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Amulet or Watchman Device for Percutaneous Left Atrial Appendage Closure: Primary Results of the SWISS-APERO Randomized Clinical Trial

Running Title: *Galea et al.; SWISS-APERO trial*

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Abstract

Background. No study has so far compared Amulet with the new Watchman FLX in terms of residual left atrial appendage (LAA) patency or clinical outcomes in patients undergoing percutaneous LAA closure (LAAC).

Methods. In the investigator-initiated SWISS APERO trial, patients undergoing LAAC were randomized (1:1) open-label to receive Amulet or Watchman 2.5 or FLX (Watchman) across 8 European centres. The primary endpoint was the composite of justified crossover to a non-randomized device during LAAC procedure or residual LAA patency detected by cardiac computed tomography angiography (CCTA) at 45 days. The secondary endpoints included procedural complications, device related thrombus (DRT), peridevice leak (PDL) at transesophageal echocardiography (TEE) and clinical outcomes at 45 days.

Results. Between June 2018, and May 2021, 221 patients were randomly assigned to Amulet (111 [50.2%]) or Watchman (110 [49.8%]), of whom 25 (22.7%) patients included before October 2019 received Watchman 2.5, and 85 (77.3%) patients received Watchman FLX. The primary endpoint was assessable in 205 (92.8%) patients and occurred in 71 (67.6%) Amulet and 70 (70.0%) Watchman patients respectively (risk ratio [RR] 0.97 [95% CI 0.80- 1.16]; P=0.713). A single justified cross-over occurred in an Amulet patient who fulfilled LAA patency criteria at 45-day CCTA. Major procedure related complications occurred more frequently in the Amulet group (9.0% vs. 2.7%; P=0.047), owing to more frequent bleeding (7.2% vs.1.8%). At 45 days, the PDL rate at TEE was higher with Watchman than Amulet (27.5% vs. 13.7%, p=0.020), albeit none was major (i.e. > 5 mm), whereas DRT was detected in 1 (0.9%) patient with Amulet and 3 (3.0%) patients with Watchman at CCTA and in 2 (2.1%) and 5 (5.5%) patients at TEE, respectively. Clinical outcomes at 45 days did not differ between the groups.

Conclusions. Amulet was not associated with lower rate of the composite of crossover or residual LAA patency compared with Watchman at 45-day CCTA. Amulet, was however associated with lower PDL rates at TEE, higher procedural complications and similar clinical outcomes at 45 days compared with Watchman. The clinical relevance of CCTA-detected LAA patency requires further investigation.

Clinical Trial Registration: URL https://clinicaltrials.gov Unique Identifier NCT03399851

Key Words: left atrial appendage closure, Amulet, Watchman FLX, cardiac computed tomography angiography, leak

Nonstandard Abbreviations and Acronyms

AF, Atrial Fibrillation; ASA, AcetylSalicylic Acid; BARC, Bleeding Academic Research Consortium; CCTA, Cardiac Computed Tomography Angiography; CEC, Clinical Events Committee; CV, CardioVascular; DRT, Device Related Thrombus; HU, Hounsfield unit; IDL, Intra Device Leak; IFU, Instructions for Use; LA, Left Atrium; LAA, Left Atrial Appendage; LAAC, Left Atrial Appendage Closure; MI, Myocardial Infarction; MIL, MIxed Leak; OAC, Oral AntiCoagulants; NPA, Non Patent left atrial Appendage; PA, Patent left atrial Appendage; PANVL, Patent left atrial Appendage with No Visible Leak; PDL, PeriDevice Leak; RCT, Randomized Clinical Trial; TEE, Transesophageal Echocardiography; VKA, Vitamin-K Antagonist

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Clinical Perspective

What is new?

- The SWISSAPERO trial is the first multicenter randomized, controlled trial comparing Amulet with Watchman FLX devices in terms of sealing capacity as evaluated by CCTA, procedural complications and short-term clinical outcomes.
- Amulet was not superior to Watchman in terms of LAA patency at 45-day CCTA or need to cross-over to the non-randomly allocated device. However, the mechanism underlying LAA patency significantly differ between the two devices, with mixed leaks and patent appendages with no visible leak being more frequent with Watchman and intradevice leaks with Amulet. PDLs at TEE were also higher with Watchman than Amulet
- Procedural complications were significantly higher in Amulet compared with Watchman groups, largely driven by higher rate of bleeding and pericardial effusions.
- At 45 days, clinical outcomes were similar between the two device groups

What are the clinical implications?

- At 45 days after LAAC, only a minority of LAAs are entirely sealed at CCTA with either Amulet or Watchman FLX.
- Both Amulet and Watchman can be successfully implanted in almost all LAAs deemed suitable for both devices as evaluated by pre-periprocedural TEE.
- The role of type of LAA leaks remain unclear but Amulet with a dual sealing system appears less prone to side leaks, yet to greater intradevice leaks and pericardial effusions.

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Introduction

Non-valvular atrial fibrillation (AF) is associated with a 5-fold risk of cardioembolic events[1]. Concomitant treatment with oral anticoagulation (OAC) decreases cardioembolic risk by almost 70% in AF patients, but is associated with higher rates of major extracranial bleeding and intracranial hemorrhage[2]. Percutaneous left atrial appendage (LAA) closure (LAAC) has been investigated as an alternative therapeutic option to OAC for preventing thromboembolism in patients with AF [3-5]. LAAC devices are meant to accomplishing complete LAA sealing, thereby excluding the main source of cardiac thrombi from the circulation[6]. However, residual LAA patency after intervention may undermine LAAC therapeutic principle and it is therefore routinely assessed after intervention, by means of transesophageal echocardiography (TEE) or cardiac computed tomography angiography (CCTA)[7].

The Watchman (Boston Scientific, USA) and Amplatzer Amulet (Abbott, USA) devices are the two most frequently used devices for LAAC worldwide. The recent Amulet IDE trial was the first head-to-head randomized comparison of Amulet versus Watchman 2.5 and showed the superiority of the former over the latter in terms of LAA occlusion rate at 45–day TEE[8]. In March 2019, the second-generation Watchman FLX was released with design iterations aiming at improving LAA sealing and facilitate device implantation in complex LAA anatomies. No RCT has so far compared the new Watchman FLX versus the Amulet in terms of residual LAA patency, rates of periprocedural complications or short-term clinical outcomes.

Methods

Study Design

The “Comparison of Amulet vs Watchman/FLX devices in patients undergoing left atrial appendage closure” (SWISS-APERO, clinicaltrial.gov NCT03399851) is an investigator-

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initiated, open-label, multicentre, randomized superiority clinical trial designed to assess whether Amulet is superior to Watchman 2.5/FLX (Watchman) in terms of need of crossover to another device or complete LAA sealing, as assessed by means of CCTA 45 days after implantation. The study rationale and design have been reported previously[9]. The trial was designed by the principal investigator (MV) and sponsored by the University Hospital of Bern, Switzerland, which was responsible for implementing, conducting, analysing and reporting trial procedures and findings. This study was partially supported by a research grant from Abbott to the study sponsor. All statistical analyses were performed by an independent academic Clinical Trial Unit located in Bern, Switzerland. The Ethics Committee (EC) of each participating site approved the study protocol and all patients provided written informed consent. All participating centres, trial personnel and the study protocol are reported in Supplement (pp 2, 21).

Participants

All patients undergoing a clinically indicated LAAC at participating centres were screened for inclusion. Patients with non-valvular AF and clinical indication for LAAC were eligible if were 18 years or older, capable to provide written informed consent, with CHA2DS2-VASc score ≥ 2 and either HAS-BLED score ≥3 or presence of high bleeding risk features as defined by Munich consensus document [10]. CHA2DS2-VASc and HAS-BLED scores have been previously defined [11, 12]. Both preprocedural CCTA and pre or intraprocedural TEE were performed before randomization to rule out LAA thrombus and confirm that LAA anatomy was suitable for both devices. Further key exclusion criteria included creatinine clearance of <30 ml/min and enrolment in another cardiovascular device or investigational drug trial [9]. Detailed inclusion and exclusion criteria are shown in the Supplement (pp 4).

Randomisation and masking

Patients who met all the inclusion criteria and none of the exclusion criteria were entered into a database by using a secure web interface (ICE-Advice Pharma, available at https://trials-

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ice.advicepharma.com/laacapero) and were randomly assigned in a 1:1 ratio, with block sizes of 4-6 and stratified by center, to receive Amulet or Watchman device immediately before the procedure. The Watchman FLX iteration became available to study centers in October 2019. Therefore, all patients randomized to the Watchman group before October 2019 received Watchman 2.5, whereas all patients randomized to the Watchman group after October 2019, received Watchman FLX. All clinical events and cross-overs were adjudicated by the independent Clinical Events Committee (CEC) members who were blinded to patient allocation.

Procedures

LAAC Procedures were performed under angiographic and echocardiographic guidance[13,14] and according to the instructions for use (IFU). Operators had to be familiar with both devices and to have successfully completed company-specified physician training programs of both devices. Procedural data, including duration, dose of contrast medium, radiation exposure, number of implantation attempts, crossover to the other device were recorded. After LAAC, the recommended antithrombotic therapy consisted of acetylsalicylic acid (ASA) and clopidogrel or OAC for three months followed by ASA alone until 12 months after LAAC. However, post-implantation drug regimen was left at discretion of the treating physician according to the bleeding risk, the stroke risk and post-device release echocardiography evaluation.

45-day follow-up

At 45 (±7) days after procedure, patients underwent an on-site clinical visit and CCTA/TEE examinations. The CCTA protocol was previously described in detail[9]. Briefly, a 64- to 320-detector scanner was used, with a multiphasic acquisition in arterial and venous phase. A prospective high-pitch flash mode or broad coverage single shot/step and shoot ECG-gated CT acquisition technique typically at 70 % of R–R interval or a retrospectively ECG gated CT-acquisition at 30–70% of R–R interval was used. Images were reconstructed using

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iterative reconstruction or filtered back-projection at 0.75 mm slice width, 0.5 mm slice increment. The standard scan (arterial phase) was performed using a bolus tracking technique by placement of a region of interest (ROI) on the ascending aorta for optimal scan acquisition timing. The delayed scan (venous phase) was executed 60 seconds following the beginning of the standard scan to allow contrast equilibration within the blood pool. TEE were performed, according to the previously described protocol[9] and reported on the Supplement (pp 14), in order to assess the presence and size of peridevice leak (PDL) and device related thrombus (DRT). Once the images were acquired, were sent to the coordinating centre for the central assessment by the Imaging Core Lab.

Study outcomes

The primary endpoint was the composite of justified crossover to the non-randomly allocated device or 45-day LAA patency rate at CCTA. The justified crossover was defined as the implantation of the non-randomized device based on morphological/anatomical considerations during device implantation after at least an attempt to implant the assigned device. LAA was defined as patent (PA) if LAA density ≥ 100 HU or ≥ 25% of that of the LA[15]. In patients with PA, visible leaks were further categorized as intradevice leak if there was passage of contrast inside the device lobe or as PDL or mixed leak if passage of contrast was visible along the lobe margins for the entire length, or part of it, respectively. If none of the above entities was detected, PAs with no visible leak were adjudicated. LAA patency and type of leaks were centrally adjudicated by the Imaging Core Lab (**Figure 1**). More details regarding endpoint definitions, adjudication methods and Imaging Core Lab inter-reader agreement were previously described [9] and are reported in the Supplement. Secondary endpoints included LAA patency at 45-day TEE, any (the composite of death, cerebrovascular event, systemic or pulmonary embolism, air embolism, any bleeding, any pericardial effusion, vascular access complication, device related complication or acute kidney injury occurring within 7 days or thereafter if deemed procedure-related) or major (as the composite of death,

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cerebrovascular event, systemic embolism, BARC 3 or 5 bleeding, clinically relevant pericardial effusion, device embolization and acute kidney injury within 7 days or thereafter if deemed procedure-related) procedure-related complications, DRT at 45 days with CCTA and TEE, LAA patency on the venous phase (the latter defined as a LAA density ≥ 100 HU or ≥ 150% of that measured at the same site on arterial phase)[16] and clinical outcomes in terms of all cause or cardiovascular death, overall, ischemic or hemorrhagic stroke, systemic or pulmonary embolism, spontaneous myocardial infarction and BARC type bleeding. The definitions of all endpoints are detailed in the appendix and are in agreement with the latest consensus document on definitions, endpoints, and data collection requirements for LAAC clinical studies[10]. All clinical endpoints and cross-overs were centrally adjudicated by the CEC members who were blinded to the treatment assignment.

Statistical analysis

The primary hypothesis was that Amulet device would be superior to Watchman for the primary endpoint. The primary analysis was prespecified to be performed on an intention-to treat (ITT) basis, including all randomized patients with 45-day CCTA follow-up analyzable data. Based on previous observational studies, we anticipated an incidence of the primary composite endpoint in the range of 50% in the Watchman cohort [16-21]. As a consequence, we determined with difference of proportion power calculation for binomial distribution that a minimum of 200 study participants with a primary endpoint reached would have provided > 80% power to detect a 40% relative risk reduction corresponding to an event rate in the range of 30% in the Amulet cohort with standard 5% type I error. The trial statistical analysis plan is reported on the Supplement. Standard descriptive statistical methods were used: absolute and relative frequencies for categorical data and the median (interquartile range [IQR]) or mean ± standard deviation for continuous data. The study endpoints were analyzed using risk ratio or, if no events were reported in one randomization arm, Fisher's exact test. The following subgroups were pre-specified in the statistical analysis plan for additional analyses of study

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endpoints: age with cut-off of 75 years old, gender, left ventricular ejection fraction with cut-off of 40%, diabetes mellitus, prior bleeding, prior cerebrovascular event, Watchman 2.5 or FLX in the comparator arm, pre-procedural antithrombotic regimen. The Mantel-Haenszel test of homogeneity has been performed to test the homogeneity of risk ratios across strata. Statistical tests were performed using Stata (Stata Statistical Software: College Station, TX: Stata Corp LP). This study was registered with ClinicalTrials.gov, NCT03399851.

Data availability

The SWISS-APERO trial will continue following up the patients until 2026 to accrue 5-year data. No individual participant data will be available before the end of the study. Any relevant inquiries should be sent to the corresponding author.

Results

Between June 19, 2018, and May 18, 2021, 423 consecutive patients undergoing LAAC were screened at 8 centres across 4 European countries and 221 patients were randomly assigned to either Amulet (111 [50.2%]) or Watchman (110 [49.8%]) groups. Reasons for excluding patients from the trial are shown in **Figure 2**. The baseline characteristics were well-balanced between groups (**Table 1**). The mean age was 76.9 years, and 65 (29.4%) patients were women. The mean CHA2DS2-VASc score was 4.3 ± 1.4 and the mean HASBLED score 3.1 ± 0.9. History of relevant bleeding was reported in 194 (87.8%) patients, either gastrointestinal (78 [35.3%]) or intracranial (72 [32.6%]). A total of 87 (39.4%) patients had a prior cerebrovascular event. Overall, 108 [48.9%]) patients were on oral anticoagulation at the time of randomization, whereas the remaining patients were treated with antiplatelet therapy (55 [24.9%]) or did not receive any antithrombotic drug (58 [26.2%]).

One hundred seven (96.4%) patients randomized to Amulet received the allocated device. In one patient, a Watchman FLX was implanted after several attempts to deliver an Amulet 34mm with unsatisfactory results. In two additional patients, a Watchman FLX was

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directly implanted due to operator's decision not to follow randomisation owing to unavailability of Amulet devices on shelf. The remaining LAAC was aborted due the cardiac tamponade after several attempts to implant Amulet 28 mm and 25 mm devices. All 110 patients randomized to Watchman received the allocated device. Of them, 25 (22.7%) patients were included before October 2019 and received Watchman 2.5, whereas the remaining 85 (77.3%) patients received Watchman FLX. The procedural characteristics were well balanced between the groups (**Table 2**).

Primary endpoint and other 45-day CCTA findings

At 45 days, 6 patients died, in 6 additional patients CCTA was not performed, due to COVID-19 pandemic in 4, and worsened kidney function in 2; in 3 patients CCTA was performed but yielded insufficient quality images and one patient withdrew informed consent. Therefore, primary endpoint ascertainment was complete in 205 (92.8%) patients [105 (94.6%) with Amulet and 100 (90.9%) with Watchman]. The primary endpoint occurred in 71 (67.6%) patients in the Amulet and in 70 patients (70.0%) in the Watchman groups (risk ratio [RR] 0.97 [95% CI 0.80- 1.16]; P=0.713) (**Figure 3**). The single adjudicated justified cross-over occurred in an Amulet patient who fulfilled PA criteria at CCTA.

The primary endpoint results were consistent across all prespecified subgroups (**Supplemental Figure 1**, pp 17), including type of Watchman used (Amulet vs Watchman 2.5 [54.2% vs. 65.2%; p=0.440] and Amulet vs. Watchman FLX [71.6% vs. 71.4%; p=0.980]).

When the type of LAA patency was further analyzed, visible leaks at device sides (peridevice or mixed leaks) trended higher in the Watchman group (34% vs. 22.9%; p = 0.077) due to a significantly higher rate of mixed leaks (14% vs. 3.8%; p=0.010). The rates of PAs with no visible leak were also more frequent with Watchman (21.0% vs. 9.5%; p=0.022), whereas intradevice leaks were more common in the Amulet arm (44.8% vs. 23.0%; p = 0.001) (**Table 3**). Definite DRT was detected in one (0.9%) patient with Amulet and 3 (3.0%)

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patients with Watchman (p=0.285). The composite of definite or possible DRT trended higher in Watchman group (9.9% vs. 3.7%; p=0.076). PA rates, as assessed on the venous phase, at per protocol or as treated analyses yielded entirely consistent results (**Supplemental Table 5-6**, pp 15-16). CCTA findings stratified based on type of Watchman devices are shown in **Supplemental Table 7-8.**

45-day TEE findings

PDL rates were two-fold higher with Watchman compared with Amulet (27.5% vs. 13.7%; p = 0.020). However, no leak greater than 5 mm was visible in either group. There were two (2.1%) DRT with Amulet and 5 (5.5%) with Watchman (P=0.225). TEE findings stratified based on type of Watchman devices are shown in **Supplemental Table 7-8.**

Procedure related complications

The prespecified composite of any periprocedural complication was higher in the Amulet group (32.4% vs. 19.1%; p = 0.023), mainly driven by a higher rate of pericardial effusion (17.1% vs. 6.4%; p = 0.013) and bleeding (25.2% vs. 13.6%; p = 0.030), mostly consisting of non-clinically relevant pericardial effusion (14.4% vs. 6.4%; p = 0.05) (**Table 4**). Major periprocedural complications were also higher in the Amulet group (9.0% vs. 2.7%; p = 0.047). There were two periprocedural deaths, both observed in the Amulet group at day 4 and 5 after LAAC, one due to air-embolism, which led to ischemic stroke and cardiovascular death and one due to a clinically relevant pericardial effusion treated by pericardiocentesis, but further complicated by hemoperitoneum and haemorrhagic shock. Two strokes occurred, one due to air-embolism as described above and a second one observed few hours after Amulet implantation and PCI completion in a combined procedure. Two device embolizations were observed, one in each treatment group.

45-day clinical outcomes

At 45 days, six deaths occurred (2.7%), 2 in Amulet, which were periprocedural as described above, and 4 in Watchman group (1.8% vs. 3.6%; p = 0.409), of which 3 were fatal bleeding

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(1 haemorrhagic stroke at 30 days, 1 haemorrhagic transformation of an ischemic stroke following thrombolysis 24 days after LAAC and 1 haemorrhagic shock 10 days after LAAC). The remaining fatal event occurred as sudden death at home 30 days after LAAC. The rate of cerebrovascular events or systemic/pulmonary embolisms was identical in the two study groups at 1.8% and 0.9%, respectively (**Table 4**).

Discussion

To the best of our knowledge, SWISS-APERO is the first RCT comparing residual LAA patency, procedural success and short-term clinical outcome between Amulet and the new Watchman FLX devices. The main findings of the study can be summarized as follows (**Figure 4**):

- Amulet was not superior to Watchman in terms of LAA patency at 45-day CCTA, which was highly prevalent in both treatment groups, or need to cross-over to the non-randomly allocated device, which occurred in a single patient.
- The mechanism leading to LAA patency at CCTA markedly differ between the two devices: mixed leaks and patent appendages with no visible leaks were more frequent with Watchman whereas intradevice leaks were more frequent with Amulet.
- Any or major procedural complications were higher in Amulet group, largely driven by higher rate of pericardial effusion and bleeding complications, mostly consisting of non-clinically relevant pericardial effusions.
- At 45-day TEE, Watchman implantation was associated with a higher PDL rate compared with Amulet, although no PDL leak greater than 5 mm were not observed in either group.
- At 45 days, clinical outcomes were comparable between the two device groups.

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Observational studies including surgical LAA ligation and hybrid LAAC showed a significant higher risk of thromboembolic events in patients with as compared to those without incomplete LAA sealing at imaging follow-up [22, 23]. However, the prognostic implication of device leaks after percutaneous LAAC remains controversial. This might reflect the retrospective and underpowered nature of studies assessing the impact of residual leaks after LAAC, the current practice of continuing or restarting OAC in patients with visible leaks or the high mortality rate of LAAC patients (competing risk scenario), precluding the assessment of the association between residual LAA patency and cerebrovascular events. However, evidence regarding the clinical implications of LAA leaks after percutaneous closure continues to accrue and a recent retrospective study suggested that new PDL identified at 45 to 90 days using transesophageal echocardiography is associated with 2-fold greater combined outcome of failure to stop OAC, transient ischemic attack or stroke, device-related thrombi, and need for PDL closure [24] .

Follow-up imaging after LAAC is recommended in order to assess residual leaks and device-related thrombosis by means of either TEE or CCTA[25]. CCTA has potential to replace or complement TEE for assessing LAA residual patency due to higher sensitivity and greater spatial resolution, allowing deeper understanding of the mechanisms underpinning residual LAA patency.

No study has so far compared Amulet with Watchman in terms of LAA residual patency at CCTA after LAAC and no controlled data of Amulet versus Watchman FLX, the most recent Watchman iteration, exists.

Our study showed a similar percentage of PA between the two groups (67.6% Amulet vs. 70.0% Watchman; p=0.713). The rate of PA observed in the Amulet group was similar to those previously described (47.8-69.2%) [15, 16, 21, 26-28]. Conversely, the PA rate detected in the Watchman group was higher in our trial compared with the only single-arm study which has assessed PA at CCTA after Watchman FLX [29], but similar with prior studies in which

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Watchman 2.5 was investigated [15, 16, 21, 27, 28]. This apparent inconsistency may derive from multiple factors, including single versus multicenter study set-up, core-lab versus investigator-reported assessment, the different timings of CCTA at follow-up, and some additional methodological considerations such as the fact that in our study, LAA HU was assessed placing the region of interest in the highest visually estimated contrast density point[9]; which may increase the likelihood of PA detection.

As shown in this and prior studies [7, 21, 30], CCTA is a very sensitive tool to detect PA, which is found in more than 1 every two patients who underwent apparently successful LAAC. This finding should be interpreted by taking into account that CCTA-based PA criteria have been mainly developed to maximize sensitivity over TEE and suffer from low specificity for the detection of leaks of at least 3 or 5 mm, which are more likely to carry clinical implications[26].

Nevertheless, CCTA provides comprehensive operator-independent assessment of PA after intervention and may help unravelling clinically meaningful differences between LAAC devices with respect to their sealing capabilities and better investigate the role of LAAC for stroke prevention over time. Interestingly, a recent study was a somewhat greater association between PDL detection at CCTA than TEE with clinical outcomes[26].

We found no inconsistent treatment effects for the primary endpoint across prespecified subgroups, including Amulet versus Watchman 2.5 or FLX. Therefore, our study does not provide clear evidence that the new Watchman FLX iteration provides superior LAA sealing compared with the earlier generation device. While Watchman FLX may be more suitable than Watchman 2.5 in complex anatomies, such as LAA with large and short neck, this was not reflected in our screening log in which roughly 50% of the screened patients were enrolled in the study both before and after Watchman FLX availability.

Of note, the mechanism underlying PA significantly differed between Amulet and Watchman: intradevice leaks were more frequent with Amulet (44.8% vs. 23.0%; p = 0.001)

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whereas mixed leaks and patent appendages with no visible leak were more frequent with Watchman (14.0% vs. 3.8%; p = 0.010 and 21.0% vs. 9.5%; p=0.022, respectively). Amulet lobe is shorter than Watchman FLX (10-12mm vs.14-35mm) and unlike Watchman, not covered by fabric, which may make the former more susceptible to intradevice leaks. It is likely that re-endothelization of the device may mitigate the presence of intradevice leaks over time, resulting in improved LAA sealing. Yet, this phenomenon remains to be investigated. The Watchman device, due to its single-lobe occluder system and the concave shape of the proximal polyethylene terephthalate membrane continuing along the side of the lobe only for few millimeters, is by geometry more susceptible to side gap leaks related to passage of contrast medium initially at the side and then inside the lobe once the side portion of the PET membrane is terminated. Leaks where LAA patency is detected in absence of a visible continuity of contrast between LA and LAA, likely reflects small (<0.75 mm) mixed or peridevice leaks which are not detectable by CCTA (our CCTA protocol included 0.75 mm slice width). Future studies should assess whether the type of LAA leaks after closure, on top of their magnitude, may carry differential clinical implications and whether different leak types may be subjected to differential evolution overtime.

In 4 patients in the Amulet group, the allocated device was not implanted whereas all patients in the Watchman group received the allocated treatment. In one Amulet case, crossover to Watchman was justified by poor device stability. In the other 3 cases, the procedure was either aborted due to a periprocedural complication which arose after attempting to implant the device or Amulet was not implanted because of device unavailability. Thus, our study provides evidence that technical success rates are high with both devices. This observation is reflected in our primary endpoint which was entirely driven by LAA patency rates at 45-day CCTA, considering that the only justified cross-over occurred in a patient fulfilling CCTA-patency criteria. The percentage of aborted procedure observed in our study (0.5%) was lower than those reported in the largest multicentre

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observation studies so far available (0.9-2.7%) [31-34]. Successful release of device was achieved more frequently in Amulet/ACP compared to Watchman groups (99% vs. 96%; p=0.007) in a prospective multicentre observational study including 641 consecutive clinically indicated LAACs[19]. However, Watchman FLX was not investigated in this registry, at variance with our study.

The occurrence of any periprocedural complication was higher in the Amulet compared with Watchman (32.4% vs. 19.1%; p = 0.023). There was an excess of bleedings and pericardial effusions with Amulet, the majority of which were minor bleedings or non-clinically relevant pericardial effusions. This observation is consistent with the Amulet IDE findings where the rate of pericardial effusion was two-fold higher with Amulet compared with Watchman[8]. Major procedure related complications were also more frequent in Amulet compared with Watchman group (9.0% vs. 2.7%; p = 0.047). This difference accrued again mainly due an excess of 4 clinically relevant pericardial bleedings in the Amulet group, of which 3 occurred within 7 days and one was detected later during follow-up. In our study all recruiting sites had large experience with the Amulet device, therefore it is unlikely that this may have driven by limited operator experience with the device. We observed a single episode of device embolization with both devices.

Unlike CCTA, TEE detects LAA leaks by the direct visualization of high velocity flows (50-60 cm/sec) adjacent to the device lobe regardless if they continue along all the entire lobe length or part of it. Under these premises, leaks, which are identified by TEE, largely correspond to mixed and/or peridevice leaks detected at CCTA. This explains why the 45-day TEE analysis showed a significantly higher rate of leaks in the Watchman compared with Amulet groups (27.5% vs. 13.7%; p=0.020). Furthermore, the only two cases with multiple leaks were observed in the Watchman arm. These observations corroborate the results of the Amulet IDE cohort[8], where residual PDLs were detected at 45-day TEE in 37% of Amulet and 53.9% of Watchman 2.5 patients. Consistently with these findings, the rate of PDL

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detected by LAA angiography and/or periprocedural TEE after device release trended higher in the Watchman compared with Amulet groups (11.8% vs. 4.5%; p=0.053).

The rates of DRT were numerically albeit not significantly higher in the Watchman group as assessed by TEE (5.5% vs. 2.1%; p = 0.225) or CCTA (3% vs. 0.9%; p = 0.285) at 45 days. Furthermore, the composite of definite or possible DRT trended higher in the Watchman compared with the Amulet groups (9.9% vs. 3.7%; p = 0.076). This finding is also consistent with the Amulet IDE results[8].

Interestingly, in our study, unlike Amulet IDE, the choice of anti-thrombotic therapy was left to investigators' discretion in both device groups, reflecting the updated IFUs for Watchman in Europe. As a result, the majority of patients in both groups did not receive OAC after LAAC.

Finally, we observed a very similar rates of clinical endpoints, such as mortality or cerebrovascular accidents in both groups at 45 days.

Trial Limitations

Our findings need also to be interpreted in the light of several limitations. First, the two devices, due to the different structural characteristics, can be easily distinguished during CCTA and TEE assessment. Therefore, the readers adjudicating imaging endpoints could not be blinded to the device which was finally implanted. Second, the trial was not powered to show differences with regard to clinical endpoints. Third, the new Watchman FLX became available in October 2019, therefore a minority yet sizable proportion of patients received Watchman 2.5. However, results were consistent between type of Watchman devices. Fourth, the observed rates of procedural complications in both arms in our study were higher compared to those reported by previous studies (0.5-5%)[19, 31-35]. Our primary definition of the procedure related complications included minor events, such as BARC 1-2 bleeding or any pericardial effusion, with or without clinical relevance. In addition, we counted as procedural complications events which occurred later than 7 days after LAAC if they were deemed

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procedural related. For example, all the DRTs detected by TEE after LAAC or pericardial effusions even if they occurred remotely from intervention (i.e. detected at 45 days) were all included in the composite periprocedural endpoints. Fifth, the prognostic significance of residual PA after percutaneous LAAC remains unclear. Finally, follow-up is limited at 45 days, which precludes meaningful evaluations of differences in both long-term clinical and clinical implications of imaging findings.

Conclusions

Among patients undergoing clinically indicated LAAC and in whom LAA anatomy was deemed suitable to both Amulet and Watchman, the former was not associated with lower residual LAA patency compared with the latter device at 45-day CCTA. Amulet, was however associated with lower PDL rates at TEE, higher procedural complications and similar clinical outcomes at 45 days compared with Watchman. The prognostic implications of CCTA-based LAA patency rates and types warrant further investigations.

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Acknowledgements

MV conceived and designed the study. MV, RG, FBB and DH acquired the data and participated in data analysis and data interpretation. All authors participated in enrolment of patients and performed clinical follow-up, along with revising the draft critically for important intellectual content. MV and RG wrote the first draft, reviewed, and revised the manuscript. All authors approved the final version of the manuscript and ensured that the accuracy or integrity of any part of the work is appropriately investigated and resolved. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication. Images of Amplatzer Amulet device are reproduced with permission of

Abbott, © 2021. All rights reserved. Images of Watchman FLX have been provided courtesy of Boston Scientific, ©2021 Boston Scientific Corporation or its affiliates. All rights reserved.

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Supplemental Materials

Expanded methods

Supplemental Tables I-VIII

Supplemental Figures I

References 36-40

Study Protocol – Study Analysis Plan

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Table 1. Baseline Patient Characteristics

	Amulet N = 111	**Watchman** N = 110
Age (years), mean ±SD	n = 111, 76.5 ± 7.1	n = 110, 77.3 ± 8.4
Male sex, no. (%)	n = 111, 79 (71.2%)	n = 110, 77 (70.0%)
BMI (kg/m²), mean ±SD	n = 111, 26.3 ± 4.8	n = 110, 27.4 ± 5.0
Arterial Hypertension, no. (%)	n = 111, 87 (78.4%)	n = 110, 90 (81.8%)
Diabetes mellitus, no. (%)	n = 111, 24 (21.6%)	n = 110, 34 (30.9%)
Chronic kidney disease *, no. (%)	n = 111, 3 (2.7%)	n = 110, 4 (3.6%)
History of coronary heart disease, no. (%)	n = 111, 39 (35.1%)	n = 110, 41 (37.3%)
Previous myocardial infarction, no. (%)	n = 111, 10 (9.0%)	n = 110, 14 (12.7%)
Prior Cerebrovascular event, no. (%)	n = 111, 45 (40.5%)	n = 110, 42 (38.2%)
History of arterial embolism, no. (%)	n = 111, 3 (2.7%)	n = 110, 2 (1.8%)
History of heart failure, no. (%)	n = 111, 5 (4.5%)	n = 110, 5 (4.5%)
Left ventricular function (%), mean ±SD	n = 108, 54.5 ± 12.6	n = 109, 55.7 ± 11.2
Paroxysmal atrial fibrillation, no. (%)	n = 111, 43 (38.7%)	n = 110, 44 (40.0%)
CHA2DS2Vasc score, mean ±SD	n = 111, 4.2 ± 1.4	n = 110, 4.4 ± 1.4
Bleeding risk features		
HASBLED score, mean ±SD	n = 111, 3.1 ± 0.8	n = 110, 3.2 ± 1.0
History of relevant bleeding†, no. (%)	n = 111, 98 (88.3%)	n = 110, 96 (87.3%)
Intracranial, no. (%)	n = 111, 39 (35.1%)	n = 110, 33 (30.0%)
Gastrointestinal, no. (%)	n = 111, 31 (27.9%)	n = 110, 47 (42.7%)
Haematuria, no. (%)	n = 111, 11 (9.9%)	n = 110, 6 (5.5%)
Epistaxis, no. (%)	n = 111, 10 (9.0%)	n = 110, 4 (3.6%)
Documented anaemia‡, no. (%)	n = 111, 34 (30.6%)	n = 110, 31 (28.2%)
Need for additional DAPT due to CAD and/or stenting, no. (%)	n = 111, 17 (15.3%)	n = 110, 13 (11.8%)
Diffuse intracranial amyloid angiopathy, no. (%)	n = 111, 9 (8.1%)	n = 110, 8 (7.3%)
Bowel angiodysplasia, no. (%)	n = 111, 17 (15.3%)	n = 110, 25 (22.7%)
Blood cell dyscrasia associated with increased bleeding risk, no. (%)	n = 111, 9 (8.1%)	n = 110, 6 (5.5%)
Recurrent falls with head trauma and significant musculoskeletal injury, no. (%)	n = 111, 2 (1.8%)	n = 110, 12 (10.9%)
Antiplatelet/Anticoagulant therapy at baseline		
No Antiplatelet/anticoagulant drugs, no. (%)	n = 111, 31 (27.9%)	n = 110, 27 (24.5%)
Any SAPT, no. (%)	n = 111, 25 (22.5%)	n = 110, 17 (15.5%)
Any DAPT, no. (%)	n = 111, 4 (3.6%)	n = 110, 9 (8.2%)
Any single-anticoagulant therapy, no. (%)	n = 111, 37 (33.3%)	n = 110, 45 (40.9%)
Any SAPT plus anticoagulant therapy, no. (%)	n = 111, 10 (9.0%)	n = 110, 10 (9.1%)
Any triple therapy, no. (%)	n = 111, 4 (3.6%)	n = 110, 2 (1.8%)

* Chronic Kidney Disease is defined if at least one of the following criteria is met: <30 eGFR mL/min per 1.73m2 (using the Modification of Diet in Renal Disease formula) and/or blood creatinine value >200 mcmol/l and/or dialysis or history of kidney transplantation
† History of relevant bleeding is defined as bleeding requiring medical attention and/or prompting evaluation
‡ Documented anaemia is defined as repeated haemoglobin levels <11g/dl or transfusion within 4 weeks before inclusion
BMI, Body Mass Index; SD, Standard Deviation; DAPT, Dual Antiplatelet Therapy; CAD, Coronary Artery Disease; SAPT, Single Antiplatelet Therapy.

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Table 2. Procedural Characteristics and Anti-thrombotic Medications

	Amulet N = 111	**Watchman** N = 110	**p value**
Randomization			
Time between device randomization and LAAC (days), mean ± SD	n = 111, 0.1 ± 0.5	n = 110, 0.1 ± 0.5	0.880
Procedure			
Sinus rhythm at the begin of procedure, no. (%)	n = 111, 57 (51.4%)	n = 110, 51 (46.4%)	0.683
General anaesthesia, no. (%)	n = 111, 46 (41.4%)	n = 110, 43 (39.1%)	0.784
Mean left atrial pressure before implantation, (mmHg), mean ± SD	n = 99, 14.9 ± 4.8	n = 100, 15.3 ± 5.7	0.620
Intracardiac echocardiography, no. (%)	n = 111, 3 (2.7%)	n = 110, 2 (1.8%)	1.000
Procedure time (min), mean ± SD	n = 111, 45.9 ± 25.1	n = 110, 43.0 ± 23.1	0.371
Fluoroscopy time (min), mean ± SD	n = 111, 12.3 ± 8.1	n = 110, 12.8 ± 9.2	0.628
Contrast medium (ml), mean ± SD	n = 108, 60.1 ± 42.7	n = 109, 62.9 ± 45.3	0.643
X-ray dose (cGy.cm2), med(IQR)	n = 107, 2777 (699; 5673)	n = 109, 2768 (1075; 5762)	0.634
Concomitant procedure, no. (%)	n = 111, 21 (18.9%)	n = 110, 16 (14.5%)	0.472
First device implantation attempt successful, no. (%)	n = 111, 74 (66.7%)	n = 110, 63 (57.3%)	0.167
First device used successfully implanted, no. (%)	n = 111, 105 (94.6%)	n = 110, 107 (97.3%)	0.499
Procedure aborted, no. (%)	n = 111, 1 (0.9%)	n = 110, 0 (0.0%)	1.000
Assessment at the end of procedure			
Any PDL detected by TEE or Angiography, no. (%)	n = 111, 5 (4.5%)	n = 110, 13 (11.8%)	0.053
Any PDL detected by TEE only, no. (%)	n = 111, 3 (2.7%)	n = 110, 6 (5.5%)	0.332
Any PDL detected by Angiography only, no. (%)	n = 87, 3 (3.4%)	n = 86, 8 (9.3%)	0.132
Any PDL detected by TEE and Angiography, no. (%)	n = 87, 1 (1.1%)	n = 86, 1 (1.2%)	1.000
Antiplatelet/Anticoagulant therapy at discharge			
No Antiplatelet/anticoagulant drugs, no. (%)	n = 109, 0 (0.0%)	n = 109, 1 (0.9%)	1.000
Any SAPT, no. (%)	n = 109, 22 (20.2%)	n = 109, 23 (21.1%)	1.000
Any DAPT, no. (%)	n = 109, 78 (71.6%)	n = 109, 77 (70.6%)	1.000
Any single-anticoagulant therapy, no. (%)	n = 109, 8 (7.3%)	n = 109, 4 (3.7%)	0.374
Any SAPT plus anticoagulant therapy, no. (%)	n = 109, 1 (0.9%)	n = 109, 3 (2.8%)	0.622
Any triple therapy, no. (%)	n = 109, 0 (0.0%)	n = 109, 1 (0.9%)	1.000
Antiplatelet/Anticoagulant therapy at 45 days			
No Antiplatelet/anticoagulant drugs, no. (%)	n =108, 5 (4.6%)	n =106, 6 (5.7%)	0.767
Any SAPT, no. (%)	n =108, 47 (43.5%)	n =106, 40 (37.7%)	0.407
Any DAPT, no. (%)	n =108, 49 (45.4%)	n =106, 55 (51.9%)	0.412
Any single-anticoagulant therapy, no. (%)	n =108, 5 (4.6%)	n =106, 2 (1.9%)	0.445
Any SAPT plus anticoagulant therapy, no. (%)	n =108, 2 (1.9%)	n =106, 3 (2.8%)	0.682
Any triple therapy, no. (%)	n =108, 0 (0.0%)	n =106, 0 (0.0%)	

LAAC, Left Atrial Appendage Closure; SD, Standard Deviation; IQR, interquartile range; PDL, Peridevice Leak; TEE, Transesophageal Echocardiography; SAPT, Single Antiplatelet Therapy; DAPT, Dual Antiplatelet Therapy.

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Table 3. Secondary imaging endpoints at 45 days after LAAC

	Amulet N = 111	**Watchman** N = 110	**Amulet vs Watchman Risk Ratio (95% CI)**	**P value**
45-day CCTA centrally assessed				
45day CCTA performed*, no. (%)	n = 111, 107 (96.4%)	n = 110, 101 (91.8%)		
Patent Appendage†, no. (%)	n = 105, 71 (67.6%)	n = 100, 70 (70.0%)	0.97 (0.80; 1.16)	0.713
IDL, no. (%)	n = 105, 47 (44.8%)	n = 100, 23 (23.0%)	1.95 (1.28; 2.95)	0.001
PDL, no. (%)	n = 105, 20 (19.0%)	n = 100, 20 (20.0%)	0.95 (0.55; 1.66)	0.863
MIL, no. (%)	n = 105, 4 (3.8%)	n = 100, 14 (14.0%)	0.27 (0.09; 0.80)	0.010
PDL or MIL, no. (%)	n = 105, 24 (22.9%)	n = 100, 34 (34.0%)	0.67 (0.43; 1.05)	0.077
PANVL, no. (%)	n = 105, 10 (9.5%)	n = 100, 21 (21.0%)	0.45 (0.22; 0.91)	0.022
Venous phase LAA patency‡, no.(%)	n = 97, 89 (91.8%)	n = 90, 83 (92.2%)	0.99 (0.91; 1.08)	0.906
Definite DRT, no. (%)	n = 107, 1 (0.9%)	n = 101, 3 (3.0%)	0.31 (0.03; 2.98)	0.285
Possible DRT, no. (%)	n = 107, 3 (2.8%)	n = 101, 7 (6.9%)	0.40 (0.11; 1.52)	0.164
Definite or possible DRT, no. (%)	n = 107, 4 (3.7%)	n = 101, 10 (9.9%)	0.38 (0.12; 1.17)	0.076
45-day TEE locally assessed				
45-day TEE performed, no. (%)	n = 111, 95 (85.6%)	n = 110, 91 (82.7%)		
Any PDL, no. (%)	n = 95, 13 (13.7%)	n = 91, 25 (27.5%)	0.50 (0.27; 0.91)	0.020
Multiple leaks, no. (%)	n = 95, 0 (0.0%)	n = 91, 2 (2.2%)		0.238
Largest PDL width (mm), mean	n = 13, 2.7 ± 0.8	n = 25, 2.2 ± 0.9		0.104
DRT, no. (%)	n = 95, 2 (2.1%)	n = 91, 5 (5.5%)	0.38 (0.08; 1.93)	0.225

* The images of three 45-day CCTAs were considered by the Imaging Core Lab not assessable for PA adjudication
† Patent Appendage was defined as LAA density ≥ 100 HU or ≥ 25% of that of the LA
‡ Venous phase LAA patency was defined as a LAA density ≥ 100 HU or ≥ 150% of that measured at the same site on arterial phase. In 21 CCTAs no venous phase was acquired
CCTA, Cardiac Computed Tomography Angiography; IDL, Intra-Device Leak; PDL, Peridevice Leak; MIL, MIxed Leak; PANVL, Patent Appendage with No Visible Leak; LAA, Left Atrial Appendage; DRT, Device Related Thrombus; TEE, Trans-Esophageal Echocardiography.

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Table 4. Clinical events at 45 days after LAAC

	Amulet N = 111	**Watchman** N = 110	**Amulet vs Watchman Risk ratio (95% CI)**	**P value**
Procedure-related events				
Any procedure-related complication*, no. (%)	n = 111, 36 (32.4%)	n = 110, 21 (19.1%)	1.70 (1.06;1.72)	0.023
Major procedure related complication†, no. (%)	n = 111, 10 (9.0%)	n = 110, 3 (2.7%)	3.30 (0.93; 11.68)	0.047
Death, no. (%)	n = 111, 2 (1.8%)	n = 110, 0 (0.0%)		0.498
Cerebrovascular event, no. (%)	n = 111, 2 (1.8%)	n = 110, 0 (0.0%)		0.498
Systemic or pulmonary embolism, no. (%)	n = 111, 1 (0.9%)	n = 110, 0 (0.0%)		1
Air embolism, no. (%)	n = 111, 2 (1.8%)	n = 110, 0 (0.0%)		0.498
Any bleeding, no. (%)	n = 111, 28 (25.2%)	n = 110, 15 (13.6%)	1.85 (1.05; 3.27)	0.03
-Minor bleeding (BARC 1-2), no. (%)	n = 111, 22 (19.8%)	n = 110, 13 (11.8%)	1.68 (0.89; 3.16)	0.103
-Major bleeding (BARC 3-5), no. (%)	n = 111, 8 (7.2%)	n = 110, 2 (1.8%)	3.96 (0.86; 18.25)	0.054
Any pericardial effusion (new onset)‡, no. (%)	n = 111, 19 (17.1%)	n = 110, 7 (6.4%)	2.69 (1.18; 6.14)	0.013
-non clinically relevant, no‡. (%)	n = 111, 16 (14.4%)	n = 110, 7 (6.4%)	2.27 (0.97; 5.29)	0.05
-clinically relevant‡, no. (%)	n = 111, 3 (2.7%)	n = 110, 0 (0.0%)		0.247
Vascular access site complication, no. (%)	n = 111, 6 (5.4%)	n = 110, 5 (4.5%)	1.19 (0.37; 3.78)	0.769
Device related complication, no. (%)	n = 111, 5 (4.5%)	n = 110, 6 (5.5%)	0.83 (0.26; 2.63)	0.745
Acute kidney injury, no. (%)	n = 111, 0 (0.0%)	n = 110, 0 (0.0%)		
Non procedure-related events				
Death, no. (%)	n = 111, 0 (0.0%)	n = 110, 4 (3.6%)		0.06
Cardiovascular death, no. (%)	n = 111, 0 (0.0%)	n = 110, 4 (3.6%)		0.06
Cerebrovascular event, no. (%)	n = 111, 0 (0.0%)	n = 110, 2 (1.8%)		0.247
Systemic or pulmonary embolism, no. (%)	n = 111, 0 (0.0%)	n = 110, 1 (0.9%)		0.498
Any bleeding, no. (%)	n = 111, 8 (7.2%)	n = 110, 10 (9.1%)	0.79 (0.33; 1.93)	0.609
-Minor bleeding (BARC 1-2), no. (%)	n = 111, 7 (6.3%)	n = 110, 6 (5.5%)	1.16 (0.4; 3.33)	0.788
-Major bleeding (BARC 3-5), no. (%)	n = 111, 1 (0.9%)	n = 110, 5 (4.5%)	0.2 (0.02; 1.67)	0.096
All clinical events at 45 days after LAAC				
Composite of CV death, stroke or systemic embolism, no. (%)	n = 111, 3 (2.7%)	n = 110, 5 (4.5%)	0.59 (0.15; 2.43)	0.463
Composite of death, stroke, systemic or pulmonary embolism and spontaneous MI, no. (%)	n = 111, 4 (2.7%)	n = 110, 5 (4.5%)	0.80 (0.22; 2.87)	0.723
Death, no. (%)	n = 111, 2 (1.8%)	n = 110, 4 (3.6%)	0.50 (0.09; 2.72)	0.409
Cardiovascular death, no. (%)	n = 111, 2 (1.8%)	n = 110, 4 (3.6%)	0.50 (0.09; 2.72)	0.409
Cerebrovascular event, no. (%)	n = 111, 2 (1.8%)	n = 110, 2 (1.8%)	1.00 (0.14; 7.16)	0.998
-Stroke, no. (%)	n = 111, 2 (1.8%)	n = 110, 2 (1.8%)	1.00 (0.14; 7.10)	0.996
Ischaemic stroke, no. (%)	n = 111, 2 (1.8%)	n = 110, 1 (0.9%)	2.00 (0.18; 22.30)	0.565
Haemorrhagic stroke, no. (%)	n = 111, 0 (0.0%)	n = 110, 1 (0.9%)		0.498
-TIA, no. (%)	n = 111, 0 (0.0%)	n = 110, 0 (0.0%)		
Systemic or pulmonary embolism, no. (%)	n = 111, 1 (0.9%)	n = 110, 1 (0.9%)	0.99 (0.06; 16.04)	0.995
Myocardial infarction, no. (%)	n = 111, 0 (0.0%)	n = 110, 0 (0.0%)		
Any bleeding, no. (%)	n = 111, 36 (32.4%)	n = 110, 25 (22.7%)	1.43 (0.92; 2.21)	0.107
-Minor bleeding (BARC 1-2), no. (%)	n = 111, 29 (26.1%)	n = 110, 19 (17.3%)	1.51 (0.9; 2.53)	0.11
-Major bleeding (BARC 3-5), no. (%)	n = 111, 9 (8.1%)	n = 110, 7 (6.4%)	1.27 (0.49; 3.3)	0.617
Any pericardial effusion (new onset), no. (%)	n = 111, 22 (19.8%)	n = 110, 8 (7.3%)	3.09 (1.32; 7.27)	0.006
-non clinically relevant, no. (%)	n = 111, 18 (16.2%)	n = 110, 8 (7.3%)	2.23 (1.01; 4.91)	0.039
-clinically relevant, no. (%)	n = 111, 4 (3.6%)	n = 110, 0 (0.0%)		0.122

* Procedure-related complications are defined as the composite of death, cerebrovascular event, systemic or pulmonary embolism, air embolism, any bleeding, any pericardial effusion, vascular access complication, device related complication or acute kidney injury occurring within 7 days or thereafter if deemed procedure-related. The definition of each component is detailed in the Supplement.

† Major procedure related complications are defined as composite of death, cerebrovascular event, systemic embolism, major bleeding (BARC 3-5), clinically relevant pericardial effusion, device embolization, or acute kidney injury occurring within 7 days or thereafter if deemed procedure-related. The definition of each component is detailed in the Supplement.

‡In the Amulet group 19 events occurred within 7 days and 3 beyond 7 days after LAAC; in the Watchman group, 7 events occurred within 7 days and one beyond 7 days after LAAC.

BARC, Bleeding Academic Research Consortium; CV, Cardiovascular; TIA, Transient Ischemic Attack.

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Figures Legends

Figure 1.

Classification of LAA based on 45-day CCTA assessment. If LAA density measured distal to the device ≥ 100 HU or ≥ 25% of that of the LA, LAA was defined as patent LAA (PA), otherwise non patent LAA (NPA). PA were considered PAVL if a leak, defined as continuity of contrast between LA and LAA, was visualized through the device (IDL) or at the device sides (gap leaks) along the entire (PDL) or a portion (MIL) of the length of the device; the remaining PAs without visible leak were considered PANVL.

LAA, left atrial appendage; CCTA, cardiac computed tomography angiography; HU, linear attenuation coefficient; LA, left atrium; PA, patent LAA; NPA, non-patent LAA; PAVL, patent appendage with visible leak; PDL, peridevice leak; IDL, intradevice leak; MIL, mixed leak; PANVL, patent appendage with no visible leak.

Circulation

Figure 2. SWISS-APERO flowchart.

Flow diagram of the progress through the study (screening, enrolment, allocation, exclusion or withdrawal, and follow-up). *n=1 LAAC procedure randomized to Amulet had to be aborted after several attempts with Amulet 28mm and Amulet 25mm devices due to pericardial effusion needing percutaneous drainage; patient deceased before 45 days visit. ¥n=3 patients randomized to Amulet implanted Watchman FLX. In only one case first operator attempted Amulet implantation (Amulet 34mm) without reaching acceptable device stability before successfully implanting Watchman FLX 35mm, as a consequence it was adjudicated by CEC as justified crossover. ¶n=1 Amulet and n=1 Watchman/FLX performed 45-day CCTA without contrast medium due to kidney dysfunction whereas in n=1 Amulet patient the arterial phase imaging was not captured correctly.

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LAAC, left atrial appendage closure; LAA, left atrial appendage; CCTA, cardiac computed tomography angiography.

Figure 3. Primary endpoint analysis.

The 45-day CCTA images of 93% of study population were considered for primary endpoint analysis. The rate of PA was similar between the two groups. However, the underlying mechanisms significantly differ between the two arms with IDL prevailing in Amulet and MIL and PANVL in Watchman/FLX.

CCTA, cardiac computed tomography angiography; RR, risk ratio; PANVL, patent appendage with no visible leak; IDL, intradevice leak; MIL, mixed leak; PDL, peridevice leak.

Figure 4. Graphical Abstract of SWISS-APERO Trial.

Summary of the main findings of the study.

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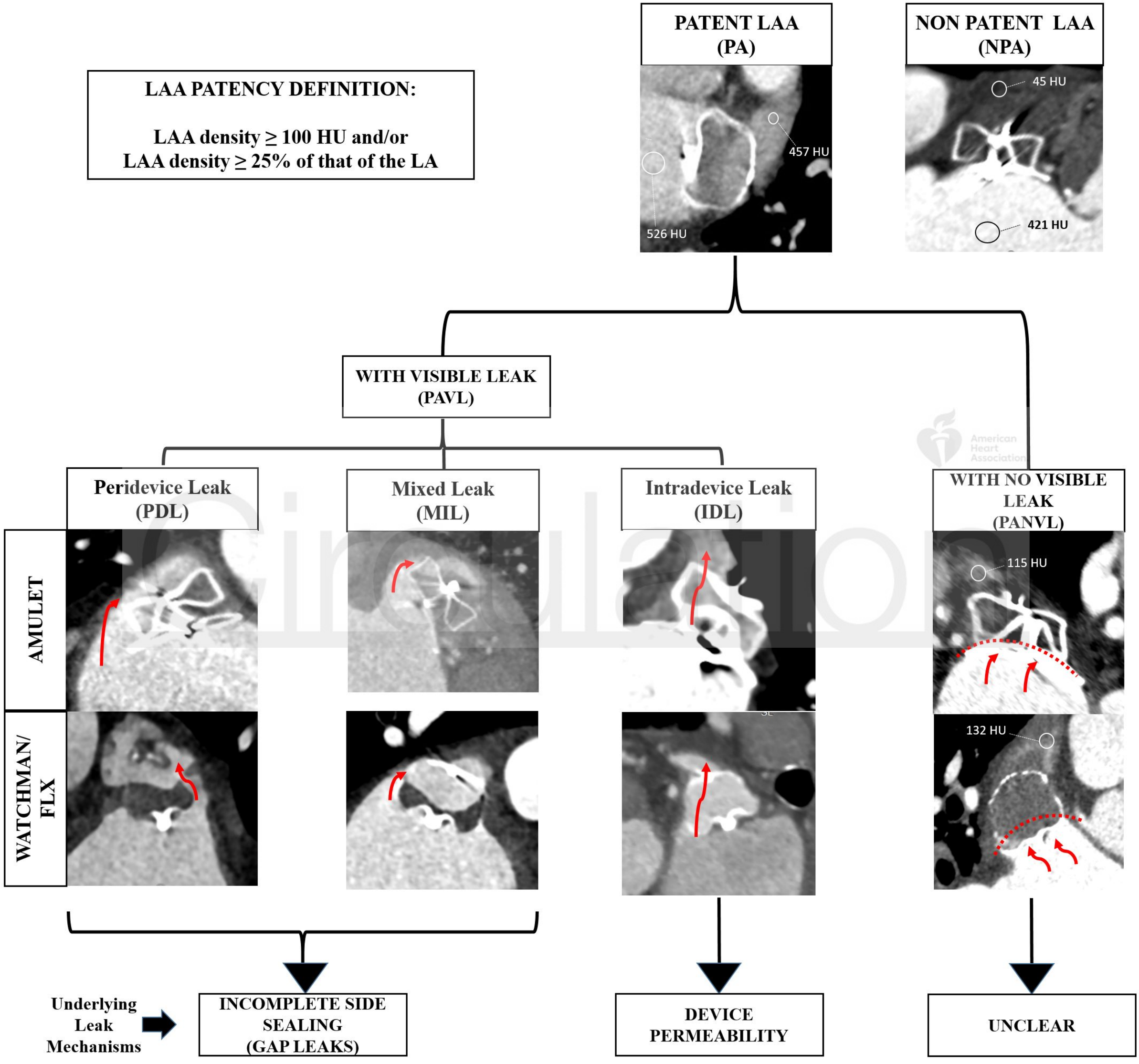

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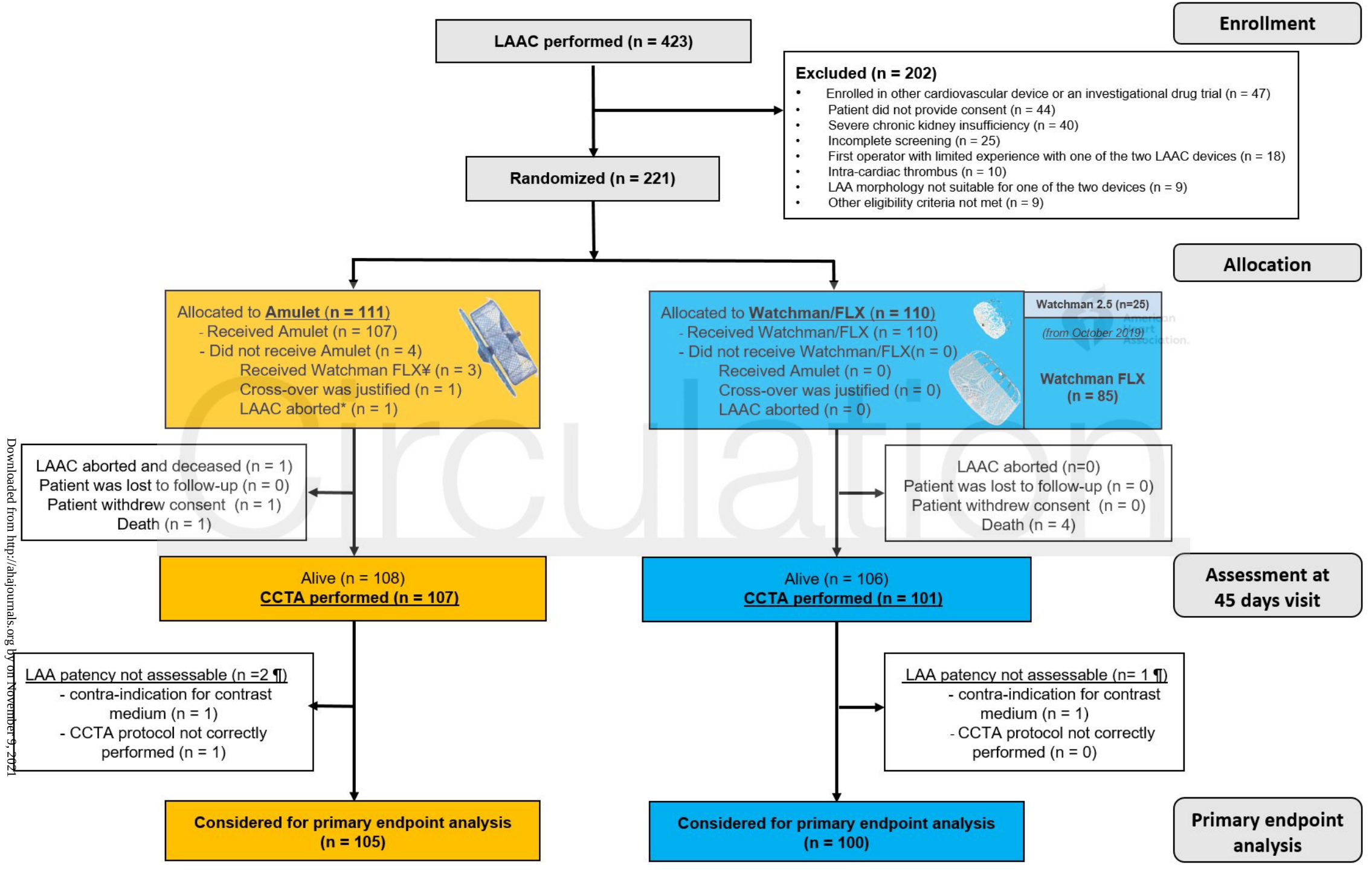

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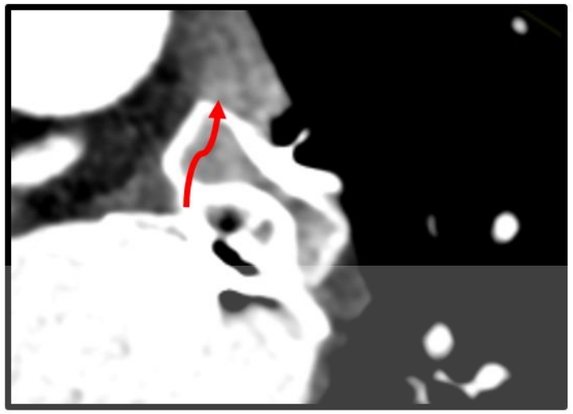
PATENT APPENDAGE Rates at 45-day CCTA

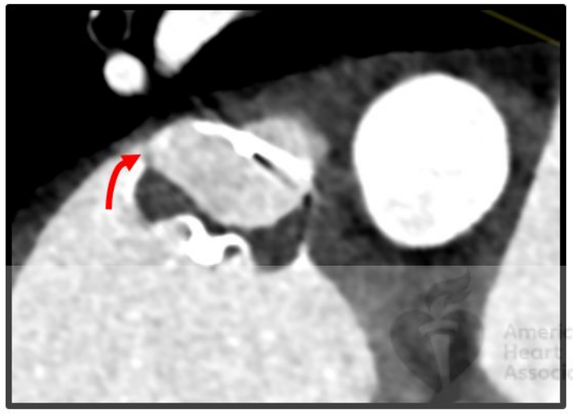
AMULET
67.6%
(n=71/105)

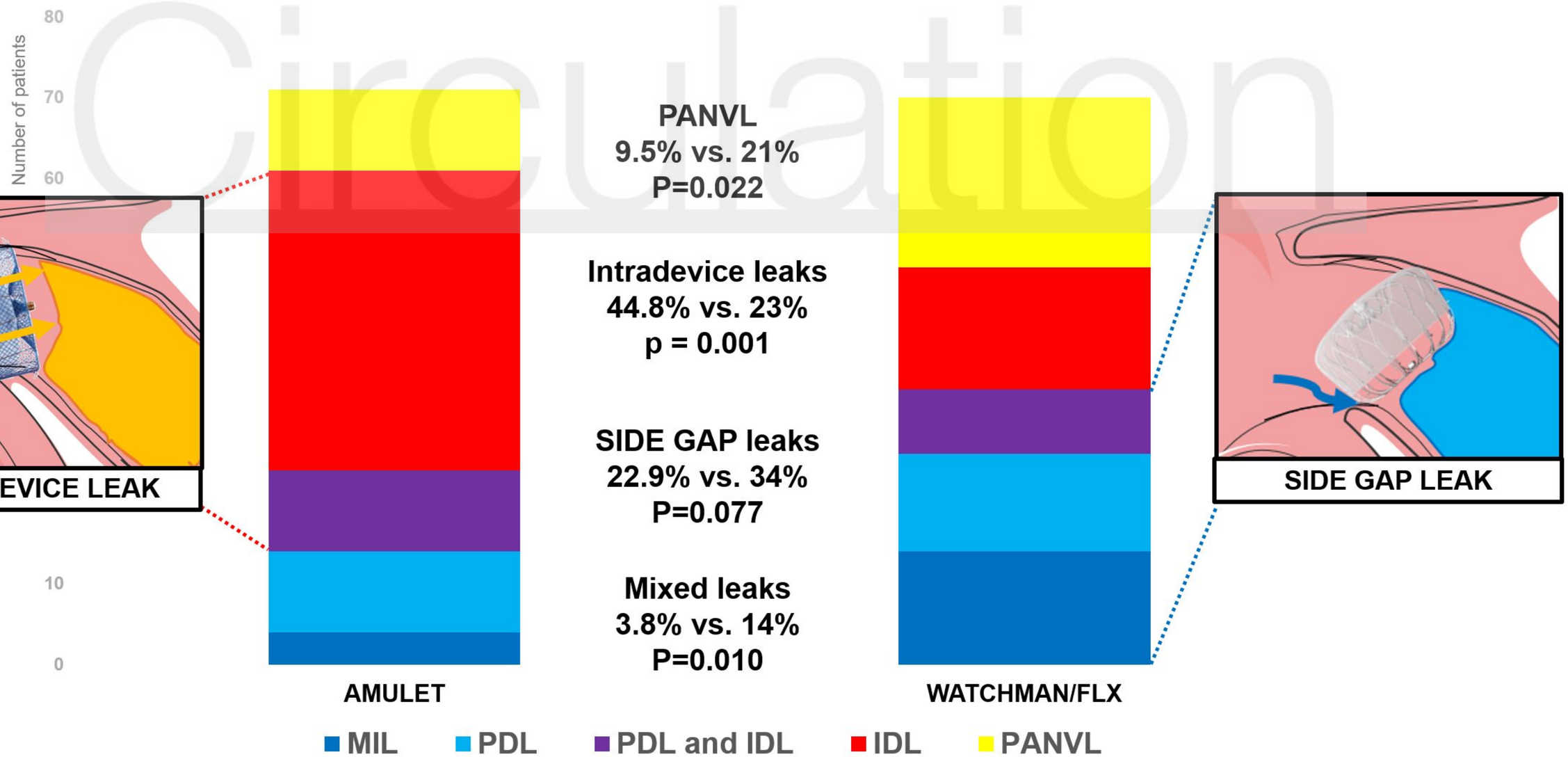
VS.

WATCHMAN/FLX
70%
(n=70/100)



RR(95%CI):
0.97 (0.80-1.16);
p value = **0.713**





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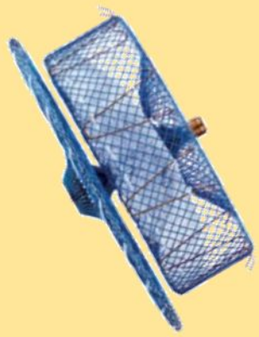
221 Patients with High Risk AF and Clinical Indication to LAAC

Aged **76.9** (± 7.8) years

29.4% women

39.4% with prior stroke/TIA
CHA2DS2VASC Score **4.3 ± 1.4**

87.8% with prior relevant bleeding
HASBLED Score **3.1 ± 0.9**



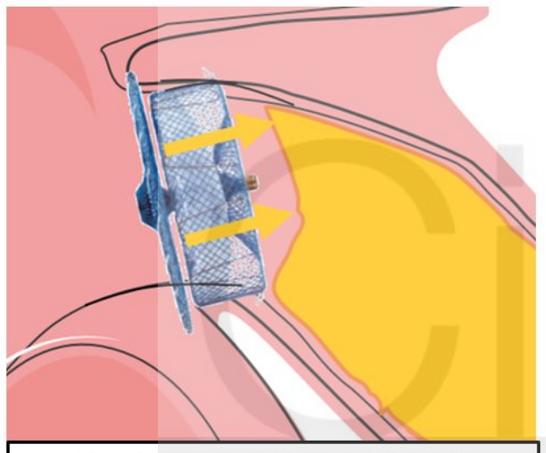
RANDOMIZED

Watchman 2.5
(n=25)
BEFORE October 2019

AMULET
(n=111)

WATCHMAN FLX
(n=85)

45-day LAA Patency

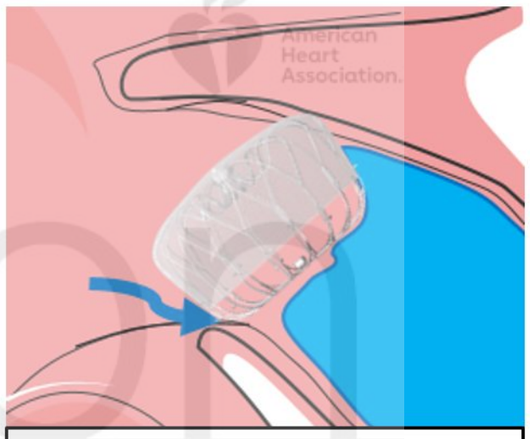


INTRADEVICE LEAK

44.8% vs. 23%; p= 0.001

CCTA
(Primary Endpoint)

67.6% = **70%**



MIXED LEAKS

3.8% vs. 14%; p=0.010

Peridevice Leak **13.7%** < **TEE** (Secondary Endpoint) < **27.5%** **Peridevice Leak**

Clinical outcomes
(Secondary Endpoints)

Major Bleeding 7.2%
Cardiac Tamponade 2.7%
9.0% > **Procedural Complications** > **2.7%**
1.8% Major Bleeding
0% Cardiac Tamponade

CVD/Stroke/SE **2.7%** = **45-day clinical outcomes** = **4.5%** **CVD/Stroke/SE**
Major Bleeding **8.1%** = = **6.4%** **Major Bleeding**

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