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Effects of implantation of quadripolar left ventricular leads on CRT response

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Abstract

Background The use of quadripolar (QP) left ventricular leads for cardiac resynchronization therapy (CRT) is intended to improve outcomes compared with conventional bipolar leads (BP). Hence, the number of implanted quadripolar CRT systems is increasing despite limited long-term data.

Purpose The aim of this study is to evaluate clinical response and long-term outcomes of CRT recipients who were implanted with quadripolar versus bipolar left ventricular leads.

Methods Data from consecutive patients receiving a CRT defibrillator in one German and one Hungarian tertiary referral center were retrospectively collected. Long-term survival and response to CRT were analyzed.

Results A total of 536 patients with structural heart disease and a mean left ventricular ejection fraction (LVEF) of 25% received a CRT defibrillator (CRT-D) system for primary (79%) or secondary (21%) prevention of sudden death. Comorbidities did not differ significantly between patients receiving a QP ($n = 123$) or a BP lead ($n = 413$). Procedure (101 vs. 120 min) and fluoroscopy times (14 vs. 20 min) were shorter in patients implanted with QP compared with BP (both $p < 0.001$). At 6 months follow-up, QP patients were more likely to respond to CRT measured as improvement in the New York Heart Association (NYHA) functional class (77% vs. 63%; $p < 0.001$). Use of QP left ventricle/left ventricular (LV) leads was associated with greater reduction in QRS duration compared with patients implanted with BP LV leads (-21 ± 30 vs. -8 ± 35 ms, $p = 0.004$). Mortality was not significantly different between patients with QP and patients with BP LV leads at a mean follow-up of 39 ± 31 months.

Conclusion Implantation of quadripolar left ventricular leads was associated with better CRT response compared with bipolar left ventricular leads.

Keywords Cardiac resynchronization therapy · CRT · CRT-D · Quadripolar lead · Bipolar lead · Response

Abbreviations

ACE-inhibitor	Angiotensin-converting-enzyme inhibitor
ARB	Angiotensin receptor blocker
ASA	Acetylsalicylacid
BP	Bipolar
BiVPace	Biventricular pacing percentage
CAD	Coronary artery disease
CI	Confidence interval
CKD	Chronic kidney disease (stage III KDIGO, GFR ≤ 59 ml/min)
CRT	Cardiac resynchronization therapy
CRT-D	Implantable cardioverter defibrillator with CRT
FDA	Federal drug association
HR	Hazard ratio
ICD	Implantable cardioverter defibrillator
IRB	Institutional review board
LBBB	Left bundle branch block
LMWH	Low-molecular-weight heparin
LV	Left ventricle/left ventricular
LVEF	Left ventricular ejection fraction
LVEDD	Left ventricular end diastolic diameter
MRAs	Mineralocorticoid receptor antagonists

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NOAC	Non-VKA oral anticoagulant
NYHA	New York Heart Association functional classification
PAD	Peripheral artery disease
QP	Quadripolar
SCD	Sudden cardiac death
SD	Standard deviation
VKA	Vitamin K antagonist

1 Introduction

Cardiac resynchronization therapy (CRT) for selected patients with heart failure has been shown to reduce both hospitalization rates [1–6] and mortality [7]. Hence, current European Society of Cardiology (ESC) guidelines on heart failure therapy recommend implantable cardioverter defibrillator with CRT (CRT-D) implantation for symptomatic heart failure patients in sinus rhythm with left bundle branch block (LBBB) of > 150 ms and LVEF < 35% despite optimal medical therapy as a class IA indication [8]. The American guidelines recommend implantation of a CRT-D for symptomatic heart failure patients (NYHA II, LVEF ≤ 35%) with a broad LBBB with QRS duration > 150 ms as a class IB indication [9]. Left ventricular (LV) electrodes used in the abovementioned trials were mostly unipolar and bipolar (BP) electrodes [1–7]. In 2011, the first quadripolar (QP) LV lead was approved allowing for LV pacing from up to 10 unique pacing vectors via four electrodes. Since that time, QP leads have been used more frequently as standard LV leads when implanting CRT systems [10, 11]. Some retrospective and prospective trials as well as one randomized controlled trial suggest less LV lead failure with the use of QP versus BP LV leads in CRT recipients [10–18]. Nonetheless, there are conflicting data concerning CRT implantation duration and fluoroscopy time [12, 14, 17] as well as response to CRT [14, 18] in patients fitted with QP and BP LV leads. Therefore, data on CRT patients implanted at two European tertiary centers receiving either QP or BP LV leads were analyzed with respect to CRT response and long-term clinical outcomes.

2 Methods

2.1 Patient population

Implantation and outcome data were retrospectively collected from a prospective registry from consecutive patients undergoing CRT implantation at the University Hospital Frankfurt, Goethe University (Frankfurt, Germany) and at the Medical Centre of Hungarian Defence Forces (Budapest, Hungary) between 2005 and 2016. CRT was considered for patients on optimized medical treatment with heart failure of NYHA functional class from II to IV, LVEF ≤ 35%, and QRS width > 120 ms [8, 9, 19]. Furthermore, patients with previously implanted pacemakers or implantable cardioverter defibrillators (ICDs) who developed the abovementioned criteria were also considered for CRT upgrade. The study was approved by the institutional review boards (IRBs) of both the enrolling institutions and complies with the ethical guidelines of the Declaration of Helsinki.

2.2 Device implantation

CRT-ICDs from various manufacturers were used (Biotronik, Germany; ELA/Sorin, Italy; Guidant/Boston Scientific, USA; Medtronic, USA; St. Jude Medical, USA). Left ventricular leads were implanted transvenously, preferably in a lateral or posterolateral vein or a side-branch in close proximity to the posterolateral area. Implantation of quadripolar left ventricular leads commenced after FDA approval in 2011 (SJM/Abbott Quartet™, Medtronic Attain Performa™, Boston Scientific Acuity X4™, Biotronik Sentus Pro MRI™). A minority of bipolar leads ($n = 4$) were implanted epicardial after a futile transvenous approach. Use of bipolar or quadripolar electrodes was left at the discretion of the implanting operator. Patients implanted with unipolar LV leads were excluded from the current analysis. Patients were followed-up in the outpatient clinic of the participating hospitals in 6 month intervals or when clinically indicated.

2.3 Study endpoints

Outcome measures were clinical response to CRT and long-term mortality in patients receiving quadripolar leads as compared with those with bipolar LV leads. Patients were considered to be responders to CRT if they survived the 6 month follow-up visit with an improvement of at least one NYHA functional class. In addition, echocardiographic (LVEF, LVEDD) and electrocardiographic data (QRS width, biventricular pacing percentage) were collected. Technical data during CRT-D implantation (fluoroscopy time, implantation time) were also assessed.

2.4 Statistical analysis

Statistical analysis was performed using SPSS Statistics software, version 24.0 (IBM, USA). The Kolmogorov-Smirnov test was used to evaluate the normal distribution of continuous data. The Chi-square test was used for categorical variables and the two-sample t test or the Mann-Whitney U test for continuous variables among patient groups.

The effects of baseline parameters on CRT response rate were assessed by the Chi-square test and by a multivariate logistic regression model. To assess the effect of implantation of a quadripolar or bipolar LV lead, statistical models were

adjusted for potential baseline confounders, which reached a p level of < 0.10 on univariate analysis: age, gender, primary/secondary ICD indication, structural heart disease, hypertension, atrial fibrillation, chronic kidney disease, peripheral artery disease (PAD), NYHA class at implantation, upgrade procedure, anticoagulation therapy, diuretic therapy, use of amiodarone. Survival curves were constructed according to the Kaplan-Meier method and compared with the Cox proportional hazard model and the Wald test for multivariate analysis. As QP LV leads were introduced in 2011, a sensitivity analysis was performed including only patients implanted from 2011 to 2016. Two-sided p values < 0.05 were considered statistically significant.

3 Results

3.1 Patient characteristics

A total of 536 CRT-D recipients (Budapest 227, Frankfurt 309) were included in the current analysis of whom 123 (23%) received a QP LV and 413 (77%) a BP LV lead. Patient characteristics are detailed in Tables 1 and 2. Mean age was 66 years (± 11 years) and 65% ($n = 421$) were male. The majority of patients had ischemic cardiomyopathy as the underlying heart disease ($n = 302$; 56%) and underwent CRT-D implantation for primary prevention of sudden death ($n = 423$; 79%).

3.2 CRT-D implantation procedures

Implantation of QP LV leads was associated with shorter fluoroscopy times (14 min vs. 20 min; $p < 0.001$) and doses (23 Gy/cm^2 vs. 29 Gy/cm^2; $p = 0.03$) (Table 3). Aiming for a lateral LV lead position, a lateral/posterolateral/anterolateral branch of the coronary sinus could be reached as the final target vein in 72% of patients implanted with QP leads and in 71% of patients implanted with BP leads ($p = 0.15$). There was no difference in the rate of non-apical positions between the two groups (73% vs 78%, $p = 0.18$) (Table 3).

3.3 Response to CRT

Patients implanted with a QP LV lead were more likely to respond to CRT compared with patients implanted with BP LV lead (77% vs. 63%; $p < 0.001$) (Table 4). After adjusting for potential baseline confounders, better NYHA response rates persisted in patients receiving QP LV leads (OR = 2.30; 95% CI 1.37–3.85; $p = 0.002$) (Fig. 1). Six months after implantation, LVEF improved by a mean of 6 ± 9% and LVEDD decreased by a mean of 1 ± 12 mm without significant differences between

Table 1 Patient baseline characteristics at CRT-D implantation

Variables	All patients, $n = 536$	Patients with quadripolar LV lead[†], $n = 123$	Patients with bipolar LV lead[‡], $n = 413$	p value
Age mean (SD) (years)	66 (11)	67 (10)	66 (11)	0.21
Male gender n (%)	421 (65)	100 (81)	321 (78)	0.37
Body weight mean (SD) (kg)	76 (22)	74 (38)	77 (20)	0.32
Primary prevention n (%)	423 (79)	96 (78)	327 (79)	0.69
Secondary prevention n (%)	111 (21)	27 (22)	84 (20)	
Structural heart disease n (%)	534 (99)	121 (98)	413 (100)	0.17
CAD	302 (56)	76 (62)	226 (55)	
Non-ischemic	234 (44)	47 (38)	187 (45)	
Upgrade n (%)	180 (28)	33 (27)	147 (36)	0.07
Bundle branch block n (%)				0.07
LBBB	406 (76)	98 (80)	308 (75)	
Non-LBBB	130 (24)	25 (20)	105 (25)	
Hypertension n (%)	381 (59)	85 (69)	296 (72)	0.58
Atrial fibrillation n (%)	185 (35)	44 (36)	141 (34)	0.74
Diabetes mellitus n (%)	188 (35)	42 (34)	146 (35)	0.81
Chronic kidney disease n (%)	238 (45)	51 (41)	187 (45)	0.67
PAD n (%)	53 (10)	14 (11)	39 (9)	0.53
NYHA classification at implantation (%)				0.57
0 + I	22 (4)	5 (4)	17 (5)	
II	166 (31)	34 (28)	132 (33)	
III	300 (56)	68 (55)	232 (53)	
IV	47 (9)	15 (12)	32 (8)	
LVEF at implantation mean % (SD)	25 (7)	27 (7)	25 (7)	0.04
LVEDD at implantation mean (mm) (SD)	66 (10)	65 (10)	66 (10)	0.06
QRS width at implantation mean (SD) (ms)	159 (29)	158 (29)	159 (29)	0.60

[*] All abbreviations are explained in the abbreviations table

[†] Implantation period: 2011–2016

[‡] Implantation period: 2005–2016

Table 2 Patient baseline characteristics at CRT-D implantation

Variables	All patients, $n = 536$	Patients with quadripolar LV lead, $n = 123$	Patients with bipolar LV lead, $n = 413$	p value
Antiplatelet therapy n (%)	302 (47)	67 (54)	235 (57)	0.68
Anticoagulation n (%)	212 (39)	69 (56)	142 (34)	0.14
NOAC n (%)	39 (6)	14 (11)	24 (6)	
VKA n (%)	172 (32)	55 (45)	117 (28)	
LMWH n (%)	1 (1)	0 (0)	1 (0)	
Beta blocker n (%)	519 (97)	119 (97)	400 (97)	> 0.99
ACE inhibitor n (%)	428 (80)	96 (78)	332 (80)	0.57
Angiotensin receptor blocker n (%)	92 (17)	23 (19)	69 (17)	0.61
Mineralocorticoid receptor antagonist n (%)	434 (81)	108 (88)	326 (79)	0.04
Diuretics n (%)	481 (90)	110 (89)	371 (90)	0.87
Digitalis n (%)	179 (34)	20 (16)	159 (38)	< 0.001
Amiodarone n (%)	136 (26)	31 (25)	105 (25)	0.96
Statin n (%)	367 (69)	82 (67)	285 (69)	0.62

* All abbreviations are explained in the abbreviations table

the two patient groups ($p = 0.13$; $p = 0.57$) (Table 4; Fig. 2a, b). Regarding QRS width and morphology, 76% of the patients ($n = 407$) had an intrinsic left bundle branch block (mean QRS width 159 ± 29 ms) at CRT-D implantation. Six months after CRT implantation the use of QP LV leads was associated with greater reduction in QRS duration compared with patients implanted with BP LV leads (− 21 ± 30 vs. − 8 ± 35 ms, p univariate = 0.004; p multivariate < 0.0001) (Table 4). Mean biventricular pacing percentage was 92% at six months after CRT-D implantation and not significantly different between both patient groups (QP 93% vs. BP 91%; $p = 0.20$).

3.4 Mortality during follow-up

Within a follow-up period of 39 (± 31) months, 172 patients (27%) died. More patients implanted with bipolar LV leads died (37% vs. 16%) but this difference was not statistically significant on a time-to-event analysis (HR = 0.81; 95% CI 0.51–1.31) (Fig. 3). After adjusting for potential clinical confounders, the adjusted HR was 0.71 (95% C I 0.44–1.15). Independent predictors of mortality were age, chronic kidney disease, PAD, and an upgrade procedure to CRT-D (Table 5). Cause-specific mortality was similar between patients fitted with a QP or a BP LV leads (Table 6).

3.5 Sensitivity analysis

As quadripolar LV leads were introduced in 2011, we performed a subgroup analysis of all patients implanted from 2011 to 2016. Fluoroscopy times were significantly lower in patients receiving QP LV leads compared with patients receiving BP LV leads ($p = 0.003$). Furthermore, patients implanted

Table 3 Implantation data and LV lead positions

Variables	All patients, $n = 536$	Patients with quadripolar LV lead, $n = 123$	Patients with bipolar LV lead, $n = 413$	p value
Fluoroscopy time mean (SD) (min)	19 ± 14	14 ± 10	20 ± 15	< 0.001
Dose area product mean (SD) (Gy/cm^2)	29 ± 28	23 ± 25	29 ± 28	0.03
Implantation duration mean (SD) (min)	116 ± 46	101 ± 37	120 ± 48	< 0.001
LV lead position n (%)				0.15
Lateral	384 (72)	89 (72)	295 (71)	
Non-lateral	148 (27)	34 (27)	114 (27)	
Epicardial	4 (1)	0 (0)	4 (1)	
LV lead projection n (%)				0.18
Non-apical	411 (77)	90 (73)	321 (78)	
Apical	115 (21)	33 (27)	82 (20)	
Epicardial	4 (1)	0 (0)	4 (1)	

* All abbreviations are explained in the abbreviations table

Table 4 Clinical parameters during follow-up

Variables	All patients, $n = 536$	Patients with quadripolar LV lead, $n = 123$	Patients with bipolar LV lead, $n = 413$	Univariate p value	Multivariate p value
NYHA response n (%)	355 (66)	95 (77)	260 (63)	0.001	0.002
Δ LVEF mean % (SD)	+ 6 (9)	+ 4 (8)	+ 6 (9)	0.13	n/a
Δ LVEDD mean (SD) (mm)	− 1 (12)	− 1 (11)	− 1 (12)	0.57	n/a
Δ QRS mean (SD) (ms)	− 11 (− 10)	− 21 (30)	− 8 (35)	0.004	< 0.001

* All abbreviations are explained in the abbreviations table

with QP LV leads improved significantly more often their NYHA functional class as well as LVEF 6 months after CRT implantation compared with patients implanted with BP LV leads, respectively ($p = 0.006$; $p = 0.04$). Mortality was not significantly different between both LV lead patient group both on crude and adjusted analysis over a mean follow-up time of 28 (± 19) months (HR crude = 0.68; 95% CI 0.40–1.17; $p = 0.16$; HR adjusted = 0.60; 95% CI 0.35–1.05; $p = 0.08$).

4 Discussion

4.1 Main findings

The main findings of our real-life, long-term outcome study of CRT-D patients, implanted with either a quadripolar or bipolar LV lead, are: (1) significantly shorter procedural and fluoroscopy times are associated with implantation of quadripolar LV leads; (2) response rates to CRT are significantly higher in patients with QP LV leads at 6 months; and (3) long-term survival in patients receiving QP LV leads compared with patients with BP LV leads was not significantly different.

4.2 Implantation and fluoroscopy times

In a prospective study, Boriani and colleagues randomly assigned patients in a 2:1 fashion either to QP or BP CRT systems [14]. Fluoroscopy duration and procedure times were comparable between the two LV lead groups [14]. In agreement with our observations, another prospective study found a mean implantation duration of 110 ± 31 min and a mean fluoroscopy time of 18 ± 10 min, for patients with QP LV leads versus 120.5 ± 37.3 min implantation duration ($p = 0.007$) and 23 ± 16 min fluoroscopy time ($p = 0.001$) for patients with BP LV leads [17]. Other smaller studies reported similar observations [13]. In essence, use of QP LV electrodes seems to be associated with shorter procedure/fluoroscopy times.

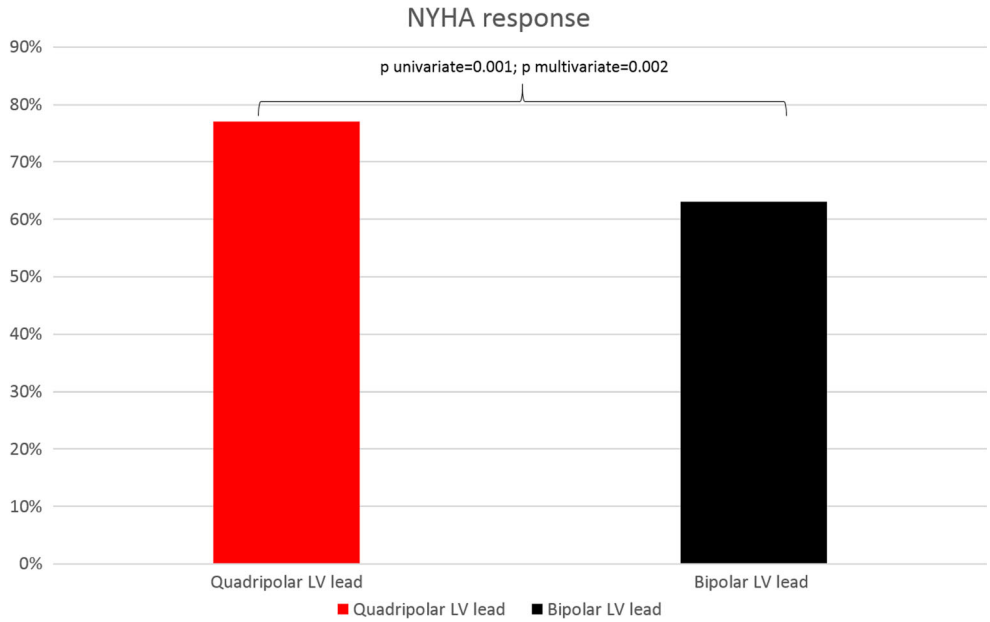
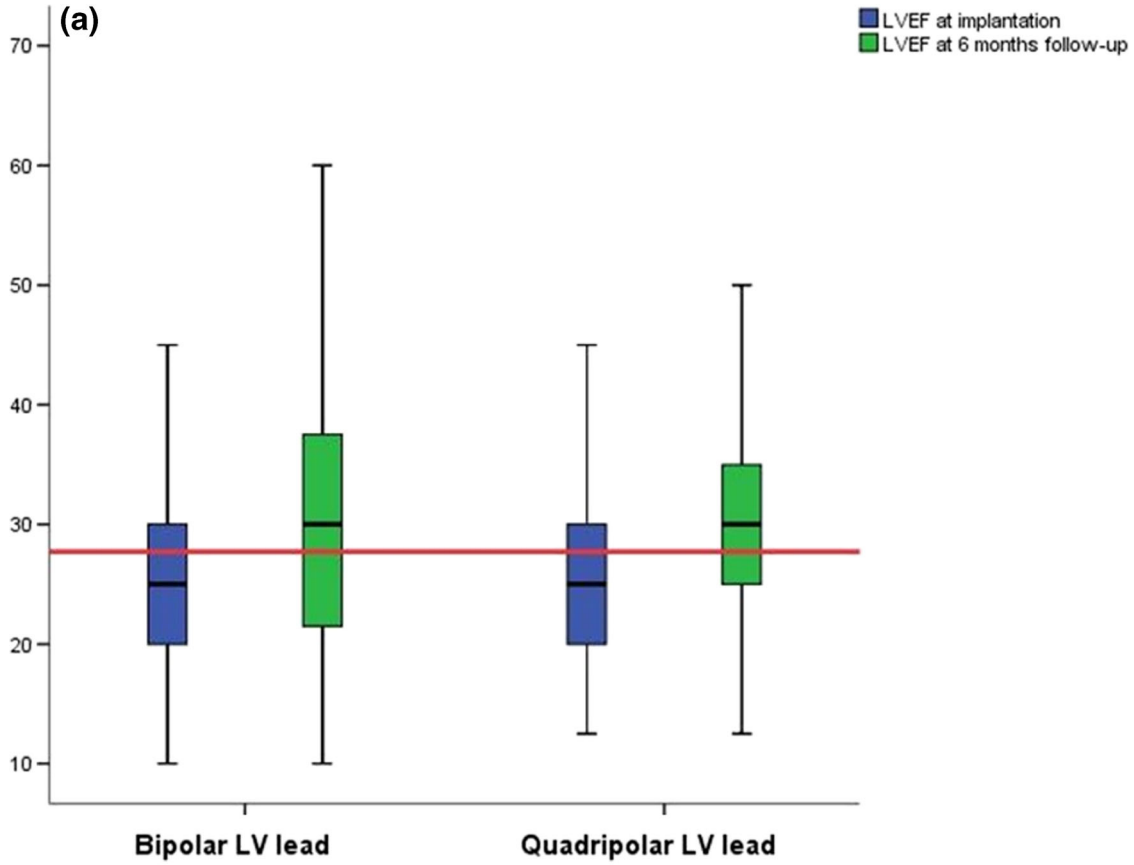
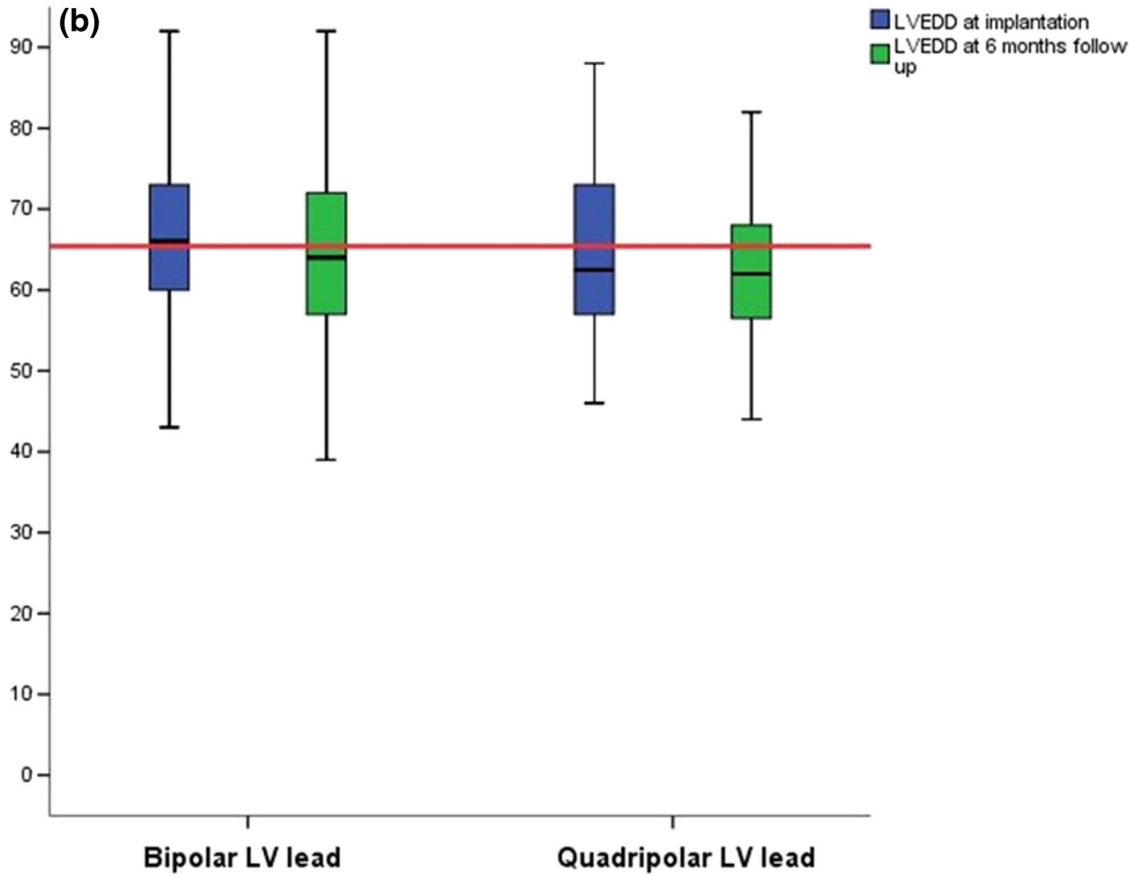


Fig. 1 Bar graphs showing NYHA response comparing patients with QP and BP LV leads on univariate and multivariate analysis at 6 months follow-up


(a)
LVEF at implantation
LVEF at 6 months follow-up
70
60
50
40
30
20
10
Bipolar LV lead
Quadripolar LV lead


(b)
LVEDD at implantation
LVEDD at 6 months follow up
90
80
70
60
50
40
30
20
10
0
Bipolar LV lead
Quadripolar LV lead

◀ **Fig. 2** **a** Box plots of LVEF at implantation and LVEF 6 months after implantation comparing patients with QP and BP LV leads; red line indicates mean LVEF. **b** Box plots comparing LVEDD at implantation and LVEDD 6 months after implantation comparing patients with QP and BP LV leads; red line indicates mean LVEDD

4.3 CRT response

Similar to the MORE-CRT Trial [14], CRT response in our study was defined as improvement in NYHA functional class. Whereas in that study, no significant difference in CRT response in patients with QP LV leads (62%) versus BP LV leads (56%; $p = 0.13$) was observed within a relatively short follow-up period [14]. More patients implanted with QP LV leads in our study had improved significantly their NYHA functional status by at least one class compared with patients with BP LV leads. These results are in line with the findings of Bencardino and colleagues, who randomized 43 patients undergoing CRT implantation to receive either QP ($n = 23$) or BP ($n = 20$) LV leads. After the 3 month follow-up, more patients with QP LV leads improved their NYHA class by at least one class compared with patients implanted with BP LV leads [18]. Moreover, the absolute LVEF values were higher in this small patient cohort after implantation of QP vs. BP LV leads (35 ± 13% vs. 31 ± 4%; $p = 0.001$) [18]. In our study cohort, a comparable improvement in LVEF as well as in LVEDD occurred at 6 months after CRT implantation either with QP or BP LV leads. Although shortening of the QRS complex due to biventricular pacing is not considered a CRT response marker, it might reflect more effective biventricular pacing. In the present study, a greater QRS shortening was observed in patients with QP LV leads compared with patients with BP LV leads ($p = 0.004$).

4.4 Mortality

Behar and colleagues were the first to describe a survival benefit associated with implantation of QP LV leads in

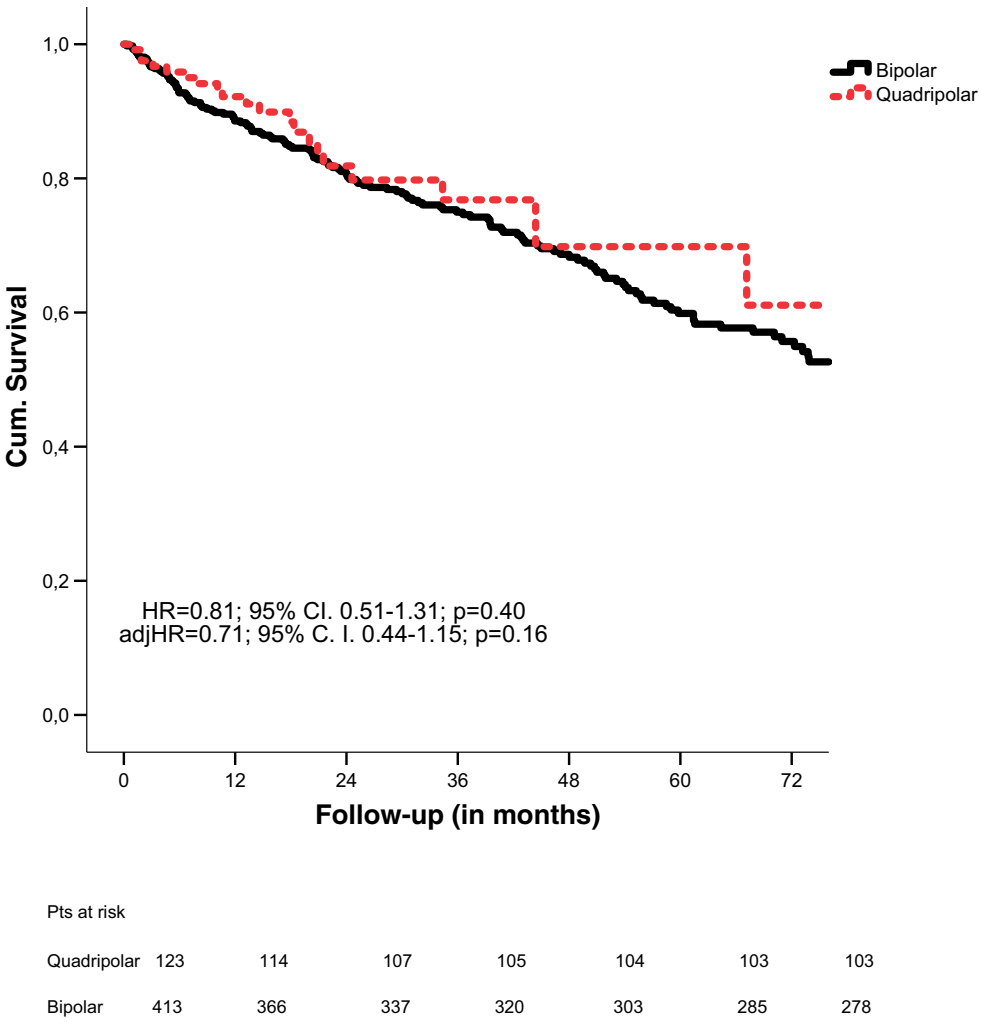


Fig. 3 Kaplan-Meier curves of survival by QP and BP LV leads

Table 5 Predictors of mortality as identified on multivariate analysis

Variables	Unadjusted HR; 95% CI	Adjusted HR; 95% CI**
QP LV lead	0.81; 0.51–1.31	0.71;.0.44–1.15
Age	1.05; 1.03–1.07	1.04; 1.02–1.05
Chronic kidney disease	2.46; 1.84–3.29	1.80; 1.32–2.45
Upgrade to CRT-D	2.02; 1.50–2.72	1.69; 1.24–2.32
PAD	2.32; 1.55–3.49	1.79; 1.17–2.74

* All abbreviations are explained in the abbreviations table

** Parameters used for adjustment on multivariate analysis: age, gender, primary/secondary ICD indication, structural heart disease, upgrade procedure, hypertension, atrial fibrillation, chronic kidney disease, PAD, NYHA class at implantation, anticoagulation therapy, diuretic therapy, and amiodarone

direct comparison with BP LV leads in 721 CRT-patients implanted in three UK centers (adjusted HR 0.66, 95% CI 0.46–0.95) [13]. The largest study to date reported registry data of 23,570 CRT patients [15], of whom 18,406 were implanted with QP LV leads and 5164 with BP LV leads. The authors reported a significant survival benefit in CRT patients receiving QP LV leads compared with BP LV leads in both unadjusted and adjusted Cox regression analysis (HR = 0.74; 95% CI 0.66–0.82; adjusted HR = 0.77; 95% CI 0.69–0.86;) [15]. In our study, we found that numerically more patients implanted with bipolar LV leads died (37% versus 16%); however, these results did not reach statistical significance on multivariate time-to-event analysis.

Although clinical response to CRT in patients implanted with QP LV leads compared with patients with BP LV leads was better in this study, mortality was not significantly reduced in patients with QP LV leads. However, given the observed 95% confidence intervals, this may be due to a power issue which could be overcome by a larger patient sample.

4.5 Limitations

Since our study comprises a non-randomized patient population, residual bias cannot be excluded with certainty. Further, there was no systematic collection of data on phrenic nerve stimulation as well as CRT reprogramming during outpatient clinic visits. Echocardiographic measurements were routinely performed in the implanting centers by independent investigators not participating in the study analysis. These measurements have not been analyzed by a core center. We aimed to minimize potential confounding by carefully adjusting our data to important patient characteristics possibly associated with worse outcomes. Intraoperative measurement of RV-LV delay or CRT optimization during follow-up was left at the discretion of the implanting operator/center; however, these data were not collected in a systematic fashion. It should be also noted that implantation of QP LV lead as a newer technology emerged; physicians might have been more familiar and experienced with the CRT implantation procedure, which might also have influenced procedure and fluoroscopy times. However, in the sensitivity analysis of patients implanted after 2011 (after introduction of quadripolar leads), results remained consistent.

5 Conclusions

In this two-center observational study, implantation of quadripolar CRT systems was associated with shorter fluoroscopy times at implantation and higher CRT response rates during follow-up compared with bipolar CRT systems. Larger randomized controlled studies are warranted to confirm these findings.

Table 6 Cause-specific mortality

Variables	All patients, $n = 536$	Patients with quadripolar LV lead, $n = 123$	Patients with bipolar LV lead, $n = 413$	p value
Pts died n (%)	171 (27)	20 (16)	151 (37)	n/a
Died within 6 months after CRT-D implant n (%)	34 (5)	5 (4)	29 (7)	n/a
Cardiac non-arrhythmic n (%)	38 (6)	3 (2)	35 (9)	0.40
Cardiac arrhythmic n (%)	10 (2)	1 (1)	9 (2)	0.86
Other cardiovascular n (%)	9 (1)	1 (1)	8 (2)	0.95
Non-cardiovascular n (%)	39 (6)	2 (2)	37 (9)	0.14
Unknown	75 (12)	13 (11)	62 (15)	0.04

Compliance with ethical standards

Conflict of interest J. W. E. reports receiving consulting fees, travel support, and lecture fees from ZOLL Medical, travel grants from St. Jude Medical/Abbott, and lecture fees from Servier and is a fellow of the Boston Scientific Heart Rhythm fellowship program outside the submitted work.

M.V. reports receiving lecture/consulting fees from Bayer, BMS, Daiichi Sankyo, and Pfizer and support attending scientific meetings from Bayer, Daiichi-Sankyo, Egis, Pfizer, and SJM, outside the submitted work.

D. D. has nothing to disclose.

A. P. B. has nothing to disclose.

Z.B. has nothing to disclose.

P. B. has nothing to disclose.

G.Z.D. reports speakers' bureau from Medtronic, Biotronik, SJM, and Johnson & Johnson outside the submitted work.

S.H.H. reports receiving consulting fees from Bayer, BI, Boston Scientific, BMS, Gilead, J&J, Medtronic, Pfizer, SJM, Sanofi-Aventis, ZOLL Medical, and Cardiome outside the submitted work.

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