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5-Year Results From the AMPLATZER Amulet Left Atrial Appendage Occluder Randomized Controlled Trial

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ABSTRACT

BACKGROUND The Amulet IDE trial (AMPLATZER Amulet Left Atrial Appendage Occluder [LAAO] Investigational Device Exemption [IDE] Trial) evaluated the safety and effectiveness of the Amulet occluder (Abbott) in patients with nonvalvular atrial fibrillation. The Amulet IDE trial is the largest randomized LAAO trial, comparing the Amulet occluder with the Watchman 2.5 device (Boston Scientific).

OBJECTIVES This analysis presents the 5-year results from the trial comparing the 2 devices head to head.

METHODS Patients enrolled in the Amulet IDE trial were at a high risk of stroke or systemic embolism defined as a CHADS2 score ≥2 or CHA2DS2-VASc score ≥3. Oral anticoagulation (OAC) use and key clinical outcomes are presented through 5 years.

RESULTS A total of 1,878 patients were randomized, with 1,833 undergoing a device implantation attempt (n = 917, Amulet occluder; and n = 916, Watchman device). A significantly higher percentage of patients were free of OAC in the Amulet occluder group at each follow-up visit, with 94.0% and 90.9% free of OAC at the last 5-year follow-up visit in the Amulet and Watchman device groups, respectively ($P = 0.009$). The 5-year clinical outcomes were similar between the Amulet and Watchman devices, including the composite of ischemic stroke or systemic embolism (7.4% vs 7.1%; $P = 0.851$), the composite of stroke, systemic embolism, or cardiovascular death (20.3% vs 20.7%; $P = 0.666$), major bleeding (20.1% vs 20.0%; $P = 0.882$), cardiovascular (CV) death (14.3% vs 15.4%; $P = 0.429$), and all-cause death (28.7% vs 31.1%; $P = 0.217$). Annualized ischemic stroke rates at 5 years were low and the same for Amulet (1.6%/y) and Watchman (1.6%/y) devices. Strokes in patients with the Amulet occluder were less severe (n = 38, nondisabling; n = 11, disabling; n = 11, fatal; n = 12, unknown) than strokes in patients with the Watchman device (n = 19, nondisabling; n = 22, disabling; n = 17, fatal; n = 10, unknown). Moreover, device factors (device-related thrombus or peridevice leak ≥3 mm) preceded stroke events and CV deaths more frequently in patients with the Watchman device (n = 63) compared with patients with the Amulet occluder (n = 31).

CONCLUSIONS The 5-year outcomes from the largest randomized LAAO clinical trial demonstrated the long-term safety and effectiveness of the Amulet occluder and Watchman 2.5 devices. The dual-seal Amulet occluder reduces atrial fibrillation–related thromboembolic events while eliminating the need for long-term OAC. (AMPLATZER Amulet Left Atrial Appendage Occluder [LAAO] Investigational Device Exemption [IDE] Trial [Amulet IDE trial]; NCT02879448) (JACC. 2024;■:■-■) © 2024 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

CV = cardiovascular

DAPT = dual antiplatelet therapy

DOAC = direct oral anticoagulation

DRT = device-related thrombus

FDA = U.S. Food and Drug Administration

LAA = left atrial appendage

LAAO = left atrial appendage occlusion

mRS = modified Rankin Scale

NVAF = nonvalvular atrial fibrillation

OAC = oral anticoagulation

PDL = peridevice leak

TEE = transesophageal echocardiography

TIA = transient ischemic attack

The left atrial appendage (LAA) is the primary source of thrombus formation in patients with nonvalvular atrial fibrillation (NVAF), and LAA closure can effectively reduce the risk of thromboembolic events.[1,2] Percutaneous LAA occlusion (LAAO) has emerged as a viable alternative to oral anticoagulation (OAC) for stroke reduction in patients with nonvalvular NVAF.[3,4] Over the past decade, LAAO devices have shown promising results in reducing stroke risk while avoiding the bleeding complications associated with long-term OAC. The Watchman 2.5 LAA closure device (Boston Scientific) demonstrated comparable stroke rates between LAAO and warfarin with reduced bleeding events compared with OAC in long-term pooled 5-year follow-up.[5] The Watchman 2.5 device uses a single lobe to plug the LAA.

The Amulet IDE trial (AMPLATZER Amulet Left Atrial Appendage Occluder [LAAO] Investigational Device Exemption [IDE] Trial; NCT02879448) is a prospective, global, multicenter, randomized, controlled trial designed to evaluate the safety and effectiveness of the AMPLATZER Amulet LAA occluder (Abbott) by demonstrating noninferiority against the control Watchman 2.5 device in patients with NVAF. The Amulet occluder uses dual-seal technology to seal the LAA at both the ostium (disc) and the neck (lobe). Initial results from the Amulet IDE trial demonstrated noninferiority of the Amulet occluder in terms of safety and effectiveness at 12 and 18 months,[6] respectively, with superiority in achieving complete LAA closure at 45 days[6] and 12 months.[7] This result led to U.S. Food and Drug Administration (FDA) approval of the Amulet occluder in August 2021. Although 3-year results from the trial showed continued long-term safety and effectiveness of both devices,[8] extended long-term data through 5-year follow-up are important to understand the comparative effectiveness and safety profile of these devices fully. This analysis presents the 5-year results from the Amulet IDE trial, thereby providing a comprehensive head-to-head comparison of the Amulet occluder and Watchman device over an extended follow-up period.

METHODS

AMULET IDE TRIAL DESIGN. Details of the design[9] and primary results[6] from the Amulet IDE trial have been presented previously. The protocol was approved by the Institutional Review Board at each participating center, along with written informed consent from each patient before enrollment. An independent data and safety monitoring board monitored the safety of the trial, and adverse events were adjudicated by a blinded independent clinical events committee. The corresponding author had full access to all the data in the study and takes responsibility for their integrity and data analyses.

Eligible patients aged 18 years or older with documented paroxysmal, persistent, or permanent NVAF and at high risk of stroke or systemic embolism ($CHADS_2$ score ≥2 or CHA2DS2-VASc score ≥3) were randomized 1:1 to receive an Amulet occluder or a Watchman 2.5 device. As required by the Watchman 2.5 device directions for use, patients had to be suitable candidates for OAC for 6 months and have appropriate rationale to seek a nonpharmacologic alternative. A complete list of the inclusion and exclusion criteria can be found in the Amulet IDE trial design publication.[9]

IMPLANTATION PROCEDURES. LAAO implantation procedures were guided by transesophageal echocardiography (TEE) and fluoroscopy. According to the protocol, patients who underwent implantation of an Amulet occluder were discharged on either dual antiplatelet therapy (DAPT) or aspirin combined with OAC at the discretion of the investigator. OAC was required if residual jet flow was >5 mm post-implantation. Patients who underwent implantation of a Watchman device were discharged on aspirin combined with OAC according to the device directions for use. If a residual jet ≤5 mm was confirmed at the 45-day visit by TEE, cessation of OAC was required for all patients. Patients in both groups were instructed to take DAPT until the 6-month visit, at which time clopidogrel was discontinued and aspirin was continued indefinitely. The medication regimens were documented at baseline, discharge, and during site trial visits through 5 years.

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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CARDIAC IMAGING. Patients were screened with TEE to ensure suitable LAA anatomy for implanting either device before enrollment. Additional TEE images were required at baseline, procedure, 45-day, 6-month (if a residual jet was >5 mm at 45 days), and 12-month visits or if a stroke was diagnosed. An independent echocardiography core laboratory (Cardiovascular Research Foundation) reviewed all TEE images to assess for the presence or absence of device-related factors (device-related thrombus [DRTs] or peridevice leaks [PDLs]). A PDL size of ≥3 mm was chosen for this analysis on the basis of a previous subanalysis showing increased clinical outcome risks associated with this cutoff size in the Amulet IDE trial.[7]

OUTCOMES. Primary, secondary, and descriptive endpoints from the Amulet IDE trial are presented through 5 years. They include the following: 1) composite of ischemic stroke or systemic embolism (primary effectiveness endpoint); 2) composite of all stroke (ischemic, hemorrhagic, or undetermined), systemic embolism, or cardiovascular (CV)/unexplained death (secondary endpoint); 3) transient ischemic attack (TIA; descriptive endpoint); 4) major bleeding (Bleeding Academic Research Consortium type 3 or higher, including any transfusion with overt bleeding and a hemoglobin drop of ≥3 g/dL)[10] (secondary endpoint); and 5) all-cause death and CV death (descriptive endpoints).

If a stroke or TIA was suspected, the patient was required to be seen by a neurologist for further evaluation, including completion of magnetic resonance imaging within 10 days of the event. If ischemic stroke was confirmed, TEE was required within 7 days along with a neurologic assessment (eg, modified Rankin Scale [mRS] score), immediately and after 90 days of the event. Strokes were categorized into different severity levels on the basis of the Munich consensus document definitions.[11] Fatal strokes were defined if the adjudicated cause of death was related to the stroke. A disabling stroke was defined if the mRS score was ≥2 during the stroke assessment (90 days after the index event), with an increase of ≥1 point compared with the prestroke baseline. A nondisabling stroke was defined if the mRS score was <2 at the 90-day stroke assessment or ≥2 without an increase of at least 1 point compared with the prestroke baseline. Strokes unable to be classified into 1 of the foregoing categories as a result of missing data (eg, missing mRS scores) were labeled as unknown. The neurologists who performed the neurologic assessment at the sites and data analytics were not blinded to the trial.

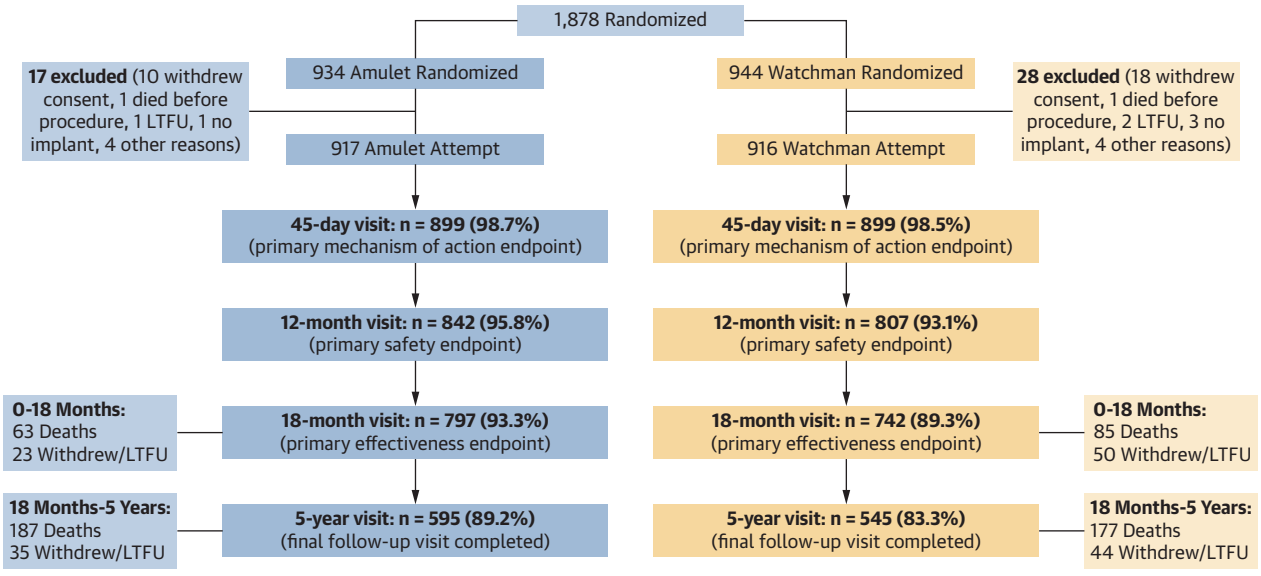
After discharge, clinical follow-up occurred at 45 days, at 3, 6, 9, 12, and 18 months, and then annually by telephone for years 2 through 5 post-LAAO implantation. Unless otherwise specified, the patients in this analysis included randomized patients who underwent a device implantation attempt regardless of whether the device was attempted to be implanted or actually implanted.

STATISTICAL ANALYSIS. The baseline characteristics, medication, stroke severity, and device factors were summarized using descriptive statistics. The *t*-test for continuous variables and the chi-square test or Fisher exact test for categorical variables were used to identify differences in patient characteristics and OAC use between the device groups. The Kaplan-Meier method was used to calculate event rates at 5 years post-procedure. Cox regression HRs and 95% CIs were calculated for the 5-year clinical outcomes, and no covariates were adjusted for because there were no statistical differences in the baseline characteristics between the 2 device groups. Annualized ischemic stroke rates (events/patient-years) were compared with the anticipated rate by baseline CHA2DS2-VASc score for patients with NVAF who were not treated with OAC through 5 years.[12] All statistical analyses were performed using SAS software version 9.4 (SAS Institute).

RESULTS

PATIENT FOLLOW-UP AND BASELINE CHARACTERISTICS. A total of 1,878 patients at 109 sites were randomized from September 2016 through March 2019, and the 1,833 patients who underwent a device implantation attempt (n = 917, Amulet occluder; and n = 916, Watchman device) were included in this analysis (**Figure 1**). The follow-up visit rate was >80% in both device groups for the final 5-year visit (89.2%; n = 595 in the Amulet occluder group and 83.3%; n = 545 in the Watchman device group). As mentioned previously, differences in withdrawal rates between the 2 device groups seemed to be mostly driven by device-specific reasons early on and in patients with particularly high numbers of comorbid conditions.[8] Baseline characteristics were well matched between the 2 device groups, as shown previously[6] (**Table 1**). The average age was 75 years, 40% were female (60% male), 55% of patients had a history of paroxysmal atrial fibrillation, average CHA2DS2-VASc score of 4.6, 27% had a previous stroke/TIA/or thromboembolism, average HAS-BLED score of 3.3, and 75% of patients had an indication for LAAO for a bleeding-associated concern.

FIGURE 1 **Number of Patients Randomized and Those Who Underwent an Implantation Attempt in the AMPLATZER Amulet Left Atrial Appendage Occluder Investigational Device Exemption Trial With Either the Amulet Occluder (Abbott) or the Watchman Device (Boston Scientific)**



Follow-up at the primary endpoint time points (45-day, 12-month, and 18-month points) and at the final 5-year required visits are provided. The follow-up rate percentage is calculated as follows: - Visit Complete / (Visit Complete + Missed or Overdue Visits + Withdrawal [cumulative] + LTFU [cumulative]). The number of deaths and withdrawals through 5 years at each time point is provided for each device. LTFU = lost to follow-up.

ORAL ANTICOAGULATION USE. The postimplant OAC use rates at discharge, 45 days, 6 months, 18 months, 2 years, 3 years, 4 years, and 5 years for both device groups are shown in **Figure 2**. At discharge, there were 78.9% of patients immediately free of OAC in the Amulet occluder group and 4.2% of patients in the Watchman device group ($P < 0.01$). At each follow-up visit, there was a significantly higher percentage of patients receiving OAC in the Watchman device group compared with the Amulet occluder group at all time points ($P < 0.05$). At 5 years, 94.0% of the Amulet occluder group and 90.9% of the Watchman device group were free of OAC ($P = 0.009$).

CLINICAL OUTCOMES. The primary results demonstrated that the Amulet occluder was noninferior to the Watchman device through 18 months for the safety and effectiveness primary endpoints, and superior closure was achieved at 45 days for the primary mechanism of action endpoint.[6] Clinical outcome rates through 5 years post-LAAO implantation are shown in **Table 2**, along with the corresponding Kaplan-Meier curves in **Figures 3A to 3F**. All measured clinical outcomes were similar between the Amulet and Watchman device groups, including the composite of ischemic stroke or systemic embolism (7.4% vs 7.1%; HR: 1.04; 95% CI: 0.71-1.50; $P = 0.851$), the composite of stroke, systemic embolism, or CV death (20.3% vs 20.7%; HR: 0.95; 95% CI: 0.77-1.19; $P = 0.666$), all stroke (8.1% vs 7.8%; HR: 1.01; 95% CI: 0.71-1.44; $P = 0.951$), major bleeding (20.1% vs 20.0%; HR: 1.02; 95% CI: 0.82-1.26; $P = 0.882$), CV death (14.3% vs 15.4%; HR: 0.90; 95% CI: 0.70-1.17; $P = 0.429$), and all-cause death (28.7% vs 31.1%; HR: 0.90; 95% CI: 0.75-1.07; $P = 0.217$). When adjusting for differences in withdrawals in the trial, all Amulet occluder clinical outcome rates were numerically lower or equal to Watchman device clinical outcome rates but with no significant differences between the device groups (Supplemental Table 1). A similar finding was observed when excluding patients who were receiving OAC after 45 days; all Amulet occluder clinical outcome rates were numerically lower than the Watchman device clinical outcome rates but with no significant differences between the device groups (Supplemental Table 2).

There were 228 major bleeding events in 169 Amulet occluder group patients and 210 major bleeding events in 162 Watchman device group patients, resulting in 5-year annualized major bleeding

rates (events/patients-years follow-up) of 6.0%/y and 5.9%/y for the Amulet and Watchman devices, respectively. For the Amulet occluder, the annualized rate of major bleeding decreased from 22.2%/y over the first 6 months (instructed to continue DAPT) to 3.8%/y from 6 months to 5 years (instructed to continue aspirin only). A similar trend was observed with the Watchman device, with an annualized rate of major bleeding of 18.7%/y in the first 6 months (instructed to continue OAC through 45 days and DAPT through 6 months) decreasing to 4.0%/y from 6 months to 5 years (instructed to continue aspirin only). In both device groups, patients who experienced a major bleeding event were at high risk for bleeding before the trial (average HAS-BLED score of 3.4 and an 86% history of bleeding), with a majority of major bleeding events in the trial being gastrointestinal related (56.6% Amulet occluder and 58.6% Watchman device) (Supplemental Table 3).

Through 5 years, 63 patients in the Amulet occluder group and 59 patients in the Watchman device group experienced a stroke event (Table 3). In both device groups, these patients were at increased risk for stroke before the trial with a high CHA2DS2-VASc score (average score: 4.8) and a history of previous stroke (average: 33%). Device-related factors (DRT or PDL) were identified before the stroke events in more patients in the Watchman device group (6 DRT and 18 PDL) compared with the Amulet occluder group (3 DRT and 4 PDL). A similar observation was observed in patients with CV death where these patients were at high risk for stroke (average CHA2DS2-VASc score: 5.0) and bleeding (average HAS-BLED score: 3.4) in both device groups, with a higher number of device-related factors preceding CV death in the Watchman device group (8 DRT and 31 PDL) compared with the Amulet occluder group (7 DRT and 17 PDL) (Table 4).

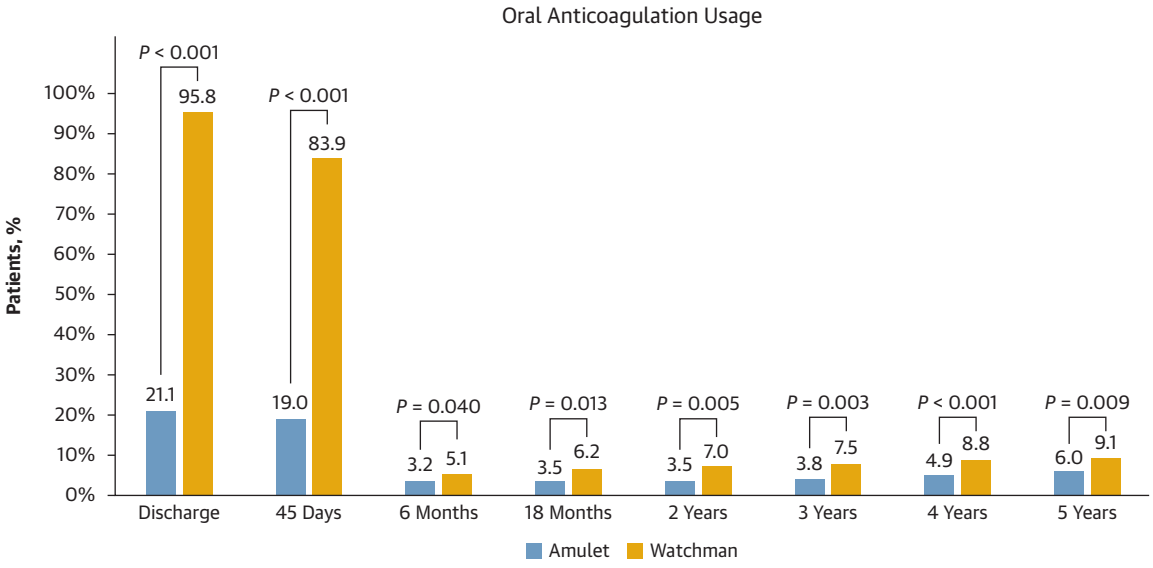
TABLE 1 Baseline Characteristics and Demographics

	Amulet Occluder (Abbott) (n = 917)	Watchman Device (Boston Scientific) (n = 916)
Age, y	75.0 ± 7.6	75.2 ± 7.6
Male	58.6	61.4
Body mass index, kg/m^2	30.0 ± 6.3	30.0 ± 6.5
AF classification		
Paroxysmal	56.7	54.1
Persistent	26.6	29.1
Permanent	16.7	16.8
Rhythm at start of procedure		
Atrial fibrillation	39.7	40.8
Sinus rhythm	60.3	59.2
CHADS2 score	2.7 ± 1.1	2.8 ± 1.2
CHA2DS2-VASc score	4.5 ± 1.3	4.7 ± 1.4
Congestive heart failure	34.0	39.5
Hypertension	92.3	93.3
Diabetes	35.0	34.8
Previous stroke or TIA or thromboembolism	25.5	28.9
Vascular disease	49.6	52.6
Previous bleeding (major or minor)	72.2	71.8
HAS-BLED score	3.2 ± 1.0	3.3 ± 1.0
Renal or urinary disorder	5.1	5.6
NYHA functional class		
No heart failure	50.6	46.3
I	16.0	18.0
II	26.8	27.7
III	6.6	8.0
Primary reason for LAAO as alternative to long-term oral anticoagulation		
History of major or minor bleeding	55.2	53.4
High bleeding risk	21.6	20.7
Risk of falls	11.5	13.4
Patient's preference or lifestyle	5.6	3.8
Previous stroke during oral anticoagulation	2.0	3.3
Labile or unstable international normalized ratio	1.6	2.9
Drug interactions	1.3	1.2
Renal or hepatic disease	0.7	0.4
Other	0.7	0.8

Values are mean ± SD or % of patient group.
AF = atrial fibrillation; LAAO = left atrial appendage occlusion; TIA = transient ischemic attack.

STROKE SEVERITY. Annualized ischemic stroke rates at 5 years were similar for the Amulet (1.6%/y) and Watchman (1.6%/y) devices, resulting in a 78% and 79% reduction in the risk of stroke compared with the predicted rates of 7.2% and 7.6%, respectively, on the basis of the CHA2DS2-VASc scores. Strokes (ischemic and hemorrhagic) were placed into different categories according to severity level (fatal, disabling, or nondisabling) for each device group (Figure 4). The Watchman device group had significantly more strokes that were fatal (n = 17) or disabling (n = 22) compared with the Amulet occluder group (11 fatal and 11 disabling; $P = 0.030$). Most of the strokes in the Amulet occluder group were non-disabling (38 of the 72 stroke events). This led to 5-year annualized ischemic stroke rates of 0.6%/y and 1.1%/y for Amulet and Watchman devices, respectively, when considering severe strokes only (fatal, disabling, or unknown). Of the 140 total stroke events (72 Amulet and 68 Watchman), 121 were ischemic strokes (63 Amulet and 58 Watchman) and 19 were hemorrhagic strokes (9 Amulet and 10 Watchman). For the ischemic strokes, most were nondisabling (36 Amulet and 19 Watchman), with 47 fatal or disabling (16 Amulet and 31 Watchman) and 19 with unknown status (11 Amulet and 8 Watchman). For the hemorrhagic strokes, most

FIGURE 2 Percentage of Patients Receiving Oral Anticoagulation at Each Follow-Up Visit Through 5 Years Post Amulet Occluder (Abbott) or Watchman Device (Boston Scientific) Implantation in the AMPLATZER Amulet Left Atrial Appendage Occluder Investigational Device Exemption Trial



were fatal or disabling (6 Amulet and 8 Watchman), with only 2 nondisabling (both in Amulet) and 3 with unknown status (1 Amulet and 2 Watchman).

Of the fatal or disabling strokes in the Watchman device group (n = 39), 19 patients (48.7%) had a device-related factor (DRT or PDL) before the stroke event compared with 5 device factors occurring before the 19 nondisabling stroke events (26.3%). In the Amulet occluder group, 4 of the 22 patients (18.2%) had a device-related factor before a fatal or disabling stroke event, and only 3 of the 38 patients in the Amulet occluder group (7.9%) had a device-related factor before the nondisabling stroke event. A similar number of strokes was not able to be categorized into a severity level because of missing mRS scores during the stroke assessment follow-up (n = 12, Amulet occluder group; and n = 10, Watchman device group).

TABLE 2 Clinical Outcomes Through 5 Years

	Amulet Occluder (Abbott) (n = 917)	Watchman Device (Boston Scientific) (n = 916)	HR (95% CI)[a]	*P* Value
IS or SE	7.4 (1.0)	7.1 (0.9)	1.04 (0.71-1.50)	0.851
Ischemic stroke	7.1 (0.9)	6.8 (0.9)	1.02 (0.70-1.49)	0.916
Systemic embolism	0.3 (0.2)	0.4 (0.2)	0.97 (0.20-4.82)	0.972
Stroke, SE, or CV death	20.3 (1.4)	20.7 (1.5)	0.95 (0.77-1.19)	0.666
Stroke	8.1 (1.0)	7.8 (1.0)	1.01 (0.71-1.44)	0.951
Systemic embolism	0.3 (0.2)	0.4 (0.2)	0.97 (0.20-4.82)	0.972
CV death	14.3 (1.3)	15.4 (1.3)	0.90 (0.70-1.17)	0.429
TIA	2.5 (0.6)	2.7 (0.6)	0.88 (0.48-1.60)]	0.667
Major bleeding	20.1 (1.4)	20.0 (1.4)	1.02 (0.82-1.26)	0.882
Non-procedure-related	17.4 (1.3)	18.2 (1.4)	0.96 (0.76-1.21)	0.709
All-cause death	28.7 (1.6)	31.1 (1.6)	0.90 (0.75-1.07)	0.217

Values are Kaplan Meir rate % (% standard error) unless otherwise indicated. [a]Amulet occluder vs Watchman device HR.

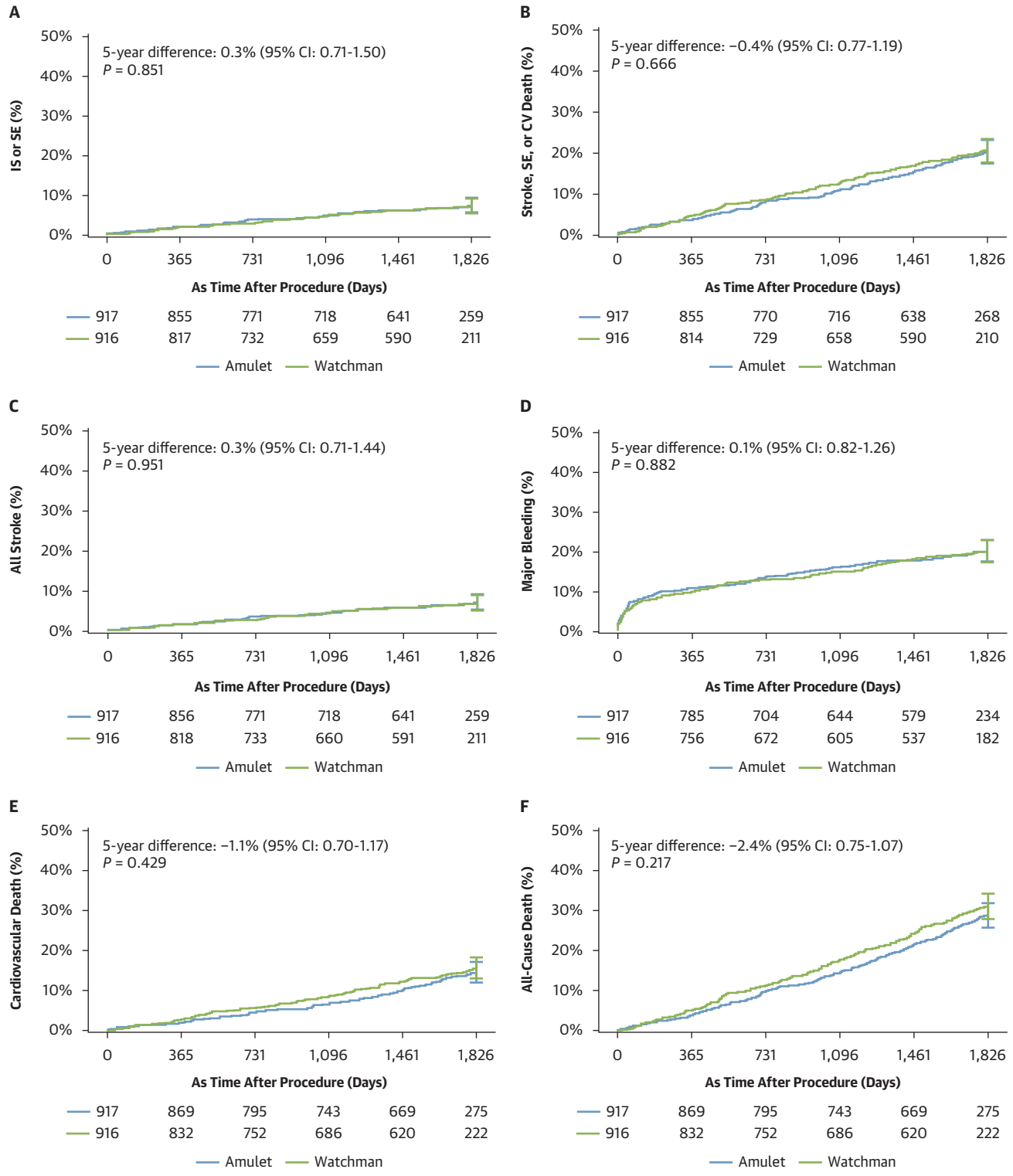
CV = cardiovascular; IS = ischemic stroke; SE = systemic embolism; TIA = transient ischemic attack.

DISCUSSION

The Amulet IDE trial prospectively evaluated the safety and effectiveness of the AMPLATZER Amulet LAA occluder compared with the commercially available Watchman 2.5 device to prevent thrombus embolization from the LAA in patients with NVAF. This was the largest global, randomized controlled head-to-head LAAO clinical trial comparing a single-lobe plug device vs a dual-seal disc and lobe device. The primary results demonstrated that the Amulet occluder was noninferior to the Watchman device for the safety and effectiveness primary endpoints through 18 months,[6] with superiority in LAA closure achieved through 45 days[6] and 12 months.[7]

Following the successful primary results through 18 months, the Amulet occluder was approved by the FDA, and patients continued follow-up through

FIGURE 3 Kaplan Meier Curves Through 5 Years in the AMPLATZER Amulet Left Atrial Appendage Occluder Investigational Device Exemption Trial



(A) The composite of ischemic stroke (IS) or systemic embolism (SE), (B) the composite of stroke, systemic embolism, or cardiovascular (CV) death, (C) all stroke, (D) major bleeding, (E) cardiovascular death, and (F) all-cause death. Differences, 95% CIs, and *P* values between the Amulet occluder (Abbott) and Watchman device (Boston Scientific) groups are provided.

TABLE 3 Details on Patients With Stroke Through 5 Years

	Amulet Occluder (Abbott) (n = 63)	Watchman Device (Boston Scientific) (n = 59)
Patient-related factors		
Age	75.6 ± 7.6	75.1 ± 8.9
CHA2DS2-VASc score	4.9 ± 1.3	4.7 ± 1.4
Previous stroke	33.3	32.2
HAS-BLED score	3.5 ± 1.1	3.3 ± 1.0
Previous major or minor bleeding	76.2	67.7
Device-related factors		
Device-related thrombus	3	6
Peridevice leak (≥3 mm)	4	18

Values are mean ± SD, %, or n and represent the number of stroke patients with the baseline patient-related factor or who experienced a device-related factor before the stroke occurrence through 5 years. Numbers are not mutually exclusive. Follow-up imaging to assess for device factors was available in 60 of the 63 patients in the Amulet group and in 57 of the 59 patients in the Watchman group.

5 years to characterize long-term outcomes of LAAO. The current analysis is the first to report Amulet IDE trial outcomes through 5 years. Main findings include the following: 1) more patients were free from OAC through 5 years with the Amulet occluder compared with the Watchman device; 2) similar low rates of clinical outcomes were observed at 5 years with both devices; 3) fewer fatal or disabling strokes occurred in patients with the Amulet occluder; and 4) more device-related factors preceded stroke or CV deaths in the Watchman device group compared with the Amulet occluder group (Central Illustration).

FREEDOM FROM ORAL ANTICOAGULATION THERAPY. Patients in the Amulet occluder group were discharged on either DAPT or OAC combined with aspirin according to the physician's discretion, whereas patients in the Watchman device group were required to be discharged on OAC combined with aspirin according to the manufacturer's directions for use at the time. At 45 days, patients in both groups were instructed to stop using OAC if adequate closure was obtained (PDL ≤5 mm), at which time DAPT was required through 6 months. After 6 months, patients continued to take aspirin indefinitely. A high degree of acute implant success was achieved in the Amulet occluder group (98.4%),[6] with no patients having PDL >5 mm post-implantation. This allowed for >78% of patients to be free of OAC at hospital discharge. At each follow-up visit, patients in the Amulet occluder group had significantly lower use of OAC than the Watchman device group, with 94.0% and 90.9% free of OAC at 5 years in the Amulet and Watchman device groups, respectively ($P = 0.009$). Possible differences in OAC use between the 2 device groups have been previously discussed.[8] Increased numbers of PDLs and late DRTs identified in the Watchman device group are possible reasons that a higher number of patients resumed OAC after 45 days. With an LAAO therapy goal of stroke prophylaxis without the need for OAC, the Amulet occluder allowed a high percentage of patients to remove OAC medications immediately and maintain freedom from OAC through 5 years.

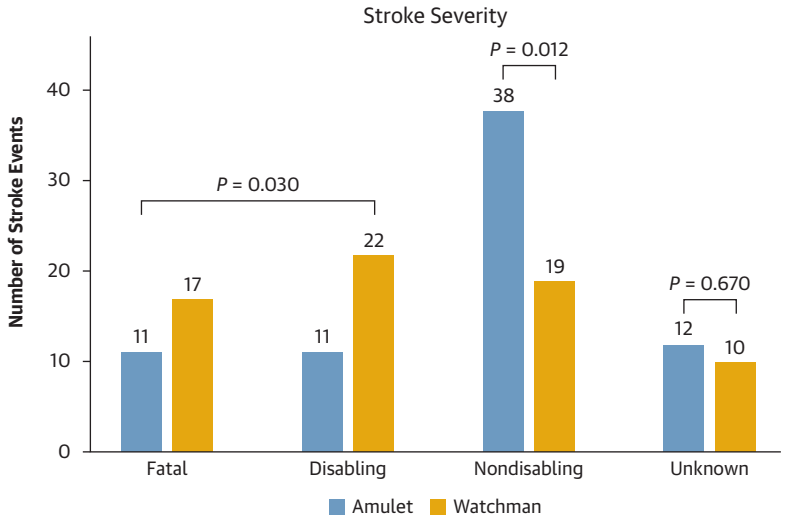
TABLE 4 Details on Patients With Cardiovascular Death Through 5 Years

	Amulet Occluder (Abbott) (n = 112)	Watchman Device (Boston Scientific) (n = 117)
Patient-related factors		
Age	76.9 ± 6.7	77.1 ± 8.2
CHA2DS2-VASc score	5.1 ± 1.4	4.9 ± 1.4
Previous stroke	20.6	19.7
HAS-BLED score	3.5 ± 1.1	3.3 ± 1.0
Previous major or minor bleeding	86.6	76.9
Device-related factors		
Device-related thrombus	7	8
Peridevice leak (≥3 mm)	17	31
Pericardial effusion requiring intervention leading to death	0	1

Values are mean ± SD, %, or n and represent the number of cardiovascular death patients with the baseline patient-related factor or who experienced a device-related factor before death through 5 years. Numbers are not mutually exclusive. Follow-up imaging to assess for device factors was available in 105 of the 112 patients in the Amulet group and in 109 of the 117 patients in the Watchman group.

LONG-TERM CLINICAL OUTCOMES. There are limited data on follow-up in patients post-LAAO, with most data on long-term follow-up only through 1 or 2 years. Reddy et al[5] presented the 5-year outcomes from the pivotal Watchman 2.5 device comparison with warfarin. At 18 months, the first coprimary endpoint composite of stroke, systemic embolism, or CV death was not achieved in the PREVAIL trial. However, at 5 years, the composite endpoint was similar between the device group and control warfarin group in the meta-analysis of patients taken from both the PROTECT AF (WATCHMAN Left Atrial Appendage System for Embolic Protection in Patients With Atrial Fibrillation) and PREVAIL (Evaluation of the WATCHMAN LAA Closure Device in Patients With Atrial Fibrillation Versus Long Term Warfarin Therapy) trials. In addition, thromboembolic and major bleeding event rates were similar between the device and medication groups, with significantly fewer disabling strokes and all-cause deaths in the device group through 5 years. These investigators concluded that the Watchman 2.5 device offers a viable alternative to warfarin for stroke prevention in patients with NVAF, with additional benefits in reducing major bleeding events and

FIGURE 4 **Number of Stroke Events (Ischemic Stroke, Hemorrhagic Stroke, or Undetermined Stroke) Classified Either Fatal, Disabling, or Nondisabling That Occurred in Patients With an Amulet Occluder (Abbott) or Watchman Device (Boston Scientific) Through 5 Years in the AMPLATZER Amulet Left Atrial Appendage Occluder Investigational Device Exemption Trial**



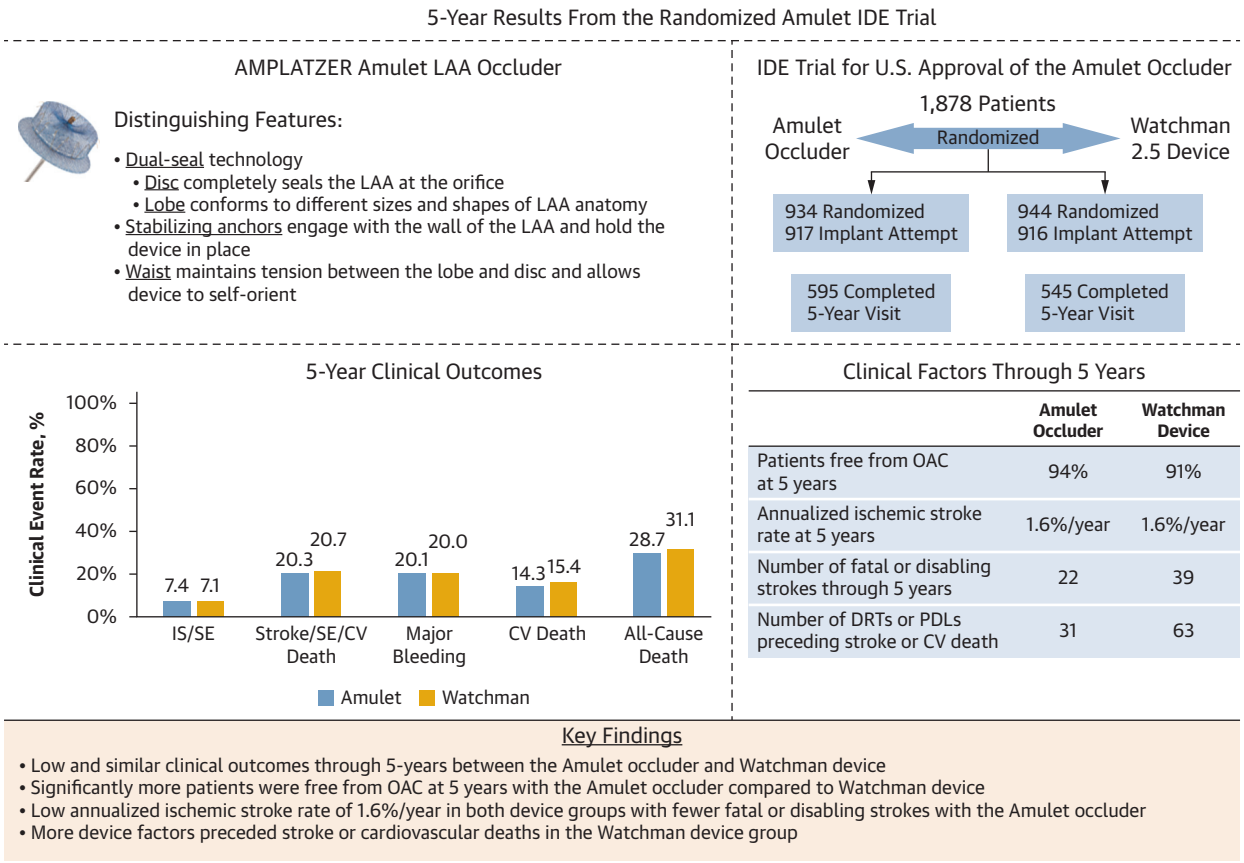
Fatal strokes were defined if the adjudicated cause of death was related to the stroke, disabling if the modified Rankin Scale (mRS) score was ≥2 at the 90-day stroke assessment and increased ≥1 point compared with the prestroke baseline, nondisabling if the mRS score was <2 at the 90-day stroke assessment or ≥2 without an increase of at least 1 point compared with the prestroke baseline, and unknown if there was missing mRS assessment.

mortality over the long term. More recently, Hildick-Smith et al[13] presented the full 2-year results of the global observational study on LAAO with the Amulet occluder. In this study, ischemic stroke was reduced by 67% compared with the predicted rate, whereas most patients (93.4%) were free of OAC, a finding suggesting that the Amulet occluder is effective in preventing strokes in high-risk patients with atrial fibrillation. Longer-term data are essential to assess comprehensively the safety, effectiveness, and risk and benefits of LAAO therapy.

In the Amulet IDE trial, patients enrolled were at high risk for stroke (average CHA2DS2-VASc score of 4.6, and 27% had history of thromboembolic event) and bleeding (average HAS-BLED score of 3.3, and 75% of patients with an indication for LAAO had a bleeding-associated concern). Despite this risk, patients in both device groups experienced low and similar rates of clinical events through 5 years. At 5 years, an annualized ischemic stroke rate of 1.6%/y was achieved in both device groups, and this was ≥78% lower than the rate for patients with NVAF without OAC predicted by the baseline CHA2DS2-VASc score. Other thromboembolic events were rare, including TIA (2.5%-2.7%) and systemic embolism (0.3%-0.4%). Several factors limit comparison of rates to other studies, including patient risk factors and antithrombotic regimens. However, the observed annualized ischemic stroke rates in the Amulet IDE trial were consistent with other Watchman device studies (1.4%-1.7% per year, representing a 73%-74% stroke risk reduction) through 5 years.[5] In comparison with direct OAC (DOAC) therapy only, the Amulet IDE trial had lower rates of ischemic stroke (6.8%-7.1%) than DOAC (15%) at 5 years in a group of patients with a similar stroke risk (CHA2DS2-VASc score, 4.8).[14] Melillo et al[15] also reported significantly higher bleeding rates in patients taking DOAC agents compared to LAAO through 5 years (25.0% vs 13.7%; $P = .048$). A similar finding was observed in the PRAGUE-17 (Left Atrial Appendage Closure vs Novel Anticoagulation Agents in Atrial Fibrillation) trial comparing DOAC with LAAO (Amulet or Watchman), which showed that LAAO remained noninferior to DOAC for preventing thromboembolic events through 4 years.[16]

The long-term clinical benefit of LAAO is to reduce bleeding events by offering stroke prophylaxis without the need for antithrombotic medications. The major bleeding annualized rates remained

CENTRAL ILLUSTRATION Results From the 5-Year Follow-Up of the AMPLATZER Amulet Left Atrial Appendage Occluder Investigational Device Exemption Trial



Lakkireddy D, et al. JACC. 2024;■(■):■-■.

A total of 1,878 patients were randomized in the trial, with 917 patients undergoing an Amulet occluder (Abbott) implantation attempt and 916 patients undergoing a Watchman device (Boston Scientific) implantation attempt. The number of patients remaining on oral anticoagulation (OAC), the annualized ischemic stroke (IS) at 5 years, the severity of strokes, device factors (device-related thrombus [DRL] and peridevice leak [PDL] ≥3mm), and clinical outcomes through 5 years are provided. CV = cardiovascular; IDE = investigational device exemption; LAA = left atrial appendage; SE = systemic embolism.

noninferior between the device groups through 5 years (5.9%-6.0%/y), with the highest rates occurring during the first 6 months, when patients were following more intense antithrombotic medication regimens (18.7%-22.2%/y). Fewer bleeding events occurred after 6 months with a mostly aspirin monotherapy regimen (3.8%-4.0%/y), with >85% of major bleeding events adjudicated as unrelated to the procedure throughout the entire trial. Although there were significantly more patients receiving OAC with the Watchman device throughout the trial, this did not translate to a higher major bleeding rate than with the Amulet occluder at 5 years. Previous studies have shown that patients at high bleeding risk who receive DAPT may have similar or even higher bleeding rates than patients receiving OAC alone.[17,18] Therefore, it is important to ensure that patients at high risk for bleeding start single antiplatelet therapy only or discontinue antithrombotic medications altogether as soon as possible post-LAAO.

In a previous analysis at 3 years, deaths (all-cause and CV-related) were numerically higher in the Watchman device group compared with the Amulet occluder group.[8] At 5 years, the mortality rate was similar between the device groups. In comparison with a similar patient group with atrial fibrillation, the all-cause death rate in both device groups (Amulet, 28.7%; and Watchman, 31.1%) was lower

than the predicted mortality rate of 35% irrespective of OAC status on the basis of CHA2DS2-VASc scores.[19] Although the primary results showed that the Amulet occluder was associated with more pericardial effusions, none of the pericardial effusions led to death, whereas 1 fatal pericardial effusion was observed after Watchman device implantation. Future trials comparing LAAO vs antithrombotic medication such as CATALYST (Clinical trial of atrial fibrillation patients comparing left atrial appendage occlusion therapy to non-vitamin K antagonist oral anticoagulants) and CHAMPION-AF (WATCHMAN FLX Versus NOAC for Embolic ProtectION in in the Management of Patients With Non-Valvular Atrial Fibrillation) will be critical to demonstrate the continued long-term benefits of LAAO therapy.

CLINICAL SIGNIFICANCE OF DEVICE-RELATED FACTOR DIFFERENCES. Device-related factors such as PDL and DRT are events associated with adverse complications after LAAO. Previous analyses have shown an increased risk for thromboembolic events or CV deaths in patients with PDL ≥3 mm[7,20,21] or DRT.[22-24] Moreover, the presence of PDL ≤5 mm at 1-year has shown to increase the risk of stroke or systemic embolism at 5 years.[25] In the Amulet IDE trial, the Amulet occluder demonstrated significantly fewer PDLs at both 45 days and 12 months than the Watchman 2.5 device, along with numerically lower DRT events. However, the newer-generation Watchman FLX device has shown reduced periprocedural and device-related factor outcomes compared with the Watchman 2.5 device,[26] but more PDLs and DRTs compared with the Amulet occluder in the SWISS-APERO randomized clinical trial.[27]

Although stroke rates were similar between the 2 device groups in the Amulet IDE trial through 5 years, patients with the Watchman device had >3 times as many device-related factors (PDLs or DRTs) preceding the stroke event compared with the Amulet occluder group (Amulet, n = 7; and Watchman, n = 24). A similar trend was observed for more device-related factors preceding CV deaths in the Watchman device group (n = 39) compared with the Amulet occluder group (n = 24). Additionally, strokes that occurred in patients with the Amulet occluder were less severe (n = 38, nondisabling; n = 11, disabling; n = 11, fatal) than strokes in patients with the Watchman device (n = 19, nondisabling; n = 22, disabling; n = 17, fatal). It is hypothesized that the increased number of device-related factors (PDLs or DRTs) with the Watchman device resulted in worse strokes either from the device factor itself (ischemic stroke) or the result of resumption of OAC (hemorrhagic stroke). Turagam et al[28] demonstrated that patients with LAAO only had less severe strokes compared with patients receiving OAC therapy. As mentioned earlier, patients with the Watchman device received OAC more often than patients with the Amulet occluder, thus resulting in potentially more severe strokes. Therefore, although stroke rates were similar between the 2 devices, strokes in patients with the Amulet occluder were less often fatal or disabling and may be attributed more to the high-risk patient baseline characteristics than to the device itself. This finding highlights that device-related factors such as PDL and DRT not only increase the incidence of thromboembolic events but may also influence stroke severity. The long-term 5-year outcomes presented in this analysis offer valuable insights into the durability of LAAO and help guide clinical decision making for stroke reduction in patients with NVAF.

STUDY LIMITATIONS. First among the potential limitations of this study is that, the trial used the Watchman 2.5 device because this was the only available device on the market at the time of enrollment. Newer-generation Watchman devices (Watchman FLX and Watchman FLX Pro) are now available and have shown improved short-term clinical outcomes.[26,29] However, the overall design between the different versions of the Watchman devices (single occlusive plug type) is still the same, which makes the long-term comparative analysis between a single-seal device and a dual-seal device design remain relevant in the largest randomized LAAO trial available to date. The second limitations is that the Amulet IDE trial was powered for the primary endpoints through 18 months but not for long-term clinical outcomes at 5 years. Third, as with any clinical trial with long-term follow-up, there is a possibility of incomplete or missing data that could limit generalizability of the findings. Fourth, direct comparison between LAAO and antithrombotic medications only for stroke prevention is needed to confirm the benefits of LAAO. Finally, follow-up with the Amulet occluder in the real world is needed to confirm the safety and effectiveness of the device. Early results from the EMERGE LAA postapproval study demonstrated favorable short-term implant success and safety through 45 days during early U.S. commercial experience.[30] Continued follow-up of patients in EMERGE LAA is needed to characterize the use of the Amulet occluder and its long-term safety and effectiveness.

CONCLUSIONS

The dual-seal Amulet LAA occluder demonstrated noninferior safety and effectiveness with superior LAA occlusion rates compared with the first-generation Watchman device in the primary results of the largest randomized head-to-head LAAO clinical trial. Long-term clinical benefits of the Amulet occluder were sustained in the Amulet IDE trial through 5 years, thus allowing for reduction of atrial fibrillation–related thromboembolic events without the need for OAC.

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KEY WORDS Amulet, atrial fibrillation, left atrial appendage occlusion, stroke, Watchman

APPENDIX For supplemental tables, please see the online version of this paper.