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# Left atrial appendage closure with the II generation Ultraseal device: An international registry. The LIGATE study

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## Abstract

**Objectives:** To assess feasibility and safety of second-generation left atrial appendage closure (LAAC) Ultraseal device in patients with nonvalvular atrial fibrillation (NVAF).

**Background:** LAAC with first-generation Ultraseal device (Cardia, Eagan, Minnesota) has been shown to be a feasible therapeutic option in patients with NVAF. However, there is a paucity of data regarding the novel second-generation Ultraseal device.

**Methods:** All patients with NVAF undergoing second-generation Ultraseal device implantation between February 2018 and September 2020 were included in a multicenter international registry. Periprocedural and post-discharge events were collected through 6-month follow-up. Co-primary efficacy endpoints were device success and technical success while primary safety endpoint was in-hospital major adverse event (MAE) occurrence.

**Results:** A total of 52 patients were included: mean age 75 ± 8, 30.8% women, mean HAS-BLED 3 ± 1. The device was successfully implanted in all patients. Technical success was achieved in 50 patients (96.1%). In-hospital MAEs occurred in three patients (5.8%). The incidence of 6-month all-cause death and major bleeding was 11.6% and 2.1%, respectively. No strokes, transient ischemic attacks, systemic embolisms, or device embolization were reported after discharge.

**Conclusions:** Second-generation Ultraseal device implantation was associated with high success rates and a low incidence of peri-procedural complications. Larger studies with longer follow-up are warranted to further evaluate the safety and the efficacy of this device, especially at long-term follow-up.

## 1 | INTRODUCTION

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia[1] and about one out of three subjects will experience at least one episode by the age of 55 years.[2] AF confers a five-fold increased risk of ischemic stroke which partially explains the poor survival rate of this patient subset.[3] Of note, left atrial appendage (LAA) is the most common site of thrombus formation whose embolization into the systemic circulation may cause stroke.[4] Although oral anticoagulants (OACs) have been shown to reduce the incidence of stroke and all-cause mortality, they are associated with a significant bleeding risk.[5–7] Because of this concern, OACs are currently underprescribed by physicians and patients' adherence to medication compliance remains poor.[8] Furthermore, people ≥75 years old, who are known to be at high risk of bleedings, are also expected to represent the majority of AF patients in the forthcoming years with an impact on the occurrence of such complication and underscoring the importance of bleeding avoidance strategy.[9–11]

Left atrial appendage closure (LAAC) might represent a valid alternative to chronic OAC for stroke prophylaxis in patients with nonvalvular AF[12] and may be considered in those with a contraindication to OAC as recommended by current international guidelines (class of recommendation IIb, level of evidence B in the European guidelines; class of recommendation IIb, level of evidence B-Not Randomized in the American guidelines).[13,14]

Among available devices,[15] the Ultraseal (CARDIA Inc.) is a self-expandable bulb-and-sail device designed for transcatheter LAAC. If the first generation has been evaluated in a prior small registry providing good short-term efficacy and safety profile,[16] there is little data regarding the second generation of this novel device.[17] Therefore, our aim was to evaluate the feasibility and safety profile of the second-generation Ultraseal LAAC device in patients with nonvalvular AF.

## 2 | MATERIALS AND METHODS

### 2.1 | Study population

The LAAC with the II generation Ultraseal device (LIGATE) was an investigator-initiated, retrospective, single-arm study across seven centers in Europe.

Subjects meeting all the following criteria were eligible: (1) nonvalvular AF, (2) undergoing an attempt of LAAC with the second-generation Ultraseal device, and (3) age >18 years old. No exclusion criteria were applied. The study protocol complied with the Declaration of Helsinki and was approved by the Institutional Review Boards or ethics committees of the individual collaborating sites. Each patient provided informed consent for participation in the study.

### 2.2 | Data collection, endpoint, and event adjudication

Baseline, periprocedural, and post-discharge events were systematically collected in each participating center and the anonymized data were sent to the study coordinators for analysis. Transthoracic echocardiography was performed before discharge and clinical follow-up was performed by visit or telephone contact. Transesophageal echocardiographic (TEE) follow-up was routinely performed in four of the seven centers involved. In the remaining three centers, TEE was only performed if clinically indicated and routine follow-up otherwise included transthoracic echocardiography only. The co-primary efficacy endpoints were (1) device success, defined as successful device deployment and implantation in the correct position, and (2) technical success, defined as LAA exclusion in the absence of device-related complications (device embolization, erosion, interference with surrounding structures, thrombus, fracture, infection, perforation, or allergy) and additionally, no leak >5 mm on color Doppler TEE during the procedure at index hospitalization, in accordance with the Munich consensus statement.[18] Peri-device leak severity was graded measuring the diameter of the color jet around the sail: trace (<1 mm), mild (1–3 mm), moderate (3–5 mm), and severe (>5 mm).[18,19]

The primary safety outcome was in-hospital major adverse event (MAE), a composite of all-cause death, stroke or transient ischemic attack, systemic embolism, major bleeding (defined as type ≥3 of Bleeding Academic Research Consortium),[20] myocardial infarction, major vascular complication according to the Valve Academic Research Consortium criteria,[21] or device embolization. Secondary study endpoints were procedural success (defined as technical success plus absence of procedure-related complications)[18] as well as the individual endpoints of the composite and cardiovascular events during follow-up, including death, stroke, transient ischemic attack, systemic embolization, major bleeding, and device-related complications.

### 2.3 | Device characteristics and implantation

The second-generation Ultraseal LAA occluder is a self-expandable nitinol device composed of three main parts, namely a distal bulb with 12 hooks, a proximal sail, and an articulating joint. The device is available in 10 sizes, ranging from 16 to 34 mm, and is provided with distal radiopaque markers. In the second-generation Ultraseal LAA occluder, the distal center post has been removed from the bulb, making the bulb more flexible with a lower radial force as compared with the first-generation device. In addition, the overall length of the device has been decreased from 15 to 21 mm to 10 to 18 mm. Finally, the sail covering has been modified inverting the polyester layer (now

proximal). Device characteristics are depicted in Figure 1, enlightening main differences between second- and first-generation . Main procedural steps are described below.

The introducer allows the introduction of the device into the delivery sheath, which ranges from 9F to 12F and is available in a single 45° or double 45° × 45° preformed curve. The delivery forceps hold the device from a knob in the center of the proximal sail. Under TEE and fluoroscopic guidance, transeptal puncture is performed. Preprocedural TEE and computed tomography together with the intraprocedural echocardiographic exam and angiography allow operator to choose the right device size, measuring the maximum diameter at the intended landing zone. A bulb-to-landing zone oversizing of 10%–20% is recommended and a minimum LAA depth of 12 mm is ideal. After having positioned the sheath in correspondence of the landing zone, the bulb is released. The sail is then easily deployed by pulling back on the sheath; forceps may be gently retracted to check device stability at any time. After angiographic and echocardiographic sealing assessment, if stability or sealing are deemed to be unsatisfactory the operator can partially or totally retrieve and reimplant the device up to five times. After having achieved the optimal result, opening the forceps releases the device for final deployment; Figure 2 shows angiography and echocardiographic monitoring during LAAC with second-generation Ultraseal LAA occluder. Although it is technically feasible to retrieve the device more than five times, it is suggested that a different device or another size should be used in these situations.

In the present study, all operators were interventional cardiologists with previous experience in LAAC (>25 procedures). The antithrombotic therapy during the procedure and follow-up was left to the operator's preference.

## 2.4 | Statistical analysis

Categorical data are reported as percentages (counts divided by the number of patients who could be evaluated). Continuous variables are reported as mean ± standard deviation or median and interquartile range (IQR). Survival curves for the secondary endpoints were constructed for time-to-event variables using Kaplan–Meier estimates. STATA version 16.0 (StataCorp) was used to perform the statistical analysis.

## 3 | RESULTS

### 3.1 | Baseline clinical and procedural characteristics

A total of 52 consecutive patients from seven European centers were included between February 2018 and September 2020. Main baseline clinical characteristics of the population are listed in Table 1 while anti-thrombotic therapy at discharge is reported in Table 2. Mean age was 75 ± 8 years, and 30.8% were women. The mean congestive heart failure history, hypertension history, age ≥75 years, diabetes mellitus, prior stroke or transient ischemic attack, vascular disease, age 65–74 years, sex category (CHA$_2$-DS$_2$-VASc) score was 4 ± 1, with a mean hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly, drugs/alcohol (HAS-BLED) score of 3 ± 1. Most patients had a history of bleeding (80.1%); only 11 patients (21.2%) had a history of ischemic stroke. Half of the patients suffered from chronic kidney disease, with a high prevalence of patients on dialysis (15.4%). Most patients (84.6%) were discharged on dual antiplatelet therapy (DAPT) that was recommended for a duration of 1 and 3 months in 34.1% and 52.3% of the cases, respectively. Three patients were discharged on single antiplatelet therapy, three on OACs, and three on low-molecular-weight heparin. None was discharged on warfarin. One patient with history of intracranial bleeding was discharged without anti-thrombotic treatment.

Procedural details are reported in Table 3. All the procedures were performed under TEE guidance. The mean device size was 23.8 ± 3.5 mm, with a mean oversizing of 29 ± 20%. No retrieval of the device was required in 36 (69.2%) cases, while 1 to 3 retrievals were performed in 16 (30.8%) cases before the final release. Only one device was used in 49 (94.2%) procedures, while a second device
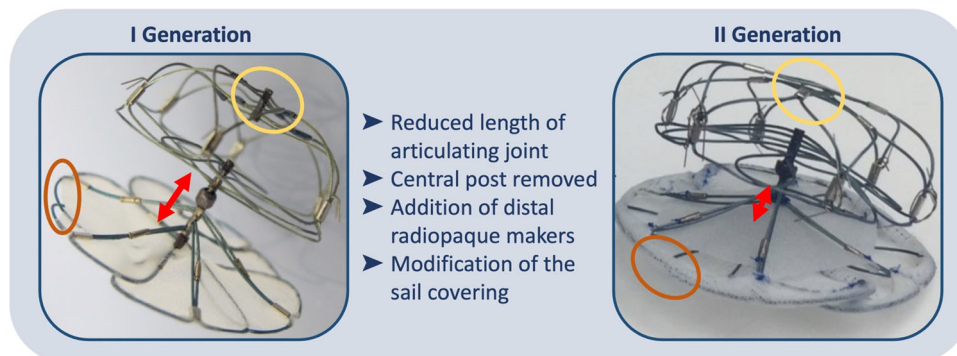


**FIGURE 1** First- and second-generation Ultraseal device for left atrial appendage closure. Comparison of first- and second-generation Ultraseal device. [Color figure can be viewed at wileyonlinelibrary.com]
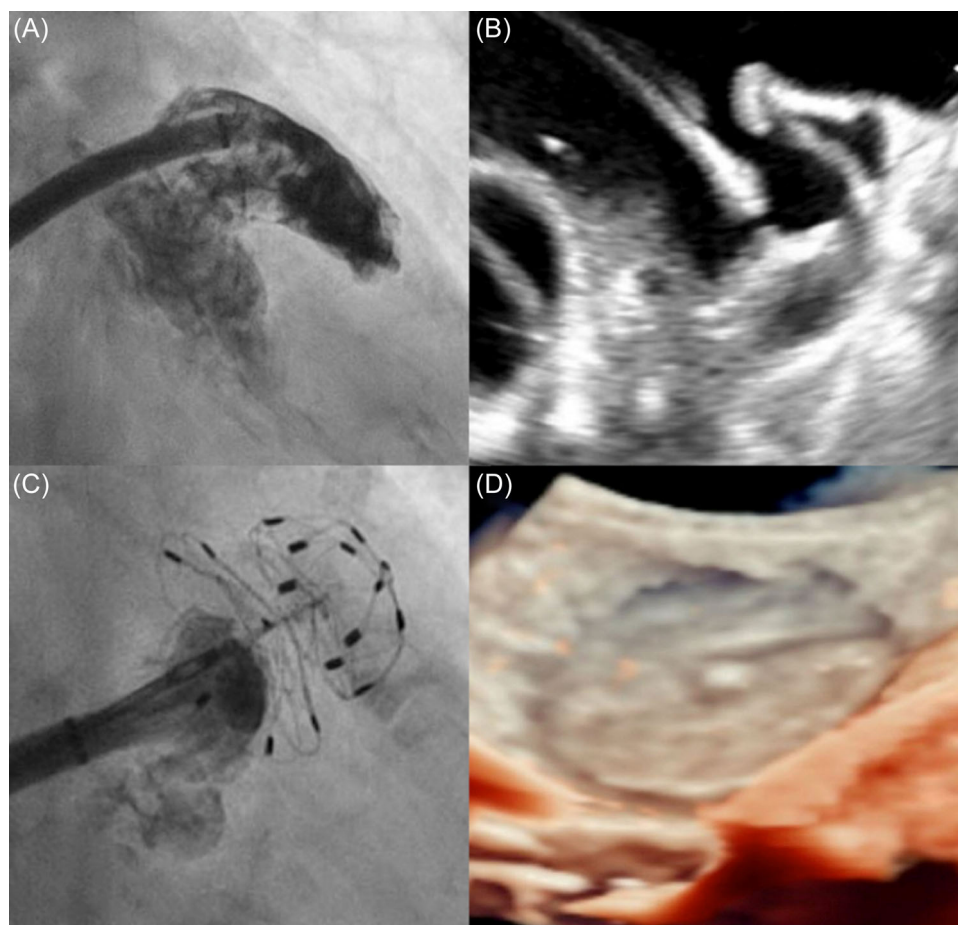
**FIGURE 2** Left atrial appendage (LAA) closure with second-generation Ultraseal device. (A) LAA angiography. (B) Transesophageal guidance for device positioning. (C) Angiography showing correct LAA sealing. (D) Transesophageal echocardiography 3D reconstruction showing correct LAA sealing. [Color figure can be viewed at wileyonlinelibrary.com]

resizing occurred in 3 (5.8%) procedures. At the end of the procedure, two significant (i.e., ≥moderate) residual leaks were observed at TEE: one (1.9%) moderate and one (1.9%) severe.

## 3.2 | In-hospital outcomes

Main outcomes during index hospitalization are summarized in Table 4. Device success was accomplished in all 52 cases (100%), while technical success was achieved in 50 (96.1%) cases due to one severe leak and one patient who experienced a device-related complication (i.e., perforation). In-hospital MAE occurred in three patients (5.8%): one patient had a minor stroke, and two patients had a major bleeding. Of note, MAE occurred in all those patients who did not achieve technical success: the minor stroke occurred in the patient with the severe leak assessed at the end of the procedure, while the device-related perforation caused pericardial effusion which eventually required pericardiocentesis. As a result, procedural success was achieved in 49 (94.2%) of patients. During hospitalization, there were no episodes of myocardial infarction, device

embolization, major vascular complications, or death. Median hospital stay after procedure was 2 days (IQR: 1–7 days).

## 3.3 | Outcomes during follow-up

Clinical outcomes and trans-esophageal echocardiographic findings at follow-up are reported in Table 5. Follow-up was available for 48 out of 52 patients (92.3%), median 117 (IQR: 57–219) days. The incidence of cardiovascular events at 6-month follow-up was 11.6%. Three patients died: one experienced fatal bleeding at Day 27 while still on DAPT, one died from cardiogenic shock at Day 149, and the remaining patient died at Day 135 after femur fracture. None of the deaths were considered related to the device, and no device-related adverse events occurred during follow-up. Among the 43 patients with an echocardiographic follow-up (median follow-up: 79 days; IQR: 47–182 days), 34 underwent TEE (median follow-up: 61 days; IQR: 47–125 days). Peri-device leak was detected in 5 (14.7%) patients but only one (2.9%) of those was classified as severe (>5 mm). In the remaining eight patients evaluated with transthoracic

**TABLE 1** Baseline clinical characteristics

| Baseline and demographic characteristics (N = 52) | |
| --- | --- |
| Age, years | 75 ± 8 |
| Women | 16 (30.8) |
| Hypertension | 46 (88.5) |
| Diabetes mellitus | 12 (23.1) |
| Dyslipidemia | 28 (53.8) |
| Coronary artery disease | 25 (48.1) |
| Congestive heart failure | 19 (36.5) |
| LVEF, % | 53 ± 7.5 |
| Peripheral artery disease | 6 (11.5) |
| Chronic kidney disease | 26 (50) |
| Dialysis | 8 (15.4) |
| Anemia | 22 (42.3) |
| *Atrial fibrillation type* | |
| Paroxysmal | 14 (26.9) |
| Persistent/permanent | 38 (73.1) |
| Prior stroke | 11 (21.2) |
| Prior transient ischemic attack | 12 (23.1) |
| Prior bleeding | 42 (80.1) |
| CHA$_2$-DS$_2$-VASc score | 4 ± 1 |
| HAS-BLED score | 3 ± 1 |

*Note*: Values are mean ± standard deviation, median (interquartile range), or number (%).

Abbreviations: CHA$_2$-DS$_2$-VASc, congestive heart failure history, hypertension history, age ≥75 years, diabetes mellitus, prior stroke or transient ischemic attack, vascular disease, age 65–74 years, sex category; HAS-BLED, hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly, drugs/alcohol; LVEF, left ventricular ejection fraction.

**TABLE 2** Antithrombotic treatment at discharge

| Discharge antithrombotic treatment (N = 52) | |
| --- | --- |
| None | 1 (1.9) |
| Single antiplatelet therapy | 3 (5.8) |
| DAPT | 44 (84.6) |
| *DAPT duration, months* | |
| 1 | 15 (34.1) |
| 3 | 23 (52.3) |
| 6 | 5 (11.4) |
| 12 | 1 (2.3) |
| Direct oral anticoagulant | 3 (5.8) |
| Low-molecular-weight heparin | 3 (5.8) |

*Note*: Values are number (%).

Abbreviation: DAPT, dual antiplatelet therapy.

**TABLE 3** Procedural characteristics

| Procedural characteristics (N = 52) | |
| --- | --- |
| *LAA morphology* | |
| Chicken-wing | 22 (42.3) |
| Windsock | 13 (25) |
| Cactus | 9 (17.3) |
| Cauliflower | 5 (9.6) |
| LAA ostium, mm | 20.8 ± 3.1 |
| LAA landing zone, mm | 18.7 ± 3.6 |
| LAA length, mm | 27.2 ± 6.3 |
| *Device size, mm* | |
| 16 | 2 (3.9) |
| 18 | 4 (7.7) |
| 22 | 14 (26.9) |
| 24 | 17 (32.7) |
| 26 | 7 (13.5) |
| 28 | 3 (5.8) |
| 30 | 4 (7.7) |
| 32 | 1 (1.9) |
| Oversizing, % | 29 ± 20 |
| *Number of devices per procedure* | |
| 1 | 49 (94.2) |
| 2 | 3 (5.8) |
| *Number of retrievals* | |
| 0 | 36 (69.2) |
| 1 | 10 (19.2) |
| 2 | 5 (9.6) |
| 3 | 1 (1.9) |
| Contrast volume, ml | 84 ± 74 |
| Procedure time, min | 87 ± 43 |
| *Residual leak at the end of the procedure* | |
| Moderate (3–5 mm) | 1 (1.9) |
| Severe (>5 mm) | 1 (1.9) |

*Note*: Values are mean ± standard deviation or number (%).

Abbreviation: LAA, left atrial appendage.

echocardiography during follow-up, there were no residual leaks. No thrombosis or fractures of the device were observed in the study.

## 4 | DISCUSSION

This study reports the first experience of transcatheter LAAC with the second-generation Ultraseal device in patients suffering from nonvalvular AF across seven European centers. Device success was

**TABLE 4** Procedural results and in-hospital outcomes

| Procedural results and in-hospital outcomes (N = 52) | |
| --- | --- |
| *Procedural results* | |
| Device success[a] | 52 (100) |
| Technical success[b] | 50 (96.1) |
| Procedural success[c] | 49 (94.2) |
| *In-hospital outcomes* | |
| MAEs[d] | 3 (5.8) |
| Death | 0 |
| Stroke | 1 (1.9) |
| Transient ischemic attack | 0 |
| Major bleeding (BARC type ≥3) | 2 (3.8) |
| Pericardial effusion requiring pericardiocentesis | 1 (1.9) |
| Myocardial infarction | 0 |
| Major vascular complications (VARC-2) | 0 |
| Device embolization | 0 |
| Hospital length of stay, days | 2 (1–7) |

*Note*: Values are median (interquartile range) or number (%).

Abbreviations: BARC, Bleeding Academic Research Consortium; LAA, left atrial appendage; MAE, major adverse event; TEE, transesophageal echocardiography; VARC, Valve Academic Research Consortium.

[a]Device success was defined as successful device implantation in correct position.

[b]Technical success was defined as LAA exclusion in the absence of device-related complications (device embolization, device erosion, interference, thrombus, fracture, infection, perforation, allergy) and no leak >5 mm on color Doppler TEE during the procedure and index hospitalization.

[c]Procedural success was defined as technical success plus absence of procedure-related complications.

[d]In-hospital MAEs were the composite of all-cause death, stroke, or transient ischemic attack, systemic embolism, major bleeding (defined as type ≥3 of BARC),[17] myocardial infarction, major vascular complication according to the VARC- criteria,[18] or device embolization.

**TABLE 5** Events at follow-up

| Adverse events at 6-month follow-up (N= 48) | |
| --- | --- |
| Follow-up duration, days | 117 (57–219) |
| Cardiovascular events[a] | 3 (11.6) |
| All-cause death[a] | 3 (11.6) |
| Cardiovascular death[a] | 1 (5.0) |
| Stroke[a] | 0 |
| Transient ischemic attack[a] | 0 |
| Systemic embolism[a] | 0 |
| Device embolization[a] | 0 |
| Major bleeding[a] | 1 (2.1) |
| *TEE findings (N = 34)* | |
| Residual leak | 5 (14.7) |
| Trace (<1 mm) | 0 |
| Mild (1–3 mm) | 3 (8.8) |
| Moderate (3–5 mm) | 1 (2.9) |
| Severe (>5mm) | 1 (2.9) |
| Device-related thrombosis | 0 |

*Note*: Values are median (interquartile range) or number (%).

Abbreviation: TEE, transesophageal echocardiography.

[a]Event rates are Kaplan–Meier estimates.

achieved in all 52 (100%) of patients enrolled, and technical success was achieved in 50 (96.1%) of them. These efficacy outcomes compare favorably with those of the first generation of the Ultraseal device reported by Asmarats et al., namely 96.8% and 94.4%, respectively.[16]

The Ultraseal device is inspired by the "pacifier" principle (i.e., endovascular delivery of a device with a lobe or anchor and an additional disc to seal the ostium of the LAA from the left atrial side). Specifically, the second-generation Ultraseal consists of a distal bulb, which anchors the device in the LAA landing zone, and a larger proximal sail, which conforms to the LAA ostium achieving isolation of the LAA from the atrial cavity after its endothelialization. The bulb and the sail are connected by an articulating joint. Although both generations of the Ultraseal device can be recaptured up to five times, the second-generation device incorporates some iterations that may increase device success rate: the articulating joint has a lesser degree of movement to facilitate the deployment and retrieval, while the distal center post has been removed so that the bulb is more flexible with a lower radial force allowing for less dependence on oversizing and a safer deep implant. These two modifications reduce the overall length of the device (from 15 to 21 mm of the first generation to 10 to 18 mm of the second generation) and therefore the minimum required length of the LAA (from 16 to 12 mm). Finally, the sail covering has been modified inverting the polyester layer making it the luminal surface of the LAA ostium. Whether these iterations actually translate into better procedural outcomes has not previously been studied, however, in this first experience, results are encouraging. The distal anchoring bulb of the Ultraseal device is not covered by fabric as compared with other devices inspired by the "pacifier" principle, such as the Amplatzer Amulet (Abbott Medical). This is noteworthy, because the covered bulb, acting as a second closure mechanism, is considered to explain the superior LAAC rate of the Amplatzer Amulet compared to the Watchman occluder (Boston Scientific), not featuring the "pacifier" principle.[23] However, in the SWISS-APERO and Amulet-IDE randomized controlled trials, the Amplatzer Amulet had also been associated with the downside of more procedural-related complications, namely pericardial effusions and device embolization.[24,25] If the flexible and uncovered distal bulb of the second-generation Ultraseal device might provide a better trade-off (between LAAC and procedural-related complication risk) is unknown and needs to be prospectively tested in an adequately powered randomized controlled trial. Furthermore,

compared to the Amplatzer Amulet, provided with a stretchable nitinol connector, the articulating joint of the Ultraseal device is more rigid and may limit the successful implantation in most complex anatomies. Still, we herein report a device success of 100% despite different LAA morphologies.

As it relates to thrombogenicity of the new device, there was one periprocedural minor stroke occurring after technical failure because of severe leak but no device-related thrombosis, stroke, or transient ischemic attacks occurred during follow-up. In the prior experience with the first-generation Ultraseal device, Asmarts et al. reported an incidence of device-related thrombosis of 5.6% and an incidence of stroke/TIA of 1.6% through a similar follow-up.[16]

Intrahospital MAEs occurred in 5.8% of the patients, higher than the rate reported by Asmarts et al. (i.e., 2.4%),[16] but in line with the initial experience with other LAA occluders (from 3.3% to 8.7%).[12] We observed a rather high incidence of all-cause death (11.6%), however, none of these events were related to the device or the procedure performed. More specifically, one of the deaths was secondary to a fatal bleeding event that occurred while the patient was on DAPT. In the present study, most patients were discharged on DAPT, which was continued for at least 3 months following the procedure. In this period, patients are actually at high risk of bleeding events; however, antithrombotic therapy is recommended until devices are completely endothelialized and LAA sealed. As of today, European guidelines recommend a DAPT regimen up to 6 months after the procedure, followed by aspirin thereafter.[22] There is a paucity of dedicated studies evaluating optimal DAPT duration and different antithrombotic strategies with LAA devices in general, including the Ultraseal device. Because of the high bleeding risk of patients undergoing LAA closure, a trend toward a reduced antithrombotic therapy following the procedure has been noted in more recent studies, where higher proportion of patients used a short DAPT regimen (3 months) or was even discharged on single antiplatelet therapy.[12,26–28] The Ultraseal device requires at least 30 days to be completely reendothelialized and therefore a DAPT duration of ≥30 days is needed.[29] Taken together, these findings may suggest the application of a shorter antithrombotic therapy (<6 months), however, dedicated studies are pivotal to evaluate the optimal antithrombotic therapy following the procedure as well as the comparison with direct OAC agents.[30]

Concerns about the risk of device fracture with the first Ultraseal generation were raised after Ahlgrimm et al. reported two device fractures in a case series of 18 patients.[31] However, in the present investigation, no cases of device fracture (0%) with the second-generation Ultraseal device were identified at echocardiography assessment. Design iterations of this second-generation Ultraseal device in terms of increased device flexibility and reduced size and radial force may likely have contributed to overcome this issue.

## 4.1 | Study limitations

The present study should be interpreted in view of several limitations. First, the lack of a control group prevents comparison with other LAAC devices. However, evaluation of the feasibility and safety profile of the second-generation Ultraseal LAAC device, which was the aim of this study, is not affected by this limitation. Second, we cannot exclude a reporting bias as the attempted procedures were reported voluntarily by the investigators at each center and there was no external monitoring to verify the accuracy of data reported and to reduce the risk of a selection bias. However, the protocol specified inclusion of all attempted LAA closures performed with the study device. Third, events were not ascertained by an independent Clinical Event Committee and there was no central echocardiographic core laboratory analysis. Furthermore, we cannot exclude residual leak or device-related thrombosis in the 18 patients without TEE follow-up. Finally, due to the small sample size and the short follow-up, we were underpowered for the evaluation of post-discharge outcomes.

## 5 | CONCLUSIONS

In patients with nonvalvular AF, LAAC with the second-generation Ultraseal device implantation was associated with high success rates and a low incidence of procedure-related adverse events. Larger studies with longer follow-up are required to further define the long-term efficacy and safety of this novel device.

### CONFLICTS OF INTEREST
Dr. Tarantini reports honoraria for lectures/consulting from Medtronic, Edwards Lifesciences, Boston Scientific, GADA, Abbott. Dr. Pagnotta is proctor for Cardia and Boston Scientific. Dr. Stefanini has received speaker fees from Abbott Vascular and Boston Scientific. The other authors report no conflicts of interest.

### DATA AVAILABILITY STATEMENT
The data that support the findings of this study are available from the corresponding author upon reasonable request.

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