CLINICAL SUMMARY

LAAO FOR PREVENTION OF ISCHEMIC STROKE IN AF - CLINICAL EXPERIENCE WITH AMPLATZER AMULET DEVICE

Patients with non-valvular atrial fibrillation (AF) are at increased risk for ischemic stroke. Although oral anticoagulation (OAC) including non-vitamin-K oral anticoagulant (NOAC) therapy are established therapies to prevent 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 evolved as a feasible nonpharmacological option for stroke prevention in these patients.

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. Meanwhile, the device has been replaced by the Amplatzer™ Amulet™ Left Atrial Appendage Occluder, which builds on the clinical and design experience obtained with the ACP device (see Figure 1). This document provides a summary of the major clinical evidence of LAAO with the Amulet device.

Figure 1: Amplatzer Cardiac Plug (left) and Amplatzer Amulet device (right)

SUMMARY OF CONCLUSIONS

- Amulet device achieves a 67% reduction in ischemic stroke compared to the predictive rate.
- Operators may achieve 99.1% successful implantation with a peri-procedural complication rate of 4% with an Amulet device.
- In comparison to OAC, LAAO is associated with equal effective stroke prevention at lower risk of major bleeding.

AMULET CLINICAL DATA - SUMMARY

The use of the Amulet device for prevention of ischemic stroke in AF patients was comprehensively documented by the Amplatzer Amulet observational study. This multicenter study, which enrolled 1088 high-risk patients from 61 centers in 17 countries, showed that the Amulet device was similarly safe and effective as the predecessor ACP device.

- High technical (99.1%) and procedural success (95.5%) 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 CHA2DS2-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 2 years of follow-up with the Amulet device[1,2]. 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 CHA2DS2-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 to OAC[1].

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Technical success (successful implantation of the device in the correct position) was achieved in 99.1% of the patients[2]. Major procedural adverse events within 7 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 3 deaths within 7 days after the procedure, 2 were adjudicated as device- or procedure-related. Procedural success (technical success with no periprocedural major adverse events) was achieved in 95.5% of the patients.[2]

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 2). Four ischemic strokes within 7 days from the procedure were adjudicated as procedure- or device related, and 2 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 3 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 7 days after implantation. Gastrointestinal bleeding accounted for 47.9% of all major bleeding events.[2]

Patients were most frequently discharged on dual (52.3%) or single (22.4%) APT. At 2 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 5-fold increased risk of ischemic stroke or TIA.[2]

Data regarding this global observational study are summarized in Table 1.

Table 1: Key data from the global prospective Amulet observational study[1,2]	
Patients	1088
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

Ischemic Stroke Rate

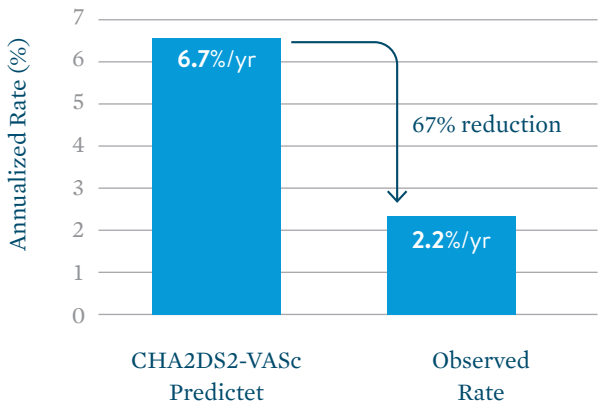

Figure 2: Expected and observed rate of ischemic stroke in the global Amulet prospective observational study at 2-year follow-up.

AMPLATZER LAAO DEVICES VERSUS OAC (ORAL ANTICOAGULANTS) - SUMMARY

Several initiatives have been deployed to compare LAAO with Amplatzer LAA occluders and long-term (OAC) oral anticoagulant therapy. Propensity score matching was applied in 2 separate studies.

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

The PRAGUE-17 study enrolled 415 patients for a randomized comparison between LAAO (performed with the Amulet 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.

Propensity score matched analyses were presented by Gloekler et al.[3] (EuroPCR 2017) and Nielsen-Kudsk et al.[4] (EuroPCR 2020). Data relevant to these analyses are summarized in Table 2 and in Figure 3. Although the definitions of the endpoints varied slightly between the 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 of LAAO compared to OAC and/or NOAC therapy. The differences in bleeding, all-cause mortality and net clinical benefit between the treatments was statistically significant in both studies.

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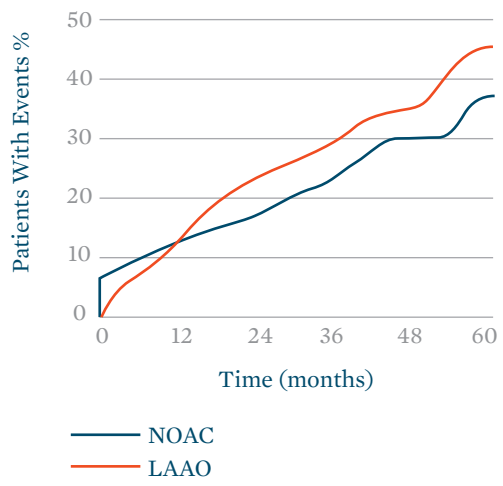
Table 2: Propensity score matched analyses of LAAO with ACP / Amulet devices versus oral anticoagulant therapy				
	Gloekler et al.[3]		Nielsen-Kudsk et al.[4]	
	LAAO	Anticoagulation	LAAO	Anticoagulation
Patients	500 (ACP/ Amulet)	500 (OAC/NOAC)	1071 (Amulet)[a]	1184 (NOAC)
CHA_2DS_2-VASc HAS-BLED	4.33 2.98	4.34 2.90	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.

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

Combined hazard endpoint



Kaplan-Meier failure estimate - primary outcome

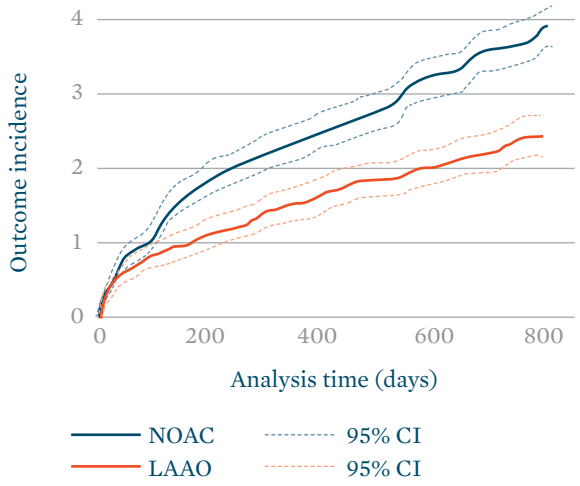


Figure 3: Propensity matched analyses comparing LAAO with ACP / Amulet occluders versus OAC/NOAC. Left: Composite of stroke, systemic embolism, cardiovascular/unexplained death, major procedural adverse events, major/life-threatening bleeding (Gloekler et al.[3]). Right: ischemic stroke, systemic embolism, major bleeding, all-cause mortality (Nielsen-Kudsk et al.[4]).

The outcomes of the PRAGUE-17 study[5] 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, which involved the Amplatzer Amulet device in the majority of patients and the Watchman ‡ device or Watchman-FLX ‡ device (Boston Scientific, St. Paul, MN). The NOAC therapy group included 202 patients, who preferably 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 3.

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Table 3: PRAGUE-17 study data[5]		
	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 2 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 in this patient population. 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.

FINAL CONCLUSIONS

- Compared with risk score-based expected rates, the Amulet device achieves a 67% reduction in ischemic stroke, as shown in the global prospective Amulet 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 Amulet device with a procedural complication rate of 4%.
- Compared to vitamin-K antagonist (i.e. warfarin) and NOAC, LAAO is associated with equally effective stroke prevention at lower risk of major bleeding. LAAO may provide an improved net clinical benefit in patients with high bleeding risk, compared to OAC/NOAC therapy.

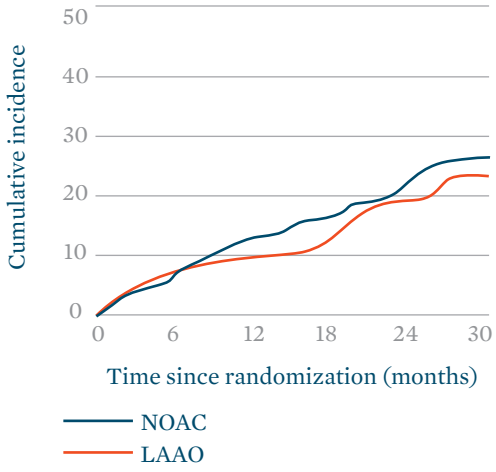

Figure 4: PRAGUE-17: primary endpoint (see Table 3). P-value for non-inferiority: 0.004.

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1. 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*.
2. 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*.
3. 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.
4. 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.
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