

# True bipolar or extended bipolar left ventricular pacing is associated with better survival in cardiac resynchronization therapy patients

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## Abstract

**Background:** Limited studies are available on the clinical significance of left ventricular (LV) lead polarity in patients undergoing cardiac resynchronization therapy (CRT), with a recent study suggesting better outcomes with LV true bipolar pacing.

**Objective:** We aimed to determine whether true bipolar LV pacing is associated with reduced mortality in a large, real-life CRT cohort, followed by remote monitoring.

**Methods:** We analyzed de-identified device data from CRT patients followed by the Boston Scientific LATITUDE remote monitoring database system. Patients with LV bipolar leads paced between the LV ring and LV tip were identified as true bipolar and those with LV bipolar leads paced between LV tip or LV ring and right ventricular (RV) coil were identified as extended bipolar. Patients with unipolar leads were identified as unipolar.

**Results:** Of the 59 046 patients included in the study, 2927 had unipolar pacing, 34 390 had extended bipolar pacing, and 21 729 had true bipolar pacing. LV true bipolar pacing was associated with a significant 30% lower risk of all-cause mortality as compared to unipolar pacing (hazards ratio [HR] = 0.70, 95% CI: 0.62-0.79,  $P < .001$ ), after adjustment for age, gender, LV lead impedance, LV pacing threshold, and BIV pacing percentage  $<95\%$ . Extended bipolar LV pacing was also associated with 24% lower risk of all-cause mortality when compared to unipolar LV pacing (HR = 0.76, 95% CI: 0.68-0.85;  $P < .001$ ). However, there were no differences in outcomes between true bipolar and extended bipolar LV pacing (HR = 0.97, 95% CI: 0.93-1.01;  $P = .198$ ).

**Conclusion:** True bipolar or extended bipolar LV pacing is associated with a lower risk of mortality in CRT patients as compared to unipolar LV pacing.

## KEYWORDS

biventricular pacing, cardiac resynchronization, death, pacing polarity

## 1 | INTRODUCTION

Cardiac resynchronization therapy (CRT) is the standard of care treatment for the management of advanced heart failure (HF) patients with severely reduced left ventricular (LV) function and a wide ventricular depolarization (QRS).<sup>1-4</sup> Optimized delivery of CRT is linked to significant LV reverse remodeling, improvement in cardiac function, and output.<sup>5</sup> Successful delivery of CRT is, however, dependent on multiple

factors, including LV lead location, scar location and extent, and device programming, including modifiable parameters.

LV lead pacing polarity is a poorly studied, modifiable parameter in CRT devices that might impact clinical outcomes. In a recent sub-study of the multicenter automatic defibrillator implantation trial-cardiac resynchronization therapy (MADIT-CRT),<sup>6</sup> we demonstrated that LBBB patients undergoing CRT with mild HF had a significantly lower risk of all-cause mortality with bipolar LV pacing compared

to unipolar pacing. We suspect our finding is secondary to a more homogenous activation of the left ventricle and reduction in mechanical dyssynchrony by bipolar LV pacing. While these data from our subgroup analysis are hypothesis generating and promising, further testing in a large, real-life cohort is warranted to validate our findings. The ALTITUDE registry is one of the largest remote monitoring databases providing real-life data on a large cohort of implantable cardioverter defibrillator (ICD) and cardiac resynchronization therapy with defibrillator (CRT-D) patients and capturing LV lead pacing polarity (Boston Scientific Corp, Natick, MA).

Given the clinical significance of this easily modifiable parameter and paucity of data on associated cardiovascular outcomes, we aimed to further study LV lead pacing polarity in a larger patient population. This study was designed to assess the association of LV lead pacing polarity and all-cause mortality in a large cohort of CRT-D patients participating in the Boston Scientific LATITUDE database.

## 2 | METHODS

### 2.1 | Study population

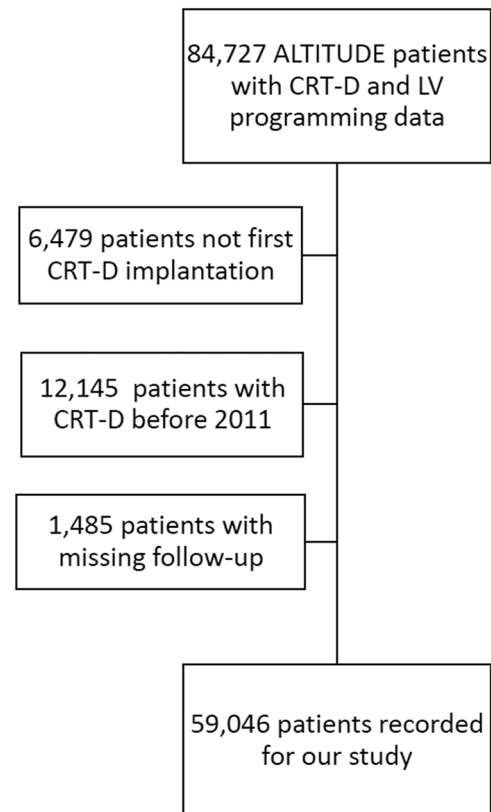
The ALTITUDE registry was established in 2008 to prospectively analyze data from ICD and CRT-D devices followed through the LATITUDE clinical remote monitoring system (Boston Scientific Corp). LATITUDE earned U.S. Food and Drug Administration approval in 2005, and since 2006, all new Boston Scientific ICD and CRT-D implants have been eligible for enrollment in this remote follow-up network. The remote interrogations may be patient initiated or performed automatically by wireless telemetry. Data are then transferred by telephone line and are accessible for routine clinical care through a secure website administered by Boston Scientific. The decision to enroll a patient in the remote follow-up system is made by the implanting physician at the time of device implantation or at routine postimplantation follow-up clinic visits.

De-identified data from the LATITUDE network form the data set for ALTITUDE studies. Investigator-initiated proposals to ALTITUDE are reviewed by an independent physician panel and projects with scientific merit are supported. Several previous studies have successfully queried the ALTITUDE database to assess arrhythmic events and survival.<sup>7-10</sup>

Patients enrolled in the LATITUDE system were eligible in this study if they had been implanted with a first CRT-D device, and they had information available on LV lead pacing polarity. Patients with not first CRT-D implant, those implanted before 2011, and those with missing follow-up were excluded from the current analysis (Figure 1). Therefore, we included de-identified device data from 59 046 HF patients with an radiofrequency (RF)-enabled CRT-D device.

### 2.2 | Device programming

Data reported in this study reflect the programming at the time of implantation. LV lead selection and LV lead pacing polarity programming were left to the discretion of the implanting physician.



**FIGURE 1** Study flowchart

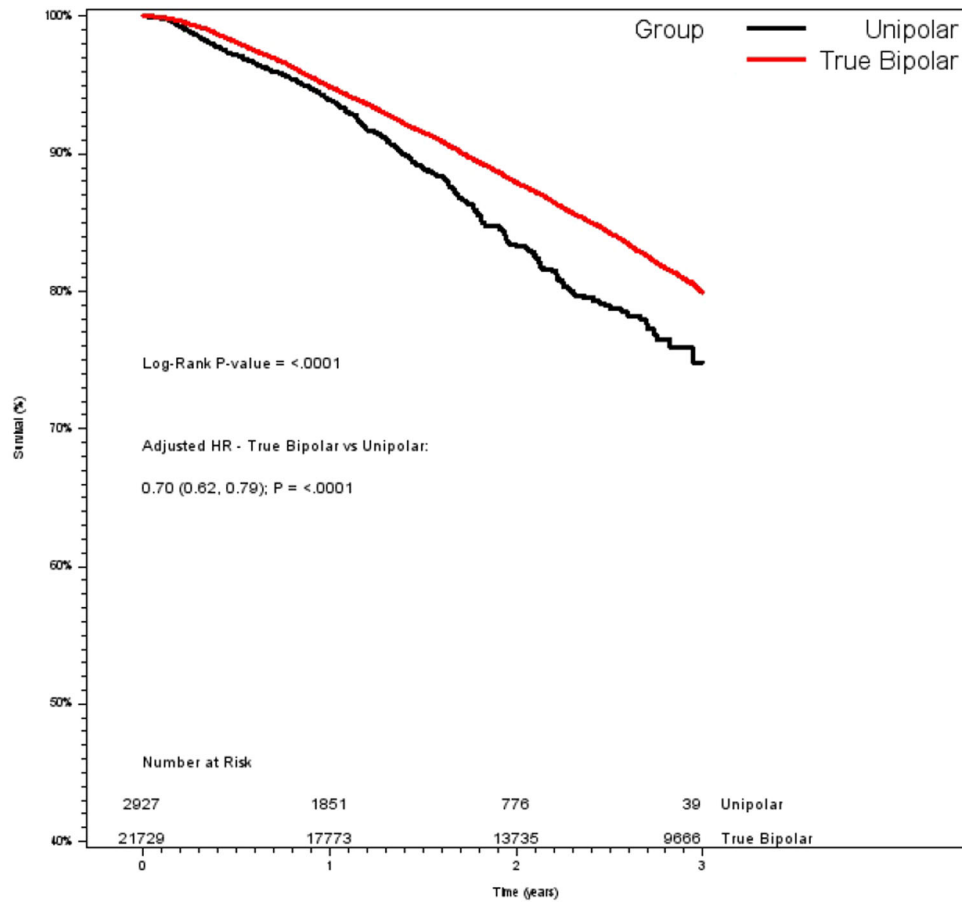
### 2.3 | Definitions, follow-up, and end points

LV pacing polarity was determined based on enrollment data collected by the LATITUDE System. Patients with LV bipolar leads paced between LV ring and LV tip were identified as true bipolar. Patients with LV bipolar leads programmed to pace between LV tip or LV ring and RV coil were identified as extended bipolar. Unipolar LV lead pacing was assessed as a separate subgroup. All-cause mortality was the primary end point of this study. De-identified patient clinical status, including death, was collected by Boston Scientific. Mean follow-up duration was  $3.3 \pm 1.6$  years.

### 2.4 | Statistical analysis

Available baseline clinical demographics, as appropriate, were compared between true bipolar, extended bipolar, and unipolar patients using analysis of variance (ANOVA) for continuous variables and  $\chi^2$  test for dichotomous variables. Kaplan-Meier method was used to demonstrate the cumulative probability of all-cause mortality by baseline LV lead pacing polarity. The log-rank test was used to compare respective cumulative rates.

Multivariate Cox proportional hazards regression analysis was used and adjusted for relevant clinical covariates. All statistical tests were two-sided, and a *P*-value of  $<.05$  was considered statistically significant. Analyses were carried out with the SAS software, version 9.3 (SAS Institute, Cary, NC).



**FIGURE 2** Cumulative probability of all-cause mortality in CRT-D patients with true bipolar versus unipolar pacing [Color figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]

**TABLE 1** Baseline clinical characteristics of patients enrolled in the LATITUDE database included in this study

Clinical characteristics	Unipolar	Extended bipolar	True bipolar
Number of patients	2927	34 390	21 729
Age at enrollment (years)	73.8 ± 11.1	75.2 ± 10.9	74.4 ± 11.5*
Female, n (%)	873 (29.8)	10 053 (29.2)	5788 (26.6)*
LV lead impedance (Ω)	603 ± 191	584 ± 192	868 ± 267*
LV lead intrinsic amplitude (V)	12.7 ± 6.1	12.4 ± 6.5	13.4 ± 6.9
LV pacing threshold (V)	1.5 ± 1.2	1.5 ± 1.2	1.3 ± 0.9*
LV pacing pulse width (ms)	0.81 ± 0.45	0.72 ± 0.40	0.62 ± 0.32*
BIV pacing <95% (%)	19.5	23.2	24.3*

Abbreviations: BIV, biventricular pacing; LV, left ventricular.

\* $P < .05$  for comparison between true bipolar versus unipolar versus extended bipolar LV pacing.

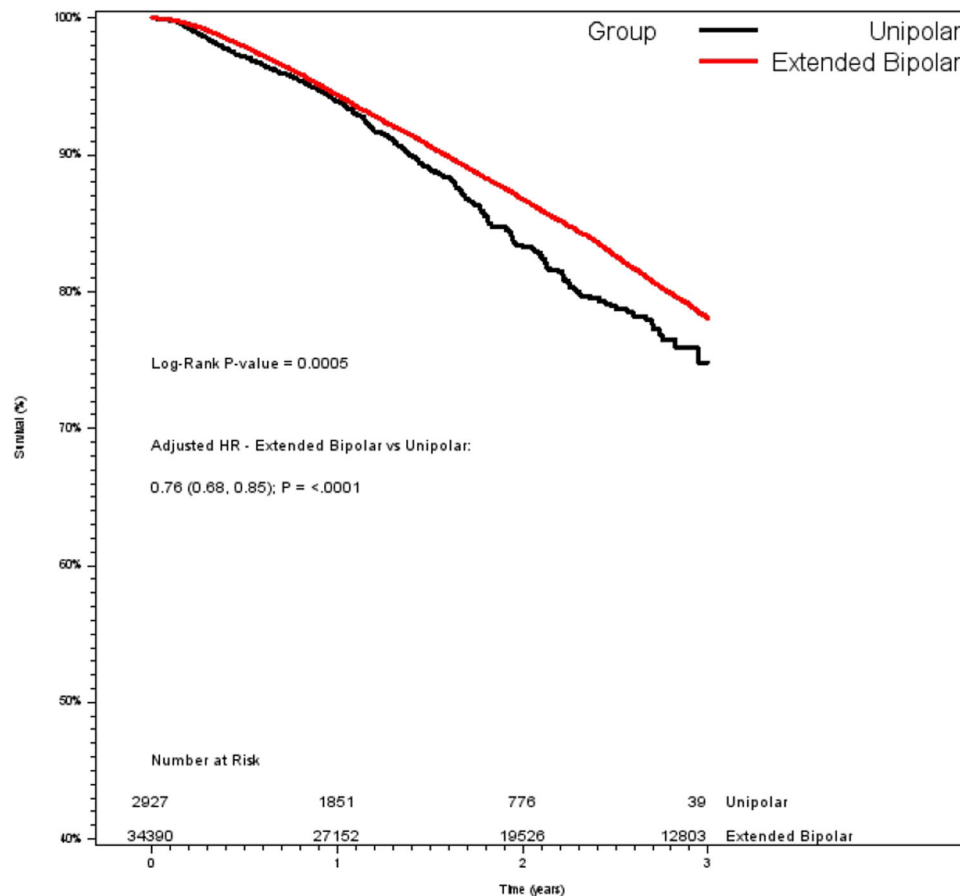
\*\*These data were collected at the first data upload at an average of 33 weeks after implant.

### 3 | RESULTS

#### 3.1 | Clinical characteristics of patients

More than half of the patients (58%) enrolled in this study had extended bipolar LV pacing (34 390), while 37% of the patients were true bipolar paced (21 729), and only 5% had unipolar LV pacing (2927). True bipolar LV paced patients were interestingly less likely

females (26.6% vs 29.8% vs 29.2%), and they had a lower LV pacing threshold (1.3 V vs 1.5 V vs 1.5 V), at a shorter pulse width, and a higher LV lead impedance (868 Ω vs 584 Ω vs 603 Ω) than patients with extended bipolar or unipolar LV pacing. In addition, patients with true bipolar LV pacing were more likely to have less than 95% biventricular pacing (24.3% vs 23.2% vs 19.5%), as compared to patients with extended bipolar LV pacing and unipolar LV pacing (Table 1).



**FIGURE 3** Cumulative probability of all-cause mortality in CRT-D patients with extended bipolar versus unipolar pacing [Color figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]

### 3.2 | Risk of mortality with true bipolar LV pacing versus unipolar LV pacing

Patients with true bipolar LV pacing had a significantly lower cumulative probability of all-cause mortality as compared to patients with unipolar LV pacing ( $P < .0001$ , Figure 2). It is relevant to note that the difference emerges after 1 year of follow-up. Multivariate Cox proportional hazards regression model after adjustment for age, gender, LV lead impedance, LV pacing threshold, and BIV pacing  $<95\%$  showed that LV true bipolar pacing was associated with a significant 28% reduction in all-cause mortality when compared to unipolar LV pacing (HR = 0.72, 95% CI: 0.62-0.79,  $P < .001$ ) (Table 2).

### 3.3 | Risk of mortality with extended bipolar LV pacing versus unipolar LV pacing

Similarly, CRT-D patients with extended bipolar LV pacing had a significantly lower cumulative probability of all-cause mortality compared to unipolar LV paced patients ( $P = .0005$ , Figure 3). Similarly, this difference emerges after 1 year of follow-up. After adjustment for age, gender, LV lead impedance, LV pacing threshold, and BIV pacing  $<95\%$ , extended bipolar LV pacing was associated with a 24% lower mortality

**TABLE 2** Multivariate analysis of all-cause mortality by pacing polarity

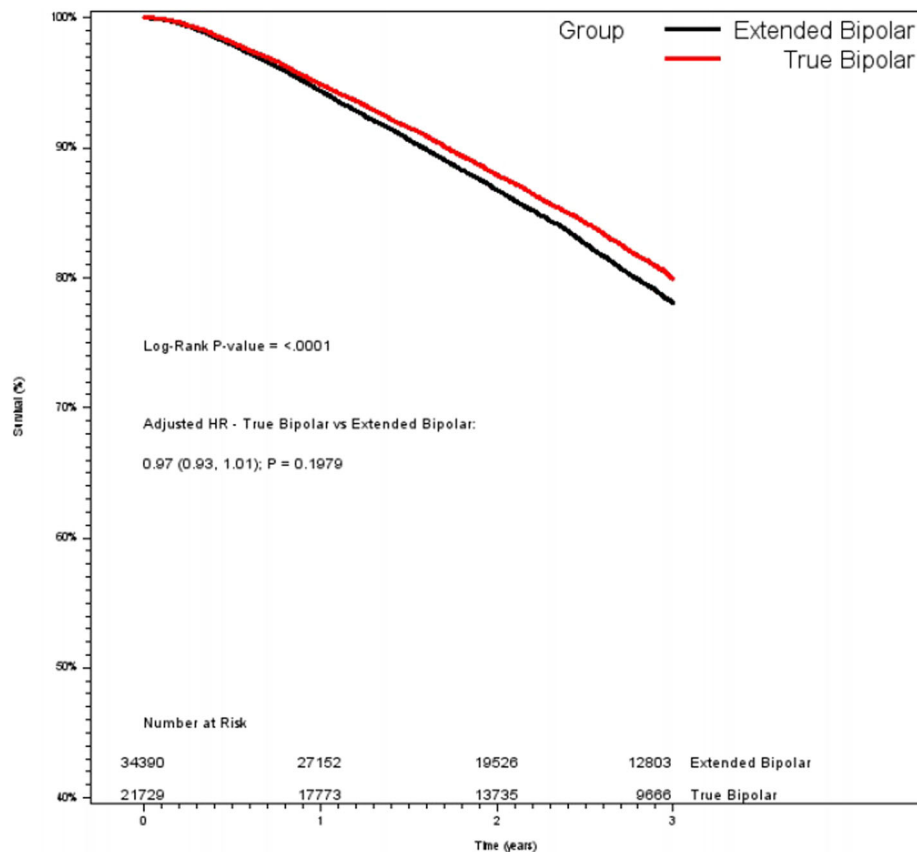
	All-cause mortality		
	HR	95% CI	P-value
True bipolar vs unipolar	0.72	0.62-0.79	$<.001$
Extended bipolar vs unipolar	0.76	0.68-0.85	$<.001$
True bipolar vs extended bipolar	0.97	0.93-1.01	.198

Abbreviations: 95% CI, 95% confidence interval; HR, hazard ratio. Models were adjusted for the following covariates: age, gender, LV lead impedance, LV pacing threshold, and BIV pacing percentage  $<95\%$ .

when compared to LV unipolar pacing (HR = 0.76, 95% CI: 0.68-0.85;  $P < .001$ ) (Table 2).

### 3.4 | Risk of mortality with true bipolar LV pacing versus extended bipolar LV pacing

Interestingly, we found no differences in the risk of all-cause mortality between true bipolar and extended bipolar LV paced patients (Figure 4), even after adjustment for age, gender, LV lead impedance, LV pacing threshold, and BIV pacing percentage less than 95% (HR = 0.97, 95% CI: 0.93-1.01;  $P = .198$ ) (Table 2).



**FIGURE 4** Cumulative probability of all-cause mortality in CRT-D patients with true bipolar versus extended bipolar pacing [Color figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]

## 4 | DISCUSSION

In our study, we demonstrate that in a large cohort of real-life CRT-D patients enrolled in the LATITUDE database, both true bipolar and extended bipolar LV pacing were associated with a significantly lower risk of all-cause mortality when compared to patients with unipolar LV pacing. Unipolar LV pacing was infrequent (5%), and patients with unipolar LV pacing presented with a higher LV pacing threshold and lower LV lead impedance. Altogether, these findings indicate that true bipolar or extended bipolar LV pacing is linked to better outcomes in CRT-D than unipolar LV pacing, and unipolar LV pacing should be avoided whenever possible.

The selection of LV lead size and polarity is typically made at the time of CRT implantation, and it is dependent on physician preference, native coronary sinus anatomy, reducing the incidence of diaphragmatic stimulation, or avoiding high pacing threshold. Clinician preferences also play a significant role, and local practice patterns can at times dictate lead selection. Importantly, once programmed at implantation, reprogramming is rarely done.

A small prior study had recently demonstrated that ventricular activation sequence of the left ventricle is dependent on pacing polarity.<sup>11</sup> In addition, we have also demonstrated in a MADIT-CRT substudy that CRT-D patients with true bipolar LV lead pacing polarity have a significantly lower risk of all-cause mortality and HF/death as com-

pared to those with unipolar and extended bipolar LV pacing.<sup>12</sup> However, MADIT-CRT was a randomized clinical trial conducted in mild HF patients, and therefore, these findings cannot be fully generalized to the overall CRT-D population. Therefore, our current study further extends previous findings by demonstrating in a very large CRT-D cohort, presumptively including both mild and advanced HF patients, that true or extended bipolar LV pacing is associated with a lower mortality risk when compared to unipolar LV pacing. This has significant relevance for clinical practice, suggesting that LV unipolar pacing should be avoided whenever possible.

When would we typically use LV unipolar pacing? Unipolar LV pacing has been useful in cases with high LV pacing thresholds in an effort to improve battery longevity. However, high LV pacing threshold could be potentially present when the lead is implanted in a scar region in the context of CRT, as shown in a previous MADIT-CRT substudy.<sup>13</sup> In addition, pacing from scar regions in CRT-D patients has been linked to worse clinical outcomes.<sup>14</sup> In addition, as our current study suggests, unipolar pacing is linked to worse survival, even when we adjust our models for LV pacing threshold. Therefore, bipolar LV pacing should be considered in such cases to improve outcomes, especially since newer devices have better device longevity even with higher pacing voltages.

How can we explain our current findings? As we previously suggested, LV bipolar pacing and extended bipolar pacing may result in

more homogenous activation of the left ventricle<sup>11</sup> and may result in less dyssynchrony. Improved dyssynchrony with CRT-D has been shown to be associated with better outcomes.<sup>15,16</sup> However, these prior findings on more homogenous LV activation have never been confirmed in a large cohort of CRT-D patients, like in our study. It might also be possible that the selection of LV unipolar pacing polarity is linked to other characteristics, such as scar in the selected LV lead area, and serves as a surrogate marker rather than representing a causal relationship. Such an association cannot be fully excluded in our current study, therefore, prospective, randomized studies would be useful to ascertain the effects of LV unipolar versus bipolar pacing in CRT-D patients.

We believe our findings have important clinical implications for the programming of LV pacing polarity in CRT-D patients. Our data from both MADIT-CRT and ALTITUDE serve a strong case for avoiding LV unipolar pacing in CRT-D patients whenever possible. By better programming of LV lead pacing polarity, patients may derive better outcomes from CRT-D.

Our current study has certain limitations. This is a post hoc analysis, LV lead pacing polarity programming was not randomized, and it could be influenced by patient characteristics and physician preferences. Due to the patient population and study design, we were unable to perform analysis by baseline QRS morphology. Therefore, this current study thus may include patients who derived less clinical benefit from CRT-D. Nevertheless, this is still one of the largest cohorts to date with data available on LV lead pacing polarity and outcomes.

## 5 | CONCLUSIONS

In a large cohort of CRT patients from the ALTITUDE study, true bipolar and extended bipolar LV pacing was associated with a significantly lower risk of all-cause mortality when compared to unipolar LV pacing. Programming true bipolar or extended bipolar LV lead pacing polarity could be favored over unipolar LV pacing in cardiac resynchronization therapy patients to improve outcomes whenever feasible.

## CONFLICT OF INTERESTS

Paul Jones, Scott Wehrenberg, and Kenneth Stein are employees of Boston Scientific, St. Paul, MN. Dr. Kutyifa received research grants from Boston Scientific, ZOLL, and Biotronik and consultation fees from ZOLL and Biotronik, unrelated to this specific analysis.

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