Leadless Ultrasound-Based Cardiac Resynchronization System in Heart Failure

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IMPORTANCE Approximately 40% of patients with heart failure (HF) who are eligible for cardiac resynchronization therapy (CRT) either fail to respond or are untreatable due to anatomical constraints.

OBJECTIVE To assess the safety and efficacy of a novel, leadless, left ventricular (LV) endocardial pacing system for patients at high risk for a CRT upgrade or whose coronary sinus (CS) lead placement/pacing with a conventional CRT system failed.

DESIGN, SETTING, AND PARTICIPANTS The SOLVE-CRT study was a prospective multicenter trial, enrolling January 2018 through September 2022, with follow-up in March 2023. Data were analyzed from DATE MONTH, YEAR, through DATE MONTH, YEAR. The trial combined data from an initial randomized, double-blind study (n = 108) and a subsequent single-arm part (n = 75). It took place at 36 centers across Australia, Europe, and the US. Participants were nonresponders, previously untreatable (PU), or high-risk upgrades (HRU). All participants contributed to the safety analysis. The primary efficacy analysis (n = 100) included 75 PU-HRU patients from the single-arm part and 25 PU-HRU patients from the randomized treatment arm.

INTERVENTIONS Patients were implanted with the WiSE CRT System (EBR Systems) consisting of a leadless LV endocardial pacing electrode stimulated with ultrasound energy delivered by a subcutaneously implanted transmitter and battery.

MAIN OUTCOMES AND MEASURES The primary safety end point was freedom from type I complications. The primary efficacy end point was a reduction in mean LV end systolic volume (LVESV).

RESULTS The study included 183 participants; mean age was 68.1 (SD, 10.3) years and 141 were male (77%). The trial was terminated at an interim analysis for meeting prespecified stopping criteria. In the safety population, patients were either New York Heart Association Class II (34.6%) or III (65.4%). The primary efficacy end point was met with a 16.4% (95% CI, −21.0% to −11.7%) reduction in mean LVESV (*P* = .003). The primary safety end point was met with an 80.9% rate of freedom from type I complications (*P* < .001), which included 12 study device system events (6.6%), 5 vascular events (2.7%), 3 strokes (1.6%), and 7 cardiac perforations which mostly occurred early in the study (3.8%).

CONCLUSIONS AND RELEVANCE The SOLVE-CRT study has demonstrated that leadless LV endocardial pacing with the WiSE CRT system is associated with a reduction in LVESV in patients with HF. This novel system may represent an alternative to conventional CRT implants in some HF patient populations

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C ardiac resynchronization therapy has conclusively demonstrated left ventricular (LV) reverse remodeling, improved functional status, and reduced hospitalizations and mortality in patients with heart failure (HF) with reduced ejection fraction (EF) and a prolonged QRS duration.[1-9]

Conventional cardiac resynchronization therapy (CRT) involves one lead in the right ventricle and another in the coronary sinus (CS). Biventricular pacing (BIVP) is rendered by pacing both simultaneously. However, positioning the lead within the coronary vein is not possible in 5% to 15% of patients due to anatomical constraints.[10] Additionally, many patients have a suboptimal lead location and 30% to 40% are nonresponders.[1,10-12] Surgical implantation of an epicardial lead is not optimal for patients with comorbidities. Moreover, evidence suggests that pacing the epicardium is not physiological.[10,11,13]

The WiSE CRT System is a novel leadless LV endocardial pacing system that delivers ultrasonic energy to a wireless receiver electrode implanted within the endocardium.[1,10,11,14] The system consists of a battery connected to an ultrasound transmitter that is implanted subcutaneously and the electrode implanted in the LV endocardium (**Figure 1**). The system requires a co-implant (eg, pacemaker, defibrillator, or CRT) capable of right ventricular (RV) pacing. The transmitter senses the RV pacing spike of the co-implant and within approximately 5 milliseconds emits an ultrasonic pulse to the electrode, which is converted into electrical energy to pace the LV. The WiSE CRT System has the potential to overcome the anatomical constraints of the coronary venous system and enable patient-specific approaches to electrode placement across the LV endocardium. We present results from the SOLVE-CRT

Key Points

Question Is leadless left ventricular (LV) endocardial pacing using ultrasound energy safe and effective for providing cardiac resynchronization therapy (CRT) to patients whose conventional CRT using a coronary sinus lead failed?

Findings In this prospective clinical trial (N = 183), 80.9% of patients were free from device- and procedure-related adverse events. The average improvement in mean LV end systolic volume was –16.4%.

Meaning In this study, for patients with failed coronary sinus lead placement for CRT, a leadless LV pacing system using ultrasound energy holds promise as a viable alternative.

study that examined the safety and efficacy of the WiSE CRT System.[15,16]

Methods

The SOLVE-CRT study was a prospective multicenter trial combining data from an initial randomized, double-blind study and a subsequent single-arm study and follows the reporting guidelines for nonrandomized studies as applicable.[17] It was originally designed as a randomized, multinational, double-blind study to enroll 350 patients from up to 45 centers. There were 3 groups of patients, including nonresponders, previously untreatable (PU), or high-risk upgrades (HRU) (eTable 1 in Supplement 1). Previously untreated patients had a full or partial CRT system but were not receiving CRT because of a failed LV lead

Figure 1. WiSE Cardiac Resynchronization Therapy (CRT) System
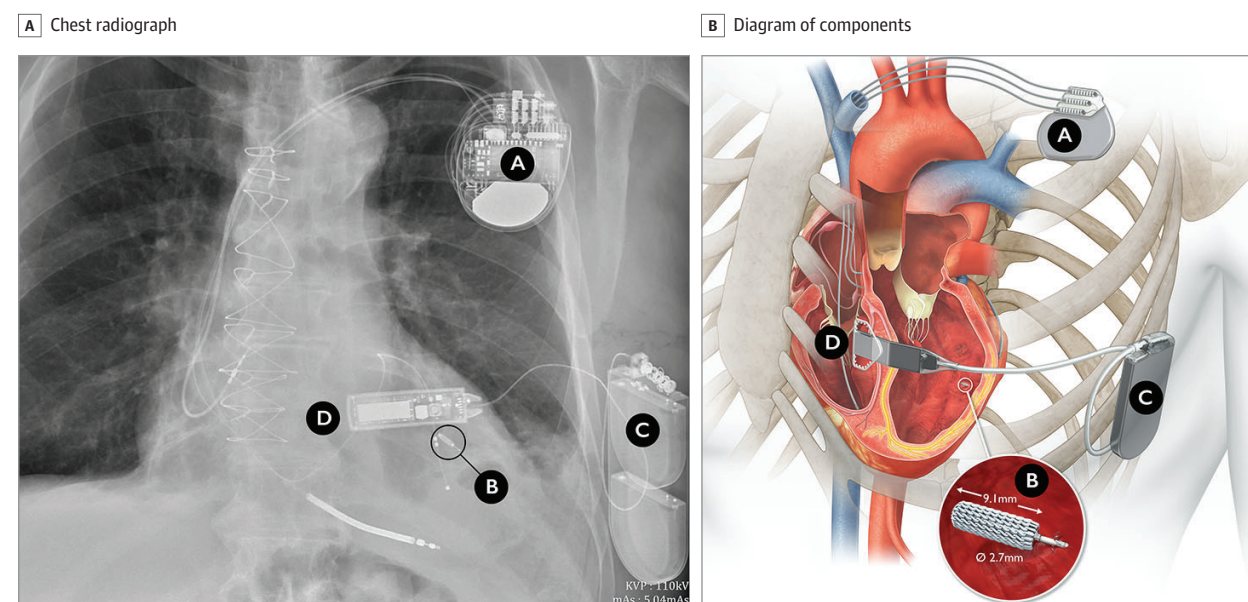
Existing co-implant device (pacemaker, implantable cardioverter defibrillator of CRT) providing right ventricular pacing (A); the receiver-electrode converts ultrasound into electrical energy to pace the LV from the endocardium (B); the battery powers the transmitter; implanted subcutaneously at the left midaxillary line (C); the phase array transmitter that is synchronized with right ventricular pacing pulse and transmits ultrasound energy to the receiver-electrode (D).

Figure 2. Modified Study Design and Patient Disposition at 6 Months
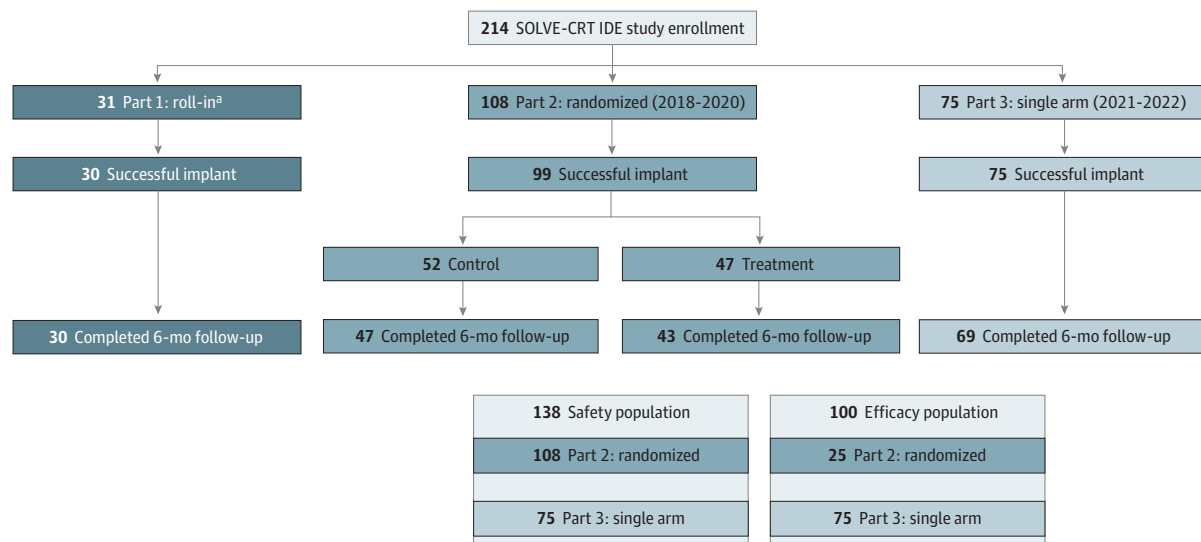
Part 2, randomization phase, was suspended in March 2020 due to the COVID-19 pandemic with 108 patients enrolled. To accommodate COVID-19 restrictions, the single-arm part (part 3) was instituted, and the inclusion criteria no longer included nonresponders. Twenty-five patients from part 2 were in the treatment arm subset of previously untreatable or high-risk upgrade patients. Seventy-five patients were enrolled in part 3, single arm. The safety population

includes all patients enrolled in part 2 and part 3, while the efficacy population includes all patients enrolled in part 3 plus the subset of part 2 matching the indication.

[a] Not included in the analysis.

implantation or lead issues that resulted in the CS lead programmed "off" due to high threshold, noncapture, phrenic nerve pacing, or lead failure.

Patients in the HRU group included those in whom standard CRT upgrade was not advisable due to relative contraindication, such as risk of venous occlusion, pocket infection, or comorbidities. This group also included patients with a leadless intracardiac pacemaker requiring upgrade to CRT. A complete listing of inclusion and exclusion criteria[16] are listed in eTable 1 in Supplement 1.

All patients underwent device implantation and were then randomized in a 1:1 ratio to treatment (system-on) or control (system-off) groups. At 6 months, patients were unblinded and the control group could have their device activated. Unblinded follow-up continued at 6-month intervals through year 2 and at 12-month intervals thereafter.

The first patient was enrolled in SOLVE-CRT in January 2018. Enrollment was severely impacted by the COVID-19 pandemic and was paused in March 2020 after 108 patients were enrolled. At that time, the investigators worked with the US Food and Drug Administration (FDA) to revise the clinical protocol, implementing a single-arm nonrandomized part to complete the study.[16] Central to this strategy was a differentiation of the 3 original patient groups and the requirements for demonstration of safety and efficacy. For the patients in the PU and HRU groups, CRT was an approved therapy and the WiSE CRT System could be viewed as an alternate method of providing CRT when conventional CRT was not possible, so a single-arm study with an objective performance goal was appropriate. In contrast, the nonresponder group had suboptimal responses to conventional CRT due to a diverse set of

pathophysiologic mechanisms. Thus, there was a different threshold for scientifically acceptable evidence for safety and effectiveness and this group was excluded from the study continuation.[16] All versions of the study protocol were approved by relevant institutional review boards and the FDA under an Investigational Device Exemption application. All patients provided written informed consent.

Patient Disposition and Study Populations

The modified study design and patient disposition are shown in **Figure 2**. Overall, the SOLVE-CRT study enrolled 214 patients. Part 1 (roll-in) was designed for centers without prior experience and enrolled 31 patients. These results were published.[18] Part 2 (randomized) enrolled 108 patients; 99 had successful implants with 52 randomized to control and 47 to treatment. In the control group, 48 completed the 6-month follow-up (3 died, 1 withdrew) and in the treatment group, 43 completed 6-month follow-up (3 died, 1 withdrew). Part 3 (single-arm) enrolled 75 patients; all had successful implants and 69 completed the 6-month follow-up (1 died, 5 withdrew).

Data from all participants in the randomized and single-arm parts were included in the prespecified interim safety analysis (n = 183; 108 randomized and 75 single-arm). The efficacy analysis was composed of only patients in the PU and HRU groups, including all single-arm patients (n = 75) and patients randomized to the treatment group from the PU and HRU groups (n = 25) for a total of 100 patients.

Study End Points

Primary Safety

The primary safety end point for the SOLVE-CRT study was freedom from type I complications (T1Cs) through 6 months compared with a performance goal of 70%.[16] Type I complications included adverse events caused by any component of the investigational system (transmitter, battery, electrode, delivery catheter, or programming software) or specific procedure-related events, such as electrode complications, vascular events, stroke, pericardial effusion, and pocket-related events. Type II complications included other procedure-related events not specifically caused by the study device, type III included events related to new disease, and type IV included events related to preexisting conditions (eMethods 6 in Supplement 1).

The performance goal was based on a review of the incidence rate of possible complications incurred by each device component and a literature search of related technologies, such as CRT, percutaneous coronary interventions, ventricular tachycardia ablations, and transcatheter aortic valve replacements (eTables 2 and 3 in Supplement 1).[16]

Primary Efficacy

The primary efficacy end point for the SOLVE-CRT study was the mean relative (percentage) change in LVESV from baseline to 6 months compared with a performance goal of −9.3%. All echocardiograms were evaluated by a blinded echocardiographic core lab.

The rationale for this end point was based on evidence that it is the most reliable measure of clinical benefit of CRT.[19-22] The performance goal of −9.3% relative reduction was derived from the lower confidence bound of a meta-analysis of LVESV reduction in control groups reported in 4 randomized CRT trials (eTable 4 and eFigure 1 in Supplement 1).[8,23-25]

Secondary Efficacy End Points

Secondary efficacy end points were measured at 6 months and included the proportion of patients with an acoustic pacing capture threshold (APCT) less than 2.9 mJ, the proportion of patients with APCT stability (defined as a less than a 3 × relative change from predischarge), percent BIVP (ejection fraction responder analysis for 5% or more absolute increase), and Kansas City Cardiomyopathy Questionnaire (KCCQ) responder analysis for 5 points or more absolute increase.

Statistical Analysis

The overall sample size was driven by the requirements for the primary safety end point. The expected rate of freedom from T1Cs was 77% (lower confidence limit = 70%). The sample size of 300 patients provided approximately 85% power for a fixed sample-size analysis, based on an exact binomial test of proportions with a 1-sided .05 α level.

Spending across the analysis points was controlled using the O'Brien-Fleming spending function. The critical 1-sided α levels for testing safety at the interim and final analyses were 0.0121 and 0.0463. Based on these parameters, a 1-sided 98.8% CI was constructed for the primary safety end point at this interim analysis.

A gatekeeping approach was used to control the type I error rate for the 2 primary end points (eTable 5 though eTable 7 in Supplement 1). The final efficacy and interim safety analyses were conducted after completion of the 6-month follow-up visit for the first 75 patients enrolled in the single-arm part. This yielded 100 patients for the primary efficacy analysis (25 randomized; 75 single arm) and 183 patients for the interim safety analysis (108 randomized; 75 single arm).

The comparison of the mean percent change in LVESV with the performance goal of −9.3 was based on the upper bound of a 95% 2-sided CI using the *t* distribution. Primary safety analysis consisted of calculating the 1-sided lower confidence bound from the exact binomial distribution and comparing that to the 70% freedom from T1Cs performance goal. Secondary end points were assessed in the efficacy population and reported as frequencies and proportions or means and SDs, as appropriate, with nominal 95% CIs for the mean or proportion. The widths of CIs for secondary end points and other exploratory analyses were not adjusted for multiplicity.

Results

Baseline Characteristics

Baseline characteristics of the 183 patients in the safety analysis and 100 patients in the efficacy analysis are presented in **Table 1**. The safety and efficacy populations were similar. In the safety population, the mean age was 68.1 years and 141 patients were male (77%), 63 patients had New York Heart Association (NYHA) Class II disease (34.6%), and 119 had Class III disease (65.4%). The etiology of cardiomyopathy was similarly distributed between ischemic and nonischemic causes. Baseline LVEF (LV ejection fraction), LV end diastolic volume (LVEDV), and LVESV were consistent with patients with advanced HF (eTable 8 and eTable 9 in Supplement 1).

Background medical therapy reflected contemporary medication trends. Notably, 168 patients were taking an ACE, ARB, or ARNI (91.8%). Sixty-eight patients (68%) were taking ARNI (37.2%), 115 (62.8%) were taking aldosterone antagonists, and 174 (95.1%) were taking β-blockers, consistent with maximal.

Indications for CRT and Patient Classifications

There were Class I indications for CRT in 68.9% and Class IIa in 31.1% of patients (Table 1).[26] Among the 183 patients in the safety analysis, there were 44 nonresponders, 110 PU, and 29 HRU. Among the 100 patients in the efficacy analysis, there were 75 PU and 25 HRU (eTable 10 in Supplement 1).

Patient Follow-Up

Of the 183 safety patients, 162 were followed up through 6 months (88.5%), 10 patients died (5.5%), 5 were withdrawn due to unsuccessful implant attempts (2.7%), and 6 were withdrawn for reasons such as heart transplant (3.1%). Of the 100 efficacy patients, 91 completed 6-month follow-up (91.0%), 3 died (3.0%), 3 had an unsuccessful implant attempt (3.0%), and 3 were withdrew due to infection or LV assist device (3.0%).

Table 1. Baseline Characteristics

	No. (%)	
Variable	Safety population (n = 183)	Efficacy population (n = 100)
Age, y, mean (SD)	68.1 (10.28)	68.2 (10.47)
Sex		
Female	42 (23)	24 (24)
Male	141 (77.0)	76 (76.0)
BMI,ᵃ mean (SD)	30.8 (5.75)	30.6 (5.45)
SBP, mm Hg, mean (SD)	119.2 (18.69)	117.5 (17.68)
DBP, mm Hg, mean (SD)	70.3 (10.58)	69.5 (10.45)
HR, bpm, mean (SD)	70.0 (10.59)	70.4 (10.25)
CRT indication		
Class I	126 (68.9)	64 (64.0)
Class IIa	57 (31.2)	36 (36.0)
Patient subpopulations		
Nonresponder	44 (24.6)	0 (0)
Previously untreatable	110 (60.1)	75 (75.0)
Failed CS lead implant	68 (37.2)	48 (48.0)
CS lead turned off	42 (23.0)	27 (27.0)
High-risk upgrade	29 (15.8)	25 (25.0)
NYHA Class		
Class II	63 (34.6)	35 (35.0)
Class III	119 (65.4)	65 (65.0)
Rhythm disorders		
History of atrial tachyarrhythmia	92 (50.3)	52 (52.0)
History of ventricular tachyarrhythmia	67 (36.6)	34 (34.0)
Type of cardiomyopathy		
Nonischemic cardiomyopathy	94 (51.4)	50 (50.0)
Ischemic cardiomyopathy	87 (47.5)	50 (50.0%)
Co-implant	183 (100.0)	100 (100.0)
Pacemaker	28 (15.3)	21 (21.0)
ICD	69 (37.7)	48 (48.0)
CRT-P	11 (6.0)	4 (4.0)
CRT-D	124 (67.8)	59 (59.0)
Medical condition/prior surgery		
Cardiac valve surgical history	19 (10.4)	14 (14.0)
Cerebrovascular disease history	28 (15.3)	16 (16.0)
Baseline kidney function (eGFR), mean (SD)	64.3 (22.20)	64.3 (21.95)
Chronic obstructive pulmonary disease	25 (13.7)	11 (11.0)
Systemic hypertension	99 (54.1)	63 (63.0)
Diabetes	64 (35.0)	31 (31.0)
Insulin dependent	21 (11.5)	8 (8.0)
Noninsulin dependent	43 (23.5)	23 (23.0)
Sleep apnea	43 (23.5)	24 (24.0)
Echo, baseline, mean (SD)		
LVESV, mL	151.1 (67.21)	146.3)71.51)
LVEDV, mL	210.4 (77.76)	206.8 (83.58)
LVEF, %	29.8 (7.90)	31.1 (7.89)
Other baseline measures, mean (SD)		
Paced QRS, ms	183.8 (25.94)	184.9 (24.72)
KCCQ Overall Summary Score	54.7 (22.90)	57.2 (21.38)

(continued)

Table 1. Baseline Characteristics (continued)

	No. (%)	
Variable	Safety population (n = 183)	Efficacy population (n = 100)
NT-proBNP, pg/mL	1626.2 (2172.41)	1761.6 (2463.09)
Baseline medications		
ACE or ARB or ARNI	168 (91.8)	96 (96.0)
ACE inhibitor	59 (32.8)	30 (30.0)
Angiotensin receptor blocker	74 (40.4)	38 (38.0)
Angiotensin receptor-neprilysin inhibitor	68 (37.2)	44 (44.0)
β-Blocker	174 (95.1)	94 (94.0)
Aldosterone antagonist	115 (62.8)	58 (58.0)
Sodium-glucose cotransporter-2 inhibitor	6 (3.3)	6 (6.0)
Diuretic	145 (79.2)	81 (81.0)
Digitalis	11 (6.0)	6 (6.0)

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blockers; ARNI, angiotensin receptor/neprilysin inhibitor; BMI, body mass index; CS, coronary sinus; CRT, cardiac resynchronization therapy; CRT-D, CRT-defibrillator; CRT-P, CRT-pacemaker; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HR, heart rate; ICD, implantable cardioverter defibrillator; LVEF, left ventricular ejection fraction; LVEDV, left ventricular end diastolic volume; LVESV, left ventricular end systolic volume; KCCQ, Kansas City Cardiomyopathy Questionnaire; NT-proBNP, N-terminal pro b-type natriuretic peptide; NYHA, New York Heart Association; SBP, systolic blood pressure.

ᵃ Calculated as weight in kilograms divided by height in meters squared.

Procedure Times

In the safety population, mean procedure times were 1.4 (SD, 0.6) hours for transmitter/battery implantation and 1.1 (SD, 0.6) hours for electrode placement. The electrode was placed via either a retrograde transaortic approach (57.3%) or an atrial transseptal approach (42.7%).

Primary End Points

In the efficacy population, the mean percent change in LVESV was −16.4% (95% CI, −21.0% to −11.7%) with an upper confidence bound below the −9.3% performance goal (*P* = .003), meeting the final primary efficacy end point (**Figure** 3A). In the safety population, there was an 80.9% (148 of 183) rate of freedom from T1Cs with a lower bound of the 1-sided 98.8% CI of 73.4%, above the 70% performance goal (*P* < .001), meeting the interim primary safety end point (eTable 11 in Supplement 1). Since both the prespecified interim safety and final efficacy end points were met, the trial was concluded.

Table 2 provides additional details on T1Cs at 6 months. There were 12 patients with study device system events (6.6%), including 7 in whom the electrode was not anchored, 3 who did not achieve BIVP due to difficulties with the acoustic window, 1 transmitter revision, and 1 episode of ventricular tachycardia requiring cardioversion. Five patients had vascular events (2.7%), including 2 groin hematomas, 1 ischemic limb, and 2 retroperitoneal bleeds. Three patients had strokes (1.6%). The strokes occurred early in the study (2018 to 2019); 2 led to the patient's death and 1 resolved with sequalae.

Figure 3. Percent Change in Left Ventricular End Systolic Volume (LVESV) at 6 Months vs Performance Goal and LVESV, Left Ventricular End Diastolic Volume (LVEDV), and Left Ventricular Ejection Fraction (LVEF) Baseline vs 6-Month Follow-Up
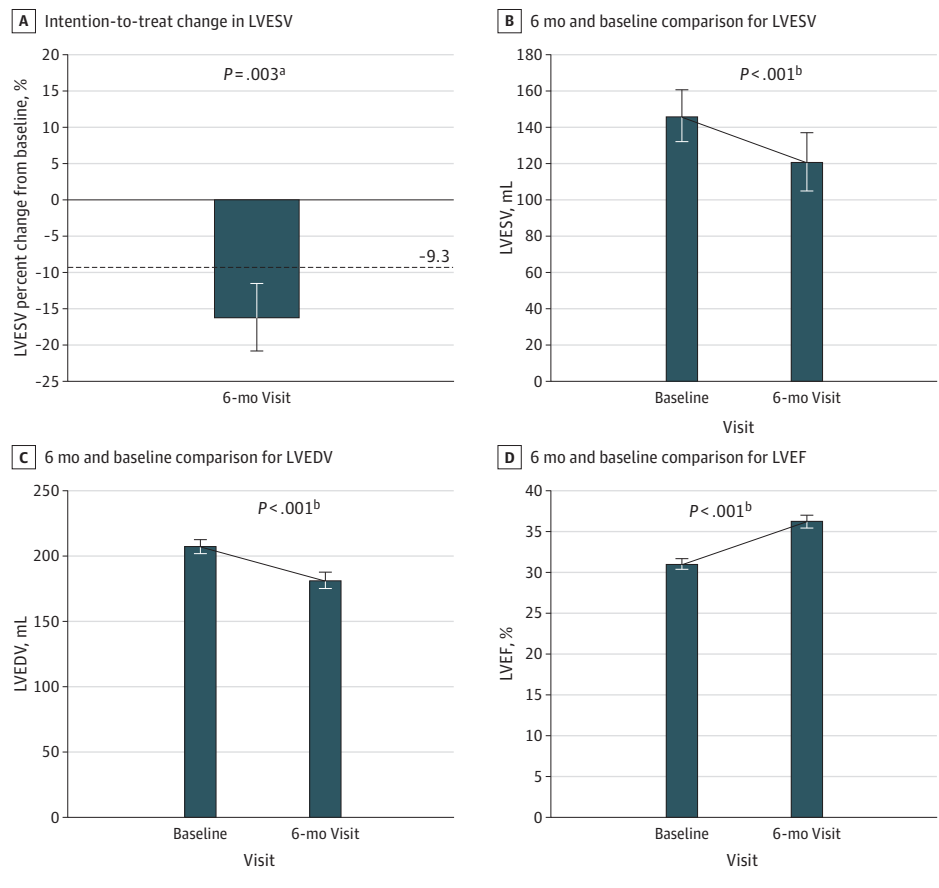
A, The intent-to-treat change in LVESV of −16.4% is shown. The upper boundary of the 2-sided 95% CI was used as the cutoff for meeting the prespecified efficacy objective.

[a] The P value is based on a 1-sample t test.

[b] The nominal P values are based on paired t tests comparing 6 months with baseline values for LVESV (mL), LVEDV (mL), and LVEF (%). These nominal P values are not adjusted for multiplicity.

In addition, 7 patients had cardiac perforations (3.8%). Four perforations required surgical intervention (2.2%) and 3 were treated with pericardiocentesis (1.6%). The cardiac perforations occurred early in the study (2018 to 2019) and in response, refresher training on an implant simulator prior to every implant and use of real-time echocardiography were implemented. These mitigations reduced the rate of cardiac perforations, with only 2 reported in the single-arm part of the study (2.7%), neither of which required surgical intervention. Twelve patients had pocket events (6.6%), including 4 infections, 4 hematomas, 2 transmitter revisions, and 2 battery revisions.

Secondary End Points

An APCT of less than 2.9 mJ was achieved in 95.2% (95% CI, 88.1%-98.7%) of participants, demonstrating that thresholds were sufficiently low. The percentage BIVP was 93.1% (95% CI, 90.3%-95.9%). For responder analyses, 46.1% of participants had 5% or less increase in LVEF (95% CI, 35.4%-57.0%) and 65.5% had a 5-point increase or more in KCCQ (95% CI, 54.6%-75.4%). The mean increase in KCCQ score was 15.3 (95% CI, 11.2%-19.5%). Other echocardiographic changes included the absolute reduction in LVESV of −25.1 mL (95% CI, −32.4 to −17.9) (Figure 3B) and in LVEDV of −25.4 mL (95% CI, −28.4 to −22.5)

(Figure 3C). The mean absolute increase in LVEF was 5.2% (95% CI, 4.7%-5.7%) (Figure 3D) (eTable 12, eFigure 2, and eFigure 3 in Supplement 1.

Overall, 55% of participants' NYHA class improved, 41% were unchanged, and 3.4% worsened by 1 class (eFigure 4 in Supplement 1). The paced QRS duration shortened by a mean of 39.3 (SD, 23.3) milliseconds (eFigure 5 in Supplement 1).

Discussion

The SOLVE-CRT study prospectively evaluated the role of a novel leadless LV endocardial CRT system (WiSE CRT System) in patients whose conventional CRT implant failed due to lead issues (PU) or who could not be upgraded to a standard CRT system due to known contraindications (HRU). This study showed that leadless ultrasound-based endocardial pacing is feasible and clinically efficacious with a high implant success rate (95.5%), an 80.9% freedom from T1Cs, enhanced functional status of patients as reflected by NYHA class and KCCQ scores, evidence of LV reverse remodeling with a mean reduction of 16.4% in LVESV, and shortening of QRS duration by a mean of 39.3 milliseconds.

Table 2. Summary of Type I Complications

Type I complications[a]	No. of patients (%) [No. of events]
Type I	35 (19.1) [43]
Study device system event	12 (6.6) [12]
Electrode not anchored	7 (3.8)
No biventricular capture	3 (1.6)
Transmitter revision	1 (0.5)
Ventricular tachycardia	1 (0.5)
Vascular event	5 (2.7) [5]
Groin hematoma	2 (1.1)
Ischemic leg	1 (0.5)
Retroperitoneal bleed	2 (1.1)
Stroke and other thromboembolic events (eg, TIA)	3 (1.6) [3]
Cardiac perforation	7 (3.8) [7]
Surgically repaired	4 (2.2) [4]
Pericardiocentesis	3 (1.6) [3]
Pocket events	12 (6.6) [15]
Hematoma, conservative treatment	3 (1.6)
Hematoma requiring transfusion	1 (0.5)
Infection	4 (2.2)
Transmitter revision, uneventful	1 (0.5)
Transmitter revision, pneumothorax	1 (0.5)
Battery revision due to erosion	2 (1.1)
Other (anemia postoperative)	1 (0.5) [1]

Abbreviation: TIA, transient ischemic attack.

[a] Six months after the electrode implant procedure, per statistical analysis plan.

Epicardial Lead Location vs Endocardial Electrode Placement and Physiology

Traditional CRT implant involves placing a lead in the CS; however, 30% to 40% of patients do not respond.[1,10-12] Furthermore, an additional 10% are unable to receive CRT due to anatomical challenges limiting access to the CS, phrenic nerve stimulation, or high-pacing thresholds.[27,28] Previous strategies to overcome these challenges included surgically placed epicardial leads or transvenous LV endocardial leads, which are both associated with multiple complications.[29,30]

The WiSE CRT electrode implanted within the left ventricle is small (0.91 cm in length; 0.27 cm in diameter) with a woven polyester jacket that promotes endothelialization[31,32] to prevent clot formation. The WiSE CRT System enables patient-specific endocardial positioning of the electrode, unconstrained by the coronary venous anatomy and without the risks of lead fractures, venous obstruction, mitral regurgitation, and endocarditis.

The present study has demonstrated that the WiSE CRT System can produce equivalent clinical results as seen with conventional CRT in terms of reverse remodeling and improved functional status in patients who were unable to be treated or upgraded with their conventional pacing devices. As such, the WiSE CRT System fills an important unmet need.

Value of Endocardial Pacing

Conventional CS pacing is nonphysiological as the electrical wavefront starts in the epicardium and moves to the endocar-

dium. Normal physiological activation of the heart is the opposite. There is increased interest in pacing the endocardium directly due to the immediate capture of the conduction system and superior hemodynamic effects.[11,13,29] Additional comparisons are needed.[14]

Complications

Adverse events were adjudicated by an independent clinical events committee. The results are comparable with prior studies of patients undergoing an upgrade to CRT who had a major complication rate of 18.7%[33] and for patients treated with a transvenous LV endocardial lead who had a complication rate of 17.8%.[29]

As is typical in initial studies with a novel device, observed complication rates were higher in the early phases and decreased over time. This can be attributed to a protocol change that allowed transseptal access, which reduced the complications associated with arterial access, enhanced training including the use of simulator models, and mandated use of real-time echocardiography.

Clinical Implications

This novel technology using ultrasound energy disrupts the conventional pacing paradigm while allowing for leadless pacing within the LV endocardium. There are several aspects of the WiSE CRT System that favorably impact the leadless future for cardiac pacing. The electrode implanted in the LV is efficiently endothelialized—without the need for prolonged anticoagulant therapy. The system has been used in Europe and Australia in patients with an intracardiac RV pacemaker who are eligible for a CRT upgrade to provide totally leadless CRT pacing.[34,35]

A feasibility study has shown promise in delivering the WiSE electrode directly into the left bundle branch area to achieve conduction system pacing.[36] Compared with conventional epicardial CRT, this is considered more physiologic and may have greater efficacy. Additional clinical studies are needed to evaluate the effects of the WiSE CRT System in CSP.

Limitations

The SOLVE-CRT study was initiated as a randomized clinical trial. Through the challenges of the COVID-19 pandemic, the protocol was revised with approval from the FDA to include a single-arm part that no longer included the nonresponder cohort.[16] This trial is limited by the absence of randomization, a limited overall trial size, and a 6-month follow-up period, so robust conclusions regarding comparative efficacy with other implant strategies cannot be drawn. Furthermore, in the absence of blinding, it is very difficult to interpret the changes in NYHA and KCCQ. Also, patients who were considered nonresponders were not included in the efficacy analysis, so this study cannot make any comment on clinical efficacy in nonresponders.

There are some technological challenges worth noting. The system requires a focused beam of ultrasound energy to target the electrode and, thus, is dependent on implanting the transmitter in an intercostal space that is free of lung encroachment. Also, the battery and transmitter are additional compo-

nents that the patient must carry, requiring 2 separate chest wall incisions.

Conclusions

In this nonrandomized study, the SOLVE-CRT study has demonstrated that leadless ultrasound-based LV endocardial pac-

ing with the WiSE CRT system is associated with a reduction in LVESV. This is a novel technology that allows the delivery of CRT in patients with HF who meet the standard criteria for CRT but who cannot be treated with conventional CRT.

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Data Sharing Statement: See Supplement 5.

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