



February 25, 2026

JoAnna Baldwin
Coverage and Analysis Group
Centers for Medicare and Medicaid Services
7500 Security Boulevard
Baltimore, MD 212454

RE: A Formal Request for a National Coverage Determination

Dear Ms. Baldwin,

EBR Systems formally requests that the Centers for Medicare and Medicaid Services (CMS) consider our request for a national coverage determination for implantable leadless left ventricular pacing for cardiac resynchronization therapy (CRT).

EBR Systems is a cardiac rhythm management company on a clear mission: to transform the lives of people with heart failure by helping physicians deliver optimal cardiac pacing. The WiSE System received Food and Drug Administration (FDA) approval on April 11, 2025 and is the first and only FDA-approved system for leadless left ventricular endocardial pacing (LVEP) in CRT.

The FDA designated the WiSE System as a breakthrough device on July 18, 2019 because it provides a more effective treatment for patients suffering from heart failure who have been considered non-treatable or high risk for traditional CRT. The WiSE System represents a breakthrough technology because of its leadless pacing mechanism; the accessible location of the battery; the ability to provide pacing site selection; the potential benefits of left ventricular (LV) endocardial stimulation; and the unique method of providing such pacing. No current therapies are true alternatives for patients that fail conventional CRT because other alternatives are highly invasive, raising safety and viability concerns.

EBR Systems is pleased to have been the first company selected to participate in the Transitional Coverage for Emerging Technologies (TCET) program. We appreciate the diligence and effort on the part of the Coverage Analysis Group in developing the Evidence Preview and providing feedback on the Evidence Development Plan that will provide additional evidence on patient outcomes for WiSE System patients.

In addition to this formal request for a national coverage determination through the TCET pathway, we have attached the following items:

1. Summary of safety and effectiveness from the WiSE System premarket approval application.
2. FDA approval letter for the WiSE System.
3. The instructions for use for the WiSE System and patient booklet.
4. Evidence Development Plan for the WiSE System, including the Coverage with Evidence Development study protocol.

We believe that our submission constitutes a complete and formal request for a national coverage determination for the WiSE System. EBR Systems looks forward to working with CMS to provide national coverage for the WiSE System as expeditiously as possible. Please reach out to me at jcrockett@ebrwise.com or +1 662 550-0808 if you have any questions.

Sincerely,

A handwritten signature in black ink, appearing to read 'JC', with a horizontal line extending to the right.

Justin Crockett
Vice President
Global Vice President of Marketing and Market Access
EBR Systems

CC: Dhritiman Mukherjee
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Formal NCD Request for Implantable Leadless Left Ventricular Endocardial Pacing (LVEP) for Cardiac Resynchronization Therapy (CRT)

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1. Request

A. Scope

EBR Systems, Inc. (EBR) is formally requesting that CMS initiate a National Coverage Analysis (NCA) for the purpose of developing a National Coverage Determination (NCD) for Implantable Leadless Left Ventricular Endocardial Pacing (LVEP) for Cardiac Resynchronization Therapy (CRT). We request that CMS limit its NCA and NCD to devices that meet this description, and which are FDA approved. This request for coverage is specific to the WiSE® (Wireless Stimulation of the Endocardium Technology) for the CRT (Cardiac Resynchronization Therapy) System, which received FDA approval on April 11, 2025. At the time of this request, WiSE System is the only FDA approved implantable leadless LVEP device for CRT.

CRT is a well-established treatment for heart failure (HF) in which the right and left ventricles are paced synchronously (biventricular pacing) via transvenous leads. In CRT, the right ventricle (RV) lead is placed directly in the RV endocardium. Stimulation of the left ventricle (LV) would ideally be achieved via endocardial pacing, akin to procedures for the RV. However, endocardial placement of leads in the LV raises significant concerns regarding thromboembolism, prompting the standard practice of placing the lead within the coronary sinus (CS), on the epicardial surface of the LV.

Unfortunately, the CS lead has long been recognized as a primary shortcoming and point of failure of CRT. As a result, there is a significant unmet clinical need to provide an alternative approach to stimulating the left ventricle for CRT that the WiSE CRT System aims to solve. The WiSE System introduces a novel approach to LVEP for CRT, with the potential to provide CRT for Medicare beneficiaries with HF who cannot benefit from conventional CRT systems and avoid progression to late-stage HF for which indicated treatments include left ventricular assist devices or transplantation.

These beneficiaries, especially those with New York Heart Association (NYHA) Class II, III, and IV HF who may be appropriate candidates for the WiSE System, suffer from diminished quality of life. They may have slight, marked, or significant limitations on physical activity, including carrying out activities of daily living. They may experience shortness of breath, fatigue, weight changes, swelling, and confusion. These patients often can't engage in simple everyday activities like taking a walk or spending time with family. They may even struggle with basic tasks such as walking to the bathroom or through a grocery store.

Based upon the body of peer reviewed published evidence, we request Medicare coverage for implantable leadless LVEP for CRT in patients with heart failure when furnished according to an FDA market-authorized indication. The current indications for use for the WiSE System may be found in Section 2. FDA Information, Subsection A. Indications for Use.

B. Benefit categories

The following Medicare benefit categories to apply to the WiSE System:

- Inpatient hospital services (Social Security Act §1812; §1861(b)).

- Outpatient hospital services (Social Security Act §1832; §1861(s)(2)(B)).
- Physician services (Social Security Act §1832; §1861(q), and (r)).;

C. Proposed NCD question

EBR proposes that the CMS Coverage & Analysis Group (CAG) address the following pertinent question relating to evaluation of the WiSE System:

Q1. Is the evidence sufficient to conclude that implantation and use of an implantable leadless LVEP device is reasonable and necessary for the treatment of Medicare beneficiaries who meet the FDA indication of being at least 22 years of age, are indicated for CRT, have an existing or are eligible for an implanted RV pacing system, and are in one of the following two categories:

1. Patients in whom previous CS lead implantation was unsuccessful, or where an implanted lead has been turned off, referred to as “previously untreatable”; or
2. Patients with previously implanted pacemakers or Implantable Cardioverter-Defibrillators (ICDs) in whom standard CRT upgrade is not advisable due to known relative contraindications for CS lead or CRT device implantation, referred to as “high risk upgrades”?

2. FDA information

On April 11, 2025, the FDA approved the Premarket Approval (PMA) application for the WiSE System. The FDA has posted the approval order, the Summary of Safety and Effectiveness Data (SSED), Instructions for Use (IFU), and the Post-Approval Study (PAS) on its website: <https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=p240028>. We have also sent the SSED and complete set of WiSE System IFUs under separate cover at the same time as submitting our formal request.

The FDA indications and patient selection considerations can be found below.

A. Indications for use

The WiSE System is indicated for adult patients who are at least 22 years of age, are indicated for CRT, have an existing or are eligible for an implanted RV pacing system, and are in one of the following two categories:

- Patients in whom previous CS lead implantation was unsuccessful, or where an implanted lead has been turned off, referred to as “previously untreatable”; or
- Patients with previously implanted pacemakers or ICDs in whom standard CRT upgrade is not advisable due to known relative contraindications for CS lead or CRT device implantation, referred to as “high risk upgrades”.

These categories are defined as follows:

Previously Untreatable: Patients who have a full or partial CRT system and are deemed as “previously untreatable” for one of the following reasons:

- CS lead implant was attempted but abandoned due any of the following: difficult CS access or anatomy, inadequate lead location, inadequate pacing thresholds, phrenic nerve stimulation (PNS), or other procedural challenges; or
- LV lead that was implanted but not operational including patients in whom the LV lead is inoperative or programmed off due to improper function such as high threshold, non-capture, PNS, lead failure, lead dislodgement, or suboptimal LV lead location.

High Risk Upgrades: Patients in whom standard CRT upgrade is not advisable due to known relative contraindication to CS lead implant, for example:

- Risk of venous occlusion or lesion precluding implant (e.g., multiple existing leads in situ);
- Risk of pocket infection at co-implanted device site (e.g., co-implant initial placement or battery change within last 12 months); and
- Considered high risk for CS implant due to co-morbidities (e.g., history of Ischemic Cardiomyopathy or Ventricular Tachycardia (VT) with risk of epicardial pacing induced VT).

B. Patient selection considerations

Conventional transvenous CRT improves outcomes for many patients with heart failure and electrical dyssynchrony; however, 30–40% of recipients do not experience meaningful clinical response, with pooled analyses demonstrating an average nonresponse rate of approximately 34%. Contributing factors include suboptimal patient selection, inability to position the LV lead at the site of latest electrical activation due to coronary sinus anatomy, and lead-related complications. Coronary venous anatomy is highly variable and may be absent, inaccessible, or unsuitable for optimal lead placement. In addition, transvenous systems carry inherent risks including lead dislodgement, phrenic nerve stimulation, infection, venous obstruction, tricuspid valve injury, and long-term lead failure, all of which may necessitate repeat procedures and increase morbidity.

These limitations define two populations of patients who meet guideline-based CRT criteria but cannot benefit from conventional therapy. The first includes previously untreatable patients in whom CRT implantation failed or resulted in lead revision or abandonment due to anatomic constraints or complications. The second includes high-risk upgrade candidates, such as patients with existing pacemakers or ICDs who develop indications for CRT but face limited venous access, need for high-risk extraction, recurrent device infection, generator pocket complications, severe tricuspid valve disease, or the presence of a leadless pacemaker. In the absence of effective resynchronization, these patients remain at risk for progressive heart failure, recurrent hospitalization, and increased mortality.

Leadless left ventricular endocardial pacing (LVEP) addresses these barriers by eliminating the need for a transvenous LV lead and enabling endocardial stimulation at sites optimized for electrical and hemodynamic response. By circumventing coronary sinus anatomic limitations and reducing dependence on transvenous hardware, LVEP offers a resynchronization strategy for patients otherwise unable to receive effective CRT. The WiSE System is the first and only FDA-approved technology delivering leadless LV endocardial pacing and is specifically indicated for

patients who are previously untreatable with conventional CRT or for whom standard CRT upgrade is inadvisable due to anatomic or clinical contraindications.

3. Supporting medical and scientific evidence

A. General background on HF

HF affects approximately 6.7 million American adults, with prevalence projected to rise to 11.4 million by 2050.¹ The lifetime risk of HF is now 1 in 4, and despite advances in therapy, mortality has increased since 2012, with a sharp rise during the COVID-19 pandemic. In 2021, HF contributed to over 425,000 deaths, representing 45 percent of all cardiovascular-related deaths nationally. Hospitalizations, which had declined until 2014, have since increased, particularly among older adults and Black patients, and HF remains a leading driver of healthcare costs, accounting for \$46 billion annually (\$32 billion in direct costs and \$14 billion in indirect costs) with projections to exceed \$140 billion (\$121 billion in direct costs and \$22 billion in indirect costs) by 2050.

After the age of 65, HF incidence rises sharply, reaching 26.5 per 1,000 person-years compared to a range of 6.0-7.9 per 1,000 person-years for those aged 45-65. Prevalence is expected to rise to 8.5 percent among older adults aged 65-70. Outcomes following hospitalization are poor; 35 percent of patients die within one year of discharge. In an analysis of Medicare patients following HF hospitalization, average total costs for patients ranged from \$38,977 to \$41,747 per beneficiary.

i. HF Definition

Several working definitions of HF have been formulated to develop clinical guidelines for diagnosis and treatment. The Heart Failure Society of America (HFSA), in collaboration with the Heart Failure Association (HFA) of the European Society of Cardiology (ESC) and the Japanese Heart Failure Society (JHFS), defines HF as “a clinical syndrome with symptoms and/or signs caused by a structural and/or functional cardiac abnormality and corroborated by elevated natriuretic peptide levels and/or objective evidence of pulmonary or systemic congestion.”² The

¹ Bozkurt, B., Ahmad, T., Alexander, K., Baker, W. L., Bosak, K., Breathett, K., Carter, S., Drazner, M. H., Dunlay, S. M., Fonarow, G. C., Greene, S. J., Heidenreich, P., Ho, J. E., Hsieh, E., Ibrahim, N. E., Jones, L. M., Khan, S. S., Khazanie, P., Koelling, T., Lee, C. S., ... WRITING COMMITTEE MEMBERS (2025). HF STATS 2024: Heart Failure Epidemiology and Outcomes Statistics An Updated 2024 Report from the Heart Failure Society of America. *Journal of cardiac failure*, 31(1), 66–116.
<https://doi.org/10.1016/j.cardfail.2024.07.001>.

² Bozkurt, B., Coats, A. J. S., Tsutsui, H., Abdelhamid, C. M., Adamopoulos, S., Albert, N., Anker, S. D., Atherton, J., Böhm, M., Butler, J., Drazner, M. H., Michael Felker, G., Filippatos, G., Fiuzat, M., Fonarow, G. C., Gomez-Mesa, J. E., Heidenreich, P., Imamura, T., Jankowska, E. A., Januzzi, J., ... Zieroth, S. (2021). Universal definition and classification of heart failure: a report of the Heart Failure Society of America, Heart Failure Association of the European Society of Cardiology, Japanese Heart Failure Society and Writing Committee of the Universal Definition of Heart Failure: Endorsed by the Canadian Heart Failure Society, Heart Failure Association of India, Cardiac Society of Australia and New Zealand, and Chinese Heart Failure Association. *European journal of heart failure*, 23(3), 352–380.
<https://doi.org/10.1002/ejhf.2115>.

American College of Cardiology Foundation / American Heart Association (ACCF/AHA) guidelines define HF as “a complex clinical syndrome with symptoms and signs that result from any structural or functional impairment of ventricular filling or ejection of blood.”³ General consensus in all guideline documents suggests that HF management goals should be focused on those medical and device therapies designed to prolong life and improve heart performance within months of diagnosis; and in preventing decompensation, which occurs when excessive volume buildup leads to symptoms of congestion and hospitalization. It is also consensus that congestive symptoms are associated directly with elevated cardiac filling pressures.

Furthermore, HF can be categorized as acute or chronic HF based on the timing of onset, with myocardial infarction or acute valvular lesion considered as causes of acute HF, and systemic hypertension, myocardial infarction, valvular lesions, or cardiomyopathies causing chronic HF. Symptoms of acute HF can include tachycardia, hypotension, dyspnea, and pulmonary and systemic edema. Symptoms of chronic HF can include exertional dyspnea, systemic edema, cardiomegaly, fatigue, and orthopnea.⁴

There are several types of HF based on the location of the functional deficit, including LV, RV, or biventricular HF, as well as functional status, including preserved or reduced ejection fraction. LV failure is the most common. This occurs when the LV doesn't pump enough blood through the body, resulting in vital organs not receiving enough oxygen, causing a host of other conditions. LV failure can be further subdivided into diastolic HF or HF with preserved ejection fraction (HFpEF) with ejection fraction over 50 percent; systolic HF or HF with reduced ejection fraction (HFrEF) with ejection fraction less than 40 percent; and HF with mid-range ejection fraction, with ejection fraction between 41 and 49 percent.⁵ EF is considered important in classification of patients with HF because of differing patient demographics, comorbid conditions, prognosis, and response to therapies⁶ and because most clinical trials selected patients based on EF.

Multiple diseases result in impaired heart function, but most commonly myocardial infarctions, valvular heart disease, hypertension and inflammation of the heart muscle, or myocarditis are causative. The term acute decompensated heart failure (ADHF) typically describes a change from a stable, chronic HF syndrome to unstable worsening symptoms of shortness of breath with

³ Heidenreich, P. A., Bozkurt, B., Aguilar, D., Allen, L. A., Byun, J. J., Colvin, M. M., Deswal, A., Drazner, M. H., Dunlay, S. M., Evers, L. R., Fang, J. C., Fedson, S. E., Fonarow, G. C., Hayek, S. S., Hernandez, A. F., Khazanie, P., Kittleson, M. M., Lee, C. S., Link, M. S., Milano, C. A., ... Yancy, C. W. (2022). 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Journal of the American College of Cardiology*, 79(17), e263–e421. <https://doi.org/10.1016/j.jacc.2021.12.012>.

⁴ Rogers, C., & Bush, N. (2015). Heart Failure: Pathophysiology, Diagnosis, Medical Treatment Guidelines, and Nursing Management. *The Nursing clinics of North America*, 50(4), 787–799. <https://doi.org/10.1016/j.cnur.2015.07.012>.

⁵ Chahine J, Alvey H. Left Ventricular Failure. [Updated 2023 Jun 26]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan-. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK537098/>.

⁶ McDonagh, T. A., Metra, M., Adamo, M., Gardner, R. S., Baumbach, A., Böhm, M., Burri, H., Butler, J., Čelutkienė, J., Chioncel, O., Cleland, J. G. F., Coats, A. J. S., Crespo-Leiro, M. G., Farmakis, D., Gilard, M., Heymans, S., Hoes, A. W., Jaarsma, T., Jankowska, E. A., Lainscak, M., ... ESC Scientific Document Group (2021). 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *European heart journal*, 42(36), 3599–3726. <https://doi.org/10.1093/eurheartj/ehab368>.

minimal exertion or at rest. Many patients with ADHF require intravenous medical therapies while monitored in the hospital to re-establish clinical stability. When patients with chronic HF experience acute decompensation, the heart muscle may be further damaged and the cardiovascular system may worsen, leading to progression of heart impairment.

More patients are living with HF than ever before given the reduction in short-term mortality and improvement in long-term survival because of advances in treatment.⁷ Yet, the prognosis for HF patients remains poor, with approximately 50 percent dying within five years.^{8,9} According to a report from the American Heart Association, in 2015, the US had 5.8 million people with HF. In 2035 this number is expected to rise an additional 3 million. Further, costs attributed to HF are expected to increase to \$45 billion in 2035.¹⁰

ii. HF Classifications

To help understand the treatment needs of patients, and to track progression of the disease, the American College of Cardiology Foundation (ACCF) and the American Heart Association (AHA) have identified four stages (A through D) of HF.¹¹ Patients meeting stage C or D criteria, more advanced stages of HF, are further distinguished by their class of the disease. The New York Heart Association (NYHA) Functional Classification System is the most used classification system which places patients in one of four categories (I-IV) based on how much they are limited during physical activity; and via an objective assessment of disease (Table 1).¹²

⁷ Savarese G, Becher PM, Lund LH, Seferovic P, Rosano GMC, Coats AJS. Global burden of heart failure: a comprehensive and updated review of epidemiology. *Cardiovasc Res* 2023;118(17):3272-3287. DOI: 10.1093/cvr/cvac013.

⁸ Berliner D, Hanselmann A, Bauersachs J. The Treatment of Heart Failure with Reduced Ejection Fraction. *Dtsch Arztebl Int* 2020;117(21):376-386. DOI: 10.3238/arztebl.2020.0376.

⁹ Sidhu BS, Gould J, Sieniewicz BJ, Porter B, Rinaldi CA. Complications associated with cardiac resynchronization therapy upgrades versus de novo implantations. *Expert Rev Cardiovasc Ther* 2018;16(8):607-615. DOI: 10.1080/14779072.2018.1498783.

¹⁰ Khavjou, Olga, Phelps, Diana, Leib, Alyssa. 2016. *Projections of Cardiovascular Disease Prevalence and Costs: 2015–2035*. <https://www.heart.org/-/media/Files/Get-Involved/Advocacy/Burden-Report-Technical-Report.pdf>.

¹¹ Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure: A report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. *J Am Coll Cardiol* 2013; 62:e147.

¹² Dolgin M, Association NYH, Fox AC, Gorlin R, Levin RI, New York Heart Association. Criteria Committee. *Nomenclature and criteria for diagnosis of diseases of the heart and great vessels*. 9th ed. Boston, MA: Lippincott Williams and Wilkins; March 1, 1994.

Table 1. Comparison of ACCF/AHA Stages of HF and NYHA Functional Classification

ACCF/AHA Stages of HF		NYHA Functional Classification	
A	At high risk for HF but without structural heart disease or symptoms of HF	None	
B	Structural heart disease but without signs or symptoms of HF	I	No limitation of physical activity. Ordinary physical activity does not cause symptoms of HF.
C	Structural heart disease with prior or current symptoms of HF	I	No limitation of physical activity. Ordinary physical activity does not cause symptoms of HF.
		II	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in symptoms of HF.
		III	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes symptoms of HF.
		IV	Unable to carry on any physical activity without symptoms of HF, or symptoms of HF at rest.
D	Refractory HF requiring specialized interventions	IV	Unable to carry on any physical activity without symptoms of HF, or symptoms of HF at rest.

A diagnosis of HF with NYHA Class II, III, or IV disease is associated with reduced quality of life characterized by shortness of breath, fatigue, weakness, edema, weight changes, and slightly to severely limited physical activity that contribute to decreased engagement in activities of daily living (Inamdar & Inamdar, 2016). Exercise intolerance, high NYHA functional class, reduced left ventricular ejection fraction (LVEF) and systolic blood pressure, and comorbid diabetes among other cardiac-related biomarkers are associated with poor outcomes among patients with chronic heart failure, particularly for older adults (Inamdar & Inamdar, 2016).

iii. HF Treatment and CRT

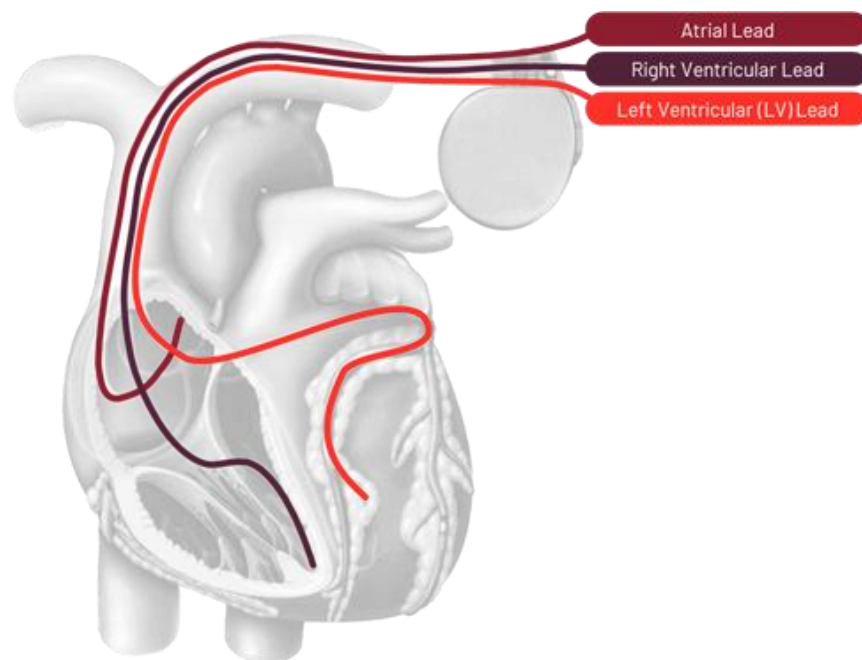
Treatment of HF may depend on the cause and can include lifestyle changes and/or medications. Often a combination of medications is used. The specific medications used depend on the cause of HF and the patient's symptoms. Some common medications for HF include angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), angiotensin receptor plus neprilysin inhibitors (ARNIs), and beta blockers. Surgery, such as coronary bypass surgery, heart valve repair or replacement, and heart transplant may be required in some patients. In addition, numerous cardiac implantable electronic devices (CIEDs) are used to treat HF including ventricular assist devices (VADs), and CRT (lead-based or leadless).^{13,14}

¹³ Truby LK, Rogers JG. Advanced Heart Failure: Epidemiology, Diagnosis, and Therapeutic Approaches. *JACC Heart Fail.* 2020 Jul;8(7):523-536. doi: 10.1016/j.jchf.2020.01.014. Epub 2020 Jun 10. PMID: 32535126.

¹⁴ Klotz S, Scheld HH. Surgical approach to end-stage heart failure. *Curr Opin Anaesthesiol.* 2011 Feb;24(1):86-91. doi: 10.1097/ACO.0b013e328340ff64. PMID: 21084985.

CRT is a well-established treatment for HF, particularly for patients with dyssynchronous heart contractions, and has been shown to improve clinical status and reduce HF hospitalizations and mortality.^{15,16,17} While traditional pacemakers, both lead and leadless, primarily address arrhythmias within the right side of the heart, CRT devices extend this therapeutic approach. By synchronizing the contractions of both the left and right ventricles through electrical stimulation, CRT enhances the heart's efficiency and overall function.

Figure 1. Illustration of Atrial and Ventricular Leads for CRT



CRT can be achieved by transvenous placement of a LV lead into a tributary vein of the CS.¹⁸ However, this approach carries high risk, particularly in heart failure patients who often present with multiple comorbidities. Common causes for unsuccessful CS lead position/placement include venous occlusion, nonviable coronary sinus anatomy, myocardial scar, or phrenic nerve

¹⁵ McAlister FA, Ezekowitz J, Hooton N, et al. Cardiac resynchronization therapy for patients with left ventricular systolic dysfunction: a systematic review. *Jama* 2007;297(22):2502-14. (In eng). DOI: 10.1001/jama.297.22.2502.

¹⁶ Linde C, Abraham WT, Gold MR, et al. Randomized trial of cardiac resynchronization in mildly symptomatic heart failure patients and in asymptomatic patients with left ventricular dysfunction and previous heart failure symptoms. *J Am Coll Cardiol* 2008;52(23):1834-1843. DOI: 10.1016/j.jacc.2008.08.027.

¹⁷ Moss AJ, Hall WJ, Cannom DS, et al. Cardiac-resynchronization therapy for the prevention of heart-failure events. *N Engl J Med* 2009;361(14):1329-38. DOI: 10.1056/NEJMoa0906431.

¹⁸ León, A. R., Abraham, W. T., Curtis, A. B., Daubert, J. P., Fisher, W. G., Gurley, J., Hayes, D. L., Lieberman, R., Petersen-Stejskal, S., Wheelan, K., & MIRACLE Study Program (2005). Safety of transvenous cardiac resynchronization system implantation in patients with chronic heart failure: combined results of over 2,000 patients from a multicenter study program. *Journal of the American College of Cardiology*, 46(12), 2348–2356. <https://doi.org/10.1016/j.jacc.2005.08.031>.

stimulation.^{19,20} As a result of these challenges, 30% to 40% of patients do not respond to conventional CRT,^{21,22,23} and 5% to 10% of patients cannot be treated with a transvenous lead-based system largely due to a persistent rate of LV lead issues.^{24,25}

An alternative that has been explored is lead implantation through an atrial transseptal route to pace an appropriate LV endocardial site. However, because of significant life-threatening thromboembolic risk and increased rates of stroke, this approach has not been adopted as an acceptable method of providing CRT. Consequently, there remains a critical unmet need for an alternative approach to LV stimulation in CRT, which the WiSE System seeks to address.²⁶

B. Wireless Stimulation Endocardially (WiSE) for Cardiac Resynchronization Therapy (CRT) System: device overview

The WiSE System is an implantable cardiac pacing system capable of delivering pacing level energy to the heart without using a lead/wire. The technology used to achieve this leadless, wireless pacing is based on converting ultrasound energy to electrical energy. A subcutaneously implanted ultrasound transmitter initiates an ultrasonic energy pulse that travels through the tissue to a receiver electrode implanted in the heart. The electrode converts the ultrasound energy received to electrical energy at sufficient amplitudes to pace/ stimulate cardiac tissue for CRT. The intensity of the ultrasound energy used is very low, even in comparison to levels used for echocardiographic imaging.

¹⁹ Chung, E. S., Leon, A. R., Tavazzi, L., Sun, J. P., Nihoyannopoulos, P., Merlino, J., Abraham, W. T., Ghio, S., Leclercq, C., Bax, J. J., Yu, C. M., Gorcsan, J., 3rd, St John Sutton, M., De Sutter, J., & Murillo, J. (2008). Results of the Predictors of Response to CRT (PROSPECT) trial. *Circulation*, 117(20), 2608–2616. <https://doi.org/10.1161/CIRCULATIONAHA.107.743120>.

²⁰ León AR, Abraham WT, Curtis AB, et al. Safety of transvenous cardiac resynchronization system implantation in patients with chronic heart failure: combined results of over 2,000 patients from a multicenter study program. *J Am Coll Cardiol*. 2005;46:2348–2356. doi: 10.1016/j.jacc.2005.08.031.

²¹ Auricchio A, Prinzen FW. Non-responders to cardiac resynchronization therapy: the magnitude of the problem and the issues. *Circ J* 2011;75(3):521-7. (In eng). DOI: 10.1253/circj.cj-10-1268.

²² Butter C, Georgi C, Stockburger M. Optimal CRT Implantation-Where and How To Place the Left-Ventricular Lead? *Curr Heart Fail Rep* 2021;18(5):329-344. DOI: 10.1007/s11897-021-00528-9.

²³ Vijayaraman P, Herweg B, Verma A, et al. Rescue left bundle branch area pacing in coronary venous lead failure or nonresponse to biventricular pacing: Results from International LBBAP Collaborative Study Group. *Heart Rhythm* 2022;19(8):1272-1280. (In eng). DOI: 10.1016/j.hrthm.2022.04.024.

²⁴ Linde C, Abraham WT, Gold MR, et al. Randomized trial of cardiac resynchronization in mildly symptomatic heart failure patients and in asymptomatic patients with left ventricular dysfunction and previous heart failure symptoms. *J Am Coll Cardiol* 2008;52(23):1834-1843. DOI: 10.1016/j.jacc.2008.08.027.

²⁵ Vijayaraman P, Herweg B, Verma A, et al. Rescue left bundle branch area pacing in coronary venous lead failure or nonresponse to biventricular pacing: Results from International LBBAP Collaborative Study Group. *Heart Rhythm* 2022;19(8):1272-1280. (In eng). DOI: 10.1016/j.hrthm.2022.04.024.

²⁶ Garrigue S, Jais P, Espil G, Labeque IN, Hocini M, Shah DC, Haissaguerre M, Clement J. Comparison of chronic biventricular pacing between epicardial and endocardial left ventricular stimulation using Doppler tissue imaging in patients with heart failure. *Am J Cardiol* 2001;88:858–862

i. Technology description

The WiSE CRT System has five main components:

1. **M1000 – Electrode Catheter:** A single use catheter used to implant the Electrode, comprising the Electrode and Delivery Catheter (or Electrode Catheter or Catheter). The Electrode is implanted in the LV; it receives ultrasound energy and converts it into electrical energy for endocardial pacing.



2. **M2000 – Delivery Sheath:** An acute use deflectable guide Sheath used in combination with the Electrode Catheter.



3. **M3100 – Battery:** A power source implanted subcutaneously in the mid-axial area of the left thorax, connected to the Transmitter by a cable (when combined with the Transmitter may be referred to as Pulse Generator).



4. **M4100 – Transmitter:** An ultrasound energy device implanted subcutaneously in the thorax cable (when combined with the Battery may be referred to as Pulse Generator).

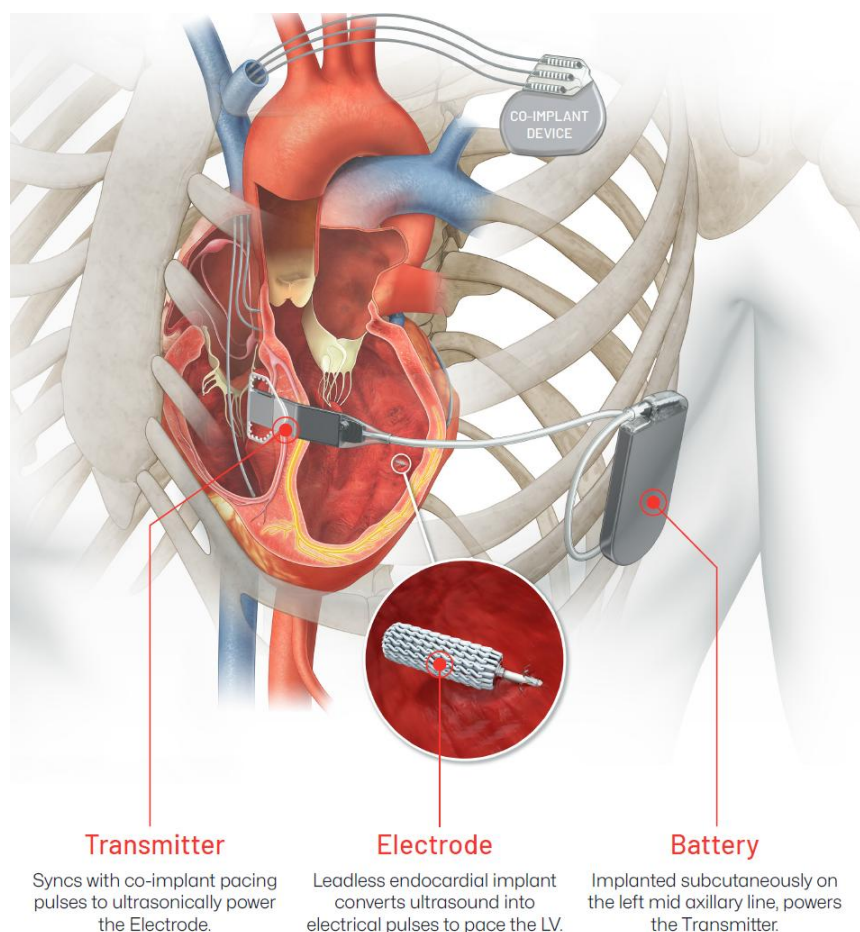


5. **M5100 – Programmer:** An external portable touch screen tablet with a communication module used to adjust parameters on the Pulse Generator and to assist with implant and follow-up of the System.



The WiSE CRT System is an implantable cardiac device capable of pacing the heart without a lead. The WiSE CRT System is not intended to be a life-sustaining device. A subcutaneously implanted Transmitter generates ultrasonic pulses that travel to a receiver, also known as the Electrode, implanted in the heart. The Electrode converts ultrasonic waves into electrical energy to stimulate cardiac tissue. The WiSE CRT System applies this leadless technology to stimulate the endocardial surface of the LV. Working in conjunction with standard, commercially available implanted pacemakers (with or without leads) or defibrillators already implanted in the patient, the WiSE System replaces the pacing function of a CS lead to achieve CRT. The WiSE System synchronizes with the co-implant using sensing electrodes in the Transmitter and Battery. As the co-implant paces the RV, the Transmitter generates ultrasound pulses that are received by the Electrode and converted to electrical energy to pace the LV. The sequence of sensing, transmitting, receiving, and stimulating the LV is essentially simultaneous with the co-implanted device's RV pacing output and provide biventricular pacing, an operation analogous to standard CRT pacing devices. The EBR Systems Programmer is used to program the WiSE System. As with other cardiac implants, programming is done by trained personnel.

Figure 2. Implanted WiSE System Components with Co-Implant Device



ii. WISE CRT System implant procedure

The Pulse Generator (battery and transmitter) are implanted first to locate the appropriate implanting site for the Electrode. Staged implantation now typically occurs in one day with Battery, Transmitter, and Electrode. In some circumstances, the Battery and Transmitter may be implanted on day 1 and the Electrode on day 2. The appropriate intercostal location to implant the transmitter is verified by preimplant transthoracic echocardiogram (TTE) of the LV.²⁷ Skin is then prepped and draped. The transmitter pocket is dissected to the level of the intercostal muscle, then the appropriate acoustic window is reconfirmed with intraoperative TTE before the Transmitter is securely sutured to the costal cartilage. A subcutaneous battery pocket in the left lateral thoracic area is created in the same intercostal space at the midaxillary line. A transmitter cable is tunneled from the transmitter pocket to the battery pocket.

Either retrograde transaortic approach via the femoral artery or transseptal approach via the femoral vein is selected based on the physician's experience and the patient's clinical characteristics. Transseptal approach is used if patients had peripheral artery disease or a prosthetic aortic valve. Retrograde transaortic approach requires a 12F introducer sheath, whereas atrial transseptal approach requires a long steerable sheath (with an inner 12F lumen).

²⁷ Future label may provide option to use computed tomography (CT) scan.

The Delivery Sheath is then advanced to the LV, and a balloon at the distal end of the Electrode Delivery Sheath is inflated with diluted contrast. At the time the Electrode Delivery Sheath is inserted into the introducer, the patient's ACT should be a minimum of 200 seconds and maintain at or above this minimum until the Electrode delivery system is withdrawn. The Delivery Sheath is then advanced to the LV endocardium while contrast is injected to ascertain adequate contact and alignment with the endocardial surface. Real time echocardiographic imaging of the left ventricle is used to assist with identifying the Delivery Sheath position relative to the cardiac structures that may impede the manipulation of the Delivery Sheath. An 8F electrode catheter is advanced inside the Delivery Sheath until approximately 25% of the Electrode body is exposed outside the delivery sheath tip. Generally, the mid to basal lateral LV segments are primarily targeted for electrode placement; however, the other locations may be selected to meet preanchoring requirements, including adequate pacing threshold (<2.5 V at the pulse width of 0.5 ms) and transmitter-electrode relation (distance <10 cm and angulation $<30^\circ$). At this time a measurement of left ventricular activation time (e.g., QLV or LVAT) is performed and recorded. Adequate electrode anchoring is confirmed with 2 orthogonal cine views with contrast injection, intracardiac electrogram, and electrical parameters before detachment of the Electrode.

iii. Post-procedure considerations

Patients who receive the WiSE System will still require programming/interrogation of their existing co-implanted device. In addition, these patients will also require programming/interrogation of the WiSE System. The WiSE System is programmed and interrogated in a similar way as standard devices today with its own unique separate programmer and settings. It is anticipated that the follow-up schedule for the WiSE System will be the same as the co-implanted device. The WiSE System uses a separate programmer but the follow-up procedure is similar in process and duration as the co-implant devices.

Based on physician assessment of individual patient characteristics, including bleeding risk, thromboembolic risk, and patient preference, post-implant antiplatelet therapy may be initiated. For patients prescribed Dual Antiplatelet Therapy (DAPT) alone, a minimum duration of three months is recommended, in accordance with current clinical guidelines and institutional protocols.

iv. WiSE System physician training

Physicians must undergo a mandatory training program to receive a certificate of completion to implant the WiSE System. The comprehensive curriculum consists of educational modules, based on procedural best practices and hands-on training activities. Educational elements are delivered in the form of didactic materials, training videos, bench model training, and practical sessions which include hands-on surgical training and the "Electrode Implant Simulator." The training program is structured in a modular approach to provide a deep understanding of WiSE technology, patient screening procedures, procedural steps and techniques, and post-implantation device follow-up.

C. Supporting clinical evidence

This section provides a comprehensive review of the clinical evidence supporting the safety and effectiveness of the WiSE System. We first present an overview of the pivotal clinical trials

conducted, followed by a detailed summary of the published clinical data evaluating its performance in relevant patient populations. We then summarize unpublished clinical evidence available to date. Next, we describe ongoing studies designed to further evaluate long-term outcomes and effectiveness. A summary table of individual case reports is included in **Error! Reference source not found.** to illustrate specific clinical scenarios and complement the broader evidence base.

i. Overview

EBR sponsored clinical studies to establish a reasonable assurance of safety and effectiveness of the WiSE System for the delivery of biventricular pacing for CRT in patients with advanced HF in the US, European Union, United Kingdom, and Australia. These studies include the SELECT-LV, WICS-LV, SOLVE-CRT and WISE-CRT studies.

The **SELECT-LV** (Safety and Performance of Electrodes implanted in the Left Ventricle) study was a prospective multicenter, non-randomized study that assessed the safety and efficacy of the WiSE System. The study enrolled patients from six European centers and assessed echocardiographic outcomes, changes in NYHA class, and patient-reported outcomes using global assessment. The study's primary performance endpoint was evidence of biventricular pacing at 1 month. The primary safety endpoints were device-related complications from implant to 24 hours and from 24 hours to 30 days. The secondary endpoints included changes in heart failure clinical composite score at 6 months; and changes in LVESV, LVEDV, and LVEF at six months. The study defined LVESV responders as having greater than or equal to a 15% relative reduction, LVEDV responders as having greater than or equal to a 10% relative reduction, and LVEF responders as having greater than or equal to a 5% absolute increase. Safety outcomes were assessed at less than 24 hours, between 24 hours and 1 month, and 1 to 6 months (Reddy et al., 2017).

The study enrolled 35 patients with a mean (SD) age of 65.4 (7.9) years at baseline. The study had 29 (85.0%) male patients, and the mean (SD) BMI was 29.9 (5.2) kg/m². The indication for WiSE CRT implantation was difficult coronary sinus anatomy/access in 12 (34.0%) patients, failure to respond to CRT in 10 (29.0%) patients, high CS threshold or phrenic nerve capture in five (14.0%) patients, coronary sinus lead dislodgement or lead failure in three (9.0%) patients, prior infection or upper extremity occlusion in three (9.0%) patients, and other reasons for two (6.0%) patients. In the study population, 20 (57.1%) patients had hypertension, 11 (31.4%) had diabetes, and 12 (34.3%) had chronic kidney disease. The mean (SD) NYHA class at baseline was 2.6 (0.6). The mean (SD) QRS duration was 169.9 (29.2) ms for intrinsic conduction and 187.2 (30.3) ms for RV pacing. The mean (SD) LVEF, LVEDV, and LVESV were 25.9 (6.4)%, 243.1 (70.7) ml, and 183.8 (62.9) ml, respectively (Reddy et al., 2017).

Among the 35 patients who underwent an attempted implant, the primary performance endpoint was met in 97.1% (33 of 34) at 1 month and in 93.9% (31 of 33) at 6 months. Biventricular pacing was not demonstrated in two patients at the 6-month follow-up due to transmitter malfunctions; the devices were later replaced. At 6 months, 84.8% (28 of 33) of patients showed an improvement in the clinical composite score, 9.1% (3 of 33) had no change, and 5.9% (2 of 33) worsened. At 6 months, the study reported LVESV, LVEDV, and LVEF of 157.0 (75.7) ml, 222.4 (77.0) ml, and 33.0 (10.3)%, respectively. All three echocardiographic outcomes showed

statistically significant improvements from baseline, with p-values of 0.007, 0.02, and 0.0001, respectively. The proportions of LVESV, LVEDV, and LVEF responders were 52%, 40%, and 66%, respectively. The intrinsic and RV-paced QRS duration at 6 months were 142.6 (27.3) ms and 182.0 (32.2) ms, respectively. Change in intrinsic QRS duration was statistically significant ($p < 0.001$), while change in RV-paced QRS duration was not ($p = 0.21$). The mean (SD) increase in NYHA class was 0.8 (0.8) at 6 months, with 67% of patients achieving greater than or equal to 1 class improvement. For the global assessment, 42.4% of patients reported marked improvement, 27.3% of patients reported moderate improvement, 6.1% of patients reported mild improvement, 15.2% of patients reported no change, 0.0% of patients reported slight worsening, 3.0% of patients reported moderate worsening, and 6.1% of patients reported marked worsening. In total, 70% of patients responded with marked or moderate improvement in the global assessment (Reddy et al., 2017).

Among the 35 patients who underwent an attempted system implantation, serious procedure- or device-related events occurred in 3 patients (8.6%) within 24 hours, 8 patients (22.9%) between 24 hours and 1 month, and 3 patients (8.6%) between 1 and 6 months. There were three complications within 24 hours of the procedure, including one (2.9%) ventricular fibrillation during catheter contact with LV endocardium, one (2.9%) electrode embolization to the lower extremity, and one (2.9%) femoral artery fistula requiring surgical repair. In the 24-hour to 1-month time frame, the study reported eight complications, including one (2.9%) acute cerebrovascular accident, two (5.7%) femoral pseudoaneurysms, one (2.9%) pocket hematoma (generator), three (8.6%) suspected infections (generator site), and one (2.9%) death following ventricular fibrillation during the initial implant procedure. Three (8.6%) cases of defective transmitter circuitry were reported in the 1 to 6 month timeframe (Reddy et al., 2017).

The study concluded that the WiSE System demonstrated clinical feasibility for eligible patients who were untreated or non-responders. The study reported a high implant success rate of 97%, improvement in heart failure CCS in 85% of patients, LVESV response in 52% of patients at 6 months (Reddy et al., 2017).

The **WICS-LV** was a European post-market surveillance study to assess the WiSE System's real-world clinical safety and efficacy. The study prospectively enrolled patients from the WICS post-market surveillance registry. Patient data were collected from 14 European centers. The study follow-up was 6 months and evaluated procedural success, a clinical composite score, echocardiographic outcomes, and proportion of patients with greater than 15% relative reduction in LVESV. The study also assessed safety outcomes at three distinct time points: acute (< 24 hours), Intermediate (> 24 hours to 1 month), and Chronic (1 – 6 months) (Sieniewicz et al., 2020).

In total, 90 patients who were implanted with WiSE CRT were enrolled in the study. The mean (SD) age was 68.2 (10.5) years, with 72 (80.0%) males. Indication of WiSE CRT implantation included 44 (48.9%) patients with failed traditional LV lead implant, 34 (37.8%) patients with complex upgrade, and 12 (13.3%) patients who failed to respond to CRT. The study included 33 (36.7%) patients classified as NYHA class II and 56 (62.2%) classified as NYHA class III. No patients were classified as NYHA class IV, and 1 (1.1%) patient was classified as NYHA class I. Baseline characteristics included a mean (SD) QRS duration, LVEF, LVEDV, and LVESV of 180.7 (27.0) ms, 30.6 (8.9)%, 185.7 (93.0) ml, and 130.4 (78.5) ml, respectively (Sieniewicz et al., 2020).

Biventricular pacing was confirmed in 85 (94.4%) of patients. At the 6-month time point, 60 (69.8%) patients had improved CCS, 12 (14.0%) had no change in CCS, and four (4.7%) had worsened CCS. Echocardiographic outcomes at 6 months for LVESV, LVEDV, LVEF, and QRS duration were 107.0 (71.6) ml, 161.0 (83.3) ml, 37.0 (11.5%), and 136.2 (84.3) ms, respectively. All evaluated echocardiographic outcomes showed statistically significant improvement from baseline. The mean (SD) NYHA class at 6 months was 2.1 (0.7); statistical comparison against the baseline NYHA class was not reported. The number of patients with > 15% relative reduction in LVESV at 6 months was 49 (54.5%) (Sieniewicz et al., 2020).

During the study, three (3.3%) procedure-related deaths and two (2.2%) non-procedure-related deaths were reported. The study reported four acute (within < 24 hours) complications, which included two (2.2%) cardiac tamponades and two (2.2%) pneumothorax/pleural effusions. For complications categorized as intermediate (within 24 hours to 1 month), the study reported 17 events, including one (1.1%) death, four (4.4%) arterial access complications, four (4.4%) pocket hematomas (generator), three (3.3%) post-procedure chest sepsis cases, three (3.3%) pocket infections (generator), and two (2.2%) acute kidney injuries. For chronic (1 to 6 months) complications, the study reported four (4.4%) deaths, one (1.1%) cerebral infarct, and one (1.1%) extra-stimulation during transthoracic echocardiography (Sieniewicz et al., 2020).

The study concluded that the WiSE System achieved procedural success, with BiV endocardial pacing observed in greater than 94% of patients. However, there were a significant number of patients with device/procedural-related adverse events, including three (3.3%) patients with procedural-related deaths and four (4.4%) patients with procedural-related complications within 24 hours of WISE CRT implantation. Furthermore, the study observed 18.8% of patients with intermediate complications and 6.7% of patients with chronic complications. The WiSE System was associated with a favorable clinical response rate of 70% at 6 months, similar to that observed in studies of traditional transvenous lead-based BiV pacing systems (Sieniewicz et al., 2020).

The **SOLVE-CRT** (Stimulation Of the Left Ventricular Endocardium for Cardiac Resynchronization Therapy in Non-Responders, Previously Untreatable and High Risk Upgrade Patients) was a prospective multicenter trial that was initially designed as a randomized, multinational, double-blind study to enroll 350 patients from up to 45 centers. However, due to COVID-19 pandemic-related restrictions, the study protocol was revised to implement a prospective nonrandomized single-arm trial in order to complete the study. At 6 months, data from patients in the randomized and single-arm phase of the study were aggregated into interim safety and efficacy analysis groups. The interim safety analysis group included 108 patients from the randomized phase and 75 patients from the single-arm phase of the study. The interim efficacy analysis group included previously untreated and high-risk upgrade patients, of which 75 patients were enrolled in the single-arm phase, and 25 patients were from the randomized phase of the study. The study's objective was to assess the safety and efficacy of WiSE-CRT in patients for whom CRT upgrade was deemed high risk or patients with failed conventional CRT systems. The primary safety endpoint was freedom from type I complications at 6 months, with a performance goal of 70%. Type I complications included adverse events caused by any component of the investigational system or specific procedure-related events. The primary efficacy endpoint was the mean relative change in left ventricular end-systolic volume (LVESV) from baseline at 6 months with a performance goal of -9.3% change (Singh et al., 2024).

The study included 183 patients in the safety subgroup. The patients had a mean (SD) age of 68.1 (10.28) years at baseline. The number of male patients was 141 (77.0%). The mean (SD) BMI was 30.8 (5.75) kg/m². Patients in the safety subgroup were primarily White (85.8%) and deemed previously untreatable (60.1%). Baseline characteristics also included 92 (50.3%) with a history of atrial tachycardia, 67 (36.6%) with a history of ventricular tachycardia, 94 (51.4%) with nonischemic cardiomyopathy, 87 (47.5%) with ischemic cardiomyopathy, and 183 (100%) patients with a co-implant. Comorbidities included chronic obstructive pulmonary disease (COPD) in 13.7%, systemic hypertension in 54.1%, dyslipidemia in 51.4%, hyperthyroidism in 2.7%, sleep apnea in 23.5%, pulmonary arterial hypertension (PAH) in 6.0%, peripheral vascular disease in 8.7%, cancer in 14.8%, and diabetes in 35.0%. Among the patients in the safety subgroup, 63 (34.6%) were NYHA class II, and 119 (65.4%) were NYHA class III. The mean (SD) QRS duration, left ventricular ejection fraction (LVEF), left ventricular end-diastolic volume (LVEDV), and LVESV at baseline were 183.8 (25.94) ms, 29.8 (7.90)%, 210.4 (77.76) mL, and 151.1 (67.21) mL, respectively (Singh et al., 2024).

The study included 100 patients in the efficacy subgroup. The patients had a mean (SD) age of 68.2 (10.47) years at baseline. The number of male patients was 76 (76.0%). The mean (SD) BMI was 30.6 (5.45) kg/m². Patients in the efficacy subgroup were primarily White (82.0%) and deemed previously untreatable (75.0%). Baseline characteristics also included 52 (52.0%) with a history of atrial tachycardia, 34 (34.0%) with a history of ventricular tachycardia, 50 (50.0%) with nonischemic cardiomyopathy, 50 (50.0%) with ischemic cardiomyopathy, and 100 (100%) patients with a co-implant. Comorbidities included COPD in 11 (11.0%), systemic hypertension in 63 (63.0%), dyslipidemia in 50 (50.0%), hyperthyroidism in 5 (5.0%), sleep apnea in 24 (24.0%), PAH in 3 (3.0%), peripheral vascular disease in 8 (8.0%), cancer in 15 (15.0%), and diabetes in 31 (31.0%). Among the patients in the efficacy subgroup, 35 (35.0%) were in NYHA class II, and 65 (65.0%) were in NYHA class III. The mean (SD) QRS duration, LVEF, LVEDV, and LVESV at baseline were 184.9 (24.72) ms, 31.1 (7.89)%, 206.8 (83.58) mL, and 146.3 (71.51) mL, respectively (Singh et al., 2024).

The mean (SD) absolute and relative changes in the primary efficacy endpoint LVESV at 6 months were -25.1 (34.3) ml ($p < 0.001$) and -17.7 (21.7)% ($p = 0.003$), respectively. Secondary endpoints included changes in LVEDV, QRS duration, LVEF, NT-proBNP, and NYHA class as reported below. For LVEDV, the absolute and relative mean (SD) CFB at 6 months were -25.4 (41.1) ml ($p < 0.001$) and -11.9 (18.5)%. The mean (SD) (95% CI) CFB in QRS duration at 6 months was -39.3 (23.3) (-44.5, -34.2) ms. The mean (SD) relative CFB in LVEF was -5.2 (6.8)% ($p < 0.001$), while a -0.02 (0.4) cm decrease was observed for the TAPSE outcome. The mean (SD) CFB in NT-proBNP was -385.1 (1,489.4) pg/ml at 6 months. At 6 months, eight (9.1%) of patients reported improvement of 2 NYHA classes, 41 (46.6%) of patients reported improvement of 1 NYHA class, 36 (40.9%) of patients reported no change, and three (3.4%) of patients reported a decline in 1 NYHA class (Singh et al., 2024).

The primary safety endpoint of freedom from type I complications was 80.6%, above the investigators' performance threshold of 70%. In total, 35 (19.1%) patients experienced 43 type I complication events at 6 months. These included 12 study device system events in 12 (6.6%) patients, five vascular events in five (2.7%) patients, three stroke and other thromboembolic events in three (1.6%) patients, seven cardiac perforation events in seven (3.8%) patients, and 15 pocket events in 12 (6.6%) patients (Singh et al., 2024).

Although the study did not provide statistical analysis for all outcomes, it reported absolute and relative improvements in all efficacy outcomes. The study reported meeting both the prespecified primary efficacy and safety endpoints. The study reported statistically significant improvement in relative and absolute CFB in LVESV, absolute CFB in LVEDV, and absolute CFB in LVEF (Singh et al., 2024).

Okabe et al., 2022 reported the safety and efficacy outcomes of 31 patients from the nonrandomized single-arm roll-in phase of the SOLVE-CRT study. The study was composed of CRT nonresponders, CRT-eligible patients previously untreated with CRT, and CRT-eligible patients at high risk for conventional transvenous CRT upgrade. The SOLVE-CRT study's interim safety and efficacy population did not include these patients. The roll-in phase was conducted in study centers with no prior implanting experience. The study assessed the short-term efficacy outcome at 1, 3, and 6 months and the safety outcome at a mean follow-up duration of 17 months (Okabe et al., 2022).

The study included 31 patients with a mean (SD) age of 65.5 (10.6) years at baseline. The study population included 18 (58.1% male patients). The mean age (SD) was 65.5 (10.6) and a mean (SD) BMI of 29.2 (5.6) kg/m². The indication for CRT upgrade was a combination of NYHA class II-IV symptoms, EF ≤ 35%, and LBBB with QRS width ≥ 150 ms for 16 (51.6%) patients. Reported comorbidities included arrhythmia history 29 (93.5%), cardiomyopathy 31 (100%), co-implant 31 (100%), and coronary artery disease 20 (64.5%). Other reported comorbidities in patients included nine (29.0%) renal dysfunction, seven (22.6%) COPD, 20 (64.5%) hypertension, 10 (32.3%) diabetes, nine (29.0%) sleep apnea, five (16.1%) pulmonary hypertension, and three (9.7%) peripheral vascular disease cases. There were no NYHA class I patients; nine (29.0%) patients were NYHA class II, 21 (67.7%) patients were NYHA class III, and one (3.2%) patient was NYHA class IV. The baseline LVEF, LVEDV, and LVESV were 28.3 (6.7)%, 185.4 (58.8) ml, and 134.9 (51.3) ml, respectively (Okabe et al., 2022).

The study reported that 14 (46.7%) patients had NYHA class improvement of ≥ 1 class, and 17 (54.8%) patients had no change. The mean (SD) CFB in each KCCQ domain score at 6 months was 14.2 (26.3) for the physical limitation score ($p = 0.0111$), 10.7 (32.9) for symptom stability score ($p = 0.0966$), 16.9 (18.3) for symptom frequency score ($p < 0.0001$), 17.3 (24.5) for symptom burden score ($p = 0.0001$), 3.1 (13.9) for self-efficacy score ($p = 0.2436$), 26.8 (26.3) for quality of life score ($p < 0.0001$), 24.7 (34.3) for social limitation score ($p = 0.0009$), 15.4 (21.8) for clinical summary score ($p = 0.0009$), and 20.4 (23.0) for overall summary score ($p < 0.0001$). The study reported a statistically significant improvement in all evaluated domains except the self-efficacy and symptom stability scores. The mean (SD) CFB at 6 months for LVEF, LVEDV, and LVESV were 5.2 (5.8)% ($p < 0.001$), -20.5 (31.9) ml ($p = 0.0017$), and -23.7 (31.7) ml ($p = 0.0004$), respectively. All echocardiographic outcomes showed statistically significant improvements from baseline at 6 months. The mean (SD) QRS duration for RV pacing and BiV pacing at 6 months were 177.4 (26.5) ms and 152.3 (30.5) ms, respectively. Comparison between RV vs. BiV pacing showed a statistically significant difference ($p = 0.0002$) (Okabe et al., 2022).

At 17 months, the study reported nine complications in total. These complications included three device-related acute and subacute complications (type I) and six procedure-related complications. The device-related complications included one intermittent loss of capture, one LV electrode embolization, and one wound infection treated with oral antibiotics. Procedure-related

complications included one iliac artery aneurysm, one hypotension treated with IV fluid, one acute congestive heart failure, one urosepsis treated with IV and oral antibiotics, one respiratory suppression related to pain medication, and one ventricular tachycardia triggered by crossing the aortic valve with the delivery catheter (Okabe et al., 2022).

The study concluded that in the roll-in phase of the SOLVE-CRT trial, patients showed statistically significant improvements from baseline at 6 months in 9 of the 10 KCCQ domains. Additionally, all evaluated echocardiographic outcomes showed statistically significant improvements from baseline at 6 months. There were no procedure-related deaths or incidents of cardiac tamponade (Okabe et al., 2022).

The **WISE-CRT** study was a prospective multicenter observational feasibility study that enrolled patients from six European centers. The study aimed to identify the feasibility, safety, and short-term outcome of WiSE CRT in heart failure patients. The study had a follow-up duration of 6 months and evaluated echocardiographic outcomes at 1 and 6 months. It also assessed changes in NYHA classification and global assessment outcomes. Furthermore, the study recorded complications at the 6-month time point (Auricchio et al., 2014).

The study included 17 patients with a mean age of 69 years at baseline, and 14 (82.4%) patients were male. Indications for WiSE CRT were upgrades for eight (47.1%) patients, “untreated” in seven (41.2%) patients, and “non-response” for two (11.8%) patients. Among the included patients, eight (47.0%) had atrial fibrillation, 11 (65.0%) had arterial hypertension, and seven (41.0%) had diabetes. No patients were classified as NYHA class I. One (5.9%) patient was classified as NYHA class II, 14 (82.4%) were classified as NYHA class III, and two (11.8%) were classified as NYHA class IV. The baseline characteristics for QRS duration and LVEF were not reported in aggregate but were provided per patient (Auricchio et al., 2014).

Although aggregate baseline values were not reported, the study reported aggregate statistical results for efficacy outcomes at different time points. At 1 month follow-up, successful and consistent biventricular pacing was observed on 12-lead ECG in 10 of 12 evaluable patients (83%). At 6 month follow-up, this was observed in 11 of 12 patients (92%). At 1 month, mean (SD) RV and BiV-paced QRS durations were reported as 202 (32.3) ms and 161 (31.8) ms, respectively. There was a statistically significant difference between the two pacing methods ($p = 0.0002$). At 6 months, mean (SD) LVEF was 31 (7.0)% and was improved from baseline 25 (4.0)% ($p < 0.01$). For the QRS duration at 6 months, RV-paced, and BiV-paced QRS durations were 185.0 (42.0) ms and 148 (25.4) ms, respectively. There was again a statistically significant difference between BiV pacing and RV pacing ($p = 0.0011$). NYHA improvement of greater than or equal to 1 classification was observed in eight (66.6%) patients at 6 months. For global assessment, the study reported six (50.0%) patients with moderate to marked improvement, two (16.7%) patients with mild change, three (25.0%) patients with no change, and one (8.3%) patient with worsening symptoms (Auricchio et al., 2014).

At 6 months, the study reported 12 serious adverse events unrelated to the procedure or system. However, one groin hematoma and three pericardial effusions related to the procedure were reported. Among the pericardial effusion events, one resulted in death. Two losses of BiV pacing requiring transmitter position revision and one battery replacement event were reported (Auricchio et al., 2014).

The study concluded that using the WiSE System for endocardial stimulation for CRT was feasible. The study also demonstrated statistically significant improvement in LVEF at 6 months, with most patients achieving moderate to marked improvement and NYHA improvement of greater than or equal to 1 NYHA class (Auricchio et al., 2014).

ii. Summary of published clinical data

Multiple studies have since been conducted to evaluate the safety and feasibility of the WiSE System for the treatment of heart failure patients who are candidates for CRT but have failed systems, are contraindicated for or are poor responders to CS lead placement. Early studies demonstrated the technical feasibility and clinical benefit of wireless LVEP, showing significant improvements in LV ejection fraction, NYHA functional class and QRS narrowing. Subsequent studies confirmed the system's safety and procedural success. These studies are summarized below and key outcomes are outlined in Appendix 1. Study Characteristics and Outcomes of Peer-Reviewed Clinical Studies. Collectively, these studies demonstrate that the WiSE System is safe and associated with improved clinical outcomes for patients who cannot be treated with conventional CRT.

- **Wijesuriya et al., 2025** – 6-month LVESV response rate was 46%; significant improvement in response rate in quartile 4 (longest Q-LV 64%) compared to quartile 1 (shortest Q-LV 28%) ($P < .01$).
- **Singh et al., 2024** – 16.4% reduction in mean LV endo-systolic volume (LVESV) (95% CI, -21.0% to -11.7%, $P = .003$); 80.9% rate of freedom from type I complications ($P < .001$).
- **Wijesuriya et al., 2024** – 23.7% improvement in BiVAT-90 ($P = .002$); 43.3% improvement in BiVAT-90 ($P = .0001$) observed at the optimal pacing mode (OPM) in both patients with lateral (43.3%; $P = .0001$; $n = 5$) and septal (42.4%; $P = .009$; $n = 5$) LV implants.
- **Elliott et al., 2022** – 100% successful implantation; significant reduction in QRS duration (187.1 ± 33.8 ms vs 149.5 ± 15.7 ms, $p = 0.009$); device function was satisfactory in 7 patients; median LV pacing percentage was 98.5% (IQR: 86.5 - 100%); 5 patients reported improvement in HF symptoms.
- **Okabe et al., 2022** – 100% successful implantation; 46.7% demonstrated ≥ 1 NYHA class improvement; improvements in LV ejection fraction ($28.3\% \pm 6.7\%$ to $33.5\% \pm 6.9\%$, $p < 0.001$), LVESV (134.9 ± 51.3 ml to 111.1 ± 40.3 ml, $p = 0.0004$), and LV endo-diastolic volume (LVEDV) (185.4 ± 58.8 ml to 164.9 ± 50.6 ml, $p = 0.0017$).
- **Sidhu et al., 2021** – 97.1% successful implantation (vs. 97.5% for CS upgrades); similar improvements in CCS (76.3% vs 68.5%, $p = 0.210$) and reduction in LVESV $\geq 15\%$ (54.2% vs 56.3%, $p = 0.835$) at 6 months; procedure-related mortality observed in 1.9%.
- **Sieniewicz et al., 2020** – 94.4% successful implantation; decreased procedural risk with operator experience.
- **Sidhu et al., 2020** – 90.9% successful implantation and confirmation of biventricular pacing; significant reduction in QRS duration (26.6 ± 24.4 ms, $p = 0.002$); significant improvement in LV ejection fraction ($4.7 \pm 7.9\%$, $p = 0.021$); 55.6% of patients had improvement in CCS; 66.7% had reduction in LVESV $\geq 15\%$ and/or absolute improvement in LVEF $\geq 5\%$.
- **Carabelli et al., 2020** – 100% successful implantation, detection of the Micra PM pacing output, and training to deliver synchronous LVEP; QRS reduction was observed in all

patients (204.4 ± 30.3 vs 137.5 ± 24.8 ms, $p = 0.012$); LV ejection fraction improved ($+11.3 \pm 8.5\%$, $p = 0.018$); no evidence of reverse remodeling or significant change in NYHA class, LVEDV or LVESV.

- **Sieniewicz et al., 2018** – 71% showed LV reverse modeling; significant in QRS duration (163.8 ± 26.7 ms vs 134.8 ± 25.6 ms, $p = 0.002$) and LVESV (11.7 ± 64.4 vs 85.9 ± 52.3 , $p < 0.0001$). LV ejection fraction significantly increased compared to baseline ($34.2 \pm 7.8\%$ to $39 \pm 9.8\%$; $p = 0.008$).
- **Reddy et al., 2017** – 97.1% successful implantation; biventricular pacing was achieved in 97% of patients; 8.6% serious device/procedure events within 24 hours; demonstrated feasibility and efficacy in CRT nonresponders.
- **Auricchio et al., 2014** – 76.5% successful implantation; biventricular pacing was achieved in 92% of patients; LV ejection fraction increased by 6 points at 6-month follow-up.
- **DeFaria Yeh et al., 2011** – 97.6% of enrolled patients had appropriate acoustic windows.
- **Lee et al., 2009** – Ultrasound-mediated pacing was achieved in 100% of patients tested.
- **Lee et al., 2007** – Ultrasound-mediated testing was achieved at 97.6% of sites.

iii. Summary of unpublished clinical evidence

Database searches in PubMed and Embase identified 12 conference abstracts for consideration as unpublished evidence. Among the conference abstracts, one abstract reported on the SOLVE-CRT study, two abstracts reported on the WICS-LV study, and nine abstracts reported on stand-alone studies. These studies are summarized below, and key outcomes are outlined in Appendix 2. Study Characteristics and Outcomes of Unpublished/ Non-peer-reviewed Evidence.

- **Sharma et al., 2024** – A post hoc analysis of the SOLVE-CRT study that aimed to analyze the effect of WiSE CRT on mitral regurgitation. At 6 months, the study reported stable mitral regurgitation in 62 (71.0%) patients, improved mitral regurgitation in 21 (24.0%) patients, and worsening mitral regurgitation in four (5.0%) patients. Patients with improved mitral regurgitation also had significant improvement in the NYHA classification at 6 months, but a p-value was not provided. The findings suggest that 95% of patients who received the WiSE-CRT implant experienced either stable or improved mitral regurgitation.
- **Defaye et al., 2023** – A stand-alone prospective nonrandomized single-arm study that aimed to assess the technical feasibility of achieving leadless CRT using a Micra device (Medtronic, Minneapolis, MN) and WiSE System. 100% (14) of WiSE CRT devices detected the Micra pacing output and delivered synchronous LVEP. The study concluded that the combination of WiSE CRT and Micra was feasible, with a WiSE System representing the only available option for a leadless upgrade of a Micra or Aveir (Abbott, Chicago, IL) pacemaker.
- **Sidhu et al., 2019a** – A stand-alone retrospective observational study that aimed to identify patient outcomes of WiSE CRT in non-responder patients. At 6 months, 10 (58.8%) patients had improvement in their clinical composite score (CCS); 9 (53.3%) patients had LVESV improvement $\geq 15\%$; and 11 (64.7%) patients had an absolute increase in LVEF $\geq 5\%$. One (5.9%) patient had a pocket hematoma, but no patients had

acute complications. The study concluded that the WiSE CRT led to improvements in the CCS and reverse LV remodeling in the high-risk non-responder patients.

- **Sidhu et al., 2019b** – A stand-alone retrospective observational study that aimed to compare the safety and efficacy of WiSE CRT against epicardial CRT upgrades. At 6 months, 26 (69.0%) patients in the WiSE CRT cohort had improved LVESV $\geq 15\%$ (not statistically significant). Complications were not reported in the study. The study concluded that patients undergoing high-risk CRT upgrades with WiSE CRT had comparable outcomes for improvement in CCS, absolute change in LVEF, and improvement in LVESV, with no statistically significant differences when compared to epicardial CRT implant.
- **Sieniewicz et al., 2019a** – Based on the WICS-LV post-market surveillance study, 5 (5.6%) patients experienced acute complications and 17 (18.9%) patients had complications within 30 days. At 6 months, 70 (78.0%) patients reported an improvement with the system, and 50 (55.4%) patients had a relative LVESV reduction $>15\%$.
- **Sieniewicz et al., 2019b** – A total of four (4.5%) patients experienced acute complications, and 17 (18.9%) patients had complications within 30 days and 18 (20.2%) patients had complications within 30 days, including one (1.1%) case of cardiac tamponade and four (5.6%) arterial access complications. At 6 months, 76.0% of patients reported an improvement with the system, and 49 (55.4%) patients had a relative LVESV reduction $>15\%$. The study also reported statistically significant changes from baseline in NYHA class, LVEF, LVEDV, and LVESV outcomes. The study's results provided further insights into the safety profile and clinical efficacy of the system, highlighting both positive outcomes and some complications observed during the follow-up period.
- **Fehrendt et al., 2019** – A stand-alone retrospective observational study that was conducted in Germany to assess the long-term clinical efficacy of WiSE CRT. The mean (SD) NYHA class at 3 months, 6 months, 2 years, and 5 years was 2.6 (0.5), 2.2 (0.7), 2.4 (0.7), and 1.7 (0.6), respectively, with statistically significant improvements observed at 6 months, 2 years, and 5 years ($p \leq 0.05$). The mean (SD) intrinsic QRS duration at 3 months, 6 months, 2 years, and 5 years was 169.0 (25.0) ms, 158.0 (11.0) ms, 176.0 (32.0) ms, and 160.0 (34.0) ms, respectively, with statistically significant improvements at 6 months and 5 years ($p \leq 0.05$). The mean (SD) paced QRS duration at 3 months, 6 months, 2 years, and 5 years was 154.0 (26.0) ms, 146.0 (22.0) ms, 155.0 (27.0) ms, and 141.0 (17.0) ms, respectively, with statistically significant improvement observed at 3 months ($p \leq 0.01$). The mean (SD) LVEF at 6 months, 2 years, and 5 years was 32.2 (10.0)%, 28.0 (10.5)%, and 33.0 (1.0)%, respectively, with statistically significant improvement observed at 6 months and 5 years ($p \leq 0.05$). The mean (SD) LVEDD at 6 months, 2 years, and 5 years was 62.0 (7.7) mm, 61.7 (14.8) mm, and 62.3 (63.0) mm, respectively, with statistically significant improvement observed at 6 months and 2 years ($p \leq 0.01$) and 5 years ($p \leq 0.05$). The mean (SD) LVEDV at 6 months, 2 years, and 5 years was 193.0 (73.0) ml, 192.0 (114.0) ml, and 181 (63.0) ml, respectively, with statistically significant improvement at 5 years ($p \leq 0.05$). The mean (SD) BiV pacing rate at 3 months, 6 months, 2 years, and 5 years was 74.0 (35.0)%, 82.0 (26.0)%, 93.3 (6.8)%, and 95.7 (3.8)%, respectively, with statistically significant improvement observed at 2 and 5 years ($p \leq 0.01$). The study did not report safety outcomes. The study reported statistically significant improvements at 2 years for the NYHA class, LVEF, LVEDD, and BiV pacing rate outcomes. At 5 years, statistically significant improvements were reported

for NYHA class, intrinsic QRS duration, LVEF, LVEDD, LVEDV, and BiV pacing rate outcomes.

- **Fehrendt et al., 2017** – A stand-alone retrospective observational study that was conducted in Germany to identify the long-term clinical efficacy of WiSE CRT. The mean (SD) NYHA class at 6 months, 2 years, and 5 years was 2.0 (0.4), 2.0 (0.6), and 1.7 (0.6), respectively, with statistically significant improvement from baseline ($p < 0.05$ at 6 months and 2 years; $p < 0.03$ at 5 years). The mean (SD) intrinsic QRS duration at 6 months, 2 years, and 5 years was 159.0 (12.0), 176.0 (26.0), and 160.0 (34.0) ms, respectively, without statistically significant improvement from baseline ($p = 0.1$). The mean (SD) paced QRS duration at 6 months, 2 years, and 5 years was 148.0 (22.0), 158.0 (33.0), and 141.0 (17.0) ms, respectively, without statistically significant improvement from baseline ($p = 0.9$). The mean (SD) LVEF at 6 months, 2 years, and 5 years were 33.6 (10.0), 34.2 (6.8), and 33.0 (1.0)%, respectively, with statistically significant improvement from baseline ($p = 0.001$). The mean (SD) LVEDD at 6 months, 2 years, and 5 years was 61.4 (8.0), 57.8 (16.2), and 62.3 (12.0) mm, respectively, with statistically significant improvement from baseline ($p < 0.05$) at 6 months and 2 years. The mean (SD) LVEDV at 6 months, 2 years, and 5 years were 198.0 (77.0), 159.0 (112.0), and 181.0 (63.0) ml, respectively, without statistically significant improvement from baseline ($p = 0.8$). The mean (SD) NTproBNP at 6 months, 2 years, and 5 years was 2,073 (1,882), 1,715 (854), and 1,951 (890) pg/ml, respectively, without statistically significant improvement from baseline ($p = 0.5$). The mean (SD) BiV pacing rate at 6 months, 2 years, and 5 years was 80.0 (28.0), 95.2 (5.7), and 95.7 (3.8)%, respectively ($p = 0.001$ at all time points). The study did not report complication outcomes. Overall, the study concluded that the WiSE System showed favorable long-term outcomes, with statistically significant improvements in NYHA class, LVEF, and LVEDD. Statistically significant CFB was not observed for intrinsic QRS duration, LVEDV, or NTproBNP levels.
- **Behar et al., 2017** – A stand-alone prospective, multicenter, observational study that was conducted in the UK aimed to evaluate the safety and efficacy of WiSE CRT with a follow-up duration of 6 months. The mean (SD) CFB in acute hemodynamic response at 6 months was 16.0 (13.0%), with statistically significant improvement against baseline ($p < 0.001$). The mean (SD) QRS duration at 6 months was 138.0 (27.0) ms, with statistically significant improvement compared with baseline ($p < 0.001$). The mean (SD) NYHA class at 6 months was 1.6 (0.7), with statistically significant improvement compared with baseline ($p = 0.01$). The study also reported three acute complications, including one (3.3%) inability to track an electrode at implant, one (3.3%) cardiac tamponade, and one (3.3%) pneumothorax. In total, four complications were reported after 24 hours, including one (3.3%) pseudo-aneurysm, one (3.3%) slow flow in the femoral artery, one (3.3%) retroperitoneal bleed, and one (3.3%) battery pocket infection that required explant and reimplantation. The study concluded that the WiSE System is a feasible alternative for patients who failed conventional CRT (Behar et al., 2017).
- **Neuzil et al., 2016a** – A prospective observational study that evaluated the efficacy and safety of WiSE CRT with a 12-month follow-up duration. The study included 34 patients with a mean (SD) age of 65.8 (8.6) years, and 25 (73.5%) male patients. All patients were indicated for CRT but were untreated because of various difficulties. The mean (SD) BMI was 29.7 (4.8) kg/m² with a mean (SD) NYHA class of 2.7 (0.6) at baseline. Baseline characteristics for intrinsic QRS duration, RV pacing QRS duration, and LVEF were 163.0

(32.0) ms, 180.0 (30.0) ms, and 27.4 (5.4%), respectively. The number of patients who achieved consistent CRT at 1 month, 6 months, and 12 months, was 34 (100.0%), 33 (97.0%), and 24 (96.0%), respectively. The mean (SD) BiV-paced QRS duration at 1 month, 6 months, and 12 months was 129.0 (22.0), 129.0 (13.0), and 124.0 (17.0) ms, respectively. For patients followed for 12 months, mean (SD) CFB in QRS duration was -34.0 (27.0) ms at 1 month, -34.0 (28.0) ms at 6 months, and -39.0 (40.0) ms at 12 months. By 12 months there were 2 deaths, 1 acute MI, 5 episodes of cardiac decompensation in 4 patients, and a resolved CVA in 1 patient who failed to follow post-op anticoagulation regimen. The study did not indicate if any of these adverse events were procedure- or device-related. There were no instances of cardiac perforation or LV electrode dislodgement. The number of patients with improved, unchanged, and worsened CCS at 6 months was 29 (84.0%), four (12.0%), and one (4.0%), respectively.

- **Neuzil et al., 2016b** – A post hoc analysis of the Neuzil et al., 2016a study analyzing the Holmolce and Aalborg hospital patient subgroups. The number of patients achieving consistent CRT at 1 month, 6 months, and 12 months was 22 (100%), 20 (91%), and 19 (94%), respectively. The mean (SD) BiV-paced QRS duration at 1 month, 6 months, and 12 months was 133.0 (25.0), 131.0 (23.0), and 127.0 (20.0) ms, respectively, corresponding to mean (SD) CFB in QRS duration of -40.0 (26.0) ms at 1 month, -41.0 (30.0) ms at 6 months, and -48.0 (33.0) ms at 12 months. The number of patients with improved, unchanged, and worsened CCS at 6 months were 17 (77.0%), four (18.6%), and one (4.5%), respectively. The study reported five complications at 12 months, including one (4.5%) death, one (4.5%) acute myocardial infarction, two (9.1%) heart failure admissions, and one (4.5%) resolved cardiovascular accident. There were no incidents of cardiac perforation or LV electrode dislodgement (Neuzil et al., 2016b). Overall, the study concluded that WiSE CRT showed clinical benefits in patients who were previously untreated by CRT. The study also found that at 12 months, BiV pacing was maintained with observation of continued reverse electrical remodeling.
- **Butter et al., 2014** – A stand-alone prospective nonrandomized single-arm study that evaluated the safety and efficacy of WiSE CRT. The mean (SD) LVEF at 12 months increased to 33.2 (7.8%), with one (10.0%) patient observed to have a reduction from baseline. The mean (SD) NYHA class at 12 months was 2.1 (0.6), with eight (80.0%) patients having a reduction of greater than or equal to 1 class and two (20.0%) patients having no change. The mean (SD) BiV pacing QRS duration at 12 months was lowered to 141.0 (43.0) ms. The study reported one (7.7%) death and two (15.4%) high pacing thresholds during the study. The study concluded that WiSE CRT successfully provided CRT to 10 of 13 patients over 12 months.

v. Ongoing studies

To add to the clinical data supporting the WiSE System, EBR plans to collect additional patient outcomes data through several clinical studies that are currently planned. These studies are summarized in the Evidence Development Plan described in Section 5. Proposed Evidence Generation Plan below. Additionally, the WiSE System will be included in the ACC Electrophysiology Device Implant Registry beginning in 2025, presenting an opportunity for additional study of WiSE System implantation in real-world settings.

4. Benefits and relevance to Medicare population

The prevalence and burden of HF in the Medicare population lends importance to CMS's consideration of Medicare coverage for the WiSE System. By 2030, more than 6 million Americans aged 65 and older will have HF, representing more than 70% of all HF patients in the US.²⁸ HF is the most frequent cause of hospitalization among individuals >65 years of age.²⁹ Mortality among HF patients is high, with 50% of Medicare beneficiaries not surviving 3 years after an HF hospitalization.³⁰

Based on the aging of the US population and the overall increasing prevalence of HF in the US, direct and indirect costs attributable to HF are projected to significantly increase from \$20.9 billion in 2012 to \$53.1 billion in 2030 – a 2.5-fold increase. Among HF patients >65 years of age, the increase is projected to be three-fold, with a majority of costs linked with hospitalizations (>70%).³¹

CRT is a well-established treatment for HF and has been shown to improve clinical status and reduce HF hospitalizations and mortality. From 2002-2010, nearly 375,000 CRT devices were implanted, with the majority in patients >65 years of age.³²

For most of these patients, CRT provides a lifeline, stabilizing or reversing progressive HF. However, for a significant subset of these patients, CRT has not been a viable treatment option. For example, in 5% to 15% of patients otherwise eligible for CRT, positioning a lead in the coronary vein is not possible due to anatomical constraints, and these patients are deemed untreatable.³³ For another subset of HF patients otherwise eligible, standard CRT is considered

²⁸ Heidenreich PA, Albert NM, Allen LA, Bluemke DA, Butler J, Fonarow GC, Ikonomidis JS, Khavjou O, Konstam MA, Maddox TM, Nichol G, Pham M, Piña IL, Trogon JG; American Heart Association Advocacy Coordinating Committee; Council on Arteriosclerosis, Thrombosis and Vascular Biology; Council on Cardiovascular Radiology Circ Heart Fail. 2013 May;6(3):606-19. doi: 10.1161/HHF.0b013e318291329a. Epub 2013 Apr 24. PMID: 23616602; PMCID: PMC3908895.

²⁹ Savarese G, Becher PM, Lund LH, Seferovic P, Rosano GMC, Coats AJS. Global burden of heart failure: a comprehensive and updated review of epidemiology. Cardiovasc Res. 2023 Jan 18;118(17):3272-3287. doi: 10.1093/cvr/cvac013. Erratum in: Cardiovasc Res. 2023 Jun 13;119(6):1453. doi: 10.1093/cvr/cvad026. PMID: 35150240.

³⁰ Barker WH, Mullooly JP, Getchell W. Changing incidence and survival for heart failure in a well-defined older population, 1970-1974 and 1990-1994. Circulation. 2006 Feb 14;113(6):799-805. doi: 10.1161/CIRCULATIONAHA.104.492033. Epub 2006 Feb 6. PMID: 16461823.

³¹ Heidenreich PA, Albert NM, Allen LA, Bluemke DA, Butler J, Fonarow GC, Ikonomidis JS, Khavjou O, Konstam MA, Maddox TM, Nichol G, Pham M, Piña IL, Trogon JG; American Heart Association Advocacy Coordinating Committee; Council on Arteriosclerosis, Thrombosis and Vascular Biology; Council on Cardiovascular Radiology and Intervention; Council on Clinical Cardiology; Council on Epidemiology and Prevention; Stroke Council. Forecasting the impact of heart failure in the United States: a policy statement from the American Heart Association. Circ Heart Fail. 2013 May;6(3):606-19. doi: 10.1161/HHF.0b013e318291329a. Epub 2013 Apr 24. PMID: 23616602; PMCID: PMC3908895.

³² Sridhar AR, Yarlagadda V, Parasa S, Reddy YM, Patel D, Lakkireddy D, Wilkoff BL, Dawn B. Cardiac Resynchronization Therapy: US Trends and Disparities in Utilization and Outcomes. Circ Arrhythm Electrophysiol. 2016 Mar;9(3):e003108. doi: 10.1161/CIRCEP.115.003108. PMID: 26921376.

³³ Singh JP, Rinaldi CA, Sanders P, Kubo SH, James S, Niazi IK, Betts T, Butter C, Okabe T, Cunnane R, Aziz E, Biffi M, Zaidi A, Alison J, Defaye P, Aurricchio A, Gold MR, Lindenfeld J, Rogers T, Walsh MN; SOLVE-CRT Investigators. Leadless Ultrasound-Based Cardiac Resynchronization System in Heart

high-risk. Approximately 25% of all CRT implants are classified as upgrades from other cardiac pacing devices.^{34,35} Based on studies published in the American Heart Association Journal and the Heart Rhythm Journal, approximately 60% of these upgrades are considered high risk, which translates to 15% of all CRT implants being upgrades.^{36,37,38}

The WiSE System provides a further treatment option for these previously untreatable and high-risk CRT patients. Of critical importance for the Medicare population, two-thirds of SOLVE-CRT study participants were 65 years of age or older, and no statistically significant differences were observed for these participants relative to the other participants in the study.³⁹ Based on the Medicare Physician & Other Practitioners - by Geography and Service 2022 claims data, 26,000 Medicare beneficiaries had left lower leads implanted for pacemaker or defibrillator.⁴⁰ We estimate that approximately 20 percent of these patients would be appropriate candidates for the WiSE System.

5. Proposed Evidence Development Plan

CMS has identified evidentiary gaps in the WiSE System clinical evidence. To support Medicare beneficiary access while addressing these evidentiary needs, we are proposing the attached Evidence Development Plan (EDP) for national coverage through the Transitional Coverage for Emerging Technologies (TCET) pathway. This plan outlines a structured approach to prospective data collection, including study objectives, outcomes, and data sources, and is designed to ensure transparent, high-quality evidence generation.

Failure. *JAMA Cardiol.* 2024 Jul 31:e242050. doi: 10.1001/jamacardio.2024.2050. Epub ahead of print. PMID: 39083254; PMCID: PMC11292567.

³⁴ Michael Glikson, Jens Cosedis Nielsen, Mads Brix Kronborg, et al., 2021 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy, <https://doi.org/10.1093/eurheartj/ehab364>

³⁵ Bogale, N., Priori, S., Gitt, A., Alings, M., Linde, C., Dickstein, K., et al., 2011. The European cardiac resynchronization therapy survey: Patient selection and implantation practice vary according to centre volume. *EP Europace*, 13(10), 1445–1453. <https://doi.org/10.1093/europace/eur173>

³⁶ Abu-El-Haija B, Bhavé PD, Campbell DN, Mazur A, Hodgson-Zingman DM, Cotarlan V, Giudici MC. Venous Stenosis After Transvenous Lead Placement: A Study of Outcomes and Risk Factors in 212 Consecutive Patients. *J Am Heart Assoc.* 2015 Jul 31;4(8):e001878. doi: 10.1161/JAHA.115.001878. PMID: 26231843; PMCID: PMC4599456.

³⁷ Johansen JB, Jørgensen OD, Møller M, Arnsbo P, Mortensen PT, Nielsen JC. Infection after pacemaker implantation: infection rates and risk factors associated with infection in a population-based cohort study of 46299 consecutive patients. *Eur Heart J.* 2011 Apr;32(8):991-8. doi: 10.1093/eurheartj/ehq497. Epub 2011 Jan 20. PMID: 21252172; PMCID: PMC3076667.

³⁸ Mendonca Costa C, Neic A, Gillette K, Porter B, Gould J, Sidhu B, Chen Z, Elliott M, Mehta V, Plank G, Rinaldi CA, Bishop MJ, Niederer SA. Left ventricular endocardial pacing is less arrhythmogenic than conventional epicardial pacing when pacing in proximity to scar. *Heart Rhythm.* 2020 Aug;17(8):1262-1270. doi: 10.1016/j.hrthm.2020.03.021. Epub 2020 Apr 6. PMID: 32272230; PMCID: PMC7397521.

^{39,39,39} Singh JP, Rinaldi CA, Sanders P, et al. Leadless Ultrasound-Based Cardiac Resynchronization System in Heart Failure. *JAMA Cardiol.* Published online July 31, 2024. doi:10.1001/jamacardio.2024.2050

⁴⁰ CMS Data: Medicare Physician & Other Practitioners - by Geography and Service, available at: <https://data.cms.gov/provider-summary-by-type-of-service/medicare-physician-other-practitioners/medicare-physician-other-practitioners-by-geography-and-service/data>

The WiSE-CHOICE Study (The WiSE System: Coverage & Health Outcomes & Impact in Clinical Evidence Study) will be propensity-matched prospective observational cohort study comparing Medicare fee-for-service (FFS) beneficiaries with HF who receive the WiSE System with those who meet clinical eligibility criteria for the Previously Untreatable or High-Risk Upgrade phenotype but did not receive the WiSE System. We have attached a full and complete protocol as required to obtain a national coverage determination through the TCET pathway.

The WiSE-UP Study is a prospective, observational post-approval study comprising commercial payer WiSE System patients. The WiSE-UP QoL Analysis will be a prospective, observational sub-analysis of WiSE-UP patients who receive a WiSE System. The SOLVE-RWE will be a propensity-matched hybrid cohort study comparing SOLVE-CRT trial patients aged ≥ 65 years from US sites who received the WiSE System with Medicare FFS beneficiaries who met clinical eligibility criteria for the Previously Untreatable or High-Risk Upgrade phenotype but did not receive the WiSE System. To avoid interruption of beneficiary access during the transition between completion of the WiSE-CHOICE CED Study and CMS's subsequent national coverage reconsideration decision, EBR System commits to developing and submitting a protocol for a continued access study.

6. Proposed coverage determination: Implantable Leadless LVEP for CRT

Coverage for implantable leadless LVEP for CRT is reasonable and necessary when furnished with an FDA-approved system, such as the WiSE System, and all the following additional safeguards are demonstrated to be in place:

1. Selection of Appropriate Patients:
 - a. Previously untreatable: Patients in whom previous CS lead implantation was unsuccessful, or where an implanted lead has been abandoned or deemed not operational.
 - b. High risk upgrades: Patients with previously implanted pacemakers or ICDs in whom standard CRT upgrade is not advisable due to known relative contraindications for CS lead or CRT device implantation.
2. Requirements for Facility and Clinician Education and Training:
 - a. Physicians who have undergone formal, documented manufacturer-supported training.

Appendices

- Appendix 1. Study Characteristics and Outcomes of Peer-Reviewed Clinical Studies
- Appendix 2. Study Characteristics and Outcomes of Unpublished/ Non-peer-reviewed Evidence

Appendix 1. Study Characteristics and Outcomes of Peer-Reviewed Clinical Studies

First Author	Year	N	Objective	Population Baseline Status	Results	Complications		Follow-Up	Conclusions
						Rate	Type		
Wijesuriya et al. ⁴¹	2025	122	The purpose of this study was to examine the association between Q-LV and echocardiographic remodeling response to leadless CRT delivered with the WiSE-CRT system.	QRSd, ms, median (IQR): 168 (154 – 188) LVEF, %, mean (SD): 29.9 (8.0) LVEDV, mL, median (IQR): 190 (154 – 243)	Complete Q-LV data were available for 122 of 153 patients (80%) in the active arms SOLVE-CRT. Overall, the 6-month LVESV response rate was 46%. Logistic regression identified Q-LV as an independent response predictor with borderline significance (adjusted odds ratio 1.015; P = .05). Analysis by Q-LV quartile demonstrated a significant improvement in response rate in quartile 4 (longest Q-LV 64%) compared to quartile 1			6 mons	Increased Q-LV was associated with improved reverse remodeling following leadless CRT. Targeting LV endocardial sites of high Q-LV may deliver additional benefit compared to empirical LV electrode implantation.

⁴¹ Wijesuriya N, Mehta V, De Vere F, et al. Left ventricular electrical delay predicts volumetric response to leadless cardiac resynchronization therapy. Heart Rhythm. 2025;22(2):357-364. doi:10.1016/j.hrthm.2024.08.050

First Author	Year	N	Objective	Population Baseline Status	Results	Complications		Follow-Up	Conclusions
						Rate	Type		
					(shortest Q-LV 28%) (P <.01). This association was primarily driven by strong Q-LV-response correlation in patients with ischemic cardiomyopathy, demonstrated by subgroup logistic regression (adjusted odds ratio 1.034; P = .004).				
Singh et al. ⁴²	2024	183	To assess the safety and efficacy of a novel, leadless LV endocardial pacing system for patients at high risk for a CRT upgrade or whose CS lead placement/pacing with a conventional CRT system failed.	LVESV, mL: 151.1 (67.21) – Safety Population 146.3 (71.51) – Efficacy Population LVEF, %:	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)	6.6% 2.7% 1.6% 3.8%	Study device system events Vascular events (2.7%) Strokes Cardiac perforations	5 years	The SOLVE-CRT study has demonstrated that leadless LV endocardial pacing with the WiSE System is associated with a reduction in LVESV in patients with HF. This novel system may represent an alternative to conventional CRT

⁴² Singh JP, Rinaldi CA, Sanders P, Kubo SH, James S, Niazi IK, Betts T, Butter C, Okabe T, Cunnane R, Aziz E, Biffi M, Zaidi A, Alison J, Defaye P, Aurricchio A, Gold MR, Lindenfeld J, Rogers T, Walsh MN; SOLVE-CRT Investigators. Leadless Ultrasound-Based Cardiac Resynchronization System in Heart Failure. JAMA Cardiol. 2024 Jul 31:e242050. doi: 10.1001/jamacardio.2024.2050.

First Author	Year	N	Objective	Population Baseline Status	Results	Complications		Follow-Up	Conclusions
						Rate	Type		
				29.8 (7.90) – Safety Population 31.1 (7.89)- Efficacy Population					implants in some HF patient populations
Okabe et al. ⁴³	2022	31	Evaluation of safety and efficacy of WiSE System in Part I (Roll-In Patients) of the SOLVE-CRT Study	LVEF: 28.1 ± 6.5% NYHA class: II/III/IV	The WiSE System was implanted successfully in 100% of patients. 30 patients completed the 6-mo follow up (1 patient underwent heart transplantation 1 mo after implantation and was excluded). 14 (46.7%) patients demonstrated ≥ 1 NYHA class improvement. TTE data were available in 29 patients. There was improvement in LVEF (28.3% ± 6.7% to 33.5% ± 6.9%,	9.7% 3.2% 16.1%	3 Type I complications (intermittent loss of capture, embolization of inadequately anchored LV electrode, wound infection) 1 iliac artery aneurysm 5 periprocedural cardiopulmonary events	6 mos	Results from roll-in phase (Phase I) of the SOLVE-CRT (Stimulation of the Left Ventricular Endocardium for Cardiac Resynchronization Therapy in Non-Responders and Previously Untreatable Patients) study of the WiSE System; results showed a high success rate of LV endocardial electrode placement in centers with no prior implanting experience and favorable clinical

⁴³ Okabe T, Hummel JD, Bank AJ, et al. Leadless left ventricular stimulation with WiSE-CRT System - Initial experience and results from phase I of SOLVE-CRT Study (nonrandomized, roll-in phase). Heart Rhythm 2022;19(1):22-29. (In eng). DOI: 10.1016/j.hrthm.2021.06.1195.

First Author	Year	N	Objective	Population Baseline Status	Results	Complications		Follow-Up	Conclusions
						Rate	Type		
					p < 0.001), LVESV (134.9 ± 51.3 ml to 111.1 ± 40.3 ml, p = 0.0004), and LVEDV (185.4 ± 58.8 ml to 164.9 ± 50.6 ml, p = 0.0017).				response and significant LV reverse remodeling
Sidhu et al. ⁴⁴	2021	CS CRT: 121	Evaluate use of the WiSE System for leadless LV endocardial pacing for CRT upgrades in comparison with CS CRT upgrades	LVEF: 29.5 ± 8.6% QRSd 170.6 ± 27.8 ms NYHA class: 2.8 ± 0.7	Patients receiving the WiSE System tended to have more comorbidities and prior cardiac surgery but similar LVEF values. WiSE CRT upgrades were successful in 97.1% of patients. CS upgrades were successful in 97.5% of cases. At 6 mos, 91 WiSE CRT upgrades and 107 CS upgrades had similar improvements in CCS (76.3% vs 68.5%, p = 0.210)	2.5% 5.6%	CS dissection Malfunction/ displacement	6 mos	Despite prior failed upgrades and high-risk patients with more comorbidities, WiSE CRT upgrades had high rates of procedural success and similar improvements in CCS and LV remodeling compared with CS upgrades.
		WiSE CRT: 104		LVEF: 30.0 ± 8.3% QRSd: 181.9 ± 30.2 ms NYHA class: 2.6 ± 0.5		1.9%	Procedure-related mortality		

⁴⁴ Sidhu BS, Sieniewicz B, Gould J, et al. Leadless left ventricular endocardial pacing for CRT upgrades in previously failed and high-risk patients in comparison with coronary sinus CRT upgrades. EP Europace 2021;23(10):1577-1585. (In en). DOI: 10.1093/europace/euab156.

First Author	Year	N	Objective	Population Baseline Status	Results	Complications		Follow-Up	Conclusions
						Rate	Type		
					and reduction in LVESV $\geq 15\%$ (54.2% vs 56.3%, $p = 0.835$).				
Carabelli et al.	2021	8	The study describes the technical feasibility and first insights into the safety and efficacy of Micra and WiSE CRT combination in European experience.						The Micra and the WiSE-CRT systems can successfully operate together to deliver total leadless CRT to a patient. Moreover, the WiSE-CRT system provides the only means to upgrade the large population of Micra patients to CRT capability without replacing the Micra. The range of application of this combination could broaden in the future with the upcoming developments of leadless cardiac pacing.

First Author	Year	N	Objective	Population Baseline Status	Results	Complications		Follow-Up	Conclusions
						Rate	Type		
Sieniewicz et al. ⁴⁵	2020	90	Evaluate performance and safety of the WiSE Systems in real-world settings	LVEF: 30.6% QRSd: 180.7 ms NYHA class: II/III	Implantation of the WiSE System was successful in 94.4% of patients.	4.4% 18.8% 6.7%	<24 hrs (cardiac tamponade (2), pneumothorax/pleural effusion (2)) 24 hrs - 1 mo (death) 1_ access complication (4), pocket hematoma (4), chest sepsis (3), pocket infection (3), acute kidney injury (2)) 1-6 mos (death (4), CVA (1), extrastimulation during TTE (1))	6 mos	BiV endocardial pacing with the WiSE System is technically feasible with a high success rate. Procedural complications mandate adequate operator training and implantation at centers with immediately available cardiothoracic and vascular surgical support
Sidhu et al. ⁴⁶	2020	22	Evaluate WiSE System in CRT non-responders	LVEF: 26.5% QRSd: 167.2 ms NYHA class: mean 2.9	20 patients underwent successful implantation of the WiSE System and confirmation of BiV pacing (failure of electrode capture in 2 patients). 18 patients	13.6% 22.7%	Early (<1 week) (1 femoral artery fistula, 1 femoral pseudo-aneurysm, 1 cellulitis) Late (1 week - 6 months) (1 pocket hematoma, 1 cellulitis, 2 system revisions, 1 pocket infection)	6 mos	The WiSE System can provide improvement in CCS and can lead to reverse remodeling in patients who did not respond to conventional CRT, a group that

⁴⁵ Sieniewicz BJ, Betts TR, James S, et al. Real-world experience of leadless left ventricular endocardial cardiac resynchronization therapy: A multicenter international registry of the WiSE-CRT pacing system. Heart Rhythm 2020;17(8):1291-1297. (In en). DOI: 10.1016/j.hrthm.2020.03.002.

⁴⁶ Sidhu BS, Porter B, Gould J, et al. Leadless left ventricular endocardial pacing in nonresponders to conventional cardiac resynchronization therapy. Pacing Clin Electrophysiol 2020;43(9):966-973. (In en). DOI: 10.1111/pace.13926.

First Author	Year	N	Objective	Population Baseline Status	Results	Complications		Follow-Up	Conclusions
						Rate	Type		
					proceeded to the 6-mo follow up. There was significant reduction in QRSd compared with intrinsic QRSd (26.6 ± 24.4 ms, $p = 0.002$) and improvement in LVEF ($4.7 \pm 7.9\%$, $p = 0.021$). There were no significant improvements in LVESV or LVEDV. 55.6% of patients had improvement in CCS and 66.7% had reduction in LVESV $\geq 15\%$ and/or absolute improvement in LVEF $\geq 5\%$.				has few remaining treatment options.
Carabelli et al. ⁴⁷	2020	8	Evaluate totally leadless CRT System using Micra PM and WiSE System	LVEF: 28.4% QRSd: 204.4 ms NYHA class: mean 2.63	All 8 implanted WiSE Systems were able to detect the Micra PM pacing output and be trained to deliver	12.5% 0%	Patient death at 4 mos due to acute heart failure No complications related to the procedure or device	6 mos	The Micra PM and WiSE System can successfully operate together to deliver totally leadless CRT. The WiSE

⁴⁷ Carabelli A, Jabeur M, Jacon P, et al. European experience with a first totally leadless cardiac resynchronization therapy pacemaker system. *Europace* 2020;23(5):740-747. DOI: 10.1093/europace/euaa342.

First Author	Year	N	Objective	Population Baseline Status	Results	Complications		Follow-Up	Conclusions
						Rate	Type		
					synchronous LV endocardial pacing (100%). Acute QRS reduction was observed in all 8 patients after WiSE System implantation (204.4 ± 30.3 vs 137.5 ± 24.8 ms, $p = 0.012$) and LVEF was improved ($+11.3 \pm 8.5\%$, $p = 0.018$). There was no evidence of reverse remodeling or significant change in NYHA class; LVEDV, or LVESV. 7 patients were evaluated at 6 mos.		occurred in the first 6 mos		System is the only means to upgrade the large population of Mica PM patients to CRT capability without replace the Micra PM.
Sieniewicz et al. ⁴⁸	2018	26	Evaluate guided implants for improvements in acute markers of contractility and chronic markers of CRT response	LVEF: $34.2 \pm 7.8\%$ QRSd: 163.8 ± 26.7 ms	It was technically feasible to selectively target and deploy the WiSE CRT Electrode in a chosen	Not reported	Similar complication rate to that observed during indiscriminate BiV endocardial pacing	6 mos	Guided endocardial implants of the WiSE System were associated with a higher degree of chronic

⁴⁸ Sieniewicz BJ, Behar JM, Gould J, et al. Guidance for Optimal Site Selection of a Leadless Left Ventricular Endocardial Electrode Improves Acute Hemodynamic Response and Chronic Remodeling. JACC Clin Electrophysiol 2018;4(7):860-868. DOI: 10.1016/j.jacep.2018.03.011.

First Author	Year	N	Objective	Population Baseline Status	Results	Complications		Follow-Up	Conclusions
						Rate	Type		
					endocardial segment in almost all cases. 90% of patients met the definition of echocardiographic responder and reverse remodeling was observed in 71%. At six months, 21 patients were evaluable. There were significant reductions compared to baseline in QRSd (163.8 ± 26.7 ms vs 134.8 ± 25.6 ms, $p = 0.002$) and LVESV (11.7 ± 64.4 vs 85.9 ± 52.3 , $p < 0.0001$). LVEF significantly increased compared to baseline ($34.2 \pm 7.8\%$ to $39 \pm 9.8\%$; $p = 0.008$).				LV remodeling compared with historical nonguided approaches.

First Author	Year	N	Objective	Population Baseline Status	Results	Complications		Follow-Up	Conclusions
						Rate	Type		
Reddy et al. ⁴⁹	2017	35	Feasibility and safety of WiSE System (SELECT-LV Study)	LVEF: 26.0 ± 6.2% NYHA class: 2.6 ± 0.6	Implantation of the System was successful in 97.1% of attempted implants. At 1 month, BiV pacing was achieved in 33 of 34 patients (97.1%). A total of 28 patients (84.8%) had improvement in CCS at 6 months and 21 (66%) demonstrated a positive echocardiographic response.	8.6% 22.3% 8.6%	<24 hrs (VF (1), Electrode embolization to lower extremity (1), femoral artery fistula (1)) 24 hrs to 1 mo (Acute CVA (1), femoral pseudoaneurysm (2), pocket hematoma (1), suspected infection (3), death (1)) 1 to 6 mos (defective transmitter circuitry (3))	1 & 6 mos	Results of the SELECT-LV Study demonstrate the clinical feasibility for the WiSE System. Clinical benefit was provided to the majority of patients within an otherwise “failed” CRT population
Auricchio et al. ⁵⁰	2014	17	Feasibility and safety of WiCS LV System (WiSE-CRT Study)	LVEF: 19 -33% QRSd: 120 - 240 ms NYHA class: III/IV	Of the 17 patients, 13 were implanted with the WiCS LV System (76.5%). BiV pacing was achieved in 10 of those 13 (79.6%). In 2, BiV pacing was achieved after correction.	23.1%	Pericardial effusion	6 mos	Results show the feasibility of providing an endocardial stimulation for CRT with a novel leadless technology.

⁴⁹ Reddy VY, Miller MA, Neuzil P, et al. Cardiac Resynchronization Therapy With Wireless Left Ventricular Endocardial Pacing: The SELECT-LV Study. J Am Coll Cardiol 2017;69(17):2119-2129. DOI: 10.1016/j.jacc.2017.02.059.

⁵⁰ Auricchio A, Delnoy PP, Butter C, et al. Feasibility, safety, and short-term outcome of leadless ultrasound-based endocardial left ventricular resynchronization in heart failure patients: results of the wireless stimulation endocardially for CRT (WiSE-CRT) study. Europace 2014;16(5):681-8. DOI: 10.1093/europace/eut435.

First Author	Year	N	Objective	Population Baseline Status	Results	Complications		Follow-Up	Conclusions
						Rate	Type		
					BiV pacing was recorded in 83% and 92% of patients and 1 and 6 months. A majority of patients had improvement in NYHA class and LVEF.				
DeFaria Yeh et al. ⁵¹	2011	42	Identification of Acoustic Window	LVEF: ≤35% QRSd: 133 ±35 ms NYHA class: III/IV	Of the 42 patients enrolled, appropriate AWs were identified in 41 patients (97.6%)	Not reported	Not reported	Acute study	Results show that adequate acoustic windows for transmitter implantation were present in nearly all patients
Lee et al. ⁵²	2009	10	Ultrasound-mediated pacing (acute)	LVEF: ≤35% NYHA class: III/IV	Ultrasound-mediated pacing was achieved in the 10 patients tested (100%)	0%	No complications reported related to ultrasound-mediated pacing	Acute study	Results show the feasibility of leadless LV stimulation acutely in HF patients. Further, the acoustic window validated by CT was predicted by TTE.

⁵¹ DeFaria Yeh D, Lonergan KL, Fu D, Yeh RW, Echt DS, Foster E. Clinical factors and echocardiographic techniques related to the presence, size, and location of acoustic windows for leadless cardiac pacing. *Europace* 2011;13(12):1760-5. DOI: 10.1093/europace/eur199.

⁵² Lee KL, Tse HF, Echt DS, Lau CP. Temporary leadless pacing in heart failure patients with ultrasound-mediated stimulation energy and effects on the acoustic window. *Heart Rhythm* 2009;6(6):742-8. DOI: 10.1016/j.hrthm.2009.02.025.

First Author	Year	N	Objective	Population Baseline Status	Results	Complications		Follow-Up	Conclusions
						Rate	Type		
Lee et al. ⁵³	2007	24	Ultrasound-mediated pacing (acute)	Not reported	Of 82 sites across 24 patients, ultrasound-mediated testing was achieved at 80 sites ((97.6%))	0%	No complications reported related to ultrasound-mediated pacing	Acute study	Results demonstrated feasibility and safety of using energy transfer to achieve cardiac stimulation without the use of leads in humans

⁵³ Lee KL, Lau CP, Tse HF, et al. First human demonstration of cardiac stimulation with transcutaneous ultrasound energy delivery: implications for wireless pacing with implantable devices. J Am Coll Cardiol 2007;50(9):877-83. DOI: 10.1016/j.jacc.2007.04.081.

Appendix 2. Study Characteristics and Outcomes of Unpublished/ Non-peer-reviewed Evidence

Study Characteristics	Subgroup	Intervention(s) and Patient Characteristics	Outcomes	
Reference: Sharma et al., 2024 (SOLVE CRT; NCT02922036) Country: Europe Study Design: Post-hoc analysis of SOLVE CRT Purpose: This analysis studies the effect of the WiSE CRT left ventricular (LV) endocardial pacing on MR in the SOLVE-CRT Trial cohort. Conclusion: This analysis of the SOLVE-CRT trial demonstrates stable or improved MR in the vast majority of patients who received the novel endocardial WiSE-CRT device. Funding Source: NR Quality: Only conference abstract was available. No formal quality assessment was performed.	Study population	Intervention: WiSE CRT Comparator: NR Length of follow-up: 6 months Patients (N): 87 Age, years, mean (SD): 67 (NR) Sex, male, n (%): 67 (77.0) BMI, kg/m², mean (SD): NR Race, n (%): NR Indication, n (%): Class I or IIA: 87 (100.0) Not received prior treatment: 64 (74.0) High risk upgrade: 23 (26.0) Comorbidities, n (%): NR NYHA class, n (%): NYHA class II: 31 (36.0) NYHA class III: 58 (66.6) QRSd, ms, mean (SD): LVEF, %, mean (SD): 31 (NR) LVEDV, mL, mean (SD): 209 (NR) LVESV, cm³, mean (SD): NR	Mitral regurgitation at 6 months, n (%): Stable MR: 62 (71.0) Improved MR: 21 (24.0) Worsening of MR: 4 (5.0) Mean vena contracta and E-wave velocity both had statistically significant reduction at 6 months (p-value NR) Patients with improved MR had significant improvement in NYHA classification at 6 months (p-value NR)	NR

Study Characteristics	Subgroup	Intervention(s) and Patient Characteristics	Outcomes	
Reference: Defaye et al., 2023 (Stand-alone study; NR) Country: Multinational Study Design: Prospective nonrandomized single-arm study Purpose: The study aimed to assess the technical feasibility of achieving totally leadless CRT using the Micra and WiSE System. Conclusion: Achieving totally leadless CRT using a combination of a Micra and WiSE CRT is technically feasible. Further work is required to assess the efficacy and safety of this combination. The WiSE System remains the only means to upgrade the expanding population of Micra and Aveir patients to CRT without replacing the leadless device. Funding Source: NR Quality: Only conference abstract was available. No formal quality	Study population	Intervention: WiSE CRT + Micra Comparator: NA Length of follow-up: NR Patients (N): 14 Age, years, mean (SD): NR Sex, male, n (%): NR BMI, kg/m², mean (SD): NR Race, n (%): NR Indication, n (%): Infection of the conventional CRT: 5 (35.7) Upgrade of a chronic Micra: 6 (42.9) De novo implant: 2 (14.3) High pacing threshold: 1 (7.1) Comorbidities, n (%): NR NYHA class, n (%): NR QRSd, ms, mean (SD): NR LVEF, %, mean (SD): NR LVEDV, cm³, mean (SD): NR LVESV, cm³, mean (SD): NR	No unforeseen device to device interactions were observed.	Acute complication, n (%): Premature detachment of an unanchored WiSE electrode: 1 (7.1)

Study Characteristics	Subgroup	Intervention(s) and Patient Characteristics	Outcomes	
assessment was performed.				
Reference: Sidhu et al., 2019a (Stand-alone study; NR) Country: UK Study Design: Retrospective observational study Purpose: To identify patient outcome of WiSE CRT in CRT non-responder population Conclusion: Study analysis showed that in the high risk non-responder patient group, the WiSE System results in a considerable improvement in the clinical composite score and leads to reverse left ventricular remodeling. These encouraging results suggest an important role for the WiSE System in the management of CRT non-responders. Funding Source: NR Quality: Only conference abstract was available. No formal quality	Study population	Intervention: WiSE CRT Comparator: NA Length of follow-up: 6 months Patients (N): 17 Age, years, mean (SD): 68.2 (7.9) Sex, male, n (%): 16 (94.1) BMI, kg/m², mean (SD): NR Race, n (%): NR Indication, n (%): NR Comorbidities, n (%): NR NYHA class, mean (SD): 2.8 (0.4) QRSd, ms, mean (SD): 169.1 (23.8) LVEF, %, mean (SD): 25.6 (8.0) LVEDV, cm³, mean (SD): NR LVESV, cm³, mean (SD): NR	Improvement in CCS (alive, no HF hospitalizations, improvement in NYHA or patient global assessment), n (%): 10 (58.8) ESV improvement of ≥ 15%, n (%): 9 (53.3) Absolute increase in LVEF of ≥ 5% or improvement in ESV of ≥ 15%: 11 (64.7)	Acute complication, n (%): 0 (0.0) Complication, n (%): Pocket hematoma: 1 (5.9)

Study Characteristics	Subgroup	Intervention(s) and Patient Characteristics	Outcomes	
assessment was performed.				
Reference: Sidhu et al., 2019b (Stand-alone study; NR) Country: UK Study Design: Retrospective observational study Purpose: To compare safety and efficacy of patients undergoing high-risk CRT upgrade using WiSE CRT against patients undergoing epicardial CRT upgrades. Conclusion: Patients undergoing high-risk CRT upgrades with WiSE-CRT have comparable outcomes with those patients undergoing epicardial CRT upgrades. There is a tendency towards improved LV remodeling following WiSE CRT, however further studies are required to determine if this reaches significance in a larger cohort Funding Source: NR	Endocardial CRT subgroup	Intervention: WiSE CRT Comparator: Epicardial CRT upgrade Length of follow-up: 6 months Patients (N): 37 Age, years, mean (SD): 67.9 (11.4) Sex, male, n (%): 31 (83.8) BMI, kg/m², mean (SD): NR Race, n (%): NR Indication, n (%): NR Comorbidities, n (%): NR NYHA class, n (%): QRSd, ms, mean (SD): 182.4 (29.0) LVEF, %, mean (SD): 29.7 (7.9) LVEDV, cm³, mean (SD): NR LVESV, cm³, mean (SD): NR	Improvement in clinical composite score (alive, no HF hospitalization, improvement in NYHA or global assessment), n (%): WiSE CRT: 29 (78.0) Epicardial CRT: 47 (81.0) WiSE CRT vs. Epicardial CRT: p = 0.784 Absolute change in LVEF ≥ 5%, n (%): WiSE CRT: 27 (73.5) Epicardial CRT: 38 (66.0) WiSE CRT vs. Epicardial CRT: p = 0.367 Improvement in LVESV ≥ 15%: WiSE CRT: 26 (69.0) Epicardial CRT: 31 (52.8) WiSE CRT vs. Epicardial CRT: p = 0.185	NR

Study Characteristics	Subgroup	Intervention(s) and Patient Characteristics	Outcomes	
Quality: Only conference abstract was available. No formal quality assessment was performed.				
Reference: Sieniewicz et al., 2019a (WICS-LV; NCT02610673); Sieniewicz et al., 2019b (WICS-LV; NCT02610673) *Note: 2019a was published in May 2019 while 2019b was published in March 2019; thus, the more recent reprinted data from 2019a supersedes data from 2019b Country: Europe Study Design: Prospective observational study (Post Market Surveillance) Purpose: The study sought to assess the safety & efficacy of the WiSE-CRT system during real world clinical use in an international registry. Conclusion: BiV ENDO pacing with the WiSE System appears technically feasible and	Study population	Intervention: WiSE CRT Comparator: NA Length of follow-up: 6 months Patients (N): 90 Age, years, mean (SD): 68.1 (10.5) Sex, male, n (%): NR BMI, kg/m², mean (SD): NR Race, n (%): NR Indication, n (%): Failed attempt at CRT delivery: 44 (49.4) Complex upgrade: 34 (38.2) Non-responders to prior CRT: 11 (12.4) Comorbidities, n (%): NR NYHA class, mean (SD): 2.6 (0.5) QRSd, ms, mean (SD): 180.3 (26.8) LVEF, %, mean (SD): 30.2 (8.8) LVEDV, ml, mean (SD): 186.9 (90.0) LVESV, ml, mean (SD): 132.3 (84.3)	Subjective improvement in system, n (%): 70 (78.0) NYHA class at 6 months, mean (SD), p-value: 2.1 (0.7), p < 0.0001 Echocardiographic outcome at 6 months, mean (SD), p-value: LVEF, %: 37.2 (12.0), p < 0.0001 LVEDV, ml: 160.0 (83.4), p < 0.0001 LVESV, ml: 105.3 (73.1), p = 0.0004 Echocardiographic responders (LVESV > 15% relative reduction), n (%): 50 (55.4)	Acute complication within < 24 hours, n (%): 5 (5.6) 30 day complication, n (%): 17 (18.9) Cardiac tamponade: 1 (1.1) Arterial access complication: 4 (5.6)

Study Characteristics	Subgroup	Intervention(s) and Patient Characteristics	Outcomes	
offers a safe and effective therapeutic option for patients who have either failed to improve following transvenous, epicardial CRT or who are unable to receive effective traditional resynchronisation pacing, whilst avoiding the need for long term anticoagulation. Funding Source: NR Quality: Only conference abstract was available. No formal quality assessment was performed.				
Reference: Fehrendt et al., 2019 (Stand-alone study; NR) Country: Germany Study Design: Retrospective observational study Purpose: To identify the long term clinical and paraclinical heart failure parameter of WiSE CRT. Conclusion: The WiSE CRT shows good long-term performance in	Study population	Intervention: WiSE CRT Comparator: NA Length of follow-up, mean (SD): 2.1 (1.9) Patients (N): 14 Age, years, mean (SD): 68.6 (12.0) Sex, male, n (%): 12 (85.7) BMI, kg/m², mean (SD): NR Race, n (%): NR Indication, n (%): NR	NYHA class, mean (SD), p-value: At 3 months: 2.6 (0.5), NR At 6 months: 2.2 (0.7), P =< 0.05 At 2 years: 2.4 (0.7), p =< 0.05 At 5 years: 1.7 (0.6), p =< 0.01 Intrinsic QRS, ms, mean (SD), p-value: At 3 months: 169.0 (25.0), NR At 6 months: 158.0 (11.0), p=< 0.05 At 2 years: 176.0 (32.0), NR At 5 years: 160.0 (34.0), p =< 0.05 QRS under CRT, ms, mean (SD), p-value: At 3 months: 154.0 (26.0), p =< 0.01 At 6 months: 146.0 (22.0), NR At 2 years: 155.0 (27.0), NR At 5 years: 141.0 (17.0), NR	NR

Study Characteristics	Subgroup	Intervention(s) and Patient Characteristics	Outcomes	
patients who cannot be treated with conventional CRT. With this new system, the clinical and paraclinical improvement is comparable with conventional CRT. Funding Source: NR Quality: Only conference abstract was available. No formal quality assessment was performed.		Comorbidities, n (%): NR NYHA class, mean (SD): 2.8 (0.4) QRSd, ms, mean (SD): 170.0 (19.0) LVEF, %, mean (SD): 24.2 (7.8) LVEDV, ml, mean (SD): 199.0 (95.0) LVEDD, mm, mean (SD): 67 (13.5)	LVEF, %, mean (SD), p-value: At 3 months: NR At 6 months: 32.2 (10.0), p = < 0.05 At 2 years: 28.0 (10.5), NR At 5 years: 33.0 (1.0), p = < 0.05 LVEDD, mm, mean (SD), p-value: At 3 months: NR At 6 months: 62.0 (7.7), p = < 0.01 At 2 years: 61.7 (14.8), p = < 0.01 At 5 years: 62.3 (63.0), p = < 0.05 LVEDV, ml, mean (SD), p-value: At 3 months: NR At 6 months: 193.0 (73.0), NR At 2 years: 192.0 (114.0), NR At 5 years: 181.0 (63.0), p < 0.05 BiV pacing rate, %, mean (SD), p-value: 3 months: 74.0 (35.0), NR 6 months: 82.0 (26.0), NR 2 years: 93.3 (6.8), p < 0.01 5 years: 95.7 (3.8), p < 0.01	
Reference: Behar et al., 2017 (Stand-alone study; NR) Country: UK Study Design: Prospective observational study Purpose: The study evaluated the clinical effectiveness and safety of a wireless intracardiac LV electrode pacing	Study population	Intervention: WiSE CRT Comparator: NA Length of follow-up: 6 months Patients (N): 30 Age, years, mean (SD): 69.0 (8.0) Sex, male, n (%): 6 (20.0) BMI, kg/m², mean (SD): NR Race, n (%): NR	CFB in acute hemodynamic response at 6 months, %, mean (SD), p-value: 16.0 (13.0), p < 0.001 QRSd at 6 months, ms, mean (SD), p-value: 138.0 (27.0), p < 0.001 NYHA class at 6 months, mean (SD), p-value: 1.6 (0.7), p = 0.01 Abstract notes that there was a non-significant trend towards improvement in 6MWT, MLHFq, LV volume and ejection fraction.	Acute complication within < 24 hours, n (%): Inability to track an electrode at implant: 1 (3.3) Cardiac tamponade: 1 (3.3) Pneumothorax: 1 (3.3) Complication > 24 hours, n (%): Pseudo-aneurysm: 1 (3.3) Slow flow in the femoral artery: 1 (3.3) Retroperitoneal bleed: 1 (3.3) Battery pocket infection requiring explant and reimplantation: 1 (3.3)

Study Characteristics	Subgroup	Intervention(s) and Patient Characteristics	Outcomes	
system, for delivery of CRT (WiSE-CRT). Conclusion: The WiSE-CRT pacing system offers a feasible alternative with promising clinical results for patients who fail to derive benefit from conventional CRT. Longer term data is required to evaluate the prevalence of adverse events and any concerns about generator longevity. The ability to target most regions of the LV endocardium irrespective of coronary venous anatomy, without the presence of a longstanding lead in the arterial system remains a unique advantage. Funding Source: NR Quality: Only conference abstract was available. No formal quality assessment was performed.		Indication, n (%): Failed LV lead (displacement, deactivation: 13 (43.3) High risk upgrade (central venous occlusion, infection, comorbidities: 13 (43.3) Non-responders to conventional CRT: 4 (13.3) Comorbidities, n (%): NR NYHA class, mean (SD): 2.6 (0.5) QRSd, ms, mean (SD): 161.0 (23.0) LVEF, %, mean (SD): 24.0 (16.0) LVEDV, cm³, mean (SD): NR LVESV, cm³, mean (SD): NR MLHFq score, mean (SD): 49.0 (24.0) 6MWD, meters, mean (SD): 243.0 (116.0)		
Reference: Fehrendt et al., 2017 (Stand-alone study; NR) Country: Germany	Study population	Intervention: WiSE CRT Comparator: NA Length of follow-up, mean (SD): 2.2 (1.9) years	NYHA class, mean (SD): At 6 months: 2.0 (0.4), p<0.05 At 2 years: 2.0 (0.6), p<0.05 At 5 years: 1.7 (0.6), p<0.03 Overall: p<0.05	NR

Study Characteristics	Subgroup	Intervention(s) and Patient Characteristics	Outcomes
Study Design: Retrospective observational study Purpose: To identify the long term performance of WiSE CRT in terms of clinical and echocardiographic heart failure parameters as well as NT-proBNP levels. Conclusion: The WiSE-CRT system shows a good long term performance in patients with failed conventional CRT implantation. Larger randomized registers and studies are necessary to prove this innovative therapy to be as effective or even more effective than conventional CRT Funding Source: NR Quality: Only conference abstract was available. No formal quality assessment was performed.		Patients (N): 12 Age, years, mean (SD): 67.0 (12.0) Sex, male, n (%): 10 (83.3) BMI, kg/m², mean (SD): NR Race, n (%): NR Indication, n (%): NR Comorbidities, n (%): NR NYHA class, mean (SD): 2.9 (0.3) QRSd, ms, mean (SD): Intrinsic QRSd: 174.0 (18.6) QRSd with CRT: 153.0 (20.0) LVEF, %, mean (SD): 22.6 (7.2) LVEDV, ml, mean (SD): 210.0 (86.0) LVEDD, mm, mean (SD): 71.4 (12.4) NTproBNP, pg/ml, mean (SD): 2,005 (1,172) BiV rate, %, mean (SD): 0.0 (0.0)	Intrinsic QRSd, ms, mean (SD): At 6 months: 159.0 (12.0) At 2 years: 176.0 (26.0) At 5 years: 160.0 (34.0) Overall: p = 0.1 QRS with CRT, ms, mean (SD): At 6 months: 148.0 (22.0) At 2 years: 158.0 (33.0) At 5 years: 141.0 (17.0) Overall: p = 0.9 LVEF, %, mean (SD): At 6 months: 33.6 (10.0) At 2 years: 34.2 (6.8) At 5 years: 33.0 (1.0) Overall: p = 0.001 LVEDD, mm, mean (SD): At 6 months: 61.4 (8.0), p < 0.05 At 2 years: 57.8 (16.2), p < 0.05 At 5 years: 62.3 (12.0) LVEDV, ml, mean (SD): At 6 months: 198.0 (77.0) At 2 years: 159.0 (112.0) At 5 years: 181.0 (63.0) Overall: p = 0.8 NTproBNP, pg/ml, mean (SD): At 6 months: 2,073 (1,882) At 2 years: 1,715 (854) At 5 years: 1,951 (890) Overall: p = 0.5 BiV pacing rate, %, mean (SD): At 6 months: 80.0 (28.0), p = 0.001 At 2 years: 95.2 (5.7), p = 0.001 At 5 years: 95.7 (3.8), p = 0.001 Overall: p = 0.001

Study Characteristics	Subgroup	Intervention(s) and Patient Characteristics	Outcomes	
Reference: Neuzil et al., 2016a (Stand-alone study; NR); Neuzil et al., 2016b (Stand-alone study; NR) Country: Multinational Study Design: Prospective observational study Purpose: To evaluate the clinical efficacy and safety of WiSE CRT Conclusion: Wireless endocardial LV pacing is an alternative approach to CRT. These 12 months data demonstrate the clinical benefit to our pts, previously untreated by CRT. BiV pacing is maintained with reverse electrical remodeling continuing to be evident 12 months post implant. Funding Source: NR	Study population	Intervention: WiSE CRT Comparator: NA Length of follow-up: 12 months Patients (N): 34 Age, years, mean (SD): 65.8 (8.6) Sex, male, n (%): 25 (73.5) BMI, kg/m², mean (SD): 29.7 (4.8) Race, n (%): NR Indication, n (%): NR Comorbidities, n (%): NR NYHA class, mean (SD): 2.7 (0.6) QRSd, ms, mean (SD): Intrinsic pacing: 163.0 (32.0) RV pacing: 180.0 (30.0) LVEF, %, mean (SD): 27.4 (5.4) LVEDV, cm³, mean (SD): NR LVESV, cm³, mean (SD): NR	Consistent CRT achieved, n (%): At 1 month: 34 (100.0) At 6 months: 33 (97.0) At 12 months: 24 (96.0) BiV QRSd, ms, mean (SD): At 1 month: 129.0 (22.0) At 6 months: 129.0 (13.0) At 12 months: 124.0 (17.0) CFB in BiV QRSd, ms, mean (SD): At 1 month: -34.0 (27.0) At 6 months: -34.0 (28.0) At 12 months: -39.0 (40.0) Clinical composite score at 6 months, n (%): Improved CCS: 29 (84.0) Unchanged CCS: 4 (12.0) Worsened CCS: 1 (4.0)	NR
Quality: Only conference abstract was available. No formal quality assessment was performed.	Holmolce and Aalborg Hospital subgroup	Intervention: WiSE CRT Comparator: NA Length of follow-up: 12 months Patients (N): 22 Age, years, mean (SD): 67.3 (6.4)	Consistent CRT achieved, n (%): At 1 month: 22 (100.0) At 6 months: 20 (91.0) At 12 months: 19 (94.0) BiV QRSd, ms, mean (SD): At 1 month: 133.0 (25.0) At 6 months: 131.0 (23.0) At 12 months: 127.0 (20.0)	Complication at 12 months, n (%): Death: 1 (4.5) Acute MI: 1 (4.5) HF admission: 2 (9.1) Resolved CVA: 1 (4.5) Cardiac perforation: 0 (0.0) LV electrode dislodgement: 0 (0.0)

Study Characteristics	Subgroup	Intervention(s) and Patient Characteristics	Outcomes	
		Sex, male, n (%): 19 (86.4) BMI, kg/m², mean (SD): 29.5 (4.5) Race, n (%): NR Indication, n (%): NR Comorbidities, n (%): NR NYHA class, mean (SD): 2.4 (0.7) QRSd, ms, mean (SD): Intrinsic pacing: 174.0 (31.0) RV pacing: 193.0 (23.0) LVEF, %, mean (SD): 26.6 (6.0) LVEDV, cm³, mean (SD): NR LVESV, cm³, mean (SD): NR	CFB in BiV QRSd, ms, mean (SD): At 1 month: -40.0 (26.0) At 6 months: -41.0 (30.0) At 12 months: -48.0 (33.0) Clinical composite score at 6 months, n (%): Improved CCS: 17 (77.0) Unchanged CCS: 4 (18.6) Worsened CCS: 1 (4.5)	
Reference: Butter et al., 2014 (Stand-alone study; NR) Country: Multinational Study Design: Prospective nonrandomized single-arm study Purpose: To identify the efficacy and safety of WiSE CRT Conclusion: WICS-LV has provided CRT	Study population	Intervention: WiSE CRT Comparator: NA Length of follow-up: 12 months Patients (N): 13 Age, years, mean (SD): 66.7 (7.8) Sex, male, n (%): NR BMI, kg/m², mean (SD): NR Race, n (%): NR Indication, n (%): NR	LVEF at 12 months, %, mean (SD): 33.2 (7.8) Reduction in LVEF at 12 months, n (%): 1 (10.0) NYHA class at 12 months, mean (SD): 2.1 (0.6) NYHA class reduction of ≥ 1 class, n (%): 8 (80.0) NYHA class no change, n (%): 2 (20.0) QRSd with BiV pacing at 12 months, ms, mean (SD): 141.0 (43.0)	Complications, n (%): Death: 1 (7.7) High threshold: 2 (15.4)

Study Characteristics	Subgroup	Intervention(s) and Patient Characteristics	Outcomes	
successfully over 12 months in 10 pts, including 5 (50%) pts who could not have otherwise received CRT therapy due to failed implant attempt(s) or no response to conventional CRT therapy. Funding Source: NR Quality: Only conference abstract was available. No formal quality assessment was performed.		Comorbidities, n (%): NR NYHA class, n (%): NYHA class III: 13 (100.0) QRSd, ms, mean (SD): Intrinsic QRSd: 188.0 (32.0) LVEF, %, mean (SD): 24.6 (4.7) LVEDV, cm³, mean (SD): NR LVESV, cm³, mean (SD): NR		
Abbreviation: BiV: biventricular; BMI: body mass index; CCS: clinical composite score; CHF: congestive heart failure; COPD: chronic obstructive pulmonary disease; CRT: cardiac resynchronization therapy; CS: coronary sinus; CVA: cardiovascular accident; HF: heart failure; HRU: high risk upgrade; KCCQ: Kansas City Cardiomyopathy Questionnaire; LV: left ventricular; LVEDD: left ventricular end-diastolic diameter; LVEDV: left ventricular end-diastolic volume; LVEF: left ventricular ejection fraction; LVESV: left ventricular end-systolic volume; MI: myocardial infarction; NT-proBNP: N-Terminal Pro-Brain Natriuretic Peptide; NYHA: New York Heart Association; PAH: pulmonary arterial hypertension; PVD: peripheral vascular disease; Q-LV: Q-wave to left ventricular depolarization; QRSd: QRS duration; RCT: randomized controlled trial; RV: right ventricular; SD: standard deviation; SAE: serious adverse event; TAPSE: tricuspid annular plane systolic excursion; VF: ventricular fibrillation.				