JACC: CLINICAL ELECTROPHYSIOLOGY VOL. ■, NO. ■, 2021

Intracardiac Echocardiography-Guided Left Atrial Appendage Closure With a Novel Foam-Based Conformable Device

Safety and 1-Year Outcomes

Mohit K. Turagam, MD,[a] Petr Neuzil, MD, PhD,[b] Pavel Hala, MD,[b] Tomas Mraz, MD,[b] Srinivas R. Dukkipati, MD,[a] Vivek Y. Reddy, MD[a,b]

ABSTRACT

OBJECTIVES This is a first report of the safety and 1-year outcomes of left atrial appendage closure (LAAC) using a novel foam-based conformable device, guided by intracardiac echocardiography (ICE).

BACKGROUND Limitations of current transcatheter LAAC devices include the need for precise coaxial delivery into the left atrial appendage (LAA), potential for traumatic implantation, incomplete LAA seal, and device-related thrombus.

METHODS The device (Conformal Left Atrial Appendage Seal, Conformal Medical Inc) is a self-expanding occluder consisting of a cylindrical nitinol endoskeleton with low-profile anchor barbs around the midpoint, covered with a porous foam cup. In a prospective single-center series, under conscious sedation, the device was delivered under fluoroscopic and ICE guidance. After positioning, a transesophageal echocardiography probe was placed to confirm ICE findings before device release. After closure, dual antiplatelet therapy was administered for 6 months. Follow-up imaging was planned for 45 days and 6 and 12 months.

RESULTS A total of 15 patients (age 71.3 ± 10.8 years, 33% men, CHA_2DS_2-VASc 4.1 ± 1.7, HAS-BLED 3.4 ± 1.4) underwent LAAC, 100% successfully. There were no procedure/device-related complications requiring intervention. Asymptomatic pericardial effusion occurred in 2 patients. The 45-day, 6-month, and 12-month follow-up imaging in 11, 9, and 13 patients, respectively, revealed adequate LAA seal (leak ≤5 mm) in all patients; device-related thrombus was detected in 1 patient at 6 months. Over 1-year follow-up, there were no ischemic strokes and 1 minor bleed. Nonprocedure-/device-related death occurred in 2 patients.

CONCLUSIONS This first report indicates that LAAC with the conformable implant guided by ICE imaging is feasible with encouraging 1-year clinical outcomes. (The Conformal Prague Study; NCT04193826)
(J Am Coll Cardiol EP 2021;■:■–■) © 2021 Published by Elsevier on behalf of the American College of Cardiology Foundation.

Echocardiographic evidence that the left atrial appendage (LAA) is the source of thrombi in ~98% of patients with nonvalvular atrial fibrillation (AF) supports the development of transcatheter therapies to occlude the LAA, thereby preventing stroke and systemic thromboembolism (1-3). The Watchman Left Atrial Appendage Closure Device (Boston Scientific Corporation) received U.S. Food and Drug Administration approval in March 2015 based on data from the PROTECT-AF and PREVAIL randomized clinical trials and associated continued access registries, which demonstrated that the device

From the [a]Helmsley Electrophysiology Center, Icahn School of Medicine at Mount Sinai, New York, New York, USA; and the [b]Department of Cardiology, Homolka Hospital, Prague, Czech Republic.

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

Manuscript received July 19, 2021; revised manuscript received September 22, 2021, accepted October 8, 2021.

ISSN 2405-500X/$36.00 https://doi.org/10.1016/j.jacep.2021.10.001

ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation

DRT = device-related thrombus

ICE = intracardiac echocardiography

LAA = left atrial appendage

LAAC = left atrial appendage closure

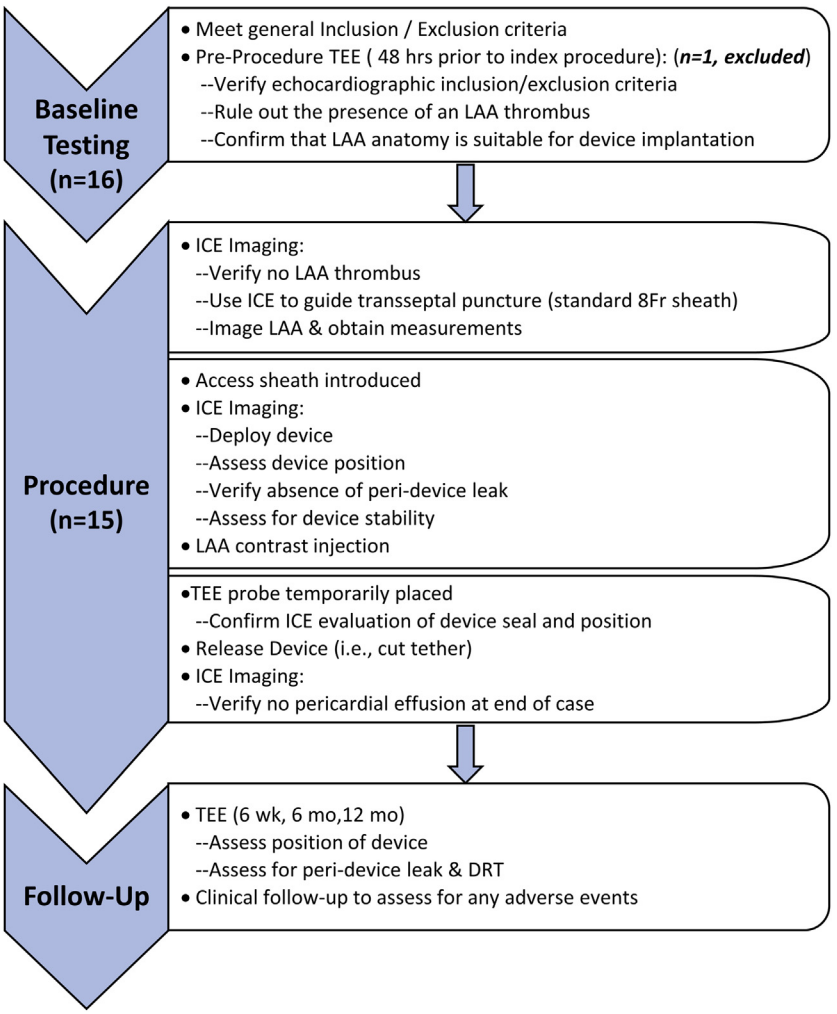
TEE = transesophageal echocardiography

TIA = transient ischemic attack

was noninferior to warfarin for the primary composite endpoint of stroke, systemic embolism, or cardiovascular death (4,5). In addition, a recent meta-analysis of 3 randomized clinical trials—PROTECT-AF, PREVAIL, and PRAGUE-17—demonstrated acceptable benefit to risk ratios for left atrial appendage closure (LAAC) in patients with nonvalvular AF and a high risk for stroke or systemic embolism. Device implantation was associated with a ~78% reduction in hemorrhagic stroke and a 47% reduction in cardiovascular death at a mean follow-up of 38 ± 17 months (6). Furthermore, other LAAC devices such as Amplatzer Cardiac Plug (Abbott Laboratories) (7,8) and LAmbre (Lifetech Scientific) (9) showed favorable efficacy for the prevention of AF-related thromboembolism.

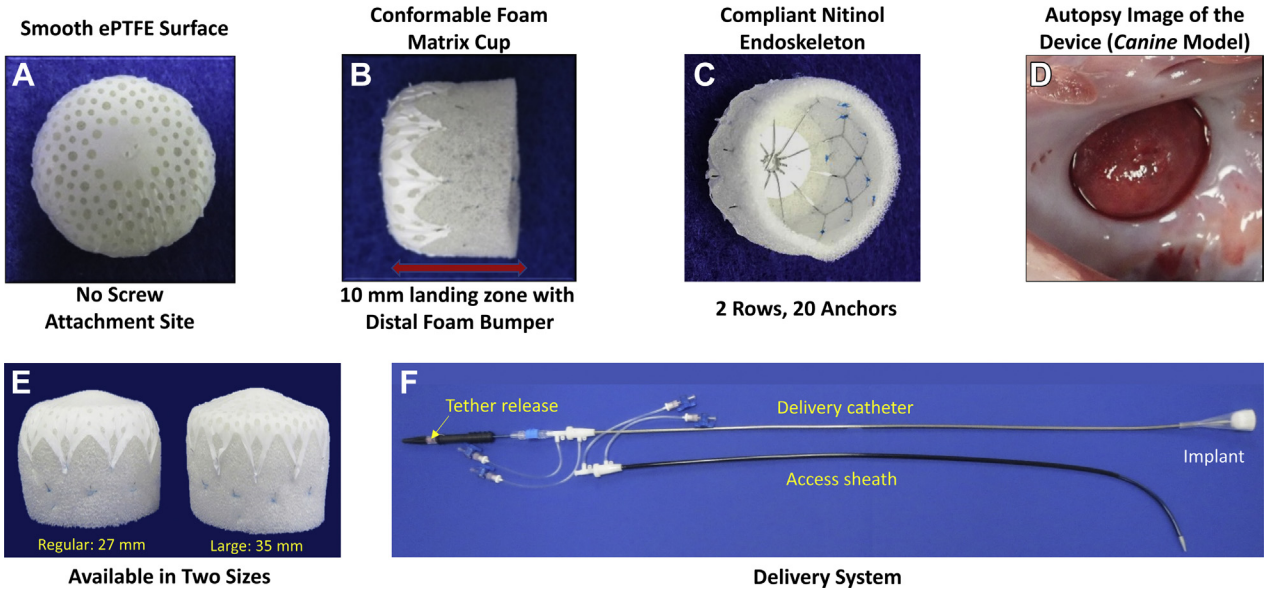
Although LAAC with these various devices represents an important advance in stroke prevention for patients with AF, important limitations and opportunities for improvement exist. This includes addressing the technical challenges of implantation (coaxial delivery of the implant), restrictions of the types of LAA anatomies that can be effectively sealed, minimizing trauma during implantation, lowering the rate of residual peridevice leak, and device-related thrombus (DRT). In addition, there is a current need to perform extensive imaging involving a transesophageal echocardiography (TEE), which requires

FIGURE 1 Study Enrollment and Follow-Up



DRT = device-related thrombus; ICE = intracardiac echocardiography; LAA = left atrial appendage; TEE = transesophageal echocardiography.

FIGURE 2 Conformal Device



(A) Left atrial face with polytetrafluoroethylene (ePTFE) cover. **(B)** Side view showing anchors and ePTFE attachment. **(C)** Inside view showing the nitinol endoskeleton, foam, ePTFE inner cover, and tether pin. **(D)** Autopsy image of the implanted device. **(E)** Available in 2 sizes: 27 and 35 mm. **(F)** Delivery system.

general anesthesia for precise device sizing and implantation. Accordingly, in a nonrandomized, prospective single-center study, we examined feasibility, safety, and effectiveness of LAAC using a novel foam-based conformable device. Further, we assessed its implantation guided by intracardiac echocardiography (ICE) as an alternative to TEE guidance.

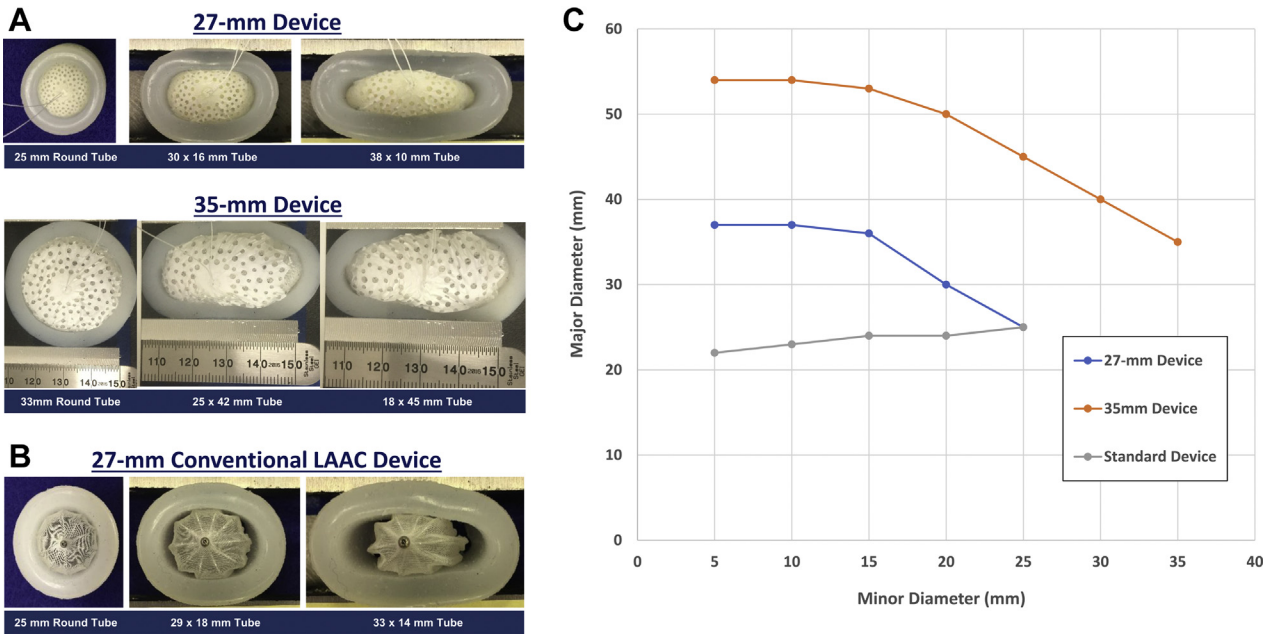
METHODS

STUDY DESIGN AND POPULATION. This prospective, single-center, open-label, single-arm study (NCT04193826) was performed to evaluate the safety and technical performance of the foam-based LAAC device (Conformal Left Atrial Appendage Seal—CLAAS; Conformal Medical Inc). The study cohort included patients with nonvalvular AF who were at increased risk for thromboembolism based on CHA_2DS_2-VASc scores and who were recommended for oral anticoagulation therapy, but who had an appropriate rationale to seek a nonpharmacologic alternative to oral anticoagulation. In this prospective registry, consecutive patients who met the study inclusion/exclusion criteria underwent the procedure in accordance with the manufacturer's guidelines between December 2019 and March 2020, using ICE to guide device implantation under local anesthesia with moderate sedation (Figure 1). Written and informed consent was obtained from each patient, and the study was approved by the Homolka Hospital institutional ethical committee and country regulatory authorities.

STUDY INCLUSION/EXCLUSION CRITERIA. The patient cohort had a diagnosis of nonvalvular AF (paroxysmal, persistent, or permanent), were ≥18 years of age, had CHA_2DS_2-VASC ≥2, had an appropriate rationale to seek a nonpharmacological alternative to OAC, had a patient condition that allows adequate ICE/TEE assessment, and provided IRB-approved written informed consent.

Study exclusion criteria included the following: 1) prior patent foramen ovale, atrial septal defect, LAA ligation, or prior implanted closure device; 2) a history of medical condition that mandates long-term oral anticoagulation (pulmonary embolism or deep vein thrombosis or mechanical heart valve); 3) severe heart failure with left ventricular ejection fraction <30%, NYHA functional class III-IV; 4) history of coagulopathy or bleeding diathesis with contraindication to antithrombotic therapy; 5) documented severe carotid stenosis (>50% stenosis with prior ipsilateral stroke/TIA or >70% asymptomatic stenosis); 6) recent history of stroke/transient ischemic attack (within 60 days) or myocardial

FIGURE 3 Conformability Testing



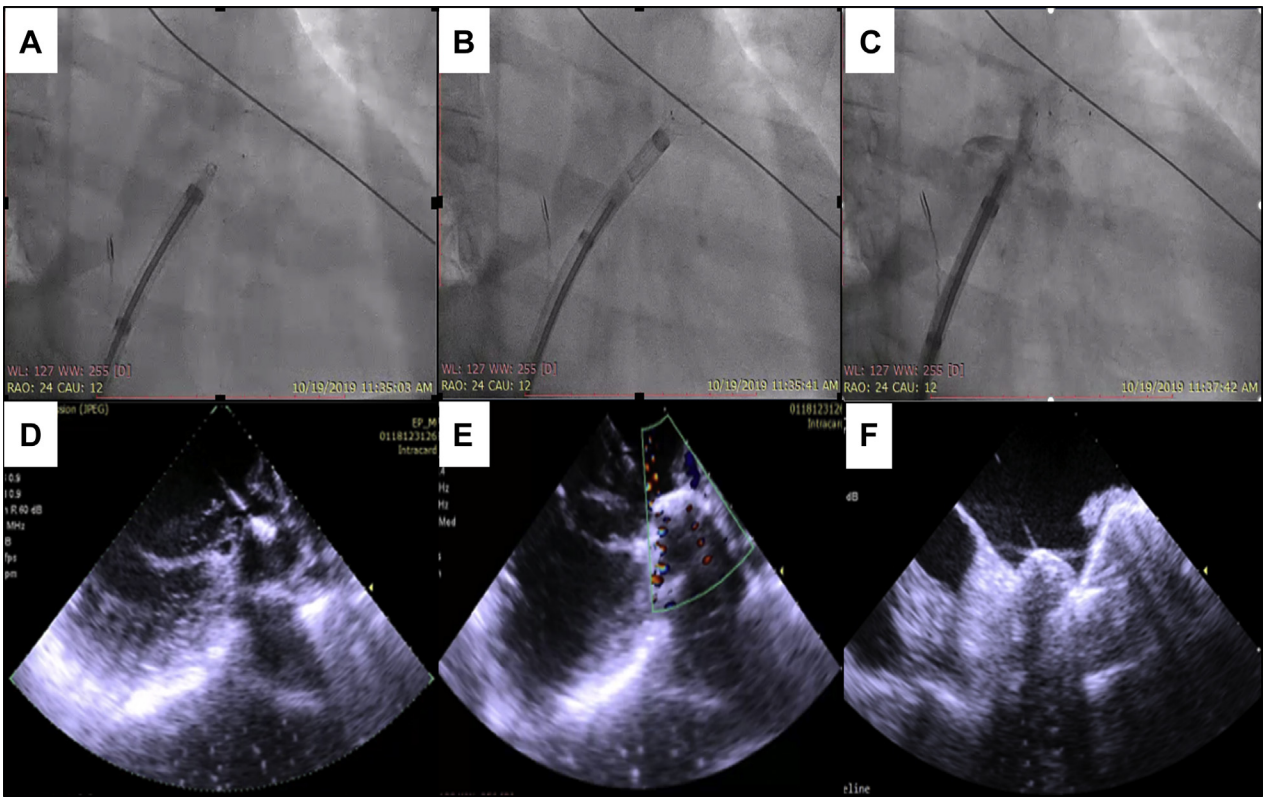
(A) Conformability testing utilizing an appropriately sized silicone tube submerged in a water bath at 37°C showing a 27- and 35-mm Conformal implant going from round to oval and able to conform to the shape of the tube. **(B)** Conformability testing utilizing an appropriately sized silicone tube submerged in a water bath at 37°C showing a 27-mm Watchman 2.5 LAAC device that does not conform to the shape of the tube. **(C)** Graphical depiction showing response of Conformal and Watchman 2.5 devices to compression.

infarction (within 90 days); 7) severe renal insufficiency (estimated glomerular filtration rate <30 mL/min/1.73 m^2) or dialysis; 8) presence of dense spontaneous echo contrast or LAA thrombus; 9) moderate-severe mitral valve stenosis (mitral valve area <1.5 cm^2); 10) complex mobile plaque of the aorta; 11) symptomatic or asymptomatic pericardial effusion (>1 cm) or signs and symptoms of pericarditis; and 12) LAA anatomy unable to accommodate the device.

FOAM-BASED LAAC DEVICE CHARACTERISTICS. The LAAC device system is comprised of an implant and a delivery system. The implant is a self-expanding occluder consisting of a cylindrical nitinol endoskeleton (with low-profile anchor barbs around the midpoint) covered with a porous foam cup made up of polyurethane-carbonate matrix foam (Figure 2). The foam is highly conformable, is porous, and promotes tissue ingrowth to permanently close off the LAA, with an endothelial layer eventually covering the implant. The foam also provides an atraumatic distal tip for procedure safety during implantation. The proximal face of the porous foam cup has a polytetrafluoroethylene (ePTFE) fabric cover to provide a thromboresistant outer surface, and the distal portion of the cup extends beyond the endoskeleton to serve as an atraumatic leading edge. The implant is available in 2 sizes that are 27 mm (regular) and 35 mm (large) in diameter, with a landing zone of 10 mm. The endoskeleton has 2 rows of anchors: 10 each in the regular and 12 each in the large device. The device is recapturable and redeployable before final release from the delivery system (available as single-curve and double-curve tips) via a flexible suture/tether that attaches to a tether pin on the endoskeleton and allows the surface to be metal free. A 27-mm device can be used for a mean LAA diameter ranging from 13-25 mm whereas a 35-mm device can be used for a mean LAA diameter ranging from 20-32 mm (10).

BASELINE TESTING. As shown in the protocol flowchart (Figure 1), all patients underwent preprocedure TEE imaging within 24-48 hours of the procedure to both ensure the absence of an LAA thrombus and evaluate echocardiographic eligibility, including calculation of the LAA dimensions for device sizing.

FIGURE 4 **Implantation of Conformal LAAC**



(A) Implantation of Conformal LAAC device on fluoroscopy. **(B)** Device recapture on fluoroscopy. **(C)** Fluoroscopy imaging with contrast injection demonstrating device stability. **(D)** Advancement of the Conformal device into the LAA using ICE imaging. **(E)** Assessment of leak: assessment of peridevice leak using Doppler color imaging. **(F)** ICE imaging demonstrates a well seated Conformal device. LAAC = left atrial appendage closure; other abbreviations as in Figure 1.

No computed tomography (CT)/cardiac magnetic resonance imaging or 3-dimensional reconstruction software was used. Regarding the latter, because of the relationship of the foam with the nitinol endoskeleton, this device is unlike many other LAAC devices in that compression in one dimension will result in expansion in the perpendicular dimension (Figure 3).

PROCEDURE CHARACTERISTICS. All patients received a loading dose of aspirin 81-100 mg 1 day before the procedure. Percutaneous femoral vein access and transseptal puncture were performed using a standard commercially available transseptal access system using ICE and fluoroscopy. Intravenous heparin was given prepuncture as a bolus to maintain an activated clotting time of 250-350 seconds. A 10-Fr AcuNav ICE catheter (Siemens) was advanced first into the proximal pulmonary artery to exclude LAA thrombus. The ICE catheter was then advanced through the transeptal hole into the left atrium to visualize the LAA. LAA dimensions were obtained with the ICE catheter positioned retroflexed facing the LAA (analogous to the 45° TEE view), retroflexed and rotated to across the mitral valve facing "upwards" toward the LAA (analogous to the 135° TEE view) and in the left superior pulmonary vein visualizing the LAA across the ridge. A pigtail catheter was positioned in the LAA, and contrast was injected to assess LAA morphology. LAA sizing and device landing zone were assessed using preprocedure TEE, ICE, and fluoroscopy.

After selecting the appropriate LAAC device size, it was inserted using ICE and fluoroscopy guidance (Supplemental Appendix, Videos 1, 2, 3, 4, 5, 6, 7, 8). Peridevice leak was assessed with angiography and Doppler imaging. Partial and full device recaptures were performed if necessary to achieve optimal LAA seal (≤5 mm). A tug-test was performed to ensure device stability (Figure 4).

TABLE 1 Baseline Demographics (n = 15)

Age, y	71.3 ± 10.8
Men	5 (33)
Age ≥75 y	7
CHA_2DS_2-VAS_c score	4.1 ± 1.7
HAS-BLED score	3.4 ± 1.4
Reason for LAA closure	
Ocular bleeding	1
Fall risk	1
Stroke	1
GI bleeding	4
Stroke/TIA	3
LAA thrombus	1
Epistaxis	2
Other	2
Antithrombotic agents	
Aspirin	2
Aspirin/clopidogrel	1
Aspirin/dabigatran	5
Aspirin/apixaban	6
Dabigatran	1
Stroke assessments	
Questionnaire for verifying stroke-free Status	10 (67)
Modified Rankin scale	0.8 ± 1.2
NIH stroke scale	0.8 ± 1.5

Values are n, n (%), or mean ± SD.
LAA = left atrial appendage; NIH = National Institutes of Health.

TABLE 2 Procedure Details (n = 15)

Least LAA depth, mm	22 ± 7.4
LAA orifice diameter, mm	21.7 ± 4.5
Device size, mm • Regular (27 mm) • Large (35 mm)	 11 4
Device success	15 (100)
Number of devices/procedure	1.4 ± 0.7
First choice[a] of device (n = 11) • Full recaptures • Partial recaptures	14 0
Second choice[a] of device (n = 2) • Full recaptures • Partial recaptures	2 3
Third choice[a] of device (n = 2) • Full recaptures • Partial recaptures	3 7
Procedure duration, min	55.1 ± 20.6
Fluoroscopy duration, min	6 ± 2.4
Contrast volume, mL	41.5 ± 14.5
Peak activated clotting time, min	298 ± 45
LAA leak • Residual flow 0-2 mm • Residual flow ≥3 mm	 1 0
Acute complications	0
Device-related thrombus	0

Values are mean ± SD or n. [a]Choice = device size. Two patients required a second device size. Two other patients required 3 devices (2 devices were damaged in 1 patient requiring a third device, while in the second patient a large device was used initially followed by a regular device and subsequently a large device caused by a difficult LAA anatomy).
LAA = left atrial appendage.

At the point of being ready to release the tether, TEE imaging was performed: 1) to confirm implant location and proximal sealing of the LAA ostium; 2) evaluate peridevice leaks; and 3) to test the stability of the device by checking the movement of the implant relative to the LAA before release. Once confirmed, the tether was cut and removed, thereby deploying the device.

FOLLOW-UP. Patients were hospitalized overnight and underwent TTE imaging before discharge for evaluation of pericardial effusion. All patients underwent a stroke assessment, which included a Questionnaire for Verifying Stroke-Free Status (QVSFS) and a National Institutes of Health Stroke Scale (NIHSS), performed by a neurologist or NIHSS-certified research staff before discharge and at 7-day, 45-day, 6-month, and 1-year follow-up. Patients in whom a neurological event was suspected based on the QVSFS, NIHSS, or other signs or symptoms underwent a complete neurological examination and evaluation performed by a neurologist. In patients with confirmed stroke, modified Rankin scale was documented and repeated at 3 months postevent to assess disability.

TEE/CT was scheduled at 45 days, 6 months, and 12 months to assess device position, peridevice LAA flow, and DRT. All patients with adequate seal (residual leak ≤5 mm) at implantation received dual antiplatelet therapy (aspirin 75-100 mg daily and clopidogrel 75 mg daily) until 45 days based on a prior preclinical study (10). If 45-day TEE/CT demonstrated adequate closure, dual antiplatelet therapy (DAPT) was continued for 6 months. If a 6-month TEE/CT demonstrated adequate closure, DAPT was replaced by a single antiplatelet agent (aspirin or $P2Y_{12}$ inhibitor) to 12 months postprocedure.

CLINICAL OUTCOME MEASURES. The primary safety endpoint was freedom from major adverse events, evaluated at hospital discharge or at 7 days post-procedure (whichever occurs later), and defined as absence of the composite of all-cause mortality, ischemic stroke, systemic thromboembolism, and device- or procedure-related adverse events requiring open cardiac surgery or major endovascular intervention such as arteriovenous fistula repair, pseudoaneurysm repair, or another major endovascular repair. Percutaneous drainage of pericardial effusion was also included in this endpoint.

The primary performance endpoint was closure success, defined as implantation success followed by

complete closure or peridevice residual leak ≤5 mm in width on TEE/CT at 45 days postprocedure.

The secondary safety endpoints included the following: 1) major procedure-related complications, defined as the composite of cardiac perforation, pericardial effusion with tamponade, ischemic stroke, device embolization, major bleeding (Bleeding Academic Research Consortium type 3-5), or vascular complications requiring surgical repair or thrombin injection evaluated in-hospital; and 2) major safety events, defined as the composite of all-cause mortality, overt central nervous system injury (Neuro ARC defined), major bleeding (Bleeding Academic Research Consortium type 3-5), DRT, device embolization, pericardial effusion resulting in invasive intervention (open cardiac surgery or percutaneous drainage), or vascular complications requiring surgical repair or thrombin injection evaluated at 45 days and 6 and 12 months.

Secondary performance endpoints included the following: 1) device success, defined as successful implantation of the device in the LAA with acceptable position and seal (peridevice residual leak ≤5 mm in width on ICE postprocedure); 2) procedure success, defined as device success without major in-hospital procedure-related complications during hospital stay or at 7 days, whichever is longer; and 3) closure success, defined as closure or peridevice residual leak ≤5 mm in width on TEE at 12 months postprocedure.

STATISTICAL ANALYSIS. Categorical variables were expressed as counts or percentages, while continuous variables were expressed as mean ± SD. All endpoints are reported using appropriate descriptive statistics in the primary analysis population, and no hypothesis testing was performed. The intention to treat analysis population was defined as all subjects enrolled in the study (the point of enrollment is introduction of the access sheath into the patient's body), regardless of the treatment received.

As a secondary analysis, all endpoints were evaluated in the implanted patient population, defined as all subjects who leave the catheterization laboratory with an implanted device. As this was an early feasibility study, sample size testing was not performed.

RESULTS

BASELINE CHARACTERISTICS. A total of 16 patients were screened and enrolled. One patient met study exclusion criteria after preprocedure TEE imaging revealed a surgically resected LAA. A total of 15 patients underwent LAAC with the device. No patients were excluded before introducing the delivery sheath. The mean age was 71.3 ± 10.8 years (range 52-87 years), and 67% were woman (Table 1). The average CHA_2DS_2-VAS_c and HAS-BLED scores were 4.1 ± 1.7 (range 2-7) and 3.4 ± 1.4 (range 1-6), respectively. Prior major bleeding occurred in 47%. Screening stroke assessment including QVSFS was negative in 10 (67%) patients. Baseline values for modified Rankin scale and NIHSS were 0.8 ± 1.2 and 0.8 ± 1.5, respectively.

TABLE 3 Clinical Outcomes

Primary safety endpoint (in hospital and ≤7 days postprocedure), %	
• All-cause mortality	0%
• Ischemic stroke/systemic thromboembolism	0%
• Device/procedure-related adverse events requiring open cardiac surgery or major endovascular interventions (including cardiac tamponade and vascular injury/groin complications)	0%
Primary performance endpoint (Complete closure or peridevice residual leak ≤5 mm in width on TEE at 45 days postprocedure)	
• Closure success	15 (100)
Secondary safety endpoints (events evaluated at 45 days and 6 and 12 months)	
• Major procedure-related complications	0%
• Major safety events (mortality, stroke, major bleeding, DRT)	3 (20)
Secondary performance endpoints	
• Device success (peridevice residual leak ≤5 mm in width on ICE/TEE post procedure)	15 (100)
• Procedure success (device success without major complications in hospital or ≤7 days postprocedure)	15 (100)
• Closure success (peridevice residual leak ≤5 mm in width on TEE/CT at 12 months postprocedure)	13 (100)
Minor safety events	
• Pericardial effusion (no intervention)	2 (18)
• Minor bleeding	1 (6.6)
Other measures	
• Ability to accurately assess device position and seal using ICE	15 (100)

Values are % or n (%).
CT = computed tomography; ICE = intracardiac echocardiography; TEE = transesophageal echocardiography.

IMPLANTATION PROCEDURE. The average maximal LAA orifice diameter on ICE imaging was 21.7 ± 4.5 mm (range 12-31 mm) and minimal LAA depth was 22 ± 7.4 mm (range 13-38 mm) (Table 2). The LAA was successfully occluded by the LAAC device in all 15 patients (*device success* = 100%). In 73% (11 of 15) of the successful cases, device implantation was managed with the first device selected; in 13% (2 of 15), a second device was selected; and in 13% (2 of 15), a third device was employed. First choice, second choice, and third choice devices were completely retrieved and redeployed in 14, 2, and 3 instances, respectively. The smaller 27-mm device was used in 11 (73%) patients, whereas the larger 35-mm device was used in 4 (27%) patients. A peridevice leak of <3 mm was detected on ICE imaging in 6.6% (1 of 15) of patients. No residual flow ≥3 mm was detected in any patient. The average procedure duration was 55.1 ± 20.6 min, and the average contrast volume

TABLE 4 TEE/CT Examination on Follow-Up

TEE/CT on Follow-Up	n
LAA seal at 45 days (n = 11)	
No residual flow	9
Residual flow 1-2 mm	2
Residual flow 3-4 mm	0
Residual flow ≥5 mm	0
Device-related thrombus	0
Pericardial effusion (not tamponade)	2
LAA seal at 6 months (n = 9)	
No residual flow	8
Residual flow 1-2 mm	1
Residual flow 3-4 mm	0
Residual flow ≥5mm	0
Device-related thrombus	1
Pericardial effusion (not tamponade)	0
LAA seal at 12 months (n = 13)	
No residual flow	12
Residual flow 1-2 mm	1
Residual flow 3-4 mm	0
Residual flow ≥5 mm	0
Device-related thrombus	0
Pericardial effusion (not tamponade)	0

LAA = left atrial appendage; other abbreviations as in Table 3.

used was 41.5 ± 14.5 mL. There were no major procedure-related complications in the entire cohort.

In combination with fluoroscopy, ICE was able to successfully guide implantation and accurately assess device position and seal in all 15 patients during the index procedure; the latter was confirmed by prerelease TEE imaging. For the single patient with a small residual leak, the leak *was identified* by ICE, but because of the inability with reducing this leak further despite repositioning, it was decided to accept this position (since the leak was small, <3 mm); again, prerelease TEE imaging confirmed this leak.

CLINICAL OUTCOMES. The primary safety endpoint occurred in 0% of patients. Primary performance endpoint measured of LAAC success was 100% (15 of 15). Follow-up 45-day TEE imaging demonstrated 100% device and procedure success with no peridevice leak ≥5 mm in any patient (Table 3). All devices remained stable at the site of deployment. In 11 of 11 patients (4 missed TEE caused by COVID-19), TEE at 45 days revealed adequate seal (9 patients had no leak, 1 patient had a 1-mm leak, and 1 patient had a 2-mm leak) and no DRT (Table 4). There were no instances of stroke/TIA, device embolization, vascular injury/groin complications, or DRT. Two patients had asymptomatic pericardial effusion (3 and 4 mm in size) on day 7 (on TTE) and day 45 (on TEE), both of which resolved without intervention. The former occurred during a temporary pacemaker insertion for complete heart block (day 7).

In 9 patients (6 patients missed TEE because of COVID-19), TEE imaging at 6 months revealed adequate seal in 100% (8 patients had no leak, 1 patient had a 1-mm leak). One patient had a moderate-sized DRT that was successfully treated with subcutaneous enoxaparin (Supplemental Figure 1). TEE or CT at 1 year was performed in 13 patients (TEE in 11 patients and CT in 2 patients), revealing no instances of peridevice leaks in 12 patients and a small leak in 1 patient on CT imaging (Table 4). There were no device- or procedure-related serious adverse events. There were 2 deaths: 1 patient died at 6 months because of heart failure and 1 patient had a sudden death at 12-month follow-up. Both deaths were not procedure or device related.

There were no strokes/TIA or major bleeding at any of the time points during follow-up. One patient had minor bleeding from epistaxis at 6-month follow-up, which resolved without intervention.

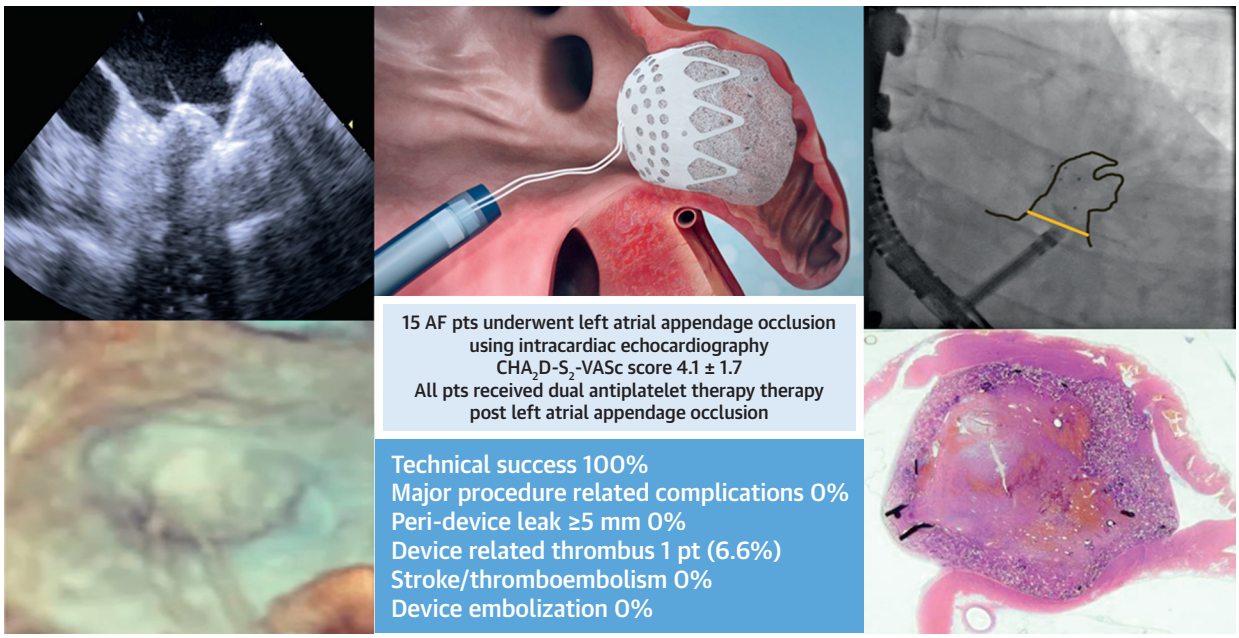
DISCUSSION

In this first-in-human experience, ICE-guided LAAC with the conformable LAAC device was feasible and safe, with encouraging 1-year clinical outcomes among patients with nonvalvular AF (Central Illustration).

CLINICAL EFFICACY. We achieved 100% procedure and LAA device success with no in-hospital complications or instances of residual leak ≥5 mm on midterm follow-up. The encouraging results can be attributed to the ability of the conformal device to expand in width during compression and effectively seal a variety of LAA anatomies (10). Similar favorable short-term and long-term results were shown using this novel conformable LAAC device in a preclinical canine study. Importantly, the animal explants demonstrated good apposition and complete sealing of the LAA with an appropriate inflammatory response to the implant at 60 days despite the use of DAPT (10).

CLINICAL SAFETY. The self-expanding, cylindrical nitinol endoskeleton of this conformable device covered with a porous foam cup is atraumatic and is designed to minimize the risk of acute procedural complications, especially cardiac perforation. In our study, there were no instances of procedure-related cardiac perforation despite 19 full recaptures and 10 partial recaptures before final release, implying significant manipulation of the device within the LAA. Two patients were found to have an asymptomatic

CENTRAL ILLUSTRATION **Left Atrial Appendage Occlusion With the Novel Conformable Device Using Intracardiac Echocardiography**



Turagam, M.K. et al. J Am Coll Cardiol EP. 2021;■(■):■-■.

AF = atrial fibrillation.

pericardial effusion on follow-up imaging at 7 (related to a temporary pacemaker) and 45 days, which were managed conservatively. The mechanism of these late effusions is unknown, but is potentially caused by inflammation—although one cannot rule out the possibility of transient accumulation of blood from micropuncture of the atrial wall by the device fixation barbs.

Device embolization is a rare but serious complication associated with transcatheter LAAC. In our small series, there were no early or late device embolization. This is attributed to the foam-based design, which is inherently occlusive, and the porous ePTFE cover, which enables blood to flow at arterial pressure avoiding device embolization.

There were also no instances of device displacement or peridevice leaks of ≥5 mm either at the 45-day, 6-month, or 1-year follow-up imaging. In addition, only 18% (2 of 9), 11% (1 of 9), and 7.7% (1 of 13) of patients had any peridevice flow ≤5 mm at 45-day and 6- and 12-month follow-up. This is consistent with the device's ability to conform to both shallow and irregular LAA anatomy while maintaining secure fixation over a wide range of LAA diameters (13-32 mm). Unlike the other available LAAC devices, this conformable implant seals even when off axis and therefore does not require the delivery sheath to be precisely oriented coaxial to the LAA ostium.

Periprocedural and stroke at 1 year is reported to occur with an incidence of 0%-0.9% and 0.5%-2.2% among patients receiving transcatheter LAAO (11-16). DRT occurred in 1 patient (6.6%) after 6 months of follow-up; none of the patients had any stroke or thromboembolic events. This occurred against the backdrop of a postimplant regimen of 6 weeks of DAPT as seen in the recent Amulet registry (8,16), and compared with the combination of warfarin and aspirin in the PROTECT-AF and PREVAIL clinical trials and NOAC and aspirin in the PINNACLE FLX (Protection Against Embolism for Nonvalvular AF Patients: Investigational Device Evaluation of the Watchman FLX LAA Closure Technology) study. The thrombogenicity of the conformable device is thought to be low because of both the less thrombogenic ePTFE covering and the flexible tether, which eliminates any exposed metal central insert attachment site. However, because of a small number of patients with limited follow-up, any firm conclusions as to the risk of DRT are premature.

ROLE OF ICE. Intraprocedural imaging with TEE has been the gold standard for implantation of transcatheter LAAC devices because it provides high-resolution multiplanar imaging, allows 3-dimensional visualization, and is a familiar technique among cardiologists. However, TEE has several limitations, such as the need for a dedicated echocardiographer, endotracheal intubation, and general anesthesia (GA), which may potentially increase the risk of complications and thus adversely affect patient satisfaction and outcomes (17). ICE has evolved as a powerful imaging modality in certain structural heart interventions, thereby eliminating the need for GA and instead using local anesthesia or moderate sedation. Prior observational studies have explored the role of ICE-guided percutaneous LAAC and found good correlation between LAA ostium size and landing zone measured by ICE, TEE imaging, and fluoroscopy (18-20). Subsequently, several observational studies and meta-analyses have assessed the role of TEE vs ICE for LAAC and found no differences in clinical outcomes (19,21-27).

An important advantage of ICE-guided LAAC under local anesthesia or moderate sedation is the expeditious procedure turnaround time and resource savings related to anesthesia (25). Of course, it should be acknowledged that general anesthesia is not necessary for TEE and can be performed with deep sedation; however, this requires careful patient selection and close monitoring and is not accepted at many institutions. In our study, ICE was used to guide transeptal puncture and provided relatively high-resolution images for LAAC device implantation without general anesthesia. The ICE images were comparable in quality to TEE imaging. More importantly, the measurements of LAA both ostial diameter and depth, which are crucial for device sizing, were consistent between the 2 imaging modalities. In our experience, the LAA dimensions can be accurately estimated by ICE directly facing the LAA ostium, from the left superior pulmonary vein, or retroflexed below the mitral valve. Although preoperative TEE was obtained in all patients to exclude LAA thrombus and assess for eligibility, placing a probe in the right ventricular outflow tract or pulmonary artery before transeptal puncture can reliably exclude thrombus with a concordance rate of 97% in the left atrium and 92% in the LAA when compared with TEE imaging (28).

In addition to our study, there is a multicenter U.S. Food and Drug Administration Early Feasibility Study (ClinicalTrials.gov: NCT03616028) including ~45 patients underway in the United States, with a primary endpoint of freedom from major adverse events. A pivotal large randomized controlled trial comparing the conformable LAAC device to the Watchman-FLX device is planned to commence later in 2021.

STUDY LIMITATIONS. First, the study is a single-center, nonrandomized study with no control group. Second, obtaining adequate images with ICE depends on operator experience. Third, given that this is a research study of an investigational device, both TEE and ICE imaging were used in all cases, which does not reflect real-world clinical practice. Fourth, all patients enrolled in the study were unable to obtain follow-up TEE imaging at 45 days and 6 months because of logistic issues related to the ongoing COVID-19 pandemic. Fifth, although necropsy studies have demonstrated safety of the foam-based device at 60 days, the long-term effects on the blood stream are yet to be determined (10). Finally, although this study is sufficient to prove the feasibility of this novel LAAC device, adequate interpretation of rare adverse events such as DRT and device embolization are not possible because of the small sample size.

CONCLUSIONS

Under conscious sedation, ICE-guided LAAC with a novel conformable device implant is safely feasible and results in good appendage seal at 1-year follow-up.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

Conformal Medical, Inc, provided funding for this study. Dr Neuzil has received grants from Conformal Medical Inc and Biosense Webster Inc. Dr Dukkipati has received a grant from Biosense Webster. Dr Reddy has served as an unpaid consultant to Conformal Medical Inc and Biosense Webster Inc; has served as a consultant for and has equity in Ablacon, Acutus Medical, Affera, Apama Medical, Aquaheart, Atacor, Autonomix, Backbeat, BioSig, Circa Scientific, Corvia Medical, Dinova-Hangzhou Nuomao Medtech Co, Ltd, East End Medical, EPD, Epix Therapeutics, EpiEP, Eximo, Fire1, Javelin, Kardium, Keystone Heart, LuxCath, Medlumics, Middlepeak, Nuvera, Sirona Medical, and Valcare unrelated to this work; has served as a consultant for Abbott, Axon, Biotronik, Cardiofocus, Cardionomic, CardioNXT/AFTx, EBR, Impulse Dynamics, Medtronic, Philips, Pulse Biosciences, Stimda, and Thermedical unrelated to this work; and has equity in Manual Surgical Sciences, Newpace, Surecor, and Vizaramed unrelated to this work. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

ADDRESS FOR CORRESPONDENCE: Dr Vivek Y. Reddy, Helmsley Electrophysiology Center, Icahn School of Medicine at Mount Sinai, One Gustave L. Levy Place, Box 1030, New York, New York 10029, USA. E-mail: vivek.reddy@mountsinai.org. Twitter: @vivekreddymd, @mohitkturagam.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: The novel foam-based conformable device can be safely implanted with intraprocedural ICE imaging substituting for TEE.

TRANSLATIONAL OUTLOOK: Although, ICE-guided implantation of the novel foam-based conformable device is associated with excellent procedural success and low risk of complications on midterm follow-up, future studies should explore the safety and efficacy of this device on long-term follow-up.

REFERENCES

1. Blackshear JL, Odell JA. Appendage obliteration to reduce stroke in cardiac surgical patients with atrial fibrillation. *Ann Thorac Surg*. 1996;61:755–759.

2. Turagam MK, Velagapudi P, Kar S, et al. Cardiovascular therapies targeting left atrial appendage. *J Am Coll Cardiol*. 2018;72:448–463.

3. Cresti A, García-Fernández MA, Sievert H, et al. Prevalence of extra-appendage thrombosis in non-valvular atrial fibrillation and atrial flutter in patients undergoing cardioversion: a large trans-oesophageal echo study. *EuroIntervention*. 2019;15:e225–e230.

4. 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;374:534–542.

5. 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.

6. Turagam MK, Osmancik P, Neuzil P, Dukkipati SR, Reddy VY. Left atrial appendage closure versus oral anticoagulants in atrial fibrillation: a meta-analysis of randomized trials. *J Am Coll Cardiol*. 2020;76:2795–2797.

7. 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;11:1170–1179.

8. Lakkireddy D, Thaler D, Ellis CR, et al. Amplatzer™ Amulet™ Left Atrial Appendage Occluder Versus Watchman™ Device for Stroke Prophylaxis (AMULET IDE): a randomized controlled trial. *Circulation*. Published online August 30, 2021. https://doi.org/10.1161/CIRCULATIONAHA.121.057063

9. 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;10:2188–2194.

10. Sommer RJ, Lamport R, Melanson D, et al. Preclinical assessment of a novel conformable foam-based left atrial appendage closure device. *Biomed Res Int*. 2021;2021, 4556400-4556400.

11. Freeman JV, Varosy P, Price MJ, et al. The NCDR left atrial appendage occlusion registry. *J Am Coll Cardiol*. 2020;75:1503–1518.

12. 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;69:253–261.

13. Glikson M, Wolff R, Hindricks G, et al. EHRA/EAPCI expert consensus statement on catheter-based left atrial appendage occlusion - an update. *EuroIntervention*. 2020;15(13):1133–1180. https://doi.org/10.4244/EIJY19M08_0

14. Kar S, Doshi SK, Sadhu A, et al. Primary outcome evaluation of a next-generation left atrial appendage closure device: results from the PINNACLE FLX Trial. *Circulation*. 2021;143:1754–1762.

15. Friedman D, Chengan D, Wang Y, et al. Outcomes of left atrial appendage occlusion with watchman in contemporary clinical practice compared with clinical trials: a pooled analysis of PROTECT-AF, PREVAIL, and the NCDR LAAO Registry (abstract). *Heart Rhythm*. 2021;18(S, Suppl 2):s252.

16. Hildick-Smith D, Landmesser U, Camm AJ, et al. Left atrial appendage occlusion with the Amplatzer™ Amulet™ device: full results of the prospective global observational study. *Eur Heart J*. 2020;41:2894–2901.

17. Freitas-Ferraz AB, Bernier M, Vaillancourt R, et al. Safety of transesophageal echocardiography to guide structural cardiac interventions. *J Am Coll Cardiol*. 2020;75:3164–3173.

18. Matsuo Y, Neuzil P, Petru J, et al. Left atrial appendage closure under intracardiac echocardiographic guidance: feasibility and comparison with transesophageal echocardiography. *J Am Heart Assoc*. 2016;5(10):e003695.

19. Berti S, Pastormerlo LE, Santoro G, et al. Intracardiac versus transesophageal echocardiographic guidance for left atrial appendage occlusion: the LAAO Italian Multicenter Registry. *J Am Coll Cardiol Intv*. 2018;11:1086–1092.

20. Ho IC, Neuzil P, Mraz T, et al. Use of intracardiac echocardiography to guide implantation of a left atrial appendage occlusion device (PLAATO). *Heart Rhythm*. 2007;4:567–571.

21. Frangieh AH, Alibegovic J, Templin C, et al. Intracardiac versus transesophageal echocardiography for left atrial appendage occlusion with watchman. *Catheter Cardiovasc Interv*. 2017;90:331–338.

22. Kim DY, Shin SY, Kim JS, Kim SH, Kim YH, Lim HE. Feasibility of intracardiac echocardiography imaging from the left superior pulmonary vein for left atrial appendage occlusion. *Int J Cardiovasc Imaging*. 2018;34:1571–1579.

23. Korsholm K, Jensen JM, Nielsen-Kudsk JE. Intracardiac echocardiography from the left atrium for procedural guidance of transcatheter left atrial appendage occlusion. *J Am Coll Cardiol Intv*. 2017;10:2198–2206.

24. Nielsen-Kudsk JE, Berti S, De Backer O, et al. Use of intracardiac compared with transesophageal echocardiography for left atrial appendage occlusion in the Amulet Observational Study. *J Am Coll Cardiol Intv*. 2019;12:1030–1039.

25. Hemam ME, Kuroki K, Schurmann PA, et al. Left atrial appendage closure with the Watchman device using intracardiac vs transesophageal echocardiography: Procedural and cost considerations. *Heart Rhythm*. 2019;16:334–342.

26. Akella K, Murtaza G, Turagam M, et al. Evaluating the role of transesophageal echocardiography (TEE) or intracardiac echocardiography (ICE) in left atrial appendage occlusion: a meta-analysis. *J Interv Card Electrophysiol*. 2021;60(1):41–48.

27. Velagapudi P, Turagam MK, Kolte D, et al. Intracardiac vs transesophageal echocardiography for percutaneous left atrial appendage occlusion: a meta-analysis. *J Card Electrophysiol*. 2019;30:461–467.

28. Saksena S, Sra J, Jordaens L, et al. A prospective comparison of cardiac imaging using intracardiac echocardiography with transesophageal echocardiography in patients with atrial fibrillation: the Intracardiac Echocardiography Guided Cardioversion Helps Interventional Procedures Study. *Circ Arrhythm Electrophysiol*. 2010;3:571–577.

KEY WORDS amulet, intracardiac echocardiography, left atrial appendage occlusion, stroke prevention, Watchman FLX

APPENDIX For supplemental videos and a supplemental figure, please see the online version of this paper.