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The SELECT-LV Study

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ABSTRACT

BACKGROUND A total of 30% to 40% of patients with congestive heart failure eligible for cardiac resynchronization therapy (CRT) either do not respond to conventional CRT or remain untreated due to an inability or impediment to coronary sinus (CS) lead implantation. The WiSE-CRT system (EBR Systems, Sunnyvale, California) was developed to address this at-risk patient population by performing biventricular pacing via a wireless left ventricular (LV) endocardial pacing electrode.

OBJECTIVES The SELECT-LV (Safety and Performance of Electrodes implanted in the Left Ventricle) study is a prospective multicenter non-randomized trial assessing the safety and performance of the WiSE-CRT system.

METHODS A total of 35 patients indicated for CRT who had "failed" conventional CRT underwent implantation of an LV endocardial pacing electrode and a subcutaneous pulse generator. System performance, clinical efficacy, and safety events were assessed out to 6 months post-implant.

RESULTS The procedure was successful in 97.1% (n = 34) of attempted implants. The most common indications for endocardial LV pacing were difficult CS anatomy (n =12), failure to respond to conventional CRT (n = 10), and a high CS pacing threshold or phrenic nerve capture (n = 5). The primary performance endpoint, biventricular pacing on the 12-lead electrocardiogram at 1 month, was achieved in 33 of 34 patients. A total of 28 patients (84.8%) had improvement in the clinical composite score at 6 months, and 21 (66%) demonstrated a positive echocardiographic CRT response (≥5% absolute increase in LV ejection fraction). There were no pericardial effusions, but serious procedure/device-related events occurred in 3 patients (8.6%) within 24 h, and 8 patients (22.9%) between 24 h and 1 month.

CONCLUSIONS The SELECT-LV study demonstrates the clinical feasibility for the WiSE-CRT system, and provided clinical benefits to a majority of patients within an otherwise "failed" CRT population. (Safety and Performance of Electrodes Implanted in the Left Ventricle [SELECT-LV]; NCT01905670) (J Am Coll Cardiol 2017;69:2119–29) © 2017 by the American College of Cardiology Foundation.

Cardiac resynchronization therapy (CRT) can improve mortality and quality of life in patients with depressed left ventricular ejection fraction (LVEF), mild to severe heart failure (HF) symptoms, and prolonged intraventricular conduction time (1). Left ventricular (LV) pacing via an implanted coronary sinus (CS) lead is the first-line approach for achieving CRT, but 30% to 40% of patients do not respond to this conventional CRT (2). Furthermore, an additional 8% to 10% of eligible patients do not receive CRT due to anatomical constraints, such as the absence of appropriate CS targets, occlusion of the upper extremity venous system, phrenic nerve stimulation, or high pacing threshold in areas of diffuse scar (3,4). Prior approaches to achieve ventricular resynchronization in patients who have either not responded or failed CS implantation have included surgical epicardial lead placement and transseptal implantation of endocardial LV pacing leads (5). However, surgical epicardial lead placement is inherently more invasive than the percutaneous approach, can be especially challenging in patients with prior cardiac surgery (pericardial adhesions), and is associated with lower lead survival rates compared with transvenous leads (6). Although transseptal LV endocardial stimulation may offer the benefits of providing more physiological endocardial ventricular activation and may even be less proarrhythmic compared with epicardial LV pacing, this approach is limited by the thromboembolic risk, need for lifelong systemic anticoagulation, and concern for mechanical effects on the mitral valve.

A system that performs endocardial LV stimulation to achieve biventricular pacing, but does not require a thoracotomy or systemic anticoagulation, would be an attractive option for resynchronization therapy. In this context, a novel wireless cardiac resynchronization system (WiSE-CRT, EBR Systems, Sunnyvale, California) was developed to pace the LV endocardium with a small wireless pacing electrode. The WiSE-CRT system provides wireless pacing by transmitting acoustic (ultrasonic) energy from a pulse generator transmitter, implanted subcutaneously over the ribcage, to a receiver electrode implanted in the LV. The WiSE-CRT System functions in conjunction with a coimplanted standard right ventricular (RV) pacing system. Biventricular pacing is achieved by sensing the RV pacing output of the coimplant, followed by the system immediately transmitting acoustic energy to the electrode, thus achieving nearly simultaneous pacing of the RV and LV. The transmitter is a phased array ultrasound system that focuses the acoustic energy on the electrode. Herein, we present the 6-month outcomes of the prospective multicenter clinical trial of the WiSE-CRT system in the SELECT-LV (Safety and Performance of Electrodes implanted in the Left Ventricle) study.

METHODS

STUDY DESIGN. The SELECT-LV study (NCT01905670) was a multicenter (n = 6 centers), prospective evaluation of the performance and safety of the WiSE-CRT System in patients indicated for CRT who had "failed" conventional CRT. Patients were eligible for inclusion if they had a standard indication for CRT and at least 1 of the following criteria: 1) "upgrades": CS lead implantation was not advisable/feasible due to perceived risk (e.g., infection) or impediment (e.g., venous obstruction); 2) "untreated": coronary sinus lead implantation attempted but failed (e.g., difficult CS anatomy, phrenic nerve capture); or 3) "nonresponders": previously implanted conventional CRT device with worsening of symptoms or worsening of New York Heart Association (NYHA) functional class after 6 months of CRT treatment. Patients were excluded if they had nonambulatory (or unstable) NYHA functional class IV HF symptoms, a contraindication to heparin, a contraindication to long-term anticoagulation and antiplatelet agents, stage 4 or 5 chronic kidney disease, major cardiac surgery within the prior month, or noncardiac implanted electrical stimulation devices. A serious adverse event was defined as any event that led to death, serious deterioration that resulted in a life-threatening illness or injury, permanent impairment of body structure or function, hospitalization or prolongation of existing hospitalization, or a medical or surgical intervention.

ENDPOINTS. The primary performance endpoint was evidence of biventricular pacing (on 12-lead electrocardiogram [ECG]) at 1 month. If the patient was not pacemaker dependent, 12-lead ECGs were to be obtained without pacing (intrinsic), during RV-only pacing (by temporarily programming off the WiSE-CRT system), and during biventricular pacing. Biventricular capture was confirmed by comparing the paced QRS morphology during biventricular pacing with that during RV-only pacing. To meet this endpoint, 2 performance criteria had to be met: appropriate recognition of the sensed coimplant RV pacing output (successful detection) and LV pacing (successful capture). The primary performance endpoint was based on the number of patients

FIGURE 1 Wireless Endocardial Left Ventricular Pacing
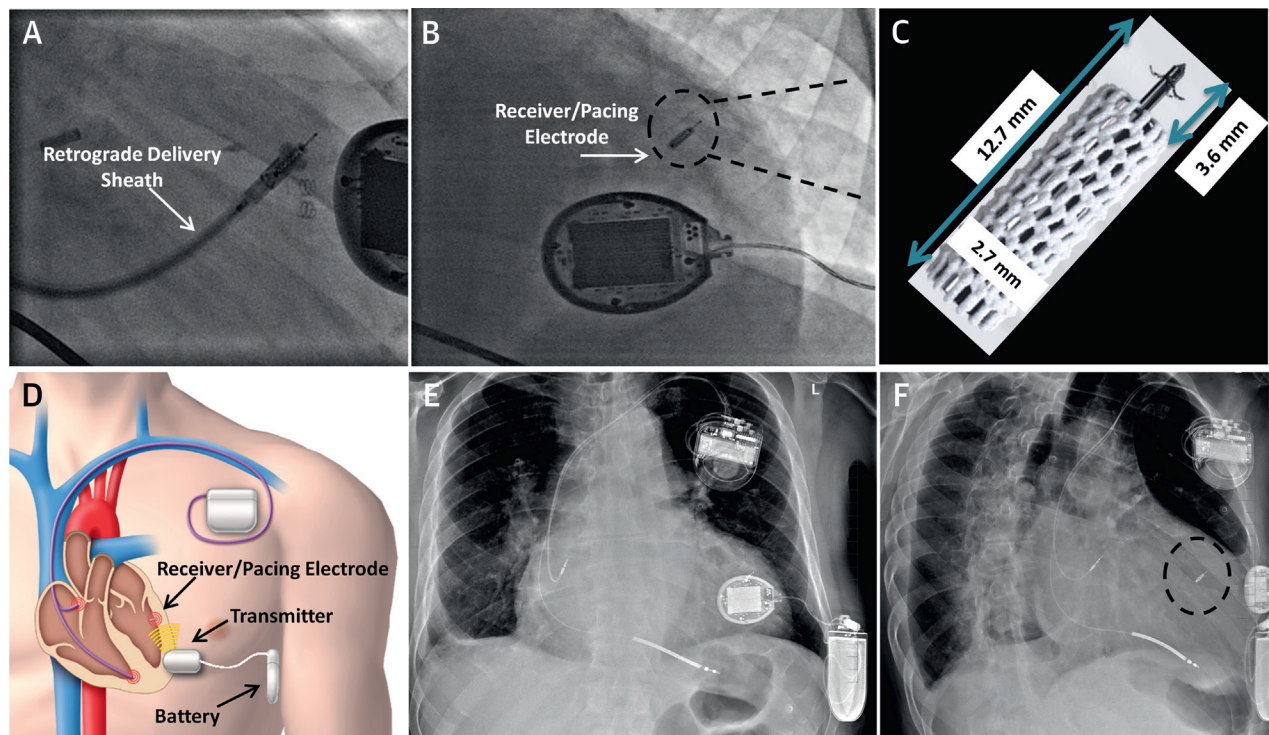
(A and B) Fluoroscopic images of the retrograde delivery sheath and pacing electrode engaged into the myocardium and following deployment. **(C)** Photograph and dimensions of the pacing electrode. **(D to F)** Schematic representations of the implanted system and posteroanterior/lateral chest x-rays the day after implant. The **dashed line** encircles the receiver/pacing electrode.

who underwent implantation of the complete system (n = 34). The primary safety endpoints were device-related complications at 2 time frames: from implant to 24 h post-implant, and from 24 h to 30 days. The safety endpoints were based on intention to treat (number of patients who underwent an attempt at system implantation; n = 35).

The secondary efficacy endpoints included: 1) change in the HF clinical composite score (all-cause mortality, HF hospitalization, NYHA functional class, and patient global assessment) at 6 months; and 2) change in echocardiographic left ventricular end-systolic volume (LVESV), left ventricular end-diastolic volume (LVEDV), and LVEF at 6 months (3,7). The clinical composite score classifies the patient as improved, unchanged, or worsened (8). The global assessment score is a 7-point rating scale, allowing for the evaluation of the patient's own perspective of overall health compared with a previous point in time (9). Positive responses to CRT between baseline and at 6 months were defined as: 1) reduction in LVESV by ≥15%; 2) reduction in LVEDV by ≥10%; 3) improvement in LVEF by ≥5%; and 4)

improvement of NYHA functional class by ≥1 (3). The intrinsic and RV-paced QRS durations at baseline (pre-CRT) were compared with the intrinsic, RV-paced, and biventricular-paced QRS durations at 6 months; the delta QRS was defined as the intrinsic QRS duration (ms) at baseline minus the biventricular-paced QRS at 6 months. Secondary safety endpoints included device-related complications between 1 and 6 months. All serious adverse events were reviewed and adjudicated by an independent clinical events committee. In-person follow-up was performed at pre-discharge and at 1 week, 1 month, 2 months, and 6 months post-implant.

SYSTEM DETAILS AND IMPLANTATION. As shown in **Figure 1**, the WiSE-CRT system consists of 4 components: 1) a 12-F steerable delivery catheter system with an atraumatic inflatable polyester balloon at the catheter tip; 2) an 8-F retractable delivery catheter with a pre-mounted receiver electrode (volume = 0.05 ml); the electrode is an ultrasound receiver and energy converter, and is implanted in the LV via a transaortic retrograde approach; 3) a

pulse generator that consists of an ultrasound energy pulse transmitter and a battery, both of which are implanted subcutaneously; and 4) the programmer.

Implanting the WiSE system is a 2-step process. Surgical subcutaneous implantation of the pulse generator system is followed by catheter placement of the LV pacing electrode. These 2 steps were performed on consecutive days. To implant the pulse generator, 2 surgical incisions are required: 1 for the transmitter, and 1 for the battery. The battery pocket is created at the midaxillary line. The location for the transmitter requires an acoustic window, a lung- and bone-free acoustic line of sight from the implant location to the LV. This is most commonly located in the 4th to 6th intercostal spaces lateral to the left parasternal border and can be identified in pre-procedure screening using transthoracic echocardiography. In general, an acoustic window of 3 cm^2 is sufficient for nominal use of the system. After cut down to the level of the intercostal muscle, an echocardiogram probe in a sterile sleeve is used to further assess the acoustic window prior to securing the transmitter in the location. An accessory is secured to the intercostal muscle using helical sutures, then the transmitter is inserted into the accessory and sutured. Additionally, a subcutaneous channel between the 2 pockets is created to pass and connect the cable between the transmitter and the battery. The cable length is 30 cm. As mentioned previously, the WiSE-CRT system requires coimplantation of a commercially available standard pacemaker, transvenous defibrillator, or conventional CRT device to synchronize biventricular pacing. Sensing electrodes on the outside surface of the transmitter and battery enclosures are used to detect RV pacing pulses from the coimplanted device. Immediately after sensing the RV pacing output, the WiSE-CRT system triggers an ultrasound pulse that is received and transduced to electrical energy to pace the LV. This occurs essentially simultaneously to achieve biventricular pacing (average time delay between RV pace sensing and LV pacing is typically 3 to 5 ms).

For placement of the LV pacing electrode prior to delivery sheath insertion, heparin is administered to maintain an activated clotting time of 200 to 250 s. The delivery sheath is advanced retrograde to the LV, and then the delivery catheter with a pre-loaded electrode is advanced until it is 5 to 10 mm proximal to the tip of the delivery sheath. The cathode of the electrode is connected through the delivery catheter so that local electrogram signals can be monitored and electrical pacing thresholds can be tested. By advancing the electrode to the very distal end of the

TABLE 1 Demographics and Indications for LV Endocardial Wireless Pacing (n = 35)	
Age, yrs	65.4 ± 7.9
Male	29 (85)
BMI, kg/m^2	29.9 ± 5.2
Cardiomyopathy	
Ischemic	15 (42.9)
Nonischemic	16 (45.7)
Mixed	4 (11.4)
NYHA functional class	2.6 ± 0.6
LVEF, %	26.0 ± 6.2
Hypertension	20 (57.1)
Diabetes	11 (31.4)
Chronic kidney disease	12 (34.3)
Coimplanted system	
Single-chamber ICD	1 (2.9)
Dual-chamber PPM	1 (2.9)
Dual-chamber ICD	4 (11.4)
CRT-P	6 (17.1)
CRT-D	23 (65.75)
Indication for LV endocardial pacing implant	
Difficult CS anatomy/access	12 (34.0)
Failure to respond to CRT	10 (29.0)
High CS threshold or phrenic nerve capture	5 (14.0)
CS lead dislodgement or lead failure	3 (9.0)
Prior infection or upper extremity occlusion	3 (9.0)
Other	2 (6.0)

Values are mean ± SD or n (%).

BMI = body mass index; CRT = cardiac resynchronization therapy; CS = coronary sinus; D = defibrillator; ICD = implantable cardioverter-defibrillator; LV = left ventricular; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; P = pacemaker; PPM = permanent pacemaker.

sheath, multiple endocardial pacing sites can be tested prior to anchoring the electrode. Under fluoroscopic guidance, the pacing site evaluation includes a combination of echocardiographic considerations, electrical timing using local electrogram signals, and pacing thresholds. The location, distance, and angle of the electrode are tracked in real time during implantation, as reported through the programmer by the transmitter's tracking algorithm. This confirms that selected sites can be targeted relative to the implant location of the transmitter. The transmitter has a 2-dimensional phased array, providing angular steering of the ultrasound beam along 2 orthogonal directions. The transmitter uses this angular steering to focus transmitted ultrasound at the location of the electrode. If the angular location coincides with the electrode, the electrode will produce an electrical pulse that can be detected by the transmitter, indicating the angular location of the electrode. Furthermore, the time lag between transmission of the ultrasound impulse and detection of electrical output is used to determine the distance between the transmitter and electrode. The real-time information

TABLE 2   Clinical Efficacy Endpoints and Response to CRT

Parameter	Baseline	6 Months	Change	p Value	Response Definition	Response Rate at 6 Months (%)
LVESV, ml (n = 25)	183.8 ± 62.9	157.0 ± 75.7	−26.8 ± 45.1	0.007	≥15% relative reduction	52
LVEDV, ml (n = 25)	243.1 ± 70.7	222.4 ± 77.0	−20.6 ± 41.5	0.02	≥10% relative reduction	40
LVEF, % (n = 32)	25.9 ± 6.4	33.0 ± 10.3	+7.1 ± 8.0	<0.0001	≥5% absolute increase	66
NYHA functional class I/II/III/IV	3/24/73/0	24/67/3/6	+0.8 ± 0.8		≥1 class improvement	67
Global assessment			Markedly improved: 42.4% Moderately improved: 27.3% Mild improvement: 6.1% No change: 15.2% Slightly worse: 0.0% Moderately worse: 3.0% Markedly worse: 6.1%		Markedly or moderately improved	70

Values are mean ± SD or %.

LVEDV = left ventricular end-diastolic volume; LVESV = left ventricular end-systolic volume; other abbreviations as in **Table 1**.

of the angular location as well as distance from transmitter to electrode is presented to the user by a graphic/data display during the site selection process. Once an appropriate endocardial LV pacing site is identified, the electrode is deployed/anchored into the LV endocardium by advancing the catheter to push the anchor of the electrode into the endocardial surface.

Following implantation, patients were prescribed aspirin 75 to 325 mg daily throughout the study duration (6 months), and clopidogrel 75 mg daily for 3 months post-implant. For patients taking long-term warfarin therapy for other indications (e.g., atrial fibrillation, and so on), based on the center's standard practice, warfarin was permitted to be discontinued 2 to 3 days pre-procedure and reinitiated afterwards; in these long-term warfarin patients, the addition of antiplatelet agents was not required.

STATISTICAL ANALYSIS. Continuous variables are expressed as mean ± SD. We used a paired Student *t* test to compare performance values between implant (baseline) and follow-up intervals. A p value <0.05 was considered indicative of statistical significance. Statistical calculations were performed by using SPSS version 12.0 (SPSS Inc., Chicago, Illinois).
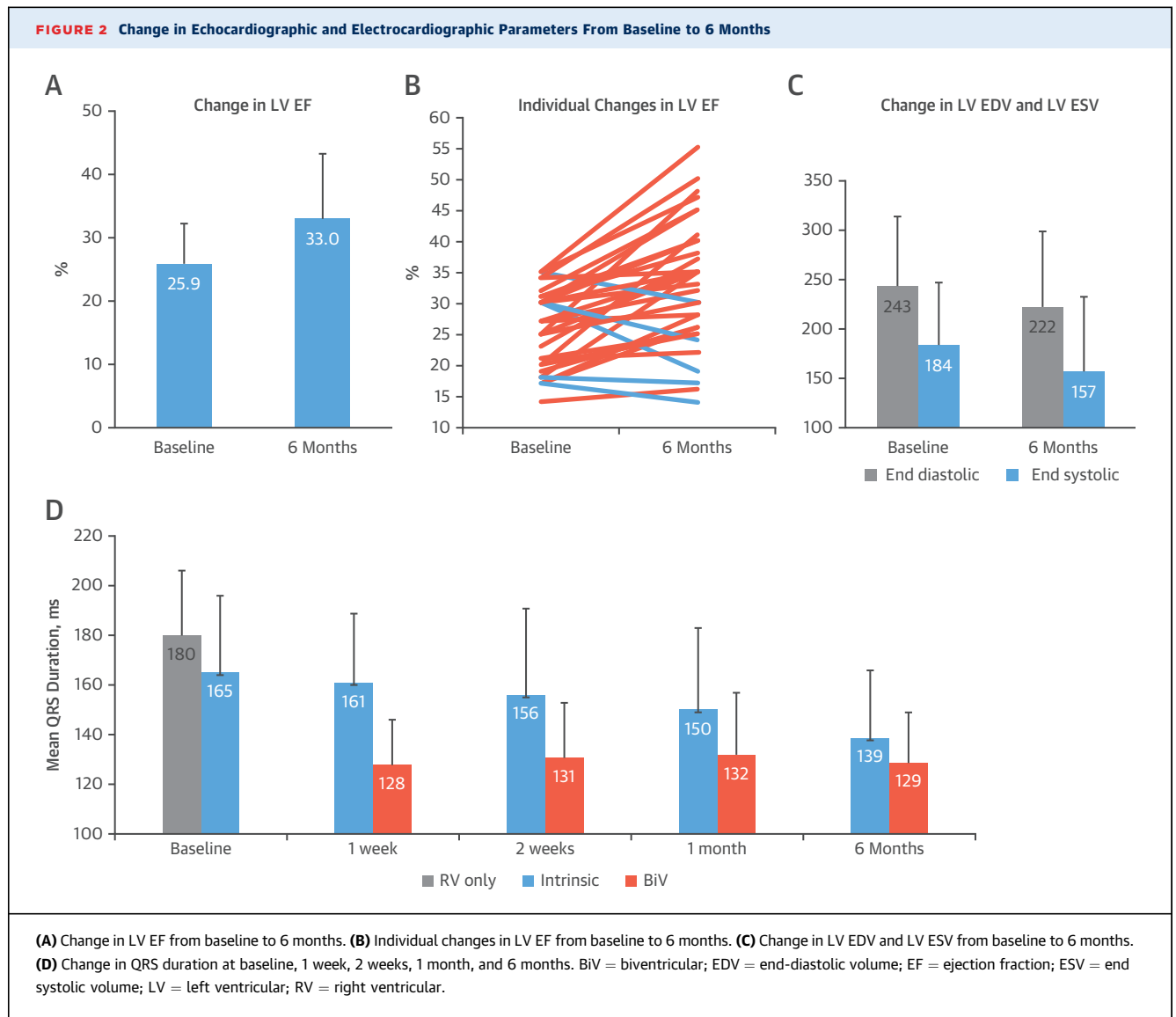
RESULTS

BASELINE DEMOGRAPHICS AND INDICATIONS FOR ENDOCARDIAL LV PACING. The clinical characteristics of the patients are shown in **Table 1**. Of the patients enrolled in the clinical trial (n = 39), 35 patients (89.7%) underwent the procedure. The remaining patients (n = 4) did not undergo a procedure because of either an inadequate acoustic window (n = 3) or patient withdrawal prior to the planned implant procedure (n = 1). The mean age of

the cohort (n = 35) was 65.4 ± 7.9 years. The prevalence of ischemic cardiomyopathy, non-ischemic cardiomyopathy, and mixed cardiomyopathy was 43% (n = 15), 46% (n = 16), and 11% (n = 4), respectively. More than one-half of the patients had hypertension (57%; n = 20), and approximately one-third had diabetes (31%; n = 11) and chronic kidney disease (34%; n = 12). Approximately two-thirds of the patients had been receiving oral anticoagulation with warfarin.

With regard to the standard coimplanted system, the devices included biventricular implantable cardioverter-defibrillators (n = 23), biventricular pacemakers (n = 6), single/dual-chamber implantable cardioverter-defibrillators (n = 4), and dual-chamber pacemaker (n = 1). These coimplanted systems were from 5 commercially available device companies, including Medtronic (n = 12), St. Jude Medical (n = 10), Boston Scientific (n = 6), Biotronik (n = 5), and Sorin (n = 1). The most common indications for endocardial LV pacing were for difficult CS anatomy (n = 12; 34%), failure to respond to conventional CRT (n = 10; 29%), and a high CS pacing threshold or phrenic nerve capture at low outputs (n = 5; 14%). Additional reasons included CS lead dislodgment or lead failure (n = 3; 9%), prior infection or upper extremity venous occlusion (n = 3; 9%), and other (n = 2; 6%). Completed follow-up was available for 34 patients at 1 month and for 33 patients at 6 months (1 patient required system removal, as discussed in the following text).

PROCEDURAL DETAILS. Of patients who underwent an attempted implant (n = 35), the procedure was successful in 97.1% (n = 34). One patient did not have the electrode implanted due to ventricular arrhythmia during the implantation procedure

FIGURE 2 Change in Echocardiographic and Electrocardiographic Parameters From Baseline to 6 Months

(A) Change in LV EF from baseline to 6 months. **(B)** Individual changes in LV EF from baseline to 6 months. **(C)** Change in LV EDV and LV ESV from baseline to 6 months. **(D)** Change in QRS duration at baseline, 1 week, 2 weeks, 1 month, and 6 months. BiV = biventricular; EDV = end-diastolic volume; EF = ejection fraction; ESV = end systolic volume; LV = left ventricular; RV = right ventricular.

(see the following text). The mean procedure durations for implanting the pulse generator (i.e., transmitter and battery) and pacing electrode, including time for ACT to meet the 200- to 250-s target were 85 ± 35 min and 58 ± 24 min, respectively. The optimal acoustic window for pulse generator implant was most commonly in the 6th intercostal space (60%; n = 21), followed by the 7th (17%; n = 6), 5th (14%; n = 5) and 4th (9%; n = 3) intercostal spaces. The mean distance from the transmitter to the pacing electrode was 8.5 ± 1.6 cm.

PERFORMANCE, CLINICAL RESPONSE, AND REMODELING ENDPOINTS. The primary performance endpoint, biventricular pacing on the 12-lead ECG, was achieved in 97.1% (n = 33 of 34) of

patients at 1 month and 93.9% (n = 31 of 33) at 6 months. Biventricular pacing could not be demonstrated in 2 patients at the 6-month follow-up due to defective transmitters, which were subsequently replaced. A majority of the patients (n = 28 of 33; 84.8%) had an improvement in the clinical composite score at 6 months, whereas a minority were either unchanged (n = 3; 9.1%) or worsened (n = 2; 5.9%). As shown in Table 2, two-thirds of the patients experienced an improvement in NYHA functional class by ≥1 (n = 22; 66.7%) and an improvement in quality-of-life scores (n = 23; 69.7%). One patient was rehospitalized for HF (n = 1; 3.0%) on 2 separate occasions.

As shown in Figure 2, there were significant improvements between baseline and 6 months in

FIGURE 3 Representative Example of QRS Shortening With Left Ventricular Endocardial Wireless Pacing and Resynchronization Therapy
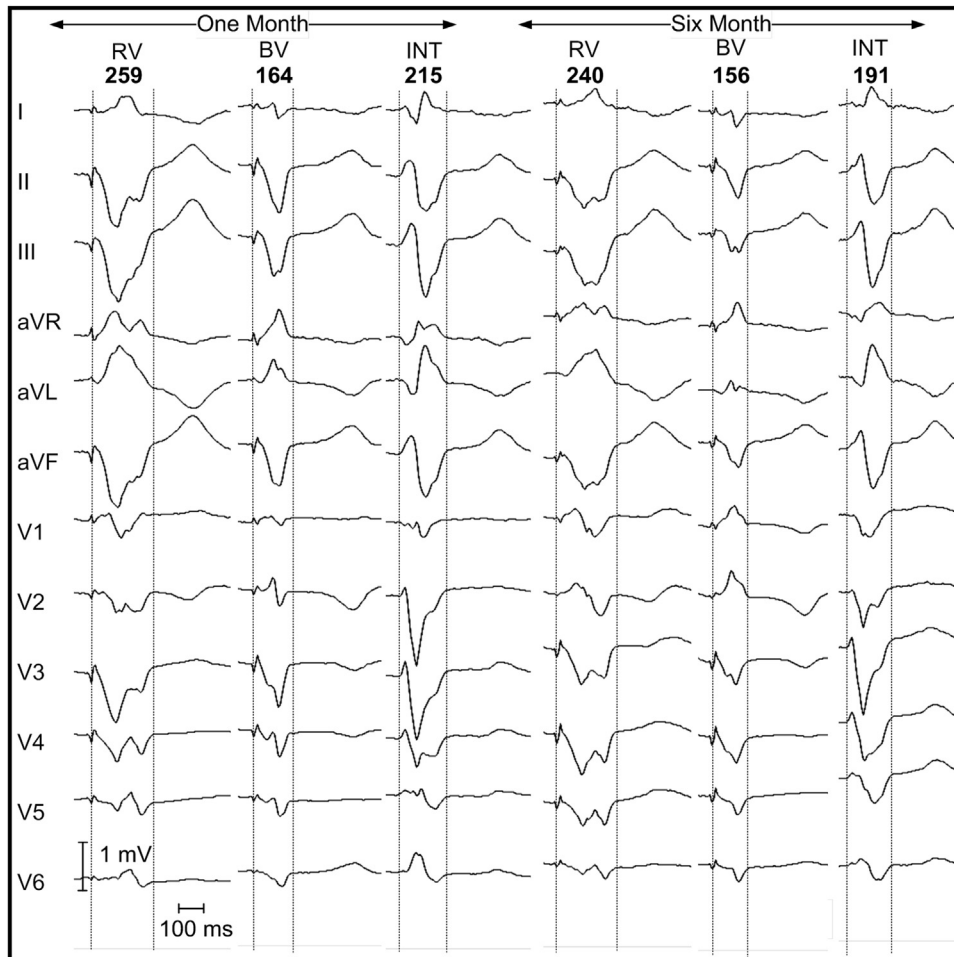
BV = biventricular; INT = intrinsic; RV = right ventricular.

LVEF (25.9 ± 6.4% vs. 33.0 ± 10.3%, respectively; p < 0.001), LVEDV (243 ± 71 ml vs. 224 ± 77 ml, respectively; p = 0.02), and the LVESV (184 ± 63 ml vs. 157 ± 76 ml, respectively; p = 0.006). Using the responder criteria for LVESV (≥15% relative reduction), LVEDV (≥10% relative reduction), and LVEF (≥5% absolute increase), positive echocardiographic responses to CRT were observed in 52% (n = 13), 40% (n = 10), and 66% (n = 21) of patients, respectively (Table 2). As compared with the baseline QRS duration, there were significant reductions in the 6-month intrinsic QRS (169.9 ± 29.2 ms vs. 142.6 ± 27.3 ms, p < 0.001) but not in RV-paced QRS (187.2 ± 30.3 ms vs. 182.0 ± 32.2 ms, p = 0.21) durations. In patients where intrinsic QRS data was available at baseline and at 6 months (n = 20), there were significant reductions in the intrinsic QRS duration (Figure 2D).

An illustrative example from a patient implanted with the WiSE-CRT system, demonstrating a narrower QRS compared with RV-paced and intrinsic rhythm, and QRS shortening over time (from 1 to 6 months) is shown in Figure 3.

SAFETY. As shown in Table 3, the primary safety endpoint of serious procedure- or device-related events occurred in 3 patients (8.6%) within the first 24 h. One patient developed ventricular fibrillation during the electrode implant procedure (following contact of the delivery catheter with the LV endocardium), which required prolonged resuscitation (37 min). This patient died 4 days later due to complications from the cardiac arrest. In 1 patient, the electrode embolized to the left tibial artery during an exchange of the dilator and catheter, prior to introduction of the sheath into the LV. Following

TABLE 3 Device- or Procedure-Related Adverse Events (n = 35)	
<24 h	3 (8.6%)
VF during catheter contact with LV endocardium	1
Electrode embolization to lower extremity	1
Femoral artery fistula (required surgical repair)	1
24 h to 1 month	8 (22.3)
Acute CVA (AF noncompliant with anticoagulation)	1
Femoral pseudoaneurysm	2
Pocket hematoma (generator)	1
Suspected infection (generator site)	3
Death (following VF during initial implant procedure)	1
1 to 6 months	3 (8.6)
Defective transmitter circuitry	3

Values are n (%) or n.

AF = atrial fibrillation; CVA = cerebrovascular accident; LV = left ventricular; VF = ventricular fibrillation.

angiography and surgical consultation, it was deemed not necessary to retrieve the embolized electrode because of the absence of angiographic occlusion or clinical symptoms. Another electrode was then placed in the LV with acceptable pacing parameters. The third patient developed a femoral artery fistula that required surgical repair.
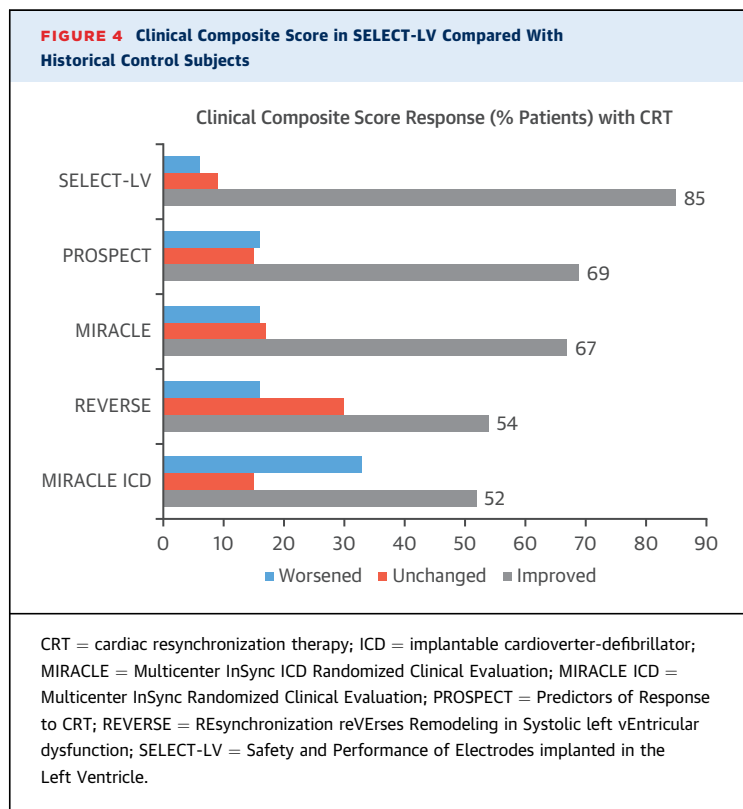
The other primary safety endpoint of serious procedure- or device-related events between 24 h and

FIGURE 4 Clinical Composite Score in SELECT-LV Compared With Historical Control Subjects

CRT = cardiac resynchronization therapy; ICD = implantable cardioverter-defibrillator; MIRACLE = Multicenter InSync ICD Randomized Clinical Evaluation; MIRACLE ICD = Multicenter InSync Randomized Clinical Evaluation; PROSPECT = Predictors of Response to CRT; REVERSE = REsynchronization reVErses Remodeling in Systolic left vEntricular dysfunction; SELECT-LV = Safety and Performance of Electrodes implanted in the Left Ventricle.
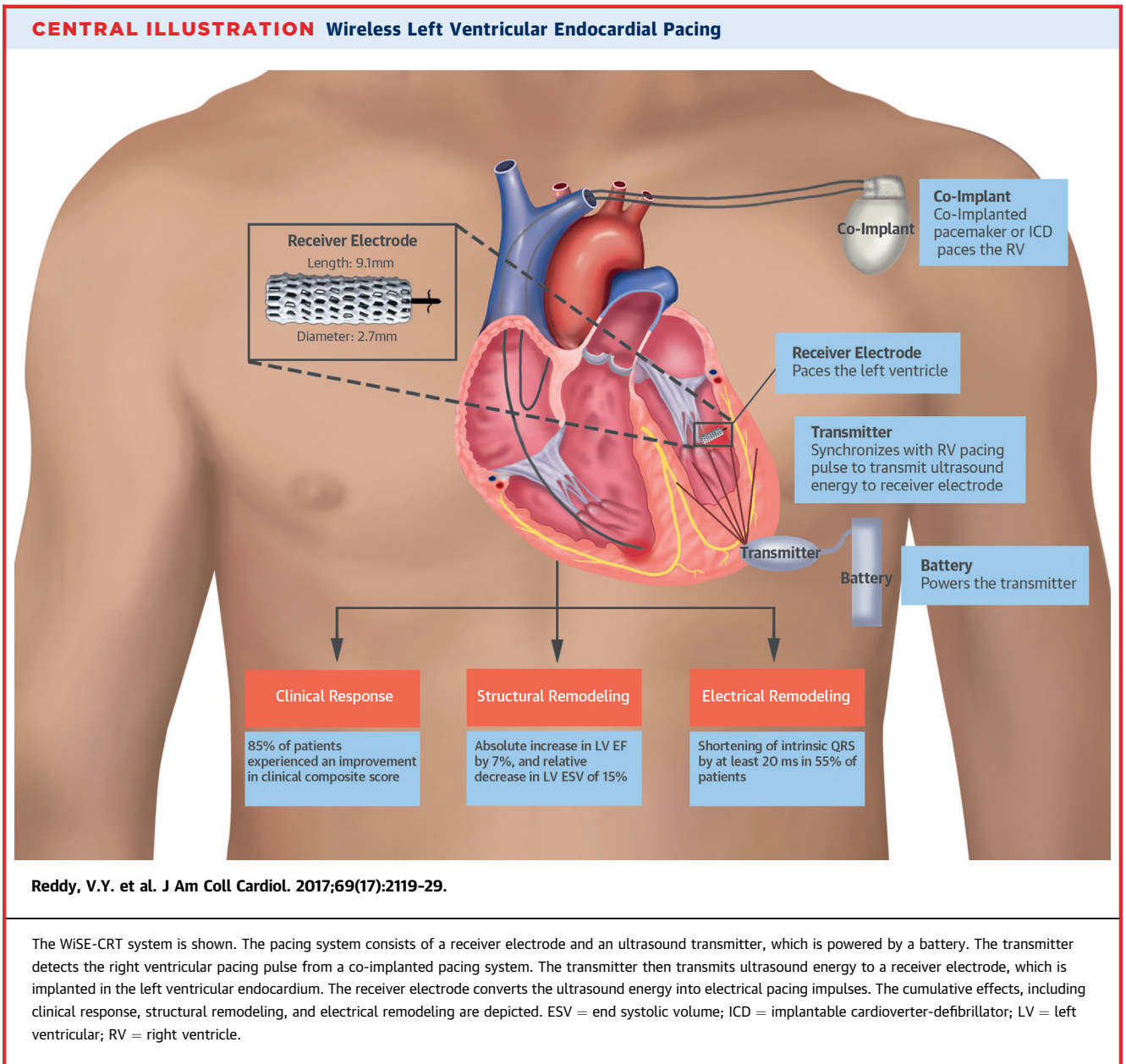
1 month occurred in 8 patients (22.9%) (Table 3). As mentioned previously, 1 patient died 4 days following catheter-induced VF. One patient with AF developed a stroke (basilar artery) 3 days after the implant, in the context of warfarin noncompliance (international normalized ratio = 1.1 at time of stroke). This patient recovered without residual neurological deficit. There were 3 suspected or proven infections: 1 patient did not require additional treatment, but the patient was hospitalized for 1 day of observation; 1 patient was treated with oral and IV antibiotics for suspected infection at the battery pocket surgical site; and 1 patient required removal of the WiSE-CRT system due to draining fluid from the transmitter pocket. There were 2 femoral artery pseudoaneurysms, 1 of which was repaired percutaneously, and the other required surgical correction.

DISCUSSION

In a population of failed conventional CRT patients, the SELECT-LV trial demonstrated that cardiac resynchronization with endocardial LV stimulation via a novel leadless pacing electrode was technically feasible and efficacious. We demonstrated: 1) a high implant success rate (97%); 2) improvements in the HF clinical composite score in 85% of patients; and 3) a positive echocardiographic CRT response (reduction in LVESV ≥15%) in 52% of patients at 6 months. As shown in **Figure 4**, these clinical outcomes compared quite favorably to the clinical and structural improvements observed in conventional CRT trials. For example, in the intervention arm of the PROSPECT (Predictors of Response to CRT) trial, the clinical composite score improved in 69% of patients and LVESV decreased by ≥15% in 56% of patients (3,10,11). Additionally, in the SELECT-LV trial, there was also evidence of resynchronization-induced electrical remodeling, which is believed to be associated with better clinical and structural response (12). In patients where intrinsic QRS data was available at baseline and at 6 months, there were significant reductions in the intrinsic QRS duration: 55% (11 of 20) patients were noted to have a shortening of the intrinsic QRS duration by at least 20 ms (**Central Illustration**). Overall, the biventricular paced QRS at 6 months was 51 ms shorter than the RV-paced QRS at baseline and 36 ms shorter than the intrinsic QRS at baseline. These data are particularly compelling given that the enrolled cohort were largely patients who failed or were poor candidates for conventional CRT.

To date, there have been various strategies utilized to offer CRT to patients who are not candidates for conventional coronary sinus pacing. Perhaps the most

CENTRAL ILLUSTRATION Wireless Left Ventricular Endocardial Pacing

Reddy, V.Y. et al. J Am Coll Cardiol. 2017;69(17):2119-29.

The WiSE-CRT system is shown. The pacing system consists of a receiver electrode and an ultrasound transmitter, which is powered by a battery. The transmitter detects the right ventricular pacing pulse from a co-implanted pacing system. The transmitter then transmits ultrasound energy to a receiver electrode, which is implanted in the left ventricular endocardium. The receiver electrode converts the ultrasound energy into electrical pacing impulses. The cumulative effects, including clinical response, structural remodeling, and electrical remodeling are depicted. ESV = end systolic volume; ICD = implantable cardioverter-defibrillator; LV = left ventricular; RV = right ventricle.

commonly employed approach is surgical placement of an epicardial lead. However, this procedure is limited by need for a thoracotomy, poor long-term performance of epicardial pacing leads, and limited access to optimal LV pacing sites (basal). An alternative technique for achieving nonconventional resynchronization therapy is transseptal (either interatrial or interventricular) implantation of a transvenous pacing lead. However, this approach can be associated with a concerning high thromboembolic risk (10%) despite a relatively high international normalized ratio goal (2.5 to 4.5), a requirement for lifelong anticoagulation

therapy, and the potential for long-term negative effects of these conventional pacing leads on adjacent structures (e.g., the mitral valve) (13). Nonetheless, as demonstrated in the ALSYNC (ALternate Site Cardiac ResYNChronization) study, which evaluated atrial transseptal LV pacing, there are some important potential benefits of LV endocardial pacing. Nearly one-half (42%) of the ALSYNC trial patients were nonresponders with conventional CRT, but converted to CRT responders with transseptal endocardial LV pacing; 55% of patients had significant (≥15%) reductions in LV end-systolic volume, and 59% of

patients achieved an improvement of at least 1 NYHA functional class at 6 months (14). Given these intriguing data of several potential advantages of endocardial LV pacing over conventional epicardial LV pacing, including faster ventricular activation and superior hemodynamic performance, it is reasonable to postulate that endocardial LV pacing could eventually become a first-line option in patients requiring CRT—if the safety profile and implantation techniques were in line with current standards.

An earlier version of the wireless LV endocardial pacing system was limited by prohibitive safety concerns. Specifically, the WiSE-CRT study was stopped after only 17 patients because of a very high incidence of pericardial tamponade (n = 3; 18%), which was fatal in 1 patient (15). The delivery system used in the SELECT-LV trial was redesigned such that the distal portion of the delivery sheath was equipped with a balloon to facilitate atraumatic engagement with the LV endocardium; indeed, there were no pericardial effusions in the SELECT-LV study (16). However, it should be noted that there was 1 occurrence of ventricular fibrillation due to delivery catheter-induced ventricular ectopy (prior to extrusion of the pacing electrode), which resulted in a prolonged resuscitation and eventual death. Furthermore, there were 2 confirmed infections related to the subcutaneous pulse generator. Although 1 was successfully treated with antibiotics, the other required system removal. Future planned enhancements such as a smaller pulse generator are in development; this may reduce the risk of infection and hematoma formation.

STUDY LIMITATIONS. Although prospective, this was a nonrandomized trial without a control cohort, so robust conclusions cannot be drawn as to its comparative efficacy. Clinical response measures are subject to the placebo effect, and the absence of a core echocardiography reading laboratory introduces the possibility of reader bias. Although various clinical, ECG, and cardiac function characteristics have been shown to predict CRT response, these various methods to assess CRT response often do not yield similar response rates (17-19). Nevertheless, there was objective evidence of resynchronization response, as demonstrated by the improvements in both echocardiographic and electrical measures of reverse remodeling. The WiSE-CRT system requires 2 chest wall incisions, which can predispose to infectious complications, as well as retrograde arterial access, which can result in vascular complications. Fortunately, the absence of a direct conduit to the endocardium reduces the likelihood of resulting endocarditis. Torturous

arterial access could potentially complicate the implant success rate, although a high implantation success rate was observed in this trial. This study did not account for the potential effect of newer quadripolar coronary sinus pacing leads, which have been shown to be effective (compared with bipolar coronary sinus leads) for managing complications such as phrenic nerve stimulation and high pacing thresholds, and reduce the need for lead repositioning (20). Although only seen in 1 patient (who was in chronic AF and subtherapeutic on warfarin), thromboembolic complications do remain a concern with a foreign body (albeit small) within the LV. The optimal anticoagulation strategy (antiplatelets vs. systemic oral anticoagulation) remains to be determined. Endocardial scar and inadequate acoustic windows could negatively affect the performance and battery life of the system. In this study, 7.7% of the patients enrolled (3 of 39) in the study did not have an adequate acoustic window, and therefore did not undergo an attempt at system implant. Although the final location of the wireless pacing electrode in the LV was typically the lateral wall or midbasal posterolateral, the primary objective in this study was to find a suitable location as determined by pacing threshold, electrogram, and an adequate acoustic window, and the methods of the study did not include optimal site selection strategies in the LV or emphasize concurrence of "clinical" site selection with acoustic windows. The need for and ability to retrieve a long-term implanted pacing electrode remains untested. Many of these concerns will be addressed in an upcoming larger, multicenter Food and Drug Administration trial to start in the United States and Europe in late 2016.

CONCLUSIONS

The SELECT-LV study has demonstrated the clinical feasibility for the WiSE-CRT system. This approach provided clinical benefits in patients with a standard indication for CRT who met the criteria of upgrade, untreated, or nonresponder, a "failed" CRT population. Additional studies within post-market surveillance registries or randomized controlled trials are needed to understand long-term outcomes, compare additional outcomes, and explore different techniques for selecting the optimal endocardial pacing site.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: CRT reduces mortality and HF hospitalization and improves quality of life in patients with HF, reduced LVEF and left bundle-branch block, or a high burden of RV pacing. When biventricular pacing is indicated but cannot be provided because of difficulty establishing stable pacing from the coronary sinus, resynchronization can be achieved with a leadless LV endocardial pacemaker.

TRANSLATIONAL OUTLOOK: Larger trials are needed to confirm the safety, efficacy, and long-term clinical benefit of wireless LV endocardial pacing.

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KEY WORDS cardiac resynchronization therapy, leadless pacemaker