and WATCHMAN devices, was presented by Yu et al.[101] during the 2018 EuroPCR congress. Using data from two registries, patients were matched regarding their stroke and bleeding risk, resulting in 2 groups of 250 patients each, implanted with one of the devices and comprising a total follow-up duration of 1270 patient years. The study did not find a difference between the devices in the primary composite safety endpoint of major periprocedural adverse events and major, life-threatening or fatal bleeding (annual rates: 5.6% vs. 4.4% for WATCHMAN and Amplatzer devices, respectively; *P*=0.35). The rate of the primary efficacy endpoint (composite of stroke, systemic embolism and cardiovascular or unexplained death) was also similar (5.7% vs. 6.1% for WATCHMAN and Amplatzer, respectively; *P*=0.74). As a result, both devices achieved similar net clinical benefit (combining safety and efficacy endpoints) of at annual rates of 10.6% and 9.6% for WATCHMAN and Amplatzer devices, respectively (*P*=0.24). Compared with WATCHMAN

devices, Amplatzer devices were associated with lower annual rates of all-cause stroke and TIA and a slightly higher rate of systemic embolism, but none of the differences reached statistical significance. Survival analysis revealed a significantly lower risk of major, life-threatening and fatal bleeding with the Amplatzer devices, compared with WATCHMAN devices (hazard ratio: 0.51, 95% confidence interval: 0.27 – 1.0, *P*=0.036). Comparison of antithrombotic therapy showed that OAC was used by significantly more patients implanted with the WATCHMAN device, compared with Amplatzer devices (10.8% vs. 2%, *P*<0.0001).

A step-by-step approach of LAA occlusion with the Amulet™ device was described by Tzikas et al. [102], reflecting the expert consensus with regard to device implantation. This publication provides recommendations and best practices regarding the essential steps of the device implantation procedure, including vascular access, device sizing, fluoroscopy views during implantation, sheath exchange, device deployment and confirmation of appropriate device implantation. In addition, specific procedural challenges are discussed, such as recapturing the device and the sandwich technique to implant a device in case of a chicken wing anatomy.

Learning curve effects

Both the implant success rate and the procedural complication rate are associated with a learning curve effect. For instance, a higher level of experience in the ACP Post Market Observational Study resulted in fewer periprocedural complications compared to the initial European registry (2.9% versus 7.3%) and fewer device exchanges due to inappropriate device sizing (7.4% versus 18.2%)[59]. Increased success rates, more appropriate device sizing and reduced complication rates with increasing operator experience are also reported by other authors [103 104]. In a study that specifically addressed this learning curve, three major procedural complications occurred in the first ten ACP implantations, while implantation of the next 11 devices was uneventful [104]. The importance of operator experience was also underlined by an analysis of 268 LAAO procedures (primarily with the WATCHMAN™ device) performed between 2006 and 2010 in the USA [105]. Centers with a relatively high LAAO volume were associated with lower procedural complication rates and mortality, compared with lower volume centers. Specifically, centers performing ≥18 procedures per year achieved significantly lower mortality and complication rates than centers with ≤2 procedures annually (3% vs. 46%, *P*<0.001).

LAAO in specific sub-populations

Several studies have evaluated the outcomes of LAAO in specific sub-populations. Gafoor et al. [106] performed LAA occlusion in octogenarians, and concluded that, like other devices used in this study, the ACP device is safe and efficacious for stroke prevention in elderly AF patients.

A number of additional analyses were performed on the multicenter cohort reported by Tzikas et al. [94] to evaluate LAAO in specific sub-populations. Freixa et al. [107] found similar major adverse event rates between patients <75 years and ≥75 years of age, although the rate of cardiac tamponade was significantly higher in older patients. At follow-up, all-cause and non-cardiovascular mortality were significantly higher and cardiovascular mortality was non-significantly higher in older patients. Nevertheless, with regard to stroke reduction, similar reductions in stroke and bleeding compared to expected rates were observed among the groups (stroke reduction: 69 vs 74.9%, bleeding risk reduction: 75.5 vs. 69.2% for patients <75 and ≥75 years, respectively). Overall, these results indicate that LAAO should not be discouraged on the basis of age.

With regard to patients with chronic kidney disease (CKD), Kefer et al. [108] reported that the procedural safety of LAA occlusion with the ACP device was similarly high in these patients compared with those with normal renal function. A significantly lower overall survival was observed in patients with end-stage renal failure (eGFR < 30 ml/min/1.73m^2, 84 vs. 93% at 2 years), but the rate of non-fatal major adverse events during follow-up was similar (4.05 vs 4.5%). Irrespective of the stage of chronic kidney disease (CKD), LAAO provided a reduction in stroke rate and bleeding rate compared with the expected rates based on the patients' risk score. Overall, in the sub-cohort of patients with CKD the annual rates of stroke/TIA and major bleeding were 2.3% and 2.1%, respectively, representing a reduction of 62% and 60%, compared with risk-based estimations. This outcome was achieved in a CKD population at high risk for bleeding with 96.3% of the patients off OAC.

Another sub-study using the data from the multicenter ACP cohort involved the comparison of 198 patients with prior intracranial bleeding versus 849 other patients enrolled for this study [109]. While LAAO was shown to be equally safe in both subgroups, it was associated with a reduction of cerebrovascular events and hemorrhagic events, compared with the expected rates according to the CHA_2DS_2-VASc and HAS-BLED risk scores. Moreover, reductions were higher in patients with prior intracranial bleeding than in other patients (annual stroke rate reduction: 75% vs. 59%; bleeding rate reduction: 89% vs. 60%). At follow-up, patients with prior intracranial bleeding were more frequently prescribed aspirin monotherapy and were less frequently on dual antiplatelet therapy. In addition, none of these patients were on VKA or NOAC therapy. Despite the less intensive antithrombotic therapy in patients with prior intracranial bleeding, no higher rate of device-related thrombus was found in this subgroup.

A total of 151 patients (14.4%) enrolled in this multicenter registry had a history of major GI bleeding. Lempereur et al. [110] compared outcomes in this subgroup of patients with those in patients without prior major GI bleeding (n=896). Compared with patients without prior major GI bleeding, a history of GI bleeding was associated with a significantly higher incidence of periprocedural bleeding (4.0% vs. 0.8%, *P*=0.001) and major bleeding during follow-up (6.0% vs. 2.1%, *P*=0.006). No significant differences were found between the subgroups with regard to death, stroke and TIA. With the inclusion of procedural events, the annual stroke rate in patients with prior GI bleeding was reduced by 61.4%, when compared with the expected rate based on the patients' risk score. This reduction was similar to the reduction in patients without prior GI bleeding (62.7%). Patients with a history of GI bleeding had a lower reduction in major bleeding than those without prior GI bleeding (20.1% vs. 71.1%), but their bleeding rate was still reduced compared to the HAS BLED-predicted rate.

AF patients indicated for OAC who had intracranial bleeding constitute a particularly difficult group with respect to their stroke risk management. In many occasions these patients do not receive anticoagulant therapy due to concerns for recurrent intracranial bleeding or intracerebral hemorrhage (ICH). Fahmy et al. [109] reported the outcome of LAA occlusion in 26 patients with prior intracranial or intraocular bleeding, using the ACP (n=12), Amulet™ (n=5) and WATCHMAN™ (n=9) devices. All devices were successfully implanted, although one ACP device appeared to be embolized at one day after the procedure. Patients were discharged on single or dual antiplatelet therapy, which was discontinued at one to three months in the majority of patients. Over a mean follow-up of 11.9 months, no strokes, systemic embolism or bleeding occurred. One patient had a TIA of unknown cause at 21 months after the procedure. These results suggest that LAA occlusion is a feasible alternative for patients with prior intracranial bleeding.

Similar results were reported from a propensity score matched study including a larger sample obtained from 13 Nordic LAA occlusion centers [112]. From 172 patients implanted with the ACP or Amulet™ device and 787 AF patients with prior intracerebral hemorrhage a propensity score matched cohort was created, including 151 patients receiving standard care and 151 patients who underwent LAA occlusion. Patients were matched with regard to their stroke risk (CHA_2DS_2-VASc score) and bleeding risk (HAS-BLED score). Compared to standard care, LAA occlusion achieved a significantly higher survival from composite endpoint events, including all-cause mortality, acute ischemic stroke and major bleeding (6 vs. 33 events, event rate: 53.3 vs 366.7 events per 1000 patient-years). This translated into a relative risk reduction of 84% associated with LAA occlusion versus standard care (HR: 0.16, 95% CI: 0.07 – 0.37, $P<0.05$). While all elements of the composite endpoint occurred less frequently in the LAA occlusion group than in the group receiving standard care, the most marked difference was observed for mortality, showing a significant reduction of the relative risk by 89%. Further analysis was performed by including only patients in the standard care group who initiated OAC therapy within 180 days after the index event, i.e. those patients who received the most effective antithrombotic therapy. In this comparison, LAA occlusion still achieved a significant relative risk reduction for the composite endpoint of 74%, with a 72% reduction in the relative risk for mortality. These results suggested that LAA occlusion may be of major clinical benefit for stroke prevention in AF patients with prior ICH. To confirm these results, the randomized controlled STROKECLOSE trial is currently ongoing. In this trial, AF patients who had an ICH are randomized to LAA occlusion or medical treatment.

Device-related aspects

Freixa et al. [113] found a lower degree of oversizing of the ACP device to be associated with residual leaks at follow-up. The shape of the implanted device did not appear to influence the presence of residual leaks and neither the shape nor the degree of oversizing were related to a particular clinical outcome.

In a Korean multicenter registry [114], 96 patients underwent LAA occlusion with the ACP device (n=50) or the WATCHMAN™ device (n=46). Peri-device leaks were more frequently found in the Watchman™ device, compared to the ACP device. Post-implant TEE detected leaks in 15.2% and 37.0% of the ACP and WATCHMAN™ devices, respectively (P=0.004). Similarly, at TEE follow-up within six months, peri-device leaks were present in 14.9% and 37.0% of the cases with the ACP and WATCHMAN™ devices, respectively (P=0.015). Despite the significant differences in peri-device leakage between the devices, no differences were observed in the rates of thromboembolic events. In the WATCHMAN™ group one TIA and one minor stroke occurred, with a peri-device leak in the patient who had a TIA but not in the patient with a stroke. In the ACP group, two patients had a minor stroke, both without evidence of peri-device leakage.

Another comparison between Amplatzer™ (ACP and Amulet™) and WATCHMAN™ devices was reported by Figini et al. [115]. No marked differences between the outcomes from both devices were reported, except for a significantly higher incidence of severe peri-device leaks with the WATCHMAN™ device compared with Amplatzer™ devices (11.4% vs. 6.3%, P=0.037).

Using the highly sensitive technique of cardiac CT during follow-up at ≥3 months after implantation of the ACP device, Jaguszewski et al. [115] found peri-device leaks in 15 (62%) out of 24 patients. The leaks were small (1.5 ± 1.4 mm) and more than 90% of them located at the posterior portion of the LAA orifice. TEE identified leaks in 36% of the patients in the same cohort. Similar results were reported from a study by Saw et al. [117] including first generation ACP, Amulet™ and WATCHMAN™ devices. Among 44 patients, cardiac CT detected residual leaks in 28 (63.6%) with no significant differences between the devices. TEE showed to be less sensitive in detecting residual flow (13.6% at the end of the procedure and 34.8% at follow-up). With regard to the ACP and Amulet™ devices, both studies identified off-axis lobe orientation (not perpendicular to the LAA neck) and inappropriate lobe compression as predisposing factors for residual leaks. From these studies, there is no indication that the presence of residual leak at follow-up influences the risk of stroke or systemic embolism, although the small size of the cohorts does not allow definite conclusions regarding this influence. Berti et al. [118] used cardiac CT for the assessment of 89 ACP and Amulet™ devices at 6 months after implantation and found opacification of the appendage in 44 patients (44.9%). In only 22 of these cases an incomplete apposition of the device was observed and it was hypothesized that the remaining 22 cases could be associated with incomplete endothelialization. TEE, performed in 20 patients who could no undergo cardiac CT, a leak was found in four patients (20%).

In a cohort of 34 patients, followed for 12 months, Plicht et al.[119] observed thrombi on the ACP device in three patients before discharge and in 3 more patients at 3 months follow-up, despite dual antiplatelet therapy. A higher $CHADS_2$ score, CHA_2DS_2-VASc score and pre-interventional platelet count, and reduced ejection fraction were identified as risk factors for device thrombus. Thrombi were resolved by intravenous heparin and/or VKA-therapy. No clinically apparent thrombo-embolic events occurred during 12 months of follow-up. With regard to the formation of device-related thrombus, the study by Korsholm et al. [120] found that aspirin monotherapy after LAAO with Amplatzer devices was not associated with an increased risk of device-related thrombus, compared with dual antiplatelet therapy, which is routinely prescribed. During a median follow-up time of 2.3 years, two cases of device-related thrombus occurred.

A French multicenter study comparing thrombus formation on nitinol cage occlusion devices (WATCHMAN) versus nitinol plug devices (Amplatzer Cardiac Plug and Amulet) [120] found no significant difference in the incidence of device-related thrombus in a multivariate analysis. Although the crude rate of thrombus formation was higher for plug-type devices than for cage devices (11.0% vs. 5.5%), patients implanted with the nitinol plug device had a higher CHA_2DS_2--VASc score and were less likely to receive antithrombotic therapy after discharge. These factors, as well as a history of ischemic stroke, were found to be independent predictors for thrombus formation on the device. The study also reported that device-related thrombus was independently associated with the occurrence of stroke or TIA (hazard ratio: 4.39, 95% confidence interval: 1.05 – 18.43, P=0.04). The authors recommended active screening for early detection and treatment of device-associated thrombus after device implantation. Major limitations of this study include the fact that only 51.3% of the patients with a nitinol plug device underwent LAA imaging during follow-up, as well as the use of TEE or CT scan to assess the devices. Moreover, the authors stated that multiple confounding variables between the groups would prevent definite conclusions for comparisons between devices, despite multivariable analysis.

Long-term follow-up

Several authors have reported on the longer-term follow-up of patients implanted with the ACP device. From the large multicenter study reported on by Tzikas et al. [94] follow-up is available on 1001 patients, yielding a total follow-up experience of 1349 patient-years. Within the follow-up cohort, a composed annual rate of ischemic stroke and TIA of 2.30% was observed. This represents a reduction of 59% compared to the expected stroke rate based on the cohort's mean CHA_2DS_2-–VASc score of 4.43. Similarly, bleeding was observed at a lower rate than expected based on the patients' HAS-BLED score (5.34% vs. 2.08%, representing a reduction of 61%).

The ACP European Observational Study, including 204 patients, reported an annual stroke rate of 1.98% over a total follow-up of 101 patient years [59]. This represents a reduction of 65% relative to the expected stroke rate, based on the patients' $CHADS_2$ score. In a longer-term follow-up of 76 patients in this study [122] (211 patient years) an annual stroke rate of 0.94% was observed, compared to the CHA_2DS_2--VASc-predicted rate of 4.89%. At the final follow-up of this cohort 61 patients (80%) were receiving aspirin only.

From a cohort of 128 patients successfully implanted with the ACP device, Santoro et al. [123] reported an annual stroke rate of 0.8%, representing a reduction of 86% compared with the expected rate according to the patients' CHA_2DS_2--VASc scores. When accounting for the additional preventive effect of clopidogrel, prescribed during the first three months after implantation, the stroke reduction provided by the device is still 80%. The reduction in stroke and TIA observed in this study was 67.5% (expected: 7.7%, observed: 2.5%). Major bleeding occurred at an annual rate of 1.3%, which is similar to bleeding rates reported for patients receiving aspirin and markedly lower than the HAS BLED-expected bleeding rate of 3.1%.

Lopez-Minguez et al. [124] reported an annual rate of stroke/TIA of 2.4% over a total follow-up experience of 290 patient years. Compared to the expected rate, based on the $CHADS_2$ score (9.6%) this implies a stroke risk reduction of 75%. These authors also reported a reduction in major bleeding rate from the HAS-BLED-predicted rate of 6.6% to 3.1%, representing a 53.0% reduction.

In another study, the ACP device was implanted in 96 patients with a median CHA_2DS_2--VASc score of 5 and a median HAS BLED score of 3, representing a very high risk of both ischemic stroke and bleeding. This was also reflected by the frequencies of previous stroke (65.5%) and bleeding (61.4%) in this cohort. During a median follow-up duration of 9 months and 93.4 patient-years, one TIA and two ischemic strokes occurred. This corresponded with an observed annual rate of thromboembolic events of 3.2%, compared with an estimated annual risk of 6.7 – 10.0% for patients without warfarin, indicating a 52 – 68 % reduction. Similarly, the bleeding risk was reduced by 70 – 81%, compared to patients on warfarin with a similar HAS-BLED score.

First results from the Belgian LAA occlusion registry were published by Kefer et al. [124] in 2013, including 90 patients implanted with the ACP device and 75 patients followed for 1 year. Over a total of 75 patient-years a reduction in stroke rate of 58% was achieved (observed stroke rate: 2.14%/year vs. expected rate: 5.08%). Within the first year of follow-up, no major bleeding events occurred in this cohort with a mean HAS-BLED score of 3.3 ± 1.3. Additional data from this cohort were presented at the EuroPCR 2016 meeting [125], including 194 patients implanted with an ACP or Amulet™ device and 64 patients who received a WATCHMAN™ device and a total follow-up of 290 patient-years. Overall survival was similar in the Amplatzer™ (89 ± 3%) and WATCHMAN™ (91 ± 8%) groups (P=0.65). Devices were also associated with similar event-free survival rates (88 ± 3% and 91 ± 8% for Amplatzer™ and WATCHMAN™ devices, respectively). When data from both devices was pooled, an overall reduction in stroke rate of 81% was achieved (expected: 5.3% vs. observed: 1.03%), while the bleeding rate was reduced by 49% (expected: 4.7% vs. observed: 2.4%). At the last follow-up, 96% of the patients did not use anticoagulants. No differences between the devices were found with respect to residual leaks observed by TEE (no leaks in 92.7% and 90.6% of the Amplatzer™ and WATCHMAN™ devices, respectively).

Similar results were reported from a cohort of 107 patients who were treated with aspirin monotherapy after undergoing LAAO with the ACP and Amulet devices [120]. The median follow-up period of this cohort was 2.3 years with a cumulative follow-up experience of 265 patient years. Compared with predictions based on CHA_2DS_2--VASc and HAS-BLED scores, the annual stroke rate was reduced by 61% (observed: 2.3% vs. predicted: 5.8%) while the rate of major bleeding was reduced by 57% (observed: 3.8% vs. predicted: 8.8%).

Figini et al. [115] reported on the long-term outcome of 99 patients implanted with the ACP and Amulet™ devices. This study also included 66 patients implanted with the WATCHMAN™ device, and since the follow-up period was not specified per device group, the actual rate of thromboembolic events during follow-up cannot be estimated for this cohort. Nevertheless, during a mean follow-up period of 448 days, only a single TIA occurred in the Amplatzer™ group. With an expected event rate based on the CHA_2DS_2--VASc score of 5.9%, this indicates a substantial reduction in stroke rate.

Results from a propensity score adjusted analysis, comparing LAA occlusion with medical treatment in AF patients with a high bleeding risk were published by Budts et al. [127] Outcome data from an all-comer population of patients undergoing LAA occlusion with the ACP device were retrieved from the Belgian LAA occlusion registry. Data from an ICH survivor cohort, receiving 'suboptimal standard' treatment was used as a control. The outcome was compared after adjusting for a propensity score, reflecting the predicted probability of receiving the trial intervention (LAA occlusion) given the pattern of observed patient characteristics. In this way, the effect of LAA occlusion was estimated by accounting for covariates (age, gender, stroke risk, bleeding risk) that predict whether or not a patient will receive the therapy. Overall, 125 patients implanted with the ACP device (median follow-up: 1.0 year) were compared with a control group of 113 patients (median follow-up: 2.5 years). With propensity score adjustment, LAA occlusion was associated with a significantly higher freedom from the composite endpoint of death, ischemic and hemorrhagic stroke, TIA, systemic embolism and major bleeding, compared with the controls (HR: 2.012, P=0.021). For the combination of stroke, TIA and systemic embolism there was a clear tendency for LAA occlusion towards fewer events (P=0.052), while no significant differences were found between the groups regarding major bleeding events (P=0.083).

Propensity score matching was applied by Gloekler et al. [128] to compare the outcomes of LAAO and oral anticoagulation. For this analysis, 500 patients who underwent LAAO with Amplatzer devices were matched with 500 patients on anticoagulation therapy (VKA or NOAC). Matching criteria included gender, age, body mass index, stroke and bleeding risk, coronary artery disease, left ventricular ejection fraction, renal function and hemoglobin. Mean CHA_2DS_2-VASc scores were 4.33 and 4.34 for LAAO and OAC groups, respectively, while HAS-BLED scores were 2.98 and 2.90 for the respective groups. While the primary safety endpoint (major procedural adverse events and major/life-threatening bleeding) occurred more frequently in the LAAO group than in the OAC group, the difference was not statistically significant over a mean follow-up period of 2.7 ± 1.5 years (P=0.26), suggesting similar safety for both therapies. Freedom from primary safety endpoints was initially lower in the LAAO group, due to procedural complications. However, it exceeded the freedom from primary safety endpoints in the OAC group after approximately 2 years post-LAAO, while the survival in the OAC group gradually declined over time. A major factor with regard to safety was the overall rate of major/life-threatening bleeding, which was significantly lower in the LAAO group compared with OAC (4.5 vs. 10.2 events per 100 patient years, P<0.0001).

The primary efficacy endpoint (stroke, systemic embolism, cardiovascular/unexplained death) was significantly less frequent in the LAAO group (5.6 vs. 7.8 events per 100 patient years for LAAO and OAC, respectively, P=0.026). The rate of combined hazard endpoints (i.e. net clinical benefit, accounting for both safety and efficacy endpoints) was also significantly lower in the LAAO group (8.1 vs 10.9 events per 100 patient years, P=0.018). A

major contribution to this increased net clinical benefit was the significantly lower all-cause mortality in the LAAO group, compared with OAC (8.3 vs. 11.6 events per 100 patient years, *P*=0.007), which was mainly driven by a significantly lower rate of cardiovascular and unexplained deaths in the LAAO group. The authors concluded that this propensity score matched analysis showed that LAAO with Amplatzer devices has a net clinical benefit over OAC with VKA or NOAC, due to superior efficacy and similar safety. LAAO also showed to be associated with lower all-cause and cardiovascular mortality.

Similar reductions in stroke and TIA rates have been reported from smaller studies, with some possible overlap with the results presented by Tzikas et al. [94]. The reduction in stroke rates compared to the expected rates based on the patients' risk scores is shown for several studies in Figure 4. Additional details on these studies are provided in the appendix. Larger studies (>100 patients years of follow-up) reported a stroke reduction after implantation of the ACP device between 59 and 75% (see Figure 6 and Table 2). Overall, results from smaller studies are consistent with those from larger studies, although based on less extensive follow-up experience. In view of these results, it should be acknowledged that patients implanted with the ACP device were most commonly prescribed short-term dual antiplatelet therapy (1 to 3 months, usually a combination of clopidogrel and aspirin), followed by indefinite aspirin therapy. A 2014 review [129] underlines the need for further assessment of LAA occlusion therapy without the need for long-term antithrombotic therapy, to further reduce the bleeding risk in patients who are considered for LAA occlusion because of their vulnerability to hemorrhagic complications.

Clinical data on the Amplatzer™ Amulet™ device

The most comprehensive clinical experience on the Amulet device has been collected within the global prospective multicenter Amulet observational study [130]. Conducted to obtain a real-world representation of LAAO in a population at high risk for ischemic stroke and contraindicated to OAC, a rigorous study design was applied to ensure objective and consistent data interpretation,

TABLE 4A: 2 YEAR OBJECTIVES OF THE GLOBAL AMULET OBSERVATIONAL STUDY

PRIMARY OBJECTIVES	
Procedural serious adverse events Patients with pericardial effusion or tamponade Patients with a major vascular complication	3.2% 1.5% 0.9%
Late serious adverse events Major bleeding event Device-related thrombus rate (@ 2-years)	 0.5% 1.6%
Cardiovascular events Ischemic stroke Systemic embolism Cardiovascular death (@ 2-years)	 2.2%/year 0.0%/year 5.5%
Major bleeding events Related to the procedure or device	7.2%/year 1.7%/year
SECONDARY OBJECTIVES	
Technical success	99.1%
Procedural success	95.8%
OAC usage Discharge 2-years	 11.2% 6.6%
Adequate LAA sealing (residual flow absent or <3mm) Procedure 1-3m following implant	 99.3% 98.4%

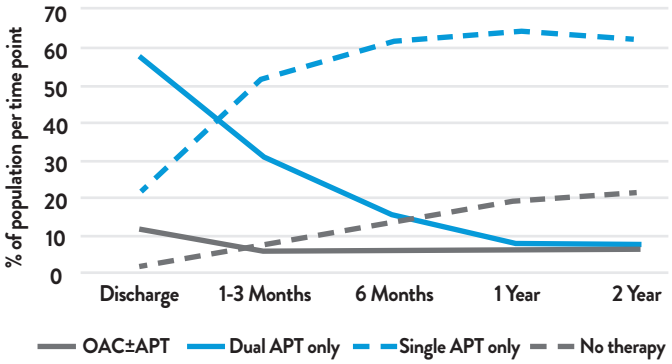


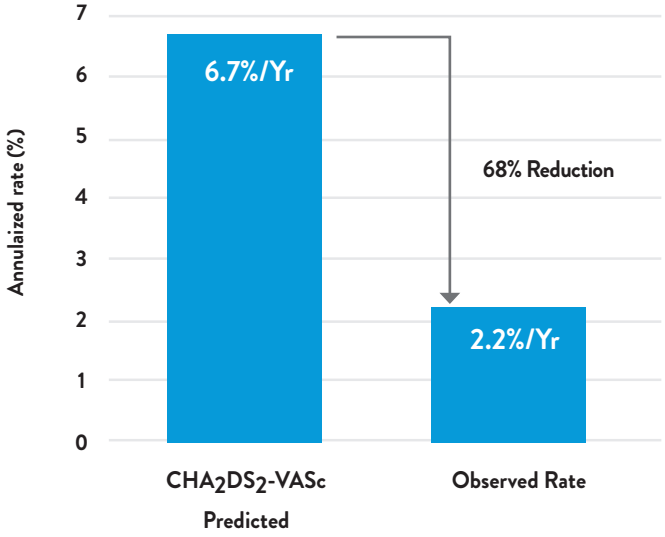
FIGURE 2A: ANTITHROMBOTIC MEDICATION USE TO 2 YEARS

and thereby obtain outcomes with high clinical significance. To this end, adverse events were adjudicated by an independent committee of clinical experts and echocardiographic images were evaluated by an independent core laboratory. Procedural and early results [131] and 1-year outcomes [131] have been published, while the Primary Results following 2 years of follow-up were presented at EuroPCR 2019 [133]. The study enrolled a total of 1088 patients with mean CHA_2DS_2-VASc and HAS-BLED scores of 4.2 ± 1.6 and 3.3

TABLE 4B: 2-YEAR OUTCOMES OF THE GLOBAL AMULET OBSERVATIONAL STUDY

ANNUALIZED RATES	
Ischemic stroke: Observed rate CHA_2DS_2-VASc predicted rate Observed vs. predicted rate	 2.2% 6.7% - 68%
Major bleeding (BARC type ≥3): Observed rate Related to procedure or device Over the 1st year Over the 2nd year	 7.2% 1.7% 10.1% 4.0%
Ischemic stroke	2.2%
Systemic embolism	0%
KAPLAN-MEIER ESTIMATES AT 2-YEARS	
Device related thrombus	1.6%
Mortality: Cardiovascular death	 5.5%

FIGURE 2B: ISCHEMIC STROKE RATE



NOTE: Results from clinical trials are not directly comparable. Information provided for educational purposes only.

± 1.1, respectively, and with 83% of the patients contraindicated to long-term OAC. As shown in Table 6a, the Amulet device was successfully implanted in 1078 patients (99.1%). Early major adverse events (during the procedure or index hospitalization) occurred in 3.6% of the patients. Adequate LAA occlusion (<3 mm jet on color Doppler echocardiography) was observed peri-procedurally in 99.3% of the patients and in 98.4% of the patients at 1 – 3 months post-implant. Most patients were able to avoid the use of dual antiplatelet or OAC therapy shortly after implantation of the Amulet device. The proportion of patients on single antiplatelet therapy or no antithrombotic medications was 84% at both 1-year and 2-years post Amulet implant, as summarized in Figure 2a.

Key outcomes at 2 years, reported from a total follow-up of 1933 patient-years, are summarized in Table 6b. LAAO with the Amulet device achieved a reduction in the annual rate of ischemic stroke of 68%, compared to the expected ischemic stroke rate in untreated patients with the same CHA_2DS_2-VASc score, as summarized in Figure 2b. The annual rate of major bleeding (BARC type ≥3) was 7.2%, which is similar to the HAS-BLED-predicted rate for a population at high risk of major bleeding. The Amulet observational study enrolled a population that was at higher risk for major bleeding than earlier large registries on LAAO, as indicated by the large proportion of patients with prior major bleeding (72%) and/or contraindications to OAC (83%) and a high HAS-BLED score (3.3). Major bleeding related to procedure or device was adjudicated at a rate of 1.7% per year, with the major bleeding rate over the first year at 10.1% per year reducing to 4.0% per year after two years. Major bleeding over the first year was higher due to procedure-related bleeds and use of DAPT post implant. Most patients were on single antiplatelet therapy or no antithrombotic medications in the second year, as summarized in Figure 2a. Device-related thrombus was an infrequent event in this population primarily discharged without OAC, with a 2-year rate of device-related thrombus of 1.6%. ,with 82% of these DRT patients not experiencing any ischemic neurologic events.[165] At 2 years, annualized death rates from cardiovascular events were 5.5% and annualized rates of ischemic stroke were 2.2%.

The results of the global Amulet observational study confirmed that the Amulet device provides effective ischemic stroke reduction in patients at high risk of ischemic stroke and contraindicated to long-term OAC. These results are of high clinical significance, supported by a study design and execution that was as rigorous as reasonably possible within a real-word registry.

Additional data from larger studies (≥40 patients) in which the Amulet™ device was used either alone or in combination with the ACP device, are provided in the appendix.

A comparative study including 50 ACP devices and 50 Amulet™ devices was reported by Gloekler et al.[134]. Procedural safety of the LAAO devices was reported to be similar (combined safety endpoint of events with need for cardiovascular bailout surgery, stroke, cardiac tamponade with need for drainage and peri-procedural death: 6% for ACP vs. 8% for the Amulet™ device). Implantation success was similar for both devices (94% and 98% for ACP and the Amulet™ device, respectively). The authors concluded that there were no substantial differences between the two devices with respect to procedural safety and device performance. Of note, in this study the devices were implanted with fluoroscopic guidance only (no use of echocardiography, which is recommended by the manufacturer).

Another comparison between the two Amplatzer™ devices was published by Abualsaud et al.[135], including 31 ACP and 28 Amulet™ devices. Exchange of the initial device for a differently sized device was required in one Amulet™ device case and five ACP cases. Three patients in the Amulet™ device group had a very large LAA with a landing zone diameter >31 mm, which were all successfully sealed with a 34 mm device. Immediate LAA sealing was observed in 97% and 100% of ACP and Amulet™ device procedures. TEE at follow-up revealed a significantly higher degree of complete LAA occlusion (i.e. absence of peri-device leaks) in the Amulet™ device group, compared to the ACP device. Two patients with an ACP device and none with an Amulet™ device suffered a stroke. The authors concluded that this initial series showed similar procedural and short-term outcome with both devices.

Al-Kassou et al.[136] compared the ACP and Amulet devices in a cohort of 196 patients. They reported favorable procedural parameters for the Amulet device (reduced fluoroscopy time, radiation dose and contrast dye use). LAAO with the Amulet device was also associated with fewer device exchanges due to sizing and peri-device leaks were less frequent with the Amulet device, compared with the ACP device.

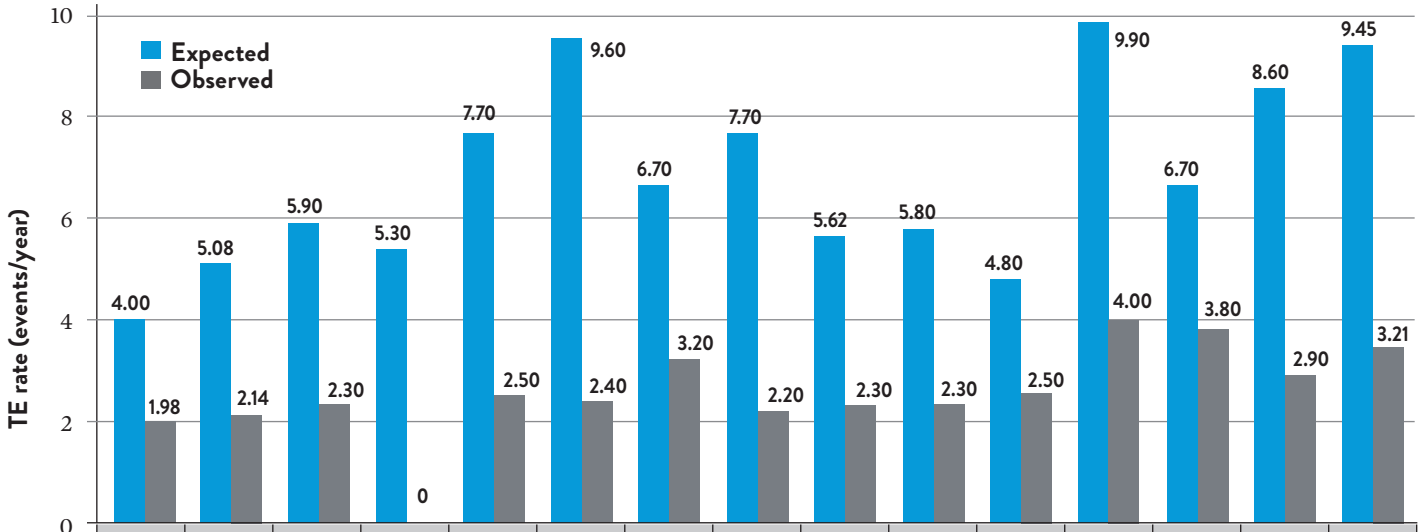
Several smaller series using the Amulet device have been reported.

Freixa et al.[137] reported successful implantation of the Amulet™ device in 24 out of 25 patients. The single unsuccessful case was in a patient with a bi-lobar, small and short LAA. Among the successful implantations, the device was implanted in three patients with a very large LAA (diameter at landing zone > 31 mm) and four patients with an extreme chicken-wing morphology of the LAA. No procedural device embolization, stroke or pericardial effusion occurred. At 2-3 months follow-up (21 patients) no stroke, peripheral embolism or bleeding had occurred and TEE showed no residual leak > 3 mm in any of the patients.

Lam et al.[138] reported on the implantation of the Amulet™ device in 17 patients. Implantation was successful in all patients. The device was fully recaptured in one case to exchange the device for a smaller device and partially recaptured in three other cases to improve the final device position. Apart from a single pericardial effusion no other procedural complications occurred. In one patient a 28 mm device was used to successfully occlude an incompletely closed LAA after implantation of a WATCHMAN™ device, three years prior. No deaths, strokes, systemic thromboembolism, myocardial infarctions, or additional bleeding complications had occurred at 90 days post-implant. TEE follow-up revealed no device associated thrombi or pericardial effusions, and only minor peri-device leaks (<2 mm) in two patients.

Successful implantation of the Amulet™ device in 20 patients was reported by Cruz-González et al.[139] with no major peri-procedural complications. During a median follow-up of 60 days one patient had a TIA, most likely due to prematurely terminated antiplatelet therapy and another patient was diagnosed with pericarditis. Echocardiography demonstrated complete LAA occlusion with no residual flow and without thrombosis or pericardial effusion in all patients.

Besides its straightforward implantation in uncomplicated anatomies, the Amulet™ device is reported to perform well in challenging LAA anatomies, such as a large diameter LAA or a "chicken-wing" morphology[139 140 141]



	Walsh	Kefer	Urena	Chun	Santoro	Lopez-Minguez	Kebernik	Berti	Tzikas	Korsholm	Szymala	Jalal	Masoud	Berti	Landmesser
Patients	204	75	52	40	128	158	89	110	1001	107	80	73	80	542	1088
Patient years	101	75	87	NR	238	290	93	264	1349	265	40	75	80	896	1934
Strokes/ TIAs	2	2	2	0	5	7	3	6	31	6	1	3	3	22	62
TE rate reduction	51%	58%	61%	–	68%	75%	52%	71%	59%	60%	48%	60%	43%	66%	66%

FIGURE 4: Expected and observed stroke rates in patients implanted with the ACP and Amulet devices, including studies with ≥40 patients. The number of patients represents the patients who completed the follow-up at which the stroke rate was determined. NR: not reported. References: Walsh et al.[59], Kefer et al.[125], Urena et al.[60], Chun et al.[96], Santoro et al.[123], Lopez-Minguez et al.[124], Kebernik et al.[142], Berti et al.[118], Tzikas et al.[94], Korsholm et al.[143], Szymala et al.[144], Jalal et al.[145], Masoud et al.[146], Berti et al.[147], Landmesser et al.[132]. Expected stroke rates are based on the patients' $CHADS_2$ or CHA_2DS_2-VASc scores. From the cohort reported on by Walsh et al.[59] long-term follow-up of a sub-cohort was reported in 2014, confirming the reduction in stroke rate[122]. In a later publication[148] on the Belgian LAA occlusion registry (Kefer et al.), a total of 8 strokes and 6 TIAs were reported from 381 ACP and Amulet devices (mean follow-up period: 589 days for the entire registry). See Table 7 in the appendix for additional details.

NOTE: Results from clinical trials are not directly comparable. Information provided for educational purposes only.

Percutaneous LAA occlusion is a feasible option for stroke reduction in AF patients at high risk for stroke who are contraindicated for anticoagulation or suffered a stroke despite OAC. With the Amplatzer Cardiac Plug, experienced operators are able to achieve an implant success rate between 95% and 100% and a procedural complication rate of 4% or lower. The most common procedure-related safety event is pericardial effusion, occurring less frequently with increasing operator experience. Longer-term follow-up results show stable and effective LAA occlusion over time and a reduction in stroke rate between approximately 60 and 75%, compared to the stroke incidence predicted by the $CHADS_2$ or CHA_2DS_2-VASc score. LAA occlusion is also associated with markedly less major bleeding than OAC. First results from the Amulet™ device show similar safety and device performance, while the device is reported to specifically perform well in challenging LAA anatomies

DISCUSSION AND CONCLUSION

Warfarin therapy is the established therapy for ischemic stroke prevention in the AF patient but it is associated with major bleeding events [20]. Non-VKA OAC drugs have a reduced bleeding risk with similar or better stroke prevention compared to warfarin. Nevertheless, OAC-related bleeding remains a clinically relevant issue, especially in patients with risk factors for bleeding [30 31 33 34]. Moreover, NOACs appear not to substantially increase the proportion of AF patients receiving pharmacological stroke prevention [35].

Percutaneous LAA occlusion may be considered as an alternative for the prevention of stroke in AF patients who are contraindicated or intolerant to OAC or who have suffered a stroke despite OAC [16 83 84 85]. Initial results from non-randomized studies indicated that this therapy reduces the stroke rate compared to the rates predicated by the patients' risk score [52 53 54 55 56 57 58 59 60]. Moreover, two randomized studies provided evidence for the non-inferiority of percutaneous LAA occlusion compared to warfarin [61 63 64]. After implantation with an LAA occlusion device, the need for OAC may be eliminated and OAC-associated bleeding events are prevented. As the procedural complication rate decreases with operator experience, the overall net benefit of this therapy improves.

Observations from several authors regarding the learning curve effect associated with device implantation underline the importance of thorough operator training and well-maintained experience with the application of the device. Based on increasing clinical experience, consensus and review documents have begun to include recommendations for operator training, proctoring, requirements for centers considering to perform LAAO and practical guidance for device implantation, imaging and follow-up [84 85]. Results reported from frequent implanters of the ACP device show implantation success rates between 95% and 100% and periprocedural complication rates between approximately 3 and 5% [59 94 123 124 147 149].

Longer-term follow-up of relatively large cohorts implanted with the ACP device shows a reduction in the rate of stroke and/or TIA between 59% and 75%, compared to the expected rate, based on the patients' risk score [59 94 123 124]. In addition, bleeding is less frequent than expected from the patients' HAS-BLED risk score [94 123 124]. Results reported from the Amulet™ device indicate similar performance in terms of safety, procedural success and effective ischemic stroke prevention [92 130 133 135 136 138 139 144] compared with the ACP device, as well as the ability of the Amulet™ device to effectively occlude large and anatomically challenging appendages [137 138 139]. Overall, the clinical data presented in this document includes information from more than 3000 patients implanted with the ACP device (see Table 5 in the appendix), and follow-up data from more than 2500 patients (see Figure 4). This number is estimated while accounting for some possible overlap in patient cohorts among the reported studies. Data on the Amulet™ device includes information from approximately 2000 patients.

In conclusion, after appropriate operator training and initial experience, implantation of the device is safe and a high procedural success rate can be achieved. Longer-term follow-up results show lower rates of stroke and significant bleeding compared to predictions based on the patient's risk factors, indicating effective protection against AF-related stroke without clinically significant bleeding.

APPENDIX: STUDIES WITH THE ACP AND AMULET DEVICES

This appendix provides an overview of studies on the ACP and Amulet devices reported in the literature. Studies are included in this overview as far as they specifically addressed the technical aspects of device implantation and/or the clinical outcome at follow-up. Only studies with ≥40 patients are included. Furthermore, reports are included only if the devices were implanted and follow-up was performed according to current clinical consensus and recommendations of the manufacturer.

Table 4a: 2-year objectives of the global Amulet Observational Study

Figure 2: Antithrombotic medication use to 2 years

Table 4b: 2-year outcomes of the global amulet Observational Study

Table 5: Overview of studies with the Amplatzer™ ACP and Amulet™ devices including 40 patients or more, with detailed results in Tables 4 and 5.

Table 5b: Overview of smaller studies with the Amplatzer™ ACP and Amulet™ devices with less than 40 patients. No detailed results are included, unless referred to in the text.

Table 6: Details on device implantation reported from various studies.

General legend to this table:

NR: not reported

Complications (major vs. minor) are listed according to the reported classification. In some cases major procedural complications are subject to interpretation (not all authors explicitly classified complications as being related to the procedure or identified during follow-up). Complications are also no consistently reported (for instance a TIA may be reported as a major or a minor procedural complication).

Successful device implantation: successful delivery, deployment and stabilization of the device in the LAA.

All percentages are related to the number of attempted occlusions unless indicated otherwise.

Table 7: Stroke and TIA events reported from follow-up of patients implanted with the ACP and Amulet™ devices.

The risk scores mentioned in this table are from the patients included in the follow-up, unless indicated otherwise (some authors only reported the mean risk score of the entire study cohort, which may include patients who were not included in the follow-up evaluation).

TABLE 5: OVERVIEW OF STUDIES WITH THE AMPLATZER™ ACP AND AMULET™ DEVICES WITH DEVICE-SPECIFIC DETAILS ON PROCEDURAL RESULTS AND FOLLOW-UP WITH ≥ 40 PATIENTS

AUTHOR, PUBLICATION YEAR	ENROLLED PATIENTS	CENTERS	DEVICE	DESCRIPTION	FU
Park 2011[150]	143	10	ACP	First European multicenter reporting on ACP device implantations. Retrospective analysis including patients with paroxysmal, persistent or permanent AF, reflecting initial experience of the operators with the device.	
Guérios 2012[151]	86	1	ACP	Experience from a single Swiss center.	✓
Walsh 2012[58]	204	13	ACP	ACP Post Market Observational Study. Results of this prospective study were presented at EuroPCR 2012 and publication of the data is currently being prepared. Longer-term follow-up of a sub-cohort was reported at EuroPCR 2014[122].	✓
Meerkin 2013[103]	100	1	ACP	Initial experience with the ACP device in a single center in Israel.	✓
Kefer 2013[125]	90	7	ACP	Belgian multicenter registry. More recent data from this registry was reported in 2017 on 318 patients implanted with ACP and Amulet devices[148]. Procedural data from this more recent report have been included in Table 6.	✓
Urena 2013[60]	52	7	ACP	Canadian multicenter study.	✓
Chun 2013[96]	40	1	ACP	Comparative study between the ACP and WATCHMAN™ devices.	✓
Nietlispach 2013[152]	120	1	ACP	10-years of experience with LAA occlusion, using ACP device in 120 patients and non-dedicated devices (PFO/septal occluders) in 32 patients	
Wiebe 2014[153]	60	1	ACP	Report on patients implanted with ACP device in a single German center.	
Berti 2014[149]	121	2	ACP	Study on ACP device implantation guided by ICE instead of TEE.	
Lopez-Minguez 2015[124]	167	12	ACP	The Iberian Registry (Spain and Portugal), reporting on implant experience and 2 year follow-up.	✓
Kebernik 2015[142]	96	1	ACP	Implantation of ACP device in high risk patients	✓
Santoro 2016[123]	134	2	ACP	Implantation and up to 4 years follow-up of the ACP device.	✓
Tzikas 2016[94]	1047	22	ACP	Multicenter experience with the ACP device	✓
Abualsaud 2016[136]	59	1	ACP Amulet	Comparison between ACP (n=31) and Amulet™ (n=28) devices.	
Figini 2016[115]	99	1	ACP Amulet	Comparison of Amplatzer™ (n=99) and WATCHMAN™ (n=66) devices	
Korsholm 2016[120]	108	1	ACP Amulet	Single center study using aspirin monotherapy after LAAO. A more recent report from Korsholm et al.[143] most likely included the 108 patients included in this 2016 publication. Procedural data from this more recent report have been included in Table 5.	✓
Berti 2016[118]	110	1	ACP Amulet	Single center study with 2.5 years of follow-up	✓
Kleinecke 2017[154]	50	1	Amulet	Procedural and 12-months outcome with Amulet device. Short-term follow-up in relatively small cohort, not suitable for characterization of reduction in thromboembolism and bleeding after LAAO with Amulet device.	
Landmesser 2017[131 132 133]	1088	61	Amulet	Global prospective multicenter Amulet registry. Procedural, short term, 1-year and 2-year outcomes reported.	✓
Nielsen-Kudsk 2017[112]	176	8	ACP Amulet	176 patients with previous ICH as an indication for LAAO among 397 LAAO procedures with ACP or Amulet in the eight largest Nordic LAAO centers. This cohort was matched with ICH survivors treated with standard care in a propensity score matched analysis.	
Al-Kassou 2017[136]	196	1	ACP Amulet	Single center study comparing ACP and Amulet devices	
Kefer 2017[148]	318	21	ACP Amulet	Results from a Belgian registry, using ACP, Amulet and Watchman devices. Results on 90 ACP devices were reported earlier[126].	
Korsholm 2017[143]	216	1	ACP Amulet	Comparison between TEE- and ICE-guided LAAO procedures. This article most likely includes the 108 patients reported earlier by Korsholm et al.[120].	
Szymala 2017[144]	80	1	ACP Amulet	Study on LAAO in patients with normal and impaired left ventricular systolic function.	✓
Jalal 2017[145]	76	2	ACP Amulet	Study on LAAO followed by single antiplatelet therapy with short- and mid-term outcomes	✓
Masoud 2017[146]	83	1	Amulet	Single center study on LAAO using the Amulet device	✓
Berti 2017[147]	613	15	ACP Amulet	Large Italian multicenter registry on Amplatzer LAA occluders	✓

NOTE: Results from clinical trials are not directly comparable. Information provided for educational purposes only.

TABLE 5B: OVERVIEW OF SMALLER STUDIES WITH THE AMPLATZER™ ACP AND AMULET™ DEVICES (<40 PATIENTS) OR OTHER STUDIES WITH NO DETAILED DATA INCLUDED FOR OTHER REASONS.

AUTHOR, PUBLICATION YEAR	ENROLLED PATIENTS	CENTERS	DEVICE	DESCRIPTION
Danna 2013[155]	37	1	ACP	Italian single center study.
Lam 2012[156]	20	2	ACP	Initial Asia-Pacific experience with the ACP device.
Streb 2013[157]	21	1	ACP	Small series reported from a Polish center.
López-Mínguez 2013[158]	35	1	ACP	Report on implantation and follow-up of the ACP device in a single Spanish center.
Plicht 2013[119]	34	1	ACP	Retrospective review of thrombus formation on devices observed by TEE follow-up
Faustino 2013[159]	20	1	ACP	Implantation of ACP device in 20 patients and WATCHMAN™ device in 2 patients
Cruz-Gonzales 2014[104]	21	1	ACP	Study on learning curve effects associated with the ACP device. This paper also reports on 10 patients implanted with the WATCHMAN™ device.
Gafoor 2013[106]	27	1	ACP	In this study on LAA occlusion in octogenarians the ACP device was used in 27 patients. Other patients were implanted with WATCHMAN™, PLAATO™, Lariat™ or Coherex™ devices.
Horstmann 2014[160]	24	1	ACP	Report from a German center on implantation of the ACP device in patients with a history of previous intracranial hemorrhage.
Freixa 2014[137]	25	1	Amulet	Initial single center experience with the Amulet device
Gloekler 2015[134]	100	1	ACP Amulet	Comparison between ACP and Amulet™ devices (50 of both). Not included because devices were implanted without fluoroscopic guidance (off-label use).
Cruz-Gonzales 2015[139]	20	1	Amulet	Initial experience with Amulet™ device
Yuniadi 2016[161]	25	1	ACP	Single center initial experience with ACP device
Aguirre 2017[162]	21	4	Amulet	Small registry on single transseptal access technique for LAAO
Sedaghat 2017[163]	24	1	Amulet	Small single center study on thrombus formation after LAAO

TABLE 6: RESULTS ON PROCEDURAL SUCCESS AND SAFETY OF PERCUTANEOUS LAA OCCLUSION WITH THE ACP AND AMULET DEVICE (≥40 PATIENTS).

Study		Park 2011[150]	Guérios 2012[151]	Walsh 2012[59]	Meerkin 2013[103]
Enrollment period		12/2008 - 12/2009	1/2009 - 9/2011	8/2009 - 9/2011	NR
Number of centers		10	1	13	1
Mean stroke risk	$CHADS_2$ CHA_2DS_2-VASc	NR	2.6 NR	2.6 NR	3.2 NR
Patients enrolled		143 (ACP)	86 (ACP)	204 (ACP)	100 (ACP)
LAA occlusion attempted		137	86	204	100
Successful device implantation		132 (96.4%)	85 (98.8%)	197 (96.6%)	100 (100%)
Initially selected device implanted		109 (79.6%)	81 (94.2%)	182 (89.2%)	82 (82.0%)
Major periprocedural complications		10 (7.3%)	4 (4.7%)	6 (2.9%)	1 (1.0%)
Stroke		3	0	0	0
TIA		0	2	0	0
MI / coronary air embolism		0	0	0	0
Device embolization		2	1	3	0
Major cardiac tamponade/perforation/effusion		5	1	3	1
Major bleeding (other than effusion)		0	0	0	0
Other		0	0	0	0
Minor periprocedural complications		7	2 (2.3%)	NR	0
LAA closure success (percentage of successful implants)		NR	3 – 6 month: 97.1%	Implant: 99.5% 1 month: 98.9% 6 months: 98.9%	Implant: 96%

NOTE: Results from clinical trials are not directly comparable. Information provided for educational purposes only.

TABLE 6: (CONT.) RESULTS ON PROCEDURAL SUCCESS AND SAFETY OF PERCUTANEOUS LAA OCCLUSION WITH THE ACP AND AMULET™ DEVICE (≥40 PATIENTS).

Study		Urena 2013 [60]	Chun 2013 [96]	Nietlispach 2013 [152]	Wiebe 2014 [153]
Enrollment period		NR	6/2010 – 6/2012	2008 - ...	1/2009 – 12/2012
Number of centers		7	1	1	1
Mean stroke risk	$CHADS_2$ CHA_2DS_2-VASc	3 (median) 5 (median)	NR 4.5	NR 3.7	2.6 4.3
Patients enrolled		52 (ACP)	40 (ACP)	120 (ACP)	60 (ACP)
LAA occlusion attempted		52	40	120	60
Successful device implantation		51 (98.1%)	40 (100%)	117 (97.5%)	57 (95.0%)
Initially selected device implanted		NR	NR	NR	NR
Major periprocedural complications		2 (3.8%)	3 (7.5%)	7 (5.8%)	5 (8.3%)
Stroke		0	0	1	0
TIA		1	0	2	0
MI / coronary air embolism		0	1 (b)	0	2
Device embolization		1	1	2	2
Major cardiac tamponade/perforation/effusion		0	1	2	1
Major bleeding		2 (a)	0	0	0
Other		0	0	0	0
Minor periprocedural complications		0	4 (10%)	0	2 (3.3%)
LAA closure success (percentage of successful implants)		At implant/ 6 months: < 3 mm jet: 100%	At implant: < 5 mm jet: 100%	(c)	At implant: no leak: 93.3% < 5 mm jet: 6.7%

Notes:
(a) In-hospital major bleeding at access site.
(b) Air embolization with ST elevation
(c) Residual shunt into LAA in 4 patients, degree of flow not specified (3 – 6 months follow-up).

TABLE 6: (CONT.) RESULTS ON PROCEDURAL SUCCESS AND SAFETY OF PERCUTANEOUS LAA OCCLUSION WITH THE ACP AND AMULET DEVICE (≥40 PATIENTS).

Study		Berti 2014 [149]	Kebernik 2015 [142]	Lopez-Minguez 2015 [124]	Tzikas 2016 [94]	Abualsaud 2016 [136]	Figini 2016 [115]
Enrollment period		1/2009 – 4/2013	3/2009 – 12/2014	3/2009 – 2013	12/2008 – 11/2013	11/2009 – 6/2012	6/2009 – 5/2015
Number of centers		2	1	12	22	1	1
Mean stroke risk	$CHADS_2$ CHA_2DS_2-VASc	NR 4.4	4 (median) 5 (median)	3 (median) 4 (median)	2.8 4.5	3.1 4.1	NR 4
Patients enrolled		121 (ACP)	96 (ACP)	167 (ACP)	1047 (ACP)	31 (ACP) 28 (Amulet)	61 (ACP) 38 (Amulet)
LAA occlusion attempted		121	96	167	1047	59	99
Successful device implantation		117 (96.7%)	96 (100%)	158 (94.6%)	1019 (97.3%)	58 (98.3%)	98 (99.4%)
Initially selected device implanted		105 (89.7%)	91 (95%)	152 (96.2%)	951 (93.3%)	52 (88.1%)	NR
Major periprocedural complications		4 (3.3%)	7 (7.3%)	9 (5.4%)	52 (5.0%)	0	7 (7.1%)
Stroke		1	1	0	9	0	1 (g)
TIA		0	1	2	0	0	0
MI / coronary air embolism		0	0	0	1	0	1
Device embolization		0	1	1	8 (c)	0	0
Major cardiac tamponade/perforation/effusion		3	4 (a)	2	13	0 (f)	1 (h)
Major bleeding (other than effusion)		0	0	0	13	0	3 (i)
Other		0	0	4 (b)	8 (d)	0	1 (j)
Minor periprocedural complications		2	0	NR	16 (e)	0	2
LAA closure success (percentage of successful implants)		NR	Follow-up: 100% (no residual leaks)	2 yr follow-up: no leak: 91.8% <3 mm jet: 8.2%	At 7 months: 98.1%	ACP (30 months) <3 mm jet: 88%	Median FU: 82 days (k) <3 mm jet: 93.8%

Notes:
(a) 4 cases of pericardial effusion, categorized as major bleeding
(b) AV fistula at vascular access site, conservatively included in major procedural complications.
(c) 1 case required surgical device removal, 7 devices were removed by snaring
(d) 8 procedural deaths (3 during the procedure, 5 after completion of the procedural but following complications during the procedure), due to major bleeding (1), cardiac tamponade (2), arrhythmia (1), MI (1), device embolization (2) and pneumonia (1)
(e) Minor complications not reported as major adverse events included TIA (4), air embolism (5), device-related thrombus (3), vascular complications (4)
(f) Mild/moderate pericardial effusion before the procedure
(g) Hemorrhagic stroke
(h) Reported as 'any pericardial effusion'
(i) Life-threatening (n=1), major (n=2)
(j) Major vascular complication
(k) Median follow-up for overall cohort, including patients implanted with WATCHMAN device. LAA closure success is reported separately for patients receiving Amplatzer devices.

NOTE: Results from clinical trials are not directly comparable. Information provided for educational purposes only.

TABLE 6: (CONT.) RESULTS ON PROCEDURAL SUCCESS AND SAFETY OF PERCUTANEOUS LAA OCCLUSION WITH THE ACP AND AMULET DEVICE (≥ 40 PATIENTS).

Study		Santoro 2016 [123]	Korsholm 2016 [120]	Berti 2016 [118] (b)	Kleinecke 2017 [154]	Landmesser 2017 [131]	Nielsen-Kudsk 2017 [112]
Enrollment period		1/2009 – 12/2012	3/2010 – 3/2015	1/2009 – 6/2014	10/2014 – 8/2015	6/2015 – 9/2016	2009 – 2/2015
Number of centers		2	1	1	1	61	8
Mean stroke risk	$CHADS_2$	NR	NR	NR	NR	NR	NR
	CHA_2DS_2-VASc	4 (median)	4.4	4.3	5.2	4.2	3.9
Patients enrolled		134 (ACP)	72 (ACP) 35 (Amulet)	91 (ACP) 19 (Amulet)	50 (Amulet)	1088 (Amulet)	172 (ACP/ Amulet)
LAA occlusion attempted		133	107	110		1088	176
Successful device implantation		128 (95.5%)	107 (a) (100%)	110 (100%)	49 (98%)	1077 (99%)	172 (97.7%)
Initially selected device implanted		114 (89.1%)	NR	108 (98.2%)	NR	93.9%	NR
Major periprocedural complications		4 (3.0%)	5 (4.7%)	5 (4.5%)	4 (8%)	35 (3.2%) (g)	7 (4.0%)
Stroke		0	1	0	0	2	0
TIA		1	0	1	0	0	0
MI / coronary air embolism		0	0	0	0	0	0
Device embolization		0	1	0	1	1	1
Major cardiac tamponade/perforation/effusion		3	0	3	2	13	1
Major bleeding (other than effusion)		0	3 (a)	1	0	26	5 (j)
Other		0	0	0	1 (e)	12 (h)	0
Minor periprocedural complications		5	NR	6 (c)	6 (f)	NR	NR
LAA closure success (percentage of successful implants)		NR	NR	6 months TEE: leak in 4/20 patients (d)	NR	procedure: 99.6% 1-3 months: 98.2%	NR

Notes:
(a) Including 1 intracranial hemorrhage and 2 extracranial major bleedings.
(b) Possible overlap with Berti 2014 [149]
(c) Minor bleeding
(d) Device assessment was primarily performed using cardiac CT
(e) Retropharyngeal hematoma from TEE probe
(f) Access site complications (n=5), acute renal injury (n=1) not classified as periprocedural major adverse event.
(g) Single patients can have multiple events. Among 26 cases of bleeding there were 13 cases of tamponade, pericardial effusion and/or perforation.
12 other complications included 2 deaths and 10 major vascular complications.

TABLE 6: (CONT.) RESULTS ON PROCEDURAL SUCCESS AND SAFETY OF PERCUTANEOUS LAA OCCLUSION WITH THE ACP AND AMULET DEVICE (≥ 40 PATIENTS).

Study		Al-Kassou 2017 [136] ACP	Al-Kassou 2017 [136] Amulet	Kefer 2017 [148]	Korsholm 2017 [143] (e)	Szymala 2017 [144]
Enrollment period		7/2014-4/2016		6/2009 – 11/2016	3/2010 – 11/2016	NR
Number of centers		1		21	1	1
Mean stroke risk	$CHADS_2$	NR	NR	2.8	NR	NR
	CHA_2DS_2-VASc	4.5	4.5	4.6	4.4	4
Patients enrolled		99	97	174 (ACP) 144 (Amulet)	318 (ACP/Amulet)	49 (ACP) 31 (Amulet)
LAA occlusion attempted		99	97	318	216	80
Successful device implantation		96 (97%)	97 (100%)	314 (98.7%) (c)	214 (99.1%)	78 (97.5%)
Initially selected device implanted		80 (83%)	91 (93.9%)	NR	NR (f)	72 (90%)
Major periprocedural complications		5 (5.1%)	4 (4.1%)	9 (2.8%) (d)	7 (2.2%)	4 (5%)
Stroke		1	0	2	2	0
TIA		0	0	0	0	0
MI / coronary air embolism		0	0	0	0	0
Device embolization		0	0	2	1	1
Major cardiac tamponade/perforation/effusion		0	1	5	2	2
Major bleeding (other than effusion)		2	3	0	2	0
Other		2 (a)	0	0	0	1 (h)
Minor periprocedural complications		3 (b)	3 (b)	NR	5 (g)	9 (i)
LAA closure success (percentage of successful implants)		At 3.1 months: only minor leaks in 15%	At 2.3 months: only minor leaks in 5%	No large leaks at implantation	At median of 55 days: >5 mm leak in 0.5%	3 months: no significant peri-device leak

Notes:
(a) Other complications included 1 procedural death and 1 death at 7 days post-procedure
(b) Vascular complications
(c) 4 failures with ACP, none with Amulet
(d) ACP: 4.5%, Amulet: 0.7%
(e) This study compared LAAO guided by TEE or ICE. Results in this table are derived by combining data reported from both imaging modalities separately.
(f) Mean number of devices used: 1.2/1.1 for TEE/ICE-guided procedures.
(g) Access related complications.
(h) Unexplained death.
(i) Vascular complication (n=1) and non-significant pericardial effusion (n=8)

NOTE: Results from clinical trials are not directly comparable. Information provided for educational purposes only.

TABLE 6: (CONT.) RESULTS ON PROCEDURAL SUCCESS AND SAFETY OF PERCUTANEOUS LAA OCCLUSION WITH THE ACP AND AMULET DEVICE (≥ 40 PATIENTS).

Study	Jalal 2017[145]	Al-Kassou 2017[145]	Berti 2017[147]
Enrollment period	1/2012 – 12/2014	NR	12/2008 – 4/2015
Number of centers	2	1	15
Mean stroke risk $CHADS_2$	NR	NR	NR
Mean stroke risk CHA_2DS_2-VASc	4.4	4	4.2
Patients enrolled	61 (ACP) 15 (Amulet)	83	613 (ACP / Amulet)
LAA occlusion attempted	76	83	613
Successful device implantation	76 (100%)	82 (98.8%)	585 (95.4%)
Initially selected device implanted	NR	68 (81.9%)	NR
Major periprocedural complications	3 (3.9%)	5 (6.0%)	38 (6.2%)
Stroke	0	0	1
TIA	0	0	3
MI / coronary air embolism	0	0	0
Device embolization	0	2 (c)	1 (f)
Major cardiac tamponade/perforation/effusion	1	0	12
Major bleeding (other than effusion)	2	2	20
Other	0	1 (d)	1 (g)
Minor periprocedural complications	3 (a)	0	NR
LAA closure success (percentage of successful implants)	(b)	At 12 months: No leaks ≥5 mm. Minor leaks in 17.1%.	At 15 months: leak >3 mm in 0.5% (e)

Notes:
(a) Minor bleeding
(b) CT (at median of 12 weeks) showed significant leaks in 38% of patients. TEE in these patients showed leaks <5 mm.
(c) Both device embolizations required surgical retrieval. One case resulted in acute kidney injury, sepsis and death.
(d) Pulmonary edema
(e) TEE assessment in 218 patients. CT found residual LAA flow in 50.5% of 101 patients, with only weak correlation with TEE findings.
(f) A total of 4 embolizations were reported, of which 1 was considered major (surgical device removal).
(g) Major access-related complication.

TABLE 7: STROKE AND TIA EVENTS DURING FOLLOW-UP OF PATIENTS IMPLANTED WITH THE ACP AND AMULET DEVICES (≥ 40 PATIENTS)

	Guérios 2012[150]	Walsh 2012[59]	Meerkin 2013[102]	Kefer 2013[124] (c)	Urena 2013[60]	Chun 2013[96]
Follow-up:						
Number of patients	69	204	30	75	52	40
Duration (months)	Mean: 4.5	Mean: 6	12 – 30	Mean: 12	Mean: 20	Median: 12
Patient years	25.9	101.2	49.9	75	86.7	NR
Patient data:						
Age (years)	NR	73.7	NR	NR	74.7	76
$CHADS_2$	NR	2.6	3.9	--	3	--
CHA_2DS_2-VASc	NR	--	--	4.4 (d)	--	4.5
TE events:						
Stroke	0	2	0	2	1	0
TIA	0	0	1	0	1	0
Annual stroke/TIA rate:						
Actual (a)	0%	1.98%	2.00%	2.14%	2.3%	0%
Predicted (b)	NR	4.0 - 5.9%	8.22%	5.08%	5.9%	5.3%

Notes:
(a) Actual annual rate of stroke and TIA calculated from the number of reported strokes and TIAs and the total number of patient years of follow-up.
(b) Rate of stroke and TIA predicted by the mean $CHADS_2$ score or CHA_2DS_2-VASc score of the patients included in the follow-up.
(c) A more recent report from the Belgian LAAO registry including 318 patients did not contain sufficient data to determine the annual stroke rate. Data in this table is from the earlier report from 2013.
(d) Risk score for the entire study cohort, not reported for follow-up cohort separately.

NOTE: Results from clinical trials are not directly comparable. Information provided for educational purposes only.

TABLE 7: (CONT.) STROKE AND TIA EVENTS DURING FOLLOW-UP OF PATIENTS IMPLANTED WITH THE ACP AND AMULET DEVICES (≥40 PATIENTS)

	López-Minguez 2015[123]	Kebernik 2015[141]	Santoro 2016[122]	Berti 2016[117]	Tzikas 2016[94]	Korsholm 2017[119] (d)
Follow-up:						
Number of patients	158	89	128	110	1001	107
Duration (months)	24	Median: 9	Mean: 22	30	Mean: 13	Median: 28
Patient years	290	93.4	238	264	1349	265
Patient data:						
Age (years)	74.7 (c)	NR	76.6 (c)	77	75	73.2
$CHADS_2$	3 (d)	--	--	--	--	--
CHA_2DS_2-VASc	--	5 (median)	4.3	4.3	4.43	4.4
TE events:						
Stroke	7 (e)	2	2	5	18	6
TIA		1	3	1	13	0
Annual stroke/TIA rate:						
Actual (a)	2.4%	3.2%	2.5%	2.2%	2.3%	2.3%
Predicted (b)	9.6%	6.7 – 10.0%	7.7%	7.7%	5.6%	5.8%

Notes:
(a) Actual annual rate of stroke and TIA calculated from the number of reported strokes and TIAs and the total number of patient years of follow-up.
(b) Rate of stroke and TIA predicted by the mean $CHADS_2$ score or CHA_2DS_2-VASc score of the patients included in the follow-up.
(c) Age of entire study cohort, not reported separately for follow-up cohort.
(d) Note that this is the earlier publication by Korsholm et al. from 2017. A later 2017 publication did not contain sufficient data to determine annual stroke rates.

TABLE 7: (CONT.) STROKE AND TIA EVENTS DURING FOLLOW-UP OF PATIENTS IMPLANTED WITH THE ACP AND AMULET DEVICES (≥40 PATIENTS)

	Szymala 2017[144]	Jalal 2017[145]	Masoud 2017[146]	Berti 2017[147]	Landmesser 2018[132]
Follow-up:					
Number of patients	80	73	80	542	1088
Duration (months)	6	13	12	19.8 (median)	11.1
Patient years	40	75	80	896	1934
Patient data:					
Age (years)	71.1	73	76.0	75.1	75.2
$CHADS_2$	NR	NR	NR	NR	NR
CHA_2DS_2-VASc	4	4.4	4	4.2	4.2
TE events:					
Stroke	0	2	3	14	42
TIA	1	1	0	8	20
Annual stroke/TIA rate:					
Actual (a)	2.5%	4.0%	3.8%	2.9%	3.2%
Predicted (b)	4.8% (c)	9.9%	6.7% (d)	8.6%	9.45%

Notes:
(a) Actual annual rate of stroke and TIA calculated from the number of reported strokes and TIAs and the total number of patient years of follow-up.
(b) Rate of stroke and TIA predicted by the mean $CHADS_2$ score or CHA_2DS_2-VASc score of the patients included in the follow-up.
(c) Stroke rate based on Friberg et al. [14].
(d) Rate of stroke, TIA and peripheral emboli in patients on antiplatelet therapy according to Friberg et al. [14]

NOTE: Results from clinical trials are not directly comparable. Information provided for educational purposes only.

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