True Bipolar or Extended Bipolar Left Ventricular Pacing is Associated with Better Survival in Cardiac Resynchronization Therapy Patients

Valentina Kutyifa[1], MD, PhD, Sina Jame[2], MD, Paul J. Wang[3], MD, Dan Musat[4], MD, Paul Jones[5], MS, Scott Wehrenberg[5], MS, Kenneth Stein[5], MD

[1]University of Rochester Medical Center, Rochester, New York, [2]University of Michigan, Ann Arbor, Michigan,[3] Stanford University, Stanford, CA, [4]Valley Hospital, NJ, [5]Boston Scientific Inc.

Address for correspondence:

Valentina Kutyifa MD, PhD

University of Rochester Medical Center

265 Crittenden Blvd., Box 653

Rochester, NY 14642

Phone: 585-275-2676

Fax: 585-273-5283

E-mail: Valentina.Kutyifa@heart.rochester.edu

Short Title: CRT Unipolar vs. Bipolar Pacing

Word count: 2559 words

Conflict of Interest/Disclosures: 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.

ABSTRACT

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

Objectives: 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 to 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, 2,927 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 (HR=0.70, 95% CI: 0.62-0.79, p<0.001), 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<0.001). However, there were no differences in outcomes between True-Bipolar or Extended-Bipolar LV pacing (HR=0.97, 95% CI: 0.93-1.01; p=0.198).

Conclusion: True-Bipolar and Extended-Bipolar LV pacing is associated with a lower risk of mortality in cardiac resynchronization therapy patients as compared to Unipolar LV pacing.

Keywords: Pacing Polarity, Cardiac Resynchronization, Biventricular Pacing, Death

INTRODUCTION

Cardiac resynchronization (CRT) is the standard of care treatment for the management of advanced heart failure patients with severely reduced left ventricular function, and a wide QRS.[1-5] Optimized delivery of CRT is linked to significant left ventricular reverse remodeling, improvement in cardiac function, and output.[6] Successful delivery of CRT is however dependent on multiple factors, including left ventricular (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),[7] we demonstrated that mild heart failure (HF), LBBB patients undergoing CRT 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 are warranted to validate our findings. The ALTITUDE registry is one of the largest remote monitoring database providing real-life data on a large cohort of ICD and 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.

METHODS

Study Population

The ALTITUDE registry was established in 2008 to prospectively analyze data from ICD and cardiac resynchronization therapy (CRT-D) devices followed through the LATITUDE clinical remote monitoring system (Boston Scientific Corp, Natick, MA). 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 post-implantation 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.[8-11]

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 RF-enabled CRT-D device.

Device Programming

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

Definitions, Follow-up, and End Points

Left Ventricular pacing polarity was determined based on enrollment data collected by the LATTITUDE System. Patients with LV bipolar leads paced between LV-ring and LV-tip were identified as True-bipolar. Those 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 sub-group. 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 ± 1.6 years.

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 χ^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 <0.05 was considered statistically significant. Analyses were carried out with the SAS software, version 9.3 (SAS institute, Cary, North Carolina).

RESULTS

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 (2,927). 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 Ohm vs. 584 Ohm vs. 603 Ohm) 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).

Risk of Mortality with True-Bipolar LV Pacing vs. 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 ($p<0.0001$, Figure 2). It is relevant to note that the difference emerges after one 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, $p<0.001$) (Table 2).

Risk of Mortality with Extended-Bipolar LV Pacing vs. 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 ($p=0.0005$, Figure 3). Similarly, this difference emerges after one 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 when compared to LV unipolar pacing (HR=0.76, 95% CI: 0.68-0.85; p<0.001) (Table 2).

Risk of Mortality with True-Bipolar LV Pacing vs. 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=0.198) (Table 2).

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 or Extended-Bipolar LV pacing was 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.[12] In addition, we have also demonstrated in a MADIT-CRT sub-study, that CRT-D patients with True-Bipolar LV lead pacing polarity have a significantly lower risk of all-cause mortality and heart failure/death as compared to those with Unipolar and Extended-Bipolar LV pacing.[13] 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 left ventricular 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 sub-study.[14] In addition, pacing from scar regions in CRT-D patients has been linked to worse clinical outcomes.[15] 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 out current findings? As we previously suggested, LV bipolar pacing and extended bipolar pacing may results in more homogenous activation of the left ventricle,[12] and may result in less dyssynchrony. Improved dyssynchrony with CRT-D has

been shown to be associated with better outcomes.[16, 17] 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 vs. 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.

CONCLUSIONS

In a large cohort of cardiac resynchronization therapy 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.

REFERENCES

[1] Bristow MR, Saxon LA, Boehmer J, Krueger S, Kass DA, De Marco T, et al. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. *The New England journal of medicine* 2004; **350**: 2140-2150.

[2] Cleland JG, Daubert JC, Erdmann E, Freemantle N, Gras D, Kappenberger L, et al. The effect of cardiac resynchronization on morbidity and mortality in heart failure. *The New England journal of medicine* 2005; **352**: 1539-1549.

[3] Moss AJ, Hall WJ, Cannom DS, Klein H, Brown MW, Daubert JP, et al. Cardiac-resynchronization therapy for the prevention of heart-failure events. *The New England journal of medicine* 2009; **361**: 1329-1338.

[4] Al-Khatib SM, Stevenson WG, Ackerman MJ, Gillis AM, Bryant WJ, Hlatky MA, et al. 2017 AHA/ACC/HRS Guideline for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. *Heart rhythm* 2017.

[5] Cleland JG, Daubert JC, Erdmann E, Freemantle N, Gras D, Kappenberger L, et al. The effect of cardiac resynchronization on morbidity and mortality in heart failure. *The New England journal of medicine* 2005; **352**: 1539-1549.

[6] Solomon SD, Foster E, Bourgoun M, Shah A, Viloria E, Brown MW, et al. Effect of cardiac resynchronization therapy on reverse remodeling and relation to outcome: multicenter automatic defibrillator implantation trial: cardiac resynchronization therapy. *Circulation* 2010; **122**: 985-992.

[7] Kutyifa V MA, Stein K, Wang PJ, Musat D, Jones P, Wehrenberg S. True Bipolar Left Ventricular Pacing is Associated With Better Survival in Cardiac Resynchronization Therapy Patients. *Circulation* 2015; **132**: A15501.

[8] Kramer DB, Mitchell SL, Monteiro J, Jones PW, Normand SL, Hayes DL, et al. Patient Activity and Survival Following Implantable Cardioverter-Defibrillator Implantation: The ALTITUDE Activity Study. *Journal of the American Heart Association* 2015; **4**.

[9] Cronin EM, Jones P, Seth MC, Varma N. Right Ventricular Pacing Increases Risk of Appropriate Implantable Cardioverter-Defibrillator Shocks Asymmetrically: An Analysis of the ALTITUDE Database. *Circulation Arrhythmia and electrophysiology* 2017; **10**.

[10] Kramer DB, Jones PW, Rogers T, Mitchell SL, Reynolds MR. Patterns of physical activity and survival following cardiac resynchronization therapy implantation: the ALTITUDE activity study. *Europace : European pacing, arrhythmias, and cardiac electrophysiology : journal of the working groups on cardiac pacing, arrhythmias, and cardiac cellular electrophysiology of the European Society of Cardiology* 2017; **19**: 1841-1847.

[11] Steinberg BA, Wehrenberg S, Jackson KP, Hayes DL, Varma N, Powell BD, et al. Atrioventricular and ventricular-to-ventricular programming in patients with cardiac resynchronization therapy: results from ALTITUDE. *J Interv Card Electrophysiol* 2015; **44**: 279-287.

[12] Yang HS, Caracciolo G, Sengupta PP, Goel R, Chandrasekaran K, Srivathsan K. Pacing polarity and left ventricular mechanical activation sequence in cardiac resynchronization therapy. *J Interv Card Electrophysiol* 2012; **35**: 101-107.

[13] Jame S, Kutyifa V, Aktas MK, McNitt S, Polonsky B, Al-Ahmad A, et al. Bipolar left ventricular pacing is associated with significant reduction in heart failure or death in CRT-D patients with LBBB. *Heart rhythm* 2016; **13**: 1468-1474.

[14] Pires LA, McNitt S, Solomon S, Goldenberg I, Zareba W, Moss AJ. Left ventricular pacing threshold and outcome in MADIT-CRT. *Journal of cardiovascular electrophysiology* 2014; **25**: 1005-1011.

[15] Delgado V, van Bommel RJ, Bertini M, Borleffs CJ, Marsan NA, Arnold CT, et al. Relative merits of left ventricular dyssynchrony, left ventricular lead position, and myocardial scar to predict long-term survival of ischemic heart failure patients undergoing cardiac resynchronization therapy. *Circulation* 2011; **123**: 70-78.

[16] Knappe D, Pouleur AC, Shah AM, Cheng S, Uno H, Hall WJ, et al. Dyssynchrony, contractile function, and response to cardiac resynchronization therapy. *Circulation Heart failure* 2011; **4**: 433-440.

[17] Kutyifa V, Pouleur AC, Knappe D, Al-Ahmad A, Gibinski M, Wang PJ, et al. Dyssynchrony and the risk of ventricular arrhythmias. *JACC Cardiovascular imaging* 2013; **6**: 432-444.

FIGURE LEGENDS

Figure 1. Study Flowchart

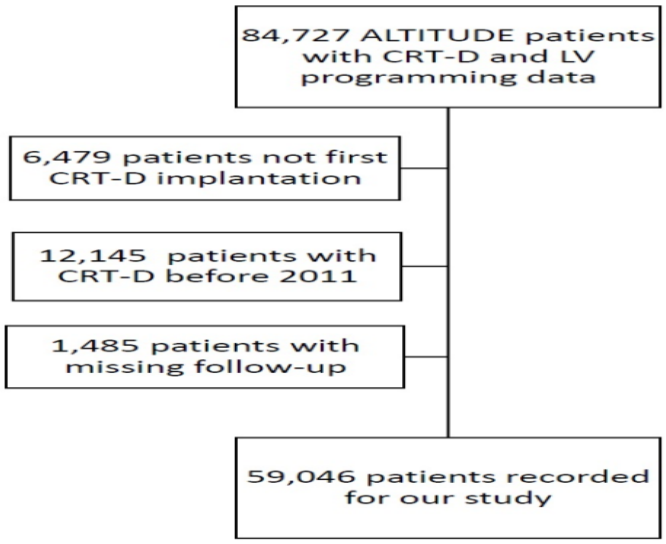

Figure 2. Cumulative Probability of All-Cause Mortality in CRT-D patients with True-Bipolar vs. Unipolar Pacing

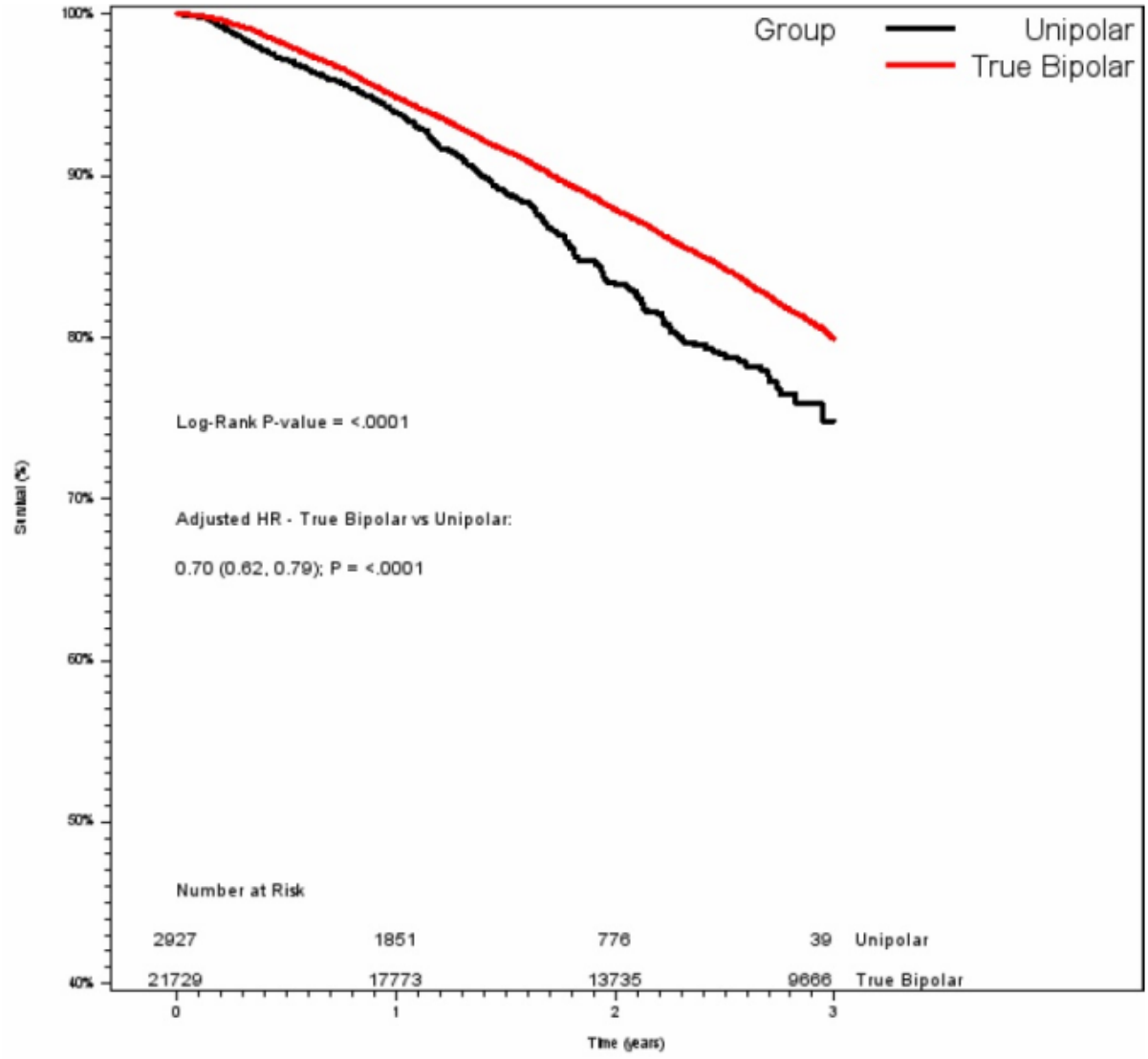

Figure 3. Cumulative Probability of All-Cause Mortality in CRT-D patients with Extended-Bipolar vs. Unipolar Pacing

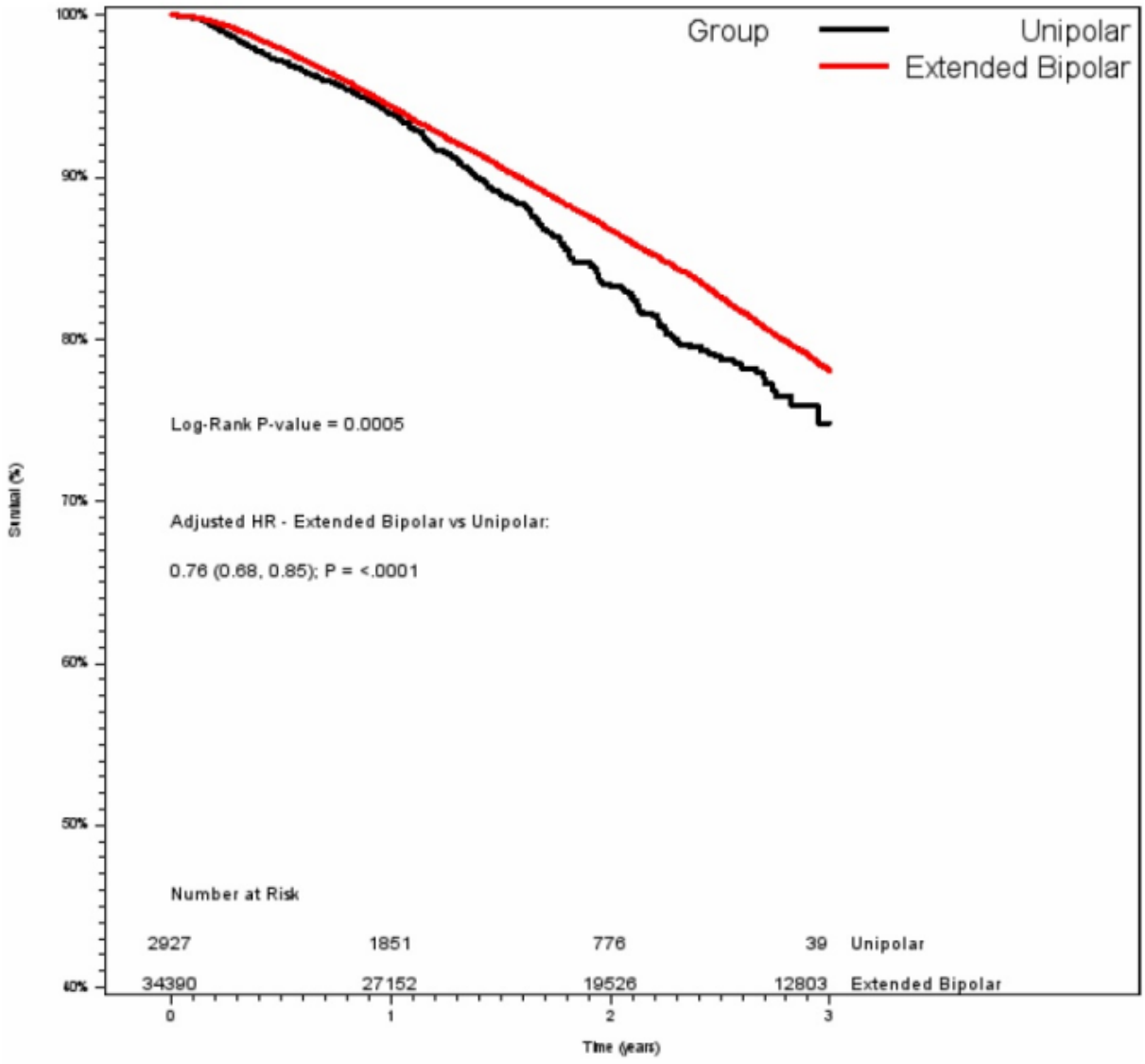

Figure 4. Cumulative Probability of All-Cause Mortality in CRT-D patients with True-Bipolar vs. Extended Bipolar Pacing

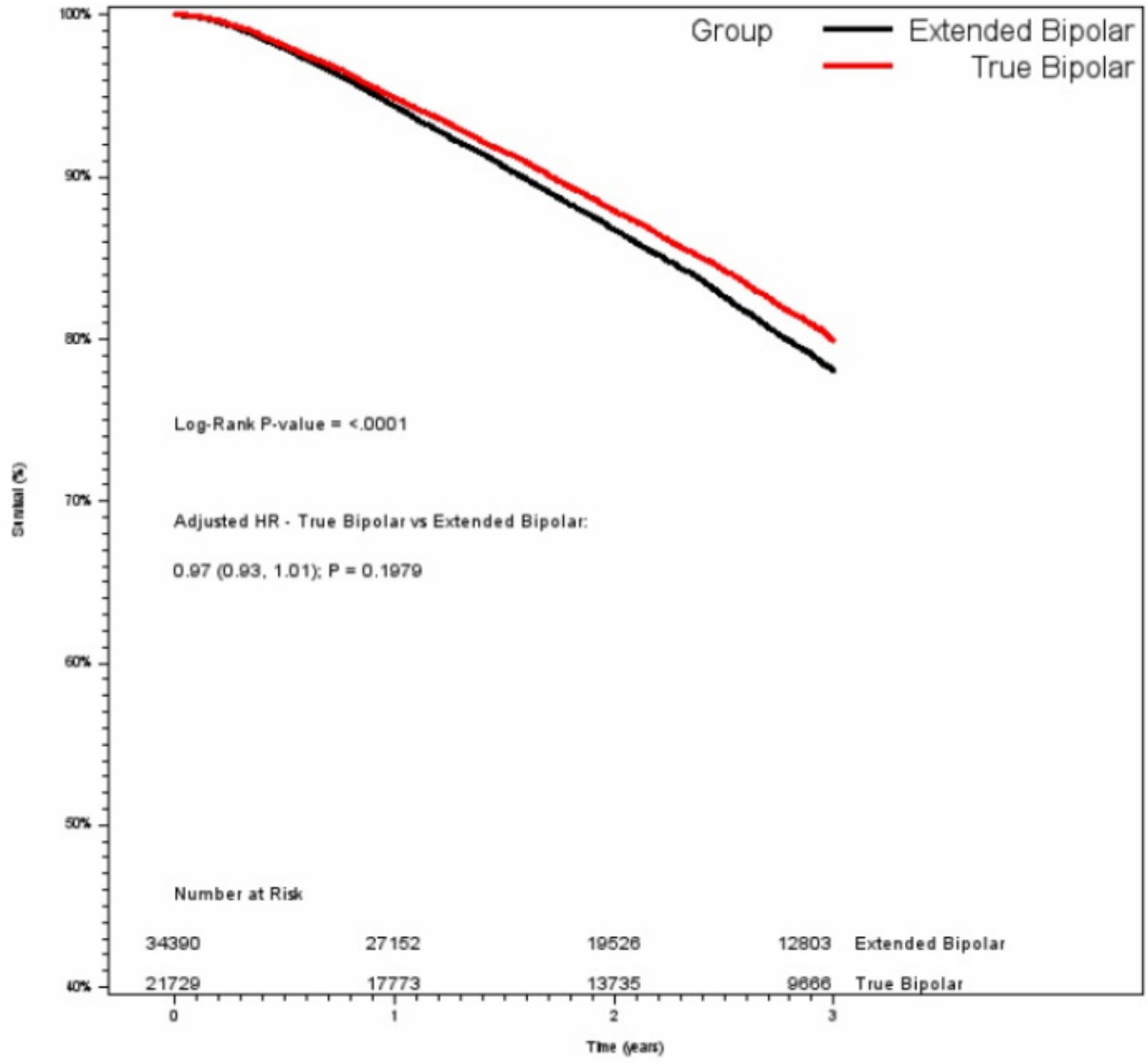

Table 1. Baseline Clinical Characteristics of Patients enrolled in the LATITUDE database included in this study

Clinical Characteristics	**Unipolar**	**Extended-Bipolar**	**True-Bipolar**
Number of patients	2,927	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)	10053 (29.2)	5788 (26.6)*
LV Lead Impedance (Ohm)	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*

*indicates $p < 0.05$ for comparison between true bipolar vs. unipolar vs. extended bipolar LV pacing

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

Abbreviations: LV– Left Ventricular**, BIV –** Biventricular Pacing

Table 2: Multivariate Analysis of All-Cause Mortality by Pacing Polarity

Table 2	All-Cause Mortality		
	HR	**95% CI**	**p-value**
True-Bipolar vs. Unipolar	0.72	0.62-0.79	<0.001
Extended-Bipolar vs. Unipolar	0.76	0.68-0.85	<0.001
True-Bipolar vs. Extended Bipolar	0.97	0.93-1.01	0.198

HR, hazard ratio; 95% CI, 95% confidence interval.

Models were adjusted for the following covariates: age, gender, LV lead impedance, LV pacing threshold, and BIV pacing percentage<95%.