

Real-world experience of leadless left ventricular endocardial cardiac resynchronization therapy: A multicenter international registry of the WiSE-CRT pacing system



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BACKGROUND Biventricular endocardial pacing (BiV ENDO) is a therapy for heart failure patients who cannot receive transvenous epicardial cardiac resynchronization therapy (CRT) or have not responded adequately to CRT. BiV ENDO CRT can be delivered by a new wireless LV ENDO pacing system (WiSE-CRT system; EBR Systems, Sunnyvale, CA), without the requirement for lifelong anticoagulation.

OBJECTIVE The purpose of this study was to assess the safety and efficacy of the WiSE-CRT system during real-world clinical use in an international registry.

METHODS Data were prospectively collected from 14 centers implanting the WiSE-CRT system as part of the WiCS-LV Post Market Surveillance Registry. ([ClinicalTrials.gov](https://clinicaltrials.gov) Identifier: NCT02610673).

RESULTS Ninety patients from 14 European centers underwent implantation with the WiSE-CRT system. Patients were predominantly male, age 68.2 ± 10.5 years, left ventricular ejection fraction $30.6\% \pm 8.9\%$, mean QRS duration 180.7 ± 27.0 ms, and 40% with ischemic etiology. Successful implantation and delivery of BiV ENDO pacing was achieved in 94.4% of patients. Acute (<24 hours), 1- to 30-day, and 1- to 6-month complications rates were 4.4%, 18.8%, and 6.7%, respectively. Five deaths (5.6%) occurred within 6 months (3 procedure related). Seventy percent of patients had improvement in heart failure symptoms.

CONCLUSION BiV ENDO pacing with the WiSE-CRT system seems to be technically feasible, with a high success rate. Three procedural deaths occurred during the study. Procedural complications mandate

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adequate operator training and implantation at centers with immediately available cardiothoracic and vascular surgical support.

KEYWORDS Cardiac resynchronization therapy; Endocardial pacing; Heart failure; Leadless pacing; Nonresponder

Introduction

Heart failure is a significant cause of morbidity and mortality,¹ with disease progression resulting in adverse left ventricular (LV) remodeling and dyssynchronous electrical and mechanical activation.² Cardiac resynchronization therapy (CRT) restores regional activation synchrony and enhances cardiac contractility.³ However, 30%–50% of patients do not show improvement with conventional CRT delivered from an epicardial LV lead within a tributary of the coronary sinus.^{4–6} In addition, implantation of an epicardial LV lead is not always possible due to technical and anatomic limitations,⁷ particularly in patients undergoing an upgrade from a pre-existing cardiac implantable electronic device because of central venous stenosis/occlusion.⁸

LV endocardial pacing is a potential therapy for patients who either cannot receive transvenous epicardial CRT or have not responded adequately to CRT.⁹ LV endocardial stimulation traditionally has been delivered via pacing leads placed transseptally, which mandates lifelong anticoagulation due to the risk of thromboembolic complications. A novel wireless LV endocardial pacing system (WiSE-CRT system; EBR Systems, Sunnyvale, CA) delivers electrical stimulation to the LV endocardial surface of the heart by transducing acoustic energy from an ultrasound (US) pulse generator implanted subcutaneously in an intercostal space (Figures 1 and 2).¹⁰ The US waves are converted to electrical stimulation energy by a small receiver electrode deployed percutaneously into the LV cavity. The receiver electrode is fully endothelialized after four weeks, avoiding the need

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for long-term anticoagulation. The stimulation is triggered by right ventricular (RV) pacing, resulting in near simultaneous (~2–5 ms) LV and RV endocardial activation. Patients must be prescreened using a combination of linear and cardiac US (echocardiography) to ensure successful delivery of consistent LV endocardial pacing from the most efficient location.

The system has undergone a first-in-man study evaluation.¹¹ More recently, in the nonrandomized SELECT-LV (Safety and Performance of Electrodes implanted in the Left Ventricle) study, 35 patients across 6 centers were implanted, and promising results were seen in terms of clinical response and LV reverse remodeling.¹² Previous work also evaluated the possibility of identifying and targeting the optimal pacing site.¹³ The WICS-LV Post Market Surveillance Registry (ClinicalTrials.gov Identifier: NCT02610673) was undertaken to assess the safety and efficacy of the WiSE-CRT system in a real-world setting. The device is CE (Conformité Européenne [French for European Conformity]) marked in Europe and is indicated for patients who are unable to receive conventional CRT or who are nonresponders to CRT.

Methods

Data collection

The WICS-LV Post Market Surveillance Registry prospectively collected data from all 14 European centers implanting the WiSE-CRT System. All patients studied provided full written consent to participate. Patient data was de-identified and collected anonymously using a uniquely identifiable study number.

Inclusion criteria

The WiSE-CRT system is CE marked for 3 approved indications¹²: (1) patients in whom LV lead deployment was not possible or had previously failed due to anatomic constraints, high capture thresholds, or phrenic nerve stimulation; (2) patients undergoing an upgrade to CRT in whom implantation of an LV lead was impractical or complex due to issues with venous access or undesirable because of previous pocket infection; and (3) patients who previously were nonresponders to conventional transvenous epicardial CRT. Nonresponders were defined as patients who had no change or had worsening of symptoms or New York Heart Association functional class after 6 months of treatment as confirmed by the treating physician. Patients were classified as having either ischemic cardiomyopathy or nonischemic cardiomyopathy using a combination of cardiac magnetic resonance imaging, electroanatomic mapping, coronary angiography, and clinical history.

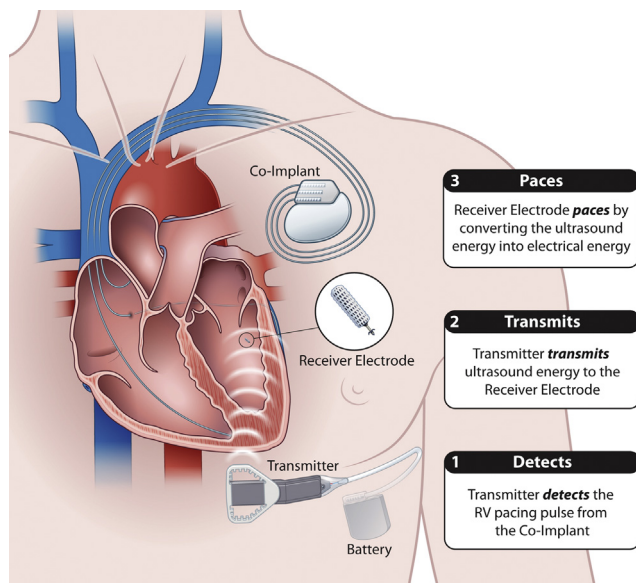


Figure 1 The WiSE-CRT pacing system.

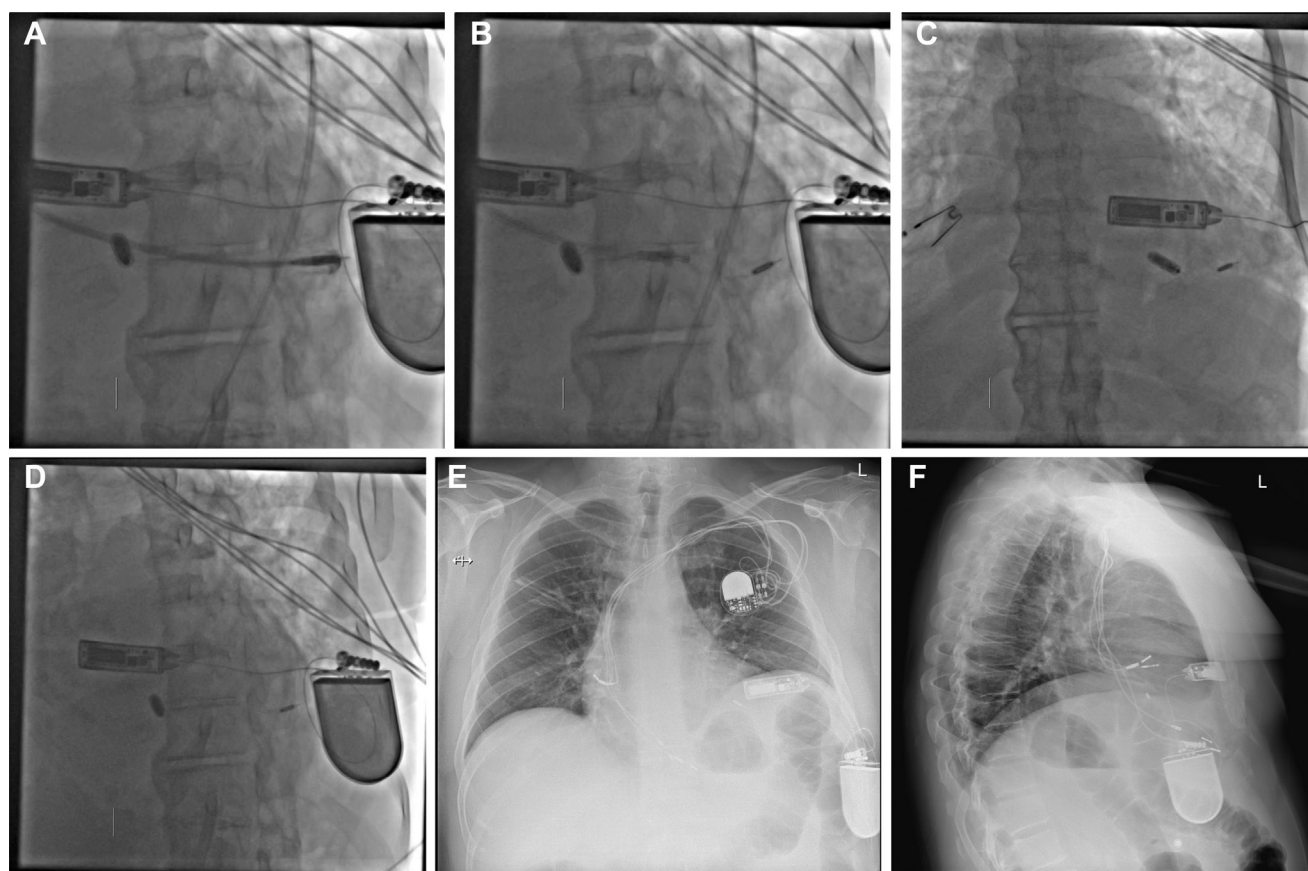


Figure 2 A: The WiSE-CRT delivery catheter across the aortic valve, with the pacing electrode advanced to the tip of the catheter and about to be deployed in the myocardium. The battery and ultrasound (US) pulse generator also are visible. B: The WiSE-CRT electrode affixed to the myocardium after release. C: Posteroanterior view of the Micra transcatheter pacing system (TPS) (Medtronic Inc, Minneapolis, MN) and the WiSE-CRT US pulse generator and pacing electrode *in situ*. D: Right anterior oblique view of the Micra TPS and WiSE-CRT US pulse generator, battery, and pacing electrode. E: Posterior chest radiograph showing the WiSE-CRT system *in situ* in combination with the Micra TPS. F: Lateral chest radiograph showing the WiSE-CRT system *in situ* in combination with the Micra TPS.

Endpoints

Three safety and efficacy assessments were prespecified: (1) Procedural success, requiring successful implantation of all WiSE-CRT components and confirmation of biventricular pacing on a postimplant 12-lead electrocardiogram. (2) Safety of the system, evaluating acute (<24 hours), intermediate (24 hours–1 month), and long-term (1–6 months) complications. Adjudication was performed by the local principal investigator at each site. (3) Clinical response to biventricular endocardial pacing, assessing the proportion of patients who experienced improvement in clinical symptoms 6 months after implantation.

Clinical response

Clinical response was assessed by a clinical composite score. This simple global assessment of symptoms classified each patient into 1 of 3 categories: improved, worsened, or unchanged.

Statistical analysis

Continuous variables with a gaussian distribution are given as mean \pm SD. Significance testing on continuous, normally

distributed paired data was performed using 2-tailed paired Student *t* tests. Significance testing on continuous, non-normally distributed paired data was performed using the Wilcoxon signed rank test. Significance testing on continuous, non-normally distributed unpaired data was performed using the Mann-Whitney U test. If both independent and dependent factors were categorical, significance testing was performed using the χ^2 test. Odds ratios were calculated using binary logistic regression. If both independent and dependent factors were continuous, odds ratios and significance testing were performed using linear regression. $P < .05$ was considered significant. Analysis was performed using PASW Statistics 24 (SPSS Inc, Chicago, IL).

Results

Patient characteristics

A total of 90 patients from 14 European centers were implanted with the WiSE-CRT system (Table 1). Patients were predominantly male (80.0%) (mean age 68.2 ± 10.5 years; mean left ventricular ejection fraction $30.6\% \pm 8.9\%$). Mean QRS duration was 180.7 ± 27.0 ms, and 40.0% of patients had an ischemic etiology. In terms of

Table 1 Patient characteristics

No. of patients	90
Age (y)	68.2 ± 10.5
Male	72 (80.0)
ICM etiology	36 (40.0)
NYHA functional class	
I	1 (1.1)
II	33 (36.7)
III	56 (62.2)
IV	0 (0)
Echocardiographic data	
LVEF (%)	30.6 ± 8.9
LVESV (ml)	130.4 ± 78.5
LVEDV (ml)	185.7 ± 93.0
ECG	
Atrial arrhythmia	47 (52.2)
QRS duration (ms)	180.7 ± 27.0
RV paced morphology	81 (90.0)
LBBB morphology	6 (6.7)
BiV paced morphology	3 (3.3)
Indication	
Failed LV lead implant	44 (48.9)
Complex upgrade	34 (37.8)
Failure to respond to CRT	12 (13.3)

Values are given as n (%) or mean ± SD unless otherwise indicated.

BiV = biventricular; ECG = electrocardiography; ICM = ischemic cardiomyopathy; LBBB = left bundle branch block; LV = left ventricle; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; LVESV = left ventricular end-systolic volume; NYHA = New York Heart Association; RV = right ventricle.

indication, 48.9% of patients had failed conventional transvenous CRT implant, 37.8% were deemed a complex upgrade, and 13.3% previously were nonresponders to epicardial CRT. Four patients (4.4%) withdrew from the registry after undergoing implantation with the system, so no follow-up data for these patients were recorded. The majority of patients (n = 82) were implanted via the femoral artery using a retrograde transaortic approach as previously described.¹⁰ In a minority of patients in whom issues with arterial patency, tortuosity, or aortic valve disease/replacement precluded a retrograde approach (n = 10), a novel transseptal approach was used.¹⁴

Procedural success

Confirmation of biventricular pacing

Biventricular pacing was confirmed by postimplantation 12-lead electrocardiogram in 85 of 90 patients (94.4%). In 5 cases (5.6%), consistent capture of the LV endocardial pacing electrode could not be achieved. Failure of the screening process to exclude 2 unsuitable patients was later confirmed: the first patient had comorbid chronic obstructive pulmonary disease with significant lung encroachment affecting the US signal between the subcutaneous transmitter array and LV endocardial pacing electrode; and the second patient had a distance between the LV pacing electrode to US array that was too large (>13 cm) to allow achievement of consistent

capture. One patient never received an LV pacing electrode due to periprocedural tamponade, which led to the implant procedure being aborted. One patient experienced suboptimal device functionality after the US transmitter displaced due to improper initial fixation, and revision with a new US transmitter resolved the issue. In the final patient, the electrode was believed to be implanted in myocardial scar, and delivery of LV stimulation resulted in intermittent capture.

Safety and complications

Acute complications

Procedural acute complications (<24 hours) occurred in 4 patients (4.4%) (Table 2). Two patients experienced cardiac tamponade after electrode placement, and 1 of these patients died 4 days later (see section on Intermediate complications). Two patients had complications related to US transmitter array/battery placement (1 pneumothorax, 1 pleural effusion). Neither patient required intervention, and both resolved with conservative management. No electrode embolizations occurred.

Intermediate complications

Intermediate complications (24 hours–1 month) occurred in 17 patients (18.8%), including 1 patient death that occurred 4 days postimplant, which was attributed to an acute LV perforation that resulted in cardiac tamponade. The most common adverse events were related to femoral arterial access in 4 patients (4.4%): 1 femoral hematoma that resolved with conservative management and 3 femoral artery pseudoaneurysms, 2 of which required surgical intervention. Four patients (4.4%) had transmitter/battery pocket hematomas, and 3 patients (3.3%) had transmitter/generator pocket infection. Three patients (3.3%) had postprocedural lower respiratory tract infection, and 2 patients had postprocedural acute kidney injury.

Table 2 Patient safety outcome data

Complication data	No. (%)
Patient deaths within the registry	5 (5.6)
Procedure related	3
Nonprocedure related	2
Acute (<24 h)	4 (4.4)
Cardiac tamponade	2
Pneumothorax/pleural effusion	2
Intermediate (>24 h–1 mo)	17 (18.8)
Death	1
Arterial access complication	4
Pocket hematoma (generator)	4
Postprocedure chest sepsis	3
Pocket infection (generator)	3
Acute kidney injury	2
Chronic (1–6 mo)	6 (6.7)
Death	4
CVA	1
Extrastimulation during TTE	1

CVA = cerebrovascular accident; TTE = transthoracic echocardiography

Chronic complications

Chronic complications (1–6 months) occurred in 6 patients, including 4 deaths (2 believed to be procedure/device related). One patient with persistent atrial fibrillation treated with apixaban suffered a cerebellar infarct 5 months postimplant. Given that the receiver electrode endothelializes within 4–6 weeks, this complication was not believed to be procedure or device related. Stimulation of the WiSE-CRT system during echocardiography was observed in 1 patient at the 6-month follow-up visit. The receiver electrode had been positioned in an LV apical position. The sonographer observed a self-terminating run of ectopic ventricular extrasystoles while obtaining an apical 4-chamber view. The run of ectopic beats stopped immediately after the probe was withdrawn, and the patient reported no symptoms.

Learning curve and success/complications

Most of the complications (76%) occurred within a center's first 10 cases, suggesting an initial learning curve when using this technology.

Patient deaths

Five patients (5.6%) died within 6 months of implantation. Three deaths (3.3%) were adjudicated to be procedure/device related, 2 of which were related to LV perforation. Details of patient deaths are given in the [Supplemental Information—Patient Deaths](#).

CRT response

Four patients who were lost to follow-up were excluded from the chronic response analysis. All 86 patients who received CRT at 6 months had data evaluating their clinical response. Sixty patients (69.8%) reported an improved clinical composite score; 12 (14.0%) had no change in composite score; and 4 (4.7%) had a worsened composite score. The group of 86 patients included 5 who experienced inconsistent LV endocardial stimulation and 5 who died during follow-up. Comprehensive echocardiographic study of LV volumes to assess remodeling was available for 43 patients and can be reviewed in the [Supplemental Information—Echocardiographic Remodeling](#) and [Supplemental Table 1](#).

Discussion

The WICS-LV Post Market Surveillance Registry is the largest experience to date of this novel technology to achieve leadless LV endocardial pacing. The registry was designed to assess the procedural success, safety, and long-term efficacy of leadless LV endocardial pacing in a real-world setting of 14 European centers.

The principal findings were as follows. (1) The WiSE-CRT system achieved procedural success, with biventricular endocardial pacing confirmed in >94% of patients. (2) Device/procedural-related adverse events occurred in a significant number of patients. Three procedural deaths (3.3%) occurred; 4.4% of patients had a procedural complication

within 24 hours of the procedure; 18.8% had a complication between 24 hours and 1 month after the procedure; and 6.7% had a complication between 1 and 6 months after the procedure. (3) At 6 months, the system was associated with a favorable clinical response rate of 70%.

Comparison with previous studies

The WiSE-CRT Post Market Surveillance Registry represents the largest evaluation of this novel pacing technology and establishes that real-world use of the WiSE-CRT LV endocardial pacing system is effective. It has a complication profile and response rate similar to those seen in the SELECT-LV study,¹² a prospective multicenter nonrandomized trial that assessed the safety and performance of the WiSE-CRT system in 35 patients. Similar to the current study, SELECT-LV reported successful implantation of the system in 97% of cases. Similar rates of clinical response of 84.8% and 70% of patients reporting an improvement in clinical composite score were observed in the SELECT-LV study and the WiSE-CRT registry, respectively.

Both studies identified a significant complication rate. No episodes of cardiac tamponade were observed in the SELECT-LV trial; however, 2 patients (2.2%) were identified in the WiSE-CRT registry and subsequently died. Serious acute (<24 hours) procedure/device-related events occurred in 4 patients (8.6%) in the SELECT-LV study compared to 4.4% in the WiSE-CRT registry. A serious procedure/device-related event occurred between 24 hours and 1 month after the procedure in 22.3% of patients in the SELECT-LV trial, with a similar rate of events (18.8%) in the WiSE-CRT registry. In the SELECT-LV trial 1 procedure-related death (2.8%) following VF at the time of electrode placement was reported, whereas in the WiSE-CRT registry 5 patient deaths (5.6%) occurred within a 6-month period, 3 (3.3%) of which were believed to be procedure related. The rate of perforation in the current registry has improved compared to the initial iteration of the device, which had an 18% tamponade rate and led to redesign of the delivery catheter.¹⁰

A lead-based system for endocardial CRT was previously analyzed in the ALSYNC (ALternate Site Cardiac ResYNChronization) study.⁹ This prospective study enrolled 138 patients who either had a failed attempt at conventional transvenous epicardial CRT or were unsuitable to undergo biventricular resynchronization pacing. The primary study objective was to investigate the safety at 6 months of delivering LV endocardial pacing via a lead placed across the atrial septum. The implant success rate was 89.4%, which is consistent with our registry findings. Freedom from complications meeting the definition of primary endpoint was 82.2% at 6 months. Fourteen transient ischemic attacks (9 patients [6.8%]), 5 nondisabling strokes (5 patients [3.8%]), and 23 deaths (17.4%) were reported. No death resulted from a primary endpoint complication. At 6 months, New York Heart Association functional class improved in 59% of patients. Therefore, the current registry has a death rate at

follow-up lower than that observed in the ALSYNC study and a significantly reduced risk of cerebrovascular events.

Vascular access complications

The most common procedural complications were related to femoral arterial access, as the WiSE-CRT system was designed to allow deployment of the pacing electrode in the LV cavity via retrograde aortic access from the femoral artery. This procedure requires large-bore 12F femoral arterial access and closure, skills not commonly required by practicing electrophysiology/complex device specialists who tend to implant this system. Three approaches have been devised to reduce the rate of femoral arterial access complications. First, vascular closure devices were used at 12 centers to minimize bleeding and ensure effective arterial closure at the end of the procedure. Eleven centers used the Perclose ProGlide, Abbott Vascular (Santa Clara, California) vascular suture system. One center used the Prostar XL (Abbott Vascular) percutaneous vascular surgical system to assist vascular hemostasis. Vascular closure systems have been shown to reduce time to hemostasis.¹⁵

Second, several operators have used pre- and periprocedural imaging to guide arterial access. Five centers used real-time US guidance to identify the femoral artery and visualize guidewire deployment. At one center, a contralateral femoral puncture was performed in order to facilitate an ipsilateral femoral angiogram before obtaining large-bore femoral access. Third, use of a transeptal approach permitting electrode deployment in the LV endocardium after initial femoral venous access has been shown to be possible.¹⁴ In a series of 10 cases, this approach obviated the requirement for femoral arterial access, achieving successful electrode deployment without a single groin or thromboembolic complication.¹⁶ This approach may be preferable among electrophysiologists who are familiar with performing transeptal punctures.

US extrastimulation

The WiSE-CRT receiver electrode typically is not sensitive to routine US imaging, but in rare instances extrastimulation of the device is possible. In our series, this event was observed in only 1 case. However, this is an important finding given the widespread use of ultrasonic imaging in medicine and specifically within the field of cardiology. Apical placement of the LV pacing electrode seems to increase the potential for extrastimulation, particularly while obtaining an apical 4-chamber view with transthoracic echocardiography, which significantly reduces the distance between the receiver electrode and the alternate US source. Other risk factors for extrastimulation include the use of high-power settings, low-frequency US (typically utilized during harmonic imaging), and thin body habitus. In order to avoid inadvertent extrastimulation of the pacing electrode, all patients are issued a medical device identification card stating they have a US-sensitive pacemaker. For cases in which apical deployment of the pacing electrode has been confirmed, an alternative echocardiography protocol has been developed

and shown to successfully prevent further extrastimulation. This document forms part of the clinical trial documents for the SOLVE CRT Clinical Trial (ClinicalTrials.gov Identifier: NCT02922036). Echocardiography Acquisition and Transfer Manual: The SOLVE-CRT Trial (Version 5.0, 19 Dec 2019).

Study limitations

The main limitation of this current analysis is that it is a registry and therefore is limited by the inherent constraints of a nonrandomized study. Importantly, neither patients nor investigators were blinded, and all suitable patients enrolled in the WiCS-LV registry were implanted with the system. Although LV reverse remodeling was selected as an endpoint, other endpoints included the subjective clinical response, which may be more open to bias. A randomized, double-blinded evaluation of the WiSE-CRT system is currently underway (Stimulation Of the Left Ventricular Endocardium for Cardiac Resynchronization Therapy in Non-Responders and Previously Untreatable Patients (SOLVE CRT; [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT02922036) Identifier: NCT02922036). This study hopefully will provide an unbiased assessment of symptomatic and echocardiographic response associated with endocardial pacing.

Unlike conventional transvenous epicardial CRT, the WiSE-CRT system is unable to determine the percentage of effective CRT pacing. When interrogating the WiSE-CRT system using the pacing system analyzer, the number of “tracked” RV pacing signals that result in generation of a US wave can be evaluated but not whether the US signal resulted in successful LV endocardial capture. LV capture can only be confirmed by assessing the paced QRS morphology for successful biventricular paced morphology. Holter monitoring can be used to confirm consistent biventricular capture when required.

Finally, comprehensive LV volume data for all patients were not available for data analysis. Comprehensive echocardiographic study of LV volumes to assess remodeling was available for 43 patients. Fourteen patients were excluded from chronic response analysis due to failure to achieve endocardial stimulation in 5, death during follow-up in 5, and loss to follow-up in 4. LV volumetric assessment either was not performed or was of insufficient quality to allow for meaningful data analysis in 33 patients.

Conclusion

The WICS-LV Post Market Surveillance Registry is the largest series of leadless LV endocardial pacing to date. Importantly it demonstrates effective real-world use with a response rate similar to those of previous nonrandomized studies, with nearly 70% of patients reporting an improvement in clinical symptoms. Response rates are equivalent to those of lead-based biventricular endocardial pacing systems while largely eliminating the risk of thromboembolic stroke.⁹ Implantation of the system can be associated with a significant complication rate, but complications will occur

less frequently as operators gain more experience with the delivery system. The risk of cardiac tamponade is in keeping with other left-sided vascular procedures such as left atrial appendage occlusion,¹⁷ and given the risk of cardiac tamponade, which may require urgent repair, implantation should be performed at centers with on-site cardiothoracic surgical facilities. Our results suggest that endocardial CRT pacing with this novel pacing system is effective treatment for a group of high-risk patients with heart failure who either cannot receive or who have not responded to conventional CRT. Implantation of the system should be performed by adequately trained operators at centers having experience with vascular and cardiothoracic complications.

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Appendix

Supplementary data

Supplementary data associated with this article can be found in the online version at <https://doi.org/10.1016/j.hrthm.2020.03.002>.

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