Clinical Insights

SUMMARY OF CLINICAL DATA

LAAO FOR REDUCING RISK OF ISCHEMIC STROKE IN AF — CLINICAL EXPERIENCE WITH AMPLATZER™ AMULET™ DEVICE

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‡ (Boston Scientific, St. Paul, MN) device.[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 That device has since been replaced by the Amplatzer™ Amulet™ Left Atrial Appendage Occluder, which builds on the clinical and design experience obtained with the ACP device.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 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 Amulet 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 device 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 non-inferior 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 by decreasing procedure-related complication rates.
- The Amplatzer Amulet device achieved similar effectiveness with limited use of OACs at discharge.

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 entire 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]

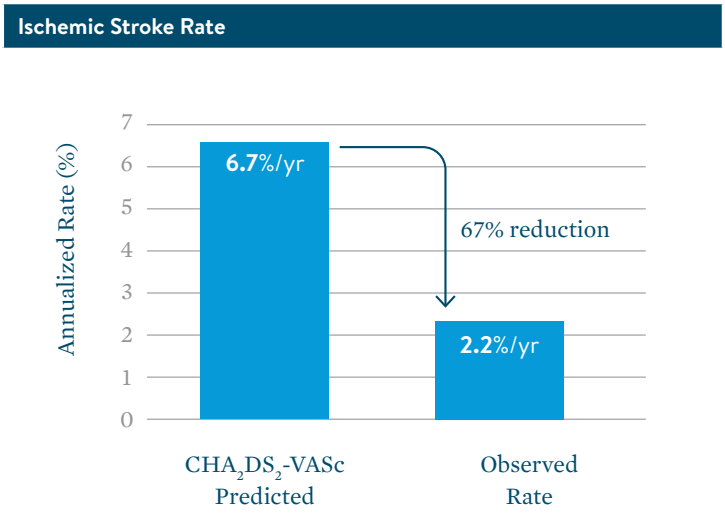


Figure 1: Expected and observed rate of ischemic stroke in the global Amplatzer Amulet prospective observational study at 2-year follow-up.

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.

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

Patients CHA_2DS_2-VASc HAS-BLED	1,088 4.2 ± 1.6 3.3 ± 1.1
Major adverse events ≤7 days Patients with major bleeding Patients with pericardial effusion or tamponade Patients with major vascular complication	4.0% 2.8% 1.4% 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) Procedure/device related Overall – 1st year Overall – 2nd year	7.2% / year 1.7% / year 10.1% / year 4.0% / year

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 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.

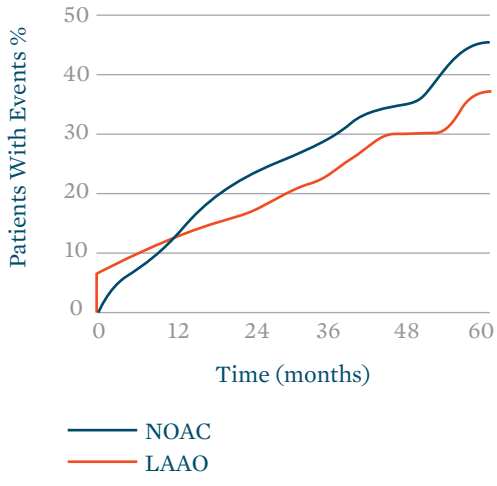
- The studies suggested: LAAO with the ACP and Amplatzer Amulet devices is equally or more effective in the prevention of ischemic stroke compared to OAC or NOAC therapy.
- LAAO is associated with a significantly lower incidence of bleeding and all-cause mortality and has an improved net clinical benefit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

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%

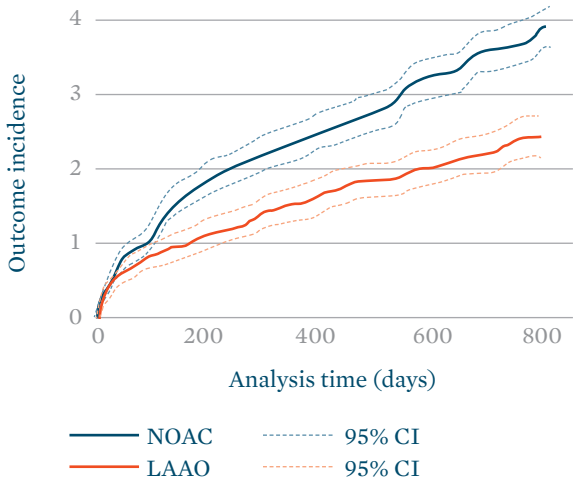
a: Data from global Amulet prospective observational study.
b: Gloekler et al.: described as 'all-cause stroke without TIA'. Nielsen-Kudsk et al.: ischemic stroke.
c: Gloekler et al.: Major, life-threatening and fatal bleeding. Nielsen-Kudsk et al.: BARC ≥3.
d: Gloekler et al.: Stroke, systemic embolism, 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.

PRAGUE-17 STUDY

The PRAGUE-17[4] 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 non-inferiority 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.

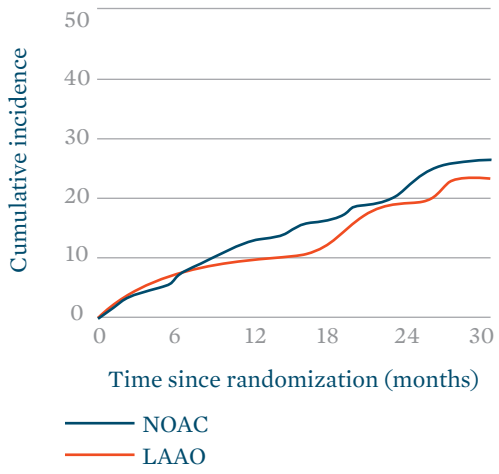


Figure 3: PRAGUE-17: primary endpoint (see Table 6). P-value for non-inferiority: 0.004.

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.

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