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CLINICAL RESEARCH

Mechanisms, predictors, and evolution of severe peri-device leaks with two different left atrial appendage occluders

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Aims Incomplete left atrial appendage occlusion (LAAO) due to peri-device leak (PDL) is a limitation of the therapy. The Amulet IDE trial is the largest randomized head-to-head trial comparing the Amulet and Watchman 2.5 LAAO devices with fundamentally different designs. The predictors and mechanistic factors impacting differences in PDLs within the Amulet IDE trial are assessed in the current analysis.

Methods and results An independent core lab analysed all images for the presence or absence of severe PDL (>5 mm). The incidence, mechanistic factors, predictors using propensity score-matched controls, and evolution of severe PDLs through 18 months were assessed. Of the 1878 patients randomized in the trial, the Amulet occluder had significantly fewer severe PDLs than the Watchman device at 45 days (1.1 vs. 3.2%, $P < 0.001$) and 12 months (0.1 vs. 1.1%, $P < 0.001$). Off-axis deployment or missed lobes were leading mechanistic PDL factors in each device group. Larger left atrial appendage (LAA) dimensions including orifice diameter, landing zone diameter, and depth predicted severe PDL with the Watchman device, with no significant anatomical limitations noted with the Amulet occluder. Procedural and device implant predictors were found with the Amulet occluder attributed to the learning curve with the device. A majority of Watchman device severe PDLs did not resolve over time through 18 months.

Conclusion The dual-occlusive Amplatzer Amulet LAA occluder provided improved LAA closure compared with the Watchman 2.5 device. Predictors and temporal observations of severe PDLs were identified in the Amulet IDE trial.

Clinical trial registration https://clinicaltrials.gov Unique identifier NCT02879448.

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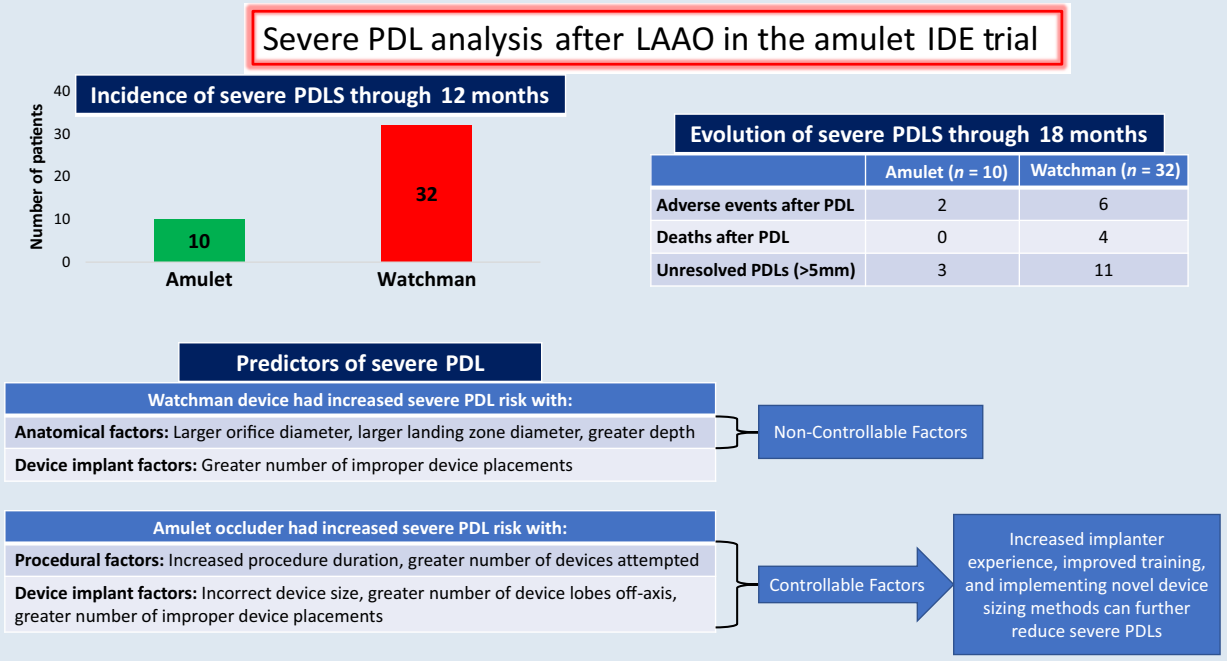
Graphical Abstract



Keywords Left atrial appendage occlusion • Peri-device leak • Stroke • Atrial fibrillation • Amulet • Watchman

What's new?

- The Amulet occluder had significantly fewer severe peri-device leaks (PDLs) through 12 months compared with the Watchman device.
- Larger left atrial appendage dimensions predicted severe PDL with the Watchman device, with no anatomical limitations noted with the Amulet occluder.
- A majority of Watchman device severe PDLs did not resolve over time, with an increased number of adverse events and deaths reported through 18 months compared with the Amulet occluder.

Introduction

Percutaneous left atrial appendage occlusion (LAAO) has emerged as an alternative therapy to reduce stroke in patients with non-valvular atrial fibrillation (NVAF) who are contraindicated to long-term oral anticoagulation (OAC).[1–3] The left atrial appendage (LAA) has a variety of shapes, sizes, and morphologies. Atypical appendages such as those with proximal lobes, large ostia, or shallow depth may be difficult to completely seal off and result in peri-device leaks (PDLs).[4] Sub-optimal deployment of the LAAO device has also been shown to increase the rate of PDLs.[5] Patients with PDLs have shown to be at increased risk for subsequent thrombo-embolism or continued use of OAC,[6–9] reducing the clinical effectiveness of LAAO. The incidence of PDLs at 45 days or 12 months ranges from <1 to 55% on transoesophageal echocardiography (TEE) depending on the leak size cut-off chosen.[1,10,11] Saw *et al.*[12] stratified PDLs depending on the residual jet size: none, no visible leak seen; minimal, <1 mm diameter jet; mild, 1–3 mm diameter jet; moderate, 3–5 mm diameter jet; and severe, >5 mm diameter jet. Physicians are often instructed to prescribe OAC to patients with a severe PDL until the leak size is reduced or a secondary procedure to plug, coil, or ablate the leak is performed.

There are two currently approved LAAO devices in the USA each with different designs and thus potentially different PDL mechanisms. The Watchman™ device (Boston Scientific, St. Paul, MN, USA) uses a single-occlusive, plug type mechanism, whereas the Amplatzer™ Amulet™ occluder (Abbott, Plymouth, MN, USA) uses dual-occlusive technology consisting of a lobe to fill and anchor in the cavity of the LAA and a disc to seal the LAA orifice. Recent evidence from the Amulet IDE trial demonstrated that the Amulet occluder provided superior closure to the Watchman 2.5 device at both 45 days and 12 months.[1,8] The objective of this *post hoc* analysis is to identify the mechanisms, predictors, and evolution of severe PDLs through 18 months in the Amulet IDE trial.

Methods

Amulet IDE trial

From September 2016 to March 2019, the Amplatzer Amulet LAA Occluder Trial (Amulet IDE trial—NCT02879448) enrolled 1878 patients with NVAF to receive either an Amulet occluder (Abbott) or a Watchman 2.5 device (Boston Scientific) in a randomized, 1:1 ratio at 108 global sites. The design of the trial[13] and primary results[1] have been published. Patients in the trial were at a high risk of stroke or systemic embolism (SE), which is defined as a $CHADS_2$ score of ≥2 or a congestive heart failure, hypertension, age, diabetes mellitus, stroke, vascular disease, age, sex category (CHA_2DS_2-VASc) score of ≥3. The trial complied with the Declaration of Helsinki, and the protocol was approved by the institutional review board at each participating centre along with written informed consent from each patient.

The antithrombotic medication regimens were documented from the time of randomization to last-known follow-up until 18 months. Patients implanted with an Amulet occluder were discharged on either aspirin plus clopidogrel Dual antiplatelet therapy (DAPT) or aspirin plus OAC (if residual flow into the LAA was >5 mm) at the discretion of the investigator, while patients implanted with a Watchman device were discharged on

aspirin plus warfarin per the device instructions for use (IFUs). If a clinically acceptable closure of the LAA was confirmed on TEE at the 45-day visit (defined as residual jet ≤5 mm), OAC cessation was required for all patients. Patients in both groups were then instructed to take DAPT until the 6-month visit at which time clopidogrel was discontinued and aspirin continued indefinitely.

Patients in analysis

The patient population used in this *post hoc* analysis included those who received a device as randomized in the Amulet IDE trial, including re-attempt procedures, and had a TEE at 45 days or 12 months evaluable for PDL by an independent core laboratory. From this set of patients, a binary analysis was used, which included those patients with severe PDL >5 mm (identified at 45 days or 12 months) and 1:2 propensity score-matched (PSM) control patients without PDL (residual flow 0 mm) through 12 months (*Figure 1*). Propensity score-matched control patients were drawn from the trial cohort with complete closure and an evaluable TEE at both 45 days and 12 months. Controls were matched through propensity score 1:2 (severe PDL:control) based on age, sex, atrial fibrillation (AF) classification, rhythm at procedure, congestive heart failure, hypertension, diabetes, prior stroke or transient ischaemic attack (TIA) or thromboembolism, vascular disease, CHA_2DS_2-VASc and hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly, drugs/alcohol concomitantly (HAS-BLED) scores, baseline left ventricular ejection fraction, and left atrial pressure at implant. A similar number of PSM control patients implanted with the Amulet occluder ($n = 46$) or Watchman device ($n = 38$) were used. This sample size ensures that at least 80% power is achieved in the analyses for each device group. The PSM control patients are referred to as 'no PDL' throughout the remainder of the text.

Echocardiograph core lab review

Protocol-mandated TEE was performed at the 45-day and 12-month post-procedure visits. Additional imaging at 6 months was required if the PDL was >5 mm at 45 days. An independent echocardiographic core laboratory (Cardiovascular Research Foundation, New York, NY, USA) analysed all TEE images for the presence or absence of PDL. Colour Doppler views at 0, 45, 90, and 135 omni-plane degrees were recommended to evaluate all quadrants of the device. If flow around the device was present, the PDL was measured at the location where the colour jet was seen exiting from the LAA into the body of the LA. Peri-device leak was graded as the single largest jet visualized around the device (passed by the entirety of the single- or dual-mechanism device) from a minimum of three Doppler views. For this analysis, a 5 mm jet size cut-off was used to define PDL (severe PDL) based on the mechanism of action endpoint published in the primary results[1] and categories of leak graded by Saw *et al.*[12] The core lab was blinded to the clinical condition of the patient and timepoint of the TEE.

Additional TEE imaging analysis was performed on baseline and follow-up timepoints of patients with severe PDL and with no PDL by the independent core laboratory. Anatomical measurements of the LAA and procedural characteristics were assessed to gather information on the patient prior to the device implanted. Ovality index (OI) was calculated from the baseline TEE by determining the ratio of long-axis LAA measurement (e.g. 135°) to the short-axis LAA (e.g. 45°). A perfectly round or circular orifice will have an OI of 1, and a highly elliptical orifice will have OI of 2 or greater. LAA morphologies were classified as chicken wing, windsock, cauliflower, or cactus shape according to previously established definitions.[14] Peri-device leak mechanisms were classified as off-axis lobe (defined as device tilting >30° from a perpendicular line from the ostium to the long axis of the LAA), missed lobe, micro-migration, or other types of device malposition according to previously established definitions.[15] Depth implant was measured between the most proximal point of the LAA device and an orthogonal line drawn through the coumadin ridge. Compression was calculated based on the deployed device diameter divided by the non-implanted native LAA landing zone diameter. Adequate sizing of the devices was determined by following the device's IFU. The independent core lab measurements were compared with the site-reported measurements, and recommendations on device sizes were provided. The position of the Amulet occluder was defined from a previously published study.[16] Briefly, the position was appropriate if the Amulet lobe was within 10–15 mm distal to the LAA orifice, too proximal if the lobe was <10 mm from the LAA orifice, and too distal if the proximal part of the lobe was located >15 mm from the LAA orifice. The Watchman device position was defined as appropriate if the plane of maximum diameter is at or just distal to and spans the entire LAA ostium.

Outcomes

Clinical events were adjudicated by an independent clinical events committee that was blinded to treatment assignment. In-hospital adverse events were reported from the index procedure to hospital discharge. Clinical outcomes through 18 months of patients with a severe PDL included ischaemic stroke (IS), SE, TIA, major bleeding (BARC ≥3, including any transfusion with overt bleeding plus a haemoglobin drop of ≥3 g/dL),[17] cardiovascular (CV) death, and all-cause death.

Statistical analysis

This analysis included the following: (i) incidence of severe PDL between device groups; (ii) baseline and procedural characteristics; (iii) PDL mechanism; (iv) anatomical, procedural, and device implant predictors of severe PDL; and (v) evolution and temporal observations of severe PDL. Baseline and procedural characteristics, PDL mechanism, and temporal observations were summarized using descriptive statistics. The *t*-test for continuous variables and χ^2 test or Fisher's exact test for categorical variables were used to identify differences in baseline, anatomical, procedural, device implant characteristics and in-hospital adverse events between patients with severe PDL and with no PDL. SAS version 9.4 (SAS Institute) software was used for analysis.

Results

Incidence of severe peri-device leaks and patient population

Of the 1878 patients randomized in the Amulet IDE trial, successful implants occurred in 903 Amulet occluder patients and 885 Watchman device patients (*Figure 1*). A similar number of patients in each device group had an evaluable TEE at 45 days (801 Amulet occluder patients and 792 Watchman device patients) and 12 months (673 Amulet occluder patients and 618 Watchman device patients). Propensity score-matched control patients were drawn from the trial cohort with complete closure and an evaluable TEE at both 45 days and 12 months, which consisted of 511 patients (297 Amulet occluder patients and 214 Watchman device patients). *Table 1* lists the incidence of all patients who had a severe PDL through 12 months. At 45 days, significantly fewer Amulet occluder-treated patients ($n = 9$; 1.1%) had a severe PDL than Watchman device ($n = 25$; 3.2%, $P < 0.001$). From 45 days to 12 months, one additional Amulet occluder-treated patient (0.1%) and seven additional Watchman device-treated patients (1.1%) had a newly discovered severe PDL ($P < 0.001$). A total of 42 severe PDLs (10 Amulet occluder and 32 Watchman device patients) were used in this analysis matched with 84 no PDL (46 Amulet occluder and 38 Watchman device patients).

Baseline characteristics of patients with severe PDL and with no PDL through 12 months are provided in *Table 2*. Patients were well matched between groups with no significant differences in any of the characteristics. In patients with a severe PDL, the average age was 75 years with mostly men (62%). Patients were at high risk for stroke and bleeding as reflected by the average CHA_2DS_2-VASc (average 4.5) and HAS-BLED (average 3.3) scores. A history of a thrombo-embolic event (stroke, TIA, or thrombo-embolism) was present in ∼31% of patients. The baseline characteristics of the individual device groups were generally well matched with opposing trends in CHA_2DS_2-VASc scores between the Amulet occluder (3.8 PDL and 4.5 no PDL; $P = 0.041$) and Watchman device (4.7 PDL and 4.0 no PDL; $P = 0.041$; see Supplementary material online, *Tables S1* and *S2*).

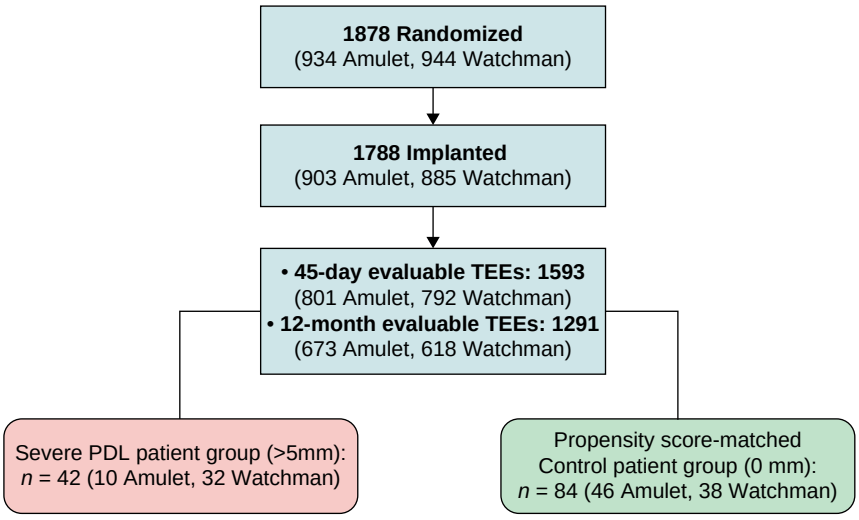


Figure 1 Flow diagram of patients used in the analysis with an Amulet occluder or a Watchman device. Flow diagram depicting the number of patients randomized and successfully implanted with the Amulet occluder or Watchman device, total evaluable 45-day and 12-month TEE images, and number of patients used in the two groups for this analysis: patients with severe PDL defined as residual flow >5 mm and PSM control patients without PDL defined as residual flow =0 mm and matched on the basis of age, sex, AF classification, rhythm at procedure, congestive heart failure, hypertension, diabetes, prior stroke or TIA or thromboembolism, vascular disease, CHA_2DS_2-VASc and HAS-BLED scores, baseline left ventricular ejection fraction, and left atrial pressure at implant. AF, atrial fibrillation; PDL, peri-device leak; PSM, propensity score matched; TEE, transoesophageal echocardiography; TIA, transient ischaemic attack.

Table 1 Incidence of severe PDL through 12 months

	Amulet	Watchman	*P*-value
45-day	1.1% (9/801)	3.2% (25/792)	<0.001
>45-day to 12-month	0.1% (1/673)	1.1% (7/618)	<0.001

Values are the number of PDLs identified (evaluable TEEs at the mentioned timepoint). This analysis includes the first PDL identified by the echocardiography core lab.
PDL, peri-device leak; TEE, transoesophageal echocardiography.

Mechanisms of severe peri-device leak

The mechanisms of severe PDLs for each device group are provided in *Figure 2*. The primary cause of PDL was off-axis implants (4 of 10 for Amulet occluder; 16 of 32 for Watchman device) or by leaving an uncovered lobe (5 of 10 for Amulet occluder; 11 of 32 for Watchman device). In each group, there was one patient who had a micro-migration leak in which the device shifted overtime from the implant to the follow-up TEE. In the Watchman device group, one patient had a leak around the entire device, one patient's mechanism of leak was caused by the implant being too distal resulting in incomplete LAA coverage, and the remaining two patients had unknown mechanisms of severe PDL.

Predictors of severe peri-device leak

Table 3 provides the anatomical, procedural, and device implant differences between patients with severe PDL and with no PDL for the Amulet occluder. For the Amulet occluder, there were no significant anatomical or in-hospital adverse event differences between patients with severe PDL and no PDL. However, compared with patients with no PDL, patients with a severe PDL had a significant increase in procedure duration (severe PDL: 55.5 ± 26.4 min vs. no PDL: 36.3 ± 19.9 min, $P = 0.025$), a greater number of devices attempted (severe PDL: 1.7 ± 0.9 vs. no PDL: 1.2 ± 0.4, $P = 0.016$), a greater number of incorrect device sizes chosen (severe PDL: 8 of 9 evaluable vs. no PDL: 11 of 36 evaluable, $P = 0.001$), a greater number of device lobes off-axis (severe PDL: 5 of 7 evaluable vs. no PDL: 2 of 20 evaluable, $P = 0.006$), and a greater number of improper device placements (severe PDL: 4 of 10 evaluable vs. no PDL: 4 of 46 evaluable, $P = 0.019$). Also, all 10 severe PDL cases were from implanters with <10 cases of prior Amulet occluder experience compared with 32 of the 46 no PDL cases ($P = 0.052$; see Supplementary material online, *Table S3*).

Patients with a severe PDL with the Watchman device had significantly larger orifice diameter (severe PDL: 20.5 ± 5.1 mm vs. no PDL: 18.1 ± 3.1 mm, $P = 0.040$), larger landing zone diameter (severe PDL: 16.8 ± 3.4 mm vs. no PDL: 14.9 ± 2.9 mm, $P = 0.036$), greater depth (severe PDL: 26.9 ± 4.6 mm vs. no PDL: 23.4 ± 4.8 mm, $P = 0.001$), and a greater number of improper device placements (severe PDL: 24 of 30 evaluable vs. no PDL: 2 of 38 evaluable, $P < 0.001$) compared with patients with no PDL (*Table 4*). There were no significant procedural characteristic or in-hospital adverse event differences between patients with severe PDL and no PDL for Watchman device.

Evolution and temporal observations of severe peri-device leak

Figure 3 shows the medication regimen, clinical events, and resolution status of PDLs through 18 months in Amulet and Watchman device-treated patients with a severe PDL. A majority of Amulet occluder patients (6 of 9) was on antiplatelet therapy (APT) at the time of identification of 45-day PDL (*Figure 3A*). Three patients were on OAC until the PDL status was resolved (≤5 mm) as instructed in the protocol. Most PDLs identified at 45 days in Watchman device-treated

Table 2 Baseline characteristics of severe PDL and propensity score-matched patients with no PDL

Characteristic	Severe PDL ($n = 42$)	No PDL ($n = 84$)	*P*-value
Age, years	75.3 ± 7.7	74.3 ± 6.6	0.481
Male	61.9%	58.3%	0.700
AF classification			0.496
Paroxysmal	47.6%	48.8%	
Persistent	40.5%	45.2%	
Permanent	11.9%	6.0%	
Rhythm at procedure			0.362
AF	42.9%	34.5%	
SR	57.1%	65.5%	
Congestive heart failure	33.3%	27.4%	0.489
Hypertension	88.1%	89.3%	1.000
Diabetes	28.6%	31.0%	0.784
Prior stroke or TIA or thrombo-embolism	31.0%	23.8%	0.390
Vascular disease	47.6%	47.6%	1.000
CHA_2DS_2-VASc	4.5 ± 1.5	4.3 ± 1.3	0.483
HAS-BLED	3.3 ± 0.9	3.3 ± 1.1	0.895
Baseline LVEF (%)	55.1 ± 6.9	56.7 ± 6.1	0.211
Left atrial pressure at implant	15.0 ± 6.6	15.5 ± 5.6	0.731
Abnormal renal function or disease[a]	9.5%	7.1%	0.316

Values are mean ± standard deviation (SD) or % of patient group.
AF, atrial fibrillation; CHA_2DS_2-VASc, congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke or transient ischaemic attack or thromboembolism, vascular disease, age 65–74 years, sex category; LVEF, left ventricular ejection fraction; SR, sinus rhythm; TIA, transient ischaemic attack; other abbreviations as in *Table 1*.
[a]Dialysis, transplant, Cr >2.26 mg/dL or >200 μmol/L.

patients (24 of 25) were on OAC, but only 3 of these patients remained on OAC until the PDL status was resolved (*Figure 3B*). There was a higher number of patients with the Watchman device who experienced newly discovered severe PDL >45 days compared with patients with the Amulet occluder ($n = 7$ Watchman device, $n = 1$ Amulet occluder). However, the Amulet occluder patient did not have the required 45-day assessment, so first detection of the severe PDL was at 12 months. For the seven Watchman device patients with a newly discovered severe PDL >45 days, one patient had a micro-migration (3.5 mm residual jet size increase) and six patients had off-axis lobe leak mechanism (1.5 ± 0.5 mm residual jet size increase).

One patient treated with the Amulet occluder experienced an IS and major bleeding event (while on APT) after identification of a PDL, while no deaths were reported in any patients with the Amulet occluder through 18 months (*Figure 3A*). In the Watchman device group, four major bleeding events (three while on APT and one on OAC), one IS (simultaneous of PDL identification), one TIA, and four deaths ($n = 2$ CV death, $n = 2$ non-CV death) occurred after identification of a PDL (*Figure 3B*). Of the patients with a follow-up TEE to assess resolution of the PDL, a higher proportion of PDLs resolved at least partially (≤5 or 0 mm) within 18 months in the Amulet occluder group ($n = 5/8$) compared with the Watchman device group ($n = 8/19$; *Figure 3*). Patients with a severe PDL (>5 mm) had a 1.5 mm decrease in jet size from 45 days to 12 months in both device groups (see Supplementary material online, *Figure S1*).

Discussion

Left atrial appendage occlusion has shown to reduce the risk of stroke irrespective of age in AF patients.[18] However, incomplete closure of the LAAO results in PDL, which have been associated with worse clinical outcomes.[6–9] If properly closed (no PDL), an annual IS rate of 1.2%/year has been achieved.[9] Prior data suggest that the dual-occlusive mechanism Amplatzer Amulet occluder has significantly lower risk of PDLs than the single-occlusive Watchman 2.5 device.[1,8] However, limited data are available on predictors and mechanistic factors that impact the differences in PDLs and evolution of PDLs over time between these two devices. This technical analysis presents the incidence and mechanistic factors of severe PDL (>5 mm), predictors of patients with severe PDL compared with PSM control patients with no PDL (0 mm), and evolution of the severe PDLs through 18 months from the largest head-to-head trial of the two FDA-approved LAAO devices utilizing an independent core lab (Amulet IDE trial).

The major findings in the analysis revealed the following: (i) the Amulet occluder had significantly fewer severe PDLs through 12 months compared with the Watchman device; (ii) mechanistic factors of severe PDL in both groups were mostly from the device being off-axis or missing a lobe; (iii) larger LAA dimensions predicted severe PDL with the Watchman device with no anatomical limitations with the Amulet occluder; and (iv) majority of Watchman device severe PDLs did not resolve over time with a greater number of adverse events and deaths through 18 months compared with the Amulet occluder.

Incidence of severe peri-device leak through 12 months

The reported incidence of PDL in LAAO varies across different studies and depends on various factors including the type of LAAO device used. Current consensus recommendation is to image at 45–90 days after LAAO to assess for PDL.[3] According to a recent meta-analysis involving 10 studies with the FDA-approved LAAO devices, the incidence ranged from 2 to 37% at 45 days depending on the type of device used, residual leak size cut-off, and imaging used to detect PDL (TEE or cardiac computed tomography angiography).[19] Data from the Amulet IDE trial showed severe PDL (>5 mm) ranged from 1 to 3% at 45 days depending on the device design in which the dual-occlusive mechanism Amulet occluder provided superior closure compared with the single-occlusive Watchman 2.5 device.[1] Superior closure with the Amulet occluder was also maintained through 12 months regardless of the residual leak size cut-off.[8] In this *post hoc* analysis, the Amulet occluder had significantly fewer severe PDLs identified through 12 months compared with the Watchman device ($n = 10$ vs. $n = 32$, $P < 0.01$).

Mechanisms of severe peri-device leak

The exact mechanism of PDL in LAAO is not fully understood. The mechanism of PDL may have important clinical implications as an uncovered deep lobe could put patients more at thrombo-embolism risk compared with leaks occurring due to non-trabeculated lobes.[15] Alkhouli *et al.*[15] identified non-coaxial device (off-axis) and multi-lobar LAA were the most common mechanistic factors of severe PDL in the Watchman device. Also, Agudelo *et al.*[20] found device-lobe misalignment (off-axis) was the leading factor for residual patency for the Amulet occluder. We observed similar results in our analysis in which both Amulet and Watchman devices most commonly had an off-axis or missed/uncovered lobe as the primary mechanisms of severe PDL with both mechanisms more prevalent in the Watchman device. The use of colour Doppler at more than the four standard views or

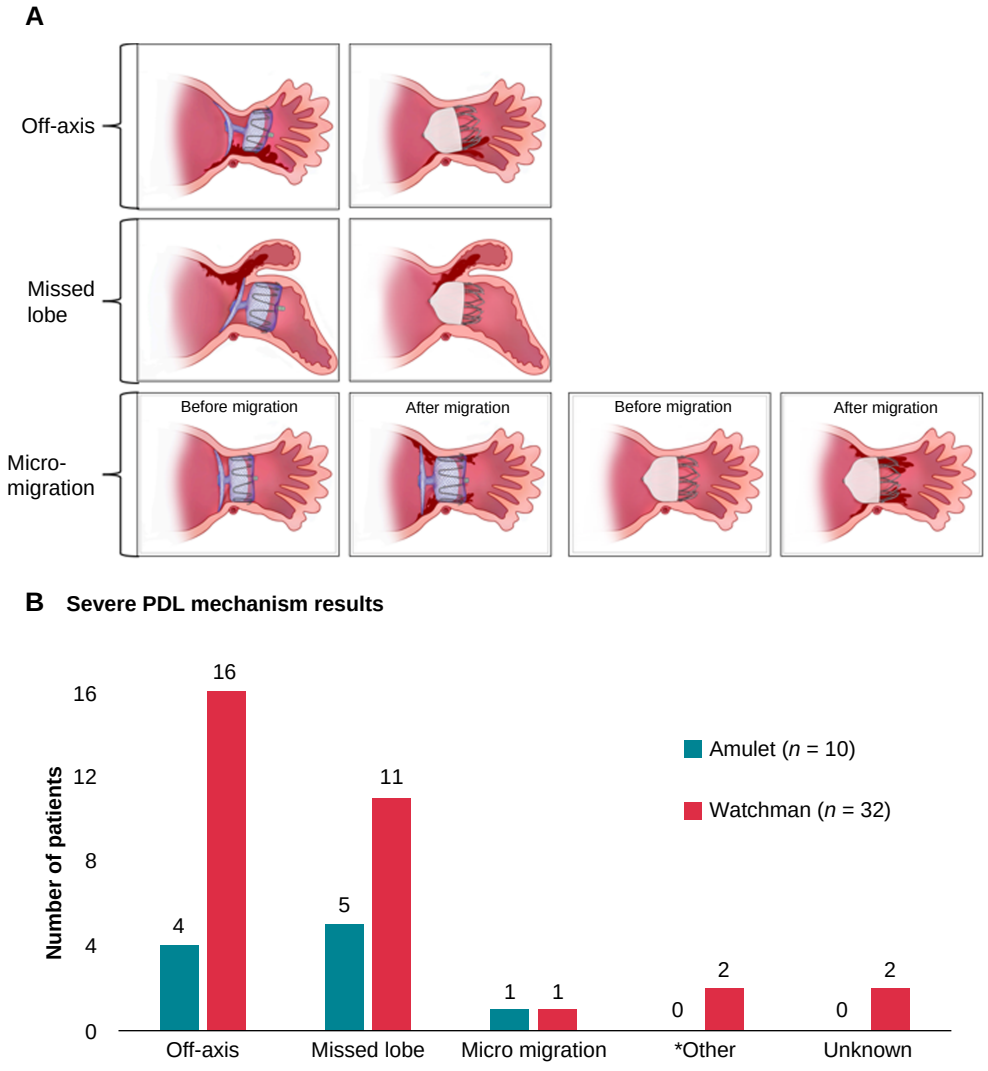


Figure 2 Mechanism of severe PDLs. (*A*) Illustration examples of the most common mechanisms of severe PDLs after LAAO. (*B*) The number of patients who were in each severe PDL mechanism category for the Amulet occluder and Watchman device during the Amulet IDE trial. *Other = one Watchman device patient had a leak around both edges of the device and one Watchman device patient had a distal implant with incomplete left atrial appendage coverage. LAAO, left atrial appendage occlusion; PDL, peri-device leak.

acquiring three-dimensional (3D) TEE datasets to evaluate for missed lobes should be an area of future investigation to further mitigate PDLs.

Anatomical and device predictors of severe peri-device leak

Several factors can contribute to the development of PDLs following LAAO including LAA anatomy, procedural factors, implanter experience, device design, and device positioning. Larger ostia have shown to increase the risk of severe PDL with the Watchman device.[15] LAAs that are irregular in shape or difficult-to-reach may also be more challenging in achieving a complete seal. Our analysis showed larger anatomical dimensions including orifice diameter (20.5 vs. 18.1 mm, $P = 0.040$), landing zone diameter (16.8 vs. 14.9 mm, $P = 0.036$), and depth (26.9 vs. 23.4 mm, $P = 0.001$) predicted severe PDL with the Watchman device. However, no anatomical predictors were discovered with the Amulet occluder, which shows the dual-occlusive disc and lobe design may provide improved closure in patients with both simple and complex anatomies.

Procedural characteristics and implanter experience may impact the risk of PDL. Procedural predictors of severe PDL with the Amulet occluder included increased procedural time (55.5 vs. 36.3 min, $P = 0.025$) and greater number of devices attempted (1.7 vs. 1.2, $P = 0.016$), while no significant procedural predictors with the Watchman device were discovered. As observed in the primary results with the Amulet occluder, procedural complications decreased with increased implanter experience.[1] A similar finding was observed in this analysis in which all 10 severe PDL cases occurred from implanters with <10 cases of prior Amulet occluder implants. The expected learning curve with the Amulet occluder procedure should therefore further improve reduction of severe PDLs resulting in decreased procedural time and devices used.

Following the IFU during the LAAO implant procedure is critical for achieving a good seal. If the device is not properly sized or positioned

Table 3 Predictors of severe PDL with the Amulet occluder

Variable	Severe PDL ($n = 10$)	No PDL ($n = 46$)	*P*-value
Anatomical			
LAA dimensions			
Orifice diameter, mm	20.0 ± 6.4 (9)	18.6 ± 4.7 (37)	0.214
Landing zone diameter, mm	16.7 ± 4.7 (9)	15.6 ± 3.7 (37)	0.148
Depth, mm	26.8 ± 7.7 (9)	24.9 ± 6.0 (37)	0.217
Ovality index (ratio)	1.5 ± 0.5 (9)	1.4 ± 0.3 (36)	0.181
Morphology of LAA			
Chicken wing (vs. other morphologies)	3 (9)	8 (38)	0.439
Windsock (vs. other morphologies)	4 (9)	23 (38)	0.385
LAA multi-lobe present	3 (9)	11 (35)	0.913
Procedural			
Procedure duration, min	55.5 ± 26.4 (10)	36.3 ± 19.9 (46)	0.025
Contrast volume, cc	117.2 ± 102.7 (10)	80.2 ± 50.5 (46)	0.116
Number of recaptures	2.2 ± 2.4 (10)	1.3 ± 2.0 (46)	0.241
Number of devices attempted	1.7 ± 0.9 (10)	1.2 ± 0.4 (46)	0.016
Smoke in LAA present	4 (9)	14 (41)	0.562
LAA flow velocity, cm/s	16.6 ± 14.8 (6)	33.6 ± 28.2 (23)	0.176
Atrial fibrillation rhythm (vs. sinus)	7 (10)	15 (36)	0.123
Device implant			
Depth of implant, mm	3.0 ± 3.7 (9)	5.1 ± 5.5 (45)	0.283
Distance between the disc and lobe, mm	5.5 ± 3.7 (10)	3.6 ± 2.0 (38)	0.061
Compression of device (min), %	2.6 (9)	7.7 (38)	0.150
Compression of device (max), %	18.1 (9)	18.5 (38)	0.911
Incorrect device size	8 (9)	11 (36)	0.001
Undersized	7 (9)	9 (36)	
Oversized	1 (9)	2 (36)	
Lobe off-axis	5 (7)	2 (20)	0.006
Improper device placement	4 (10)	4 (46)	0.019
Too distal	1 (10)	2 (46)	
Too proximal	3 (10)	2 (46)	
In-hospital adverse events			
Death	0.0% (0)	0.0% (0)	1.000
Cardiac arrest	0.0% (0)	0.0% (0)	1.000
Ischaemic stroke	0.0% (0)	0.0% (0)	1.000
Haemorrhagic stroke	0.0% (0)	0.0% (0)	1.000
Undetermined stroke	0.0% (0)	0.0% (0)	1.000
Transient ischaemic attack	0.0% (0)	0.0% (0)	1.000
Intracranial haemorrhage	0.0% (0)	0.0% (0)	1.000
Systemic embolism	0.0% (0)	0.0% (0)	1.000
Major bleeding	20.0% (2)	2.2% (1)	0.079
Major vascular complication	0.0% (0)	0.0% (0)	1.000
Myocardial infarction	0.0% (0)	0.0% (0)	1.000
Pericardial effusion requiring intervention	0.0% (0)	0.0% (0)	1.000
Device embolization	0.0% (0)	0.0% (0)	1.000

Values are mean ± SD (*N*), *n* (*N*) of total evaluable TEE images, or % (*n* of in-hospital adverse events) of patient group.
LAA, left atrial appendage; other abbreviations as in *Table 1*.

within the LAA, it may not seal completely, leading to PDL. Improper device placement was a predictor of severe PDL in both devices with 4 of 10 severe PDL cases improperly placed with the Amulet occluder and 24 of 30 severe PDL cases improperly placed with the Watchman device. Additionally, inadequate device sizing was a predictor of severe PDL with the Amulet occluder in which seven were undersized and one was oversized. Although device sizing was not a predictor of severe PDL with the Watchman device, it is important to note that over 60% of devices were incorrectly sized regardless of PDL status. Recently developed methods and technologies to improve implant procedures and sizing of devices have been reported including a novel sizing chart and method using 3D data,[21] FEops HEARTguide technology,[22] and novel steerable sheaths. Peri-procedural complication rates were also similar regardless of PDL status in both device groups. As demonstrated by Messele *et al.*,[23] high CHA_2DS_2-VASc scores (>4) could have also increased the risk of peri-procedural complications such as PDL although CHA_2DS_2-VASc scores and in-hospital adverse events were similar regardless of PDL status and devices used in this analysis.

Predictors of severe PDL in this analysis involved both anatomical and implant procedural variables. The latter is more addressable as these can be controlled through increased implanter experience, improved training on best implant practices, and implementing novel methods and technologies for device sizing and placement.

Evolution of severe peri-device leak

In this analysis, patients with a severe PDL in each device group were followed through 18 months to understand medication treatments, associated adverse events, and resolution status of the PDL over time. Patients with an Amulet occluder were instructed to be discharged on dual APT, while Watchman device patients were discharged on OAC (warfarin and aspirin) per the IFU. Therefore, most patients with an Amulet occluder were on APT (6 of 9) at the time of severe PDL identification, while most Watchman device patients were on OAC (24 of 25). The recent Society for Cardiovascular Angiography

Table 4 Predictors of severe PDL with the Watchman device

Variable	Severe PDL ($n = 32$)	No PDL ($n = 38$)	*P*-value
Anatomical			
LAA dimensions			
Orifice diameter, mm	20.5 ± 5.1 (26)	18.1 ± 3.1 (32)	0.040
Landing zone diameter, mm	16.8 ± 3.4 (26)	14.9 ± 2.9 (32)	0.036
Depth, mm	26.9 ± 4.6 (28)	23.4 ± 4.8 (33)	0.001
Ovality index (ratio)	1.3 ± 0.3 (26)	1.4 ± 0.2 (32)	0.242
Morphology of LAA			
Chicken wing (vs. other morphologies)	6 (29)	10 (31)	0.314
Windsock (vs. other morphologies)	15 (29)	17 (31)	0.809
LAA multi-lobe present	12 (27)	15 (29)	0.586
Procedural			
Procedure duration, min	29.4 ± 16.1 (32)	27.3 ± 19.7 (38)	0.629
Contrast volume, cc	89.2 ± 55.3 (31)	67.4 ± 51.4 (37)	0.101
Number of recaptures	0.7 ± 1.0 (32)	0.6 ± 1.3 (38)	0.928
Number of devices attempted	1.3 ± 0.5 (32)	1.3 ± 0.5 (38)	0.913
Smoke in LAA present	8 (30)	14 (35)	0.260
LAA flow velocity, cm/s	21.6 ± 30.2 (15)	16.9 ± 26.5 (22)	0.610
Atrial fibrillation rhythm (vs. sinus)	10 (22)	12 (33)	0.501
Device implant			
Depth of implant, mm	10.1 ± 7.5 (30)	8.4 ± 6.9 (36)	0.339
Compression of device (min), %	15.2 (27)	13.5 (35)	0.627
Compression of device (max), %	25.6 (27)	22.6 (35)	0.133
Incorrect device size	16 (26)	19 (32)	0.867
Undersized	6 (26)	4 (32)	
Oversized	10 (26)	15 (32)	
Improper device placement	24 (30)	2 (38)	<0.001
Too distal	6 (30)	0 (38)	
Too proximal	1 (30)	1 (38)	
Off-axis	17 (30)	1 (38)	
In-hospital adverse events			
Death	0.0% (0)	0.0% (0)	1.000
Cardiac arrest	0.0% (0)	0.0% (0)	1.000
Ischaemic stroke	0.0% (0)	0.0% (0)	1.000
Haemorrhagic stroke	0.0% (0)	0.0% (0)	1.000
Undetermined stroke	0.0% (0)	0.0% (0)	1.000
Transient ischaemic attack	0.0% (0)	0.0% (0)	1.000
Intracranial haemorrhage	0.0% (0)	0.0% (0)	1.000
Systemic embolism	0.0% (0)	0.0% (0)	1.000
Major bleeding	3.1% (1)	2.6% (1)	1.000
Major vascular complication	0.0% (0)	0.0% (0)	1.000
Myocardial infarction	0.0% (0)	0.0% (0)	1.000
Pericardial effusion requiring intervention	3.1% (1)	2.6% (1)	1.000
Device embolization	0.0% (0)	0.0% (0)	1.000

Values are mean ± SD (*N*), *n* (*N*) of total evaluable TEE images, or % (*n* of in-hospital adverse events) of patient group.
Abbreviations as in *Tables 1* and *3*.

& Interventions/Heart Rhythm Society Expert Consensus Statement on Transcatheter left atrial appendage closure recommends to continue on OAC after PDL identification.[3] However, only three patients with each device remained on OAC until the severe PDL was determined to be resolved (≤5 mm) through TEE as instructed in the protocol. This may be due to the clinical site's interpretation of not being a PDL >5 mm and therefore not needing OAC, whereas the independent core lab-reported data in this analysis suggest these patients had a severe PDL. Precise measurements of PDL should be performed at required follow-up timepoints to prevent this discrepancy.

Adverse events following severe PDL identification in each device group were rare, but more were observed with the Watchman device compared with the Amulet occluder (6 vs. 2). Most importantly, there were zero deaths in Amulet occluder patients with severe PDL with four deaths (two CV and two all-cause related) in the Watchman device group. In all four Watchman device patients, PDL was not resolved prior to death which may have put them at increased risk. In a prior analysis within the Amulet IDE trial, increased stroke, SE, or CV death risk was observed in patients with PDL ≥3 mm.[8] However, special precautions such as increased OAC usage, additional imaging performed, and added monitoring of patients with PDL >5 mm patients may have decreased thrombo-embolism risk.

It is believed small PDLs (≤3 mm) may resolve on their own during the natural healing process, whereas larger leaks (>3 mm) do not.[6] In our analysis, we observed five Amulet occluder severe PDLs resolved at least partially (≤5 mm) by 12 months leaving only three patients with confirmed severe PDL (two unknown status) through 18 months. One could speculate that a large leak around one part of the disc can diminish or be absent after a year if the disc undergoes scar retraction within the LA wall or pulmonary vein ridge as the entire LAA device fibroses are closed from underneath. In comparison, 8 of the 19 evaluable Watchman device severe PDLs resolved at least partially by 12 months leaving 11 unresolved and 13 with an unknown status. It was interesting to observe seven Watchman device patients with a newly discovered severe PDL after the 45-day assessment. The device may have shifted axis or position over time as these patients had either an off-axis or micro-migration mechanism of PDL. The precision of residual jet size measurement with TEE may have also played a role with a 1.5 ± 0.5 mm residual jet size increase in off-axis PDL mechanism patients. However, in both groups, there was >20% (1.5 mm) decrease

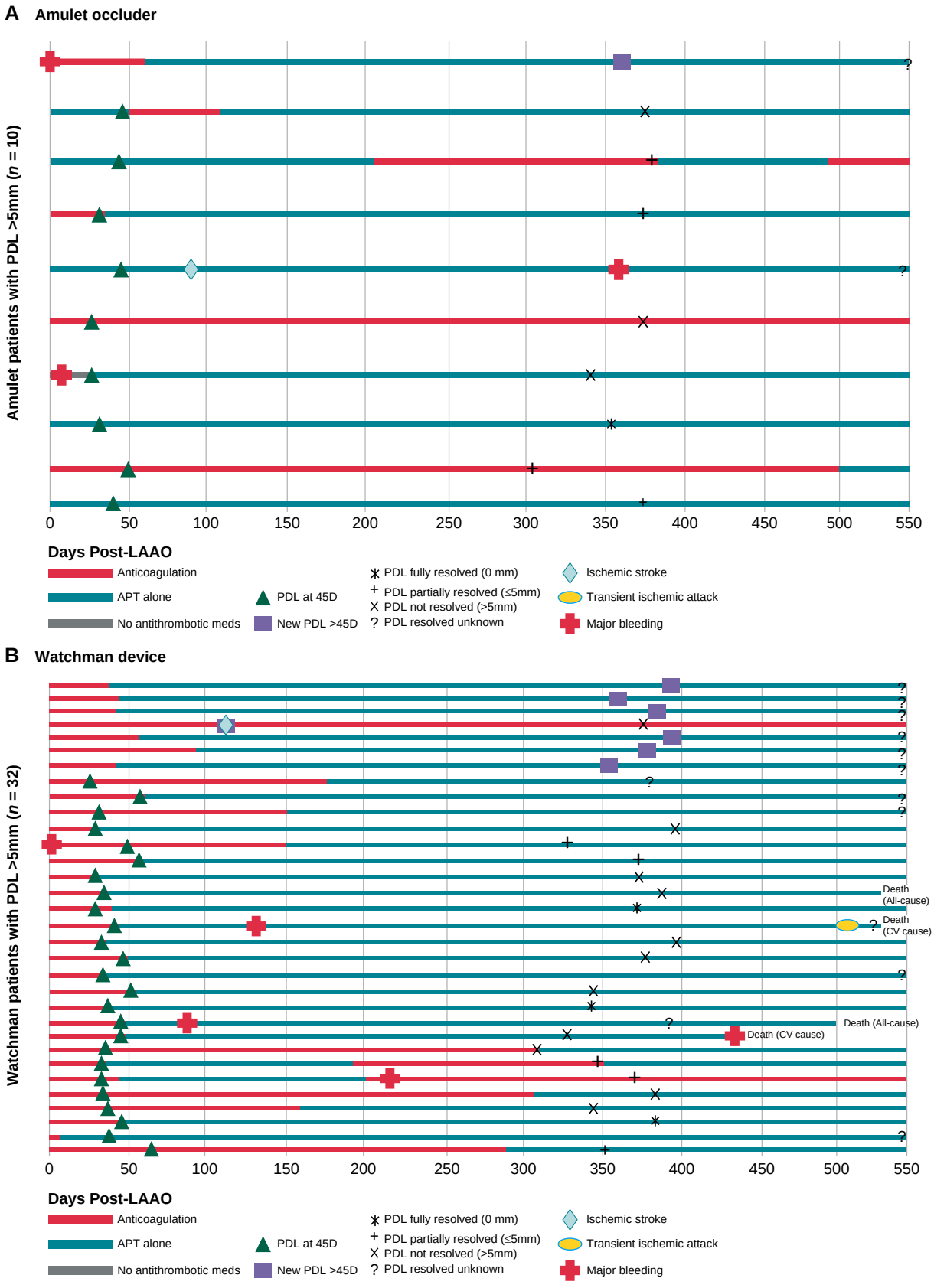


Figure 3 Evolution of patients with severe PDL. Each bar represents the follow-up duration (18 months) for a patient with a severe PDL in the Amulet IDE trial. APT, antiplatelet therapy; CV, cardiovascular; LAAO, left atrial appendage occlusion; PDL, peri-device leak.

in residual leak size from 45 days to 12 months, which remains to be seen if this has clinical impact on long-term outcomes.

Limitations

This analysis had a number of limitations: (i) The analysis compared the Amulet occluder with the Watchman 2.5, while there is now a more recent Watchman™ FLX device available that has shown improved closure.[24] However, the mechanistic design of both devices is similar (single-lobe plug type), so we believe that this analysis is relevant to identify PDL mechanisms and predictors. (ii) The residual jet size cut-off size was set at 5 mm to define PDL for this analysis in alignment with the primary mechanism of action endpoint in the protocol. The signals for PDL mechanisms and predictors for 5 mm may act as hypothesis-generating for future analyses with other clinically relevant cut-off sizes[7] and with more sensitive cardiac computed tomography (CT). (iii) There were missing data due to the fact that not all TEEs were evaluable, so the frequency and severity of PDL may be underestimated. (iv) The sample sizes used in analyses may not have been sufficiently powered because this is a *post hoc* analysis from the Amulet IDE trial. (v) Peri-device leaks were assessed by TEE in the Amulet IDE trial, which can be subjective and an operator-dependent imaging modality. As mentioned by Korsholm *et al.*,[25] cardiac CT may provide more detailed information about PDL with a better understanding of the underlying mechanism and quantification of the residual leak. (vi) Our analysis methodology only noted the single largest leak passing the entirety of the device. Further investigations of the impact of smaller multiple leaks or leaks passing through only a portion of the device, are warranted, and cardiac CT appears to be appropriate for this analysis.

Conclusions

The dual-occlusive mechanism Amulet occluder demonstrated significantly fewer severe PDLs through 12 months compared with the single-occlusive Watchman 2.5 device. Larger LAA anatomical dimensions predicted severe PDL with the Watchman device with no anatomical limitations discovered with the Amulet occluder. Further studies should address the management of unresolved severe PDLs after 18 months.

Supplementary material

Supplementary material is available at *Europace* online.

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Authorship

All authors attest that they meet the current ICMJE criteria for authorship.

Consent

All patients provided written informed consent.

Ethics statement

The study was performed in accordance with an IRB-approved protocol and adhered to the Helsinki guidelines.

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Data availability

Data used in this analysis are confidential as the Amulet IDE trial is ongoing.

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