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ORIGINAL ARTICLE

Ultra-Low Cryoablation for Scar-Related VT Ablation: Results From the US Early Feasibility Study

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BACKGROUND: A limitation of ablation for scar-related ventricular tachycardia (VT) is insufficient lesion depth to address nonendocardial substrate. Ultra-low temperature cryoablation (ULTC) at −196°C has been shown to create transmural lesions in preclinical models. Early human studies in Europe have shown safety and efficacy.

METHODS: An EFS (Early Feasibility Study) was designed in collaboration with the Food and Drug Administration as a prospective, nonrandomized evaluation of the acute safety and effectiveness of ULTC ablation for scar-related VT.

RESULTS: Twenty patients (age 63±14 years; 5% women; LVEF 36±13%; 45% ischemic and 55% nonischemic) underwent VT ablation with ULTC from September to December 2023 at 4 clinical sites. Ablation strategies included substrate modification during sinus rhythm, as well as activation and entrainment mapping when hemodynamics permitted. Mean ULTC lesions were 9.9±3.6, with a total freeze duration of 47±22 minutes. Noninducibility of the targeted VTs was observed in 13 of 14 patients with inducibility tested both pre- and postablation. There were no procedural strokes, tamponades, or deaths. One suspected cardiac perforation without tamponade was conservatively managed. One patient was excluded from the follow-up efficacy analysis due to RF use, and another lacked postacute follow-up due to death from heart failure 1 month post-procedure. Among surviving per-protocol patients, 23.7±4.3 weeks of freedom from VT and implantable cardioverter defibrillator shock were 61.1% (11/18) and 83.3% (15/18), respectively.

CONCLUSIONS: In a US EFS, ULTC therapy was safe and effective for the treatment of scar-related VT. The EFS design, in collaboration with the Food and Drug Administration, represents an important initiative to accelerate the evaluation of new medical technologies in the United States.

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

Key Words: cicatrix ■ freedom ■ heart failure ■ humans ■ temperature

Freedom from recurrent ventricular tachycardia (VT) in the setting of structural heart disease after catheter ablation remains variable, with frequent recurrences and significant clinical sequelae.[1–4] It is increasingly appreciated that reentrant VT often involves the endo-, epi-, and mid-myocardium.[5] The ventricular walls, including the intraventricular septum, frequently exceed 10 mm in thickness, and patients with structural heart disease will often demonstrate heterogeneity of tissue including healthy myocardium and fibrotic scar in the regions of arrhythmogenic substrate. Although there have been significant advances in technology and techniques for the mapping of VT circuits and identification of arrhythmogenic substrate, the limited depth of RF ablation (to as

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WHAT IS KNOWN?

- Ultra-low temperature cryoablation is a new ventricular tachycardia ablation modality capable of producing ventricular lesions with depth titratable by the duration of the freeze to over 10 mm.
- An early European-Canadian study of endocardial ultra-low temperature cryoablation demonstrated favorable safety and efficacy in a patient cohort with both ischemic and nonischemic cardiomyopathies with no statistical difference in outcomes between etiologies.

WHAT THE STUDY ADDS

- This study confirms the earlier findings in the context of an US Food and Drug Administration Early Feasibility Study in a patient population with higher prevalence of nonischemic cardiomyopathy with predominantly basal and septal substrates which often represent particular challenge for RF ablation.
- This study provides a first insight into the distribution of ablation element temperatures in the current generation of the ultra-low temperature cryoablation catheter as a function of anatomic ablation location and may therefore guide further development of the technology and instructions for use.

Nonstandard Abbreviations and Acronyms

EFS	Early Feasibility Study
FDA	Food and Drug Administration
ICD	implantable cardioverter defibrillator
MAE	Major Adverse Events
ULTC	ultra-low temperature cryoablation
VT	ventricular tachycardia

little as 3–5 mm), further attenuated by the presence of myocardial scar,[6,7] is a key factor impeding efficacy.[8]

Cryoablation has become a well-accepted approach for the treatment of atrial arrhythmias, including atrial fibrillation and some supraventricular tachycardias[9] Potential advantages of cryoenergy for VT ablation include reversibility when ablating regions at risk of causing heart block, relative safety near coronary arteries, and increased catheter stability when targeting mobile structures related to adherence to the myocardium during freezing (cryoadhesion).[10,11] Previous catheter-based cryoablation in the ventricles has been limited by insufficient cooling, as these catheters were primarily designed for atrial, rather than ventricular use.[12] Ultra-low temperature cryoablation (ULTC) is a novel technology that has the potential to overcome the limitations of previous catheter-based cryotherapy to achieve greater lesion depth. The unique properties of near-critical nitrogen refrigerant, with a boiling temperature ≈ −196°C[13] allow for much lower temperatures at the catheter-tissue interface, with the potential to titrate ablation lesions to over 10 mm depth in preclinical models including fibrotic/scar substrate.[14] Initial human experience outside the United States in the treatment of scar-related VT has been recently published, demonstrating early safety and efficacy.[15]

Challenges with efficient early technology development and evaluation in the United States have been a barrier to patient access to novel devices targeting unmet clinical needs. The EFS (Early Feasibility Study) initiative of the Food and Drug Administration (FDA) was established in 2013 with the publication of an EFS guidance document,[16] and enhanced by the passage of the 21st Century Cures Act of 2016 in an effort to promote the efficient development of new technologies in the United States.[17]

The purpose of this EFS was to assess the early safety and performance of a novel ULTC system in the United States at tertiary referral centers in patients referred for scar-related VT ablation in a mixed real-world patient cohort.

METHODS

The data that support the findings of this study are available upon reasonable request from: Adagio Medical, Inc, Laguna Hills, CA.

In collaboration with the FDA, an Early Feasibility Study (NCT05675865) was designed to prospectively evaluate initial US VT ablation experience with ULTC. The protocol was developed jointly by the sponsor and the primary investigators. Coordination of data collection and analysis was performed by the sponsor, with interpretation and adjudication of clinical events by the investigators and an independent Clinical Events Committee, and reviewed by an independent Data and Safety Monitoring Board. Patients were consented and enrolled in accordance with local IRB and standard human subjects best practices as established at each clinical site. All authors have reviewed and approved the data and article before submission for publication and attest to the accuracy and completeness of the data and to the fidelity of the trial to the protocol.

Patient Selection and Study Protocol

This was a prospective, single-arm, multicenter EFS conducted at 4 US tertiary referral centers. Patients with documented drug-refractory scar-related monomorphic VT related to either ischemic cardiomyopathy or nonischemic cardiomyopathy who were suitable for ablation were enrolled. The scheduled ablation could be either de novo or a first repeat procedure with the initial ablation at least 4 weeks prior. All patients had implantable cardioverter defibrillators (ICDs) before ablation, which allowed evaluation of pre- and postprocedure arrhythmia burden. Key exclusions included idiopathic VT, ejection fraction <20%, NYHA class IV status, significant valvular heart disease, acute coronary events or interventions within 60 days or coronary artery bypass graft surgery <6 months before ablation. A unique exclusion for ULTC is a history of cryoglobulinemia. All

patients underwent imaging with transesophageal echo, MRI, computed tomography, or intracardiac echo within 48 hours of the procedure to exclude intracardiac thrombus.

The primary safety end point was freedom from device- or procedure-related Major Adverse Events (MAEs) occurring within 7 days of the procedure. Prespecified MAEs included: death, cardiac perforation with significant effusion or tamponade, stroke or systemic embolism, major bleeding requiring transfusion, acute severe valvular damage, access site complications requiring intervention, clinically severe pericarditis, and new complete heart block requiring permanent pacing. Thirty-day MAEs were considered a secondary safety end point. All serious adverse events and MAEs, regardless of timing, were adjudicated by the independent Clinical Events Committee.

The primary performance end point was acute noninducibility of any VT induced during the procedure and targeted for ablation. Secondary performance end points included: freedom from the inducible sustained (or slower) VTs at the end of the procedure, freedom from sustained VT or appropriate ICD intervention at up to 6 months overall and in the absence of new or increased doses of antiarrhythmic drug therapies, as well as evaluation of VT burden at 6 months. Identification of VT or appropriate ICD therapy events could be made at prespecified follow-up or during unscheduled clinical visits and was documented by ICD, EKG, or monitor tracings as adjudicated by the investigators at each clinical site.

Prespecified data collection occurred at screening, periprocedure, hospital discharge, and 7 days, 1-, 3-, and 6-month post-procedure. In accordance with the EFS study design with limited sample size, no formal statistical hypothesis testing was prospectively defined. Descriptive statistics are presented according to common standards, including continuous variables presented as mean±SD, ordinal variables presented additionally with counts and percentages, and categorical variables as counts and percentages.

Ablation Procedure

All procedures were performed by experienced clinical investigators after appropriate training for the ULTC ablation system. General procedural parameters for VT ablation were left to the discretion of the operating providers. These included: use of general anesthesia or deep sedation, selection of venous/arterial femoral access, LV access via retrograde aortic and transseptal approach, and choice of 3-dimensional mapping system and diagnostic catheters. Access sheaths for the ULTC system were limited to those tested and approved for use with the study system and were ≥10 Fr. The use of intracardiac echo was encouraged but not required. Epicardial access was not permitted by protocol. All patients were heparinized targeting an activated clotting time of >350 seconds. Mapping in all procedures included evaluation of bipolar and unipolar voltage using standard criteria.[18,19] Additional mapping could be performed at operator discretion, including (and not limited to): activation mapping during tolerated VT, localization of exit sites by pace mapping, identification of late potentials or local abnormal ventricular activity, and isochronal late activation mapping to identify of deceleration zones and lines of block.[20,21]

Ablation was performed using the ULTC ablation system (Adagio Medical, Inc., Laguna Hills, CA), consisting of the ULTC console and a purpose-built VT ablation catheter. The catheter (vCLAS, Adagio Medical Inc.) features a 9 Fr, bi-directionally deflectable shaft (65 mm curve, >180° deflection) and a solid 15 mm long cryoablation element with 8 1 mm electrodes for pacing and intracardiac electrogram recording (Figure 1A). There is no contact force sensing in this first-generation catheter. The VT ablation catheter is compatible with 10 Fr fixed-curve or steerable introducer sheaths for transvenous access to the RV and both transseptal and retrograde access to the LV and can be integrated with commercial, impedance-capable electroanatomic mapping systems. The depth and lateral dimensions of ablation lesions are dependent on the duration of a freeze–thaw–freeze cycle where the freeze durations range from 1 to 5 minutes and the thaw is 1 minute (Figure 2). Investigators estimated wall thicknesses at ablation target zones using preprocedural computed tomography, magnetic resonance imaging, or intraprocedural intracardiac echocardiography, where available. Importantly, to maximize energy transfer and achieve target lesion depth, effort was made to position the entire length of the cryoablation element in contact with and parallel to the tissue whenever possible, as ascertained by surrogates for tissue contact such as fluoroscopic appearance of catheter bending, catheter visualization on the electroanatomic map, intracardiac echocardiograph imaging, and catheter intracardiac electrograms (Figure 1B and 1C). Regions targeted for ablation were left to the discretion of the operator and could include a substrate-based approach or a more limited treatment of identified critical substrate.

Pre-ablation and postablation VT inductions by ventricular programmed electrical stimulation were performed in accordance with each institution's standard of care. Postablation testing was at the discretion of the operator, based upon VT inducibility at the beginning of the procedure as well as clinical stability of the patient at the end of the procedure. Post procedure ICD programming was left to the discretion of the investigators, with the general recommendation to follow recent Heart Rhythm Society guidelines.[22,23]

RESULTS

Baseline characteristics are shown in Table 1. A total of 20 patients were enrolled and underwent ULTC ablation between September and December 2023 at 4 clinical sites. The mean age was 63±14 years, and 19 (95%) were men. Cardiomyopathy characteristics included: LVEF 36±13%, ischemic cardiomyopathy in 9 (45%), and nonischemic cardiomyopathy in 11 (55%), including 2 (10%) with hypertrophic cardiomyopathy. Failure or intolerance of antiarrhythmic drug therapy was present in 20 (100%), with 11 (55%) having been on amiodarone. Six (32%) patients had undergone prior RF ablation at least 4 weeks before the study procedure.

Procedural characteristics are shown in Table 2. Before ablation, VT was successfully induced in 17 (85%) with a median of 3±1.4 VT morphologies induced during each procedure. Of a total of 51 VTs induced in all patients, 25/51 (49%) were considered consistent with spontaneous clinical VTs, and 14/51 (28%) were hemodynamically stable. Average VT cycle length was 343±55 ms. All procedures included a combination of substrate

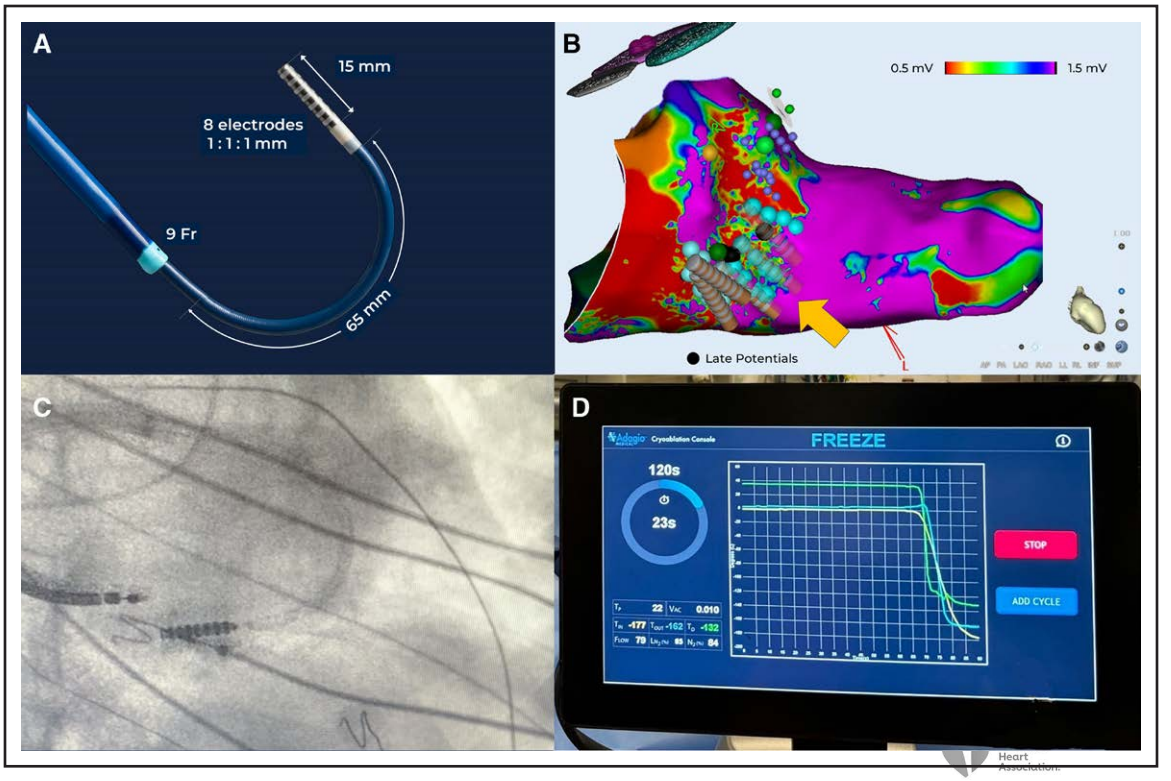

Figure 1. Ultra-low temperature cryoablation (ULTC) catheter.
A, Catheter design detail and dimensions. **B**, Fluoroscopic appearance of the catheter. **C**, Catheter appearance on electroanatomic imaging system (Carto, Biosense Webster, Inc). Blue dots designate prior lesions, identifying locations of the ablation element electrodes. **D**, Temperature profile during freeze. The ablation element reaches nadir temperatures in ≈20 to 25 seconds from freeze initiation.

mapping, pace mapping, and activation mapping with 10 (50%) having entrainment mapping of at least 1 VT. The predominant ablation strategy was substrate modification during sinus rhythm. Operators reported their ablation strategy as scar homogenization in 60% (12/20), targeting a VT isthmus or exit site in 45% (9/20), and targeting channels, local abnormal ventricular activity, or isochronal late activation mapping in 50% (10/20) of procedures.

Transeptal access to the LV was utilized in 100% (20/20) of the procedures. Additional retrograde access to the LV was implemented in 10% (2/20) of cases, and the RV was accessed in 30% (6/20) of cases. Intracardiac echo was used in all patients. The distribution of ablation locations is shown in Figure 3A. Septal ablations (both LV and RV) represented ≈60% of all energy applications, and 55% of all ablations were performed in the basal LV, reflecting the high prevalence of nonischemic patients. Overall procedure time was 245±55 minutes, with 13±8 minutes of fluoroscopy time, and freeze time of 47±22 minutes, with an average of 9.9±3.6 lesions delivered per patient.

The average temperature of the ablation element was −142±9°C. Excluding 3 cases performed by first-time operators, the temperature average was −145±5°C with minimal variability across ablation locations (Figure 3B).

Safety

There were no occurrences of predefined MAEs at 7 days post-procedure, including stroke, tamponade, major bleeding, or death. There was a single reported procedure-related nonmajor safety event of suspected myocardial perforation in the LV apex without significant pericardial effusion or tamponade in a postcoronary artery bypass graft patient with prior failed RF ablation and 5 (5) ULTC lesions created in the basal inferior and basal infero-septal segments. The suspected perforation was first identified by postprocedural bedside echocardiography and confirmed by repeat contrast computed tomography angiography based on partially visualized mild hemopericardium and moderate hemomediastinum. The hemodynamically stable patient was managed conservatively and was discharged without symptoms 3 days post-procedure. The 30-day secondary safety evaluation reported no further MAE events.

Performance

During the procedure, arrhythmia induction before ablation was performed in all patients, with 85% (17/20) induced into at least 1 monomorphic VT, with details as described above. Acute postablation noninducibility of targeted clinical VT was achieved in 92.9% (13/14) of patients with preablation inducibility and postablation

A

Freeze Time (min)	Desired Lesion Depth Range (mm)	Lesion Length (mm)
0.5	<4	15
1	4-6	
2	7-9	
3	10 and above	
4-5	May be used to maximize acute effectiveness based on physician's judgement when the target tissue thickness is >10 mm, with the understanding that the dose escalation (from the 3 min – 1 min - 3 min dose) does not reliably translate into incremental lesion depth.	
Full ablation cycle includes two freezes of stated duration separated by one (1) minute thaw.		

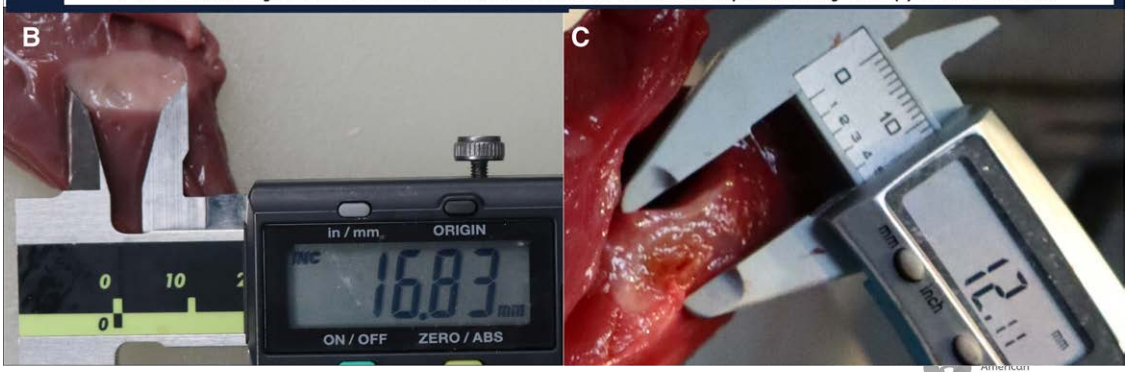

Figure 2. Ablation duration and target lesion dimensions.
A, Protocol-recommended freeze cycles based on the target tissue depth. The length of the lesion is based on the length of the ablation element and assumption of full tissue contact. **B** and **C**, Chronic Ultra-low temperature cryoablation (ULTC) lesions (endocardial surface and through-cut) in animal model on gross necropsy. Adopted from Verma et al,[15] with permission.

testing. Full noninducibility for any VT was achieved in 85.7% (12/14) of these patients (Figure 4). Three patients (15%) were noninducible preablation and 2 (10%) were not tested postablation at investigator discretion. One of the 20 patients (5%) was exited from the study—for purposes other than safety analysis—due to the additional use of an RF ablation catheter during their procedure. No epicardial access, mapping, or ablation were done in any of the patients.

At baseline, 19 (95.0%) patients were receiving Class I/III antiarrhythmic drug therapy including 11 (55.0%) receiving amiodarone. Within 30 days of the procedure antiarrhythmic drug therapies were discontinued or dose-decreased in 15 (78.9%) patients overall and in 10 (90.9%) of those receiving amiodarone.

Follow-up averaged 23.7±4.1 weeks in the prespecified 6-month follow-up window. One patient with EF=25% at the time of an otherwise uncomplicated substrate homogenization procedure, supported by a vascular assist device, died of heart failure 35 days postablation without available ICD interrogation arrhythmia data. Six patients had VT events requiring ATP or shocks, and one had low-rate symptomatic VT untreated by the device. Two patients underwent a repeat procedure 14 and 15 weeks after the index procedure. In surviving patients with index ablation performed per protocol, freedom from VT and ICD shock were 61.1% (11/18) and 83.3% (15/18), respectively. Amiodarone was restarted, and de novo mexiletine was started in 2 patients who received shocks, respectively; 1 patient with discontinued baseline amiodarone was re-ablated and received de novo mexiletine for symptomatic VT below the device detection threshold. Overall, in 18 patients treated per protocol and surviving through the duration of the follow-up, antiarrhythmic drug therapies were completely discontinued in 9 (50%), dose-decreased in 4 (22.2%), and remained steady in 2 (11.1%).

The 6-month ICD history before ablation was available in 11 (61%) of surviving, per-protocol patients, 8 (8)

Table 1. Baseline Patient Characteristics (n=20)

Age, y; mean (SD)	63±14
Male %, (n)	95% (19/20)
LVEF % ± SD	36% ± 13
Hypertension %, (n)	80% (16/20)
Diabetes %, (n)	35% (7/20)
Valvular Heart Dz %, (n)	15% (3/20)
CHF %, (n)	55% (11/20)
Ischemic CM %, (n)	45% (9/20)
Nonischemic CM %, (n)	55% (11/20)
Hypertrophic CM %, (n)	10% (2/20)
Antiarrhythmic drug %, (n)	95% (19/20)

Table 2. Procedural Strategies

Mapping strategies (n=20), average 2.9 per patient	
Substrate mapping	80% (16/20)
Pace mapping	85% (17/20)
Activation mapping	70% (14/20)
Entrainment mapping	50% (10/20)
Ablation strategies, average 2.0 per patient	
Scar homogenization	60% (12/20)
VT isthmus	45% (9/20)
VT exit Site	45% (9/20)
Scar de-channeling	25% (5/20)
Slow conduction channel	15% (3/20)
LAVA elimination	10% (2/20)
ILAM	5% (1/20)
Inducibility data	
Inducible patients	85% (17/20)
Number of VTs per patient	3.0±1.4
Hemodynamically stable VT, %	27.5% (14/51)
Clinical VT, %	49.0% (25/51)
Clinical VT cycle length, ms	343±55

of whom experienced ICD shock preablation, and 2 (2) of whom had arrhythmia recurrence, including 1 patient with shock. During 6 months post-ablation the overall VT burden in those patients decreased from a mean of 5.5 to 1.9 events per patient, and ICD shock burden decreased from a mean of 2.1 shocks to 0.1 shocks per patient.

Ongoing follow-up of EFS study patients was prespecified and they will be included for safety-only end points in the planned subsequent IDE study.

DISCUSSION

This US-based Early Feasibility Study describes the safety and performance of ULTC in the treatment of scar-related VT. In brief, an EFS is defined as a small clinical study (typically 15–25 initial subjects) designed to facilitate direct interactions between the FDA, industry sponsors, and investigators early in the product lifecycle to develop clinical insights into the performance of an innovative medical technology and inform the development and execution of subsequent pivotal studies.[16,17]

Assessment of the primary safety end point found no MAEs during the primary 7-day evaluation or the secondary 30-day evaluation periods. There was 1 of 20 (5%) nonmajor safety event. Procedure characteristics were consistent with reasonable expectations regarding duration, fluoroscopy, and ablation time in this real-world patient cohort treated with a novel ablation technology. Efficacy was favorable with acute noninducibility for tested patients of 86%, 83.3% ICD shock-free survival and notable VT burden reduction at an average of 5.5 months of follow-up.

The small sample size of the study does not allow for full elucidation of predictors of ablation success. The maximum ULTC energy transfer to target myocardium is achieved when the entire length of the cryoablation element is in contact with the tissue, which also minimizes the thermal load from the circulating blood and, theoretically, leads to lower ablation element temperature. Achieving such a parallel configuration using a 9 Fr catheter is somewhat nonintuitive for operators accustomed to performing RF ablations and may require

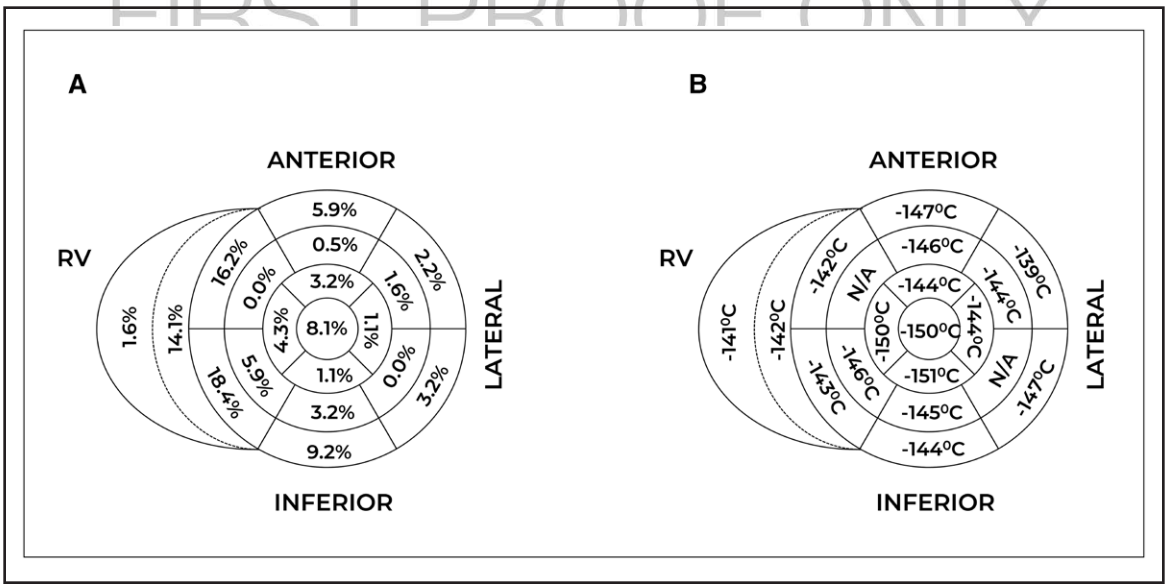

Figure 3. Distribution of lesion locations.
A, Distribution of 185 lesions locations (19 patients) in accordance to standard 17-segment model in LV and empirical segmentation of RV separating septal vs all other ablation locations. **B**, Segmental distribution of the ablation element temperatures, based on 168 lesions from 17 patients, excluding first-time operator cases.

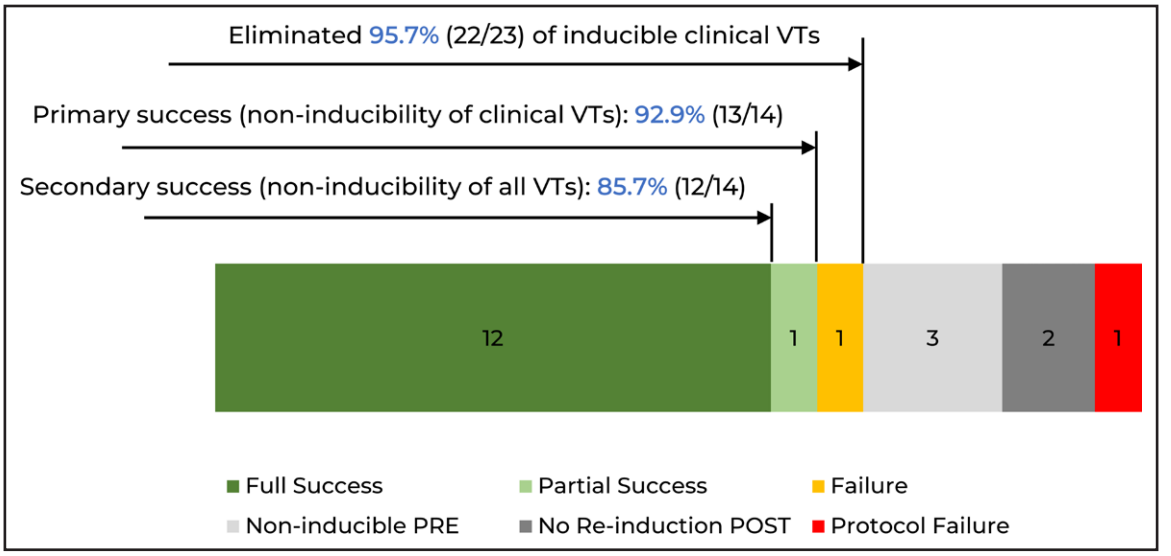

Figure 4. Acute procedural outcomes.
Noninducibility of the targeted clinical ventricular tachycardia (VT) was observed in 13 of 14 patients with inducibility tested both pre- and postablation (1 patient did not have postablation testing of 3 clinical VTs induced preablation; 3 had no VTs induced preablation; 1 was treated with additional RFA). No epicardial ablation was done.

adjustment to the traditional catheter manipulation technique, depending on the target segment and LV access. In this small study somewhat higher ablation temperatures were observed in the three procedures performed by first-time operators, potentially implying sub-optimal catheter-tissue energy transfer despite contact stability inferred by cryoadhesion. A larger sample size study, with appropriate provision for the initial operator learning curve with catheter manipulation (such as protocol-defined roll-in patients), would be required to draw any conclusions on the effect of the ablation locations, duration, and maximum ablation temperature on both acute and chronic effectiveness.

Catheter ablation of VT in patients with structural heart disease is challenging. Multicenter trials of RF ablation report recurrence rates in the range of 50%, and 9% to 21% rates of MAEs, including death, stroke, cardiac perforations, tamponade, and acute HF decompensation.[4,24,25] Intramural and subepicardial VT substrates, particularly common in nonischemic cardiomyopathy are important obstacles. While multiple methods and strategies have evolved seeking to improve outcomes, including percutaneous epicardial access, coronary venous alcohol infusion, RF with half-normal saline irrigation, RF needle ablation, and external stereotactic beam radiation,[8] VT recurrence rates and morbidity remain substantial in this patient population.

While limited sample size, patient heterogeneity, and the variety of clinical approaches limit objective comparisons with prior studies, the results of this EFS are encouraging. The findings are also consistent with the Cryocure-VT study of ULTC technology[15] conducted in Canada and Europe. Both acute and chronic efficacy of ULTC appears to be favorable despite the use of only an endocardial-only approach in a mixed patient population with a slightly higher prevalence of nonischemic cardiomyopathy, warranting consideration for future randomized comparisons of the technologies.

The completion of this EFS, in cooperation with the FDA, provides important foundational support for the ongoing evaluation of this novel ablation technology. As is consistent with the intention of the EFS program, the results of this study facilitated the initiation of a now ongoing pivotal prospective IDE trial designed to fulfill the requirements for PMA approval in the United States. The results of that larger study will provide a more definitive answer on the chronic effectiveness of ULTC ablations at both 6 (primary end point) and 12 months. The patient cohort described in this article will be incorporated into the safety end points analysis of the pivotal trial.

STUDY LIMITATIONS

By design, EFS studies are of small sample size and therefore limited in generalizability and statistical power. Findings of this study will need to be further evaluated and confirmed in larger prospective studies, as well as ongoing evaluation once the catheter becomes commercially available. With no comparator arm using traditional RF ablation, direct comparisons for relative efficacy cannot be evaluated and should be considered for future studies. Finally, there are variations in institutional protocols for collecting and assessing baseline VT burden, VT inducibility, mapping, and ICD programming across the 4 enrolling centers, which likely warrant consideration in future study design.

CONCLUSIONS

This EFS of ULTC supports its efficacy and safety in patients with scar-related VT. Moreover, the completion of the present study represents an important initiative to accelerate the evaluation of new technologies in the United States, in collaboration with the FDA, in an effort to improve VT ablation outcomes.

ARTICLE INFORMATION

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