Clinical Insights

SUMMARY OF CLINICAL DATA

AMPLATZER™ AMULET™ LAA OCCLUDER

LAAO FOR REDUCING RISK OF ISCHEMIC STROKE IN AF — CLINICAL EXPERIENCE WITH AMPLATZER™ AMULET™ LEFT ATRIAL APPENDAGE OCCLUDER

SUMMARY OF CONCLUSIONS

- The Amplatzer Amulet device achieves a 67% reduction in ischemic stroke.[1]
- Operators may achieve 99% successful implantation with a procedural complication rate of 4% with an Amplatzer Amulet device.1 Similar success rates and complication rates are achieved using TEE or ICE.[2] These outcomes were confirmed by the randomized controlled Amulet IDE trial.
- 80% of patients receiving an Amulet device were frequently discharged on either a single or dual antiplatelet therapy alone.1 The Amulet IDE trial demonstrated non-inferiority of the Amplatzer Amulet device to the Watchman‡ device (Boston Scientific, St. Paul, MN).[3]
- In comparison to oral anticoagulation, LAA occlusion is associated with equally effective stroke prevention and lower risk of major bleeding.[4]

BACKGROUND

Patients with non-valvular atrial fibrillation (NVAF) are at increased risk for ischemic stroke. Although oral anticoagulation (OAC) including non-vitamin-K oral anticoagulant (NOAC) medications are established therapies to reduce the risk of AF-related stroke, they may be less suited for patients with a high risk of bleeding. In addition, some patients suffer a stroke despite the use of oral anticoagulation. Percutaneous left atrial appendage occlusion (LAAO) has emerged as a non-invasive, permanent non-pharmacological option for prevention of AF related stroke in these patients.

OBJECTIVE OF THIS DOCUMENT

The Amplatzer™ Cardiac Plug (ACP) was one of the first devices specifically developed for LAAO, and much of the initial clinical experience with the therapy was obtained with this device. That device has since been replaced by the Amplatzer™ Amulet™ Left Atrial Appendage Occluder, which builds on the clinical and design experience obtained with the ACP device. This document provides a summary of the major clinical evidence of LAAO with the Amplatzer Amulet device.

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AMPLATZER™ AMULET™ IDE TRIAL — SUMMARY[3]

The Amulet IDE trial is a randomized controlled trial (RCT) conducted in the U.S., Canada, Europe and Australia to provide clinical evidence of LAAO with the Amplatzer Amulet device in support of FDA regulatory approval. It uses the FDA approved Watchman‡ device as a control. The primary objective of the study is to evaluate the safety and effectiveness of the Amplatzer Amulet device by demonstrating non-inferiority to the Watchman‡ device. Final assessment of the primary endpoints was performed in October 2020.[3]

An overview of the Amplatzer™ Amulet™ Left Atrial Appendage Occluder IDE trial design and endpoints is provided in Table 1. The study enrolled 1,878 patients who were randomized to LAAO using either the Amplatzer Amulet device (n=934) or the Watchman‡ device (n=944). Demographic data and medical history of the study cohort are summarized in Table 2. Study arms were similar with regard to demographic data, risk scores and medical history.

Table 1: Amulet IDE Trial

Study size	1,878 patients enrolled at 108 centers worldwide
Patients*	Paroxysmal, persistent or permanent non-valvular atrial fibrillation (NVAF). High risk of stroke or systemic embolism defined as $CHADS_2$ score of ≥2 or CHA_2DS_2-VASc score of ≥3. Appropriate rationale to seek an alternative to anticoagulant medication. Suitable for short-term warfarin therapy but deemed unable to take long-term anticoagulation. Not requiring anticoagulation therapy for a condition other than AF. Not contraindicated for, or allergic to aspirin, clopidogrel or warfarin.
Design	Randomized controlled trial (1:1 randomization). Adjudication of safety and effectiveness endpoints by clinical events committee. Core laboratory evaluation of TEE data.
Devices	*Investigational device:* Amplatzer Amulet *Control device:* Watchman‡
Primary endpoints	*Safety:* Composite of procedure-related complications, or all-cause death, or major bleeding Bleeding Academic Research Consortium (BARC) ≥3) at 12 months. *Effectiveness:* Composite of ischemic stroke or systemic embolism through 18 months of follow-up. *Mechanism of action:* Device closure (residual jet ≤5 mm as documented by TEE/TOE) at the 45-day visit.
Follow-up	5 years, with assessments at discharge, 45 days, 3, 6, 9, 12, 18, 24 months and then annually.

* Most essential criteria. A comprehensive overview of inclusion and exclusion criteria is provided by Lakkireddy et al.[5]

Table 2: Amulet IDE Trial Demographics and Medical History

	Amplatzer Amulet (n=934)	Watchman‡ (n=944)
Age (years)	75.0 ± 7.6	75.1 ± 7.6
Female	41.2%	38.7%
BMI (kg/m^2)	30.0 ± 6.3	30.0 ± 6.5
CHA_2DS_2-VASc	4.5 ± 1.3	4.7 ± 1.4
HAS-BLED	3.2 ± 1.0	3.3 ± 1.0
Prior AF ablation	30.4%	29.8%
Prior bleeding	72.2%	71.5%
Prior TIA	10.7%	12.0%
Prior stroke	18.0%	19.9%

DISCUSSION

The Amplatzer™ Amulet™ Left Atrial Appendage Occluder was demonstrated to be non-inferior to the Watchman‡ device for each of the three pre-defined primary endpoints (see Table 3). Among the pre-specified secondary endpoints, the Amplatzer Amulet device was shown to be noninferior to the Watchman‡ device for the secondary endpoint of stroke, systemic embolism and cardiovascular/unexplained death through 18 months (5.6% and 7.7% for Amplatzer Amulet and Watchman‡, respectively; p<0.0001) and the Amplatzer Amulet device was shown to be superior to the Watchman‡ device for device closure at 45 days (p=0.0025).

Table 3: Amulet IDE Trial Primary Endpoints Assessment			
	Amplatzer Amulet	**Watchman‡**	**P-value for non-inferiority**
Safety at 12 months: Composite of procedure-related complications, all-cause death or major bleeding[a]	14.5%	14.7%	0.0014
Effectiveness at 18 months: Composite of ischemic stroke or systemic embolism[b]	2.8%	2.8%	<0.0001
Mechanism of action at 45 days: Device closure (residual jet ≤5 mm on TEE/TOE)[c]	98.9%	96.8%	<0.0001

a. Non-inferiority margin: 5.8%
b. Non-inferiority margin: 3.2%
c. Non-inferiority margin: 3%

The Amplatzer Amulet device achieved a slightly higher rate of successful implantation than the Watchman‡ device. (The device deployed and implanted at the correct position during the index procedure in 98.4% vs. 96.4% of the patients.)

Non-inferiority was demonstrated for the primary safety endpoint of procedure-related complications (defined as adverse events adjudicated by the Clinical Events Committee as procedure related and requiring either invasive surgical or percutaneous intervention, all-cause death or major bleeding), all-cause death or major bleeding. While the procedure-related complication rate was numerically higher for the Amplatzer Amulet device compared with the Watchman‡ device (4.5% vs. 2.5%), confidence intervals for the difference in event rates overlapped. The devices had similar 1-year rates of major bleeding and all-cause mortality (major bleeding: 10.6% and 10.0%, all-cause death: 3.9% and 5.1% for Amplatzer Amulet and Watchman‡, respectively).

There was evidence of a learning effect contributing to the difference in procedure-related complication rates for U.S. implanters. Typically, implanters achieved lower procedural complication rates after having completed their first six cases within the study. Also, procedure-related complication rates with the Amplatzer Amulet device were lower for implanters who performed more procedures (>10 randomized cases).

At discharge, OACs were used more often in Watchman‡ cases (95.8%) compared to Amplatzer Amulet cases (21.1%). No Amplatzer Amulet patients were required to take OACs because of a peri-device leak >5mm, but implanters decided to continue OACs despite adequate device closure. Coming into the 3-month follow-up visit, dual antiplatelet therapy (DAPT) usage was similar between groups (83.5% Amplatzer Amulet and 80.9% Watchman‡). At the 9-month follow-up visit and beyond, the majority of subjects (~85%) in both groups were on single antiplatelet therapy. At 18-months, the Amplatzer Amulet device showed device-related thrombosis (DRT) rates were lower at 3.3% compared to Watchman‡ DRT rates at 4.5%.

IN SUMMARY, THE FOLLOWING IS CONCLUDED FROM THIS INITIAL EVALUATION OF THE AMPLATZER™ AMULET™ IDE TRIAL DATA:

- The Amplatzer Amulet device achieved superior device closure and non-inferiority for the composite of stroke, systemic embolism or cardiovascular death, compared with the Watchman‡ device.
- At 45 days, the device closure rate for the Amplatzer Amulet device was 98.9% vs. 96.8% for the Watchman‡ device.
- At 18 months, the ischemic stroke rate for the Amplatzer Amulet device was 2.5% vs. 2.7% for the Watchman‡ device.
- At 18 months, the systemic embolism rate for the Amplatzer Amulet device was 0.3% vs. 0.2% for the Watchman‡ device.
- At 18 months, the device-related thrombosis rate for the Amplatzer Amulet device was 3.3% vs. 4.5% for the Watchman‡ device.
- Learning effects likely contributed to a higher procedure-related complication rate for the Amplatzer Amulet device compared with the Watchman‡ device. During the trial, increased experience with the device was reflected in decreasing procedure-related complication rates.
- The Amplatzer Amulet device achieved similar effectiveness with limited use of OACs at discharge.

ADDITIONAL ANALYSES

A number of additional analyses have been performed using the Amulet IDE trial data. The incidence and outcomes of peri-device leaks (PDL) were investigated in patients who successfully received their assigned device, including 903 and 885 patients with an Amplatzer Amulet and a Watchman‡ device, respectively[A]. PDL was assessed by TEE at 45 days and 12 months after implantation and evaluated by an independent core laboratory. Outcomes are shown in Figure 1.

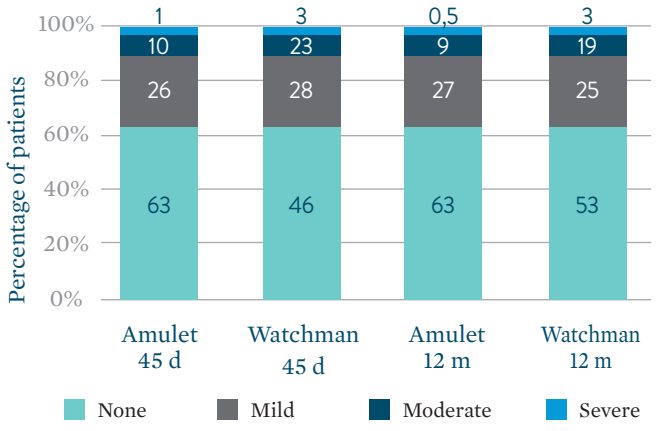


Figure 1: Degree of PDL at 45 days and 12 months after implantation in the Amulet IDE trial. Severe: >5 mm, Moderate: 3–5 mm, Mild: >0–3 mm.

The Amulet device showed superior closure over the Watchman‡ device at 45 days and 12 months post-implantation, with the Watchman‡ device associated with a 2.7-fold higher risk of moderate or severe PDL at 45 days (p<0.01 in multivariable analysis).

Moderate or severe PDL (irrespective of the implanted device) was significantly associated with a higher risk of the composite endpoint of stroke, systemic embolism, and cardiovascular death, compared to mild or no PDL (18-months hazard ratio per Kaplan-Meier analysis: 1.75; 95% CI: 1.08 – 2.83). This effect was more pronounced in the Watchman arm than in the Amulet arm. The incidence of the composite endpoint in patients with moderate or severe PDL was 9.7% and 4.5% in the Watchman and Amulet arms, respectively. While the rates of thromboembolic events alone trended higher in the patients with moderate or severe PDL, event rates were too low to demonstrate statistical significance[B].

Another analysis involved the incidence, predictors, and clinical outcomes of device-related thrombus (DRT) in the Amulet IDE trial through 18 months.[B] In the Amulet arm of this trial, 76% of the patients were discharged on dual antiplatelet therapy, while 82% of the patients implanted with the Watchman device were discharged on OAC plus aspirin. Through 18 months of follow-up, DRT occurred at similar rates in the Amulet arm (3.4%) and the Watchman arm (4.8%). Strong predictors for DRT included AF at the procedure, female gender and older age. In the Amulet arm, DRT was more frequently identified early (61% detected within 45 days), while late DRT was more common in the Watchman arm (74% detected at >45 days, see Figure 2). Accounting for all patients (irrespective of their randomization), cardiovascular mortality was significantly increased in patients with DRT compared to those without (8.7% vs. 3.9%, HR: 2.33, p=0.04).

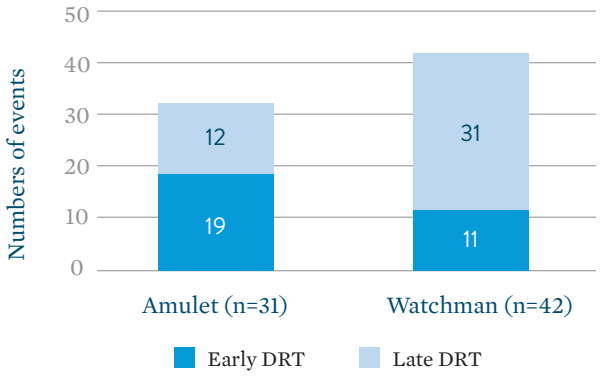


Figure 2: Early (≤45 days) and late (>45 days) DRT in the Amulet IDE trial through 18 months follow-up.

A post-hoc univariate analysis[C] of Amulet IDE trial data through 18 months identified prior stroke (p<0.01) and increased CHA_2DS_2-VASc score (p=0.04) as predictors of stroke after LAAO. Prior stroke remained a significant predictor for stroke in multiple regression analysis. The rates of stroke, TIA and systemic embolism, as well as stroke severity were similar across the devices (annualized ischemic stroke rate: 1.7%/year and 2.0%/year for the Amulet and Watchman devices, respectively). Most of the strokes occurred >45 days after implantation. Strokes in the Watchman arm (n=13) were more frequently preceded by peri-device leak or device-related thrombus than in the Amulet arm (n=2).

Across the two randomization arms, the Amulet IDE trial included 1,099 men and 734 women who underwent and LAAO implantation attempt. A post-hoc analysis[D] found similar implant success rates between men vs. women (97.4% and 97.1%, respectively), but women appeared to have increased procedural complication rates (see Figure 3).

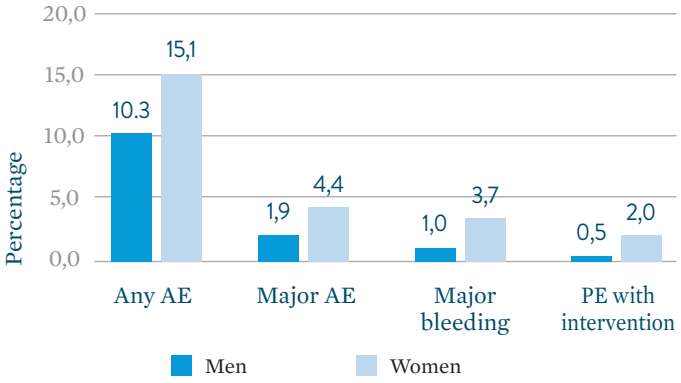


Figure 3: Peri-procedural complications in men and women in the Amulet IDE trial.

CONCLUSIONS:

The following conclusions can be drawn from additional analyses of the Amulet IDE trial data:

- The Amplatzer™ Amulet™ Left Atrial Appendage Occluder showed superior closure through 12 months compared to the Watchman device. Completeness of closure of the LAA has important implications for patient outcomes[A].
- Late DRTs were more frequent with the Watchman device due to differences in post-implant anticoagulation regiments. However, overall rates of device-related thrombus were similar for the Amulet and Watchman devices. Device-related thrombus is associated with increased cardiovascular mortality[B].
- The rates of stroke, TIA and systemic embolism are similar for both devices through 18 months. Prior stroke is a significant predictor for stroke after LAAO with either device. In the Watchman arm, stroke was more frequently preceded by peri-device leak or device-related thrombus than in the Amulet arm.
- Compared to men, women have a higher risk of procedural complications but show similar device-related and long-term clinical outcomes through 18 months.

AMPLATZER™ AMULET™ GLOBAL PROSPECTIVE OBSERVATIONAL STUDY — SUMMARY[1]

The use of the Amplatzer Amulet device for prevention of ischemic stroke in AF patients was comprehensively documented by the Amplatzer Amulet observational study. This multicenter study, which enrolled 1,088 high-risk patients, showed that the Amplatzer Amulet device was similarly safe and effective as the predecessor ACP device.

- High technical and procedural success rates were achieved with a 4% major periprocedural adverse event rate.
- At 2-year follow-up, the rate of ischemic stroke was reduced by 67% compared to the CHA_2DS_2-VASc-predicted rate.
- Major bleeding occurred at a rate similar to the HAS-BLED predicted rate, with a strong reduction in bleeding incidence during the second year after implantation.

The global prospective Amplatzer Amulet observational study was conducted to collect procedural experience and clinical outcomes through two years of follow-up with the Amplatzer Amulet device.[1,6] While conducted as a multicenter registry, the study involved a strict methodology including independent adjudication of safety and effectiveness endpoints and evaluation of echocardiographic data by a core laboratory. The study enrolled 1088 patients in 61 centers in Europe, Australia, Israel, Chile and Hong Kong, representing a real-world cohort with a high risk of ischemic stroke (mean CHA_2DS_2-VASc score: 4.2 ± 1.6) and bleeding (mean HAS-BLED score: 3.3 ± 1.1). Of the enrolled patients, 27.5% had a prior stroke and 72.4% had a history of major bleeding, with 82.8% contraindicated for OAC.6

Technical success (i.e., successful implantation of the device in the correct position) was achieved in 99.1% of the patients.3 Major procedural adverse events within seven days from the procedure occurred in 4.0% of the patients. Specifically, 1.4% of the patients experienced a pericardial effusion or tamponade and 1.3% had a major vascular complication. Of the three deaths within seven days after the procedure, two were adjudicated as device- or procedure-related. Procedural success (i.e., technical success with no periprocedural major adverse events) was achieved in 95.5% of the patients.[1]

Throughout the study, follow-up ischemic stroke occurred at a rate of 2.2% per year. This represented a 67% reduction compared with the expected ischemic stroke rate based on the mean CHA_2DS_2-VASc score (Figure 1). Four ischemic strokes within seven days from the procedure were adjudicated as procedure- or device-related, and two late strokes that occurred within the context of DRT were adjudicated as device-related. TIA occurred at a rate of 1.0% per year. With 140 major bleeding events in 110 patients, the annualized rate of major bleeding was 7.2%, which was similar to the HAS-BLED-based expected rate (6.7%). Bleeding was particularly more frequent during the first year after LAAO (10.1% per year). Most events occurred within three months after the procedure, while 75.5% of patients were on a more intensive antithrombotic therapy, with 2.8% of the patients experiencing major bleeding during the first seven days after implantation. Gastrointestinal bleeding accounted for 47.9% of all major bleeding events.[1]

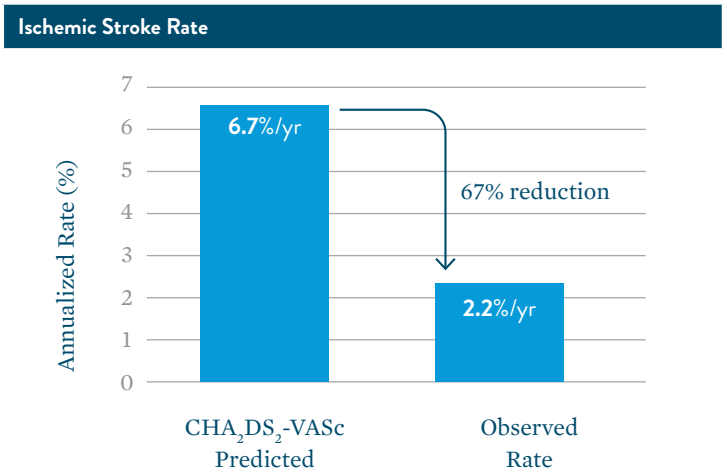


Figure 1: Expected and observed rate of ischemic stroke in the global Amplatzer Amulet prospective observational study at 2-year follow-up.

Patients were most frequently discharged on dual (57.7%) or single (22.4%) APT. At two years after the procedure, 62.8% of the patients were on single APT and 21.5% did not receive any antithrombotic therapy. DRT was observed in 1.6% of the patients and was associated with a five-fold increased risk of ischemic stroke or TIA.[1] Patients without an observed DRT event were discharged on APT therapy 80.3%, either single APT (22.7%) or dual APT (57.6%).[1] Data regarding this global observational study are summarized in Table 4.

In the Amplatzer Amulet observational study, 130 (12%) procedures were guided by intracardiac echocardiography (ICE) in the left atrium and in 955 (88%) procedures transesophageal echocardiography (TEE) was used.[2] Baseline characteristics were similar in both groups, except for a higher rate of prior stroke and a lower rate of abnormal renal function in patients undergoing ICE-guided LAAO compared to those in which TEE was used. All ICE-guided procedures were preceded by CT or TEE for pre-procedural planning and device sizing. Procedural and 1-year clinical outcomes are compared between these imaging modalities in Table 5.

Table 4: Key data from the global prospective Amplatzer Amulet observational study[1,6]

Patients	1,088
CHA_2DS_2-VASc	4.2 ± 1.6
HAS-BLED	3.3 ± 1.1
Major adverse events ≤7 days	4.0%
Patients with major bleeding	2.8%
Patients with pericardial effusion or tamponade	1.4%
Patients with major vascular complication	1.3%
Technical success	99.1%
Procedural success	95.5%
2-year follow-up	
Ischemic stroke	2.2% / year
TIA	1.0% / year
Systemic embolism	0.0% / year
Major bleeding events (BARC ≥3)	7.2% / year
Procedure/device related	1.7% / year
Overall – 1st year	10.1% / year
Overall – 2nd year	4.0% / year

Table 5: Procedural and 1 year clinical outcomes of LAAO guided by TEE or ICE[2]

	TEE	ICE	P value
Device implantation success	99%	99%	1.00
General anesthesia	66%	7%	<0.0001
Procedure duration	33 ± 21 min	40 ± 31 min	0.01
Fluoroscopic duration	15 ± 66 min	20 ± 12 min	<0.0001
Contrast	98 ± 76 mL	145 ± 157 mL	<0.001
Heparin	7,578 ± 3,502 U	7,004 ± 2,254 U	0.02
Procedure- or device-related serious adverse events	91 (10.4%)	13 (10.7%)	0.93
Vascular access serious adverse events	14 (1.5%)	1 (0.8%)	0.52
Renal complications	21 (2.4%)	1 (0.8%)	0.29
Pericardial effusion / tamponade	15 (1.7%)	3 (2.5%)	0.57
Ischemic stroke	23 (2.6%)	5 (4.1%)	0.37
TIA	7 (0.8%)	1 (0.8%)	0.98
Major bleeding event	93 (10.6%)	10 (8.2%)	0.44
All-cause death (Kaplan-Meier estimate)	79 (8.6%)	8 (6.3%)	0.39

Compared with TEE-guided LAAO, ICE-guided procedures were associated with a longer duration and a higher contrast use. Device implantation success, stroke/TIA rates and complications were similar between TEE- and ICE-guided procedures, while ICE was associated with more frequent use of local rather than general anesthesia.

Assessment of LAA sealing using TEE at 1 to 3 months after LAAO showed appropriate LAA sealing (residual flow <3 mm) in all ICE patients and in 98% of the TEE patients. ICE should not be considered a stand-alone imaging modality for LAAO and requires pre-procedural device sizing by CT.

AMPLATZER LAAO DEVICES VERSUS ORAL ANTICOAGULANTS (OAC) — SUMMARY

Several initiatives have been deployed to compare Amplatzer LAA occlusion devices with long-term OAC.

GLOEKLER AND NIELSEN-KUDSK STUDIES

Propensity score matched analyses were presented by Gloekler et al.[7] (EuroPCR 2017) and Nielsen-Kudsk et al.[8] (EuroPCR 2020). Data relevant to these analyses are summarized in Table 6 and in Figure 2. Although the definitions of the endpoints varied slightly between these two studies, both analyses showed a net clinical benefit of LAAO versus anticoagulant therapy, driven by similar or better stroke prevention, fewer bleeding events and lower all-cause mortality. The differences in bleeding, all-cause mortality and net clinical benefit between the treatments was statistically significant in both studies.

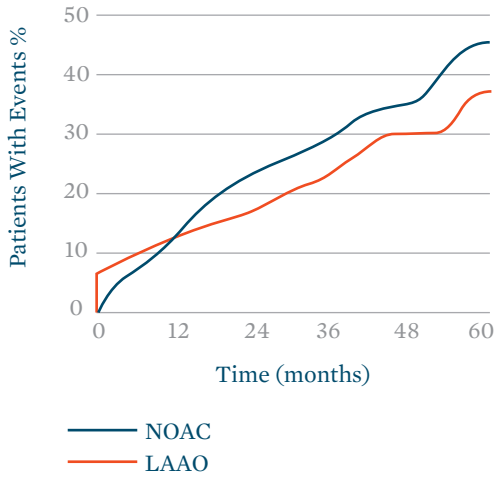
- The studies suggested: LAAO with the ACP and Amplatzer Amulet devices is equally or more effective in the prevention of ischemic stroke compared to OAC or NOAC therapy.
- LAAO is associated with a significantly lower incidence of bleeding and all-cause mortality and has an improved net clinical benefit

Table 6: Propensity score matched analyses of LAAO with Amplatzer devices versus oral anticoagulant therapy

	Gloekler et al.[7]		Nielsen-Kudsk et al.[8]	
	LAAO	**Anticoagulation**	**LAAO**	**Anticoagulation**
Patients	500 (ACP/Amulet)	500 (OAC/NOAC)	1071 (Amulet)[a]	1184 (NOAC)
CHA_2DS_2-VASc HAS-BLED	4.3 3.0	4.3 2.9	4.2 3.3	4.3 3.4
Follow-up	2.7 years		2 years	
Stroke[b]	1.6%	2.5%	2.1%	1.9%
Bleeding[c]	2.0%	5.5%	6.0%	10.0%
All-cause mortality	8.3%	11.6%	8.0%	15.3%
Net clinical benefit[d]	8.1%	10.9%	14.5%	25.7%

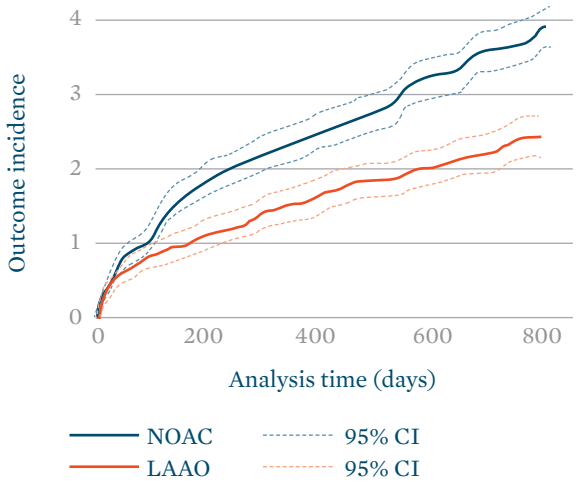
a: Data from global Amulet prospective observational study.
b: Gloekler et al.: described as 'all-cause stroke without TIA'. Nielsen-Kudsk et al.: ischemic stroke.
c: Gloekler et al.: Major, life-threatening and fatal bleeding. Nielsen-Kudsk et al.: BARC ≥3.
d: Gloekler et al.: Stroke, systemic embolism, cardiovascular/unexplained death, major procedural adverse events, major or life threatening bleeding. Nielsen-Kudsk et al.: Ischemic stroke, major bleeding, mortality.

Combined hazard endpoint



Composite of stroke, systemic embolism, cardiovascular/unexplained death, major procedural adverse events, major/life-threatening bleeding (Gloekler et al.).[7]

Kaplan-Meier failure estimate — primary outcome



Ischemic stroke, systemic embolism, major bleeding, all-cause mortality (Nielsen-Kudsk et al.).[8]

Figure 2: Propensity matched analyses comparing LAAO with ACP / Amplatzer Amulet occluders versus OAC/NOAC compared with anticoagulant therapy.

PRAGUE-17 STUDY

The PRAGUE-174 study enrolled 415 patients for a randomized comparison between LAAO (performed with the Amplatzer™ Amulet™ occluder device in 61% of the cases) and long-term NOAC therapy.

- Outcomes at 21 months of follow-up showed that LAAO was non-inferior to NOAC therapy in the prevention of primary endpoint events, including safety and effectiveness outcomes. The outcomes of the PRAGUE-17 study provide further randomized controlled evidence for the efficacy and net clinical benefit of LAAO compared with oral anticoagulant therapy. This study randomized 213 patients with AF at risk of ischemic stroke to LAAO. The majority of patients received the Amplatzer Amulet device, with the balance receiving the Watchman‡ or Watchman FLX‡ device. The NOAC therapy group included 202 patients, most of whom received Apixaban. The study was powered to demonstrate noninferiority of LAAO compared to NOAC therapy for prevention of a composed endpoint accounting for efficacy and safety aspects. Key data of this study are provided in Table 7.

Table 7: PRAGUE-17 study data[4]

	NOAC	LAAO
Patients	202 patients allocated, 201 in ITT analysis	213 patients allocated, 201 in ITT analysis
CHA_2DS_2-VASc 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%)	Amplatzer Amulet (61.3%) Watchman‡ (38.7%) 12 patients crossed over to the NOAC arm Implant success: 96.8% of attempts Complications: 4.8% (including two procedure- and/or device-related deaths)
Follow-up	20.8 ± 10.8 months	
Primary endpoint	Composite of: - Stroke or TIA - Systemic embolism - Clinically significant bleeding - Cardiovascular death - Significant peri-procedural or device-related complication	
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).	

The results of the PRAGUE-17 study suggest similar outcomes with either LAAO or NOAC therapy. While LAAO was associated with procedural complications, these risks were offset by similarly effective stroke prevention and reduced bleeding, in particular non-procedural clinically significant bleeding over a mean follow-up period of 20.8 months. Additional follow-up is warranted to reveal long-term differences between the therapies.

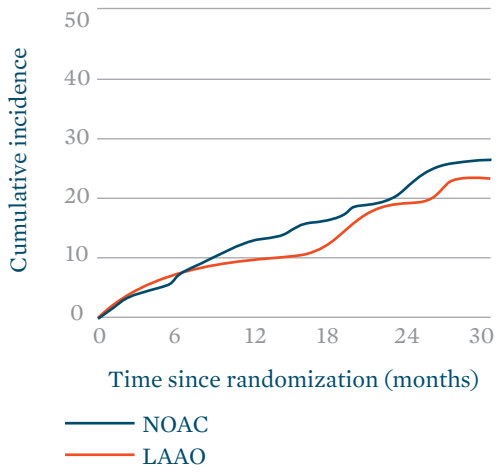


Figure 3: PRAGUE-17: primary endpoint (see Table 6). P-value for non-inferiority: 0.004.

FINAL CONCLUSIONS

- Compared with risk score-based expected rates, the Amplatzer Amulet device achieves a 67% reduction in ischemic stroke, as shown in the global Amulet prospective observational study. The overall annual rate of major bleeding was similar to the HAS-BLED-predicted rate, but tended to decrease over time.
- Experienced operators may achieve 99% successful implantation of the Amplatzer Amulet device with a procedural complication rate of 4%. Similar success rates, procedural safety and clinical outcomes are achieved using ICE or TEE during the procedure.
- The Amplatzer™ Amulet™ IDE trial demonstrated non-inferiority of the Amulet device compared to the Watchman‡ device. For device closure, the Amulet IDE trial demonstrated superiority of the Amulet device compared to the Watchman‡ device.
- LAA Occlusion (LAAO) is associated with equally effective stroke prevention and lower risk of major bleeding. LAAO may provide an improved net clinical benefit in patients with high bleeding risk, compared to OAC/NOAC therapy.

REFERENCES

1. Hildick-Smith D, Landmesser U, Camm AJ, et al. Left atrial appendage occlusion with the Amplatzer™ Amulet™ device: full results of the prospective global observational study. *European Heart Journal*. 2020.
2. Nielsen-Kudsk JE, Berti S, De Backer O, et al. Use of Intracardiac Compared With Transesophageal Echocardiography for Left Atrial Appendage Occlusion in the Amulet Observational Study. *J Am Coll Cardiol Intv 2019;12:1030-1039*
3. Amulet IDE Trial 2021 full data results on file.
4. Osmancik P, Herman D, Neuzil P, et al. Percutaneous left atrial appendage closure versus novel anticoagulation agents in high risk atrial fibrillation patients (PRAGUE 17 study). Paper presented at: ESC 2019.
5. Lakkireddy D, Windecker S, Thaler D, et al. Rationale and design for Amplatzer Amulet Left Atrial Appendage Occluder IDE randomized controlled trial (Amulet IDE Trial). *American Heart Journal*. 2019; 211:45-53.
6. Landmesser U, Schmidt B, Nielsen-Kudsk JE, et al. Left atrial appendage occlusion with the Amplatzer Amulet device: periprocedural and early clinical/echocardiographic data from a global prospective observational study. EuroIntervention: journal of EuroPCR in collaboration with the Working Group on Interventional Cardiology of the European Society of Cardiology. 2017;13(7):867-876.
7. Gloekler S, Koskinas K, Streit S, et al. Percutaneous left atrial appendage closure vs. oral anticoagulation: A propensity score matched study of 1000 patients with atrial fibrillation. Paper presented at: EuroPCR 2017.
8. Nielsen-Kudsk JE, Korsholm K, Valentin J, Johnsen S. Left atrial appendage occlusion versus novel oral anticoagulation in atrial fibrillation: A propensity score matched follow-up study based on the Amulet Observational Registry Paper presented at: EuroPCR 2020.

ADDITIONAL REFERENCES:

1. Ellis CR, Incidence and Clinical Outcomes of Peri-Device Leak After Transcatheter Left Atrial Appendage Occlusion: An Analysis of the Amulet IDE Trial. Presented at Heart Rhythm 2022, San Francisco, CA, USA
2. Schmidt B et al. Incidence, Predictors, and Clinical Outcomes of DRT in Patients Undergoing LAAO - Amulet IDE Trial. Presented at ACC 2022, Washington DC, USA
3. Thaler D et al. Stroke Predictors and Outcomes from the Amplatzer Amulet Left Atrial Appendage Occluder Randomized Controlled Trial. Presented at International Stroke Conference 2022, Dallas, TX, USA

4 Alkhouli M, Sex differences in safety and effectiveness of left atrial appendage occlusion from the Amulet IDE trial. Presented at EuroPCR 2022, Paris, France

AMPLATZER™ AMULET™ LEFT ATRIAL APPENDAGE OCCLUDER
IMPORTANT SAFETY INFORMATION

Rx ONLY

INDICATION FOR USE

The Amplatzer™ Amulet™ Left Atrial Appendage Occluder is a percutaneous transcatheter device intended to reduce the risk of thrombus embolization from the left atrial appendage (LAA) in patients who have nonvalvular atrial fibrillation and who are at increased risk for stroke and systemic embolism based on $CHADS_2$ or CHA_2DS_2-VASc scores, are suitable for short term anticoagulation therapy, and have appropriate rationale to seek a non-pharmacologic alternative to oral anticoagulation, taking into consideration the safety and effectiveness of the device.

CONTRAINDICATIONS

The Amplatzer™ Amulet™ Left Atrial Appendage (LAA) Occluder is contraindicated for patients:

- with the presence of intracardiac thrombus, with active endocarditis or other infections producing bacteremia.
- where placement of the device would interfere with any intracardiac or intravascular structures.

WARNINGS

- If the device is retracted while it is in the sheath, the device and the sheath must both be removed and replaced. Failure to replace both the device and the sheath may result in sheath and/or device malfunction.
- If the device is retracted farther than the radiopaque markers (fully recaptured), the device and the sheath must both be removed and replaced. Failure to replace both the device and the sheath may result in sheath and/or device malfunction.
- Physicians must be prepared to deal with urgent situations, such as pericardial effusion or device embolization, which can require removal of the device.
- This device should be used only by physicians who are trained in standard transcatheter techniques. The physician should determine which patients are candidates for procedures that use this device.
- Late pericardial effusion events were observed in the clinical study. The use of post-procedure anticoagulation therapy may be associated with an increased potential for a late pericardial effusion. Physicians should monitor for signs and symptoms of pericardial effusion and obtain appropriate imaging when indicated. Physicians should also consider routine echocardiography to screen for pericardial effusion.
- Remove embolized devices. Do not remove an embolized device unless the device is fully captured inside a sheath.
- The Amplatzer™ Amulet™ device contains a nickeltitanium alloy, which is generally considered safe. However, in vitro testing has demonstrated that nickel is released from this device for a minimum of 120 days. Patients who are allergic to nickel may have an allergic reaction to this device, especially those with a history of metal allergies. Certain allergic reactions can be serious; patients should be instructed to seek medical assistance immediately if they suspect they are experiencing an allergic reaction. Symptoms may include difficulty in breathing or swelling of the face or throat. While data are currently limited, it is possible that some patients may develop an allergy to nickel if this device is implanted.
- Do not use this device if the sterile package is open or damaged.
- The device was sterilized with ethylene oxide and is for single use only. Do not reuse or resterilize this device. Attempts to resterilize this device can cause a malfunction, insufficient sterilization, or harm to the patient.
- Use on or before the expiration date that is printed on the product packaging label.

PRECAUTIONS

- The physician should exercise clinical judgment in situations that involve the use of antithrombotic drugs before, during, and/or after the use of this device.
- The physician should exercise caution if implanting a device in a patient who has an implantable cardioverter defibrillator (ICD) or pacemaker leads.
- The physician should have the guidewire in the left upper pulmonary vein when making exchanges in the left atrium.
- Ensure that the vasculature is adequate for the sheath size being selected.
- The physician should exercise caution if performing ablation at or near the implant site after the device is implanted.
- Use standard interventional cardiovascular catheterization techniques when using Amplatzer™ products.
- Use in specific populations
  - Pregnancy – Minimize the radiation exposure to the fetus and the mother.
  - Nursing mothers – There has been no quantitative assessment for the presence of leachables in breast milk.

MRI SAFETY INFORMATION

MR

Non-clinical testing has demonstrated that the Amplatzer™ Amulet™ Left Atrial Appendage Occluder device is MR Conditional. A patient with the Amplatzer™Amulet™ device can be safely scanned in an MR system under the following conditions:

- Static magnetic fields of 1.5 Tesla (1.5T) and 3.0 Tesla (3.0T)
- Maximum spatial gradient field of 19 T/m (1900 G/cm)
- Maximum MR system reported, whole-body averaged specific absorption rate (SAR) of 2.0 W/kg (normal operating mode)

Under the scan conditions defined above, the device is expected to produce a maximum temperature rise of less than or equal to 4°C after 15 minutes of continuous scanning. In non-clinical testing, the image artifact caused by the device extends radially up to 20 mm from the device when imaged with a gradient echo pulse sequence in a 3.0T MR system.

POTENTIAL ADVERSE EVENTS

Potential adverse events associated with the device or implant procedure include, but are not limited to, the following:

- Airway trauma
- Allergic reaction
- Anemia
- Anesthesia reaction (nausea, vasovagal reaction, confusion/altered mental status or other)
- Arrhythmia
- Atrial septal defect
- Bleeding
- Cardiac arrest
- Cardiac tamponade
- Chest pain/discomfort
- Congestive heart failure
- Death
- Device embolization
- Device erosion
- Device malfunction
- Device malposition
- Device migration
- Device-related thrombus
- Fever
- Hematuria
- Hypertension/hypotension
- Infection
- Multi-organ failure
- Myocardial infarction
- Perforation
- Pericardial effusion
- Pleural effusion
- Renal failure/dysfunction
- Respiratory failure
- Seizure
- Significant residual flow
- Stroke
- Thrombocytopenia
- Thromboembolism: peripheral and pulmonary
- Thrombus formation
- Transient ischemic attack
- Valvular regurgitation/insufficiency
- Vascular access site injury (hematoma, pseudoaneurysm, arteriovenous fistula, groin pain or other)
- Vessel trauma/injury

CAUTION: This product is intended for use by or under the direction of a physician. Prior to use, reference the Instructions for Use, inside the product carton (when available) or at eifu.abbottvascular.com or at medical.abbott/manuals for more detailed information on Indications, Contraindications, Warnings, Precautions and Adverse Events.

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Abbott
3200 Lakeside Dr, Santa Clara, CA 95054, USA. Tel: 1.800.227.9902 www.structuralheart.abbott

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