Title: Leadless left ventricular endocardial pacing for CRT upgrades in previously failed and high-risk patients in comparison with coronary sinus CRT upgrades

Short Title: Epicardial versus coronary sinus upgrades

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What's New

- Patients undergoing cardiac resynchronization therapy (CRT) upgrades have additional co-morbidities that can increase the chance of non-response. Left ventricular endocardial pacing can be used in patients with previously failed CRT or high-risk upgrades.
- WiSE-CRT upgrades were successful in 97.1% of cases with procedure-related mortality in 1.9% and no acute strokes. There was 1 stroke during 6-month follow-up and 1 episode of sustained ventricular tachycardia.
- Coronary sinus upgrades were successful in 97.5% of cases with a 2.5% rate of coronary sinus dissection and 5.6% lead malfunction/ displacement.
- Endocardial and coronary sinus upgrades demonstrated similar improvements in clinical composite score (76.3 vs. 68.5%; $P = 0.210$) and reduction in left ventricular end-systolic volume ≥15% (54.2 vs. 56.3%; $P = 0.835$).
- These findings support the need for larger, randomized controlled trials with matched patient characteristics to determine whether endocardial pacing can lead to improved outcomes for CRT upgrades.

Abstract

Background: Cardiac resynchronization therapy (CRT) upgrades may be less likely to improve following intervention. Leadless left ventricular (LV) endocardial pacing has been used for patients with previously failed CRT or high-risk upgrades. We compared procedural and long-term outcomes in patients undergoing coronary sinus (CS) CRT upgrades with high-risk and previously failed CRT upgrades undergoing LV endocardial upgrades.

Method: Prospective consecutive CS upgrades between 2015 and 2019 were compared with those undergoing WiSE-CRT implantation. CRT response at 6-months was defined as improvement in clinical composite score (CCS) and a reduction in LV end-systolic volume (LVESV) ≥15%.

Results: 225 patients were analyzed; 121 CS and 104 endocardial upgrades. Patients receiving WiSE-CRT tended to have more comorbidities and were more likely to have previous cardiac surgery (30.9 vs. 16.5%; P=0.012), hypertension (59.2 vs. 34.7%; P<0.001), chronic obstructive airways disease (19.4 vs. 9.9%; P=0.046) and chronic kidney disease (46.4 vs. 21.5%; P<0.01) but similar LV ejection fraction (30.0±8.3%; vs. 29.5±8.6%; P=0.678). WiSE-CRT upgrades were successful in 97.1% with procedure-related mortality in 1.9%. CS upgrades were successful in 97.5% of cases with a 2.5% rate of coronary sinus dissection and 5.6% lead malfunction/ displacement. At 6 months, 91 WiSE-CRT upgrades and 107 CS upgrades had similar improvements in CCS (76.3 vs. 68.5%; P=0.210) and reduction in LVESV ≥15% (54.2 vs. 56.3%; P=0.835).

Conclusion: Despite prior failed upgrades and high-risk patients with more co-morbidities, WiSE-CRT upgrades had high rates of procedural success and similar improvements in CCS and LV remodeling with CS upgrades.

Keywords: Cardiac resynchronization therapy; Endocardial pacing, Epicardial pacing; WiSE-CRT system

Introduction

Cardiac resynchronization therapy (CRT) is an important intervention in symptomatic patients with severe left ventricular systolic impairment,(1) with CRT upgrades accounting for 28% of all implantations.(2) Patients undergoing CRT upgrades often suffer from additional co-morbidities compared to de novo implantations and may respond differently.(3, 4) Conventional CRT upgrades with epicardial left ventricular (LV) lead placement in the coronary sinus (CS) can be complicated by central venous occlusion that may require lead extraction or venoplasty to complete procedures, with additional associated risks.(5, 6) CS upgrade procedures can also be complicated by damage or displacement to previously implanted leads, leading to re-intervention with an increased risk of infection. Endocardial pacing may overcome many of these limitations allowing access to faster endocardial conduction and optimal pacing site selection avoiding myocardial scar and targeting areas of latest electrical or mechanical activation.(7, 8) Endocardial pacing has been shown to improve both left and right ventricular function.(9) The WiSE-CRT system (EBR systems, USA) is capable of providing leadless LV endocardial pacing to achieve CRT. It consists of 3 separate components: a subcutaneous transmitter connected only to a subcutaneous battery and a leadless electrode within the left ventricle. Patients must have a co-implant in-situ capable of providing continuous right ventricular pacing. Studies have demonstrated reliable biventricular pacing, resulting in improved patient symptoms and LV remodeling albeit with a risk of procedural-related major complications.(10-13) Currently, eligibility for the WiSE-CRT system mandates patients meet additional inclusion criteria than for CS pacing that may result in a sicker patient cohort. We set out to compare procedural and long-term outcomes in patients undergoing CS CRT upgrades with patients with previously failed CRT or high-risk CRT upgrades receiving endocardial CRT upgrades with the WiSE-CRT system.

Methods

Study design

The study was approved by the Health Research Authority (20/HRA/0885). A prospective registry of patients undergoing both CS and endocardial CRT upgrades between 2015 to 2019 was collated. Patients were eligible to participate if they had a standard indication for CRT upgrade.(14) In addition, patients undergoing WiSE-CRT implantation must either have been previously untreatable or considered a high-risk upgrade. Patients who were previously untreatable included those with a failed or unsuccessful coronary sinus lead placement or whose LV lead was subsequently programmed off due to a high threshold, no LV capture, phrenic nerve stimulation, lead displacement or malfunction. High-risk upgrades included patients with a relative contraindication to coronary sinus lead implantation such as venous occlusion. Consecutive patients undergoing conventional CS CRT upgrades at Guy's and St Thomas' NHS Foundation Trust were compared with those who underwent CRT upgrade (excluding prior CRT non-responders) with the WiSE-CRT system in the WiCS-LV Post Market Surveillance Registry (Clinical study number NCT02610673). **A propensity score for the CS group was calculated by a logistic regression model using demographics that were significantly different at baseline. Endocardial upgrades were matched 1:1 with CS upgrades and this analysis is provided in the Supplementary File.**

CS *CRT upgrade procedure*

CS upgrades involved transvenous lead placement of a quadripolar LV lead in the lateral or posterolateral vein, wherever possible. Procedures were performed under sedation and local anesthesia. Biventricular pacing was confirmed at the end of procedures, with devices programmed to simultaneous ventricular activation and an atrio-ventricular delay of 100-

120ms. The pacing vector that resulted in the narrowest QRS duration without phrenic nerve stimulation was chosen.

WiSE-CRT procedure

Patients with previously failed CRT or "high-risk" CRT upgrades were included. Acoustic window screening was performed to identify suitable intercostal spaces that had no lung encroachment during maximal inspiration, with an angle between the ultrasound probe and basal LV posterolateral wall of <45°, distance <12cm and LV wall thickness ≥5mm. Implantations were performed in a dual or single-stage procedure with the latter involving implantation of the transmitter, battery and receiver electrode during the same procedure. The transmitter and battery were initially implanted first to ensure the final electrode location could be tracked by the transmitter. Based on the optimal intercostal space identified during acoustic window screening, the transmitter was placed on the internal intercostal muscle and secured to the costal cartilage. Ultrasound screening intra-procedurally confirmed an adequate window and the battery was placed in the left mid-axillary line. The electrode was implanted using a retrograde aortic or transeptal approach to the LV endocardium. Intra-procedural testing to confirm right ventricular tracking and biventricular pacing was undertaken. The system only allows for simultaneous ventricular activation. Patients were discharged on dual anti-platelet therapy or if already on anticoagulation then an anti-platelet drug was added for 3-months post intervention.

Endpoints

Procedural-related major complications were collected, and patients were assessed at 6-months to determine their response to CRT on the basis of the Clinical Composite Score (CCS) and LV remodeling as defined by transthoracic echocardiography. Patients were

considered to have improved if (A) they had an improvement in their clinical composite score (CCS) consisting of alive, no heart failure hospitalizations, improvement in New York Heart Association (NYHA) functional class or global patient assessment(15) and (B) reduction in LV end-systolic volume (LVESV) ≥15%. Patients were considered to have worsened their CCS if they had died, experienced a heart failure hospitalization, worsening of NYHA functional class or global patient assessment and were considered to stabilize their CCS if they were alive, no heart failure hospitalization and no change in NYHA functional class or global patient assessment.

Statistical Analysis

Discrete data is presented as *n* values (with corresponding percentages) and continuous data as mean ± one standard deviation for normally distributed variables and median (interquartile range) for non-normally distributed variables. Discrete variables were compared using a X^2 or a Fisher's exact test if the expected cell count was less than five. The Shapiro-Wilk test was used to assess the normality of continuous data, with a *P*-value ≥ 0.05 considered normally distributed. Normally distributed data were compared with an independent t-test and non-normally distributed data with a Wilcoxon signed-rank test. A two-sided *P*-value of <0.05 was considered statistically significant. Statistical analyses were performed using Prism (GraphPad Software Inc., Version 9, CA) and SPSS (IBM Switzerland, Version 26, Switzerland).

Results

Overall, 225 patients undergoing CRT upgrade were included; 121 CS and 104 endocardial upgrades of which 65 were previously untreatable and 39 high-risk upgrades. In previously untreatable patients, 38 were due to failure of LV lead placement and 28 were due to the LV

lead being programmed off. Baseline patient demographics are described in *Table 1*. CS and endocardial upgrades were matched in terms of baseline demographics and co-morbidities including age (70.9 ± 11.7 vs. 69.1 ± 10.2 years; $P = 0.110$), male gender (80.2 vs. 78.9%; $P = 0.807$), ischemic aetiology (44.6 vs. 38.5%; $P = 0.350$), atrial fibrillation (57.9 vs. 59.6%; $P = 0.789$), diabetes mellitus (27.3 vs. 24.5; $P = 0.641$) and LV ejection fraction (29.5 ± 8.6 vs. 30.0 ± 8.3%; $P = 0.678$). Endocardial upgrades tended to have more co-morbidities and were more likely to have a history of previous cardiac surgery (30.9 vs. 16.5%; $P = 0.012$), hypertension (59.2 vs. 34.7%; $P < 0.001$), chronic obstructive airways disease (19.4 vs. 9.9%; $P = 0.046$) and chronic kidney disease (46.4 vs. 21.5%; $P <0.001$).

Procedural outcomes

CS CRT upgrades were successful in 118/121 (97.5%) patients. In 3 patients the upgrade procedure was unsuccessful due to subclavian vein occlusion, coronary sinus stenosis preventing LV lead implantation and failure of coronary sinus intubation due to an acute angle. There was evidence of subclavian vein stenosis at the entry site of the previous pacing leads in 14/121 (11.6%) patients that was overcome with either a medial puncture or a Terumo Glidewire®. In one patient the right ventricular lead was damaged requiring an extra lead to be implanted. Additionally, 3/121 (2.5%) patients suffered a coronary sinus dissection, which were all managed conservatively without pericardial drainage. There were no acute procedure related deaths, pericardial tamponades or pneumothoraxes. One patient developed vegetations on their pacing leads at 5-months and died from sepsis despite system extraction. This patient did not undergo any other recent device interventions prior to the upgrade procedure and therefore their death is likely a complication of the upgrade procedure itself. Endocardial upgrades with the WiSE-CRT system were successful in 101/104 (97.1%) patients with biventricular pacing confirmed on a 12-lead ECG post implantation. There was

inconsistent LV capture in 3 patients; 1 due to lead placed in myocardial scar, 1 had a displaced transmitter requiring revision which improved capture and 1 had inadequate capture despite transmitter revision. There were 2 (1.9%) procedure related deaths; 1 death occurred suddenly four days post procedure and a post-mortem revealed cardiac tamponade secondary to LV perforation and 1 patient presented to hospital 30 days post-procedure with septicemia which was likely procedure-related. There were no acute cerebrovascular events.

Six-month follow-up

Standard CS upgrades

One hundred and seven of 118 successfully implanted patients underwent assessment at 6-month follow-up. Four (3.3%) patients died within 6 months of implant, 5 were lost to follow-up, 1 had a displaced LV lead and 1 had phrenic nerve stimulation in the only possible pacing vector. In the patients that died, 3 died from progressive heart failure and 1 patient suffered a device related infection at 5-months requiring transvenous lead extraction and died from septicemia. In addition, 6 (5.6%) patients suffered lead malfunction or displacement in the follow-up period (2 right atrial leads, 1 right ventricular lead and 3 LV leads) with successful revision in 5 patients. At 6-month follow-up there was a significant improvement in NYHA functional class (2.7 ± 0.7 vs. 1.9 ± 0.8; P <0.001), a reduction in QRS duration (171.5 ± 30.6 vs. 151.8 ± 30.0ms; P = 0.006), improvement in LV ejection fraction (30.0 ± 8.4 vs. 40.1 ± 12.1%; P <0.001), reduction in LV end-diastolic volume (186.8 ± 55.0 vs. 166.5 ± 52.4cm^3; P < 0.001) and LVESV (129.1 ± 46.2 vs. 106.3 ± 49.3cm^3; P < 0.001) (*Table 2 and Figure 1*). Overall, 7 patients were admitted to hospital with decompensated heart failure, 68.5% showed an improvement in their CCS, 18.0% stabilized their CCS, 13.5% had worsening of their CCS and 56.3% displayed a reduction in LVESV ≥15%.

Endocardial upgrade follow-up

Ninety-one of 104 patients had 6-month follow-up. 3 patients had inconsistent LV capture and 4 were lost to follow-up. Six (5.7%) patients died within 6-months: 2 suffered procedure related deaths, 1 died at 3 months from incessant ventricular tachycardia, 1 died from an intracerebral hemorrhage at 2-months, one day after a ventricular tachycardia ablation whose arrhythmia pre-dated the WiSE-CRT implant and 2 from non-cardiac related deaths. There were no other ventricular arrhythmias or ventricular high rates reported during the follow-up period and one patient suffered a stroke 5-months post intervention. At 6-months follow-up, there was a significant reduction in NYHA functional class (2.6 ± 0.5 vs. 2.1 ± 0.6; *P* <0.001), reduction in QRS duration (181.1.5 ± 28.1 vs. 137.4 ± 28.2ms; *P* < 0.001), improvement in LV ejection fraction (30.8 ± 7.9 vs. 36.7 ± 10.4%; *P* <0.001), reduction in LV end-diastolic volume (187.1 ± 84.8 vs. 164.1 ± 75.3cm^3; *P* < 0.001) and LVESV (131.7 ± 68.1 vs. 108.8 ± 65.3cm^3; *P* < 0.001) (*Table 2 and Figure 2*). Overall, 2 patients were admitted to hospital with decompensated heart failure, 76.3% showed an improvement in their CCS, 12.4% stabilized their CCS, 11.3% had worsening of their CCS and 54.2% displayed a reduction in LVESV ≥15%. Sub-group analysis of patients who were previously untreatable or considered high-risk (*Table 2*) demonstrates a significant improvement in clinical response and LV remodeling with the WiSE-CRT system.

Comparison of CS *and endocardial upgrades*

The outcomes of patients proceeding to follow-up were compared; 107 CS and 91 endocardial upgrades (*Table 3*). Patients with endocardial upgrades had a greater absolute reduction in QRS duration (-43.7 ± 31.6 vs. -19.7 ± 35.9ms; *P* = 0.002). They both had a similar absolute reduction in LV end-diastolic volume (23.0 ± 42.2 vs. 20.3 ± 37.6cm^3; *P* = 0.736) and LVESV (-22.9 ± 35.5 vs. -22.7 ± 34.9cm^3; *P* = 0.807) but less likely to have an

absolute change in LV ejection fraction (5.9 ± 8.9 vs. 10.1 ± 10.2%; *P* = 0.008). They had similar improvements in CCS (76.3 vs. 68.5%; *P* = 0.210) and reduction in LVESV ≥15% (54.2 vs. 56.3%; *P* = 0.835). Ischemic patients undergoing endocardial and CS upgrades demonstrated similar improvements in CCS (79.0 vs. 66.0%; *P* = 0.182) and reduction in LVESV ≥15% (58.3 vs. 36.4%; *P* = 0.136). **A propensity score showed patients undergoing endocardial and CS upgrades had similar improvements in CCS (72.7 vs 70.8%; *P* = 0.804) and reduction in LVESV ≥15% (51.3 vs. 63.6%; *P* = 0.295) (Supplementary file).**

Sub-group analysis of patients previously untreatable who underwent endocardial upgrades compared with CS upgrades showed similar improvements in CCS (78.0 vs. 68.5%; *P* = 0.192) and reduction in LVESV ≥15% (39.4 vs. 56.3%; *P* = 0.138). Similarly, high-risk patients who underwent endocardial upgrades compared with CS upgrades showed similar improvement in CCS (73.7 vs. 68.5%; *P* = 0.547) and reduction in LVESV ≥15% (73.1 vs. 56.3%; *P* =0.157).

Discussion

We compared the outcomes of patients with previously failed or high-risk CRT upgrades undergoing WiSE-CRT implantation with patients undergoing standard CRT upgrades. The predominant findings were:

1. CS upgrades were successful in 97.5% of cases, with evidence of a significant venous stenosis in 11.6% and no procedure related mortality but 4.6% required re-intervention for lead malfunction/ displacement. Patients displayed significant improvement in clinical and echocardiographic outcomes following CRT.

2. Endocardial upgrades were performed in patients with more co-morbidities and were successful in 97.1% of cases with 1.9% procedure-related mortality. There were no acute stroke and during the follow-up period, 1 patient suffered a stroke and 1 patient a ventricular arrhythmia. Patients displayed significant improvement in clinical and echocardiographic outcomes following intervention.
3. Patients undergoing CS and endocardial upgrades had similar improvements in their CCS and reduction in LVESV ≥15%. CS upgrades were more likely to have an absolute change in LV ejection fraction.
4. **There was a higher burden of co-morbidities in the endocardial group, reflecting real world CRT practice(16), but the propensity matched score indicated these benefits persisted in this high-risk group.**

Comparison with previous studies

A direct comparison of CS and endocardial upgrades has not been previously investigated, to the best of our knowledge, but each intervention have been studied separately. Several trials have reported outcomes following CS upgrades.(2, 3, 17) In a European CRT Survey involving 692 upgrade procedures in 141 centres, they found 73% of patients improved their global assessment at 1 year.(2) Significant procedure related complications included 0.3% rate of cardiac tamponade, 1.7% coronary sinus dissection and 3.2% experienced a lead displacement. A prospectively collected multicenter study of 177 upgrade procedures found 57% of patients improved their NYHA functional status and overall, there was a mean improvement in LV ejection fraction of 2.9 ± 9%.(18) In the current study of 121 CS upgrade procedures, we found similar rates of coronary sinus dissection (2.5%) and lead malfunction / displacement (5.6%) but significantly better rates of clinical and echocardiographic response. Endocardial pacing using lead-based technology was investigated in a multicenter study of

138 patients.(19) The inclusion criteria was similar to the present study and also included patients who were non-responders to conventional CRT. They found a success rate of 89.4%, with 6.8% experiencing transient ischaemic attacks and 3.8% non-disabling strokes. At follow-up, 59% improved their NYHA functional class and 55% had a reduction in LVESV ≥15%. The position of the LV lead could only be fixated to the desired location in 81% of implants, arguably the greatest potential benefit of endocardial pacing. The current study compares favorably with these results since we have shown higher success rates and comparable clinical and echocardiographic improvements.

Clinical perspective

Currently, patients undergoing WiSE-CRT implantation have relatively few alternative options to achieve resynchronization, evidenced by the inclusion criteria for the device. These patients may represent a higher risk group with more co-morbidities than those felt suitable for conventional CS upgrades. Supportively, in the current study endocardial upgrade patients were significantly more likely to have had previous cardiac surgery, hypertension, and chronic kidney disease. Despite these additional co-morbidities these patients had similar improvements in CCS and reduction in LVESV ≥15% compared with CS pacing. Furthermore, 88.7% of endocardial upgrades had improvement or stabilization of their CCS which has important prognostic implications.(20) Indeed, high-risk upgrades unlike previously untreatable patients have never received resynchronization therapy and in these patients, there was a non-significant trend towards improved clinical response and LV remodeling compared with standard upgrades. Additionally, previously untreatable patients who received the WiSE-CRT system represent the highest-risk patient cohort but still had similar outcomes to CS pacing. A potential benefit of the WiSE-CRT system is the ability to pace anywhere inside the LV and provide targeted pacing, with guidance shown to improve

outcomes.(7, 8) The current study showed ischemic patients undergoing upgrades had similar improvements in CCS and LV remodeling, although there was a non-significant trend favoring endocardial pacing. This study was not powered to detect a significant difference in outcomes of ischemic patients, but endocardial pacing may potentially be more beneficial due to site specific pacing. Randomized controlled trials of matched patients undergoing each intervention will be important to further investigate outcomes and determine whether ischaemic patients are more likely to benefit with endocardial pacing. In addition, conduction system pacing may be beneficial in patients who fail conventional CRT upgrades and left bundle branch area pacing may be possible with the WiSE-CRT system. Randomized controlled trials are needed to determine whether endocardial pacing with the WiSE-CRT system or conduction system pacing may prove to be more beneficial than conventional upgrades.

Limitations

This study is subject to the same limitations as any prospectively collected data, although data collection was standardized to reduce bias. There is inclusion bias as patients undergoing WiSE-CRT implantation had either failed prior CRT upgrades or were felt to be high-risk. We did not perform a matched analysis as this would have resulted in a smaller study size which may potentially have led to bias and inaccurate results. However, both groups were matched in terms of important baseline demographics including age, sex, aetiology, atrial fibrillation, LV ejection fraction, LV end-diastolic volume and LVESV. Biventricular pacing was estimated at 6 months from device interrogation but cannot be fully relied upon without attaching a Holter monitor for QRS morphology. The procedural duration was not

documented in all patients in both arms and this would have been important since the invasive nature of WiSE-CRT procedures may have prolonged interventions. Changes in optimal medical therapy or anti-arrhythmic treatment during the study was not recorded and this would have been important as it may have influenced LV remodeling. However, all patients must have been on optimal medical therapy prior to enrolment into the study and therefore we would not expect any significant medication changes during follow-up. **The right ventricular pacing burden was not collected during the study and this would have been important to determine the relative proportion of pacing induced cardiomyopathy.**

Conclusion

Patients currently indicated for WiSE-CRT upgrades are a complex patient cohort with multiple co-morbidities and may be less likely to respond to CRT with prior failed upgrade attempts or high-risk features precluding standard upgrade. Despite this WiSE-CRT upgrades showed a high rate of procedural success with 1.9% rate of procedure-related mortality and similar rate of improvements in CCS and reduction in LVESV ≥15% compared to patients undergoing CS upgrades. These findings support the need for larger, randomized controlled trials with matched patient characteristics to determine whether endocardial pacing can lead to improved outcomes for CRT upgrades.

Data availability

The data underlying this article cannot be shared publicly due to patient confidentiality.

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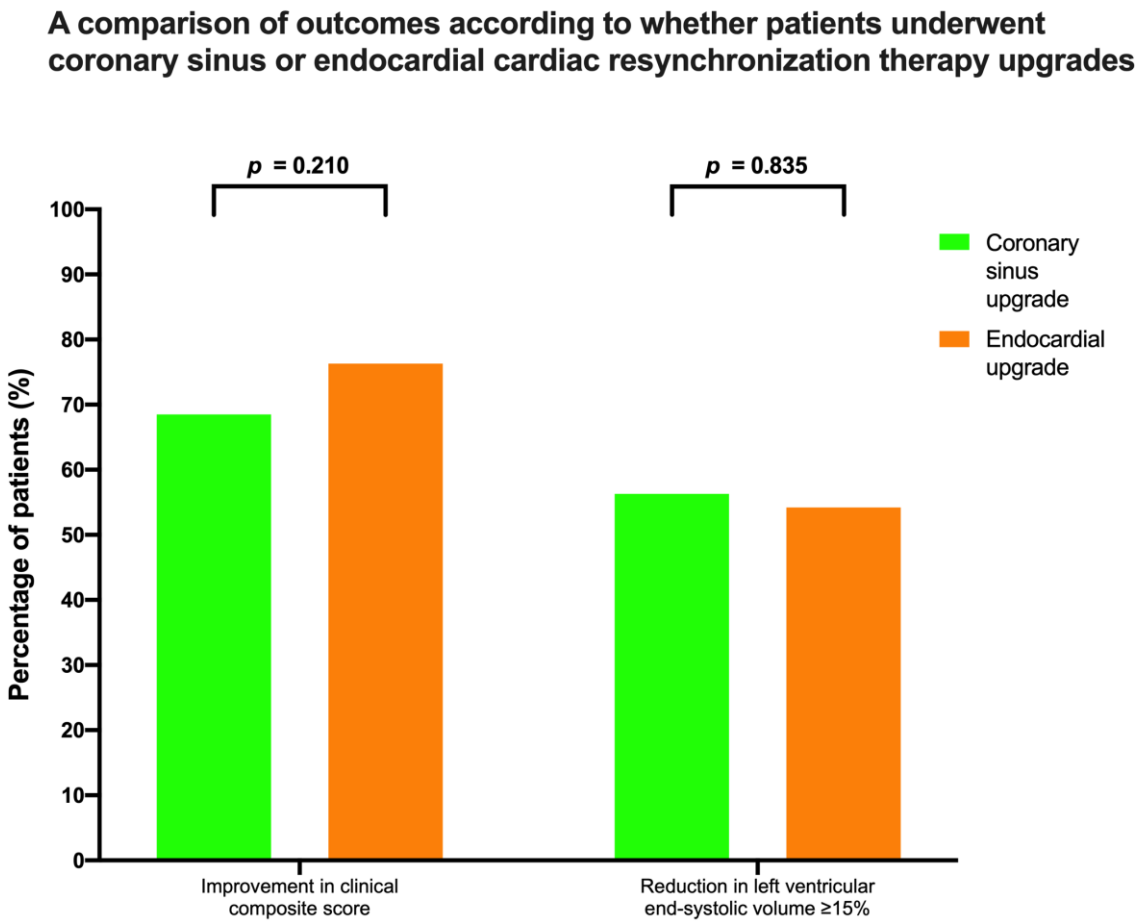
Figure legends

Figure 1. Box and whisker plots showing changes in QRS duration and left ventricular remodeling following **coronary sinus** cardiac resynchronization therapy upgrades

Figure 2. Box and whisker plots showing changes in QRS duration and left ventricular remodeling following endocardial cardiac resynchronization therapy upgrades with the WiSE-CRT system

496 **Summarizing illustration**



This graph demonstrates coronay sinus and endocardial cardiac resynchronization therapy upgrades had similar improvements in clinical composite scores and left ventricular remodeling.

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One-sentence summary

Despite prior failed upgrades and high-risk patients with more co-morbidities, WiSE-CRT upgrades had similar improvements in clinical composite score and left ventricular remodeling with conventional CRT upgrades

Declaration of Helsinki

This study complies with the Declaration of Helsinki and locally appointed ethics committees have approved the research.