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Long-Term Results of Triventricular Versus Biventricular Pacing in Heart Failure

A Propensity-Matched Comparison

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ABSTRACT

OBJECTIVES The goal of this study was to assess the impact of triventricular pacing (Tri-V) on long-term survival.

BACKGROUND Biventricular pacing (Bi-V) is an important adjunctive treatment in advanced heart failure, but almost one-third of patients experience no improvement with this therapy and are labeled as nonresponders. Adding a third ventricular lead (Tri-V) has been shown to be feasible and provides favorable acute results when assessed by using echocardiographic, hemodynamic, and clinical endpoints. However, the long-term effects of Tri-V pacing and how it affects long-term survival remains unknown.

METHODS This single-center, propensity score–matched cohort study compared 34 patients with advanced heart failure who underwent implantation with Tri-V devices versus 34 control subjects treated with Bi-V pacing. Clinical outcomes during a median of 2,478 days (IQR: 1,183 to 3,214 days) were compared.

RESULTS Tri-V–treated patients compared with Bi-V–treated patients presented with a trend for shorter battery longevity (time to box change, 1,758 ± 360 days vs. 1,993 ± 408 days; $p = 0.072$). Incidence of lead dislodgement (Tri-V vs. Bi-V, 0.86 vs. 1.10 per 100 patient-years; $p = 0.742$), device-related infection (Tri-V vs. Bi-V, 1.83 vs. 1.76 per 100 patient-years; $p = 0.996$), and refractory phrenic nerve capture (Tri-V vs. Bi-V, 0.48 vs. 1.84 per 100 patient-years; $p = 0.341$) was comparable in the 2 groups. Episodes of ventricular arrhythmia requiring implantable cardioverter-defibrillator intervention occurred more frequently in the Bi-V group versus the Tri-V group (6.55 vs. 16.88 per 100 patient-years; adjusted hazard ratio: 0.31; 95% confidence interval: 0.14 to 0.66; $p = 0.002$). Lower all-cause mortality and heart transplant was observed in the Tri-V group compared with the Bi-V group (6.99 vs. 11.92 per 100 patient-years; adjusted hazard ratio: 0.44; 95% confidence interval: 0.23 to 0.85; $p = 0.015$).

CONCLUSIONS Tri-V displayed a similar safety profile compared with Bi-V and was associated with potential benefits regarding long-term survival and ventricular arrhythmia burden. (J Am Coll Cardiol EP 2016;2:825–35)

Cardiac resynchronization therapy (CRT) has emerged as one of the major developments in the treatment of advanced heart failure, providing symptom relief and improved survival benefit (1–3). Unfortunately, almost one-third of patients experience no improvement with this therapy and are labeled as nonresponders (4).

Standard CRT consists of biventricular pacing (Bi-V) from the right ventricle and coronary sinus (CS) aiming to correct electrical dyssynchrony/delayed activation of the lateral left ventricular (LV) wall (5). There are many variables that determine patient outcome to CRT, including differences in regional myocardial response to pacing, scar burden and degree of

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ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation

ATP = antitachycardia pacing

Bi-V = biventricular pacing

CRT = cardiac resynchronization therapy

CS = coronary sinus

ICD = implantable-cardioverter defibrillator

LV = left ventricular

RV = right ventricular

Tri-V = triventricular pacing

VF = ventricular fibrillation

VT = ventricular tachycardia

myocardial recruitment, suboptimal lead positioning within scar or zones of slow conduction, and concordance with areas of latest contraction. To improve clinical outcomes and reduce the proportion of clinical nonresponders to CRT, the addition of a third ventricular lead has been used to achieve simultaneous stimulation of 3 ventricular sites and thus improve electro-mechanical synchrony (6). Compared with Bi-V pacing, this approach has been shown to improve echocardiographic and clinical responses (6,7). Whether triventricular (Tri-V) pacing affects long-term survival remains to be assessed.

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METHODS

This single-center, propensity score–matched study compared the long-term clinical outcomes of patients implanted with Tri-V and Bi-V devices. Retrospective review of relevant medical records for this analysis was performed. All Tri-V–treated patients gave full informed consent, and the procedure was approved by the local ethics committee.

SETTING AND STUDY POPULATION. All consecutive patients implanted with Bi-V or Tri-V pacing devices (with or without defibrillator) at The Heart Hospital UCLH from January 2005 to December 2008 were considered potentially eligible for this analysis.

In our institution, patients underwent implantation with CRTs at the time if they had symptomatic heart failure (New York Heart Association functional class II to IV) despite maximally tolerated medical therapy, had left ventricular ejection fraction (LVEF) <35%, and had a QRS duration ≥150 ms (or QRS <150 ms with echocardiographic evidence of mechanical dyssynchrony). Patients were not considered for the purpose of this analysis if they were <18 years of age, required intravenous inotropic drug therapy, or had an estimated life expectancy <12 months due to a cause other than heart failure. Patients with unsuccessful CS lead insertion during the procedure were also excluded to preserve homogeneity while comparing groups in this as-treated analysis.

Our center's initial experience with Tri-V pacing has been published previously (7). In the initial study, during the first 12 months' post-implantation, Tri-V devices were randomly switched between 4 different pacing configurations: Tri-V; standard Bi-V; dual site LV or right ventricular (RV) pacing; and single-site RV or LV pacing. They were then programmed with the configuration providing the best echocardiographic and clinical response. Therefore, for the purpose of this as-treated analysis, Tri-V–treated patients were considered eligible if they were programmed with all 3 ventricular leads after the first 12 months (i.e., if they were receiving true Tri-V pacing). Similarly, patients in the control group had to be alive after the first year post-implantation and should be receiving effective Bi-V pacing.

Propensity score matching with a 1:1 ratio was used to obtain a control group of standard CRT patients (Bi-V group) and assure that Tri-V and their contemporary Bi-V control subjects were similar in all baseline variables. Probabilities in the Tri-V group were matched 1:1 to the best Bi-V corresponding patient.

SAMPLE CHARACTERIZATION. All variables at the time of the procedure and during follow-up were defined and categorized. Information was collected regarding demographic characteristics, anthropometric data, baseline cardiac disease, echocardiographic data, and medication.

The following variables were used for developing the propensity score, which was used for creating a well-matched control group: device type (CRT with or without a defibrillator), age at time of implant, sex, presence of atrial fibrillation (AF), pre-existing permanent pacemaker, previous valve repair or replacement, history of cancer, previous stroke, diabetes mellitus, estimated glomerular filtration rate (calculated by using the Modified Diet in Renal Disease formula), New York Heart Association functional class, primary or secondary prevention of sudden cardiac death, QRS width, bundle branch or QRS pattern, ischemic or nonischemic cardiomyopathy, LVEF, and medication (use of oral anticoagulant agents, antiplatelet agents, beta-blockers, other antiarrhythmic agents, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, spironolactone, and loop diuretic agents).

TRI-V IMPLANT PROCEDURE. Our approach to Tri-V device implantation has been described previously (7). In summary, standard, commercially available equipment (Boston Scientific, Marlborough, Massachusetts, and St. Jude Medical, St. Paul, Minnesota) was used. Two different approaches were included: implanting 2 leads in the anterolateral branch of the CS and 1 in the right ventricle (group A), or implanting 1 lead in the anterolateral branch of the CS and 2 in the right ventricle (group B). All patients had a lead positioned in the RV apex, and all except for those in permanent AF had a lead positioned in the right atrium. The second RV leads in group B patients were positioned in the high RV septal location. Occlusive

venography of the anterolateral branch of the CS was performed to identify potential target veins for pacing. An LV lead was inserted into a lateral or posterolateral branch of the anterolateral branch of the CS; where possible, an additional lead was implanted into another lateral or anterolateral branch of the CS, or into the middle cardiac vein, aiming for maximal orthogonal separation between the pacing sites of the 3 ventricular leads. No measurement of local ventricular electrogram delay or acute hemodynamics was made during the implantation.

The leads were attached to a standard CRT device (Contak Renewal 4, Boston Scientific, and Atlas-HF, St. Jude Medical). Choice of a CRT device with a pacemaker or a CRT device with ICD was made on the basis of the patient's clinical history, risk profile, and past arrhythmic events. In patients with permanent AF, the third ventricular lead was connected to the atrial port of the device and the AV delay programmed to the minimum allowed by the device (10 ms). In those patients receiving an atrial lead, 2 ventricular leads were paired together by using a twin bipolar-to-bipolar connector (Oscor, Palm Harbor, Florida). The paired leads were connected to the LV port, and the unpaired final lead was connected to the RV port.

DEVICE PROGRAMMING. Because this study occurred in the era before the MADIT-RIT (Multicenter Automatic Defibrillator Implantation Trial-Reduce Inappropriate Therapy) study (8), all devices were programmed with 2 ventricular tachycardia (VT) zones ab initium, on the basis of patient's age and presence of previous ventricular arrhythmia events. VT zone was programmed starting at 169 ± 11 beats/min in Bi-V pacing versus 171 ± 9 beats/min in Tri-V pacing ($p = 0.435$), and the ventricular fibrillation (VF) zone was programmed starting at 209 ± 11 beats/min in Bi-V pacing versus 206 ± 9 beats/min in Tri-V pacing ($p = 0.199$). A nominal number of intervals for initial detection was used and detection was set at 2.5 to 9.0 s (depending on manufacturer) in the VT zone and 1.0 to 5.0 s in the VF zone. Supraventricular tachycardia discriminators were switched on, and high-rate timeout was turned off. Antitachycardia pacing (ATP) and shocks were programmed in the VT and VF zones. Subsequent adjustments to therapies and detection zones were performed during follow-up or after the occurrence of any arrhythmic events.

FOLLOW-UP AND OUTCOMES. Safety data and the presence of complications, including lead dislodgement, lead failure (defined as lead performing inappropriately and requiring replacement), device-related infection (whether pocket or lead infection), phrenic nerve capture refractory to electronic programming (requiring temporarily switching off the LV lead and repositioning or insertion of a new lead), pneumothorax, and hematoma requiring drainage or bleeding requiring red blood cell transfusion, was recorded. Device longevity, measured as time to box change, was compared in the 2 groups.

Mortality data (all-cause mortality) and information on patients accepted for heart transplant were collected by using hospital reports. In patients who transferred their follow-up to another hospital, long-term follow-up data were retrieved. When patients were lost to hospital follow-up, data were collected through patients' registered general practitioners.

Data from our local device clinic follow-up records and stored device electrograms during episodes of detected VT, VF, any therapy deliveries, and inappropriate shocks were analyzed by a cardiac physiologist specializing in electrophysiology and a consultant electrophysiologist or senior electrophysiology fellow. Sustained VT episodes meeting criteria for appropriate implantable cardioverter-defibrillator (ICD) intervention were classified as either VT/VF, according to the rate and detection window in which therapy was delivered. Non-sustained VT episodes that met detection criteria and were terminated before therapy was delivered were not classified as VT/VF.

Patients were classified as having had appropriate shocks, if a shock was delivered during a VT or VF event. An effective ATP therapy was defined as overdrive ventricular pacing able to restore sinus rhythm after a VT or VF episode. An appropriate ICD intervention was classified as the presence of either an appropriate shock or an effective ATP.

The incidence of inappropriate shocks delivered due to misdetection of tachycardia (either supraventricular tachycardia, sinus tachycardia, fast AF, or artifact) was also compared between the 2 treatment groups.

Data regarding multiple arrhythmia episodes (either in the VT or VF zones) and appropriate ICD therapies (ATPs and appropriate shocks) in the same patient were collected, and the mean number of episodes was compared between the 2 groups. The presence of arrhythmic storm, defined as ≥3 sustained episodes of VT, VF, or appropriate ICD therapies during a 24-h period, was also documented.

From 2011 onward, home-monitoring systems (LATITUDE [Boston Scientific] and MERLIN [St. Jude Medical]) became available in our institution and were also used for follow-up purposes.

STATISTICAL ANALYSIS. A propensity score was obtained for all participants undergoing a transvenous

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CRT implantation through binary logistic regression: CRT modality (Tri-V or Bi-V) was the binary outcome and all baseline variables (mentioned earlier) were used as covariates for estimating a probability (the propensity score). Probabilities in the Tri-V group were then matched 1:1 to the closest Bi-V patient fulfilling inclusion criteria by using the nearest neighbor matching approach. The propensity score was matched to 5 decimals whenever possible. If this outcome was not possible, we subsequently attempted matching of 4, 3, and then 2 decimals. If a treated subject could not be matched to any untreated subject on the second digit of the propensity score, the treated subject was then excluded from the matched analysis. Histograms and comparison of means and medians were used for assessing distribution and matching success.

Comparisons between Tri-V and Bi-V pacing were performed. Based on the research of Stuart (9), analyses were performed by using the groups as a whole, rather than using the individual matched pairs. Chi-square tests were used for the comparison of nominal variables. The Student *t* test, or its nonparametric equivalent (Mann-Whitney *U* test) when appropriate, was used for comparison of continuous variables; the Levene's test was used to check the homogeneity of variance. Results with p values <0.05 were regarded as significant.

Kaplan-Meier curves were traced for comparing survival (freedom from all-cause mortality or heart transplant, and ventricular arrhythmia events or ICD therapies) among the 2 intervention groups. Hazard ratios were used for assessing the existence of differences. For the endpoint of all-cause mortality or heart transplant, both an as-treated analysis (including 34 Tri-V patients treated with Tri-V pacing after the first 12 months) and an intention-to-treat analysis (including all 45 patients initially implanted with Tri-V devices) were performed. For the purpose of time to event analysis, only time to first event was considered (Kaplan-Meier analysis and Cox regression analysis). For every specific assessed endpoint, the patients were censored after their first event.

Independent predictor endpoints for mortality, cardiac transplantation, and appropriate ICD interventions were assessed through multivariate Cox regression analysis. All variables were assessed for potential inclusion in the model and were then selected by using the forward likelihood ratio method, with a probability for stepwise of 0.05.

PASW Statistics version 18.0 (IBM SPSS Statistics, IBM Corporation, Armonk, New York) was used for descriptive and inferential statistical analyses.

RESULTS

During the pre-specified time interval, 327 patients underwent implantation with CRT devices. Of 45 patients implanted with Tri-V pacing devices during the pre-specified time window, 34 met the inclusion criteria and were included in the present analysis. Among the remaining 282 contemporary patients who underwent implantation with Bi-V devices, 34 control subjects were selected through propensity matching.

Reasons for Tri-V-treated patients not being included in the as-treated analysis included: death in the first year post-implantation and consequently before being programmed as Tri-V full-time ($n = 4$), and programmed as dual LV pacing only (no RV pacing; $n = 3$) after 12 months, standard Bi-V pacing after 12 months ($n = 2$), and dual RV pacing only (no LV pacing; $n = 2$) after 12 months.

Baseline variables of the study cohort comparison of Tri-V and Bi-V groups are shown in **Table 1**. Their mean age was 67.0 ± 12.8 years, and 20.6% ($n = 14$) were women. Ischemic cardiomyopathy accounted for 54.4% of all cases, and 11 patients (16.2%) had previously existing RV devices and underwent system upgrades. The majority of patients (95.6% [$n = 65$]) underwent implantation with a defibrillator. Eleven patients (16.2%) had known AF, and 72.1% ($n = 49$) had a QRS $\geq$120 ms.

Both groups were matched for baseline variables, and no significant differences were observed for any of the baseline comparisons and medical treatment (**Tables 1 and 2**). All patients were matched with an appropriate propensity score-matched control. **Figure 1** illustrates the similar distribution of the propensity score among the 2 treatment groups. Despite this approach, a nonsignificant trend suggesting more severe disease in Tri-V-treated patients was observed with regard to ischemic disease, AF, and chronic obstructive pulmonary disease that was numerically but nonsignificantly more prevalent. Similarly, the use of beta-blockers and angiotensin-converting enzyme inhibitors/angiotensin II receptor antagonists was numerically but nonsignificantly lower.

Bi-V-treated patients not selected through propensity matching, and therefore not included in the comparison, were younger, more frequently female, had more AF, more frequently underwent implantation with CRT devices with pacemakers, had higher LVEF and estimated glomerular filtration rates, and received beta-blockers and antiplatelet agents less frequently (**Tables 1 and 2**).

TABLE 1 Baseline Variables: Tri-V Cohort Versus Propensity Matched Controls

	Global Sample (n = 68)	Tri-V Cohort (n = 34)	Matched Bi-V Controls (n = 34)	p Value (Tri-V vs. Bi-V)	Other Bi-V (n = 248)	p Value (vs. Study Sample)
Age, yrs	67.0 ± 12.8	67.4 ± 11.7	66.5 ± 13.9	0.787	62.2 ± 14.5	0.014
Female	20.6% (14)	20.6% (7)	20.6% (7)	1.000	33.9% (84)	0.036
BMI, kg/m^2	28.1 ± 6.5	29.2 ± 7.2	27.0 ± 5.6	0.201	28.4 ± 6.1	0.782
Diabetes mellitus	22.1% (15)	23.5% (8)	20.6% (7)	0.770	22.7% (56)	0.915
COPD	11.8% (8)	14.7% (5)	8.8% (3)	0.452	6.5% (16)	0.146
History of cancer	8.8% (6)	8.8% (3)	8.8% (3)	1.000	12.6% (31)	0.398
Previous stroke	8.8% (6)	8.8% (3)	8.8% (3)	1.000	9.3% (23)	0.902
Ischemic cardiomyopathy	54.4% (37)	61.8% (21)	47.1% (16)	0.331	40.3% (100)	0.014
Secondary prevention of SCD	8.8% (6)	8.8% (3)	8.8% (3)	1.000	12.9% (32)	0.360
Known AF	16.2% (11)	20.6% (7)	11.8% (4)	0.323	40.3% (100)	<0.001
CRT-P	4.4% (3)	2.9% (1)	5.9% (2)	0.555	13.7% (34)	0.035
Upgrade to CRT	16.2% (11)	14.7% (5)	17.6% (6)	0.428	26.3% (65)	0.084
Previous valve repair/surgery	1.5% (1)	0	2.9% (1)	0.314	7.7% (19)	0.062
NYHA functional class	2.8 ± 0.6	2.9 ± 0.6	2.8 ± 0.6	0.839	2.7 ± 0.7	0.037
QRS width, ms	140 ± 29	140 ± 27	140 ± 32	0.951	148 ± 34	0.090
LBBB	67.6% (46)	70.6% (24)	64.7% (22)	0.604	58.4% (143)	0.166
eGFR, ml/min	55 ± 20	56 ± 19	54 ± 21	0.621	63 ± 22	0.010
LVEF, %	24 ± 8	25 ± 5	26 ± 11	0.491	29 ± 14	0.005

Values are mean ± SD or % (n).

AF = atrial fibrillation; Bi-V = biventricular pacing; BMI = body mass index; COPD = chronic obstructive pulmonary disease; CRT = cardiac resynchronization therapy; CRT-P = cardiac resynchronization therapy with a pacemaker; eGFR = estimated glomerular filtration rate; LBBB = left bundle branch block; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association functional class; SCD = sudden cardiac death; Tri-V = triventricular pacing.

PROCEDURAL DATA/SAFETY. No pneumothorax or acute bleeding complications requiring intervention or red blood cell transfusions were observed in any of the treatment groups. Patients were followed up for a total of 413 patient-years (median 2,478 days; IQR: 1,183 to 3,214 days). Only 1 patient (1.47%) in the control group was lost to follow-up after transferring to a new Health Authority.

Four patients presented with lead dislodgment in the Tri-V group: 1 right atrial lead, 1 RV lead, and 2 CS leads, with 2 dislodging in the first month and the remainder presenting late (after 6 months). In the Bi-V group, this scenario was observed in 5 patients: 2 presented with RA lead displacement, 1 with CS lead displacement, and 2 with both RV and CS lead displacement. One case occurred in the first week, 2 more in the first 6 months, and the remainder at a later date. No significant differences were observed in the incidence of this complication between the 2 groups (Tri-V vs. Bi-V, 0.86 per 100 patient-years vs. 1.10 per 100 patient-years; p = 0.742) (Table 3).

Infection was reported in 7 patients (4 in the Tri-V group vs. 3 in the BI-V group). In all but 2 cases, infections occurred after >1 year following the initial device implantation (Tri-V vs. Bi-V, 1.83 per 100 patient-years vs. 1.76 per 100 patient-years; p = 0.996).

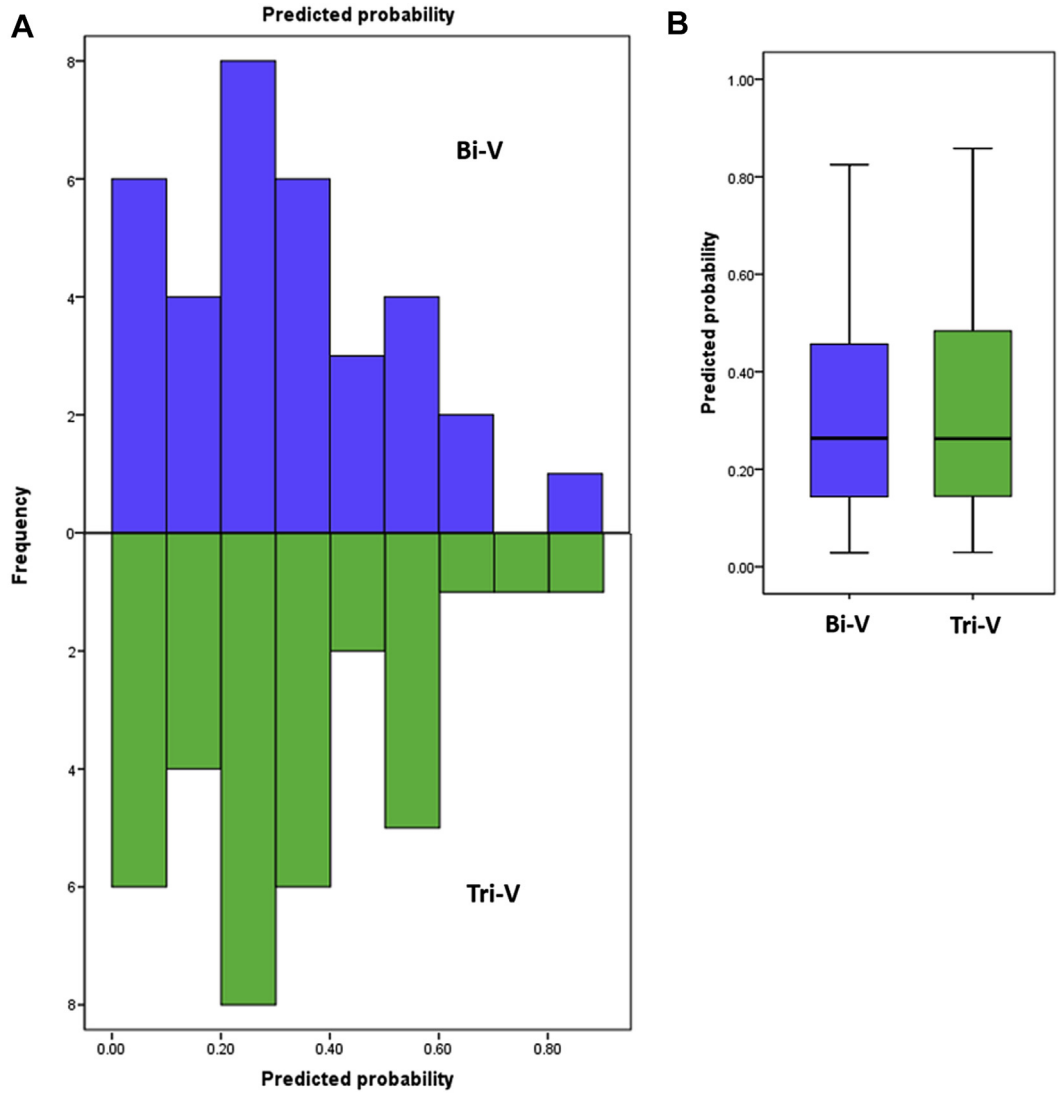
TABLE 2 Baseline Medication

	Global Sample (n = 68)	Tri-V Cohort (n = 34)	Matched Bi-V Controls (n = 34)	p Value (Tri-V vs. Bi-V)	Other Bi-V (n = 248)	p Value (vs. Study Sample)
Beta-blockers	75.0% (51)	67.6% (23)	82.4% (28)	0.161	54.1% (132)	0.002
Other AADs	16.2% (11)	17.6% (6)	14.7% (5)	0.742	29.5% (72)	0.028
ACEi/ARB-II	89.7% (61)	85.3% (29)	94.1% (32)	0.231	84.0% (205)	0.242
Spironolactone	45.6% (31)	44.1% (15)	47.1% (16)	0.808	57.0% (139)	0.096
Loop diuretics	67.6% (46)	70.6% (24)	64.7% (22)	0.604	77.5% (189)	0.097
Digoxin	25.0% (17)	26.5% (9)	23.5% (8)	0.779	22.1% (54)	0.618
Nitrates	17.0% (38)	17.8% (8)	16.8% (30)	0.871	14.8% (36)	0.568
Statins	55.9% (38)	61.8% (21)	50.0% (21)	0.329	53.3% (130)	0.703
Oral anticoagulants	38.2% (26)	41.2% (14)	35.2% (12)	0.618	43.7% (107)	0.422
Antiplatelet agents	58.8% (40)	55.9% (19)	61.8% (21)	0.622	44.7% (109)	0.039

Values are % (n).

AAD = anti-arrhythmic drug; ACEi = angiotensin-converting enzyme inhibitor; ARB-II = angiotensin II receptor blockers; other abbreviations as in Table 1.

FIGURE 1 Distribution of Propensity Scores Among the 2 Treatment Groups



(A) Histogram and **(B)** boxplot. Comparison of means (Student *t* test) shows no significant differences between the 2 groups: biventricular pacing (Bi-V), 0.31 ± 0.20; triventricular pacing (Tri-V), 0.32 ± 0.21 (p = 0.89). The same outcome was true for comparison of medians (Mann-Whitney *U* test): Bi-V pacing, 0.26 (0.14–0.49); Tri-V pacing, 0.26 (0.14-0.46) (p = 0.96).

Four patients (1 in the Tri-V group and 3 in the Bi-V control group [Tri-V, 0.48 per 100 patient-years; Bi-V, 1.84 per 100 patient-years (p = 0.341)]) presented with phrenic nerve capture, irresolvable with device reprogramming and requiring CS lead repositioning. There was a trend for shorter battery longevity in individuals implanted with Tri-V devices, with box change taking place 7 months before box change in the control Bi-V group (time to box change, Tri-V vs. Bi-V, 1,758 ± 360 days vs. 1,993 ± 408 days; p = 0.072).

Among the 11 Tri-V–treated patients not included in this as-treated analysis, several issues were observed: 1 patient had a micro-dislodgement of the CS lead with loss of capture in the first year and was left with dual RV pacing because she presented with very good hemodynamic and echocardiogram responses (still alive 3,319 days after the implant procedure); a second patient had a CS lead dislodgement at 30 days requiring repositioning, complicated by infection and system extraction at 6 months. This patient later underwent implantation with a standard

TABLE 3 Study Outcomes: Comparison of Tri-V–Treated Versus Bi-V–Treated Patients

	Incidence (Per 100 Patient-Yrs)				
	Tri-V	Bi-V	Hazard Ratio	95% CI	p Value
All-cause mortality and/or heart transplant	6.99 (4.35-11.05)	11.92 (0.80-17.39)	0.54	0.28–1.02	0.059
Heart transplant	0 (0-1.65)	0.54 (0.10-0.30)	0.14	0–139,801	0.605
All-cause mortality	6.99 (4.35-11.05)	11.38 (7.57-16.77)	0.57	0.30–1.10	0.096
Appropriate ICD intervention (ATP/shock)	6.55 (3.79-11.10)	16.88 (11.20-24.65)	0.42	0.21–0.87	0.019
ATP termination of VT/VF	4.10 (2.09-7.89)	14.12 (9.12-21.22)	0.32	0.14–0.75	0.008
Appropriate shock	2.81 (1.29-6.00)	4.37 (2.13-8.75)	0.69	0.23–2.07	0.512
Inappropriate shock	1.96 (0.77-4.93)	1.70 (0.58-4.89)	1.30	0.29–5.81	0.734
Device-related infection	1.83 (0.71-4.60)	1.76 (0.60-5.05)	1.00	0.22–4.54	0.996
Lead failure	0.86 (0.24-3.09)	1.10 (0.30-3.91)	0.72	0.10–5.11	0.742
Lead dislodgement	1.91 (0.74-4.80)	2.03 (0.87-4.66)	0.73	0.19–2.72	0.635
Refractory phrenic nerve capture	0.48 (0.08-2.65)	1.84 (0.55-4.67)	0.33	0.04–3.20	0.341

ATP = antitachycardia pacing; CI = confidence interval; ICD = implantable cardioverter-defibrillator; VT/VF = ventricular tachycardia/ventricular fibrillation.

Bi-V device and died 2,244 days after the initial Tri-V implant. A third patient, with a Tri-V device with 2 CS leads, had phrenic nerve capture with one of the CS leads, reason why he had to be programmed as a standard CRT device with ICD (i.e., the CS lead with phrenic nerve capture was switched off). This patient died 68 days after the initial Tri-V implantation procedure.

ARRHYTHMIC EVENTS. Almost one-half of patients (47.1% [n = 32]) experienced at least 1 VT/VF episode requiring an appropriate ICD intervention (incidence 9.70 per 100 patient-years; 95% confidence interval [CI]: 7.91 to 11.84). These arrhythmia episodes occurred more frequently in the Bi-V group (Tri-V 6.55 per 100 patient-years; Bi-V 16.88 per 100 patient-years [p = 0.019]; adjusted hazard ratio [HR]: 0.31; 95% CI: 0.14 to 0.66; p = 0.002) (Figure 2).

The higher incidence of arrhythmic episodes in Bi-V-treated patients was driven by a higher number of arrhythmia episodes successfully terminated with ATPs (Bi-V, 14.12 per 100 patient-years; Tri-V, 4.10 per 100 patent-years [p = 0.008]). No significant differences were observed in the incidence of arrhythmia episodes requiring termination with shock (Tri-V, 2.81 per 100 patient-years; Bi-V, 4.37 per 100 patient-years [p = 0.512]) (Table 3).

Bi-V pacing recipients presented more frequently with ventricular arrhythmia episodes in the VT zones requiring therapy (Bi-V vs. Tri-V, 52.9% vs. 29.4%; p = 0.049). The occurrence of episodes in the VF zone requiring therapy was similar in both groups (Bi-V vs. Tri-V, 14.7% vs. 11.8%; p = 0.720). The occurrence of arrhythmia storm was more frequent in the Bi-V group (2.9% vs. 17.6%; p = 0.046). One patient in the Bi-V group underwent VT ablation.

The cumulative analysis of all ventricular arrhythmia episodes revealed that Tri-V-treated patients presented with fewer sustained episodes in the VT zone requiring ICD intervention (Tri-V vs. Bi-V, 0.8 ± 1.7 vs. 3.8 ± 7.4; p = 0.027) and had a lower incidence of VT requiring ATP termination (Tri-V vs. Bi-V, 0.6 ± 1.5 vs. 3.1 ± 5.8; p = 0.018). No differences were observed regarding the incidence of detections in the VF zone requiring ICD termination (Tri-V vs. Bi-V, 0.4 ± 1.6 vs. 0.3 ± 0.9; p = 0.707) or the number of appropriate shocks for ventricular arrhythmias (Tri-V vs. Bi-V, 0.6 ± 2.1 vs. 1.0 ± 2.7; p = 0.551).

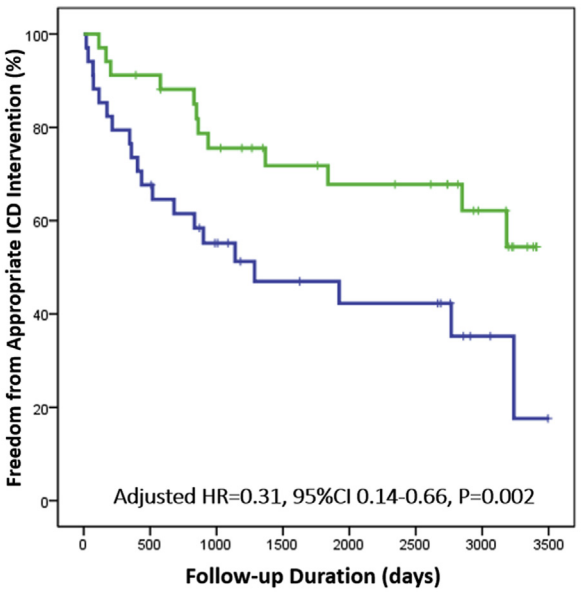
The incidence of inappropriate shocks was 1.84 per 100 patient-years (95% CI: 0.90 to 3.75) and was similar in both treatment groups (Tri-V vs. Bi-V, 1.96 per 100 patient-years vs. 1.70 per 100 patient-years; p = 0.734). These occurred mostly in the setting of AF (71.4%), with the remaining cases occurring as a result of sinus tachycardia.

LONG-TERM SURVIVAL. During follow-up, 37 patients (16 Tri-V vs. 21 Bi-V recipients) died, and 1 patient of the Bi-V group underwent heart transplantation. The overall incidence of all-cause mortality or heart transplantation was 9.17 per 100 patient-years (95% CI: 6.75 to 12.33).

A trend for lower all-cause mortality and heart transplantation was observed in the Tri-V group (Tri-V vs. Bi-V, 6.99 per 100 patient-years vs. 11.92 per 100 patient-years; p = 0.059). After adjustment, on multivariate Cox regression, treatment with Tri-V devices (HR: 0.44; 95% CI: 0.23 to 0.85; p = 0.015) and ischemic cardiomyopathy (HR: 2.54; 95% CI: 1.26 to 5.11; p = 0.009) were the only independent predictors of all-cause mortality or heart transplant (Figure 3).

Intention-to-treat analysis comparing all 45 patients implanted with Tri-V devices compared with

FIGURE 2 Incidence of Appropriate ICD Intervention Over Time in Bi-V- and Tri-V-Treated Patients



N at Risk	0	500	1000	1500	2000	2500	3000	3500
Bi-V	34	23	16	11	9	9	3	0
Tri-V	34	30	24	19	17	16	9	0

CI = confidence interval; HR = hazard ratio; ICD = implantable cardioverter-defibrillator; other abbreviations as in Figure 1.

45 Bi-V-treated control subjects (Online Figure 1) revealed lower all-cause mortality and heart transplant in the Tri-V group (log rank p = 0.027; HR: 0.55; 95% CI: 0.32 to 0.94; p = 0.029).

Subanalyses regarding baseline QRS width and presence/absence of AF and their impact on the overall survival of these patients (Online Figures 2 and 3) suggest a possible benefit of Tri-V pacing in these subsets of patients (Online Appendix). Assessment of the type of Tri-V modality (group A or group B) and interaction with survival and arrhythmic events suggests that the location of the third ventricular lead in the Tri-V group (whether RV or anterolateral branch of the CS) does not seem to affect the incidence of all-cause mortality or heart transplant, nor the ventricular arrhythmia profile (Online Figures 4 to 7).

DISCUSSION

We observed a potential benefit of Tri-V pacing compared with standard Bi-V pacing in long-term survival, ventricular arrhythmia burden, and need of ICD interventions. In addition, the incidence of safety-related events or complications with Tri-V was comparable to standard BI-V devices, with a low incidence of lead failure, lead dislodgment, and infections.

To the best of our knowledge, this study is the first demonstrating an impact of Tri-V on long-term clinical outcomes. Previous studies have reported a potential improvement in patients' heart failure symptoms (New York Heart Association functional class and quality of life score on the Minnesota Living With Heart Failure questionnaire [7,10,11], peak oxygen consumption [10], 6-min walking distance [7,10]) and hemodynamic (increase in dP/dT and cardiac output [12–14]) benefit, as well as echocardiographic evidence of reverse remodeling (improvement in LVEF [6,7,10], LV dimensions [7], and intraventricular synchrony [10]).

Bi-V pacing is believed to improve synchrony in patients with left bundle branch block by enhancing myocardial recruitment through simultaneous stimulation of the LV free wall and septum, thus reducing regional dispersions of delayed activation. However, both the hemodynamic response and progression of the depolarizing wavefront can be affected by the conduction properties of the myocardium (15). The location and extent of myocardial scarring may also influence response to Bi-V because scarred regions can prevent or delay progression of the activation wavefront and the synchronized engagement of viable tissue, or if scarring is extensive, there may be inadequate volume of healthy myocardium recruited to improve hemodynamics (16,17). The potential advantage of Tri-V pacing and the mechanism underlying the observed clinical and echocardiographic benefit may reside in the possibility of direct stimulation of wider regions of myocardial tissue simultaneously, or allowing the depolarization wavefront to bypass regions of slow conduction or scar and reaching previously delayed or remote sites more quickly (7).

Ogano et al. (18) have also suggested that Tri-V pacing might affect repolarization indexes (e.g., corrected QT interval, transmural dispersion of repolarization) and therefore exert antiarrhythmic effects leading to a reduction in ventricular arrhythmia (18). Other contributory factors can be LV reverse remodeling itself, as previously suggested in the MADIT-CRT study (19), and reduction of dispersion of refractoriness. It has been previously suggested that Bi-V pacing can prevent or reduce the induction of VT/VF (20,21). However, this outcome seems to depend on the position of the pacing site, in relation to the slow conduction area. It has been suggested

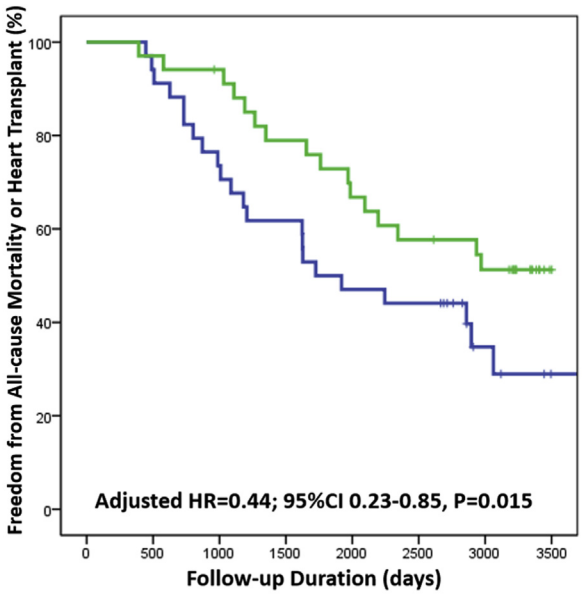
that to obtain sufficient antiarrhythmic effects, the pacing site should be positioned in the latest sites of activation that may be responsible for the development of re-entrant tachyarrhythmia. Pacing in a site nondelayed region can result in either no effects or pro-arrhythmic effects (22). Therefore, pacing with an additional lead could be beneficial in the latter group (pro-arrhythmic LV lead positioning) by making conduction more uniform or provide penetration of the wavefront into the re-entrant circuit, making the circuit less likely to develop sustained VTs. Our data show a reduction in ventricular arrhythmia events, mostly monomorphic VTs (events in the VT zone), which support the hypothesis of Tri-V pacing having some antiarrhythmic effect on these re-entrant circuits.

The impact of the third ventricular lead position to provide optimal resynchronization is a factor that still needs to be investigated, as previous studies have either included individuals with 2 RV leads (14) or 2 anterolateral branches of the CS leads (6,11,18). In our small cohort, the 2 groups are represented (group A and group B), with no difference observed in major clinical outcomes. However, this outcome needs to be interpreted with caution because our study was not powered to show minor differences among the 2 strategies of lead placement. Therefore, the comparable outcomes observed with both configurations, which in theory may lead to different electrophysiological and structural remodeling overtime, may be coincidental.

Behar et al. (23) recently reported the potential impact of the new quadripolar anterolateral branch of the CS leads on survival. Therefore, it would be important to ascertain whether multisite and multipolar LV pacing leads provide similar benefit, as the latter could be advantageous from the perspective that with fewer leads and material used, a shorter duration procedure would be needed. Therefore, the risk of complications such as lead dislodgement, lead failure, and infection would theoretically be lower.

The 3 currently ongoing randomized controlled trials (TRIUMPH CRT [Triple-site Bi-Ventricular Stimulation in the Optimization of CRT; NCT02350842], STRIVE HF [Standard Care Versus Tri-Ventricular Pacing in Heart Failure; NCT02529410], and Efficacy and Safety of Multisite Cardiac Resynchronization Therapy; NCT01966016), are feasibility studies, assessing the improvement in echocardiography parameters with Tri-V devices. Randomized clinical trials of Tri-V pacing versus Bi-V devices assessing clinical outcomes should be the next step for this promising approach. It would be of utmost importance to know if Tri-V can further improve the results of conventional CRT (Bi-V) in patients with broad complex QRS (particularly those who are classified as nonresponders to Bi-V pacing) or whether Tri-V pacing has a role in CRT devices in the population of patients with advanced heart failure and a narrow QRS complex.

FIGURE 3 All-Cause Mortality and Heart Transplant During Follow-Up (As-Treated Analysis)



N at Risk	0	500	1000	1500	2000	2500	3000	3500
Bi-V	34	32	25	21	16	15	6	2
Tri-V	34	33	31	26	22	19	16	0

CI = confidence interval; HR = hazard ratio.

STUDY LIMITATIONS. First, the results of this single-center study should be interpreted carefully in view of the small sample size and absence of randomization. The use of propensity score matching provided an appropriately matched control group, attempting to minimize that issue. However, because small samples can sometimes lead to misleading results, our findings require validation in larger samples. Second, some patients with narrow QRS complex underwent implantation on the basis of echocardiography dyssynchrony practice at the time, which was abandoned after the landmark studies PROSPECT (Predictors of Response to CRT) (24) and EchoCRT (Echocardiography Guided Cardiac Resynchronization Therapy) (25). However, groups were also

matched for that type of currently off-label patients, and some are still alive at 10 years. Third, due to the exploratory nature of this long-term cohort follow-up, there was no baseline power assessment. However, it is striking that for some of the assessed endpoints, this study was able to suggest a marked reduction and benefit in favor of Tri-V-treated patients. Lastly, even though both groups were matched for baseline variables and device brands, and they had similar cutoffs for zone programming, we cannot entirely rule out that unaccounted aspects in detection or therapy programming may have contributed in part to the observed differences in ventricular arrhythmia events.

CONCLUSIONS

In this exploratory single-center pilot study, Tri-V pacing presented promising results, and compared with Bi-V pacing, it displayed a similar safety profile and potential benefits as regard long-term survival and ventricular arrhythmia burden. These findings support the need of future long-term and sufficiently powered randomized controlled studies to assess the impact of this pacing modality on hard clinical outcomes such as mortality and arrhythmic events.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: This exploratory study raises the possibility of a survival benefit from Tri-V pacing in patients with advanced heart failure. This may be of interest because almost one-third of patients are nonresponders to conventional CRT.

TRANSLATIONAL OUTLOOK: Our cohort data confirm the promising results of multisite pacing previously observed in animal models but now with "hard" clinical endpoints, and prompt the need for future randomized controlled trials.

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KEY WORDS arrhythmia, mortality, multisite pacing, nonresponders, refractory

APPENDIX For supplemental figures, please see the online version of this article.