

# **Long-term Results of Tri-Ventricular versus Bi-Ventricular Pacing in Heart Failure: A Propensity-Matched Comparison.**

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**Short Title:** Long-term Results of Tri-V vs. Bi-V Pacing in HF

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**Abstract**      **Words:** 247

**Objective:** To Assess the impact of Tri-Ventricular pacing (Tri-V) on long-term survival.

**Background:** Bi-Ventricular pacing (Bi-V) is an important adjunctive treatment in advanced heart failure, but almost one third of patients are non-responders. Adding a third ventricular lead (Tri-V) has shown to be feasible and provide favourable acute results when assessed by echocardiographic, haemodynamic and clinical endpoints. However, the long-term effects of Tri-V pacing and how it impacts on long-term survival remains unknown.

**Methods:** Single-centre propensity score-matched cohort study comparing 34 advanced heart failure patients implanted with Tri-V devices with 34 controls treated with Bi-V comparing clinical outcomes during a median of 2,478 days (IQR=1,183-3,214).

**Results:** Tri-V patients presented with a trend for shorter battery longevity (time to Box change: Tri-V 1,758±360 vs. Bi-V 1,993±408 days; P=0.072). Incidence of lead dislodgement (Tri-V 0.86 vs. Bi-V 1.10 per 100 patient-years; P=0.742), device-related infection (Tri-V 1.83 vs. Bi-V 1.76 per 100 patient-years; P=0.996) and refractory phrenic nerve capture (Tri-V 0.48 vs. Bi-V 1.84 per 100 patient-years; P=0.341) was comparable in the two groups. Ventricular arrhythmia episodes requiring implantable cardioverter-defibrillator intervention occurred more frequently in the Bi-V group (Tri-V 6.55 vs. Bi-V 16.88 per 100 patient-years; adjusted HR=0.31, 95% CI 0.14-0.66, P=0.002). Lower all-cause mortality and heart transplant was observed in the Tri-V group (Tri-V 6.99 vs. Bi-V 11.92 per 100 patient-years; adjusted HR=0.44; 95% CI 0.23-0.85, P=0.015).

**Conclusion:** Tri-V displayed a similar safety profile when compared with Bi-V and was associated with potential benefits regarding long-term survival and ventricular arrhythmia burden.

**Keywords:** multisite pacing; non-responders; refractory; mortality; arrhythmia.

### **Condensed Abstract:**

Bi-Ventricular pacing (Bi-V) is an important adjunctive treatment in advanced heart failure, but almost one third of patients are non-responders. Adding a third ventricular lead (Tri-Ventricular pacing –Tri-V) has shown to be feasible and provide favourable acute results. However, the long-term effects of adding a third ventricular lead(Tri-Ventricular pacing –Tri-V) remain unknown. In this single-centre propensity score-matched cohort study comparing 34 advanced heart failure Tri-V patients with 34 Bi-V controls during a median of 2,478 days we observed a lower incidence of ventricular arrhythmia episodes requiring implantable cardioverter-defibrillator intervention and lower all-cause mortality and heart transplant in the Tri-V group.

### **Abbreviations**

CRT – cardiac resynchronization therapy; Bi-V – biventricular pacing; Tri-V – triventricular pacing;

RV – right ventricular; LV – left ventricular; AF – atrial fibrillation; VT – ventricular tachycardia;

VF – ventricular fibrillation; ATP – anti-tachycardia pacing; ICD – implantable cardioverter defibrillator.

## **Background**

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 do not experience any improvement with this therapy, and are labelled as non-responders [4].

Standard CRT consists of Bi-Ventricular pacing (Bi-V) from the right ventricle and coronary sinus aiming to correct electrical dyssynchrony / delayed activation of the lateral left ventricular wall [5]. Large numbers of variables exist that determine patient outcome to CRT, including differences in regional myocardial response to pacing, scar burden and degree of 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 non-responders to CRT, adding a third ventricular lead has been used to achieve simultaneous stimulation of three ventricular sites, and thus improving electro-mechanical synchrony [6]. Compared with Bi-V, this approach has shown to improve echocardiographic, and clinical response [6, 7]. Whether Tri-Ventricular pacing (Tri-V) impacts on long-term survival, remains to be assessed.

## **Methods**

This was a single-centre, propensity-matched study to compare 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 obtained from the local ethics committee. All Tri-V 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 were implanted with CRTs at the time if they had symptomatic heart failure (New York Heart Association class II to IV) despite maximally tolerated medical therapy, had left ventricular ejection fraction (LVEF) < 35%, and QRS duration  $\geq$  150ms (or QRS < 150ms with echocardiographic evidence of mechanical dyssynchrony). Patients were not considered for the purpose of this analysis if they were aged < 18, if they required intravenous inotropic drug therapy, or had an estimated life expectancy of < 12 months due to a cause other than heart failure. Patients with unsuccessful coronary sinus lead insertion during the procedure were also excluded to preserve homogeneity while comparing groups in this as-treated analysis.

Our Centre's initial experience with Tri-V pacing has been published previously [7]. In the initial study, during the first 12 months post-implant, Tri-V devices were randomly switched between four different pacing configurations: Tri-V; standard Bi-V; dual site left ventricular (LV) or right ventricular (RV) pacing; and single site RV or LV pacing; and then programmed with the configuration providing the best echocardiographic and clinical response [7]. Therefore, for the purpose of this as-treated analysis, Tri-V patients were considered eligible if they were programmed with all three ventricular leads on 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-implant 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 controls 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 demographics, anthropometric data, baseline cardiac disease, echocardiographic data and medication.

The following variables were used for creating 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, gender, 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 using the Modified Diet in Renal Disease – MDRD - formula), New York Heart Association functional class, primary or secondary prevention of sudden cardiac death, QRS width, bundle branch or QRS pattern, ischemic or non-ischemic cardiomyopathy, LVEF, and medication (use of oral anticoagulants, antiplatelet agents, beta-blockers, other anti-arrhythmic agents, angiotensin converter enzyme inhibitors or angiotensin receptor blockers, spironolactone, and loop diuretics).

### Tri-V Implant Procedure

Our approach to Tri-V device implantation has been previously described [7]. In summary, standard commercially available equipment (Boston Scientific, USA; St Jude Medical, USA) was used. Two different approaches were used: implanting two leads in the coronary sinus and one in the RV (group A) or, implanting one lead in the coronary sinus and two in the RV (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 coronary sinus was performed to identify potential target veins for

pacing. An LV lead was inserted into a lateral or posterolateral branch of the coronary sinus. Where possible, a further 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 three ventricular leads. No measurement of local ventricular electrogram delay or acute haemodynamics was made during the implantation.

The leads were attached to a standard CRT device (Contak Renewal 4, Boston Scientific, USA; Atlas-HF, St Jude Medical, USA). Choice of a CRT-P or CRT-D was based in 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 (10ms). In those patients receiving an atrial lead, two ventricular leads were paired together using a twin bipolar-to-bipolar connector (Oscor, Palm Harbor, FL, USA). The paired leads were connected to the LV port and the unpaired final lead was connected to the RV port.

### Device Programming

As this study occurred in the pre-MADIT-RIT era [8], all devices were programmed with two ventricular tachycardia zones *ab initium*, based on patient's age and presence of previous ventricular arrhythmia events. Ventricular tachycardia (VT) zone was programmed starting at  $169\pm 11$ bpm in Bi-V vs.  $171\pm 9$ bpm in Tri-V ( $P=0.435$ ) and ventricular fibrillation (VF) zone was programmed starting at  $209\pm 11$ bpm in Bi-V vs.  $206\pm 9$ bpm in Tri-V ( $P=0.199$ ). Nominal number of intervals for initial detection was used and detection was set to 2.5s–9.0s (depending on manufacturer) in the VT zone and 1.0s–5.0s in the VF zone. Supraventricular tachycardia discriminators were switched on and high-rate timeout turned off. Anti-tachycardia pacing (ATP) and shocks were programmed in the VT and VF zone. Subsequent adjustments to therapies and detection zones were performed during follow-up, or following 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 haematoma requiring drainage or bleeding requiring red blood cell transfusion was recorded. Device longevity, measured as time to box change, was compared in the two groups.

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

Data from our local device clinic follow-up records and stored device electrograms (EGMs) during episodes of detected VT, VF, any therapy deliveries, and inappropriate shocks were analysed by a cardiac physiologist specialized in electrophysiology and a Consultant Electrophysiologist or Senior Electrophysiology Fellow. Sustained ventricular tachycardia episodes meeting criteria for appropriate implantable cardioverter-defibrillator (ICD) intervention were classified as either VT/VF, according to the rate and detection window where therapy was delivered. Non sustained VT episodes which met detection criteria and 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 following 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 supra-ventricular tachycardia, sinus tachycardia, fast AF or artefact) was also compared between the two treatment groups.



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

From 2011 onwards, home-monitoring systems (LATITUDE and MERLIN) 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 CRT implantation through binary logistic regression: CRT modality (Tri-V or Bi-V) was the binary outcome and all baseline variables (mentioned above) were used as covariates for estimating a probability (the propensity score). Then, probabilities in the Tri-V group were matched 1:1 to the closest Bi-V patient fulfilling inclusion criteria using the nearest neighbour matching approach. The propensity score was matched to 5 decimals whenever possible. If this was not possible, we subsequently attempted 4, 3 and then 2 decimal matching. If a treated subject could not be matched to any untreated subject on the second digit of the propensity score, then the treated subject was discarded 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 were performed. Based on Stuart [9], analyses were performed using the groups as a whole, rather than using the individual matched pairs. Chi-square was used for the comparison of nominal variables. The student t-test, or its non-parametric equivalent, Mann-Whitney when appropriate, was used for comparison of continuous variables; the *Levene's* test was used in order to check the homogeneity of variance. Results with  $P < 0.05$  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 two intervention groups. Hazard ratio was 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 following 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). 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. All variables were assessed for potential inclusion in the model, and were then selected using the forward likelihood ratio method, with a probability for stepwise of 0.05.

PASW Statistics (SPSS Inc, Chicago, IL) version 18.0 was used for descriptive and inferential statistical analysis.

## **Results**

During the pre-specified time interval 327 patients were implanted with CRT devices. Out of 45 patients implanted with TRI-V pacing devices during the pre-specified time window, 34 filled the inclusion criteria and were included in this analysis. Among the remaining 282 contemporary patients implanted with Bi-V devices, 34 controls were selected through propensity matching.

Reasons for Tri-V patients not being included in the as-treated analysis included: death in the first year post-implant 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. Mean age was  $67.0 \pm 12.8$  years and only 20.6% (n=14) were women. Ischemic cardiomyopathy accounted for 54.4% of all cases, and 11 patients (16.2%) had previously existing right ventricular devices and underwent system upgrades. The majority of patients (95.6%, n=65) was implanted 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-matched control. Figure 1 illustrates the similar distribution of the propensity score among the two treatment groups. In spite of this, a non-significant trend suggesting more severe disease in Tri-V patients could be observed with regard to ischemic disease, AF, and COPD which were numerically but non-significantly more prevalent. Similarly, the use of Beta-blockers and ACEi/ARB-II agents was numerically, but non-significantly, lower.

Bi-V patients not selected through propensity matching, and therefore not included in the comparison, were younger, more frequently female gender, had more AF, were more frequently implanted with CRT-Ps, had higher LVEF and estimated glomerular filtration rate, and received beta-blockers and antiplatelet agents less frequently (Tables 1 and 2).

### **Procedural data / Safety**

No pneumothorax or acute bleeding complications requiring intervention or red blood cell transfusion were observed in any of the treatment groups.

Patients were followed during a total of 413 patient-years (median: 2,478 days, interquartile range 1,183 to 3,214 days). Only one 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 RA 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 was observed in 5 patients: 2 presented with RA lead displacement, 1 with CS lead displacement and two with both RV and CS lead displacement. One case happened in the first week, two 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 two groups (Tri-V 0.86 per 100 patient-years vs. Bi-V 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 patients treated with BI-V devices). In all but two cases, infections occurred following more than one year after the initial device implant (TRI-V 1.83 per 100 patient-years vs. BI-V 1.76 per 100 patient-years;  $P=0.996$ ).

Four patients (one in the TRI-V and three in the BI-V control group (Tri-V 0.48 per 100 patient-years vs. Bi-V 1.84 per 100 patient-years;  $P=0.341$ ) presented with phrenic nerve capture, irresolvable with device reprogramming and required 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 the control Bi-V group (time to Box change: TRI-V  $1,758\pm 360$  days vs. Bi-V  $1,993\pm 408$  days;  $P = 0.072$ ).

Among the 11 Tri-V patients not included in this as-treated analysis, observed issues were: one patient had a micro-dislodgement of the CS lead with loss of capture in the first year and was left with dual-RV pacing as she presented with very good haemodynamic and echo response (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 was later implanted with a standard Bi-V device and died 2,244 days following the initial Tri-V implant; A third patient, with a Tri-V 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-D. This patient died 68 days following the initial Tri-V implantation procedure.

## **Arrhythmic Events**

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

The higher incidence of arrhythmic episodes in Bi-V patients was driven by a higher number of arrhythmia episodes successfully terminated with ATPs (Bi-V 14.12 per 100 patient-years vs. Tri-V 4.10 per 100 patient-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 vs. Bi-V 4.37 per 100 patient-years; P=0.512) (Table 3).

Bi-V recipients presented more frequently with ventricular arrhythmia episodes in the VT zones requiring therapy (Bi-V 52.9% vs. Tri-V 29.4%; P=0.049). The occurrence of episodes in the VF zone requiring therapy was similar in both groups (Bi-V 14.7% vs. Tri-V 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 patients presented with less sustained episodes in the VT zone requiring ICD intervention (Tri-V  $0.8 \pm 1.7$  vs. Bi-V  $3.8 \pm 7.4$ ; P=0.027), and had a lower incidence of VT requiring ATP termination (Tri-V  $0.6 \pm 1.5$  vs. Bi-V  $3.1 \pm 5.8$ ; P=0.018). No differences were observed regarding the incidence of detections in the VF zone requiring ICD termination (Tri-V  $0.4 \pm 1.6$  vs. Bi-V  $0.3 \pm 0.9$ ; P=0.707) or number of appropriate shocks for ventricular arrhythmias (Tri-V  $0.6 \pm 2.1$  vs. Bi-V  $1.0 \pm 2.7$ ; P=0.551).

The incidence of inappropriate shocks was 1.84 per 100 patient-years (95%CI 0.90-3.75), and was similar in both treatment groups (Tri-V 1.96 per 100 patient-years vs. Bi-V 1.70 per 100 patient-years; P = 0.734). These occurred mostly in the setting of AF (71.4%), with the remaining cases occurred 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 from the Bi-V group underwent heart transplant. The overall incidence of all-cause mortality or heart transplant was 9.17 per 100 patient-years (95% CI 6.75-12.33).

A trend for lower all-cause mortality and heart transplant was observed in the Tri-V group (Tri-V 6.99 per 100 patient-years vs. Bi-V 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 0.23-0.85,  $P=0.015$ ) and ischemic cardiomyopathy (HR = 2.54; 95% CI 1.26-5.11;  $P = 0.009$ ) 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 vs. 45 Bi-V controls (Figure S-1) shows lower all-cause mortality and heart transplant in the Tri-V group (log rank  $P = 0.027$ ; HR = 0.55; 95% CI 0.32-0.94;  $P=0.029$ ).

Sub-analyses regarding baseline QRS width and presence/absence of AF and their impact on the overall survival of these patients are shown (Figures S-2 and S-3), and suggest a possible benefit of Tri-V in these subsets of patients (Supplementary Material). 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 coronary sinus) does not seem to affect the incidence of all-cause mortality or heart transplant, nor the ventricular arrhythmia profile (Figures S-4, S-5, S-6 and S7).

## **Discussion**

We have observed a potential benefit of Tri-V pacing compared with standard Bi-V in long term survival, ventricular arrhythmia burden and need of ICD interventions. Also, 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 is the first study demonstrating an impact of Tri-V on long-term clinical outcomes. Previous studies have shown a potential improvement in patients heart failure symptoms (New York Heart Association class and quality of life Minnesota Living With Heart Failure Score [7, 10, 11], peak oxygen consumption – VO<sub>2</sub>max [10], 6-minute walking distance [7, 10]) and haemodynamic (increase in dP/dT and cardiac output [12-14]) benefit, as well as echocardiographic evidence of reverse remodelling (improvement in LVEF [6, 7, 10], LV dimensions [7] and intraventricular synchrony [10]).

Bi-V pacing is thought 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 haemodynamic response and progression of the depolarizing wave-front 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, as scarred regions can prevent or delay progression of the activation wave-front and the synchronized engagement of viable tissue, or if scarring is extensive there may be inadequate volume of healthy myocardium recruited to improve haemodynamics [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 wave-front to bypass regions of slow conduction or scar and reaching previously delayed or remote sites more quickly [7].

*Ogano et al.* have also suggested that Tri-V might affect repolarization indexes (corrected QT interval, and transmural dispersion of repolarization) and therefore exert anti-arrhythmic effects leading to a reduction of ventricular arrhythmia [18]. Other contributory factors can be LV reverse remodelling 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 seems to depend on the position of the pacing site, in relation to the slow-conduction area. It has been suggested that in order to obtain sufficient anti-arrhythmic effects the pacing site should be positioned in the latest sites of activation that maybe responsible for the development of re-entrant tachyarrhythmia. Pacing in a site non-delayed 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 wave-front 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 having some anti-arrhythmic effect on these re-entrant circuits.

The impact of the third ventricular lead position to provide optimal resynchronisation is something that still needs to be fully investigated, as previous studies have either included individuals with two RV leads [14] or two coronary sinus leads [6, 11, 18]. In our small cohort, the two groups are represented (group A and group B), with no difference observed in major clinical outcomes. However, this needs to be interpreted with caution, as our study is not powered to show minor differences among the two strategies of lead placement. Therefore, the comparable outcomes observed with both configurations, which in theory may lead to different electrophysiological and structural remodelling overtime, may be coincidental.

*Behar et al.* have recently shown a potential impact of the new quadripolar coronary sinus leads on survival [23]. 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 less leads and material would be used, a shorter duration procedure would be needed, and therefore, the risk of complications like lead dislodgement, lead failure and infection would theoretically be lower.

The three currently ongoing randomized controlled trials, “*Triple-site Bi-Ventricular Stimulation in the Optimization of CRT*” (TRIUMPH CRT; NCT02350842), “*Standard Care Versus Tri-Ventricular Pacing in Heart Failure*” (STRIVE HF; 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 vs. 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, in particular in those that are classed as non responders to BiV pacing, or whether Tri-V has a role in CRT devices in the population of patients with advanced heart failure and a narrow QRS complex.

### **Study limitations**

We acknowledge several limitations in our work. First, the results of this single-centre 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, as small samples can sometimes lead to misleading results, our findings require validation in larger samples. Second, some patients with narrow QRS complex were implanted based on echocardiography dyssynchrony practice at the time, which was abandoned after the landmark studies PROSPECT [24] and EchoCRT [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, device brands and had similar cutoffs for zone programming, we cannot entirely rule out that unaccounted aspects in detection or therapy programming can have contributed in part to the observed differences in ventricular arrhythmia events.

### **Conclusion**

In this exploratory pilot single-centre study Tri-V presented promising results, and compared with Bi-V it displayed a similar safety profile and potential benefits as regards 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 like mortality and arrhythmic events.

### **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 as almost a third of patients are non-responders to conventional CRT.

**Competency in Patient Care:** These results suggest that CRT can still be improved and in the next decades we may expect better survival and outcomes in the advanced heart failure setting. However, a confirmatory randomized controlled trial confirming the positive performance of Tri-V pacing before it becomes routine practice or an alternative to Bi-V non-responders is warranted.

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## Figure Legends

**Figure 1** – A. Histogram and B. Boxplot illustrating the distribution of propensity-score among the two treatment groups.

Legend: Comparison of means (t-student) shows no significant differences between the two groups – Bi-V  $0.31 \pm 0.20$  vs. Tri-V  $0.32 \pm 0.21$ ,  $P=0.89$ . Same for comparison of medians (Mann-Whitney) – Bi-V  $0.26$  (0.14-0.49) vs. Tri-V  $0.26$  (0.14-0.46),  $P=0.96$ .

**Figure 2** – Incidence of appropriate ICD intervention over time in Bi-V and Tri-V patients.

Legend: HR – hazard ratio; CI – confidence interval.

**Figure 3** – All-cause mortality and heart transplant during follow-up (as-treated analysis).

Legend: HR – hazard ratio; CI – confidence interval.