JACC: CARDIOVASCULAR INTERVENTIONS VOL. 11, NO. 19, 2018

PUBLISHED BY ELSEVIER

Percutaneous Left Atrial Appendage Closure With the Ultraseal Device

Insights From the Initial Multicenter Experience

Lluis Asmarats, MD,[a] Jean-Bernard Masson, MD,[b] Paolo A. Pagnotta, MD,[c] Stéphane Cook, MD,[d] Mike Foresti, MD,[e] Réda Ibrahim, MD,[f] Adam Sukiennik, MD,[g] Robert Sabiniewicz, MD, PHD,[h] Diego Maffeo, MD,[i] Julio Carballo, MD,[j] Ignacio Cruz-González, MD, PHD,[k] Carmelo Grasso, MD,[l] Francesco Pisano, MD,[m] Gaetano Senatore, MD,[n] Giuseppe Tarantini, MD, PHD,[o] Adolphe Kasongo, MD,[b] Mauro Chiarito, MD,[c] Serban Puricel, MD,[d] Nathan Messas, MD,[f] Jose Carlos Moreno-Samos, MD,[k] Gilles O'Hara, MD,[a] Josep Rodés-Cabau, MD[a]

ABSTRACT

OBJECTIVES This study sought to evaluate the feasibility, safety, and efficacy of the Ultraseal device for left atrial appendage closure (LAAC) (Cardia, Eagan, Minnesota) in patients with nonvalvular atrial fibrillation at high bleeding risk.

BACKGROUND The Ultraseal device is a novel bulb-and-sail designed LAAC device, with an articulating joint enabling conformability to heterogeneous angles and shapes of appendage anatomy.

METHODS This was a multicenter study including consecutive patients undergoing LAAC with the Ultraseal device at 15 Canadian and European sites. Periprocedural and follow-up events were systematically collected, and transesophageal echocardiography at 45 to 180 days post-procedure was routinely performed in all centers but 3.

RESULTS A total of 126 patients (mean age 75 ± 8 years; mean CHA_2DS_2-VASc score 5 ± 2; mean HAS-BLED score 4 ± 1) were included. The device was successfully implanted in 97% of patients. A major periprocedural adverse event occurred in 3 (2.4%) patients (clinically relevant pericardial effusion [n = 1], stroke [n = 1], device embolization [n = 1]). Ninety percent of patients were discharged on single or dual antiplatelet therapy. Follow-up transesophageal echocardiography was available in 89 (73%) patients, with no cases of large (>5 mm) residual leak and 5 (5.6%) cases of device-related thrombosis (all successfully treated with anticoagulation therapy). At a median follow-up of 6 (interquartile range: 3 to 10) months, the rates of stroke and transient ischemic attack were 0.8% and 0.8%, respectively, with no systemic emboli. None of the events occurred in patients with device-related thrombosis.

CONCLUSIONS In this initial multicenter experience, LAAC with the Ultraseal device was associated with a high implant success rate and a very low incidence of periprocedural complications. There were no late device-related clinical events and promising efficacy results were observed regarding thromboembolic prevention at midterm follow-up. Larger studies are further warranted to confirm the long-term safety and efficacy of this novel device. (J Am Coll Cardiol Intv 2018;11:1932–41) © 2018 by the American College of Cardiology Foundation.

From the [a]Department of Cardiology, Quebec Heart & Lung Institute, Laval University, Quebec City, Canada; [b]Department of Cardiology, Centre Hospitalier de l'Université de Montreal, Montreal, Canada; [c]Department of Cardiology, Cardio Center, Humanitas Research Hospital, Rozzano-Milan, Italy; [d]Department of Cardiology, Fribourg University and Hospital, Fribourg, Switzerland; [e]Department of Cardiology, Kliniken Maria Hilf GmbH Mönchengladbach, Mönchengladbach, Germany; [f]Department of Cardiology, Montreal Heart Institute, Montreal, Canada; [g]Department of Cardiology, Nicolaus Copernicus University, Bydgoszcz, Poland; [h]Department of Cardiology, Medical University Gdansk, Gdansk, Poland; [i]Department of Cardiology, Fondazione Poliambulanza, Brescia, Italy; [j]Department of Cardiology, Hospital El Pilar-CM Teknon, Barcelona, Spain; [k]Department of Cardiology, University Hospital of Salamanca, Salamanca, Spain; [l]Department of Cardiology, Ferrarotto Hospital, Catania, Italy; [m]Department of Cardiology, Regional Hospital Aosta, Aosta, Italy; [n]Department of Cardiology, Presidio Ospedaliero di Ivrea-Ciriè, Torino, Italy; and the [o]Department of Cardiology, University of Padua Medical School, Padua, Italy. Dr. Asmarats has been supported by a grant from the Fundacion Alfonso Martin Escudero. Dr. Rodés-Cabau holds the Canadian Research Chair "Fondation Famille Jacques Larivière" for the Development of Structural Heart Disease Interventions. Dr. Pagnotta has served as a proctor for Cardia. Dr. Ibrahim has served as a consultant for Abbott, Boston Scientific, and Gore; has served as a consultant for Abbott and Boston Scientific; and has received honoraria from Medtronic. Dr. Rodés-Cabau has received institutional research grant support from Cardia. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received March 14, 2018; revised manuscript received May 1, 2018, accepted May 15, 2018.

ISSN 1936-8798/$36.00 https://doi.org/10.1016/j.jcin.2018.05.023

Anticoagulation with vitamin K antagonists or direct oral anticoagulant agents remains the mainstay of thromboembolic prevention in patients with nonvalvular atrial fibrillation (AF), with robust reductions in the risk of stroke and death (1,2). Nevertheless, oral anticoagulation has been associated with increased bleeding risk in a commonly old and comorbid population. Also, more than one-third of AF patients at high risk for stroke still fail to receive optimal thromboembolic prophylaxis in contemporary practice (3). In recent years, left atrial appendage closure (LAAC) has emerged as an alternative treatment to anticoagulation in patients with nonvalvular AF and a broad spectrum of LAAC devices have been developed, mainly targeting high-risk patients deemed ineligible for oral anticoagulation (4).

SEE PAGE 1942

The Ultraseal LAAC device (Cardia, Eagan, Minnesota) is a new, self-expandable bulb-and-sail occluder, specifically designed for transcatheter LAAC. The first-in-human experience with this device, including a total of 18 patients from 2 centers, showed promising preliminary feasibility data (5,6), and the device received Conformité Européenne mark approval in March 2016. This first multicenter international experience aimed to evaluate the safety, feasibility, and preliminary efficacy of LAAC with the Ultraseal device in a larger patient population.

METHODS

STUDY POPULATION. This multicenter study included consecutive patients with nonvalvular AF who underwent LAAC with the Ultraseal device from 15 centers in Europe and Canada between January 2015 and January 2018. All participating centers but 1 had previous LAAC experience, with a mean experience time of 4 ± 3 years and a median of 79 (interquartile range: 40 to 118) and 43 (interquartile range: 12 to 95) procedures per center and per operator, respectively. The procedure was performed by interventional cardiologists, electrophysiologists, or both in 73%, 13%, and 13% of the participating centers, respectively. Canadian patients were treated on the basis of a compassionate clinical use program and each procedure was approved by Health Canada. In Europe, all patients were treated following Conformité Européenne mark approval of the device. All patients provided informed consent for the procedures. The device was implanted on an all-comer basis in unselected patients undergoing LAAC, in the absence of LAA thrombus. Baseline and periprocedural events were collected prospectively in each participating center. Device success was defined as successful device implantation in correct position and technical success 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 transesophageal echocardiography (TEE) during the procedure and index hospitalization, in accordance to the Munich consensus statement (7). Major adverse events (MAEs) during the procedure and index hospitalization included death, stroke or transient ischemic attack, systemic embolism, major bleeding (defined as type ≥3 of Bleeding Academic Research Consortium, including cardiac tamponade) (8), myocardial infarction, major vascular complication according to the Valve Academic Research Consortium-2 criteria (9), and device embolization. Cardiovascular events during follow-up included death, stroke or transient ischemic attack, systemic embolization, major bleeding, and device-related complications.

DEVICE CHARACTERISTICS AND IMPLANTATION. The Ultraseal LAAC device is a fully retrievable and repositionable self-expandable nitinol device composed of 2 parts: a soft distal bulb that anchors the device to the LAA through 12 stabilizing hooks and a 3-leaflet multilayered sail with a proximal polyvinyl alcohol foam and a distal polyester layer, for LAA occlusion (**Figure 1**). Both sections are connected by a dual articulating joint enabling multidirectional movement and optimal adjustment to different ostium angles and shapes. The device is available in 9 different bulb sizes ranging from 16 to 32 mm (fitting landing zone measurements from 11 to 26 mm), with the proximal sail being 6 mm larger than the distal bulb diameter, and requires a minimum LAA depth of 16 mm. A bulb-to-landing zone oversizing of at least 25% is generally recommended. The bulb offers low radial force, which allows for permissive oversizing if needed.

The Cardia Delivery System includes 3 components: the delivery forceps, the introducer, and the delivery sheath. The delivery forceps is flexible and has jaws enabling holding and release of the device at a grasping knob located at the center of the proximal sail, whereas a forceps handle locking mechanism prevents device detachment. A hemostatic introducer allows introduction of the device into the delivery sheath. The Cardia delivery sheath, ranging from 10-F to 12-F, is currently available in 2 different preformed curves: single (45°) and double (45° to 45°).

ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation

DRT = device-related thrombosis

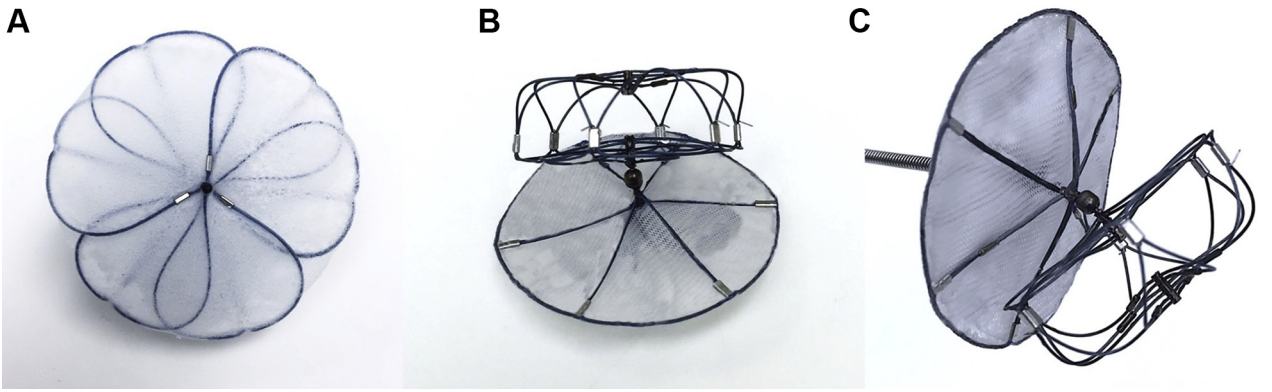
LAA = left atrial appendage

LAAC = left atrial appendage closure

MAE = major adverse event(s)

TEE = transesophageal echocardiography

FIGURE 1 The Cardia Ultraseal Device



(A) Left atrial side. The sail is made of 3 leaflets, and is covered by a proximal polyvinyl alcohol foam and a distal polyester layer. **(B)** Left atrial appendage side. A distal atraumatic bulb of stranded nitinol anchors the device into the left atrial appendage through 12 stabilizing hooks to prevent device dislodgement. **(C)** Side view. Both sections are connected by a dual articulating joint allowing multidirectional movement.

Procedures were performed under TEE or intracardiac echocardiography and fluoroscopic guidance. After transseptal puncture, heparin was administered to achieve a minimum activated clotting time ≥250 s before device insertion. Sizing of the device was performed by using the maximum measured landing zone diameter (at 10 to 12 mm from the LAA orifice) by TEE (45°, 90°, 135°) or intracardiac echocardiography, and angiographic measurements. The delivery sheath was then advanced within the LAA, so that the distal end of its radiopaque marker band was placed at the intended landing zone of the bulb hooks. The distal bulb was deployed into the LAA with a slow unsheathing movement and appropriate compression was assessed by confirming the fluoroscopic nonsymmetric shape of the bulb radiopaque markers and separation between the sail and the lobe (**Figure 2**). Subsequently, the sheath was withdrawn by further pullback to expose the proximal sail, allowing LAA ostium sealing. The device could be partially or fully retrieved and redeployed up to 5 times if implant location or stability were deemed unsatisfactory. After a subtle tug test and upon satisfactory position, the device was released by unscrewing the locking mechanism of the forceps handle.

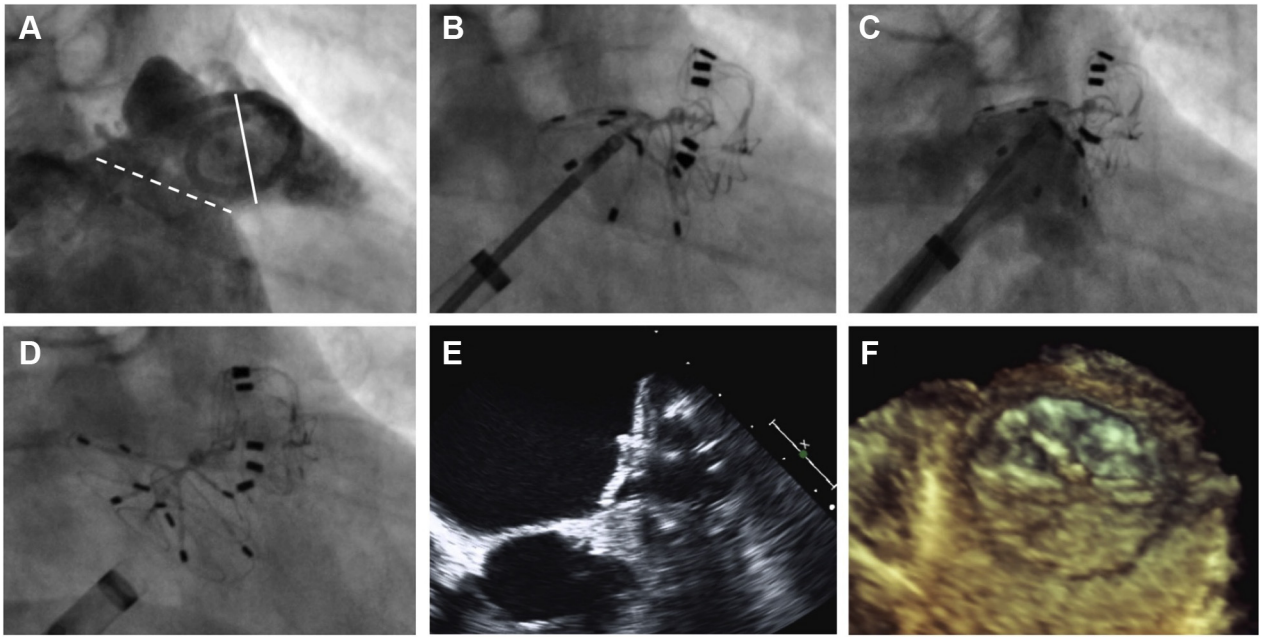
A transthoracic echocardiography examination was performed the day after the procedure. Generally, patients were discharged on dual antiplatelet therapy for 3 months followed by lifelong aspirin, or single antiplatelet monotherapy when deemed at too high bleeding risk. Routine TEE was performed at 45 to 180 days post-procedure in all participating centers but 3. Peridevice leaks were categorized according to the width of the color jet as follows: trace (<1-mm-diameter jet), mild (1 to 3 mm), moderate (>3 mm but ≤5 mm), and severe (>5 mm) (7,10).

STATISTICAL ANALYSIS. Categorical variables are reported as counts and percentages and continuous variables as mean ± SD or median (interquartile range). LAAC efficacy on thromboembolic prevention was assessed by comparing the actual annual event rate at follow-up (total number of observed events per 100 patient-years) with the predicted event rate by the $CHADS_2$ (congestive heart failure history, hypertension history, age ≥75 years, diabetes mellitus history, stroke or transient ischemic attack symptoms previously) and CHA_2DS_2-VASc (congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke or transient ischemic attack, vascular disease, age 65 to 74 years, sex category) scores (11). Risk reduction was calculated as follows: (estimated % event rate - actual % event rate)/estimated % event rate. Analyses were performed using the statistical package STATA version 14.0 (StataCorp, College Station, Texas).

RESULTS

A total of 126 consecutive patients from 15 centers were included. Only 1 patient with a very large LAA was excluded. The main baseline clinical characteristics of the study population are shown in **Table 1**. Mean age was 75 ± 8 years and 57% were men. The mean $CHADS_2$ and CHA_2DS_2-VASc score were 3 ± 1 and 5 ± 2, respectively, with an average HAS-BLED

FIGURE 2 Ultraseal Device Implantation



(A) Angiographic measurement of the landing zone in right anterior oblique cranial projection **(dashed line:** ostium; **solid line:** landing zone). **(B)** Fluoroscopic view illustrating device articulation during deployment. **(C)** Angiography showing good sealing after implantation. **(D)** Device release. **(E)** Two-dimensional and **(F)** 3-dimensional transesophageal echocardiography showing the appropriately implanted device.

(hypertension, abnormal renal or liver function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly, drugs or alcohol) score of 4 ± 1. The vast majority of patients had a history of bleeding (78%) and were ineligible for long-term oral anticoagulation (93%).

PROCEDURAL RESULTS. Chief procedural details are provided in Table 2. Most procedures were performed under TEE guidance (87%), whereas 13% were performed with intracardiac echocardiography guidance. Two patients underwent combined procedures with LAAC (1 percutaneous edge-to-edge mitral valve repair, 1 atrial septal defect closure). Successful device implantation was achieved in 122 (97%) patients and technical success—residual leak <5 mm in the absence of device-related complications—in 119 (94%) patients. The device could not be implanted in 4 patients with unsuitable anatomy due to shallow accessory lobes (n = 2) or large oval ostia (n = 2) yielding to persistent significant gaps. Additional reasons for technical failure were significant pericardial effusion requiring pericardiocentesis (n = 1), major residual leak (n = 1), and post-procedure device embolization (n = 1). The mean device size was 24 ± 4 mm, with an average oversizing of 26 ± 11%. Successful implantation was achieved with the first selected device in 102 of 122 (84%) patients, with acute complete LAA seal in 101 (83%) patients and 1 single case (0.8%) of severe (>5 mm) residual leak.

IN-HOSPITAL OUTCOMES. The main in-hospital outcomes are summarized in Table 3. The rate of periprocedural MAEs was 2.4%. There was 1 single case of serious pericardial effusion requiring pericardiocentesis (0.8%). One ischemic stroke (0.8%) occurred 48 h after the procedure in a patient undergoing concomitant MitraClip (Abbott Vascular, Santa Clara, California) and LAAC. One device embolization to the left ventricle within the hours following the procedure was reported in the very early experience. The device was retrieved surgically (due to chordae tendineae entanglement) with postoperative asymptomatic hemoglobin drop requiring transfusion. No episodes of systemic embolism, major vascular complications, myocardial infarction, or deaths occurred during the in-hospital period. Most patients (~90%) were discharged on single or dual antiplatelet therapy, whereas only 4% of patients received oral anticoagulation.

FOLLOW-UP. At a median of 6 (interquartile range: 3 to 10) months, a total of 7 deaths (5 cardiovascular

TABLE 1 Baseline Clinical Characteristics (N = 126)

Age, yrs	75 ± 8
Female	54 (42.9)
Hypertension	108 (85.7)
Diabetes mellitus	57 (45.2)
Coronary artery disease	65 (51.6)
Congestive heart failure	36 (28.6)
LVEF, %	49 ± 14
Chronic kidney disease	55/111 (49.5)
Atrial fibrillation type	
Paroxysmal	47 (37.3)
Persistent/permanent	79 (62.7)
Previous history of TIA/stroke	34 (27.0)
Prior bleeding	98 (77.8)
Contraindication to OAC	117 (92.9)
Absolute	56 (44.5)
Relative	61 (48.4)
Indication for LAAC	
Major bleeding	79 (62.7)
Minor bleeding	19 (15.1)
High bleeding risk	13 (10.3)
Stroke on OAC	2 (1.6)
Labile INR	4 (3.2)
Risk of falls	3 (2.4)
Other	6 (4.8)
$CHADS_2$ score	3 ± 1
CHA_2DS_2-VASc score	5 ± 2
HAS-BLED score	4 ± 1

Values are mean ± SD, n (%), or n/N (%).

$CHADS_2$ = congestive heart failure history, hypertension history, age ≥75 years, diabetes mellitus history, stroke or transient ischemic attack symptoms previously; CHA_2DS_2-VASc = congestive heart failure, hypertension, 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; INR = international normalized ratio; LAAC = left atrial appendage closure; LVEF = left ventricle ejection fraction; OAC = oral anticoagulation; TIA = transient ischemic attack.

TABLE 2 Procedural Findings (N = 126)

Device success	122 (96.8)
Technical success	119 (94.4)
Procedural guidance	
TEE	109 (86.5)
ICE	17 (13.5)
LAA ostium, mm	20.5 ± 4.6
LAA landing zone, mm	17.8 ± 3.9
LAA length, mm	25.1 ± 7.4
Device size, mm*	
16	5 (4.1)
18	10 (8.2)
20	19 (15.6)
22	21 (17.2)
24	23 (18.9)
26	17 (13.9)
28	13 (10.7)
30	4 (3.3)
32	10 (8.2)
Oversizing, %	26 ± 11
Number of devices per procedure*	
1	102 (83.6)
2	17 (13.9)
3	3 (2.5)
Number of recaptures*	1.6 ± 1.9
LAA seal*	
Complete	101 (82.8)
Trace leak (<1 mm)	6 (4.9)
Mild leak (1-3 mm)	11 (9.0)
Moderate leak (>3 mm but ≤5 mm)	3 (2.5)
Severe leak (>5 mm)	1 (0.8)
Procedural time, min	73 ± 29

Values are n (%) or mean ± SD. *Percentage based on 122 successfully implanted patients.

ICE = intracardiac echocardiography; LAA = left atrial appendage; TEE = transesophageal echocardiography.

events) were reported, none of them related to the device. There were 2 cerebrovascular events (1 stroke in a patient with prior history of stroke and 1 transient ischemic attack) unrelated to device-related thrombosis (DRT) or LAA patency. The annualized rates (including both periprocedural and follow-up periods) of ischemic stroke and thromboembolic events (stroke or transient ischemic attack or systemic embolism) in the study were 2.45% and 3.68%, respectively, translating into a 66% and 60% relative risk reduction for stroke, and 63% and 57% risk reduction for thromboembolic events, according to their $CHADS_2$ and CHA_2DS_2-VASc scores respectively (**Figure 3**) (11). Major bleeding events occurred in 4 patients (2 gastrointestinal, 2 anemia without overt bleeding). No episodes of device embolization occurred at follow-up.

Eighty-nine of 122 (73%) patients with successful device implantation underwent TEE within the 6 months after the index procedure (mean 90 ± 60 days). DRT was observed in 5 (5.6%) patients. Two patients were on aspirin monotherapy at the time of DRT diagnosis, whereas 3 patients were on dual antiplatelet therapy. All 5 patients received oral anticoagulation with complete thrombus resolution and remained asymptomatic with no neurological events during follow-up. Some degree of peridevice leak was found in 19 (21%) patients, and it was trace or mild in 16%, and moderate in 5.6%. No patient had severe leak (>5 mm). Late clinical outcomes and TEE findings are summarized in **Table 4**. LAA closure rates immediately after device implantation and within 6-month follow-up are depicted in **Figure 4**.

DISCUSSION

The present study is the first multicenter evaluation of transcatheter LAAC with the Ultraseal device in patients with nonvalvular AF who were deemed

TABLE 3 In-Hospital Outcomes (N = 126)

In-hospital outcomes	
Major adverse events	3 (2.4)
Death	0
Stroke/TIA	1 (0.8)
Systemic embolism	0
Major bleeding (BARC type ≥3)	2 (1.6)
Pericardial effusion requiring pericardiocentesis	1 (0.8)
Postoperative Hb drop requiring transfusion*	1 (0.8)
Myocardial infarction	0
Major vascular complications (VARC-2)	0
Device embolization*	1 (0.8)
Other adverse events	
Pericardial effusion not requiring intervention	1 (0.8)
Minor vascular complications	4 (3.2)
Hospitalization length, days	1 (1-2)
Antithrombotic treatment post-LAAC†	
None	1 (0.8)
Single antiplatelet therapy	9 (7.4)
Dual antiplatelet therapy	101 (82.8)
Oral anticoagulation	5 (4.1)
Warfarin	0
Direct OAC	5 (4.1)
Low-molecular-weight heparin	6 (4.9)

Values are n (%) or median (interquartile range). *A single patient had 2 major adverse events (device embolization and major bleeding). †Percentage based on 122 successfully implanted patients.

BARC = Bleeding Academic Research Consortium; Hb = hemoglobin; VARC = Valve Academic Research Consortium; other abbreviations as in Table 1.

poor candidates for long-term oral anticoagulation. The device was successfully implanted in 97% of patients with a low rate of major periprocedural complications (2.4%) and severe residual leaks (<1%). The rate of DRT within the months following the procedure was 5.6%, and the incidence of cerebrovascular events at midterm follow-up was lower than that expected on the basis of thromboembolic risk scores.

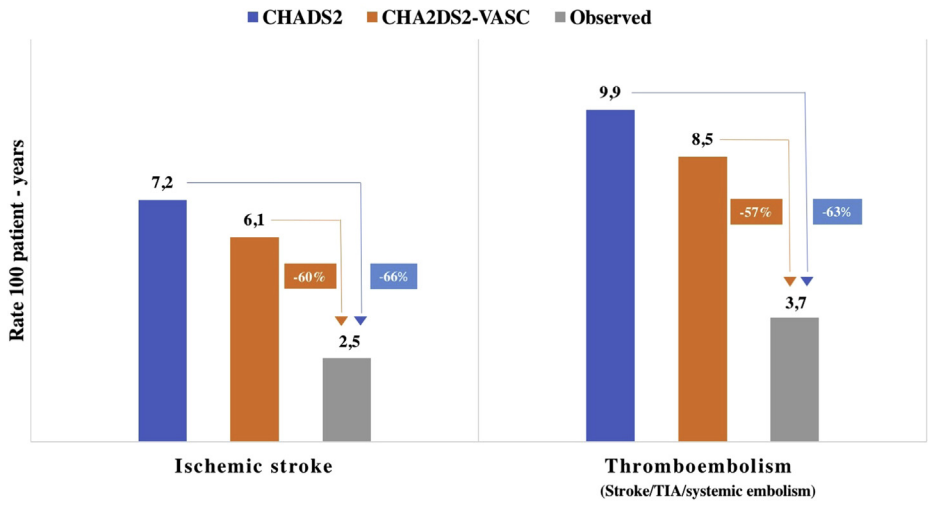
The Amplatzer Amulet (Abbott Vascular, Santa Clara, California) and the Watchman device (Boston Scientific, Natick, Massachusetts) remain the 2 most widely used endocardial LAAC devices (12–14), the latter being the only device studied in randomized clinical trials to date (15,16). However, despite continuous improvements linked to increasing operator experience and device iterations, the wide heterogeneity of LAA morphologies and sizes still limits the suitability of percutaneous LAAC in some of patients (17). This unmet need and the continuous growth of the LAAC field has fueled the development of novel LAAC technologies (4).

The Ultraseal LAAC device represents a new-generation self-expandable device with a unique bulb-and-sail design and 3 chief distinguishing features: a fully articulating joint between the distal and proximal sections allowing multidirectional movement and adjustment to different LAA angles and morphologies; a soft distal atraumatic bulb enabling safe deep entry into the LAA and very distal deployment in cases with limited usable length; and the capability of being fully retrieved and redeployed multiple times. The device may accommodate a landing zone up to 26 mm, which is slightly smaller than that recommended for other devices. However, this may be compensated by the soft and flexible characteristics of the bulb, allowing a safe deployment of the device very distal into the LAA, where the width is frequently smaller. The Ultraseal bulb-and-sail design features the previously called "pacifier principle" (18). The distal bulb anchors the device in the LAA landing zone, whereas the larger proximal sail covers the LAA ostium, akin to a baby pacifier.

The reported rate of successful implantation achieved in this study was as high as 97%, comparable to previous studies with the most commonly used commercialized devices (91% to 100%) (4). These results are encouraging considering that this series represents the initial experience with a novel device. Overall, LAAC procedures with the Ultraseal device represented 37% (126 of 345) of the total LAAC cases performed throughout the study period among all participating centers, with a slight decreased share between the first (46%) and last (35%) trimester of the inclusion period. All 4 patients with implant failure presented very challenging anatomies with reduced implantation zone or conical LAAs with oval ostia markedly larger than the LAA landing zone, leading to persistent gaps despite progressive device upsizing. Modifications of the device including wider sails for small bulbs to overcome these particularly challenging anatomies, along with increased operator experience, may potentially decrease the rate of implant failure in the future. Also, further studies addressing anatomical eligibility for the Ultraseal device are warranted.

Importantly, the results of this study demonstrated the high safety profile of the Ultraseal device, with a low rate of periprocedural MAEs (2.4%) and a very low rate of significant pericardial effusion (0.8%), similar to the safety outcomes reported in contemporary experiences with other available LAAC devices (13,14,19). Also, these results appear to compare favorably with the initial experiences with other LAAC devices, which exhibited average MAE rates of ~5% (from 3.3% to 8.7%) (15,20,21). Acute device embolization is an uncommon complication of LAAC, albeit reported to occur in up to 2% of LAAC procedures (22). Device embolization in our study occurred only in 1 (0.8%) patient, at the very beginning of the

FIGURE 3 Expected Versus Observed Ischemic Stroke Events



Effectiveness of left atrial appendage closure in reduction of ischemic stroke and thromboembolic events (stroke or transient ischemic attack [TIA] or peripheral emboli) predicted by $CHADS_2$ (congestive heart failure history, hypertension history, age ≥75 years, diabetes mellitus history, stroke or transient ischemic attack symptoms previously) and CHA_2DS_2-VASc (congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke or transient ischemic attack, vascular disease, age 65 to 74 years, sex category) scores (both periprocedural and follow-up included) (11).

experience. Overall, these safety outcomes are likely explained by the presence of a soft and flexible distal bulb with reduced risk of wall perforation, and a combination of low radial force, 12 stabilizing hooks and meaningful oversizing (~25%), which minimize device "pop out" during the implantation process and ultimately contribute to the stability of the Ultraseal device.

Incomplete sealing with any degree of peridevice leak under routine TEE surveillance has been reported in up to 41% of patients treated with the Watchman device in the PROTECT-AF (Watchman Left Atrial Appendage System for Embolic Protection in Patients With Atrial Fibrillation) study at 45 days, 34% at 6 months, or 32% at 1 year (23); 13% in the core lab-adjudicated cohort of the multicenter Amplatzer Cardiac Plug (ACP) (Abbott Vascular, Santa Clara, California) registry and 16% in the early Canadian experience with ACP at 6 months (10,24); up to 12% at 3 months with Amulet (25) or 16% at 1 year in the LAmbre (Lifetech Scientific, Shenzhen, China) multicenter study (21). Leaks may occur at the time of implantation or late after LAAC due to atrial remodeling around the device (edge effect) (26), although unlike prior surgical studies (27), this finding has not been associated with a higher risk of clinical events (10,23). In our experience, complete LAAC sealing was achieved in ~80% of patients at implantation and within 6 months, and most residual leaks (14 of 19, 74%) were small (<3 mm). Definitions of significant residual peridevice leaks have arbitrarily varied from 3 to 5 mm among different LAAC studies, with 5 mm being the widest accepted cutoff for peridevice leak severity in most studies conducted to date with either Amplatzer ACP/Amulet

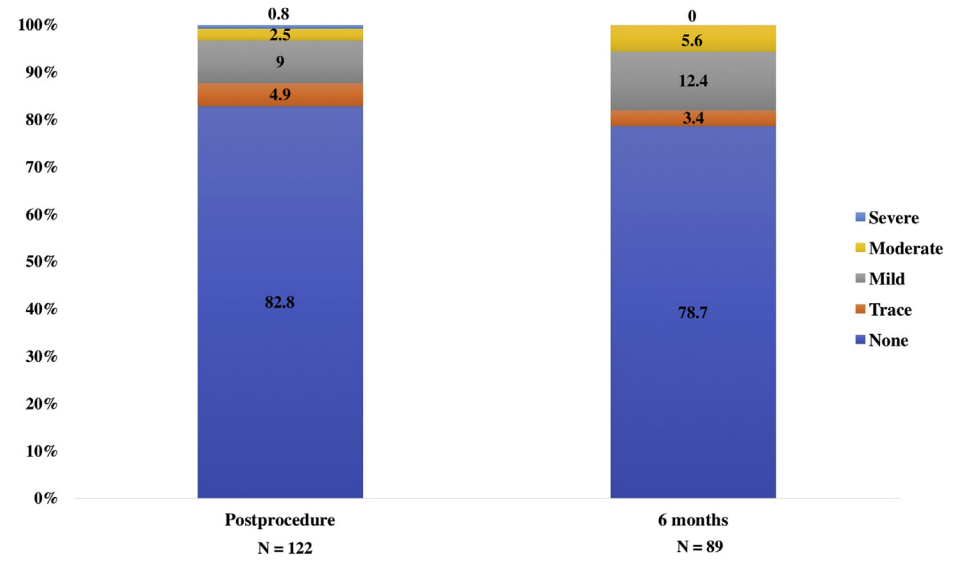
TABLE 4 Follow-Up Clinical and TEE Findings

Adverse events during follow-up	
Follow-up, months	6 (3–10)
All-cause death	7 (5.7)
Cardiovascular death	5 (4.1)
Cerebrovascular events	2 (1.6)
Stroke	1 (0.8)
TIA	1 (0.8)
Systemic embolism	0
Major bleeding*	4 (3.3)
Device embolization	0
TEE follow-up	N = 89
Residual peridevice leak	
None	70 (78.7)
Trace (<1 mm)	3 (3.4)
Mild (1–3 mm)	11 (12.4)
Moderate (3–5 mm)	5 (5.6)
Severe (>5 mm)	0
Device-related thrombosis	5 (5.6)

Values are median (interquartile range) or n (%). *Two on single and 2 on dual antiplatelet therapy (2 gastrointestinal, 2 anemia without overt bleeding).

Abbreviations as in Tables 1 and 2.

FIGURE 4 Peridevice Leak Post-Implantation and at 6-Month Follow-Up



The rate of complete left atrial appendage seal remained stable during follow-up (~80%), with no evidence of large (>5 mm) leaks assessed by transesophageal echocardiography within the first 6 months of follow-up.

(10,13) or Watchman (14-16), as well as in recent consensus documents (7). Notably, no large residual leaks (>5 mm) were observed during follow-up, leading to an adequate occlusion rate of the LAA of 100%, according to current standardized definitions (7). Albeit lobe-and-disk LAAC devices have typically been associated with lower peridevice leaks as compared with single-lobe devices likely due to the "pacifier effect" of the double-layered barrier, future head-to-head studies with other available lobe-and-disk LAA devices (e.g., Amulet) are needed to assess whether the absence of fabric covering in the distal bulb may associate with an increased risk of residual leaks.

The rate of DRT following LAAC has ranged from 0% to 25% (4,28), with wide variations depending on device type, post-procedural antithrombotic treatment, and timing of TEE surveillance imaging. In our experience, 5 (5.6%) patients developed DRT at a mean follow-up of 3 months post-LAAC. Importantly, all 5 patients experienced complete DRT resolution with oral anticoagulation, and remained asymptomatic. Uncertainty about optimal antithrombotic therapy after LAAC remains a concern in this field. Recent findings have shown a significant activation of the coagulation system very early after LAAC, suggesting a potential benefit of short-term (~4 weeks) anticoagulation following LAAC in the absence of absolute contraindications to anticoagulant agents (29). It is noteworthy that patients included in this preliminary clinical experience received more conservative antithrombotic approach (>90% discharged on single or dual antiplatelet therapy and <5% on oral anticoagulation), than most previous studies with other LAAC devices: 100% anticoagulation in the PROTECT-AF and PREVAIL (Prospective Randomized Evaluation of the Watchman LAAC Device in Patients With AF Versus Long-Term Warfarin Therapy) studies (15,16), 27% anticoagulation in EWOLUTION (Registry on Watchman Outcomes in Real-Life Utilization) study (14), and 19% anticoagulation in the Amulet Observational Study (13). Interestingly, complete healing and neointimal coverage was observed at 30 days in a canine model with the Ultraseal device (30). The low rate of post-procedural oral anticoagulation in the present real-world experience reflects the increasing trend toward less aggressive antithrombotic approaches in this high-risk population currently referred for percutaneous LAAC. Larger studies with longer follow-up are warranted to determine the real incidence of DRT, as well as to elucidate the optimal post-procedural antithrombotic therapy in this population.

STUDY LIMITATIONS. There was no independent adjudication event committee and no centralized

echo core lab in this study. Data on screen failures was not systematically collected. Post-procedural antithrombotic therapy and follow-up TEE imaging were based on each institution's standard practice and some variations were observed among different centers and physicians. However, routine surveillance imaging at intermediate follow-up (1 to 6 months) was done in most (80%) participating centers, minimizing the risk of patient selection bias regarding the incidence of residual leaks or DRT. Last, the limited sample size and follow-up prevent from drawing definite conclusions on the long-term efficacy for thromboembolic prevention.

CONCLUSIONS

In patients with nonvalvular AF at high bleeding risk, LAAC with the Ultraseal device was safe and associated with a high procedural success rate. The low incidence of cerebrovascular events at midterm follow-up provides promising efficacy data on the prevention of thromboembolic events. Larger studies with a longer-term follow-up are warranted.

ADDRESS FOR CORRESPONDENCE: Dr. Josep Rodés-Cabau, Quebec Heart & Lung Institute, Laval University, 2725 chemin Ste-Foy, G1V 4G5 Quebec City, Quebec, Canada. E-mail: josep.rodes@criucpq.ulaval.ca.

PERSPECTIVES

WHAT IS KNOWN? Isolated small case series have suggested the feasibility of LAAC with the Ultraseal device.

WHAT IS NEW? This first multicenter global experience showed a high implant success rate and a low incidence of procedure-related complications, along with a low rate of ischemic stroke at midterm follow-up.

WHAT IS NEXT? Larger studies with a longer follow-up are required to adequately define the long-term clinical efficacy of this novel device.

REFERENCES

1. Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. Ann Intern Med 2007;146:857–67.

2. Ruff CT, Giugliano RP, Braunwald E, et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. Lancet 2014;383:955–62.

3. Marzec LN, Wang J, Shah ND, et al. Influence of direct oral anticoagulants on rates of oral anticoagulation for atrial fibrillation. J Am Coll Cardiol 2017;69:2475–84.

4. Asmarats L, Rodés-Cabau J. Percutaneous left atrial appendage closure: current devices and clinical outcomes. Circ Cardiovasc Interv 2017;10:e005359.

5. Sabiniewicz R, Hiczkiewicz J, Wanczura P, Stecko W, Curzytek A. First-in-human experience with the Cardia Ultraseal left atrial appendage closure device: the feasibility study. Cardiol J 2016;23:652–4.

6. Regueiro A, Bernier M, O'Hara G, et al. Left atrial appendage closure: Initial experience with the Ultraseal device. Catheter Cardiovasc Interv 2017;90:817–23.

7. Tzikas A, Holmes DR Jr., Gafoor S, et al. Percutaneous left atrial appendage occlusion: the Munich consensus document on definitions, endpoints and data collection requirements for clinical studies. EuroIntervention 2016;12:103–11.

8. Mehran R, Rao SV, Bhatt DL, et al. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. Circulation 2011;123:2736–47.

9. Kappetein AP, Head SJ, Genereux P, et al. Updated standardized endpoint definitions for transcatheter aortic valve implantation: the Valve Academic Research Consortium-2 consensus document. J Am Coll Cardiol 2012;60:1438–54.

10. Saw J, Tzikas A, Shakir S, et al. Incidence and clinical impact of device-associated thrombus and peri-device leak following left atrial appendage closure with the Amplatzer cardiac plug. J Am Coll Cardiol Intv 2017;10:391–9.

11. Friberg L, Rosenqvist M, Lip GY. Evaluation of risk stratification schemes for ischaemic stroke and bleeding in 182 678 patients with atrial fibrillation: the Swedish Atrial Fibrillation cohort study. Eur Heart J 2012;33:1500–10.

12. Tzikas A, Shakir S, Gafoor S, et al. Left atrial appendage occlusion for stroke prevention in atrial fibrillation: multicentre experience with the AMPLATZER Cardiac Plug. EuroIntervention 2016;11:1170–9.

13. Landmesser U, Schmidt B, Nielsen-Kudsk JE, et al. Left atrial appendage occlusion with the AMPLATZER Amulet device: periprocedural and early clinical/echocardiographic data from a global prospective observational study. EuroIntervention 2017;13:867–76.

14. Boersma LV, Ince H, Kische S, et al. Efficacy and safety of left atrial appendage closure with WATCHMAN in patients with or without contraindication to oral anticoagulation: 1-year follow-up outcome data of the EWOLUTION trial. Heart Rhythm 2017;14:1302–8.

15. Holmes DR, Reddy VY, Turi ZG, et al. Percutaneous closure of the left atrial appendage versus warfarin therapy for prevention of stroke in patients with atrial fibrillation: a randomised non-inferiority trial. Lancet 2009;374:534–42.

16. Holmes DR Jr., Kar S, Price MJ, et al. Prospective randomized evaluation of the Watchman left atrial appendage closure device in patients with atrial fibrillation versus long-term warfarin therapy: the PREVAIL trial. J Am Coll Cardiol 2014;64:1–12.

17. Cabrera JA, Saremi F, Sanchez-Quintana D. Left atrial appendage: anatomy and imaging landmarks pertinent to percutaneous transcatheter occlusion. Heart 2014;100:1636–50.

18. Meier B, Palacios I, Windecker S, et al. Transcatheter left atrial appendage occlusion with Amplatzer devices to obviate anticoagulation in patients with atrial fibrillation. Catheter Cardiovasc Interv 2003;60:417–22.

19. Reddy VY, Gibson DN, Kar S, et al. Post-approval U.S. experience with left atrial appendage closure for stroke prevention in atrial fibrillation. J Am Coll Cardiol 2017;69:253–61.

20. Park JW, Bethencourt A, Sievert H, et al. Left atrial appendage closure with Amplatzer Cardiac Plug in atrial fibrillation: initial European experience. Catheter Cardiovasc Interv 2011;77:700–6.

21. Huang H, Liu Y, Xu Y, et al. Percutaneous left atrial appendage closure with the LAmbre device for stroke prevention in atrial fibrillation: a prospective, multicenter clinical study. J Am Coll Cardiol Intv 2017;10:2188–94.

22. Koskinas KC, Shakir S, Fankhauser M, et al. Predictors of early (1-week) outcomes following left atrial appendage closure with Amplatzer devices. J Am Coll Cardiol Intv 2016;9:1374–83.

23. Viles-Gonzalez JF, Kar S, Douglas P, et al. The clinical impact of incomplete left atrial appendage closure with the Watchman device in patients with atrial fibrillation: a PROTECT AF (Percutaneous Closure of the Left Atrial Appendage Versus Warfarin Therapy for Prevention of Stroke in Patients With Atrial Fibrillation) substudy. J Am Coll Cardiol 2012;59:923–9.

24. Urena M, Rodés-Cabau J, Freixa X, et al. Percutaneous left atrial appendage closure with the Amplatzer Cardiac Plug device in patients with nonvalvular atrial fibrillation and contraindications to anticoagulation therapy. J Am Coll Cardiol 2013;62:96–102.

25. Lam SC, Bertog S, Gafoor S, et al. Left atrial appendage closure using the Amulet device: an initial experience with the second generation amplatzer cardiac plug. Catheter Cardiovasc Interv 2015;85:297–303.

26. Pillarisetti J, Reddy YM, Gunda S, et al. Endocardial (Watchman) vs epicardial (Lariat) left atrial appendage exclusion devices: Understanding the differences in the location and type of leaks and their clinical implications. Heart Rhythm 2015;12:1501–7.

27. Kanderian AS, Gillinov AM, Pettersson GB, Blackstone E, Klein AL. Success of surgical left atrial appendage closure: assessment by transesophageal echocardiography. J Am Coll Cardiol 2008;52:924–9.

28. Fauchier L, Cinaud A, Brigadeau F, et al. Device-related thrombosis after percutaneous left atrial appendage occlusion for atrial fibrillation. J Am Coll Cardiol 2018;71:1528–36.

29. Rodés-Cabau J, O'Hara G, Paradis JM, et al. Changes in coagulation and platelet activation markers following transcatheter left atrial appendage closure. Am J Cardiol 2017;120:87–91.

30. Cheng Y, Conditt G, Yi G, et al. TCT-765 first in-vivo evaluation of the Ultrasept left atrial appendage closure device. J Am Coll Cardiol 2012;60 Suppl:B223.

KEY WORDS atrial fibrillation, left atrial appendage closure, stroke, Ultraseal