

ORIGINAL ARTICLE



Dual Epicardial and Endocardial Procedure (DEEP) for Persistent or Longstanding Persistent Atrial Fibrillation

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BACKGROUND: Despite advances in endocardial catheter ablation (ECA) for persistent atrial fibrillation (PersAF), undertreatment persists, especially in ECA nonresponders and in longstanding PersAF (LSPersAF), with disappointing ablation results. These patients need effective clinical treatment options.

METHODS: The DEEP (Dual Epicardial and Endocardial Procedure) was a prospective, multicenter, single-arm, investigational device exemption trial to establish the safety and effectiveness of a combined epicardial/endocardial ablation procedure with left atrial appendage exclusion for PersAF/LSPersAF. Eligibility included age 18 to 75 years; symptomatic PersAF/LSPersAF refractory to ≥ 1 Class I/III antiarrhythmic drug; and ≤ 2 previous failed ECAs. Two-stage hybrid ablation included ECA performed at 91 to 121 days after the epicardial first stage (including left atrial appendage exclusion), followed by a 90-day blanking and 90-day antiarrhythmic drug optimization period. Primary effectiveness was defined as freedom from documented atrial fibrillation/atrial flutter/atrial tachycardia episodes >30 seconds through the 12-month follow-up, absent Class I/III antiarrhythmic drugs, except previously failed antiarrhythmic drugs at doses not exceeding those previously failed. Primary safety was defined as a composite of device/procedure-related serious adverse events within 30 days of epicardial ablation and 7 days of ECA.

RESULTS: Ninety patients enrolled from February 2015 to December 2020; 83.3% (75/90) were male and mean $\pm$ SD age was 63.4 $\pm$ 7.7 years. AF classification was 83.3% (75/90) PersAF/16.7% (15/90) LSPersAF, and 47.8% (43/90) had prior ECA. The composite serious adverse events rate was 6.7% (6/90 [95% CI, 2.5%–13.9%]; $P<0.001$ versus safety goal), including 3 patients experiencing serious adverse events within 30 days of the epicardial procedure and 3 patients within 7 days of the endocardial procedure, all of whom were anticoagulated at the time of the event. Primary effectiveness through 12 months was 71.8% (61/85 [95% CI, 62.2%–81.3%]; $P=0.0134$ versus performance goal) and was 62.4% (53/85 [95% CI, 52.1%–72.7%]) through 2 years.

CONCLUSIONS: A collaborative hybrid ablation approach to treating PersAF/LSPersAF is safe and effective.

REGISTRATION: URL: <https://www.clinicaltrials.gov>; Unique identifier: NCT02393885.

GRAPHIC ABSTRACT: A graphic abstract is available for this article.

Key Words: atrial fibrillation ■ catheter ablation ■ freedom ■ goals ■ tachycardia

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WHAT IS KNOWN?

- Atrial fibrillation is the most common sustained tachyarrhythmia globally and increases risk of stroke, heart failure, and death.
- Advanced forms of atrial fibrillation can be resistant to pharmacological and endocardial ablation procedures, requiring repeated interventions.
- Quality of life is impacted by atrial fibrillation symptom burden and a return to normal sinus rhythm may improve quality of life.

WHAT THE STUDY ADDS

- The DEEP (Dual Epicardial and Endocardial Procedure) was a prospective, multicenter trial that evaluated safety and effectiveness of a 2-stage epicardial-endocardial ablation plus left atrial appendage exclusion approach in patients with persistent and longstanding persistent atrial fibrillation, including patients who had failed prior catheter ablation.
- The DEEP trial met primary safety (6.8%) and effectiveness through 12 months (71.8%), with 62.4% effectiveness through 2 years.

Nonstandard Abbreviations and Acronyms

AAD	antiarrhythmic drug
AEF	atrioesophageal fistula
AF	atrial fibrillation
AFEQT	atrial fibrillation effect on quality of life
AFL	atrial flutter
AT	atrial tachycardia
CTI	cavotricuspid isthmus
DEEP	Dual Epicardial and Endocardial Procedure
ECA	endocardial catheter ablation
IQR	interquartile range
LAAE	left atrial appendage exclusion
LAD	left atrial diameter
LSPersAF	longstanding persistent atrial fibrillation
mITT	modified intent-to-treat
PersAF	persistent atrial fibrillation
PVI	pulmonary vein isolation
PV	pulmonary vein
QOL	quality of life
SAE	serious adverse events
TEE	transesophageal echocardiography

Atrial fibrillation (AF) is the most common sustained tachyarrhythmia encountered in clinical practice and has become more prevalent with an aging population and other risk factors.¹ Patients with AF have a 4- to 5-fold higher risk of stroke and a 5-fold increased risk of

heart failure, which can lead to increased mortality.² The disease progression to persistent AF, and increased AF burden is also associated with increased risk of morbidity. This can have a negative effect on patient-reported outcomes such as quality of life (QOL) for those with early persistent and longstanding persistent AF.^{3,4} The progressive nature of AF is described by a classification scheme based on frequency and duration, with the most advanced and difficult-to-treat forms known as nonparoxysmal AF, further defined as persistent AF (PersAF) and longstanding persistent AF (LSPersAF).² Single procedure success of endocardial catheter ablation (ECA) for PersAF ranges from 55% to 62% at 12 months,⁵⁻⁷ whereas ECA success rates at 12 months for patients with LSPersAF are reported to be 25% to 41%, leaving a considerable portion of this patient population inadequately treated.⁸⁻¹² A return to normal sinus rhythm and AF symptom reduction may result in improved QOL for patients with persistent AF, as suggested by recent ablation trials, in which some have shown as much as a 26 point improvement in QOL measurement from baseline to 12 months.^{6,13,14}

Hybrid ablation is a collaborative approach between electrophysiologists and cardiothoracic surgeons effectively targeting the pulmonary veins (PVs) and atrial substrate beyond PVs through combined epicardial and endocardial ablation, also including thoracoscopic left atrial appendage exclusion (LAAE). Several contemporary trials have demonstrated the success of a hybrid ablation approach to treat persistent forms of AF.^{9,11} Most recently, in the CEASE-AF trial—a European, multicenter randomized trial of hybrid ablation with LAAE compared with ECA—71.6% of patients in the hybrid arm and 39.2% in the ECA arm met the primary effectiveness outcome of freedom from atrial arrhythmias off antiarrhythmic drugs (AADs; except AADs at doses not exceeding those previously failed) through 12 months with no significant safety differences.⁸ Another recently published prospective, randomized, single-center HARTCAP-AF trial produced similar results with 89% of patients who received hybrid ablation with LAAE meeting the primary end point of freedom from atrial arrhythmias at 12 months compared with 41% of patients who received ECA only, with similar safety profiles.¹⁵ Similarly, CONVERGE, an international, multicenter randomized IDE trial, demonstrated significantly improved effectiveness of a hybrid ablation approach compared with ECA in freedom from atrial arrhythmias, both on and off AADs, as well as improved AF burden reduction at 18 months.⁹ Although the DEEP trial (Dual Epicardial and Endocardial Procedure) was not randomized, it did allow patients with up to 2 prior ablations, while CEASE-AF, HARTCAP-AF, and CONVERGE enrolled de novo patients.

Persistent AF patients have been difficult to effectively treat and may benefit from a safe and effective

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alternative treatment approach. The hypothesis of the DEEP trial is that a minimally invasive hybrid approach that includes epicardial ablation and LAAE, followed by endocardial mapping/ablation, is safe and effective to treat patients with symptomatic persistent AF who are medical therapy nonresponders, including AADs and prior ECA.

METHODS

Study Design

The primary results of the DEEP Trial are on ClinicalTrials.gov (NCT02393885) per FDAAA 801. Five years after trial completion, partial data may be provided to qualified researchers through a direct request, including proposed research question(s), to MedAffairs@atricure.com, determined by representatives of the Sponsor's Scientific, Clinical, and Medical Affairs departments. DEEP is a prospective, multicenter, single-arm trial to establish the safety and effectiveness of a dual epicardial and endocardial ablation procedure for patients presenting with PersAF or LSPersAF utilizing the AtriCure Bipolar System and AtriClip PRO LAA Exclusion System (AtriCure, Inc, Mason, OH) in an endoscopic procedure, followed by endocardial mapping and ablation utilizing commercially available endocardial RF ablation catheters. Seventeen centers in the United States, the Netherlands, and Belgium participated. Institutional review board or ethics committee approval was obtained at each center. An independent, noninvestigator, Clinical Events Committee comprised of an independently practicing cardiothoracic surgeon, electrophysiologist, and neurologist was established to review and adjudicate safety events in the trial. A Data Safety Monitoring Board comprised of a noninvestigator cardiothoracic surgeon, electrophysiologist, and a biostatistician was established; their identities remain anonymous to investigational sites to reduce potential bias. The trial was performed in accordance with 21 CFR Part 11, 50, 54, 56, and 812, ISO 14155:2011, HIPAA, and GCP. The trial sponsor (AtriCure, Inc, Mason, OH) performed data management and monitoring in the United States. A contract research organization (Cardialysis, Rotterdam, the Netherlands) performed data monitoring in Europe. Statistical analyses were performed by NAMSA (Northwood, OH). An overview of enrollment and follow-up procedures is shown in Figure 1.

Participants

Eligible patients were between 18 and 75 years of age at the time of consent; had symptomatic PersAF or LSPersAF refractory to at least 1 Class I or Class III AAD; left atrial diameter (LAD) up to 5.5 cm; and ≤ 2 previous failed ECA. Persistent AF was defined as continuous AF, which is sustained beyond 7 days, or lasting >48 hours and less than 7 days but necessitating pharmacological or electrical cardioversion.^{16,17} Longstanding persistent AF was defined as continuous AF of >12 months' duration. Key exclusion criteria were continuous AF >10 years; an ECA procedure to treat AF within 3 months before consent; and BMI >40 kg/m². Complete inclusion and exclusion criteria are in Table S1.

Procedures

Epicardial Surgical Ablation Procedure

Preprocedure management for enrolled subjects is described in Table S2. Hybrid ablation was performed as a 2-staged sequential epicardial and endocardial procedure.

The first stage of the procedure, minimally invasive epicardial surgical ablation, was performed under general anesthesia using a dual-lumen endotracheal tube for unilateral lung ventilation. The patient was placed in the supine position with the operated hemithorax elevated. The procedure involved a bilateral thoracoscopic approach to perform the epicardial lesion set (Figure 2). Precautions were taken to prevent phrenic nerve injury when opening the pericardium. Epicardial ablation was performed bilaterally through ports placed on the right and left sides of the patient. A lighted dissector (MID1) and attached rubber tape (GPT100) were used to guide Isolator Synergy bipolar RF clamps (EMR2 [right], EML2 [left]) into place for pulmonary vein isolation (PVI). Connecting linear roof and floor lines were created using RF pens (MLP1 or MCR1). Ganglionated plexi were tested and ablated on the right and left sides, as appropriate, using RF pens (MLP1 or MAX5). Pacing and sensing were performed to evaluate entrance and exit block (when in sinus rhythm) of the PVs and LA posterior wall. From the left side, a left superior PV to LAA lesion was made with the EML2 clamp. Dissection of the ligament of Marshall was recommended. LAAE with the AtriClip PRO1 or PRO2 device was recommended in all patients if the anatomy accommodated the procedure. Intraoperative transesophageal echocardiography (TEE) was used to confirm that the LAA was excluded; these data were site-reported. A process for preoperative antithrombotic therapy was recommended for protection from bleeding or a thromboembolic event, and investigators could use their institutional procedures, or the recommended process outlined in the trial procedures (Table S2). TEE was performed before epicardial intervention to assess for thrombus in the left atrium, and none were detected. If a thrombus was present in the left atrium, the patient was excluded from the study until the thrombus resolved, although no patients had this occur.

To mitigate the risk of esophageal thermal injury, the following steps were recommended in the study protocol during epicardial ablation, and were further enhanced after the single atrioesophageal fistula (AEF): (1) the location of the esophagus was determined utilizing thoracoscopic visualization and the TEE probe; (2) before energy delivery, the TEE probe was retracted from the area of ablation to protect the esophagus and other surrounding tissue structures; (3) during ablation, the targeted lesions were visualized, and atrial tissue was elevated up and away from the posterior pericardium with the ablation device(s) to avoid collateral injury to surrounding tissue; (4) before repositioning the device and before resting the atrium onto the posterior pericardium postablation, the device remained in place for 30 seconds while simultaneously quenching the device, the ablated tissue, and the surrounding tissues with saline to allow these areas to adequately cool; and (5) a proton pump inhibitor prescription was recommended for a minimum of 7 days before the procedure and continued for a minimum of 30 days postprocedure; an H2 receptor antagonist or other acid reducing agent was recommended if proton pump inhibitors were not tolerated.

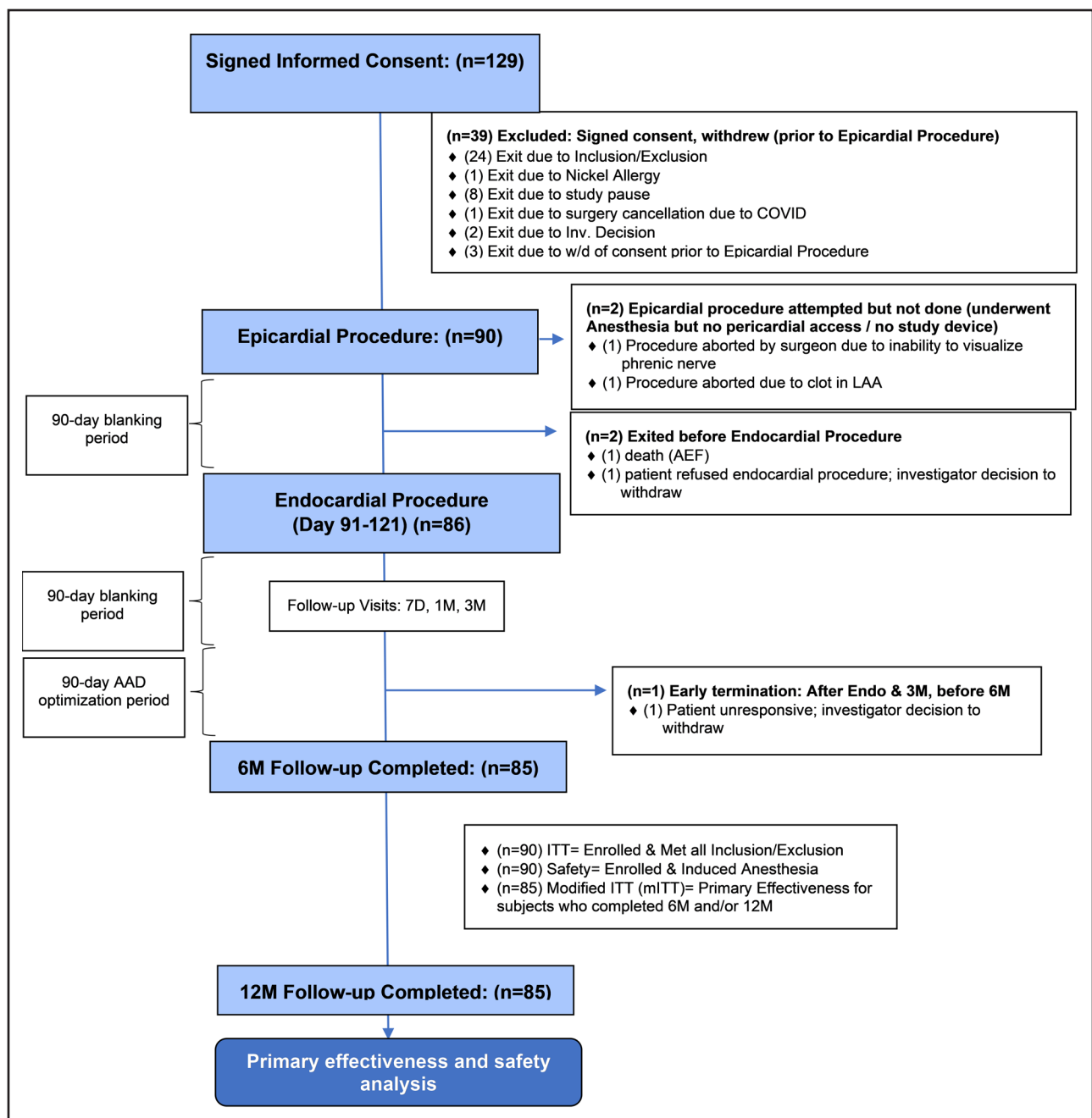


Figure 1. The DEEP trial (Dual Epicardial and Endocardial Procedure) overview.

AAD indicates antiarrhythmic drug; AEF, atrioesophageal fistula; D, day; ET, early termination; ITT, intent-to-treat; LAA, left atrial appendage; LTF, lost to follow-up; M, month; mITT, modified intent-to-treat; and WD, withdrew.

Postepicardial antithrombotic therapy was also suggested to mitigate thromboembolic events, which could be based on institutional practices and patient factors or as recommended in the trial protocol (Table S3). Longer-term oral anticoagulation was recommended until the endocardial stage of the hybrid ablation procedure.

Endocardial Ablation Procedure

Following a 90-day blanking period, the second stage ECA was done by the electrophysiologist at 91 to 121 days after the first

stage. The use of conscious sedation or general anesthesia was per institutional standard-of-care. Endocardial voltage mapping was completed preablation (Figure 3A). Endocardial ablation was performed using a commercially available irrigated RF catheter with conventional techniques for transfemoral and transseptal access to reach the left atrium. Heparin was administered in keeping with standard-of-care maintaining an ACT >300 seconds. Conduction block testing of the PV and posterior wall was performed, and gaps were mapped and ablated, if present. Endocardial voltage mapping was completed postendocardial

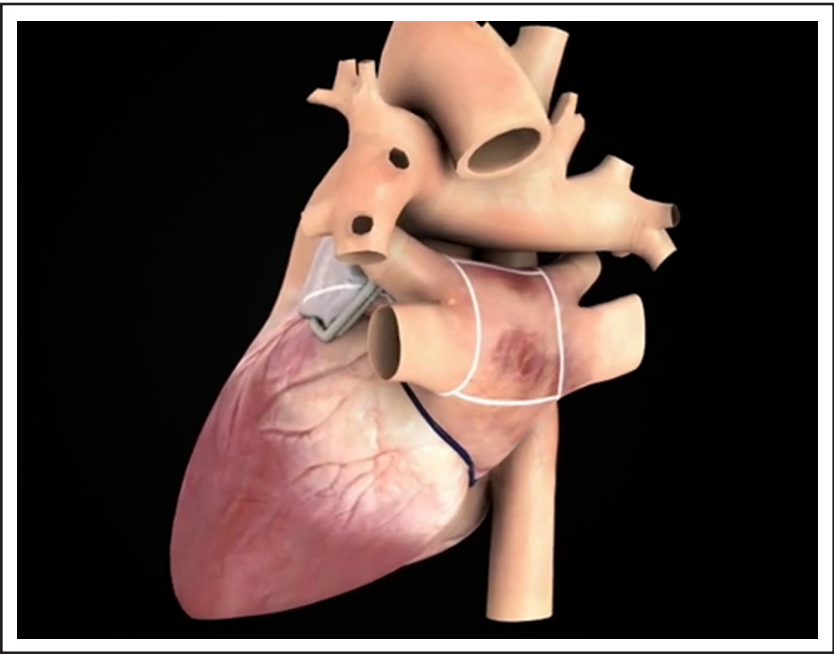


Figure 2. Epicardial (surgical) lesion set.
Surgical lesion set depicting pulmonary vein isolation (PVI), box lesion, and left atrial appendage (LAA) lesion.

ablation to confirm isolation was achieved (Figure 3B). A cavotricuspid isthmus (CTI) line was created; if the patient had a CTI line from prior endocardial ablation, the CTI line was tested for conduction block and ablated if necessary. If a peri-mitral atrial flutter (AFL) was observed, a mitral line was created. Endocardial bidirectional block via pacing maneuvers assessed the CTI and mitral isthmus lesions. During the endocardial procedure, TEE was again performed to evaluate LAEE. A process for postoperative antithrombotic therapy was implemented per institutional protocols or via recommended trial protocol to prevent postprocedural bleeding or thromboembolic events. A second 90-day blanking period followed, during which 1 repeat ECA was allowed for treating any atrial arrhythmias.

Follow-Up Visits

Follow-up visits occurred at 7 days, 1, 3, 6, and 12 months after the completion of the second stage ECA procedure. Longer-term follow-up visits occurred or will occur at 2, 3, 4, and 5 years from second stage completion. Rhythm status for effectiveness was performed via 24-hour rhythm monitoring and ECG at 6- and 12-month post-ECA. In addition, symptom driven monitoring was performed, as indicated, from 6- through 12-month post-ECA, that included patient-reported AF symptom data collection. An independent ECG core laboratory reviewed and interpreted the readings from ECGs done at follow-up study visits, 24-hour continuous rhythm monitoring, and symptom driven monitoring. Computed tomography angiography

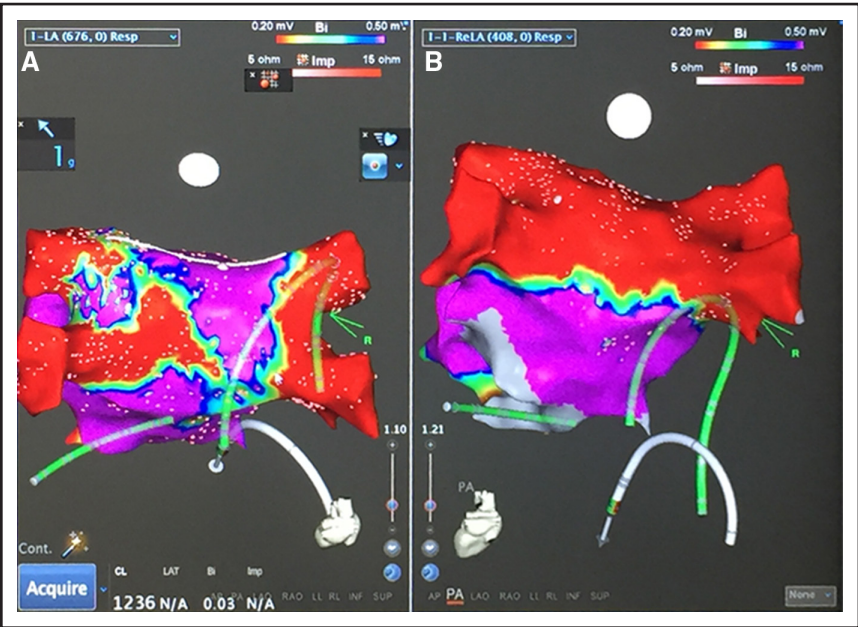


Figure 3. Endocardial voltage map.
A, Postepicardial/preendocardial. **B,** Postepicardial/postendocardial.

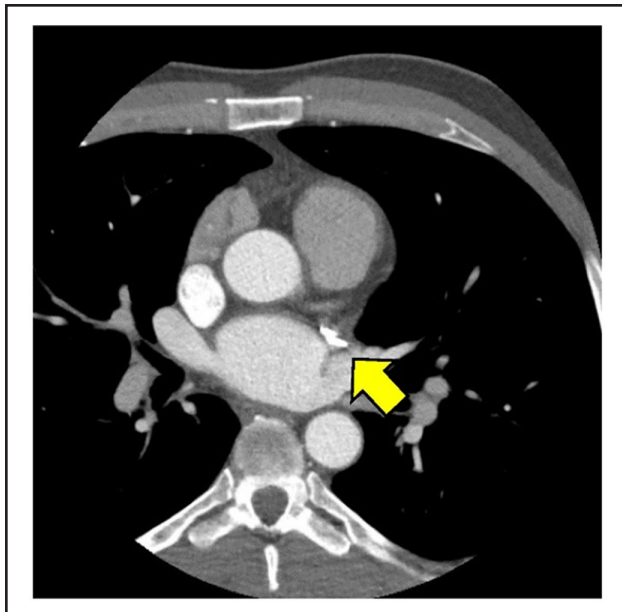


Figure 4. Computed tomography angiography (CTA) at 12 months post-AtriClip placement.
CTA depicting exclusion of the appendage.

was performed at 12-month follow-up for LAAE (Figure 4), and these results were adjudicated by an independent core laboratory.

Study End Points

The primary effectiveness end point was freedom from documented AF/AFL/atrial tachycardia (AT) episodes >30 seconds through the 12-month follow-up visit, off Class I/III AADs, except previously failed AADs at doses not exceeding those previously failed, although no patients failed the primary end point due to new/increased AADs usage. Primary effectiveness failure also included direct current cardioversion for AF, AFL, or AT between the 6- and 12-month visits; catheter or surgical ablation for AF, AFL, or AT between the 3- and 12-month visits; ≥ 2 repeat ECA within the second blanking period; and use of nonstudy device for creation of any lesions during the epicardial ablation procedure. The primary safety end point was defined as a composite of device/procedure-related serious adverse events (SAE) within 30 days of epicardial ablation and 7 days of ECA (including repeat ablation within the second blanking period). An underlying safety rate of 19%, with an upper confidence limit of <28%, was assumed to meet primary safety. Major complications are defined in Table S4.

Secondary effectiveness end points included acute procedural success after the endocardial procedure; exclusion of the LAA defined as lack of fluid communication (<3 mm residual communication with LAA and <10 mm residual pocket) between the LA and LAA at the 12-month visit; exclusion of the LAA at the endocardial ablation procedure; and change in QOL from baseline to 12 months. Acute procedural success was defined as the percentage of subjects with successful electrical isolation/conduction block of PVs, posterior wall box, and CTI (ECA only). Patient-reported QOL was measured at the baseline and 12-month visits via the AF Effect on QOL

(AFEQT) questionnaire, which includes an overall score and 4 subscales: symptoms, daily activities, treatment concern, and treatment satisfaction.¹⁸ The 20-question instrument uses a 7-point Likert scale and produces scores ranging from 0 to 100, where a score of 0 corresponds to complete disability based on extremely limited, difficult, or bothersome responses and a score of 100 corresponds to no disability based on not at all limited, difficult, or bothersome responses. The score was calculated per the AFEQT scoring manual and included the mean difference with 95% CIs using the *t*-distribution. The absolute change in QOL was measured as the total AFEQT score at 12-month follow-up minus the baseline score; paired responses in the modified intent-to-treat (mITT) population were utilized. A 5-point difference in AFEQT has been reported to be a clinically important change.¹⁹

Other reported end points include primary effectiveness by PersAF/LSPersAF subgroups; primary effectiveness by prior/no prior ablation (de novo); primary effectiveness by LAD; effectiveness through 2 years, effectiveness off amiodarone through 2 years, freedom from >30 seconds AF absent AADs (except those previously failed at doses not exceeding those previously failed) through 12 months and 2 years.

Statistical Analysis

The initial sample size calculation was based on a single-arm treatment group to determine the primary effectiveness and primary safety end points. To achieve 80% power for a 12-month performance goal of 60% and effectiveness success rate of 70% for the DEEP procedure, a 1-sided significance level of 2.5%, and a normal approximation to the binomial distribution with continuity correction, it was determined that a sample size of $n=182$ would be required. To achieve 80% power for a primary safety event rate for the DEEP procedure of <28%, which is the upper confidence limit of an underlying 19% rate, a sample size of $n=192$ subjects was required, based on a 1-sided significance level of 2.5% and a normal approximation to the binomial distribution with continuity correction assumption. Given the similar sample size requirements for both primary effectiveness and safety end points, with the effectiveness end point driving the overall sample size, and allowance for a 20% attrition rate, the sample size was determined to be $n=220$ subjects. The trial was temporarily halted due to an AEF occurrence and mitigation strategies were then developed before resuming the trial. Due to slow enrollment, the sponsor decided to terminate the trial after only 90 patients enrolled. Of the 90 enrolled patients, 90 patients had evaluable data for primary safety and 85 patients for effectiveness analyses. At the time of this decision, the Sponsor and investigators were blinded to the primary effectiveness results.

For data analysis, the ITT patient population consisted of all subjects who met all inclusion/exclusion criteria. The safety population for safety analyses included all enrolled subjects who underwent induction of anesthesia. The mITT population included enrolled subjects who had attempted epicardial procedure (induction of anesthesia) and had at least 1 post-procedure follow-up visit after the second blanking period with nonmissing primary effectiveness data in the evaluation period from 6 to 12 months; this population was used for primary effectiveness analysis. Primary imputation was conducted for follow-up analyses containing missing data. The outcomes

analyses did not differ from the mITT population to the ITT and per protocol populations, per the SAP.

Role of Funding Source

The DEEP trial was funded by AtriCure Inc, who participated in the trial design, conduct, and article editing, preparation, and submission. AtriCure was blinded throughout the study and did not conduct independent adjudication or statistical analyses.

RESULTS

A total of 90 patients were enrolled from February 2015 to December 2020 (Table 1), after the trial was stopped prematurely, short of the planned 220 patient enrollment. Several study pauses slowed enrollment, which also overlapped with the COVID-19 pandemic. The mean age was 63.4 ± 7.7 years, 83.3% (75/90) were male, mean LAD was 4.5 ± 0.6 cm and mean BMI was 29.9 ± 3.8 kg/m². The median duration of AF was 3.75 years (interquartile range [IQR], 1.4–7.3), with 83.3% (75/90) and 16.7% (15/90) of patients having PersAF and LSPersAF, respectively. The median CHA₂DS₂-VASc score was 2.0 (IQR, 1.0–3.0) and median HAS-BLED score was 1.0 (IQR, 1.0–3.0). A total of 47.8% (43/90) of patients had a prior failed ECA and 12.5% (11/88) had prior stroke or TIA. The safety population consisted of 90 patients and the mITT population consisted of 85 patients (Figure 1). Two patients did not have the epicardial procedure after induction of anesthesia and exited the study, an additional 2 patients exited the study before the endocardial procedure, and 1 patient was terminated early and withdrawn from the study after both stages were completed but before the 6-month follow-up. Baseline characteristics of the mITT population are detailed in the Table S5.

Detailed results on procedural parameters are included in Table 2. In the mITT population, all 85 patients underwent epicardial ablation and had LAEE with AtriClip. The mean epicardial ablation and LAEE duration was 184.7 minutes. After epicardial ablation, 92.9% (79/85) of patients received anticoagulation. Additional procedural summary details of the epicardial ablation are shown in Table S6. The median postprocedural length of stay was 3.2 days (IQR, 2.85–4.19). The mean time between epicardial and endocardial procedures was 104.2 days, and 85 patients underwent endocardial ablation. The mean endocardial ablation duration was 128.7 minutes (IQR, 88.5–156.0). The mean fluoroscopy time was 31.1 minutes (IQR, 12.0–31.0). The details of the endocardial ablation are shown in Table S6. The median postprocedural length of stay was 0.9 days (IQR, 0.80–1.02). No patients required repeat ECA in the first blanking period, and 2 (2.4%) patients required repeat ECA in the second blanking period.

Acute procedural success was evaluated immediately following the endocardial ablation and demonstrated nearly 100% electrical isolation, assessed using pacing

Table 1. Baseline Demographics (Safety Population)

Parameter	Outcome
Age, y; n	
Mean $\pm$ SD, n	63.4 $\pm$ 7.7 (90)
Median (Q1, Q3; n)	65.0 (59.0, 69.0; 90)
Range (min–max)	(36.0–75.0)
Sex	
Male	83.3% (75/90)
Female	15.7% (15/90)
BMI, kg/m ²	
Mean $\pm$ SD, n	29.9 $\pm$ 3.8 (90)
median (Q1, Q3; n)	29.6 (27.3–32.6; 90)
Range (min–max)	(19.6, 37.8)
Type of AF, % (n/N)	
Persistent	83.3% (75/90)
Longstanding persistent	16.7% (15/90)
Duration of AF, y	
Mean $\pm$ SD, n	5.6 $\pm$ 6.1 (90)
Median (Q1, Q3; n)	3.7 (1.4, 7.3; 90)
Range (min–max)	(0.1–32.0)
Left atrial diameter, cm	
Mean $\pm$ SD, n	4.5 $\pm$ 0.6 (89)
Median (Q1, Q3; n)	4.5 (4.1, 5.0; 89)
Range (min–max)	(3.0–5.5)
Anticoagulation use	
Yes, % (n/N)	74.4% (67/90)
No, % (n/N)	25.6% (23/90)
Class I/ III AAD use	
III	73.3% (66/90)
Ic	26.7% (24/90)
CHA ₂ DS ₂ -VASc score	
Mean $\pm$ SD (n)	1.8 $\pm$ 1.3 (88)
Median (Q1, Q3; n)	2.0 (1.0, 3.0; 88)
Range (min–max)	(0.0–5.0)
HAS-BLED score*	
Mean $\pm$ SD, n	1.1 $\pm$ 0.8 (88)
Median (Q1, Q3; n)	1.0 (1.0, 3.0; 88)
Range (min–max)	(0.0–3.0)
Prior stroke or TIA, % (n/N)	12.5% (11/88)
Prior catheter ablation, % (n/N)	47.8% (43/90)

AAD indicates antiarrhythmic drug; AF, atrial fibrillation; BMI, body mass index; and TIA, transient ischemic attack.

*The HAS-BLED Score was calculated based on available risk factors. The abnormal liver function/drug/alcohol/labile international normalized ratios were not included in the calculation since not available.

and sensing (Table S7). Where entrance and exit block were possible to assess, there was 100% (85/85) entrance block achieved for both right and left PVs, with 98.8% (84/85) and 100% (85/85) exit block achieved for right and left PVs, respectively. The posterior box entrance block was achieved in 100% (85/85) and the

Table 2. Procedural Outcomes/Success (Modified Intent-to-Treat Population)

Parameter	Outcome
Left atrial appendage exclusion with AtriClip, % (n/N)	100% (85/85)
Epicardial ablation and LAAE duration, minutes	
Mean±SD, n	184.7±52.0 (85)
median (Q1, Q3; n)	191.0 (142.0, 216.0; 85)
Range (min–max)	(88.0–356.0)
Endocardial ablation duration, minutes	
Mean±SD, n	128.7±52.4 (84)
Median (Q1, Q3; n)	117.5 (88.5, 156.0; 84)
Range (min–max)	(21.0–266.0)
Time from epicardial to endocardial procedure, d	
Mean±SD, n	104.2±16.2 (84)
Median (Q1, Q3; n)	100.0 (96.0, 108.0; 84)
Range (min–max)	(91.0–224.0)
Fluoroscopy time, min	
Mean±SD, n	31.1±53.5 (85)
Median (Q1, Q3; n)	21.0 (12.0, 31.0; 85)
Range (min–max)	(0.0–397.0)
Repeat catheter ablations in second blanking period, % (n/N)	2.4% (2/85)
Anticoagulation after epicardial ablation, % (n/N)	92.9% (79/85)

SAE indicates serious adverse events.

posterior box exit block was achieved in 100% (85/85) of patients. Overall entrance block was achieved in 100% of patients (85/85) and overall exit block was achieved in 98.8% (84/85) of patients.

For primary safety, the composite SAE rate was 6.7% (6/90 [95% CI, 2.5%–13.9%]; $P<0.001$ versus safety goal; Table 3). Three patients experienced SAEs within 30 days of the epicardial procedure. One patient experienced an atriopharyngeal fistula followed by systemic

embolism, stroke, and eventually death, after the epicardial surgical ablation. Two patients experienced a single SAE each postepicardial procedure: 1 TIA and 1 nondisabling stroke, both of whom were on anticoagulants and which resolved without sequelae. Three patients experienced SAEs within 7 days of the endocardial procedure. One patient, who was anticoagulated at the time, experienced an acute stroke and systemic embolism due to air in the mapping catheter post-ECA, with residual aphasia. Two patients experienced a single SAE each postendocardial procedure: 1 left groin pseudoaneurysm requiring intervention and 1 femoral artery aneurysm requiring intervention, which resolved without sequelae.

Of the 3 strokes, 1 occurred on postop day 9 and was related to postprocedural AF. The second occurred at the endocardial procedure due to micro air emboli in the ancillary Orion tubing. The third was observed on postop day 31 via CT imaging in the patient who had the AEF and unfortunate death. None had evidence demonstrating leaks or evidence of incomplete LAA occlusion for those who had imaging before the stroke. There were no additional strokes or TIAs through 2 years beyond those that occurred within the primary safety end point. Other nonserious AEs included pericarditis and pleural effusion. There were 5 patients who had pericarditis and 3 patients who had pleural effusion, all of which occurred after the epicardial procedure but before the endocardial procedure and resolved without sequelae. The rate of hospital readmissions through 12 months was 2.4% (2/85) and 6.1% (5/82) at 2 years.

The 12-month visit occurred at a median of 377 days (IQR, 371–385) postendocardial procedure. Freedom from AF/AFL/AT through 12 months was 71.8% (61/85 [95% CI, 62.2%–81.3%]; $P=0.0134$ versus performance goal), which met the prespecified threshold of at least 60% (Table 4; Figure 5). In a subgroup analysis by AF classification, effectiveness in patients with PersAF was 73.2% (52/71 95% CI, 62.9%–83.5%) and 64.3%

Table 3. Primary Safety end point (Safety Population)

Parameter	SAE rate, % (n/N)
Composite major adverse event rate	6.7% (95% CI, 2.5%–13.9%) (6/90); $P<0.001$
Within 30 d of epicardial procedure	3.3% (95% CI, 0.7%–9.4%) (3/90)
Transient ischemic attack (n=1)	
Atriopharyngeal fistula, stroke, systemic embolism, death* (n=1)	
Stroke (nondisabling; n=1)	
Within 7 d of endocardial procedure or blanking period repeat endocardial procedure	3.5% (95% CI, 0.7%–9.9%) (3/86)
Left groin pseudoaneurysm requiring intervention (n=1)	
Femoral artery aneurysm requiring intervention (n=1)	
Stroke and systemic embolism† (n=1)	

SAE indicates serious adverse events.

Note: The SAE rate was compared with an underlying safety rate of 19%, with an upper confidence limit of <28%, to reach statistical significance for primary safety.

*Patient experienced atriopharyngeal fistula leading to systemic embolism, stroke, and death.

†Patient experienced acute stroke and systemic embolism due to air in mapping catheter, which resolved with sequelae.

Table 4. Primary and Secondary Effectiveness End Points (Modified Intent-to-Treat Population)

Freedom from AF/AFL/AT through 12 months off AADs (except those previously failed at doses not exceeding those previously failed)	61	85	71.8% (62.2%–81.3%)	0.0134
Persistent AF	52	71	73.2% (62.9%–83.5%)	0.0114
Longstanding persistent AF	9	14	64.3% (39.2%–89.4%)	0.3717
Prior ablation at baseline	25	39	64.1% (49.0%–79.2%)	0.3005
Without prior ablation at baseline (de novo)	36	46	78.3% (66.3%–90.2%)	0.0057
LA size <4.5 cm	28	41	68.3% (54.0%–82.5%)	0.1392
LA size ≥4.5 cm	33	43	76.7% (64.1%–89.4%)	0.0125
Freedom from AF/AFL/AT through 12 months off Amiodarone	61	85	71.8% (62.2%–81.3%)	...
Freedom from AF through 12 months off AADs (except those previously failed at doses not exceeding those previously failed)	66	85	77.6% (68.8%–86.5%)	...

AAD indicates antiarrhythmic drug; AF, atrial fibrillation; AFL, atrial flutter; AT, atrial tachycardia; and LA, left atrial. Note: The effectiveness rate was compared with a prespecified 12-month performance goal of 60% and effectiveness success rate of 70%, to reach statistical significance for primary effectiveness.

(9/14 [95% CI, 39.2%–89.4%]) in patients with LSPersAF through 12 months (Table 4; Figure 5). For those who had a history of prior ablation at baseline, freedom AF/AFL/AT through 12 months was 64.1% (25/39 [95% CI, 49.0%–79.2%]), and freedom AF/AFL/AT was 78.3% (36/46 [95% CI, 66.3%–90.2%]) in those without a history of prior ablation. For those with baseline LAD less than the median of 4.5 cm, freedom AF/AFL/AT was 68.3% (28/41 [95% CI, 54.0%–82.5%]). Freedom AF/AFL/AT was 76.7% (33/43 [95% CI, 64.1%–89.4%]) in those with LAD ≥4.5 cm. Freedom AF/AFL/AT off amiodarone through 12 months was 71.8% (61/85 [95% CI, 62.2%–81.3%]). Freedom from AF only through 12 months was 77.6% (66/85 [95% CI, 68.8%–86.5%]).

LAAE was evaluated at 3 timepoints: at thoracoscopic intraprocedural, at endocardial ablation, and at 12-month follow-up (Table 5). LAAE success was defined as lack of fluid communication (<3 mm residual communication and <10 mm residual pocket) between the LA and LAA. The success rate for LAAE was 97.7% by TEE, 95.2% by TEE, and 86.4% by computed tomography angiography at 12 months, as adjudicated by an independent core laboratory (Figure 4). Eighty of 81 (98.8%) patients had exclusion with no residual communication ≥3 mm between the LAA and LA, and 86.6% (71/82) of patients had no residual pocket >10 mm.

Eighty-two patients in the mITT population completed both baseline and 12-month visit AFEQT questionnaires to assess QOL outcomes. The mean change in overall score was 30.1±19.8 (95% CI, 25.8–34.5; median 29.5, min–max: –15.4 to 78.2, $P<0.0001$; Figure 6; Table 6). Similar improvements at 12 months were seen in all 4 AFEQT subscales: symptoms, daily activities, treatment concern, and treatment satisfaction.

At 2 years, effectiveness was 62.4% (53/85 [95% CI, 52.1%–72.7%]; Table 7; Figure 5). Freedom AF/AFL/AT effectiveness off amiodarone at 2 years was 63.5%

(54/85 [95% CI, 53.3%–73.8%]). Freedom from AF only at 2 years was 68.2% (58/85 [95% CI, 58.3%–78.1%]).

DISCUSSION

Hybrid treatment of patients with refractory persistent AF has demonstrated promising results.^{20–26} In an advanced AF patient population (ie, PersAF and LSPersAF), the DEEP trial demonstrated a 71.8% primary effectiveness rate of freedom from AF/AFL/AT off new or increased dose of AADs. Freedom from AF through 12 months was 77.6%. Although there was a relatively small sample size for LSPersAF (n=14), the hybrid approach with LAAE achieved 64.3% effectiveness in this difficult-to-treat subgroup. The DEEP trial also demonstrated significant QOL improvements across all 4 AFEQT subdomains as well as overall score at 12 months compared with baseline, with the largest improvement related to treatment satisfaction. Given this trial enrolled patients with persistent AF including LSPersAF and allowed for prior ECA, these are important findings that support the need for hybrid ablation in patients who were often not considered good candidates for further ECA for failed AADs.

At 12 months, 98.8% of patients with adjudicated LAA computed tomography angiography imaging had no residual communication of ≥3 mm, as defined by the protocol. The high rates of LAAE without residual communication ≥3 mm at the evaluated timepoints demonstrate effective prevention of significant residual blood flow communication between the left atrium and LAA once the AtriClip was applied. The primary reason for 12-month LAAE end point failure was due to residual pocket size measuring ≥10 mm on computed tomography angiography, which occurred in 11 patients (11/79; 13.9%). Recent observational and randomized studies of hybrid totally thoracoscopic ablation with LAAE for patients with PersAF and LSPersAF have reported SAE

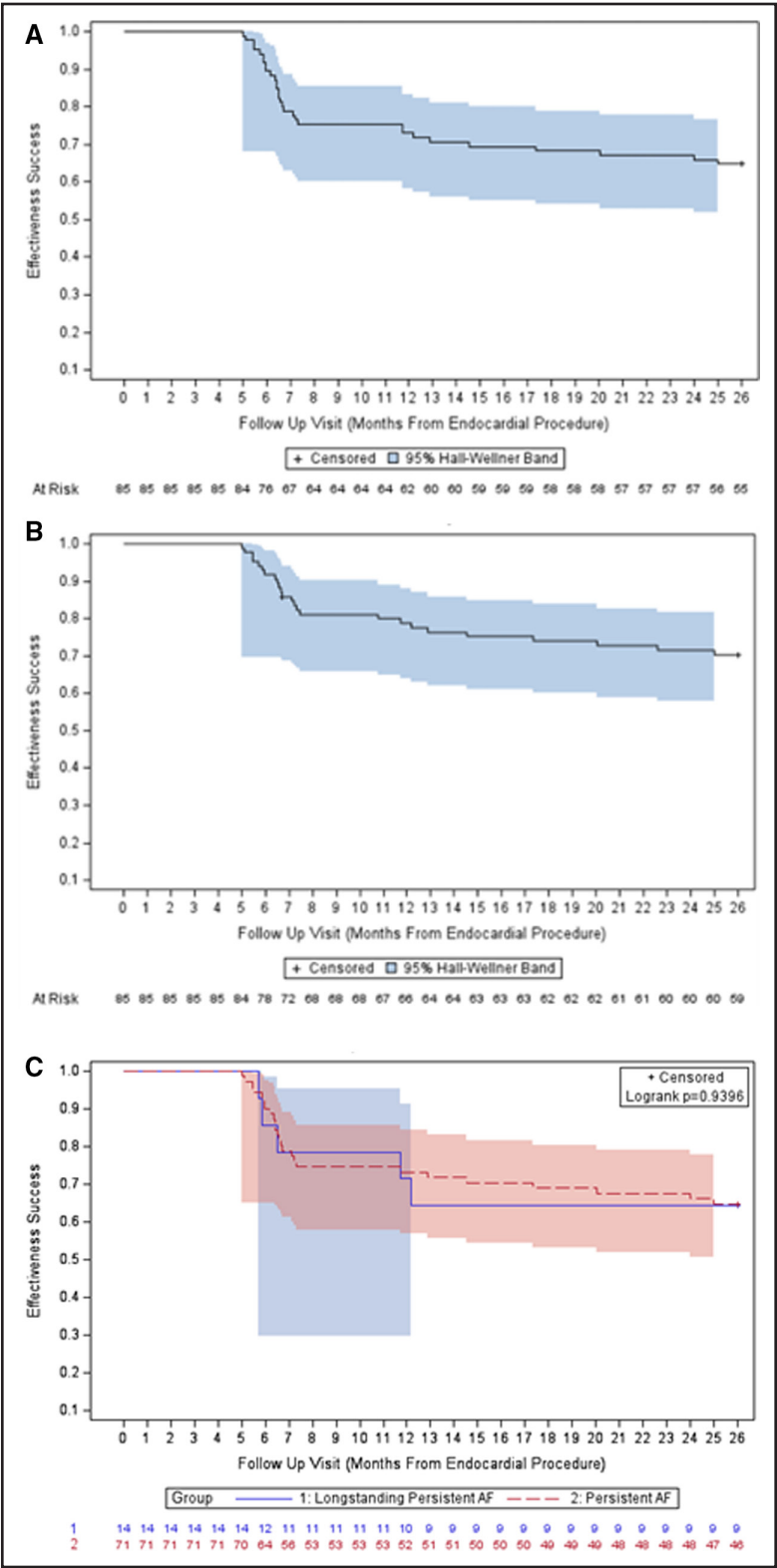


Figure 5. Kaplan-Meier analysis freedom from atrial fibrillation (AF), flutter (AFL), and tachycardia (AT) through 24 months (A, top), freedom from AF (B, middle) and freedom from AF/AFL/AT by type of AF through 24 months (C, bottom).

rates (defined by DEEP safety criteria) ranging from 0% to 10%.^{8,15,27–31} In comparison, the DEEP trial demonstrated a 6.7% SAE rate, which falls within this range. In 2 published RCTs in which ECA was a comparative

intervention to hybrid ablation, SAE rates with ECA ranged from 4.5% to 5.8% alongside poorer effectiveness outcomes, 39.2% to 41% for ECA versus 71.6% to 89% for hybrid ablation.^{8,15} While published studies

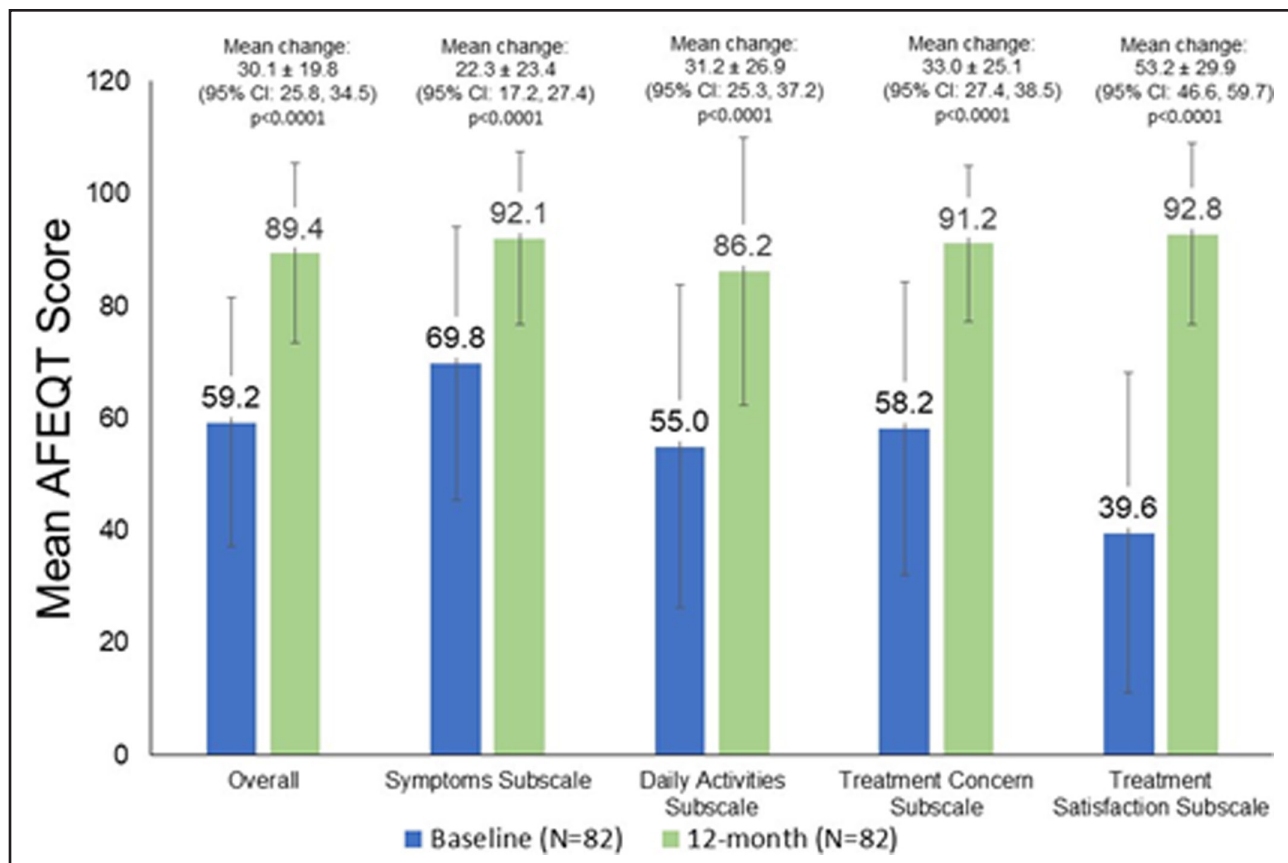
Table 5. Left Atrial Appendage Exclusion

End point	Outcome, n/N, % (95% CI)
Intraprocedural timepoint (TEE, site-reported)	
Exclusion of LAA (residual pocket <10 mm, residual communication <3 mm)	84/86 97.7% (91.9%–99.7%)
Residual pocket success (<10 mm)	84/86 97.7% (91.9%–99.7%)
Residual communication success (<3 mm)	87/87 100.0% (95.8%–100.0%)
Endocardial procedure timepoint (TEE)	
Exclusion of LAA (residual pocket <10 mm, residual communication <3 mm)	60/63 95.2% (86.7%–99.0%)
Residual pocket success (<10 mm)	62/65 95.4% (87.1%–99.0%)
Residual communication success (<3 mm)	64/64 100.0% (94.4%–100.0%)
12-month follow-up (CTA, core laboratory adjudicated)	
Exclusion of LAA (residual pocket <10 mm, residual communication <3 mm)	70/81 86.4% (77.0%–93.0%)
Residual pocket success (<10 mm)	71/82 86.6% (77.3%, 93.1%)
Residual communication success (<3 mm)	80/81 98.8% (93.3%–100.0%)

CTA indicates computed tomography angiography; LAA, left atrial appendage; and TEE, transesophageal echocardiography.

have reported stroke rates of 0% to 1% after thoracoscopic hybrid ablation, 4 patients (4.4%) in DEEP had stroke or TIA, with 3 (3.3%) occurring as primary SAEs and 1 (1.1%) additional stroke secondary to AEF. The expected range of stroke and TIA after AF ablation is 0% to 2%.⁴ In DEEP, after the AEF was reported, mitigation strategies to reduce the risk of esophageal thermal injury

were implemented into the study protocol as described in the Methods. These included preprocedure visualization of the esophagus, retraction of the TEE probe from the ablation area before energy delivery, elevation of the atrial tissue away from the posterior pericardium during ablation and quenching of the ablated area during a 30-second waiting period, and prophylactic use of proton

**Figure 6. Quality of Life (QOL) changes from baseline to 12 months after hybrid ablation.**

Note: Atrial Fibrillation Effect on Quality of Life (AFEQT) questionnaire overall and subscale scores range from 0 to 100, with 0 being extreme disability and 100 being no disability (high QOL); error bars are SD. LAA indicates left atrial appendage.

Table 6. Mean Change in Quality of Life at 12 Months (Modified Intent-to-Treat Population)

Atrial Fibrillation Effect on Quality of Life score	Baseline (n=82)	12 months (n=82)	Change from baseline to 12 months	P value
Overall				
Mean±SD	59.2±22.2	89.4±16.0	30.1±19.8	
Median (min–max)	60.1 (0.0 to 100.0)	96.8 (34.3 to 100.0)	29.5 (–15.4 to 78.2)	
95% CI for mean change			(25.8–34.5)	<0.0001
Symptoms subscale				
Mean±SD	69.8±24.3	92.1±15.3	22.3±23.4	
Median (min–max)	75.0 (0.0 to 100.0)	100.0 (16.7 to 100.0)	20.8 (–20.8 to 100.0)	
95% CI for mean change			(17.2 to 27.4)	<0.0001
Daily activities subscale				
Mean±SD	55.0±28.7	86.2±23.9	31.2±26.9	
Median (min–max)	50.0 (0.0 to 100.0)	97.9 (12.5 to 100.0)	31.1 (–30.8 to 89.6)	
95% CI for mean change			(25.3–37.2)	<0.0001
Treatment concern subscale				
Mean±SD	58.2±26.0	91.2±13.9	33.0±25.1	
Median (min–max)	61.1 (0.0 to 100.0)	94.4 (27.8 to 100.0)	31.9 (–36.1 to 100.0)	
95% CI for mean change			(27.4–38.5)	<0.0001
Treatment satisfaction subscale				
Mean±SD	39.6±28.5	92.8±16.1	53.2±29.9	
Median (min–max)	33.3 (0.0 to 100.0)	100.0 (16.7 to 100.0)	58.3 (0.0 to 100.0)	
95% CI for mean change			(46.6–59.7)	<0.0001

pump inhibitors or other acid reducers. The occurrence of this AEF was unfortunate, and mitigation steps implemented resulted in no additional AEFs observed using these strategies.

A hybrid approach allows for additional ablation to promote lesion transmural, isolation of the PVs and left atrial posterior wall, and access for LAA exclusion. It leverages the principles of the Cox-maze surgical ablation procedure, which has proven highly effective in treating persistent AF, although generally with less rigorous follow-up than in the current study.³² However, the epicardial stage of the hybrid ablation strategy in this

study differs in that it is performed thoracoscopically on the beating heart in the absence of a concomitant cardiac surgery without any right atrial ablation. This hybrid strategy may more comprehensively overcome the limitations of ECA to address the complexities of the left atrial substrate in which endocardial-epicardial asynchronous conduction leading to the epicardial layer perpetuating AF in persistent AF.^{33,34} The CEASE-AF and HARTCAP-AF trials further support the strategy of endocardial-epicardial ablation.^{8,15} A recent meta-analysis of more than 15 000 patients with persistent AF in 66 randomized controlled trials and 33 prospective

Table 7. Effectiveness Through 2 Years

Parameter	Patients achieving end point	Total patients	Effectiveness end point rate (95% CI)
Freedom from AF/AFL/AT through 2 y off AADs (except those previously failed at doses not exceeding those previously failed)	53	85	62.4% (52.1%–72.7%)
Persistent AF	44	71	62.0% (50.7%–73.3%)
Longstanding persistent AF	9	14	64.3% (39.2%–89.4%)
Prior ablation at baseline	20	39	51.3% (35.6%–67.0%)
Without prior ablation at baseline (de novo)	33	46	71.7% (58.7%–84.8%)
LA size <4.5 cm	26	41	63.4% (48.7%–78.2%)
LA size ≥4.5 cm	27	43	62.8% (48.3%–77.2%)
Freedom from AF/AFL/AT through 2 y off Amiodarone	54	85	63.5% (53.3%–73.8%)
Freedom from AF through 2 y off AADs (except those previously failed at doses not exceeding those previously failed)	58	85	68.2% (58.3%–78.1%)

AAD indicates antiarrhythmic drug; AF, atrial fibrillation; AFL, atrial flutter; AT, atrial tachycardia; and LA, left atrium.

non-RCTs from 2006 to 2023 found the 12-month pooled rate of freedom from AF/AT after ECA was 48.2%, with PVI-only ECA achieving 55.8% and PVI with adjunctive lesions achieving 44.1%.³⁵ Another contemporary meta-analysis of 8500 patients in 46 RCTs found that while adjunctive renal denervation and hybrid ablation resulted in a significant reduction in atrial arrhythmia recurrences compared with PVI alone, other adjunctive ECA strategies—including posterior wall isolation and linear ablation—did not reduce atrial arrhythmia recurrences compared with PVI alone.³⁶ Although direct comparisons are cumbersome due to variations in trial designs, the 71.8% freedom from atrial arrhythmias through 12 months observed in DEEP is favorable compared with published aggregate ECA results, particularly considering 47.8% of patients in DEEP had already failed ECA. The effectiveness through 12 months was 64.1% in patients with prior failed ECA.

The single-arm design and relatively small sample size of DEEP is a limitation, however comparable effectiveness after hybrid ablation with LAAE has been shown in recent RCTs in patients with PersAF, LSPersAF and an enlarged left atrium to have lower rates of recurrent AF at 12 and 24 months compared with patients undergoing ECA.^{8,15,37,38} These trials enrolled patients who had not received prior surgical or catheter left atrial ablation. It is not uncommon for patients with persistent AF to experience AF recurrences and need >1 repeat ECAs, with 17% to 35.8% of patients presenting for repeat ablations within 3 years.^{8,39,40} Each repeat ECA may not have the same incremental benefit to restoring and maintaining sinus rhythm. AF recurrences can occur despite durable PVI from ECA, and no additional ECA strategy confers a superior rhythm benefit.⁴¹

The rhythm monitoring modalities and schedule in DEEP included 24-hour Holter monitoring at 6 and 12 months, aligned with societal guidelines for PersAF trials at this time this trial was conducted.⁴ Although prematurely stopped due to enrollment challenges, the trial's prespecified safety and performance goals were still met.

In summary, the results of the DEEP trial demonstrate that hybrid ablation is effective for PersAF/LSPersAF when benefit-risk is deemed favorable, given this patient population's limited treatment options. The trial results add to published RCT data on hybrid ablation as a de novo procedure and provide evidence that hybrid ablation is also effective in patients who have already failed ECA.

ARTICLE INFORMATION

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Supplemental Material

Tables S1–S7

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