JACC: CLINICAL ELECTROPHYSIOLOGY
VOL. 2, NO. 2, 2016

ISSN 2405-500X/$36.00
PUBLISHED BY ELSEVIER
http://dx.doi.org/10.1016/j.jacep.2015.10.004

Cardiac Resynchronization Therapy With a Quadripolar Electrode Lead Decreases Complications at 6 Months

Results of the MORE-CRT Randomized Trial

Giuseppe Boriani, MD, PhD,[a,b] Sean Connors, MD, PhD,[c] Zbigniew Kalarus, MD,[d] Bernd Lemke, MD,[e] Wilfried Mullens, MD, PhD,[f] Joaquin Osca Asensi, MD, PhD,[g] Pekka Raatikainen, MD, PhD,[h] Carlo Gazzola, BSc,[i] Taraneh G. Farazi, PhD,[j] Christophe Leclercq, MD, PhD[k]

ABSTRACT

OBJECTIVES The aim of this study was to test the hypothesis that a quadripolar left ventricular (LV) lead results in fewer LV lead–related events than a bipolar cardiac resynchronization therapy (CRT) system in a prospective randomized trial.

BACKGROUND Bipolar LV leads cannot be implanted at the optimal site in up to 10% of patients who need CRT, because of anatomic or technical challenges (pacing threshold, phrenic stimulation, or mechanical instability).

METHODS The MORE-CRT (More Options Available With a Quadripolar LV Lead Provide In-Clinic Solutions to CRT Challenges) trial enrolled 1,078 patients. Patients with indications for CRT defibrillator therapy were randomized into 2 groups in a 1:2 ratio: a group with a bipolar CRT lead system (the BiP group; any manufacturer) and a group with a quadripolar CRT system (the Quad group; Quartet LV lead). The primary endpoint was freedom from a composite endpoint of intraoperative and post-operative LV lead–related events at 6 months.

RESULTS A total of 1,074 of 1,078 patients (99%) were randomized and contributed to the primary endpoint. Freedom from the composite endpoint was significantly greater in the Quad than the BiP group (83.0% vs. 74.4%, $p = 0.0002$). The intraoperative component of the endpoint was met less frequently by Quad group patients (6.26% Quad vs. 12.1% BiP), whereas there was no difference for the post-operative component (7.1% Quad vs. 7.6% BiP).

CONCLUSIONS The Quartet LV system significantly reduced total LV lead–related events at 6 months after implantation compared with a bipolar CRT system. The reduction in events demonstrates the superiority of this quadripolar technology to effectively manage CRT patients. (More Options Available With a Quadripolar LV Lead Provide In-Clinic Solutions to CRT Challenges [MORE-CRT]; NCT01510652) (J Am Coll Cardiol EP 2016;2:212–20)

From the [a]Institute of Cardiology, DIMES Department, University of Bologna, Bologna, Italy; [b]Cardiology Department, Modena University Hospital, University of Modena and Reggio Emilia, Modena, Italy; [c]Department of Cardiology, Memorial University of Newfoundland, St. John's, Newfoundland, Canada; [d]Department of Cardiology, Silesian Center for Heart Diseases (SCHD), Zabrze, Poland; [e]Department of Cardiology, Hospital Lüdenscheid, Lüdenscheid, Germany; [f]Department of Cardiology, Hospital Oost-Limburg, Universiteit Hasselt, Genk, Belgium; [g]Department of Cardiology, University Hospital La Fe, Valencia, Spain; [h]Department of Cardiology, Central Finland Health Care District and University of Eastern Finland, Jyväskylä, Finland; [i]SJM Coordination Center BVBA, Zaventem, Belgium; [j]St. Jude Medical Inc., Sunnyvale, California; and the [k]Hospital Pontchaillou, Rennes, France. This study was sponsored by St. Jude Medical. Prof. Boriani has received speaking fees from Biotronik, Boston Scientific, Medtronic, and St. Jude Medical. Dr. Connors has received consulting fees from St. Jude Medical; and speaking fees from St. Jude Medical, Biosense Webster, Bristol-Myers Squibb, and Boehringer-Ingelheim. Prof. Kalarus has received speaking fees from Pfizer, Eli Lilly, Boehringer-Ingelheim, Abbott, Bayer, St. Jude Medical, and Adamed; and consulting fees from Boehringer Ingelheim, Amgen, and AstraZeneca. Prof. Lemke has received speaking fees from St. Jude Medical, Medtronic, Biotronik, and Impulse Dynamic. Dr. Osca-Asensi has received consulting fees from St. Jude Medical. Prof. Raatikainen has received consulting fees from Bayer and Bristol-Myers Squibb/Pfizer; speaking fees from Biosense Webster, Bristol-Myers Squibb/Pfizer, Boehringer Ingelheim, and Cardiome; and research support from St. Jude Medical. Mr. Gazzola and Dr. Farazi are employees of St. Jude Medical. Prof. Leclercq has received consulting fees from St. Jude Medical, Medtronic, Sorin, Boston Scientific, and Biotronik. Dr. Leclerq has reported that he has no relationships relevant to the contents of this paper to disclose.

Manuscript received July 31, 2015; revised manuscript received September 14, 2015, accepted October 8, 2015.

Listen to this manuscript's audio summary by *JACC: Clinical Electrophysiology* Editor-in-Chief Dr. David J. Wilber.

Cardiac resynchronization therapy (CRT) is a recognized and rapidly expanding therapy for heart failure (HF) that has been shown to produce significant clinical benefits, including reduced mortality, fewer HF hospitalizations, and improved symptoms and quality of life (QoL) (1–7). CRT is achieved by pacing both a right ventricular lead and a left ventricular (LV) lead, which is usually placed in a tributary of the coronary sinus. Improvements in LV lead technology over the past decade have been driven by the need for leads to be placed in stable locations with adequate pacing thresholds and the absence of phrenic nerve stimulation (PNS). Despite improvements, challenges remain in consistently situating the lead in the target vein with both a stable position and an acceptable pacing threshold. Furthermore, LV leads that are displaced over time potentially lead to increased pacing thresholds, PNS, or hemodynamically suboptimal pacing sites (8–13). These complications may require lead repositioning, or they may sometimes be mitigated by post-implantation reprogramming of the LV pacing vector (13). However, an additional invasive procedure may be necessary to physically reposition the lead, with a high risk for complications in revision of CRT devices (14), or a surgical procedure may be required to implant an LV lead on the epicardium. When further invasive procedures (implant revision) are difficult or contraindicated, it may be necessary to abandon LV pacing and therefore CRT.

Recently, a novel quadripolar LV lead (Quartet, St. Jude Medical, St. Paul, Minnesota) has been introduced that has 1 distal tip electrode and 3 ring electrodes at positions along the lead progressively more proximal from the distal tip and can be programmed to pace the left ventricle in any of 10 different vectors. Several observational studies have shown that the implantation of this quadripolar LV lead has been successful in ≥95% of patients and has been associated with low rates of lead dislodgment and PNS (15–19). Therefore, the MORE-CRT (More Options Available With a Quadripolar LV Lead Provide In-Clinic Solutions to CRT Challenges) randomized clinical trial was designed to prospectively compare LV lead-related events through 6 months of follow-up in patients implanted with the Quartet-based CRT system versus any bipolar CRT system.

METHODS

PATIENTS. MORE-CRT was a prospective, randomized, parallel, multicenter, open-label trial (NCT01510652) conducted at 63 centers in 13 countries. Selection of centers was based on previous experience in CRT and quadripolar lead implantation. This study is the first large randomized controlled trial with direct comparison between quadripolar and bipolar CRT.

Patients were included if they had conventional indications for the implantation of a CRT defibrillator, were ≥18 years of age, and had life expectancies ≥12 months. Patients were excluded if, within 4 weeks before enrollment, they had myocardial infarctions, unstable angina pectoris, or coronary artery bypass grafting. In addition, patients were excluded if they were pregnant or had uncorrected primary valvular disease. All patients provided written informed consent, and the study was approved by the institutional ethics committee of each center.

ABBREVIATIONS AND ACRONYMS

BiP = bipolar left ventricular lead group

CRT = cardiac resynchronization therapy

CS = coronary sinus

HF = heart failure

LV = left ventricular

MLWHFQ = Minnesota Living With Heart Failure Questionnaire

PNS = phrenic nerve stimulation

QoL = quality of life

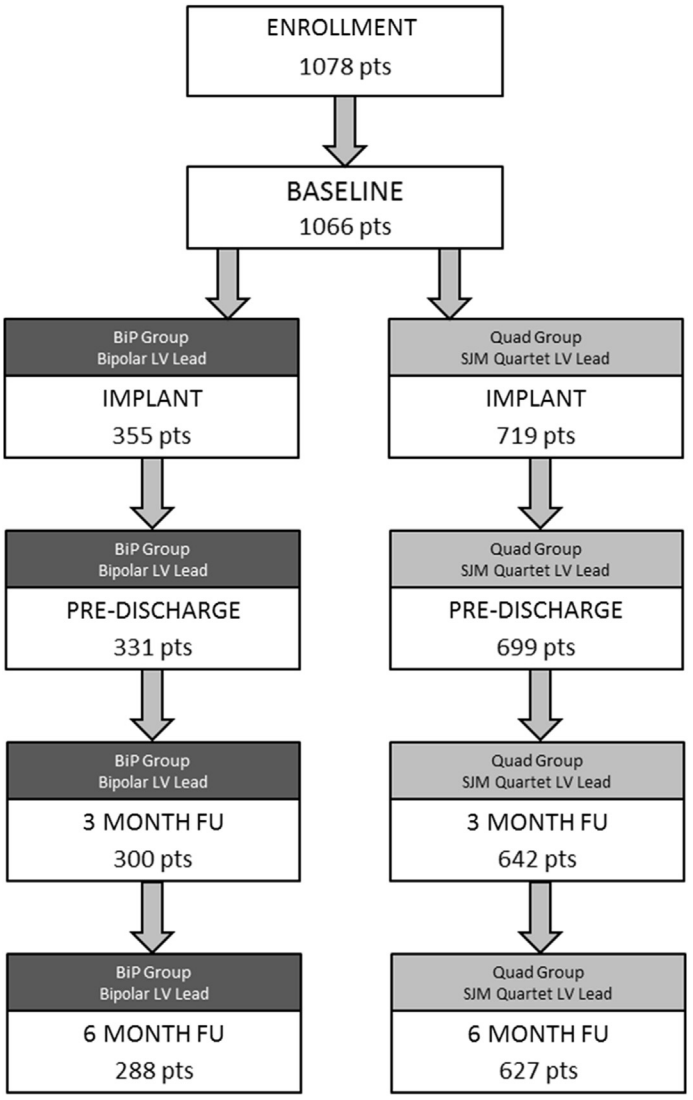
Quad = quadripolar Quartet left ventricular lead group

Patients were randomized into 1 of 2 groups in a 1:2 ratio: a group with a bipolar CRT-D system (passive-fixation LV lead; the BiP group) and a group with a quadripolar CRT-D system (Quartet LV lead; the Quad group). The BiP group was furthermore randomized in a 1:2 ratio to bipolar leads from St. Jude Medical or from other manufacturers (**Figure 1**). Initial clinical experiences with the Quartet quadripolar LV lead system have been reported (17). After successful implantation, patients were observed before hospital discharge and at 3 and 6 months post-implantation.

PRIMARY ENDPOINT. The primary endpoint of the study was freedom from a composite endpoint of intraoperative and post-operative events through 6 months after implantation. Intraoperative events included implant failure for any reason; change to a different tributary vein of the coronary sinus after target site evaluation; use of more than 1 LV lead during the procedure; and use of any device (e.g., a stent) to actively fix the lead because of PNS, mechanical lead instability, or high pacing threshold. A lead position was considered unstable when the implanting physician chose to take extra measures to avoid acute or possible future dislodgements.

Post-operative events were defined as any serious adverse device event related to the LV lead and abandoning CRT for any reason. An LV lead-related serious adverse device event was defined as an adverse event related to the LV lead that required hospitalization or medical or surgical intervention or resulted in death or serious deterioration in the health of a patient. All events were classified by the reporting investigator if the events were LV-related serious adverse device events before submission to the sponsor. All events were further assessed by trained personnel from the

FIGURE 1 Study Flowchart



A flow diagram of patients enrolled in the MORE-CRT (More Options Available With a Quadripolar LV Lead Provide In-Clinic Solutions to CRT Challenges) study. BiP = bipolar left ventricular lead group; FU = follow-up; LV = left ventricular; pts = patients; Quad = quadripolar Quartet left ventricular lead group; SJM = St. Jude Medical.

sponsor's safety team who were not involved in the study.

Additional analyses were performed among patients who underwent successful implantation to compare the number of LV lead positions that were not evaluated as satisfactory because of PNS and the PNS safety margin, defined as the difference between PNS threshold and LV pacing threshold.

SECONDARY ENDPOINTS. The intraoperative secondary endpoints included procedure duration (skin to skin), fluoroscopy time, the need to reposition the lead within the same vein (after unsatisfactory lead site evaluation), and the need to program the LV pacing amplitude to <1 V higher than the measured pacing threshold. Other secondary endpoints included freedom from hospitalization for HF and CRT system hospitalization through 6 months of follow-up, the percentage of CRT responders (defined as a reduction in LV end-systolic volume of ≥10% between baseline and 6 months), survival from all-cause mortality at 6 months, and improvement in QoL between baseline and 6-month follow-up (defined as a decrease of at least 5 points in the Minnesota Living With Heart Failure Questionnaire [MLWHFQ] score or a positive change of status on the EQ-5D test). QoL was assessed with the MLWHFQ and EQ-5D.

STATISTICAL ANALYSIS. To test the hypothesis that the Quartet quadripolar LV lead is superior to bipolar LV leads in terms of freedom from the composite endpoint and to achieve 90% power at a significance level of 5% with a randomization ratio of 1:2, it was estimated that 1,006 patients (336 patients in the BiP group and 670 patients in the Quad group) would be needed. Taking into account a dropout rate of 5%, it was further estimated a total of 1,062 patients should be enrolled in the study (354 patients in the BiP group and 708 in the Quad group).

The primary endpoint analysis was based on the intention-to-treat principle. Patients who were withdrawn from the study before implantation and those who had incomplete data for the intraoperative endpoint were imputed as failure at time of implantation. Sensitivity analysis was performed to assess the robustness of the results. Event rates for time-to-event endpoints were based on Kaplan-Meier estimation. The log-rank test was used to compare the primary outcome between the 2 groups as well as for the post-hoc subgroup analysis. The impact of subgroup covariate and its interaction with the treatment was analyzed using Cox proportional hazard regression. The assumption for proportional hazards was confirmed for each covariate in the Cox proportional hazard model. Continuous variables are summarized as mean ± SD, and categorical variables are reported as frequencies or percentages. Continuous variables were compared using unpaired Student *t* tests or Wilcoxon rank sum tests if the data were not normally distributed. Categorical variables were compared using chi-square tests or Fisher exact tests if >25% of the cells in the contingency table had expected frequencies <5. A p value <0.05 was considered to indicate statistical significance for all analyses. Statistical analyses were performed using SAS software

version 9.2 (SAS Institute Inc., Cary, North Carolina) by the study sponsor and validated per sponsor procedures.

RESULTS

A total of 1,078 patients were enrolled between November 2011 and August 2013 at 63 centers in 13 countries; 1,074 patients were randomized either to the BiP group (n = 355 [32.9%]) or to the Quad group (n = 719 [66.7%]). Of the 1,078 patients, 1,018 underwent successful implantation (including multiple attempts), and complete 6-month follow-up visits were achieved for 915 patients (84.9%). There was no significant difference between the 2 groups with regard to the proportion of patients who withdrew before the primary endpoint visit (6.9% in the Quad group vs. 9.6% in the BiP group, p = 0.12) (Online Table 1).

Baseline data were obtained in 1,066 patients (98.8%). The average age at baseline was 67.9 ± 10.1 years, and 76.8% were men. The baseline LV ejection fraction was 27.2 ± 7.7%, and 33.8%, 62.6%, and 3.6% were in New York Heart Association functional classes II, III, and IV, respectively. The average baseline QRS duration was 157 ± 28 ms. There were no differences in the demographic, echocardiographic, or electrocardiographic variables between the 2 groups (**Table 1**). There was a slightly greater prevalence of ischemic heart disease in the BiP group than the Quad group (56.3% vs. 49.2%, p = 0.0283) (**Table 2**). The higher prevalence of ischemic heart disease in the BiP group may have accounted for a higher percentage of patients with histories of coronary artery bypass grafting than in the Quad group (23.6% vs. 16.7%, p = 0.0074). Histories of other cardiac procedures, including percutaneous coronary intervention, atherectomy, and valvular repair or replacement, were not significantly different between the 2 groups. In addition, there was no difference in baseline medication use between the 2 groups (Online Table 2).

TABLE 1 Baseline Demographic, Echocardiographic, and Electrocardiographic Variables

	BiP (n = 348)	Quad (n = 718)	p Value
Age (yrs)	68.4 ± 9.7	67.6 ± 10.2	NS
Men	274 (78.7)	545 (75.9)	NS
NYHA functional class			
II	113 (32.5)	247 (34.4)	NS
III	219 (62.9)	448 (62.4)	NS
IV	16 (4.6)	23 (3.2)	NS
LVEDV (ml)	204.5 ± 72.0	200.4 ± 74.9	NS
LVESV (ml)	149.0 ± 58.3	151.2 ± 64.0	NS
LVEF (%)	27.5 ± 8.1	27.1 ± 7.6	NS
QRS duration (ms)	157 ± 27	158 ± 29	NS
Arrhythmia history			
Atrial fibrillation	58 (16.7)	114 (15.9)	NS
Atrial flutter	7 (2.0)	21 (2.9)	NS
AV block (%)			
None	242 (69.5)	484 (67.4)	NS
First-degree block	62 (17.8)	138 (19.2)	NS
Second-degree block (Mobitiz 1)	1 (0.3)	2 (0.3)	NS
Second-degree block (Mobitiz 2)	1 (0.3)	2 (0.3)	NS
Third-degree block	18 (5.2)	37 (5.1)	NS
Other findings			
None	59 (16.9)	133 (18.5)	NS
LBBB	252 (72.4)	501 (69.8)	NS
RBBB	17 (4.9)	41 (5.7)	NS
LAFB	4 (1.1)	10 (1.4)	NS
Other	14 (4.0)	28 (3.9)	NS
Coronary artery bypass graft	82 (23.6)	120 (16.7)	0.0074

Values are mean ± SD or n (%).

AV = atrioventricular; BiP = bipolar left ventricular lead group; LAFB = left anterior fascicular block; LBBB = left bundle branch block; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; LVESV = left ventricular end-systolic volume; NYHA = New York Heart Association; Quad = quadripolar Quartet left ventricular lead group; RBBB = right bundle branch block.

PRIMARY ENDPOINT. Of the 1,078 enrolled patients, 1,074 (99%) were randomized and contributed to the primary composite endpoint analysis. **Figure 1** represents the flow diagram of the enrolled patients. Of these 1,074 patients, 1,052 underwent implantation, and 22 did not because of early termination (including 2 who died before implantation, 4 who withdrew informed consent, and 5 who were withdrawn by the study investigators). The composite event occurred in 113 patients in the Quad group and 88 patients in the BiP group. Freedom from the composite endpoint was significantly greater in the Quad group than the BiP group (n = 1,074, 83.0% vs. 74.4%, p = 0.0002) (**Figure 2**). With a hazard ratio of 0.61 (95% confidence interval: 0.46 to 0.80) for the Quad group compared with the BiP group, the hazard that a patient would progress to a composite event at a time point was less for patients in the Quad group by 39%. The analysis of the best-case scenario (assuming that patients with missing endpoint data did not experience failures) showed superiority of the Quartet lead (p = 0.0038). Furthermore, the results of the analysis of available cases (excluding patients with missing endpoint data from the analysis) were consistent with those of the primary analysis (p = 0.0026). Therefore, the sensitivity analysis demonstrated consistently better outcomes for the Quartet lead regardless of how the cases with missing values were considered.

The number of patients meeting the intraoperative LV lead-related component of the composite

TABLE 2 Heart Failure Etiology at Baseline

Etiology	BiP (n = 348)	Quad (n = 718)	p Value
Ischemic HF	196 (56.3)	353 (49.2)	0.0283
CAD without MI	62 (17.8)	112 (15.6)	NS
CAD with MI	135 (38.8)	240 (33.4)	NS
Unstable angina	0 (0)	5 (0.7)	NS
Other	3 (0.9)	3 (0.4)	NS
Nonischemic HF	152 (43.7)	365 (50.8)	0.0283
Dilated CMP	66 (19.0)	155 (21.6)	NS
Idiopathic CMP	65 (18.7)	131 (18.2)	NS
Hypertrophic CMP	3 (0.9)	13 (1.8)	NS
Nonobstructive HCM	4 (1.1)	8 (1.1)	NS
Hypertensive	9 (2.6)	25 (3.5)	NS
Valvular	8 (2.3)	31 (4.3)	NS
Other	16 (4.6)	32 (4.5)	NS

Values are n (%). Patients with ischemic HF and nonischemic heart disease could be classified into more than 1 subcategory.

CAD = coronary artery disease; CMP = cardiomyopathy; HCM = hypertrophic cardiomyopathy; HF = heart failure; MI = myocardial infarction; Other abbreviations as in Table 1.

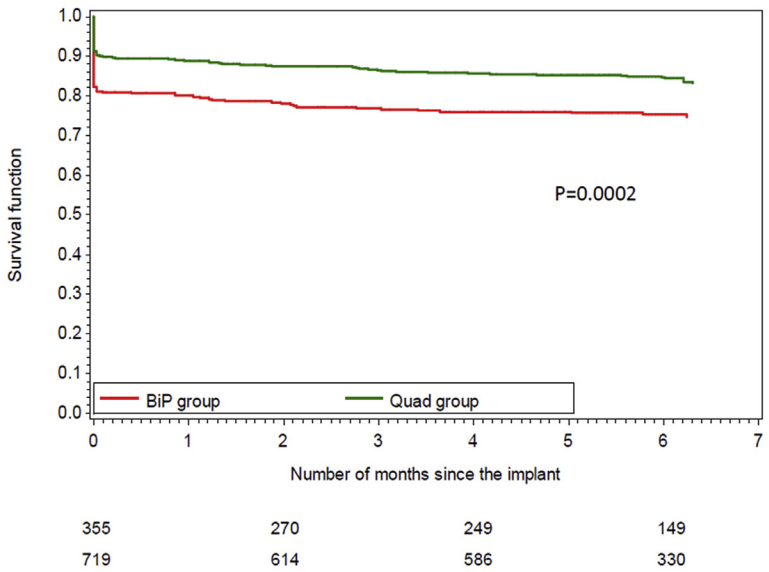
endpoint was lower in the Quad group than the BiP group (n = 1,074, 6.3% vs. 12.1%). A detailed list of all intraoperative events is shown in Table 3. This result was driven mainly by implant failure rate as well as reported events due to PNS, high pacing threshold, or mechanical instability. Once the coronary sinus was cannulated, implant-related failures were consistently lower for the Quad group than the BiP group. In addition, intraoperative events related to PNS, high pacing threshold, or mechanical instability were also in favor of the Quad group. In particular, the use of more than 1 LV lead to conclude the implantation and change to a different vein were more prevalent in the BiP group (n = 1,052, 1.3% vs. 5.3% and 1.7% vs. 3.2%, respectively).

There was no difference in the number of patients meeting the post-operative component of the composite endpoint between the Quad group and the BiP group (n = 1074, 7.1% vs 7.6%, respectively).

Among patients who underwent successful implantation and were evaluated for PNS, the proportion of patients with rejected lead positions due to PNS was significantly lower in the Quad group than the BiP group (n = 992, 2.5% vs 8.8%, p < 0.0001). Furthermore, among patients with unacceptable positions due to PNS (n = 45), patients in the Quad group had a greater PNS safety margin. Specifically, in the Quad group, 10 of 17 patients (58.9%) had safety margins >2 V, whereas only 8 of 28 (28.6%) had this safety margin in the BiP group (p = 0.0208). Finally, the overall average safety margin was significantly higher in the Quad group than the BiP group (4.5 ± 3.3 vs. 1.9 ± 3.2 V, p = 0.0279).

ADDITIONAL ANALYSIS. Post-hoc analysis was performed to examine the effect of HF etiology on the

FIGURE 2 Primary Endpoint



Kaplan-Meier survival curves in the quadripolar lead group and the bipolar lead group. The x-axis shows months of follow-up, and the y-axis shows freedom from the composite endpoint (cumulative survival). BiP = bipolar left ventricular lead group; LV = left ventricular; Quad = quadripolar Quartet left ventricular lead group.

TABLE 3 Detailed List of All Intraoperative Events

Intraoperative Event	BiP (n = 342)	Quad (n = 710)	Total (n = 1,052)
Implant failure			
Unable to cannulate CS	2 (0.6)	13 (1.8)	15 (1.4)
Unable to proceed within CS	3 (1.0)	0 (0)	3 (0.3)
Unable to reach the target vein and no other possible veins	5 (1.6)	2 (0.3)	7 (0.7)
Unable to reach any vein	1 (0.3)	1 (0.1)	2 (0.2)
No stable position found	1 (0.3)	0 (0)	1 (0.10)
Persistent SVC	1 (0.3)	2 (0.3)	3 (0.3)
Other	3 (0.9)	7 (0.9)	10 (0.9)
Total	16 (4.7)	25 (3.5)	41 (3.9)
Due to PNS, high pacing threshold, or mechanical instability			
Change to a different vein	11 (3.2)	12 (1.7)	23 (2.2)
Use more than 1 LV lead	18 (5.3)	9 (1.3)	27 (2.6)
Use of a device to fix the lead	0 (0)	1 (0.14)	1 (0.10)
Total	29 (8.5)	22 (3.1)	51 (4.85)

Values are n (%). Note that for the 3 categories "Change to a different vein," "Use more than 1 LV lead," and "Use of a device to fixate the lead," multiple choices are possible (i.e., change of vein and change of LV lead model).

CS = coronary sinus; LV = left ventricular; PNS = phrenic nerve stimulation; SVC = superior vena cava; Other abbreviations as in Table 1.

study outcome. The primary endpoint results, stratified by ischemic or nonischemic HF, showed no significant interaction between etiology and treatment (p = 0.86), and the results remained unaffected. Specifically, in patients with ischemic HF, freedom from the composite endpoint was significantly greater in the Quad group than the BiP group (83.0% vs 75.8%, p = 0.0162). Similarly, freedom from the composite endpoint in patients with a nonischemic HF etiology was greater in the Quad group than the BiP group (83.2% vs 76.0%, p = 0.0504) (**Figure 3**, Online Table 3).

The percentage of patients who responded to CRT at 6 months was 61.9% in the Quad group compared with 56.0% in the BiP group; however, this difference was not statistically significant (p = 0.1334). In addition, the percentage of patients who had improvements in QoL (according to the MLWHFQ and EQ-5D) between baseline and 6 months was 64.6% in the Quad group and 58.9% in the BiP group, although this difference was also not statistically significant (p = 0.1179). Although numbers were in favor of the Quad group, the analysis of this secondary endpoint showed no difference between the 2 groups in terms of percentage of CRT responders, percentage of patients with >90% biventricular pacing at 6 months, implantation procedure duration, fluoroscopy time, repositioning the lead within the same vein at implant (after unsatisfactory lead site evaluation), post-operative programming of LV output to <1 V higher than the measured pacing threshold, improvements in QoL (according to the MLWHFQ and EQ-5D) at 6 months, survival free of HF, CRT system-related hospitalizations, all-cause hospitalizations, and mortality at 6 months (**Table 4**).

The vectors programmed at pre-discharge visits are shown in **Table 5**. Quadripolar-exclusive vectors were programmed in 41.5% of patients in the Quad group. The vector programming decision was made by the implanting physician per the patient's status.

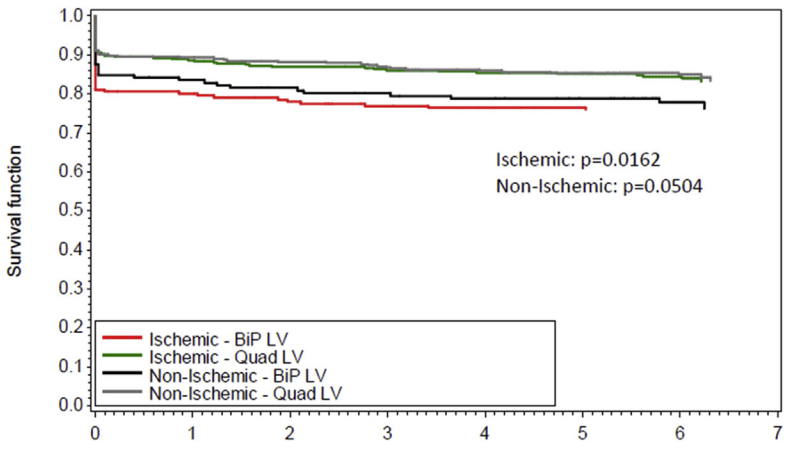
DISCUSSION

The present study is the first prospective, randomized study to compare the outcomes of CRT systems with the Quartet LV lead with those with any bipolar LV lead. Appropriate evaluation of the clinical impact of a new technology is an important step in health technology assessment (20). Because observational and uncontrolled clinical evaluations are associated with a substantial risk for bias, randomized clinical trials are the gold standard of comparative assessments, supporting the conception of the MORE-CRT trial. In this randomized trial, we observed a superior performance and safety of the Quartet LV lead compared with bipolar LV leads.

Although 60% to 70% of patients with HF with systolic dysfunction have been reported to respond to CRT therapy, LV leads could not be implanted in up to 10% of patients in studies published at the time the Quartet lead was tested (5,8,10). These implant failures are due, not to patient selection, but rather to challenges posed by coronary sinus venous anatomy, leading to lead instability, PNS, and inadequate pacing threshold (11,12). Lead repositioning in the coronary sinus branch may be needed in 26% of patients when there is poor lead stability, PNS, or unsatisfactory electric measurement (21). The use of a quadripolar LV lead constitutes a novel approach for CRT implantation. The Quartet quadripolar lead has 1 distal tip electrode and 3 ring electrodes and can be programmed to 10 different pacing vectors to help identify a pacing site with a low pacing threshold and without PNS. According to the results of prior observational studies with this quadripolar lead, implantation was successful in ≥95% of patients, and the rates of lead displacement and PNS were low (15-18).

The results of the present study showed that the primary endpoint of freedom from intraoperative and post-operative lead-related events was in favor of patients with the Quartet quadripolar LV lead compared with those with bipolar LV leads from any manufacturer. The driver of benefit was a marked reduction in intraoperative LV lead-related events, with the intraoperative event rate reduced by more

FIGURE 3 Primary Endpoint per Etiology



No. at Risk				
Ischemic				
Bipolar LV	196	149	135	84
Quadripolar LV	353	299	288	162
Non-Ischemic				
Bipolar LV	152	121	114	65
Quadripolar LV	365	315	298	168

Interaction between etiology and randomized treatment: p=0.8676

Kaplan-Meier survival curves in the quadripolar lead group and the bipolar lead group per cardiomyopathy etiology. The x-axis shows months of follow-up, and the y-axis shows freedom from the composite endpoint (cumulative survival). BiP = bipolar left ventricular lead group; LV = left ventricular; Quad = quadripolar Quartet left ventricular lead group.

TABLE 4 Results of the Analysis of Secondary Endpoints

	BiP*	Quad*	Total*	p Value
Percentage of CRT responders at 6 months	56.0 (218)	62.0 (476)	60.1 (694)	0.1334
Percentage of patients with >90% biventricular pacing at 6 mo	81.1 (233)	82.0 (500)	81.7 (733)	0.7318
Implantation procedure duration (min)	101.0 ± 51.0	100.4 ± 54.5	100.6 ± 53.3	0.6203
Implantation fluoroscopy time (min)	20.3 ± 16.8	19.7 ± 15.6	32.7 ± 16.0	0.6382
Repositioning the lead within the same vein (after unsatisfactory lead site evaluation)	8.5 (331)	8.6 (687)	8.5 (1,018)	0.9618
Programming of the LV output to <1 V above the measured pacing threshold	15.7 (70)	12.9 (240)	13.5 (310)	0.5473
Improvements in quality of life (MLWHFQ, EQ-5D) at 6 mo	59.5 (264)	64.3 (575)	62.8 (839)	0.1179
Survival free of HF hospitalization at 6 mo	5.1 (331)	5.2 (687)	5.2 (1,018)	0.9736
Survival free of CRT system-related hospitalizations at 6 mo	9.4 (331)	8.9 (687)	9.0 (1,018)	0.7715
Survival free of all-cause mortality at 6 mo	3.3 (331)	2.8 (687)	2.9 (1,018)	0.5892

Values are % (n) or mean ± SD. *Total number of patients with data available.
CRT = cardiac resynchronization therapy; HF = heart failure; Other abbreviations as in Tables 1 and 3.

than 50%. Even though the performance of the bipolar leads in MORE-CRT was superior to those observed in previous studies (8–15), the Quartet lead outperformed these results and demonstrated further superiority. The benefit was confirmed in a subanalysis that stratified patients into 2 groups on the basis of their HF etiology (ischemic or nonischemic). Furthermore, subanalysis showed that in patients who underwent successful implantation who were evaluated for PNS, the rate of any lead-related event due to PNS was significantly lower in the Quad group than the BiP group. This is a remarkable result on top of the use of electric repositioning, which already decreased the rate of PNS with bipolar LV leads (12,13). In addition, patients with the Quartet lead had a higher safety margin for PNS than those with bipolar leads.

Although none of the differences in secondary endpoints were statically significant, there was a

TABLE 5 Final Device Programming of Left Ventricular Vectors

Vector	Patients per Programmed Vector
Quad (n = 553)	
Distal 1 to mid 2	38.9 (215)
Distal 1 to proximal 4	3.8 (21)
Distal 1 to RV coil	9.0 (50)
Mid 2 to proximal 4	7.2 (40)
Mid 2 to RV coil	10.5 (58)
Mid 3 to mid 2	8.9 (49)
Mid 3 to proximal 4	8.3 (46)
Mid 3 to RV coil	7.2 (40)
Proximal 4 to mid 2	1.4 (8)
Proximal 4 to RV coil	4.7 (26)
BiP (n = 249)	
Bipolar (tip to ring)	52.2 (130)
Tip to RV coil	20.5 (51)
Ring to RV coil	27.3 (68)

Values are n (%).
RV = right ventricular; other abbreviations as in Table 1.

trend for the Quartet lead to improve the response to CRT and QoL. The lack of significance in the changes in these variables from baseline to 6 months may have been due to the limited follow-up duration and to differences in programming LV pacing vectors. Furthermore, the study was powered only for primary endpoint and not for secondary analyses.

CLINICAL IMPLICATIONS. The performance and safety of the Quartet LV lead provide more options to effectively manage common pacing complications compared with systems based on bipolar leads; thus, this lead should improve the efficiency of CRT. The use of this quadripolar lead facilitates successful completion of CRT implantation and may reduce the need for surgical revisions to reposition the lead, thereby reducing the risks associated with early reinterventions. Reinterventions are associated with high risks for complications, particularly with regard to the risks for system infection (22,23). Therefore, the use of the Quartet lead could imply, in a large number of patients, important benefits that cannot emerge in a prospective trial limited to 1,000 patients. Furthermore, the Quartet LV lead provides more options to pace at a preferred LV stimulation site without compromising lead stability. Moreover, although this study was not powered to demonstrate benefit in the secondary endpoints, the positive trends in these parameters point to potentially more efficacious CRT therapy during long-term follow-up if a quadripolar CRT system is used instead of a conventional bipolar system.

STUDY LIMITATIONS. Because patients were followed for only 6 months, studies with longer follow-up would add to the body of evidence. Absence of protocol-required CRT optimization may have contributed to the observed CRT response. Specifically, CRT optimization by echocardiography, electrocardiography, or electrogram may have led to a higher response rate in the Quad group compared with the BiP group by improving higher use of Quad-exclusive LV pacing vectors. The additional option of multipoint stimulation (i.e., simultaneous pacing from more than 2 electrodes of the quadripolar lead) (24,25) was not considered in this study, because the devices used did not allow this pacing modality.

CONCLUSIONS

In this large, prospective, randomized trial, freedom from intraoperative and post-operative LV lead-related events at 6 months was greater in patients with the Quartet quadripolar LV lead than in those with bipolar LV leads. The significant reduction in rate of LV lead-related events achieved with this quadripolar lead, which provides more pacing options to manage CRT patients, demonstrates the safety and reliability of this technology.

ACKNOWLEDGMENT The authors thank Emily Zhang for her statistical expertise.

REPRINT REQUESTS AND CORRESPONDENCE: Prof. Giuseppe Boriani, Cardiology Department, University of Modena and Reggio Emilia, Policlinico di Modena, Via del Pozzo, 71, 41124 Modena, Italy. E-mail: giuseppe.boriani@unimore.it.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: CRT is an effective treatment for appropriately selected patients with HF. CRT is achieved by pacing both a right ventricular lead and an LV lead, which is usually placed in a tributary of the coronary sinus. Despite improvements in LV lead technology, challenges remain in consistently situating the lead in the target vein with a stable position and an acceptable pacing threshold and in the absence of PNS. The use of a quadripolar lead (the Quartet LV lead) for LV stimulation provides more options to effectively manage common pacing complications compared with systems based on bipolar leads, because it facilitates successful completion of CRT implantation at a preferred LV stimulation site without compromising lead stability.

TRANSLATIONAL OUTLOOK: In view of the results of the present study, the use of a quadripolar lead (the Quartet LV lead) for LV stimulation could imply in a large number of patients additional benefits that cannot emerge in a prospective trial limited to 1,000 patients. This emphasizes the role of registries collecting information over the long term.

REFERENCES

1. Cazeau S, Leclercq C, Lavergne T, et al., for the Multisite Stimulation in Cardiomyopathies (MUSTIC) Study Investigators. Effects of multisite biventricular pacing in patients with heart failure and intraventricular conduction delay. N Engl J Med 2001;344:873–80.

2. Abraham WT, Fisher WG, Smith AL, et al. Cardiac resynchronization in chronic heart failure. N Engl J Med 2002;346:1845–53.

3. Cleland JG, Daubert JC, Erdmann E, et al. The effect of cardiac resynchronization on morbidity and mortality in heart failure. N Engl J Med 2005; 352:1539–49.

4. Linde C, Abraham WT, Gold MR, Daubert C, for the REVERSE Study Group. Cardiac resynchronization therapy in asymptomatic or mildly symptomatic heart failure patients in relation to etiology: results from the REVERSE (Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction) study. J Am Coll Cardiol 2010;56:1826–31.

5. Anand IS, Carson P, Galle E, et al. Cardiac resynchronization therapy reduces the risk of hospitalizations in patients with advanced heart failure: results from the Comparison of Medical Therapy, Pacing and Defibrillation in Heart Failure (COMPANION) trial. Circulation 2009;119:969–77.

6. Moss AJ, Hall WJ, Cannom DS, et al., for the MADIT-CRT Trial Investigators. Cardiac-resynchronization therapy for the prevention of heart-failure events. N Engl J Med 2009;361: 1329–38.

7. Tang AS, Wells GA, Talajic M, et al. Cardiac resynchronization therapy for mild-to-moderate heart failure. N Engl J Med 2010;363:2385–95.

8. Gras D, Böcker D, Lunati M, et al., for the CARE-HF Study Steering Committee and Investigators. Implantation of cardiac resynchronization therapy systems in the CARE-HF trial: procedural success rate and safety. Europace 2007;9:516–22.

9. Ypenburg C, Vanbommel R, Delgado V, et al. Optimal left ventricular lead position predicts reverse remodelling and survival after cardiac resynchronization therapy. J Am Coll Cardiol 2008;52:1402–9.

10. Dickstein K, Bogale N, Priori S, et al., for the Scientific Committee and National Coordinators. The European Cardiac Resynchronization Therapy Survey. Eur Heart J 2009;30:2450–60.

11. Borleffs CJW, van Bommel RJ, Molhoek SG, de Leeuw JG, Schalij MJ, van Erven L. Requirement for coronary sinus lead interventions and effectiveness of endovascular replacement during long-term follow-up after implantation of a resynchronization device. Europace 2009;11: 607–11.

12. Biffi M, Moschini C, Bertini M, et al. Phrenic stimulation: a challenge for cardiac resynchronization therapy. Circ Arrhythm Electrophysiol 2009;2:402–10.

13. Goetze S, Defaye P, Bauer A, et al., for the ERACE Study Investigators. Phrenic nerve stimulation in CRT patients and benefits of electronic lead repositioning: the ERACE trial. J Interv Card Electrophysiol 2013;38:1–9.

14. Poole J, Gleva M, Mela T, et al., for the REPLACE Registry Investigators. Complication rates associated with pacemaker or implantable cardioverter-defibrillator generator replacements and upgrade procedures results from the REPLACE registry. Circulation 2010;122:1553–61.

15. Klein N, Klein M, Weglage H, et al., for the Efface Phrenic Stim Study Group. Clinical efficacy of left ventricular pacing vector programmability in cardiac resynchronization therapy defibrillator patients for management of phrenic nerve stimulation and/or elevated left ventricular pacing thresholds: insights from the Efface Phrenic Stim study. Europace 2012;14:826–32.

16. Forleo GB, Mantica M, Di Biase L, et al. Clinical and procedural outcome of patients implanted with a quadripolar left ventricular lead: early results of a prospective multicenter study. Heart Rhythm 2012;9:1822–8.

17. Mehta PA, Shetty AK, Squirrel M, Bostock J, Rinaldi CA. Elimination of phrenic nerve stimulation occurring during CRT: follow-up in patients implanted with a novel quadripolar pacing lead. J Interv Card Electrophysiol 2012; 33:43–9.

18. Sperzel J, Dänschel W, Gutleben K-J, et al. First prospective, multi-centre clinical experience with a novel left ventricular quadripolar lead. Europace 2012;14:365–72.

19. Tomassoni G, Baker J, Corbisiero R, et al., for the Promote® Q CRT-D and Quartet® Left Ventricular Heart Lead Study Group. Postoperative performance of the Quartet® left ventricular heart lead. J Cardiovasc Electrophysiol 2013;24: 449–56.

20. Boriani G, Maniadakis N, Auricchio A, et al. Health technology assessment in interventional electrophysiology and device therapy: a position paper of the European Heart Rhythm Association. Eur Heart J 2013;34:1869–74.

21. Duray GZ, Hohnloser SH, Israel CW. Coronary sinus side branches for cardiac resynchronization therapy: prospective evaluation of availability, implant success, and procedural determinants. J Cardiovasc Electrophysiol 2008;19:489–94.

22. Diemberger I, Mazzotti A, Massaro G, et al. From lead management to implanted patient management: systematic review and meta-analysis of the last 15 years of experience in lead extraction. Expert Rev Med Devices 2013;10: 551–73.

23. De Maria E, Diemberger I, Vassallo PL, et al. Prevention of infections in cardiovascular implantable electronic devices beyond the antibiotic agent. J Cardiovasc Med (Hagerstown) 2014; 15:554–64.

24. Rinaldi CA, Leclercq C, Kranig W, et al. Improvement in acute contractility and hemodynamics with multipoint pacing via a left ventricular quadripolar pacing lead. J Interv Card Electrophysiol 2014;40:75–80.

25. van Everdingen WM, Cramer MJ, Doevendans PA, Meine M. Quadripolar leads in cardiac resynchronization therapy: a review. J Am Coll Cardiol EP 2015;1:225–37.

KEY WORDS **cardiac resynchronization therapy, left ventricular pacing, LV lead complications, phrenic nerve stimulation, quadripolar lead, randomized trial**

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