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STRUCTURAL

3-Year Outcomes From the Amplatzer Amulet Left Atrial Appendage Occluder Randomized Controlled Trial (Amulet IDE)

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ABSTRACT

BACKGROUND The Amulet (Abbott) left atrial appendage occluder investigational device exemption trial is the largest randomized trial evaluating the safety and effectiveness of the Amulet left atrial appendage occluder compared with the Watchman 2.5 device (Boston Scientific) through 5 years.

OBJECTIVES This analysis evaluated the device effect on 3-year outcomes in the Amulet investigational device exemption trial.

METHODS The medication regimen and key clinical outcomes were reported through 3 years including: 1) the composite of ischemic stroke or systemic embolism (SE); 2) the composite of all strokes, SE, or cardiovascular (CV) death; 3) major bleeding; and 4) all-cause death and CV death.

RESULTS A total of 1,878 patients at 108 sites were randomized. A significantly higher percentage of patients were free of oral anticoagulation usage at 3 years with Amulet (96.2%) vs Watchman (92.5%) ($P < 0.01$). Clinical outcomes were comparable for the composite of ischemic stroke or SE (5.0% vs 4.6%; $P = 0.69$); the composite of all strokes, SE, or CV death (11.1% vs 12.7%; $P = 0.31$); major bleeding (16.1% vs 14.7%; $P = 0.46$); all-cause death (14.6% vs 17.9%; $P = 0.08$); and CV death (6.6% vs 8.5%; $P = 0.14$) for Amulet and Watchman, respectively. Through 3 years, device factors (device-related thrombus or peridevice leak ≥3 mm) preceded ischemic stroke events and CV deaths more frequently in Watchman compared with Amulet patients.

CONCLUSIONS The Amulet occluder demonstrated continued safety and effectiveness with over 96% free of oral anticoagulation usage through 3 years in a high-risk population compared to the Watchman device. (AMPLATZER Amulet LAA Occluder Trial [Amulet IDE]; NCT02879448) (J Am Coll Cardiol Intv 2023;16:1902–1913) © 2023 by the American College of Cardiology Foundation.

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Percutaneous left atrial appendage occlusion (LAAO) is used for stroke reduction in patients with nonvalvular atrial fibrillation (NVAF) who have a rationale for an alternative to oral anticoagulation (OAC) therapy.[1] Published evidence supporting LAAO is provided largely by the 2 pivotal randomized controlled trials (ie, PROTECT-AF [Percutaneous Closure of the Left Atrial Appendage Versus Warfarin Therapy for Prevention of Stroke in Patients With Atrial Fibrillation] and PREVAIL [Evaluation of the WATCHMAN LAA Closure Device in Patients With Atrial Fibrillation Versus Long Term Warfarin Therapy]) comparing the Watchman 2.5 LAA closure device (Boston Scientific) to warfarin. Pooled 5-year follow-up of patients in the trials demonstrated comparable stroke rates between LAAO and warfarin with a reduced risk of thromboembolic events in patients indicated for and able to take OAC.[2] Unlike the Watchman device, which uses a single, occlusive plug-type mechanism to seal the left atrial appendage (LAA), the Amplatzer Amulet (Abbott) occluder uses a dual occlusive mechanism consisting of a lobe to anchor and seal at the neck of the LAA and a disc to close off the opening into the LAA.

Recent evidence from Amulet IDE (AMPLATZER Amulet LAA Occluder Trial) through 18 months of follow-up led to Food and Drug Administration approval of the Amplatzer Amulet occluder. The Amulet IDE trial is a prospective, global, randomized clinical trial comparing the safety and effectiveness of the Amulet occluder to the Watchman 2.5 device in patients with NVAF. The primary endpoints indicate that the Amulet occluder offered superior closure at 45 days and was noninferior for safety and effectiveness compared with the Watchman device.[3] The Amulet occluder also demonstrated sustained superior closure at 12 months compared to the Watchman device using different peridevice leak (PDL) cutoff sizes.[4] In this analysis, we report the 3-year clinical outcomes from the Amulet IDE trial.

METHODS

TRIAL DESIGN. The design and primary results from the Amulet IDE trial (NCT02879448) have been presented previously.[3,5] Briefly, the Amulet IDE trial used 1:1 randomization to compare the safety and effectiveness of the Amulet occluder to the Watchman device. Eligible patients were 18 years of age or older with documented paroxysmal, persistent, or permanent NVAF and deemed to be at high risk of stroke or systemic embolism (SE) defined as a $CHADS_2$ score ≥2 or a CHA_2DS_2-VASc score ≥3. As required by the Watchman device directions for use (DFU), patients had to be suitable for OAC with warfarin and have appropriate rationale to seek a nonpharmacologic alternative to long-term OAC. Patients were prescreened with transesophageal echocardiography (TEE) before randomization to confirm eligibility to receive both Amulet and Watchman devices. A list of the additional inclusion and exclusion criteria can be found in the trial design publication.[5]

The patient population used in this analysis (unless otherwise specified) was an as-attempted population that included randomized patients who underwent an implant attempt regardless of the device attempted or implanted to evaluate the long-term device effect (excluding those who never underwent a device attempt). The protocol was approved by the Institutional Review Board at each participating center along with written informed consent from each patient before enrollment. All adverse events were independently reviewed and adjudicated by a blinded independent clinical events committee.

PROCEDURES. Investigators were selected based on training and experience in percutaneous and transseptal procedures. LAAO procedures were guided by TEE and fluoroscopy. Patients receiving an Amulet occluder were discharged on either dual antiplatelet therapy (DAPT) or aspirin plus OAC. OAC was required if residual jet flow was >5 mm. Patients receiving the Watchman device were required to be discharged on aspirin plus OAC according to the DFU. If at the 45-day visit TEE showed adequate closure of the LAA (residual jet ≤5 mm), 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 cessation of clopidogrel was required and

ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation
CV = cardiovascular
DAPT = dual antiplatelet therapy
DFU = directions for use
DOAC = direct oral anticoagulant
DRT = device-related thrombus
IS = ischemic stroke
LAA = left atrial appendage
LAAO = left atrial appendage occlusion
NVAF = nonvalvular atrial fibrillation
OAC = oral anticoagulation
PDL = peridevice leak
SE = systemic embolism
TEE = transesophageal echocardiography
VKA = vitamin K antagonist

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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aspirin continued indefinitely. If a device-related thrombus (DRT) was detected at any time during the trial, 4 to 6 weeks of OAC was recommended followed by TEE to evaluate resolution of the DRT. The medication regimens were documented at baseline, discharge, and during site trial visits.

IMAGING. Baseline imaging was performed to ensure suitable LAA anatomy for implanting either device before enrollment. Additional TEE was required at 45-day, 6-month (if residual jet was >5 mm at 45 days), and 12-month visits or if an ischemic stroke was diagnosed. The TEE images were reviewed by an independent echo core lab (Cardiovascular Research Foundation) to determine if device factors including DRT or PDL were present. The clinically relevant PDL definition of ≥3 mm was chosen for this analysis based on our previous publication showing increased clinical outcome risks associated with this cut-off size.[4]

ENDPOINTS. Descriptive analyses of endpoints and individual components from the Amulet IDE trial are presented through 3 years. This includes: 1) the composite of ischemic stroke or SE (primary effectiveness endpoint); 2) the composite of all stroke (ischemic or hemorrhagic), SE, or cardiovascular (CV)/unexplained death (secondary endpoint); 3) major bleeding (Bleeding Academic Research Consortium ≥3, including any transfusion with overt bleeding plus a hemoglobin drop ≥3 g/dL)[6] (secondary endpoint); and 4) all-cause death and CV death (descriptive endpoints). Ischemic stroke and major bleeding are also presented as annualized rates (events/patient-years) through 3 years.

Clinical follow-up occurred at discharge; 45 days; 3, 6, 9, 12, and 18 months; and annually for years 2 through 5. Follow-up beyond 3 years is currently ongoing.

STATISTICAL ANALYSIS. The baseline characteristics and medication regimen were summarized using descriptive statistics. The *t*-test for continuous variables and the chi-square test or Fisher exact test for categoric variables were used to identify differences in characteristics and medications between the device groups. The Kaplan-Meier method was used to calculate event rates at 3 years postprocedure. Cox regression HRs and 95% CIs were calculated for the clinical outcomes. The annualized rates (events/patient-years) of ischemic stroke were compared to the anticipated rate by baseline CHA_2DS_2-VASc score for NVAF patients not treated with OAC.[7] The analyses were performed with SAS version 9.4 (SAS Institute) software.

RESULTS

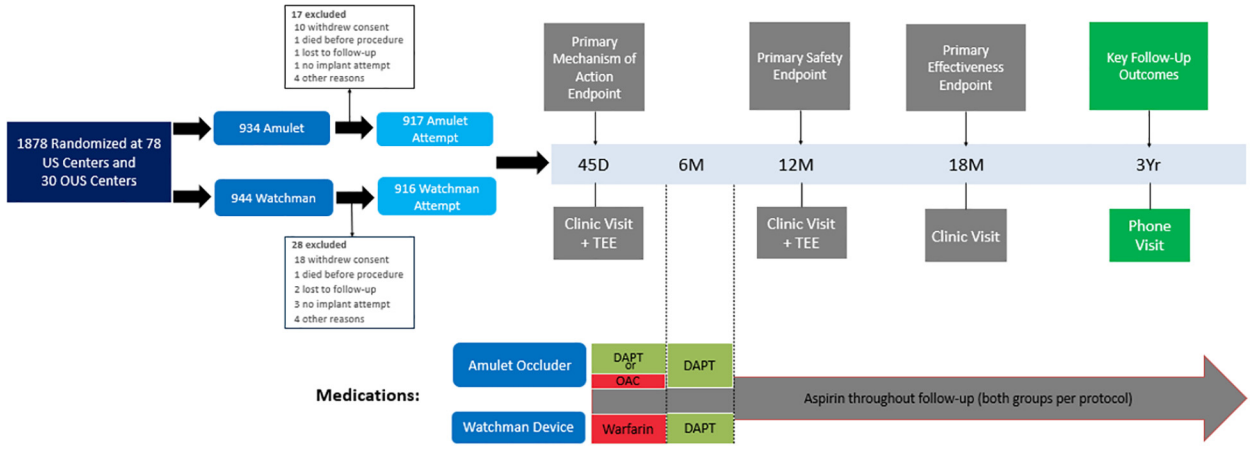
PATIENT FOLLOW-UP. A total of 1,878 patients were randomized from September 2016 through March 2019, and 1,833 underwent a device implant attempt (917 Amulet occluder group patients and 916 Watchman device group patients) (**Figure 1**). At 3 years, patients in the Amulet occluder group had a 92.0% follow-up rate, and patients in the Watchman device group had an 86.7% follow-up rate with comparable deaths and withdrawals from 18 months to 3 years (Watchman device group: 69 deaths and 30 withdrew; Amulet occluder group: 70 deaths and 19 withdrew). Additional information for patients with withdrawals is provided in the Supplemental Results and Supplemental Tables 1 and 2.

Baseline characteristics were well matched between the 2 groups, consistent with the primary results publication[3] (**Table 1**). The average age was 75 years; patients were mostly male (60%); 55% of patients had a history of paroxysmal atrial fibrillation, a CHA_2DS_2-VASc score of 4.6, and a HAS-BLED score of 3.3; and 75% of patients were indicated for LAAO for a bleeding-associated concern.

MEDICATION REGIMEN. The postimplant antithrombotic medication regimens at discharge, 45 days, 6 months, 18 months, and 3 years for both groups are presented in **Figure 2**. Most patients with an Amulet occluder were discharged on DAPT (75.7%), whereas most patients with a Watchman device were discharged on OAC (95.8%) as instructed. At 45 days, most Amulet occluder group patients were on DAPT (73.8%), whereas most Watchman device group patients were on OAC (83.9%: 6.9% direct oral anticoagulant [DOAC] and 77.0% vitamin K antagonist [VKA]). After 45 days, both groups were instructed to begin the same medication regimen (DAPT until 6 months followed by aspirin monotherapy indefinitely). At 3 years, a significantly lower prevalence of Amulet occluder group patients were on OAC (3.8%: 3.3% DOAC and 0.5% VKA) compared to Watchman device group patients (7.5%: 6.0% DOAC and 1.5% VKA; $P < 0.01$), resulting in 96.2% and 92.5% of patients free of OAC, respectively.

ISCHEMIC STROKE OR SE. The 3-year follow-up visit was completed in 1,380 patients (721 Amulet occluder group and 659 Watchman device group) with a median duration of 3.0 (IQR: 3.0-3.0) years in both devices. **Table 2** presents the clinical outcome rates through 3 years post-LAAO implantation along with the corresponding Kaplan-Meier curves in **Figure 3**. The rate of the composite of ischemic stroke or SE was similar between the Amulet and Watchman device

FIGURE 1 Patients Randomized and Disposition of Those Who Underwent an Implant Attempt in the Amulet IDE Trial With Either the Amulet Occluder or Watchman Device Used in This Analysis



The Amulet IDE trial endpoints, follow-up visits, and pre-specified medication regimens are provided. Amulet IDE = AMPLATZER Amulet LAA Occluder Trial; DAPT = dual antiplatelet therapy; OAC = oral anticoagulant; TEE = transesophageal echocardiography.

groups at 3 years (**Table 2**) (5.0% and 4.6%) (**Figure 3A**) (difference 0.4%; 95% CI: 0.70-1.70; $P = 0.69$). Using the primary results protocol analysis population (intention-to-treat), the rates remained the same between the 2 groups (5.0% and 4.6%; 95% CI: 0.70-1.70; $P = 0.69$) (Supplemental Table 3). There was a similar rate increase from 6 months to 3 years between both groups for the composite of ischemic stroke or SE (Supplemental Figure 1).

There were 39 patients in the Amulet occluder group who experienced an ischemic stroke and 36 Watchman device group patients through 3 years. Across both groups, patients who experienced ischemic stroke were at increased stroke risk with a high CHA_2DS_2-VASc score (score ≥4.8) and a history of prior stroke (28/75 patients with a stroke) (**Table 3**). Through 3 years, device factors (DRT or PDL) preceded strokes in more of the Watchman device group patients than the Amulet occluder group patients (20 Watchman device group vs 5 Amulet occluder group), with most occurring after 6 months when patients in both groups were instructed to be on aspirin monotherapy (17 Watchman device group vs 4 Amulet occluder group). In both groups, most device factors were detected within 1 year of stroke occurrence (15/20 Watchman device group and 5/5 Amulet occluder group). A low number of patients were on OAC at the time of ischemic stroke occurrence in both groups (6/36 Watchman device group patients vs 2/39 Amulet occluder group patients), with 0 Amulet occluder group patients and 1 Watchman device group patient on protocol-mandated OAC.

The 3-year annualized rate (events/patient-years follow-up) of ischemic stroke was 1.6%/y for both Amulet and Watchman device groups, representing a 78% reduction in the risk of ischemic stroke compared to the predicted rate of 7.2% and 7.6% for Amulet and Watchman devices, respectively (Supplemental Figure 2A). From 6 months to 3 years, when the majority of patients were on aspirin monotherapy, the annualized ischemic stroke rates were 1.5%/y and 1.6%/y for the Amulet and Watchman device groups, respectively.

STROKE, SE, OR CV DEATH. The rate of the composite of stroke, SE, or CV death was similar between the Amulet and Watchman device groups at 3 years (**Table 2**) (11.1% and 12.7%) (**Figure 3B**) (difference −1.6%; 95% CI: 0.66-1.14; $P = 0.31$). Using the primary results protocol analysis population (attempt as randomized), the rates remained similar between the 2 groups (11.0% and 12.7%; 95% CI: 0.65-1.13; $P = 0.28$) (Supplemental Table 3). There was a similar rate increase from 6 months to 3 years between both groups for the composite of stroke, SE, or CV death (Supplemental Figure 1).

TABLE 1 Baseline Characteristics and Demographics

	Amulet Occluder (n = 917)	Watchman Device (n = 916)
Age, y	75.0 ± 7.6	75.2 ± 7.6
Male	58.6	61.4
BMI, 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
$CHADS_2$	2.7 ± 1.1	2.8 ± 1.2
CHA_2DS_2-VASc	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
Prior 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	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/lifestyle	5.6	3.8
Prior stroke on oral anticoagulation	2.0	3.3
Labile/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 %.
AF = atrial fibrillation; BMI = body mass index; LAAO = left atrial appendage occlusion; NYHA = New York Heart Association; TIA = transient ischemic attack.

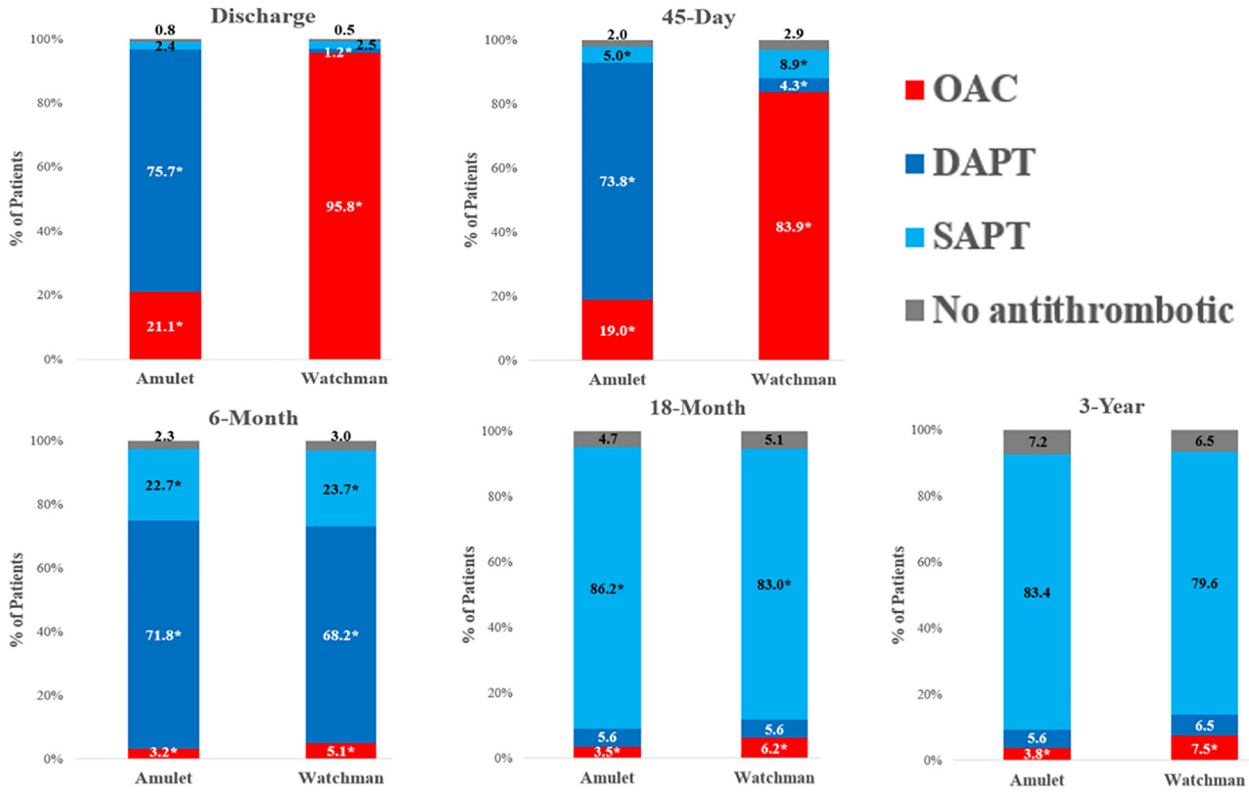
MAJOR BLEEDING. The rate of major bleeding was comparable between the 2 groups at 3 years (**Table 2**) (16.1% and 14.7%) (**Figure 3C**) (difference 1.4%; 95% CI: 0.86-1.39; $P = 0.46$) with the rate of bleeds unrelated to the procedure (13.4% and 13.0%) accounting for most events in both groups. Using the primary results protocol analysis population (per protocol), the rates remained similar between the 2 groups (15.7% and 15.0%; 95% CI: 0.82-1.34; $P = 0.80$) (Supplemental Table 3). There was a similar rate increase from 6 months to 3 years between both groups for major bleeding (Supplemental Figure 1).

There were 178 major bleeding events in 141 Amulet occluder group patients and 164 major bleeding events in 127 Watchman device group patients. Most of the major bleeding events were gastrointestinal related in both groups regardless of the time point (**Table 4**). After 6 months, most patients were on single antiplatelet therapy only at the time of the major bleeding event; only 4 Amulet and 8 Watchman device group patients with major bleeding events were on OAC at the time of the event (Supplemental Table 4). The 3-year annualized rate (events/patient-years follow-up) of major bleeding was 7.2%/y and 6.9%/y for Amulet and Watchman device groups, respectively. The highest rate of bleeding occurred within the first 6 months when both groups were on intense antithrombotic regimens and was reduced to 3.9%/y and 4.2%/y from 6 months to 3 years for Amulet and Watchman device groups, respectively, when patients were generally on aspirin monotherapy (Supplemental Figure 2B).

CV DEATH AND ALL-CAUSE DEATH. The rate of death (CV and all-cause) was numerically higher with the Watchman device group compared to the Amulet occluder group at 3 years, although the differences were not significant (CV death) (**Table 2**) (8.5% vs 6.6%) (**Figure 3D**) (difference −1.9%; 95% CI: 0.54-1.09; $P = 0.14$) and all-cause death (**Table 2**) (17.9% vs 14.6%) (**Figure 3E**) (difference −3.3%; 95% CI: 0.64-1.02; $P = 0.07$). Using the primary results protocol analysis population (attempt as randomized for CV death and per protocol for all-cause death), death continued to remain numerically higher in the Watchman device group compared to the Amulet occluder group (CV death: 8.5% and 6.5%; 95% CI: 0.53-1.08; $P = 0.12$ and all-cause death: 17.8% and 14.4%; 95% CI: 0.63-1.01; $P = 0.06$) (Supplemental Table 3). The number of additional deaths between 6 months and 3 years were similar between the 2 groups (Supplemental Figure 1).

There were 56 CV deaths in the Amulet occluder group and 70 CV deaths in the Watchman device group through 3 years. Most of the CV deaths were attributed to cardiac arrest or congestive heart failure in either group (84/126 CV deaths) (Supplemental Table 5). Patients with a CV death in both groups were at increased stroke risk (CHA_2DS_2-VASc score ≥5.0) and high bleeding risk (HAS-BLED score ≥3.0) (**Table 5**). In the primary results analysis, pericardial effusions were more frequent with the Amulet occluder compared to the Watchman device.[3]

FIGURE 2 The Antithrombotic Medication Regimen of Patients at Discharge Through 3 Years Post-Amulet Occluder or Watchman Device Implant



*$P < 0.05$ between the device and medication group. SAPT = single antiplatelet therapy; other abbreviations as in Figure 1.

However, there were no procedure-related mortalities caused by pericardial effusion in the Amulet occluder group, whereas 1 Watchman device group patient had a pericardial effusion discovered shortly after the procedure and met the definition of a procedure-related mortality. Through 3 years, device factors (DRT or PDL) preceded CV deaths in more of the Watchman device group patients than the Amulet occluder group patients (22 Watchman device group vs 8 Amulet occluder group), with most occurring after 6 months when patients in both groups were instructed to be on aspirin monotherapy (19 Watchman device group vs 6 Amulet occluder group). In both groups, most of the device factors were detected within 1 year of the CV death (15/22 Watchman device group and 5/8 Amulet occluder group). A low number of patients were on OAC at the time of CV death in both groups (8/70 Watchman device group patients vs 3/56 Amulet occluder group patients) with 0 Amulet occluder group patients and 1 Watchman device group patient on protocol-mandated OAC.

DISCUSSION

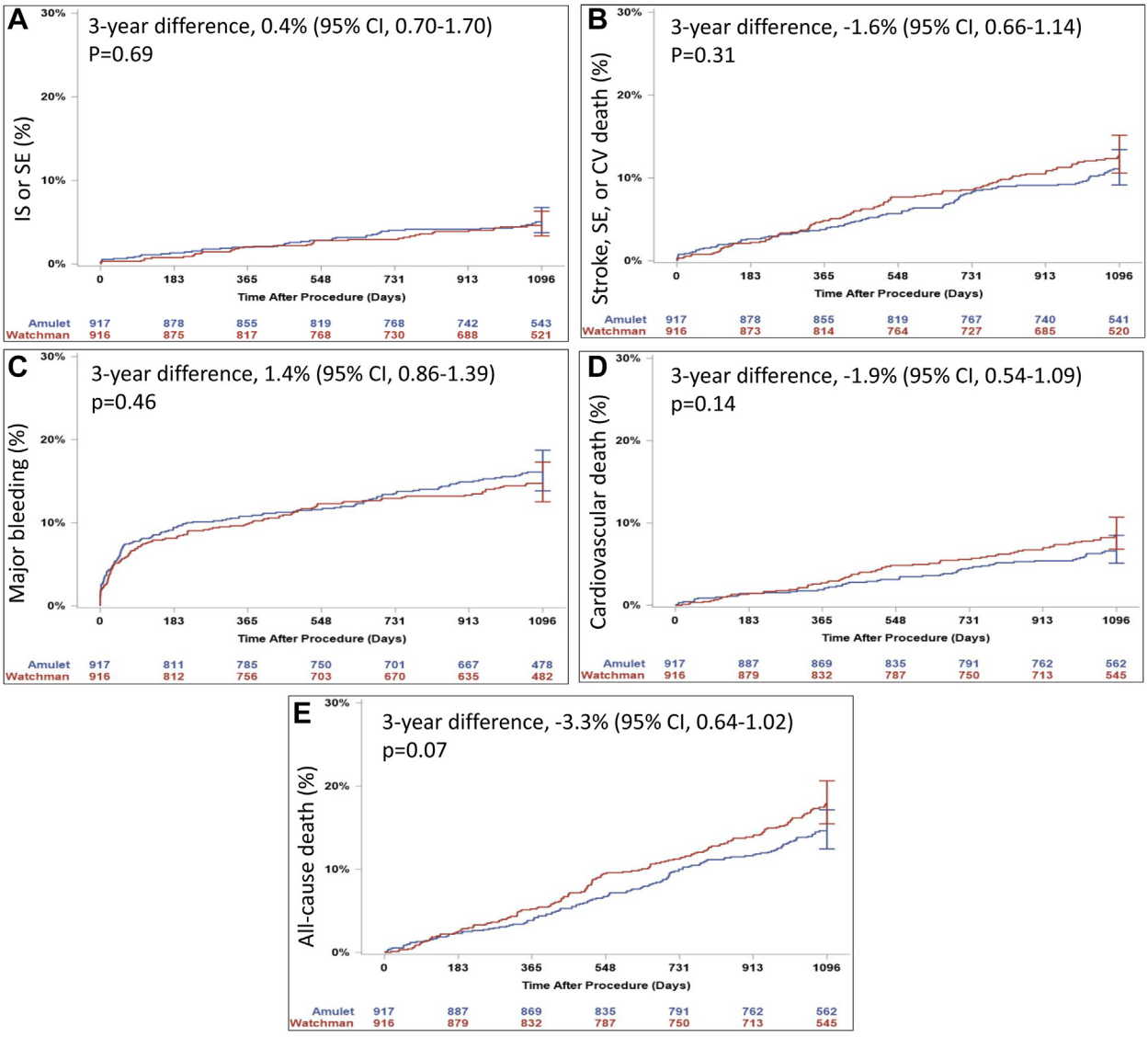
The Amulet IDE trial is the largest LAAO randomized clinical trial comparing the safety and effectiveness of the 2 commercially available devices in the United

TABLE 2 Clinical Outcomes Through 3 Years

	Amulet Occluder (n = 917)	Watchman Device (n = 916)	HR (95% CI)[a]	*P* Value
IS or SE	5.0 (42)	4.6 (37)	1.09 (0.70-1.70)	0.69
Ischemic stroke	4.7 (39)	4.5 (36)	1.04 (0.66-1.64)	0.86
Systemic embolism	0.3 (3)	0.2 (2)	1.47 (0.25-8.81)	0.67
Stroke, SE, or CV death	11.1 (95)	12.7 (105)	0.87 (0.66-1.14)	0.31
Stroke	5.3 (44)	5.2 (42)	1.01 (0.66-1.54)	0.97
Systemic embolism	0.3 (3)	0.2 (2)	1.47 (0.25-8.81)	0.67
CV death	6.6 (56)	8.5 (70)	0.77 (0.54-1.09)	0.14
Major bleeding	16.1 (141)	14.7 (127)	1.09 (0.86-1.39)	0.46
Non-procedure related	13.4 (116)	13.0 (110)	1.03 (0.79-1.34)	0.83
All-cause death	14.6 (129)	17.9 (153)	0.81 (0.64-1.02)	0.07

Values are Kaplan-Meier rate % (n of patients with events). [a]Amulet occluder vs Watchman device HR.
CV = cardiovascular; IS = ischemic stroke; SE = systemic embolism.

FIGURE 3 **Kaplan-Meier Curves for Clinical Outcomes Through 3 Years**



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

States. The dual occlusive lobe and disc mechanism device (Amulet occluder) proved to be noninferior to the single, occlusive plug-type mechanism (Watchman device) for the primary endpoints through 18 months and superior with respect to LAA closure.[3,4]

The longer-term 3-year follow-up of patients randomized in the Amulet IDE trial revealed the following: 1) more patients who had the Watchman device were on OAC compared to the Amulet occluder; 2) clinical outcomes including ischemic stroke and major bleeding rates were comparable between device groups; 3) CV and all-cause deaths were numerically higher in the Watchman device group compared to the Amulet occluder group although not significant; and 4) device factors preceded ischemic strokes and CV deaths more often after LAAO with the Watchman device compared with the Amulet occluder (**Central Illustration**).

OAC USAGE. In the Amulet IDE trial, the Watchman device DFU required patients to be discharged on aspirin plus OAC, whereas patients with the Amulet occluder were discharged on either DAPT or aspirin plus OAC. OAC cessation was required for all patients at 45 days if adequate closure of the LAA was observed from TEE (residual jet ≤5 mm) followed by DAPT until 6 months and then aspirin continued indefinitely after 6 months. In the Amulet IDE trial, a significantly higher number of patients with the Amulet occluder discontinued OAC usage from 6 months to 3 years compared with patients with the Watchman device. As discussed by Schmidt et al,[8] more patients were placed on OAC after identification of late (>6 months) DRT in the Watchman device group (n = 23) compared to the Amulet occluder group (n = 10). This increase in late DRTs with the Watchman device as well as improved closure rates with the dual occlusive mechanism Amulet occluder seemed to account for the majority of the OAC usage differences between the 2 devices after 6 months. The recommendation to prolong OAC therapy in patients with DRT or a large PDL may have been sufficient to mitigate the risk of thromboembolic events, but alternative secondary reinterventions to close the LAA could also considered in these patients. With the goal of removing OAC from patients' medication regimen through LAAO, the dual occlusive mechanism Amulet occluder allowed for immediate OAC discontinuation (>75% of patients at discharge) and freedom from OAC at 3 years (>96% of patients).

CLINICAL OUTCOMES. The patient cohort in the Amulet IDE trial was representative of a NVAF population with a high risk for stroke (mean CHA_2DS_2-VASc score of 4.6). Despite this, annualized ischemic stroke rates were low at 3 years (1.6%/y for both devices), resulting in a 78% reduction in the risk of ischemic stroke compared to the CHA_2DS_2-VASc score predicted rate. These annualized rates are comparable to prior Watchman device trials in which patients had lower CHA_2DS_2-VASc scores (mean score of 3.4 in PROTECT-AF and 3.4 in PREVAIL)[2] and the reported 1.7%/y stroke rate in the 2-year outcome PINNACLE FLX (Protection Against Embolism for Nonvalvular AF Patients: Investigational Device Evaluation of the Watchman FLX LAA Closure Technology) trial with the newer-generation Watchman FLX device.[9]

Major bleeding rates were comparable between the Amulet and Watchman devices through 3 years in a high-risk bleeding population (mean HAS-BLED score of 3.3 and >70% with prior bleeding event). Although Amulet occluder patients were instructed to be discharged on DAPT rather than OAC with Watchman patients, major bleeding rates remained similar at 6 months. This observation has been previously reported in the Active W (Active Fibrillation Clopidogrel Trial With Irbesartan for Prevention of Vascular Events) trial.[10] Most of the bleeding events that

TABLE 3 Ischemic Stroke Patient Details

	0 to 6 Months		6 Months to 3 Years	
	Amulet Occluder (n = 10)	Watchman Device (n = 7)	Amulet Occluder (n = 29)	Watchman Device (n = 29)
Patient factors				
CHA_2DS_2-Vasc score	5.6 ± 1.8	5.0 ± 1.5	4.8 ± 1.3	5.0 ± 1.5
Prior stroke	5	3	9	11
Device factors				
Device-related thrombus	0	1	1	2
Time relationship, <1 y[a]	0	1	1	1
Peridevice leak (≥3 mm)	1	2	3	15
Time relationship, <1 y[a]	1	2	3	11
Oral anticoagulation usage at time of stroke[b]	2	3	0	3

Values are mean ± SD or number of ischemic stroke patients with the baseline patient factor or experienced a device factor before the stroke occurrence through 3 years. Numbers are not mutually exclusive. [a]Patients with device factor detection and stroke occurrence <1 year apart. [b]Zero Amulet group patients and 1 Watchman group patient were on protocol-mandated oral anticoagulation.

TABLE 4 Source of Major Bleeding Events

	0 to 6 Months		6 Months to 3 Years	
	Amulet Occluder (n = 97)	Watchman Device (n = 84)	Amulet Occluder (n = 81)	Watchman Device (n = 80)
Source of bleeding				
Gastrointestinal	54	51	46	45
Pericardial effusion	20	11	3[a]	3[a]
Trauma or fall	7	5	6	17
Vascular	6	7	0	0
Hematoma	1	3	8[b]	4[b]
Intracerebral or subdural hemorrhage	4	4	5	6
Epistaxis	3	2	3	0
Hemothorax	1	0	2	0
Hematuria	1	0	2	2
Pleural effusion	0	1	0	1
Cancer	0	0	2	1
Hemoptysis	0	0	2	0
Aneurysm	0	0	1	0
Suicide	0	0	1	0
Organ failure	0	0	0	1

Values are the total number of major bleeding events that occurred through 3 years. [a]Pericardial effusion events >6 months (Amulet occluder: 2 undetermined cause and 1 other elective cardiac procedure and Watchman device: 2 secondary closure of peridevice leak and 1 other elective cardiac procedure). [b]Hematoma events >6 months occurred from other elective procedures (Amulet occluder: 3 orthopedic, 2 lumbar laminectomy, 1 aneurysm, 1 craniotomy, and 1 other and Watchman device: 1 orthopedic, 1 lumpectomy, 1 lumbar, and 1 other).

TABLE 5 Cardiovascular Death Patient Details

	0 to 6 Months		6 Months to 3 Years	
	Amulet Occluder (n = 13)	Watchman Device (n = 12)	Amulet Occluder (n = 43)	Watchman Device (n = 58)
Patient factors				
CHA_2DS_2-Vasc score	5.6 ± 1.6	5.3 ± 1.8	5.0 ± 1.6	5.0 ± 1.4
Prior stroke	6	5	4	11
HAS-BLED score	3.7 ± 0.9	3.0 ± 1.3	3.5 ± 0.9	3.4 ± 1.0
Prior major or minor bleeding	13	7	41	45
Device factors				
Device-related thrombus	1	1	1	4
Time relationship, <1 y[a]	1	1	1	3
Peridevice leak (≥3 mm)	1	2	5	15
Time relationship, <1 y[a]	1	2	2	9
Pericardial effusion[b]	0	1	0	0
Oral anticoagulation usage at time of death[c]	1	3	2	5

Values are mean ± SD or the number of cardiovascular death patients with the baseline patient factor or experienced a device factor before death through 3 years. Numbers are not mutually exclusive. [a]Patients with device factor detection and cardiovascular death <1 year apart. [b]Defined as a pericardial effusion that led to procedural mortality. [c]Zero Amulet occluder group patients and 0 Watchman device group patient were on protocol-mandated oral anticoagulation.

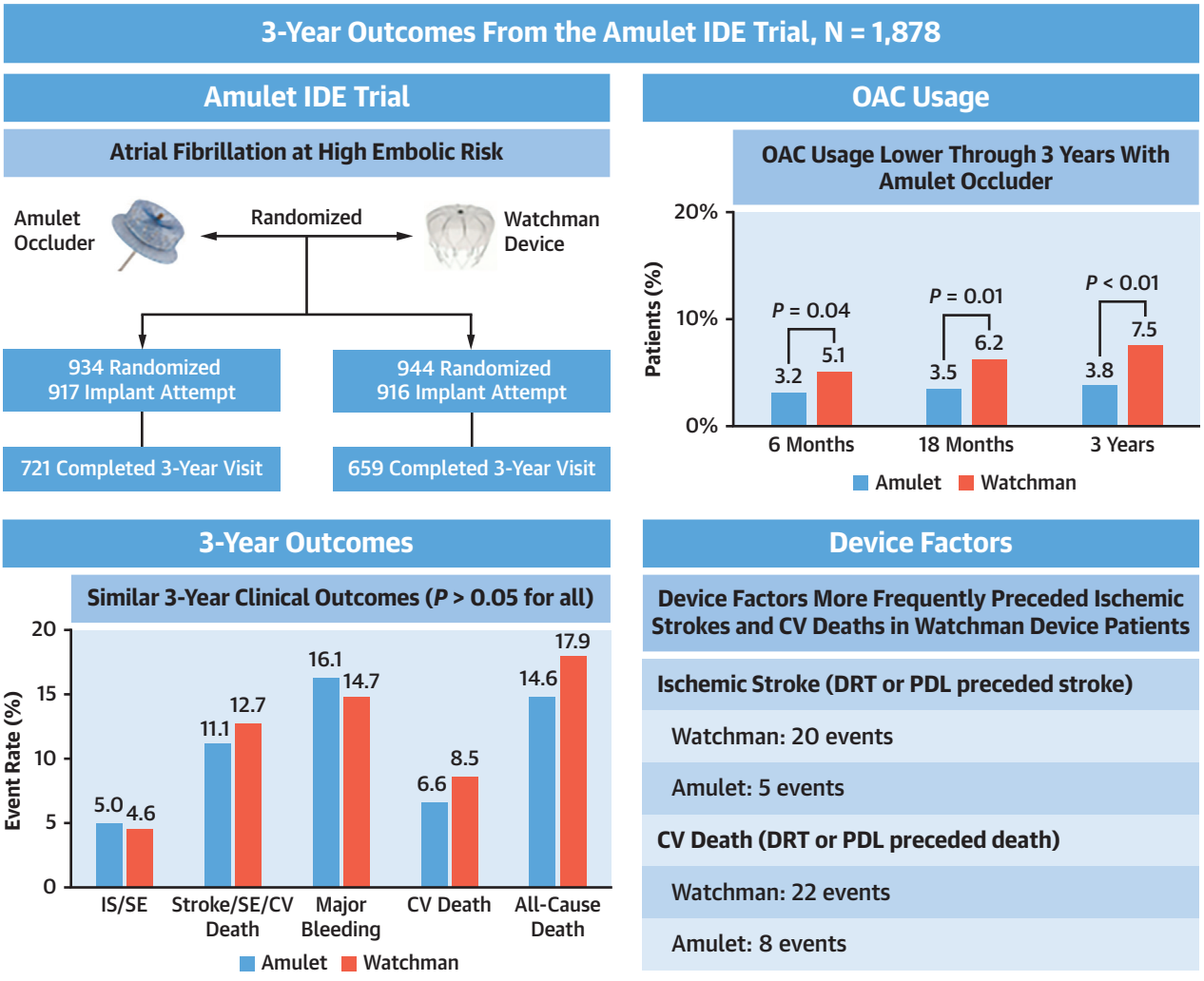
occurred through 3 years (regardless of the time point) were gastrointestinal related in both device groups. Also, there was a similar number of major bleeding events that occurred within the first 6 months during intense antithrombotic medication compared to post 6 months when patients were mostly on aspirin monotherapy or no antithrombotic medication at the time of the major bleeding event. It is interesting that the decreased OAC usage with the Amulet occluder observed through 3 years did not translate to a lower bleeding rate with annualized rates similar between the device groups after 6 months (3.9%/y vs 4.2%/y). This further emphasizes that patients in the trial were prone to bleeding before enrollment and highlights the risk for bleeding in this population even on a restrained antithrombotic regimen such as low-dose aspirin monotherapy.

Deaths (all-cause and CV related) were numerically higher in patients with the Watchman device compared to the Amulet occluder at 3 years (all-cause: 17.9% vs 14.6% and CV: 8.5% vs 6.6%). However, these did not reach statistical significance (all-cause: $P = 0.07$ and CV: $P = 0.14$). Both device groups had lower all-cause death rates than the predicted rate of 20% at 3 years in a similar patient population irrespective of OAC usage (NVAF patients with a mean CHA2DS2-VASc score of 4).[11] Although pericardial effusions were more frequently observed with the Amulet occluder,[3] importantly, fatal pericardial effusions were extremely rare in both devices (none after LAAO with the Amulet occluder and 1 after LAAO with the Watchman device). Although patients were screened with TEE in the Amulet IDE trial, recently developed preprocedural planning FEops HEARTguide technology using computed tomography angiography may have led to improved periprocedural and long-term clinical outcomes in either device group as demonstrated in recent studies.[12,13]

DEVICE FACTORS. Prior studies have shown an increased risk of thromboembolism in patients with a DRT[14-16] or PDL.[17,18] Thromboembolic events also trended higher in patients with DRT and PDL in the Amulet IDE trial, but the low overall thromboembolic event rates did not reach statistical significance through 18 months.[4,8] However, long-term thromboembolic events were nearly twice as likely through 3 years in patients with PDL in the Amulet IDE trial[19] and significantly increased in PDL patients through 5 years using combined data from the Watchman PROTECT-AF, PREVAIL, and CAP2 (Continued Access to PREVAIL) studies.[20] At 3 years, patients in both device groups who experienced an ischemic stroke were at high risk for stroke as indicated by an increased CHA_2DS_2-VASc score (>5.0) and a history of a prior stroke (>35%). It was interesting to observe similar 3-year thromboembolic rates between the 2 device groups devices despite device factors (DRT or PDL) preceding ischemic strokes 4 times more frequently in the Watchman device compared to the Amulet occluder through 3 years (20 Watchman device group vs 5 Amulet occluder group). As previously discussed, the increase in OAC use through 3 years in Watchman device group patients may have provided additional protection against thromboembolic events in patients with a device-related factor. Also, the high risk for stroke in patients in the trial could have mitigated the device-related factor differences between the 2 device groups leading to similar 3-year thromboembolic rates.

In the Amulet IDE trial, CV death was more than doubled in patients with a DRT (8.7% vs 3.9%; $P = 0.04$)[8] and numerically higher in patients with a PDL[4] (4.9% vs 2.9%; $P = 0.13$). Although Watchman device patients had an increased number of late DRTs (>6 months) in the Amulet IDE trial,[8] no additional DRTs were noted after 18 months with the last mandated TEE at 12 months. At 3 years, patients in both device groups with a CV death were at high risk for stroke (CHA2DS2-VASc score >5.0) and bleeding (HAS-BLED score >3.0). Similar to the trend observed in patients with an ischemic stroke, device factors

CENTRAL ILLUSTRATION **Results From the 3-Year Follow-Up of the AMPLATZER Amulet LAA Occluder Trial**



Lakkireddy D, et al. J Am Coll Cardiol Intv. 2023;16(15):1902–1913.

More patients were on oral anticoagulation (OAC) in the Watchman than Amulet device group through 3 years. Clinical outcomes including: 1) the composite of ischemic stroke (IS) or systemic embolism (SE); 2) the composite of stroke, SE, or cardiovascular (CV) death; 3) major bleeding; 4) CV death; 5) and all-cause death were similar between groups at 3 years with no significant differences ($P > 0.05$). Device factors (device-related thrombus [DRT] or peridevice leak [PDL] ≥3 mm) preceded ischemic strokes and CV deaths in more Watchman device patients than Amulet occluder patients through 3 years. Amulet IDE trial = AMPLATZER Amulet LAA Occluder Trial.

more frequently preceded CV deaths in Watchman device patients compared to Amulet occluder patients through 3 years (22 Watchman device group vs 8 Amulet occluder group). Although most CV deaths were likely unrelated to the device or procedure (84/126 CV deaths attributed to cardiac arrest or congestive heart failure), these device factors may have contributed in part to the higher observed mortality rate in the Watchman device group. Both devices have continued to demonstrate long-term safety and effectiveness for stroke prophylaxis in patients with NVAF, adding further evidence to the efficacy for LAAO at large.

STUDY LIMITATIONS. First, the trial included the Watchman 2.5 device, which has now been replaced by the second-generation Watchman FLX device in practice that has shown improved periprocedural

outcomes.[21] However, the mechanistic factors of the Watchman device design (single occlusive plug type) are still the same with the Watchman FLX device; hence, the comparative analysis of the mechanism of action between a single and dual occlusive device design remains very relevant. Second, the trial was powered for the primary endpoints through 18 months but not for the clinical outcomes analyzed at 3 years or to determine associations with PDL or DRT. Third, the higher follow-up rates in the Amulet occluder group could have influenced differences in clinical outcomes because more patients were in the trial at 3 years compared to patients with the Watchman device. Finally, longer-term follow-up through 5-year trial completion is needed to confirm findings observed in this analysis.

CONCLUSIONS

LAAO with either the Amulet LAA occluder or the Watchman LAA closure device resulted in comparable clinical outcomes through 3 years. A higher percentage of Amulet occluder patients were free of OAC usage during long-term follow-up compared to Watchman device patients.

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PERSPECTIVES

WHAT IS KNOWN? In the primary results of the Amulet IDE trial, the Amulet occluder was noninferior for safety and effectiveness compared to the Watchman device through 18 months and superior for LAA closure. However, the long-term device effects in the trial are unknown.

WHAT IS NEW? In this analysis, the Amulet occluder and Watchman device continued to demonstrate safety and effectiveness through 3 years. The Amulet occluder allowed for more patients to discontinue oral anticoagulation and was associated with fewer device-related issues before ischemic strokes and CV deaths compared to the Watchman device.

WHAT IS NEXT? Continued follow-up of the Amulet IDE trial through 5 years is needed to confirm the safety and effectiveness of the LAAO devices are maintained.

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

APPENDIX For an expanded Results section and supplemental tables and figures, please see the online version of this paper.