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AMPLATZER™ AMULET™ LEFT ATRIAL APPENDAGE OCCLUDER VERSUS WATCHMAN™ DEVICE FOR STROKE PROPHYLAXIS (AMULET IDE): A RANDOMIZED CONTROLLED TRIAL

Running Title: *Lakkireddy et al.; Amulet IDE trial*

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Abstract

Background: Percutaneous closure of the left atrial appendage (LAA) is an alternative to chronic oral anticoagulation to reduce stroke risk in patients with non-valvular atrial fibrillation (NVAF). The Amplatzer™ Amulet™ LAA Occluder IDE Trial (Amulet IDE Trial) was designed to evaluate the safety and effectiveness of the dual-seal mechanism of the Amulet LAA occluder compared with the Watchman™ device.

Methods: Patients with NVAF at increased risk of stroke were randomly assigned (1:1) to undergo percutaneous implantation of a LAA occluder with the Amulet occluder or Watchman device. The primary endpoints included safety (composite of procedure-related complications, all-cause death, or major bleeding at 12 months) and effectiveness (composite of ischemic stroke or systemic embolism at 18 months) and the rate of LAA occlusion at 45 days. Pre-specified secondary endpoints included a composite of all stroke, systemic embolism, or cardiovascular/unexplained death at 18 months, major bleeding at 18 months, and superiority test of the three primary endpoints.

Results: A total of 1878 patients were enrolled. The Amulet occluder was noninferior to the Watchman device for the primary safety endpoint (14.5% vs. 14.7%; difference=-0.14, 95% CI, -3.42-3.13; p<0.001 for noninferiority). Major bleeding and all-cause death were similar between groups (10.6% vs 10.0% and 3.9% vs 5.1%, respectively). Procedure-related complications were higher for the Amulet occluder (4.5% vs. 2.5%), largely related to more frequent pericardial effusion and device embolization. The Amulet occluder was noninferior to the Watchman device for the primary effectiveness endpoint (2.8% vs. 2.8%; difference=0.00, 95% CI, -1.55-1.55; p<0.001 for non-inferiority), and the composite of stroke, systemic embolism or cardiovascular/unexplained death (5.6% vs 7.7%, difference=-2.12, 95% CI, -4.45-0.21; p<0.001 for noninferiority). The rate of major bleeding was similar between groups (11.6% vs. 12.3%; difference=-0.71, 95% CI -3.72-2.31; p=0.32 for superiority). LAA occlusion was higher for the Amulet occluder compared with the Watchman device (98.9% vs. 96.8%; difference=2.03, 95% confidence interval [CI], 0.41-3.66; p<0.001 for noninferiority; p=0.003 for superiority).

Conclusions: The Amulet occluder was non-inferior for safety and effectiveness of stroke prevention for NVAF compared with the Watchman device, and superior for LAA occlusion. Procedure-related complications were higher with the Amulet device and decreased with operator experience.

Clinical Trial Registration: URL https://clinicaltrials.gov Unique Identifier NCT02879448

Key Words: Left atrial appendage closure; Stroke; Atrial Fibrillation; Stroke prevention

Nonstandard Abbreviations and Acronyms

BARC	Bleeding Academic Research Consortium
DAPT	Dual Antiplatelet Therapy
LAA	Left Atrial Appendage
LAAO	Left Atrial Appendage Occlusion
NVAF	Non-Valvular Atrial Fibrillation
OAC	Oral Anticoagulation
TEE	Transesophageal Echocardiogram
TIA	Transient Ischemic Attack

Clinical Perspective

What is new?

- The Amulet IDE trial is the first large scale randomized, multicenter, controlled trial among high-risk patients of stroke or systemic embolism to assess the Amulet occluder compared with the Watchman device.
- The dual-seal Amulet occluder was non-inferior with respect to safety and effectiveness compared with the single-seal mechanism Watchman device, and superior with respect to LAA occlusion.
- Procedure-related complications were higher for the Amulet occluder, largely related to more frequent pericardial effusion and device embolization. Procedure-related complications decreased with operator experience.

What are the clinical implications?

- The Amulet occluder met criteria for the primary safety (composite of procedure-related complications, all-cause death, or major bleeding at 12 months), and primary effectiveness (ischemic stroke or systemic embolism at 18 months) endpoints versus the Watchman device.
- Device-based successful LAA occlusion was higher with Amulet compared with Watchman, but procedural complications were higher when operators had limited experience.
- The Amulet occluder offers similar safely and efficacy as the Watchman device with the option to discharge without the use of oral anticoagulants.

Introduction

Patients with non-valvular atrial fibrillation (NVAF) are at a 3 to 5 fold increased risk of ischemic stroke[1] due to stagnation of blood flow in the left atrial appendage (LAA) that promotes local thrombus formation. Oral anticoagulation (OAC) is effective in preventing thromboembolic events; however, its use is limited by poor adherence and need for long-term treatment, side effects including bleeding, and drug interactions[2]. Percutaneous left atrial appendage occlusion (LAAO) can prevent thrombus embolization. In 2015 FDA approved the single seal mechanism Watchman™ device for LAA occlusion which requires 6 weeks of post-procedural anticoagulation. LAAO with a single seal mechanism may be incomplete due to the complex and variable anatomy of the LAA. A dual-seal device with an outer disc may overcome the limitations of anatomic heterogeneity, provide an improved seal of the LAA ostium, and reduce the risk of leak.

Long term follow-up of patients in PROTECT-AF and PREVAIL demonstrated that LAAO reduced the risk of hemorrhagic stroke, disabling/fatal stroke and death but not ischemic stroke as compared with warfarin through 5 years[3]. While there are observational studies suggesting comparable implant success, procedural outcomes, and safety events, no randomized multicenter trial comparing different devices with clinical outcome assessment has been performed. The purpose of the Amulet IDE trial was to compare the Amulet occluder to the Watchman device with respect to successful LAA occlusion as well as safety and effectiveness for stroke prevention.

Methods

Details about the design of the Amplatzer Amulet Left Atrial Appendage Occluder IDE Trial (Amulet IDE trial) have been published previously[4]. Briefly, the trial was a multi-center, open label, randomized, controlled trial evaluating the safety and effectiveness of the Amulet occluder. Details about trial organization and a list of participating centers are provided in Table I in the Supplement. The sponsor (Abbott) selected investigators qualified by training and experience in percutaneous and transseptal procedures to participate in the trial. Although all implanters met the same minimum criteria for inclusion in the trial and all had previous experience with the Watchman device, physicians outside the US were more experienced with the Amulet occluder. All physicians had previous experience with the Watchman device. To provide Amulet implant experience at US sites prior to randomization, up to 3 patients per sponsor-approved implanter could be implanted with the Amulet device as part of the roll-in phase. Patients were designated based on physician proctor assessment as a roll-in patient prior to the procedure. The results in this study represent the main cohort and not the roll-in population. Because of the sensitive nature of the data collected for this study, requests to access the dataset from qualified researchers trained in human subject confidentiality protocols require an application which may be submitted to Abbott Structural Heart at iEnvision (envisionpharma.com).

The protocol was approved by the institutional review board at each participating center. All patients provided written informed consent. An independent Data and Safety Monitoring Board monitored all safety data and was involved in decisions regarding trial continuation. Adverse events were adjudicated by an independent clinical events committee that was blinded

to treatment assignment and device implanted. An independent core laboratory was used to analyze transesophageal echocardiography (TEE) images.

Eligible patients were 18 years of age or older with documented paroxysmal, persistent, or permanent NVAF and were at increased risk of stroke or systemic embolism defined as $CHADS_2$ score ≥ 2 or a CHA_2DS_2-VASc score of ≥ 3[5, 6]. Patients were screened with TEE to ensure suitable LAA anatomy for implanting both devices prior to enrollment. As required by the directions for use for the Watchman device, patients had to be suitable for anticoagulation therapy for 6 months and have appropriate rationale to seek a non-pharmacological alternative. A complete list of enrollment criteria is provided in Table II in the Supplement. Patients were randomized in a 1:1 ratio to undergo percutaneous LAAO with the Amulet occluder (Abbott) or the Watchman device (Boston Scientific) according to a computer-generated randomization scheme (Table 1; Table III in the Supplement). Randomization was stratified by investigational site in permuted block sizes of 2, 4, and 6.

Procedures

Implant procedures were guided by TEE and fluoroscopy. Patients implanted with the Amulet occluder were discharged on either aspirin plus clopidogrel or aspirin plus OAC at the discretion of the investigator, while patients assigned to and implanted with the Watchman device received aspirin plus warfarin per the device directions for use. When LAAO was confirmed by TEE (residual jet ≤ 5mm) at the 45-day visit, cessation of OAC was required for all patients. Patients were then instructed to take aspirin and clopidogrel until the 6-month visit when clopidogrel was discontinued and aspirin continued indefinitely. Details about the trial assessments are shown in Table IV in the Supplement.

Endpoints

The *primary safety endpoint* was a composite of procedure-related complications, all-cause death, or major bleeding[7] through 12 months. The *primary effectiveness endpoint* was a composite of ischemic stroke or systemic embolism through 18 months. The primary *mechanism of action* endpoint was successful device-based LAA occlusion (residual jet around the device ≤ 5 mm) was assessed by an independent core laboratory on TEE at the 45-day visit. Pre-specified *secondary endpoints* included 1) a composite of all stroke (ischemic or hemorrhagic), systemic embolism, or cardiovascular/unexplained death at 18 months (noninferiority); 2) major bleeding at 18 months (superiority); 3) superiority test of the primary mechanism of action endpoint;4) superiority test of the primary safety endpoint; and 5) superiority test of the primary effectiveness endpoint (Tables V and VI in the Supplement).

Statistical Analysis

Assuming a composite event rate of 15% in both groups for the primary safety endpoint, the sample size required to provide 90% power to reject a non-inferiority margin of 5.8% at the 2.5% significance level was 1746 patients. The pre-specified primary analysis of the primary safety endpoint was based on the per-protocol population. In addition, sensitivity analysis was performed in the as-attempted population. Assuming a composite event rate of 4.2% in both groups for the primary effectiveness endpoint, the sample size required to provide 90% power to reject a non-inferiority margin of 3.2% at the 2.5% significance level was 1878 patients. The pre-specified primary analysis of the primary effectiveness endpoint was based on the intention-to-treat population. In addition, sensitivity analysis was performed in the per-protocol population. Both primary safety and effectiveness endpoint event rates were estimated using Kaplan-Meier method with Greenwood's formula for the variance of the estimates. Assuming a device based

LAA occlusion rate of 96% for the Amulet occluder and 95% for the Watchman device, the sample size required to provide 90% power to reject a non-inferiority margin of 3% at the 2.5% significance level was 1258 patients based on the Farrington Manning test for difference between two binomial proportions. The pre-specified primary analysis included patients who received the device as randomized and who had 45-day occlusion status determined by the core laboratory. Sensitivity analysis including unsuccessful implants was conducted to account for missing data.

Detailed descriptions of analysis populations are provided in Table VII in the Supplement. Patients who withdrew or were lost-to-follow-up without experiencing an endpoint event were censored on the date of withdrawal/loss-to-follow-up. Sensitivity analysis with multiple imputation was performed to account for missing data.

All three primary endpoints were required to be met to conclude that the trial was successful. If all three primary endpoints of non-inferiority were met, the five secondary endpoints would be tested using the Hochberg procedure[8] to adjust for multiple comparisons. Other than above, Cox regression model was used to analyze time to first event, and logistic regression was used to analyze binary outcome. A two-sided P value of less than 0.05 indicates statistical significance. All statistical analyses were performed with SAS software, version 9.4 (SAS Institute). Data collection for this analysis ended on October 26, 2020.

Role of the funding source

The sponsor (Abbott) designed the trial and was responsible for selecting and monitoring sites as well as data management and data analysis. The Steering Committee and other coauthors had full

access to the data and attest to the integrity of the trial and the accuracy and completeness of the reported data.

Results

Patient Characteristics

A total of 2592 patients were consented in the Amulet IDE Trial (Figure 1). The most common reason for screen failure was LAA anatomy not being appropriate for one or both devices. From September 2016 through March 2019, a total of 1878 patients (1598 at 78 US centers and 280 at 30 centers outside the US) at 108 sites were randomly assigned to receive either an Amulet occluder (934) or Watchman device (944). Baseline characteristics were well-matched between groups (Table 2). The average age was 75 years, and a majority were male. Patients had a high risk for stroke and bleeding as reflected by the average CHA_2DS_2-VASc (4.5 and 4.7) and HAS-BLED (3.2 and 3.3). History of stroke was present in about 20% of patients.

Procedural Outcomes

Procedural outcomes are shown in Table 3. Device implant attempt as randomized occurred in 915 Amulet patients and 916 Watchman patients. Device success[9] as randomized was similar between groups (98.4% vs 96.4%). The most common reason for unsuccessful implant was unsuitable patient anatomy, which was less common in the Amulet group (9 vs 30; Figure 1). Technical and procedural success were similar between groups (97.2% vs 95.3% and 96.0% vs 94.5%). At hospital discharge 75.7% of Amulet patients were on aspirin and clopidogrel and 20.0% were on anticoagulation plus aspirin. Most (82.0%) Watchman patients were discharged on warfarin plus aspirin. At the 9-month follow-up visit and beyond, the majority of patients

(~85%) in both groups were on single antiplatelet therapy. Details of antithrombotic medication use at each scheduled follow-up visit are provided in Figure 2.

Primary and Secondary Endpoints

Results of the primary and secondary endpoints are shown in Table 3 and Table VIII in the Supplement. The rate for the primary safety endpoint was 14.5% for the Amulet occluder and 14.7% for the Watchman device (Figure 3A; difference, -0.14, 95% CI, -3.42 to 3.13; $p<0.001$ for non-inferiority, $p=0.47$ for superiority). Similar results were observed for the as-attempted analysis (Table VIII in the Supplement). Major bleeding and all-cause death were similar between groups (10.6% vs 10.0% and 3.9% vs 5.1%, respectively). Procedure-related complications were higher for the Amulet occluder (Table 3: 4.5% vs. 2.5%), largely related to more frequent pericardial effusion and device embolization (Table IV in the Supplement). Patients discharged on anticoagulation therapy experienced a higher rate of late pericardial effusion than patients discharged on no antithrombotic therapy (Figure II in the Supplement). Procedure-related complications including pericardial effusion and device embolization generally occurred early in implanter experience with the Amulet occluder (Figure 4). Although there was a higher rate of pericardial effusion with the Amulet occluder, the event resolved without sequalae in all cases and none required emergency surgery or resulted in death. The rate for the primary effectiveness endpoint was 2.8% for both groups (Figure 3B; difference, 0.00, 95% CI, -1.55 to 1.55; $p<0.001$ for non-inferiority, $p=0.50$ for superiority). The rate of ischemic stroke and systemic embolism were comparable between groups. Similar results were observed for the per protocol analysis (Table VIII in the Supplement). The ischemic stroke rate was 1.67%/year for the Amulet occluder and 1.94%/year for the Watchman device. Successful device-based LAA occlusion was observed in 98.9% of Amulet patients and 96.8% of

Watchman patients (Figure 3C; difference, 2.03; 95% confidence interval [CI], 0.41 to 3.66; p<0.001 for non-inferiority, p=0.003 for superiority). Complete occlusion (i.e. no residual jet around the device) was observed in 63.0% of Amulet patients and 46.1% of Watchman patients (Figure I in the Supplement).

Among the secondary endpoints, the Amulet occluder was non-inferior to the Watchman device for the composite of stroke, systemic embolism or cardiovascular/unexplained death (5.6% vs 7.7%; difference, -2.12, 95% CI, -4.45 to 0.21; p<0.001 for non-inferiority; Table 3). The rate of major bleeding was similar between groups (11.6% vs 12.3%; p=0.32), therefore the secondary endpoint for superiority of major bleeding was not met.

Sensitivity analyses showed that all primary and secondary endpoint results remained robust to missing data (Table VIII in the Supplement). Prespecified subgroup analyses showed no evidence that the difference in results between groups were different across the different subgroup strata for any of the primary endpoints (Figures III, IV, and V in the Supplement).

Key Descriptive Endpoints at 18 Months

Device-related thrombosis (DRT) rates were similar between groups (3.3% vs 4.5%; Table 4). The majority of DRT events were identified during scheduled follow-up visits and most subjects in both groups were on antiplatelet therapy when the DRT was first identified. In the Watchman group two patients with DRT experienced an ischemic stroke and/or systemic embolism. In the Amulet group no patients with DRT experienced an ischemic stroke or systemic embolism. The rate of transient ischemic attack (1.6% vs 1.4%) and hemorrhagic stroke (0.3% vs 0.7%) were similar between groups.

Discussion

In the Amulet IDE trial, compared with the single seal mechanism first generation Watchman device, the dual-seal mechanism Amulet device was non-inferior with respect to safety and effectiveness endpoints, and superior with respect to LAA occlusion. Sensitivity analyses of all primary endpoints revealed that the results were robust to missing data and similar for different analysis populations.

In patients with NVAF at risk for stroke, OAC is recommended as first line therapy[10]. Percutaneous LAA occlusion with the Watchman device has been shown to be non-inferior to warfarin in NVAF patients at moderate stroke risk,(3) although direct comparison of LAA closure with the Amulet occluder to non-Vitamin K antagonists remains the subject of ongoing clinical trials. In addition, LAAO may be considered in patients with contraindications for OAC (Class IIB), those who experience major bleeding on OAC as well as patients at high bleeding risk. LAAO is associated with device-specific limitations including inability to close the appendage due to unsuitable anatomy, incomplete occlusion with leaks and device-related complications.

The Amulet device was non-inferior to the Watchman device for the composite safety endpoint of procedure-related complications, all-cause death, or major bleeding at 12 months. The rate of non-procedural bleeding was high in both groups, pointing to a high-risk bleeding population. Procedural complications were nearly twice as high with the Amulet device, and occurred early in an implanter's experience driven by pericardial effusion and device embolization. In a prospective observational study using the Amulet occluder, rates of device embolization and pericardial effusion requiring surgical or percutaneous intervention were 0.2% and 1.3%, respectively[11]. US sites had an existing Watchman program and no prior Amulet

experience, which may have contributed to higher complication rates in US sites in the Amulet arm. Moreover, Amulet patients who were discharged on OACs experienced a higher rate of late pericardial effusion than those discharged on antiplatelet therapy, suggesting that less intensive antithrombotic therapy may mitigate the risk of late pericardial effusions. Additional study will be required to determine whether rates of device complications diminish with increased operator experience. The Amulet device was non-inferior with respect to the primary effectiveness endpoint of stroke and systemic embolism as well as the composite endpoint of stroke, systemic embolism and cardiovascular/unexplained death at 18 months. DRT rates were similar between groups despite the reduced rate of post-procedure anticoagulation in the Amulet group.

The Amulet device has a dual-seal mechanism and consists of a lobe and a disc connected by a central waist with polyester patches sewn into both the lobe and disc to facilitate effective occlusion. This design may help to overcome limitations of a single seal mechanism including but not limited to short LAA length, proximal lobes near the ostium, and very large ostia. In addition, patients may be treated without the need for OAC post-procedure.

Trial Limitations

The results should be interpreted in view of the following limitations. The trial had many exclusion criteria and a high number of patients were excluded which may limit the generalizability of the findings. The echocardiographic core lab was not blinded. This trial compared the Amulet device to the first-generation Watchman device, not the newer generation of the Watchman FLX[12]. Currently, it is unknown which antithrombotic regimen provides the best balance between stroke and bleeding risk and the lowest risk for DRT. Moreover, patients continue to experience stroke despite OAC and there may be potential synergy between LAA occlusion and continuation of OAC as demonstrated in the recent LAAOS III trial.([13]) Further

studies are needed to better understand the higher occurrence of late pericardial effusion in Amulet patients receiving post-procedure OAC. Death as a competing risk for the primary efficacy endpoint was not accounted for in the primary time-to-event analyses. Finally, a direct comparison between LAA occlusion and stroke prevention based on non-Vitamin K antagonists is needed.

Conclusions

In conclusion, compared with the first generation Watchman device, LAAO with a dual-seal mechanism using the Amulet occluder demonstrated noninferior safety and effectiveness, with superior LAA occlusion rates but higher device related complications. The clinical significance of differences in LAA closure will need to be ascertained via longer-term follow-up.

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Supplemental Materials

Expanded methods

Supplemental Tables I-VIII

Supplemental Figures I-V

References

1. Ball J, Carrington MJ, McMurray JJ and Stewart S. Atrial fibrillation: profile and burden of an evolving epidemic in the 21st century. *International journal of cardiology*. 2013;167:1807-24.
2. Shameem R and Ansell J. Disadvantages of VKA and requirements for novel anticoagulants. *Best practice & research Clinical haematology*. 2013;26:103-14.
3. Reddy VY, Doshi SK, Kar S, Gibson DN, Price MJ, Huber K, Horton RP, Buchbinder M, Neuzil P, Gordon NT, Holmes DR, Jr., Prevail and Investigators PA. 5-Year Outcomes After Left Atrial Appendage Closure: From the PREVAIL and PROTECT AF Trials. *Journal of the American College of Cardiology*. 2017;70:2964-2975.
4. Lakkireddy D, Windecker S, Thaler D, Sondergaard L, Carroll J, Gold MR, Guo H, Brunner KJ, Hermiller JB, Diener HC, et al. Rationale and design for AMPLATZER Amulet Left Atrial Appendage Occluder IDE randomized controlled trial (Amulet IDE Trial). *Am Heart J*. 2019;211:45-53.
5. Gage BF, Waterman AD, Shannon W, Boechler M, Rich MW and Radford MJ. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. *Jama*. 2001;285:2864-70.
6. Lip GY, Nieuwlaat R, Pisters R, Lane DA and Crijns HJ. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. *Chest*. 2010;137:263-72.
7. Mehran R, Rao SV, Bhatt DL, Gibson CM, Caixeta A, Eikelboom J, Kaul S, Wiviott SD, Menon V, Nikolsky E, et al. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. *Circulation*. 2011;123:2736-47.
8. Hochberg Y. A sharper Bonferroni procedure for multiple tests of significance. *Biometrika*. 1988;75:800-802.
9. Tzikas A, Holmes DR, Jr., Gafoor S, Ruiz CE, Blomstrom-Lundqvist C, Diener HC, Cappato R, Kar S, Lee RJ, Byrne RA, et al. Percutaneous left atrial appendage occlusion: the Munich consensus document on definitions, endpoints, and data collection requirements for clinical studies. *Europace : European pacing, arrhythmias, and cardiac electrophysiology : journal of the working groups on cardiac pacing, arrhythmias, and cardiac cellular electrophysiology of the European Society of Cardiology*. 2017;19:4-15.
10. Hindricks G, Potpara T, Dagres N, Arbelo E, Bax JJ, Blomstrom-Lundqvist C, Boriani G, Castella M, Dan GA, Dilaveris PE, et al. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): The Task Force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. *European heart journal*. 2021;42:373-498.
11. Landmesser U, Tondo C, Camm J, Diener HC, Paul V, Schmidt B, Settergren M, Teiger E, Nielsen-Kudsk JE and Hildick-Smith D. Left atrial appendage occlusion with the AMPLATZER Amulet device: one-year follow-up from the prospective global Amulet observational registry. *EuroIntervention : journal of EuroPCR in collaboration with the Working Group on Interventional Cardiology of the European Society of Cardiology*. 2018;14:e590-e597.

12. Kar S, Doshi SK, Sadhu A, Horton R, Osorio J, Ellis C, Stone J, Jr., Shah M, Dukkipati SR, Adler S, et al. Primary Outcome Evaluation of a Next-Generation Left Atrial Appendage Closure Device: Results From the PINNACLE FLX Trial. *Circulation*. 2021;143:1754-1762.
13. Whitlock RP, Belley-Cote EP, Paparella D, Healey JS, Brady K, Sharma M, Reents W, Budera P, Baddour AJ, Fila P, et al. Left Atrial Appendage Occlusion during Cardiac Surgery to Prevent Stroke. *N Engl J Med*. 2021;384:2081-2091.

Table 1. Comparison of Devices

	Amulet	**Watchman**
Manufacturer	Abbott Medical	Boston Scientific
Mechanism of Action	Lobe of the device placed within the LAA and the disc sealing the orifice	Closes off distal body of LAA
Sizes (diameter)	16, 18, 20, 22, 25, 28, 31, and 34 mm	21, 24, 27, 30, and 33 mm

Table 2. Demographics and Baseline Characteristics

Characteristic	Amulet (N=934)	Watchman (N=944)
Age - yr	75.0 ± 7.6	75.1 ± 7.6
Male sex – no. (%)	549 (58.8)	579 (61.3)
Type of atrial fibrillation – no. (%)		
Paroxysmal	528 (56.5)	509 (53.9)
Persistent	250 (26.8)	277 (29.3)
Permanent	156 (16.7)	157 (16.6)
$CHADS_2$ Score	2.7 ± 1.1	2.8 ± 1.2
CHA_2DS_2-VASc Score	4.5 ± 1.3	4.7 ± 1.4
HAS-BLED Score	3.2 ± 1.0	3.3 ± 1.0
Medical history – no. (%)		
Minor Bleeding	310 (33.2)	320 (33.9)
Major Bleeding	271 (29.0)	250 (26.5)
Both Major and Minor Bleeding	28 (3.0)	37 (3.9)
TIA	100 (10.7)	113 (12.0)
Stroke	168 (18.0)	188 (19.9)
Systemic Embolism	57 (6.1)	53 (5.6)
Myocardial Infarction	136 (14.6)	149 (15.8)
NYHA		
No Heart Failure	469 (50.4)	437 (46.4)
I	147 (15.8)	169 (18.0)
II	251 (27.0)	259 (27.5)
III	63 (6.8)	76 (8.1)
Primary Reason for LAA occlusion as Alternative to Long-term OAC		
History of major or minor bleeding	515 (55.1)	503 (53.3)
High bleeding risk	204 (21.8)	193 (20.4)
Risk of falls	107 (11.5)	126 (13.3)
Patient's preference/lifestyle	51 (5.5)	38 (4.0)
Prior stroke on OAC	18 (1.9)	32 (3.4)
Labile/unstable International Normalized Ratio	15 (1.6)	29 (3.1)
Drug interactions	12 (1.3)	12 (1.3)
Renal or hepatic disease	6 (0.6)	4 (0.4)

Data are Mean ± SD (N) or % (n/N)

Table 3. Outcomes

Outcome	No. of patients (%)		Hazard Ratio (95% CI)	P-value for non-inferiority	P-value for superiority
	Amulet	Watchman			
Primary Safety Endpoint at 12 months	131 (14.5)	130 (14.7)	-0.14* (-3.42, 3.13)	<0.001†	0.47‡
Procedure Related Complications	41 (4.5)	22 (2.5)	1.86 (1.11, 3.12)		0.02#
Major Bleeding (Type 3 or greater)	95 (10.6)	88 (10.0)	1.07 (0.80, 1.43)		0.63#
Non-Procedure Related Major Bleeding	70 (7.9)	70 (8.0)	0.99 (0.71, 1.37)		0.94#
All-Cause Death	35 (3.9)	45 (5.1)	0.76 (0.49, 1.19)		0.23#
Primary Effectiveness Endpoint at 18 months	25 (2.8)	24 (2.8)	0.00* (-1.55, 1.55)	<0.001†	0.50‡
Ischemic Stroke	22 (2.5)	23 (2.7)	0.94 (0.52, 1.68)		0.83#
Systemic Embolism	3 (0.3)	2 (0.2)	1.48 (0.25, 8.83)		0.67#
Primary Mechanism of Action Endpoint (Device-based LAA occlusion with residual jet ≤5 mm at 45 days)	792 (98.9)	767 (96.8)	2.03* (0.41, 3.66)	<0.001§	0.003‖
Major Bleeding at 18-Months	105 (11.6)	109 (12.3)	-0.71* (-3.72, 2.31)		0.32‡
Stroke, Systemic Embolism, CV/unexplained death at 18-Months	50 (5.6)	67 (7.7)	-2.12* (-4.45, 0.21)	<0.001†	0.09#
All Stroke	24 (2.7)	29 (3.4)	0.81 (0.47, 1.39)		0.45#
Systemic Embolism	3 (0.3)	2 (0.2)	1.48 (0.25, 8.83)		0.67#
Cardiovascular/Unexplained Death	28 (3.1)	42 (4.8)	0.65 (0.40, 1.05)		0.08#

*Difference in event rates (Kaplan-Meier estimate or proportions) between groups

† The null hypothesis was tested at the 2.5% significance level (Non-inferiority margin 5.8% for safety and 3.2% for effectiveness)..

‡ The null hypothesis was tested at the 2.5% significance level (Non-inferiority margin 5.8% for safety and 3.2% for effectiveness).

§ Farrington Manning test (Non-inferiority margin 3%).

‖ The null hypothesis is tested at the 2.5% significance level.

Cox regression

Table 4. Key Descriptive Endpoints

Outcome	Amulet (N=915)	Watchman (N=916)
Device Success*	900 (98.4)	883 (96.4)
Technical Success**	889 (97.2)	873 (95.3)
Procedural Success***	878 (96.0)	866 (94.5)
Device Related Thrombus (DRT) at 18-months	30 (3.3)	40 (4.5)
Transient Ischemic Attack at 18-months	15 (1.5)	13 (1.4)
Hemorrhagic Stroke at 18-months	3 (0.3)	6 (0.7)

Data presented as No. of patients (%). *defined as device deployed and implanted in correct position at the index procedure; **exclusion of the LAA with site reported residual jet ≤5 mm and no device-related complications through discharge or 7 days whichever is earlier; ***technical success with no procedure-related complications

Figure Legends

Figure 1. Patient Flow Chart

Enrollment and disposition of patients in the Amulet IDE trial.

Figure 2. Antithrombotic Medication During Follow-up

The distribution of antithrombotic medical regimen on the day of discharge or on the day prior to each follow-up visit in the two groups is presented.

Figure 3. Primary Endpoint Results.

Panel A shows Kaplan-Meier estimated rates of the primary safety endpoint and **Panel B** shows primary effectiveness endpoint in the prespecified analysis populations (PP, ITT, respectively). **Panel C** shows the distribution of residual jet at 45 days for the images analyzed by the echo core lab.

Figure 4. US implanters' Amulet Experience and Procedure Related Complications of Pericardial Effusion and Device Embolization

Panel A shows the number of Amulet patients with procedure-related complications of device embolization and pericardial effusion by US implanter case sequence. Cases are grouped in three's by Amulet case experience across US implanters, including roll-in cases. **Panel B** shows the same type of data for pericardial effusions including only patients discharged on antiplatelet therapy (APT) or no antithrombotic medication (i.e. not discharged on OAC).