Journal of Interventional Cardiac Electrophysiology (2018) 51:237–244
https://doi.org/10.1007/s10840-018-0330-6

Response and outcomes of cardiac resynchronization therapy in patients with renal dysfunction

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Received: 19 October 2017 / Accepted: 6 February 2018 / Published online: 19 February 2018

Abstract

Purpose Renal dysfunction is often associated with chronic heart failure, leading to increased morbi-mortality. However, data regarding these patients after cardiac resynchronization therapy (CRT) is sparse. We sought to evaluate response and long-term mortality in patients with heart failure and renal dysfunction and assess renal improvement after CRT.

Methods We analyzed 178 consecutive patients who underwent successful CRT device implantation (age 64 ± 11 years; 69% male; 92% in New York Heart Association (NYHA) functional class ≥ III; 34% with ischemic cardiomyopathy). Echocardiographic response was defined as ≥ 15% reduction in left ventricular end-systolic diameter and clinical response as a sustained improvement of at least one NYHA functional class. Renal dysfunction was defined as an estimated glomerular filtration rate (eGFR) below 60 mL/min/1.73 m^2.

Results Renal dysfunction was present in 34.7%. Renal dysfunction was not an independent predictor of echocardiographic response (OR 1.109, 95% CI 0.713–1.725, p 0.646) nor clinical response (OR 1.003; 95% CI 0.997–1.010; p 0.324). During follow-up (mean 55.2 ± 32 months), patients with eGFR < 60mL/min/1.73 m^2 had higher overall mortality (HR 4.902, 95% CI 1.118–21.482, p 0.035). However, clinical response in patients with renal dysfunction was independently associated with better long-term survival (HR 0.236, 95% CI 0.073–0.767, p 0.016). Renal function was significantly improved in patients who respond to CRT (ΔeGFR + 5.5 mL/min/1.73 m^2 at baseline vs. follow-up, p 0.049), while this was not evident in nonresponders. Improvements in eGFR of at least 10 mL/min/1.73 m^2 were associated with improved survival in renal dysfunction patients (log-rank p 0.036).

Conclusion Renal dysfunction was associated with higher long-term mortality in CRT patients, though, it did not influence echocardiographic nor functional response. Despite worse overall prognosis, renal dysfunction patients who are responders showed long-term survival benefit and improvement in renal function following CRT.

Keywords Renal dysfunction · Cardiac resynchronization therapy · Chronic heart failure · Long-term outcome

1 Introduction

Cardiac resynchronization therapy (CRT) is a well-established treatment for patients with symptomatic heart failure (HF), depressed left ventricular (LV) ejection fraction (LVEF), and a prolonged QRS duration [1]. Several studies have demonstrated improvement in exercise capacity, quality of life, and LVEF, in addition to reverse remodeling, mitral regurgitation reduction, and improved survival [2–7].

Renal dysfunction, defined as an estimated glomerular filtration rate (eGFR) reduced below 60 mL/min/1.73 m^2, is often associated with chronic HF, with about one third of HF patients suffering from at least mild to moderate renal dysfunction [8–10].

Many of these heart failure patients are considered candidates for CRT. However, data regarding functional response and its effect on subsequent survival in this population is sparse. Moreover, CRT may have also a role in improving renal function, given the high degree of interaction seen in cardiorenal physiology [11, 12]. The aim of this study was to

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evaluate the response and subsequent long-term mortality in patients with HF and chronic renal dysfunction (CKD) and to understand the incidence and predictors of renal improvement after CRT.

2 Methods

2.1 Study design

This study is a single-center analysis of patients who underwent successful CRT device implantation. A total of 178 consecutive CRT recipients were included, and patient data was collected in our Cardiology Department Information System and analyzed. Extensive demographic and clinical data, including death, New York Heart Association (NYHA) class, and hospitalization for HF worsening were collected from medical records. Follow-up data were obtained by medical record reviews, outpatient clinical visits, and telephone contact.

The study protocol was approved by the local Research Ethics Board.

2.2 Patients

Patients were selected for CRT if they met the currently recommended criteria: (1) LVEF < 35%, (2) symptoms of HF, defined as NYHA classes II–IV despite optimal medical therapy, and (3) QRS duration > 120 ms.

Patients were classified as ischemic in the presence of significant coronary artery disease (> 50% stenosis of two or more epicardial vessels or left main or proximal left anterior descending coronary artery stenosis > 50% on coronary angiography and/or a history of previous myocardial infarction or revascularization). The other patients were classified as nonischemic. Clinical response to CRT was defined as a sustained improvement ≥ 1 in NYHA functional class at 6-month follow-up.

2.3 Evaluation of renal function

Estimated eGFR was calculated using the standard formula by Cockcroft and Gault and expressed in mL/min/1.73 m^2 [13]. Patients were divided into two pre-specified subgroups: eGFR < 60 mL/min/1.73 m^2 and eGFR ≥ 60 mL/min/1.73 m^2. Change in the continuous eGFR measurement was assessed, and the threshold of 10 mL/min/1.73m^2 was chosen to define renal response as in prior studies that demonstrated the relationship between changes in GFR of 10 mL/min/1.73 m^2 and cardiovascular outcomes [14, 15].

2.4 Implantation

All leads were placed transvenously via the subclavian and cephalic route using fluoroscopy. The right ventricular lead was positioned in the apex or mid septum. The LV lead was placed in the posterolateral or lateral tributary vein of the coronary sinus with an over-the-wire system depending on the ability to cannulate the veins, the pacing threshold, or the diaphragmatic stimulation. The standard settings included an atrioventricular (AV) delay of 100 ms (sensed) and 130 ms (paced), with DDD or DDDR mode and standard lower (50 beats/min) and upper (120–130 beats/min) pacing rates.

2.5 Echocardiography

Transthoracic two-dimensional echocardiography information was assessed at baseline and at 6 months of CRT device implantation. In this study, LV reverse remodeling (LVRR) was defined as an increase ≥ 15% reduction in left ventricular end-systolic dimension (LVESD). Echocardiographic cardiac dimensions and function were assessed using a commercially available ultrasound system (Vivid-7 and Vivid-E9; GE Vingmed Ultrasound, Horten, Norway) equipped with a 3.5-MHz transducer. LVESD, left ventricular end-diastolic dimension (LVEDD), and LVEF were determined according to standard techniques and digitally stored for offline analysis in cine-loop format.

2.6 Statistical analysis

Data are expressed as mean ± standard deviation (SD) for continuous variables and as frequencies and percentages for categorical variables. Data distribution was tested for normality using the Kolmogorov–Smirnov test or Shapiro–Wilk as appropriate. Missing patient-level covariates were assumed to be missing and no imputation was performed. Comparisons of baseline characteristics and outcomes were performed using the chi-square test or Fisher's exact test, when appropriate, for categorical variables and the Student's t test or the Mann–Whitney test for continuous variables. The cumulative event rates after CRT implantation were calculated using the Kaplan–Meier method and dichotomizing the population according to the renal function. The log-rank tests for time-to-event data with respect to all-cause mortality were used for statistical comparison between two patient groups. All the statistical tests were two-sided, and a p value < 0.05 was considered significant. The SPSS version 21 software (SPSS Inc., Chicago, IL) was used for computation.

3 Results

3.1 Baseline characteristics

The study included 178 consecutive patients with an average age of 63.9 ± 10.7 years; the majority of whom were men (69.3%). Most had nonischemic cardiomyopathy (65.7%), suffered from severe HF (92.1% with NYHA class ≥ III), and had poor LV function (mean LVEF 25.1 ± 6.5%).

Mean plasma creatinine level was 1.16 ± 0.47 mg/dL, and mean estimated creatinine clearance was 72.8 ± 30.1 mL/min/1.73 m^2. Renal dysfunction (eGFR < 60 mL/min/1.73 m^2) was present in 34.7% of the patients. The baseline characteristics of the two groups are shown in Table 1. Patients with renal dysfunction were older and presented a higher rate of moderate to severe mitral regurgitation. There were no significant differences in pre-implant LVEF or QRS duration.

3.2 Renal function, left ventricular reverse remodeling, and clinical response

Overall, 108 patients (60.6%) showed ≥ 15% reduction in LVESD (LVRR or echocardiographic response to CRT) at 6 months of follow-up. Echocardiographic response to CRT occurred without significant differences among patients with and without renal dysfunction (59.0 and 62.6%, respectively; $p = 0.64$). In a multivariable Cox-regression analysis, adjusting for age, sex, left bundle branch block, QRS duration > 150 ms, and etiology, renal dysfunction was not a predictor of LVRR (OR 1.109, 95% CI 0.713–1.725, p 0.646).

Although renal dysfunction was associated with less clinical response (57.1 vs. 72.8%, $p = 0.04$), in a multivariate logistic regression analysis, baseline renal dysfunction was not an independent predictor for 6-month functional response (OR 1.003; 95% CI 0.997–1.010; p 0.324), after adjusting

Table 1 Baseline clinical and echocardiographic characteristics

Baseline	All patients ($n = 178$)	eGFR < 60 mL/min/1.73m^2 ($n = 62$)	eGFR ≥ 60 mL/min/1.73m^2 ($n = 116$)	p
Age, years mean (SD)	64 ± 11	67 ± 9	61 ± 11	< 0.001
Male gender, *n* (%)	122 (69)	42 (69)	80 (69)	0.922
Ischemic etiology, *n* (%)	59 (34)	22 (37)	37 (33)	0.551
NYHA class, mean (SD)	2.9 ± 0.4	2.9 ± 0.4	2.9 ± 0.4	0.715
NYHA class ≥ III	151 (92)	54 (93)	97 (92)	0.718
BMI, mean (SD)	27 ± 4	25 ± 5	28 ± 4	< 0.001
Obesity, *n* (%)	38 (24)	6 (11)	32 (31)	0.004
Hypertension, *n* (%)	129 (76)	39 (67)	90 (81)	0.044
Dyslipidemia, *n* (%)	92 (55)	29 (50)	63 (58)	0.303
Diabetes, *n* (%)	55 (33)	18 (31)	37 (33)	0.733
History of smoking habits, *n* (%)	53 (34)	20 (36)	33 (32)	0.583
COPD, *n* (%)	29 (18)	11 (19)	18 (18)	0.919
Previous heart surgery, *n* (%)	34 (19)	9 (15)	25 (22)	0.264
Prosthetic valve, *n* (%)	15 (8)	3 (5)	12 (10)	0.212
Sinus rhythm, *n* (%)	107 (61)	36 (59)	71 (62)	0.725
LBBB, *n* (%)	128 (82)	49 (88)	79 (78)	0.151
QRS duration, ms mean (SD)	167 ± 30	166 ± 27	170 ± 32	0.969
QRS duration > 150 ms, *n* (%)	112 (72)	42 (75)	70 (70)	0.506
Mitral regurgitation grade 3+ or 4+, *n* (%)	18 (25)	13 (39)	5 (13)	0.008
LVEDD, mm mean (SD)	74 ± 10	76 ± 10	73 ± 10	0.288
LVESD, mm mean (SD)	56 ± 12	60 ± 13	54 ± 13	0.150
LVEF at baseline, mean % (SD)	25 ± 7	24 ± 6	25 ± 7	0.812
LVEF change, mean % (SD)	12 ± 10	10 ± 9	13 ± 11	0.060
Echocardiographic response (%)	108 (61)	36 (59)	72 (63)	0.641
Clinical response (%)	107 (67)	32 (57)	75 (73)	0.044

Obesity was defined as BMI ≥ 30 kg/m^2. Heart surgery includes previous valvular and/or revascularization surgery

NYHA New York Heart Association, *BMI* body mass index, *COPD* chronic obstructive pulmonary disease, *LBBB* left bundle branch block, *LVEDD* left ventricle end-diastolic diameter, *LVESD* left ventricle end-systolic diameter, *LVEF* left ventricular ejection fraction

for age, sex, left bundle branch block, QRS duration > 150 ms, and etiology.

3.3 Renal function and long-term mortality

Renal function was investigated in relation to mortality after CRT. At the end of the follow-up period (mean follow-up 55.2 ± 32 months), 51 patients (29.0%) had died. Compared to patients without renal dysfunction, patients with eGFR < 60 mL/min/1.73 m^2 had a higher mortality (45.9 vs. 20.0%, $p < 0.001$), with a 10-mL/min/1.73 m^2 lower eGFR being associated with a 20% higher risk for mortality. In patients with renal dysfunction, a cumulative 9, 18, and 26% of the patients died by 12-, 24-, and 36-month follow-ups, respectively. In contrast, a respective 2, 5, and 8% of the patients without renal dysfunction died during the same time period (log-rank p value 0.001).

Renal dysfunction was tested as an independent predictor for mortality using a Cox proportional hazards model, adjusting for age, sex, etiology of heart failure, QRS duration > 150 ms, LV dimensions, LVEF, and mitral regurgitation grade. Renal dysfunction remained a strong predictor of mortality after CRT, with a corrected hazard ratio (HR) of 5.575 (95% CI 1.470–21.147, p 0.012, Table 2).

In patients with clinical response, a lower eGFR was associated with increased mortality after follow-up (31.1 vs. 13.3%, $p = 0.03$). However, in renal dysfunction patients, those who had functional response had a better survival compared to clinical nonresponders, as can be seen in Kaplan–Meier curve (log-rank p value 0.003, Fig. 1). Furthermore, there was no significant difference regarding the amplitude of the benefit following CRT in responders with renal dysfunction by comparison to responders with normal renal function (Fig. 2). In patients with renal dysfunction, clinical responses (HR 0.236, 95% CI 0.073–0.767, $p = 0.016$) as well as female gender (HR 0.013, 95% CI 0.033–0.668, $p = 0.013$) and LVEDD (HR 0.915, 0.816–0.972, $p = 0.004$) were independent survival predictors after multivariate Cox analysis.

3.4 Renal response after CRT

In 155 patients, blood samples were available after 6-month follow-up and the effect of CRT on renal function was assessed. Overall, there was an improvement in renal function (eGFR 75.1 mL/min/1.73 m^2 at baseline vs. 80.2 mL/min/1.73 m^2 at follow-up, $p = 0.022$), including in renal dysfunction patients (43.2 mL/min/1.73 m^2 at baseline vs. 50.8 mL/min/1.73 m^2 at follow-up, $p = 0.005$). This improvement was only significant in patients who showed response to CRT (ΔeGFR + 5.5 mL/min/1.73 m^2 at baseline vs. follow-up, $p = 0.049$, for echocardiographic responders; ΔeGFR + 6.0 mL/min/1.73 m^2, $p = 0.028$, for clinical responders). In nonresponders, no significant improvement in renal function was observed (ΔeGFR + 4.2 mL/min/1.73 m^2, $p = 0.227$, for echocardiographic nonresponders; ΔeGFR + 0.6 mL/min/1.73 m^2, $p = 0.871$, for clinical nonresponders).

Renal response (improvement in eGFR of at least 10 mL/min/1.73 m^2) was observed in 35.2% of all population. In a multivariable model, age (OR 0.900, 95% CI 0.841–0.964, $p = 0.003$), male gender (OR 0.207, 95% CI 0.064–0.660, $p = 0.008$), NYHA class ≥ III at baseline (OR 29.307, 95% CI 2.413–356.028, $p = 0.008$), and change in LVEF (OR 1.06, 95% CI 1.007–1.117, p 0.027) were predictors of renal response. Each 1% improvement in LVEF between baseline and follow-up was associated with a 6% increased likelihood of renal response.

To assess the impact of renal response on survival of patients with renal dysfunction, Kaplan–Meier analysis was performed in patients stratified by presence or absence of renal response (Fig. 3). Renal response was associated with significantly improved survival in renal dysfunction patients (log-rank p value 0.036). In a multivariable Cox-regression

Table 2 Multivariable analysis of eGFR and clinical and echocardiographic factors on mortality

Dependent variable: all-cause mortality	Multivariable analysis	
	HR (95% CI)	p
eGFR < 60 mL/min/1.73 m^2	5.575 (1.470–21.147)	0.012
Age (years)	0.996 (0.920–1.014)	0.158
Male gender	1.314 (0.364–4.743)	0.677
Ischemic etiology	4.909 (1.404–17.169)	0.013
QRS duration > 150 ms	0.462 (0.141–1.510)	0.201
LVEDD	1.032 (0.967–1.103)	0.344
LVEF	1.032 (0.942–1.129)	0.502
Mitral regurgitation grade	1.300 (0.814–2.077)	0.272

HR hazards ratio, *CI* confidence intervals, *LBBB* left bundle branch block, *LVEDD* left ventricle end-diastolic diameter, *LVEF* left ventricular ejection fraction

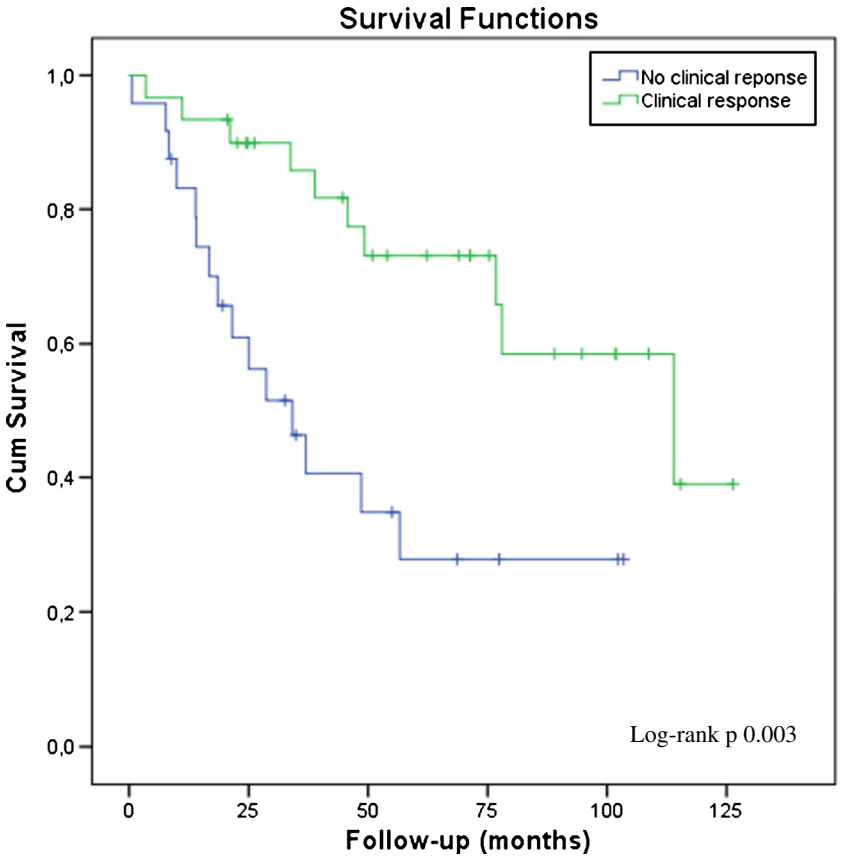

Fig. 1 Kaplan–Meier survival curves of CRT patients with renal dysfunction according to clinical response

analysis, improvement in eGFR of at least 10 mL/min/1.73 m^2 remained an important predictor of outcomes in patients with renal dysfunction (HR 0.004, 95% CI 0.000–0.667, p 0.035).

4 Discussion

The findings of the current study can be summarized as follows: (1) baseline renal dysfunction (eGFR < 60 mL/min/1.73 m2) is a strong predictor for long-term mortality in patients undergoing CRT implantation; (2) there was no significant difference in echocardiographic nor clinical response rate to CRT between patients with and without renal dysfunction; (3) renal dysfunction patients who are responders to CRT therapy show better long-term outcome; (4) CRT responders have a significant improvement in renal function; and (5) renal response (improvement in eGFR of at least 10 mL/min/1.73 m^2) is associated with improved survival in renal dysfunction patients.

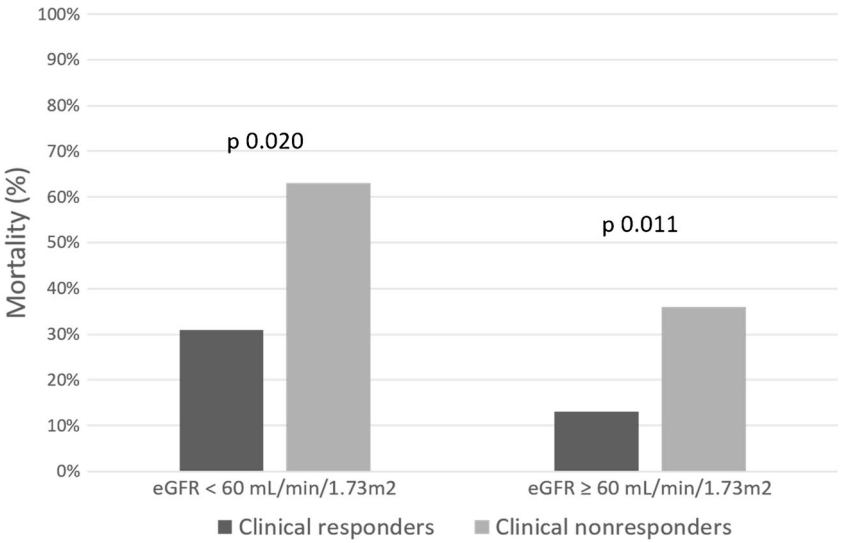

Fig. 2 Long-term all-cause mortality in each eGFR group by functional response to CRT

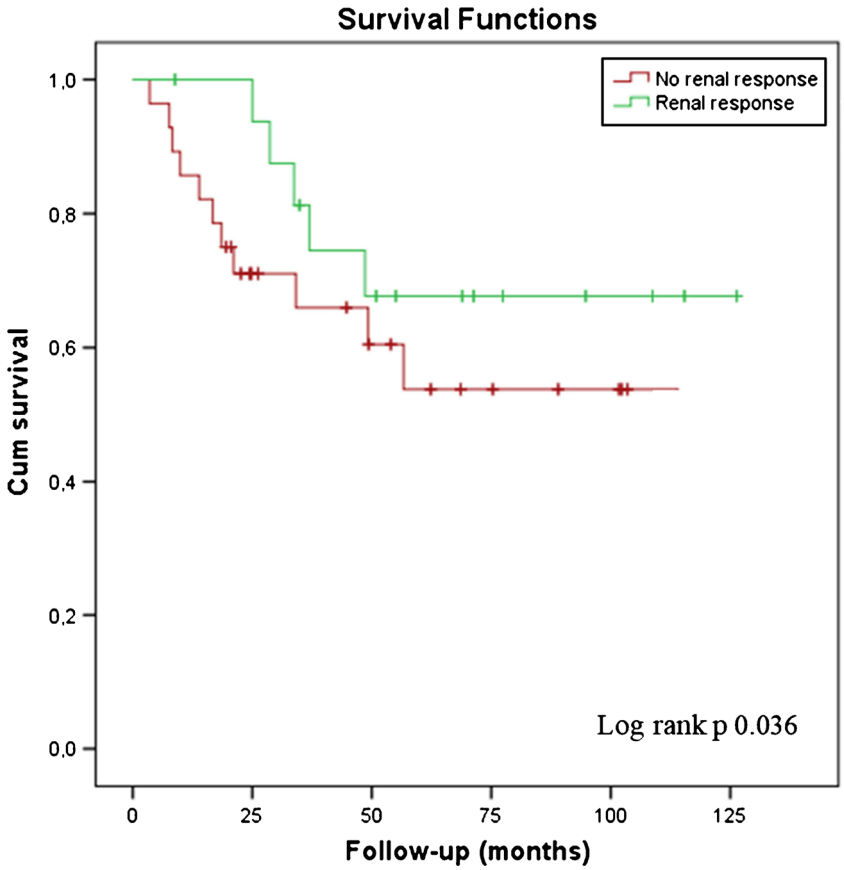

Fig. 3 Kaplan–Meier survival curves of CRT patients with renal dysfunction according to renal reponse

HF is a systemic condition affecting and being affected by several organs as a result of the bidirectional relationship between the cardiovascular symptoms and other systems, including renal, hepatic, pulmonary, central nervous, and hematopoietic systems [16–19]. HF is a risk factor for the development of CKD and vice versa, while the two conditions quite often coexist. The potential pathogenic pathways linking HF with CKD involve neuro-hormonal activation, inflammation, and coincident risk factors [20].

Renal failure is greatly prevalent among HF patients. It has been estimated that as many as 25 to 50% of patients with HF have impaired renal function (creatinine clearance < 60 mL/min/1.73 m^2) [4, 10, 21, 22]. In large trials, including the SOLVD (Studies of LV Dysfunction) [21] and CHARM (Candesartan in Heart Failure: Assessment of reduction in Mortality and Morbidity) [23], eGFR < 60 mL/min/1.73 m^2 was associated with increased mortality during long-term follow-up.

Renal dysfunction patients with CRT therapy started to be evaluated more recently. In a subanalysis of the MIRACLE (Multicenter InSync Randomized Clinical Evaluation) study [24], 452 patients were randomized to either CRT or control group. In the CRT group, patients with decreased eGFR had less mean reduction of LV dimensions. Although, authors did not test for significance of these results, this observation suggested that impaired renal function results in less LVRR after CRT. This topic was further evaluated by Van Bommel and colleagues [25] in a group of CRT recipients (NYHA class III or IV; LVEF 24 ± 8%) with a high prevalence (39%) of eGFR < 60 mL/min/m^2. In this study, renal dysfunction was a predictor for echocardiographic nonresponse, which may be an explanation for no response and higher mortality in the renal dysfunction group.

We, however, showed that echocardiographic response to CRT occurred without significant differences among patients with and without renal dysfunction and that baseline eGFR was not a predictor for 6-month echocardiographic nonresponse. Furthermore, although patients with renal dysfunction presented less clinical response, after adjusting for other clinical variables, baseline eGFR was not a predictor of functional nonresponse. These results have also been demonstrated previously by Bogdan and colleagues [26] in 179 patients with CRT (90% NYHA class III or IV, LVEF = 24.2 ± 6.2%), in which functional response rates (defined by a composite score using New York Heart Association functional class, 6-min walk test, and quality of life) did not differ significantly between patients with and without renal dysfunction. These findings suggest that the functional and echocardiographic benefit

of CRT is not diminished among patients with renal dysfunction. Additionally, we found that renal dysfunction patients who responded to CRT had a better outcome than nonresponders. In a subanalysis of MADIT-CRT trial [27], it was also demonstrated that long-term benefit from CRT was not influenced by baseline renal function. In this study, patients with left bundle brunch block derived long-term benefit form CRT, with greater absolute risk reduction in death among those with moderate renal dysfunction (absolute risk reduction of 14% for all-cause mortality in patients with eGFR < 60 mL/min/1.73m^2 vs. 6% in patients without renal dysfunction).

Finally, we also observed that patients who respond to CRT have a significantly improvement of renal function, while this is not evident in nonresponders. This renal response after CRT was also observed in patients with renal dysfunction at baseline, and it was associated with better long-term survival in these patients. CRT might improve renal function by several mechanisms, including improvement in LVEF, with consequently improvement in forward perfusion and decrease in venous congestion [11]. The fact that LVEF changes were an independent predictor of renal response in our study supports this explanation. These results were also demonstrated by Singal and colleagues [14] in a retrospective analysis where improvement in renal function occurred in patients across all CKD stages with LVEF improvement being a predictor of renal response. In this study, it was also demonstrated that renal response conferred a significant (73%) hazard reduction for 5-year death, transplant, or LV assistance device.

Taking these results into consideration, the excess mortality in the renal dysfunction group may be due to other potential causes than CRT nonresponse per se. Even milder degrees of renal impairment have been associated with increasing mortality and cardiovascular complications [15]. Renal dysfunction may also lead to other complications, such as azotemia, anemia, derangements in calcium–phosphate homeostasis, inflammation, infection, and conditions promoting coagulation [28–30], each of which may contribute to the risk for mortality, either cardiac or noncardiac.

In fact, in this population, annual mortality rate in patients with renal dysfunction was more than triple comparing with patients without renal dysfunction. This fact should be taken into consideration when deciding for CRT. However, since patients with renal dysfunction in our study derived a CRT benefit, as clinical responders had better long-term survival by comparison to nonresponders, in our opinion, patients with renal dysfunction should not be excluded from CRT.

5 Limitations

This is a retrospective, nonrandomized, and noncontrolled study, which should be considered when interpreting the results. Nonetheless, this represents a real-life group of patients. Clinical response was based only in NYHA class improvement and did not include functional capacity evaluation and quality of life scores, and the definition of LV improvement used was limited to change in dimensions, as pre- and postimplant LV volumes were not always available. Clinical and echocardiographic response was evaluated at 6 months of follow-up, and some patients may have late LVRR [31, 32]. Only a few patients had eGFR < 45 mL/min/1.73 m^2 (15.7%), and therefore one needs to be cautious when extrapolating the results to the extremes. Parameters such as position of LV lead, device programming, presence of rhythm abnormalities, extent of myocardial scar, biomarker brain natriuretic peptide, and diuretic dosage data were not addressed in this study.

6 Conclusion

Renal dysfunction (eGFR < 60 mL/min/1.73 m^2) was associated with higher long-term mortality in CRT patients. However, mild to moderate renal dysfunction did not influence echocardiographic nor functional response. Despite worse overall prognosis, responder patients with renal dysfunction still have a long-term survival benefit following CRT. Furthermore, CRT responders show an improvement in renal function which was associated with better survival. The excess mortality in mild to moderate renal dysfunction patients may be due to other potential causes than CRT nonresponse per se, and therefore, we suggest that these patients should not be excluded for CRT.

Compliance with ethical standards

The study protocol was approved by the local Research Ethics Board.

Conflict of interest The authors declare that they have no conflicts of interest.

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