Response to Cardiac Resynchronization Therapy Across Chronic Kidney Disease Stages

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ABSTRACT

Introduction: Limited data are available concerning the effect of severe chronic kidney disease (CKD) on the response to cardiac resynchronization therapy (CRT) because these patients are commonly excluded from trials. Therefore, we aimed to assess the effect of CRT on renal function, reverse remodeling and outcome across all stages of CKD in a large patient population of recipients of CRT.

Methods: We retrospectively evaluated 798 consecutive patients with heart failure who were undergoing CRT implantation between October 2008 and September 2016. Renal function data were available at baseline and at 6 months following CRT. Remodeling based on left ventricular end diastolic volume/left ventricular ejection fraction (LVESV/LVEF) and clinical outcome was assessed using a combined endpoint of all-cause mortality and hospitalization because of heart failure.

Results: Median baseline estimated glomerular filtration rate was 62.8 (43.6−77.8) mL/min/1.73 m^2. Of the patients, 33.6% were in CKD stage 3, 11.0% in stage 4 and 1.1% in stage 5. LVEF and LVESV improved across all CKD stages; however, patients with CKD stages 1 and 2 exhibited a greater degree of improvement in LVEF (median 15% vs 10%, $P < 0.001$) and LVESV (median −37.2% vs −29.9%, $P < 0.001$) compared to patients with CKD stages 3−5. Despite a greater degree of reverse remodeling in CKD stages 1 and 2, the most accurate cut-off of remodeling predicting good clinical outcome was lower for patients with CKD stage 3−5, respectively: 5.5% vs 9.5% (LVEF) and −6.67% vs −12.41% (LVESV).

Conclusions: CRT results in reverse remodeling across all stages of CKD, although to a lesser extent in patients with renal dysfunction (CKD stage 3−5). However, patients with CKD derive benefit on outcome at a lesser degree of remodeling. (*J Cardiac Fail 2019;25:803−811*)

Key Words: Cardiac resynchronization therapy, chronic kidney disease, heart failure, response.

Introduction

Renal dysfunction is 1 of the most prevalent comorbidities in patients with heart failure (HF) and is associated with poor outcome.[1] In most randomized controlled trials that have investigated therapies for HF, patients with (severe) renal dysfunction have generally been excluded from participation.[2] As a consequence, patients with HF and advanced chronic kidney disease (CKD) are commonly undertreated, in part due to this lack of knowledge and the caution expressed in guidelines.[3,4] Nevertheless, as kidney disease progresses, the absolute baseline risk for developing adverse cardiac events, including HF, disproportionally increases. Cardiac resynchronization therapy (CRT) is recommended for patients with HF and reduced ejection fraction (HFrEF) and electromechanical dyssynchrony so as to improve symptoms and outcomes.[5−8] Recently, several real-world observational studies of patients with HF have indicated that CRT is associated with greater beneficial effects on renal function and outcomes in comparison to recipients of implantable cardiac defibrillators.[9−12] Nevertheless, limited data are available concerning how chronic kidney disease modulates the response to CRT and how this translates in important clinical outcome endpoints, including the development of arrhythmias, hospitalization resulting from HF and mortality.[12] Therefore, we aimed to assess the effects of CRT on renal function, reverse remodeling and various outcome parameters across all stages of renal dysfunction in a large, contemporary real-world cohort.

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Methods

Study population

Consecutive patients with HFrEF undergoing CRT implantation in a single tertiary care center (Ziekenhuis Oost-Limburg, Genk, Belgium) between October 2008 and September 2016 were evaluated retrospectively. CRT indications were in compliance with the European Society of Cardiology guidelines.[13] For the current analysis, only patients with renal function data available at baseline were included. After implantation, all patients underwent a similar prespecified follow-up and CRT optimization protocol, as previously published.[14–18] Briefly, all patients, without exception, received optimization of HF care, such as uptitration of neurohormonal blockers and downtitration of loop diuretics, enrollment in rehabilitation, as well as echocardiographically guided atrioventricular and ventriculo-ventricular optimization of their device settings during follow-up. Patients were also included in a multidisciplinary care program, including follow-up through telemonitoring. Patients received a first follow-up appointment 6 weeks after implantation and a second follow-up at 6 months. After this, the follow-up was reduced to once every 9 months if the patient were clinically stable.

The present study is in compliance with the Declaration of Helsinki. Given the retrospective nature of the study design, the need for written informed consent was waived by the local ethics committee.

Baseline characteristics and follow-up

Baseline demographic characteristics and clinical data just before CRT placement, such as medical therapy, laboratory assessments, electrocardiography, as well as echocardiography, were retrospectively collected from the individuals' electronic medical records. Renal function was available at baseline, at 6 months and at censoring (last available laboratory analysis in the vicinity of fewer than 3 months since last clinical follow-up estimated glomerular filtration rate (eGFR) was defined using the modification of diet in renal disease equation. Stages of renal dysfunction were determined using the KDIGO (Kidney Disease Improving Global Outcomes) stages of chronic kidney disease.[19] Grade 1 indicates normal renal function (eGFR $>$ 90 mL/min/1.73 m^2); grade 2 indicates mildly decreased renal function (eGFR 60−89 mL/min/1.73 m^2); grade 3 indicates moderately decreased renal function (eGFR 30−59 mL/min/1.73 m^2); grade 4 indicates severely decreased renal function (eGFR 15−29 mL/min/1.73 m^2); and grade 5 indicates kidney failure (eGFR $<$ 15 mL/min/1.73 m^2). Renal dysfunction was defined as CKD KDIGO stages 3 through 5.

Comprehensive 2-dimensional echocardiography examinations were performed (iE33w; Philips Medical Systems, Amsterdam, the Netherlands) at the time of device implantation and after 6 months. In accordance with the recommendations of the American Society of Echocardiography, all reported measurements were averaged from 3 consecutive cycles (or 5, in cases of atrial fibrillation).

Left ventricular ejection fraction (LVEF), left ventricular end-systolic (LVESV) and end-diastolic volume (LVEDV) were obtained using the modified Simpson biplane method in the apical 2- and 4-chamber views.[20]

Endpoints

To assess the relationship between renal function and response to CRT, changes in LVEF and LVESV from baseline to 6 months after implantation of CRT were assessed as a continuous value. Additionally, for consequent analyses, response to therapy (ie, *responders*) was defined as a decrease of LVESV $>$ 15% because this change has been used traditionally in previous studies. Symptomatic response was assessed as a change in New York Heart Association class between implantation and 6 months. Furthermore, changes in renal function from baseline to 6 months were analyzed as continuous values. Additionally, *renal response* was defined as an increase in eGFR $>$ 10 mL/min/1.73 m^2.[21,22] A combined clinical outcome of all-cause mortality and hospitalization resulting from HF was studied. Additionally, to study the relationship between echocardiographic reverse remodeling and outcome, an endpoint of good clinical outcome was defined as the absence of all-cause mortality or readmission because of HF after 1 year. *Heart failure hospitalization* was defined as hospitalization for congestion (at least 2 signs or symptoms of congestion), necessitating the use of intravenous diuretics or hospitalization for low-output HF lasting at least 24 hours.

Statistics

Data are presented as mean ± standard deviation (SD) when normally distributed, as median (interquartile range) when skewed and as frequencies (percentage) when categorical. Normality of variables was evaluated graphically using histograms and normal quantile-quantile plots. Baseline characteristics were analyzed using the independent samples *t* test for normally distributed variables and the Mann-Whitney U test for skewed variables. The χ^2 test was used for categorical variables. Patients were divided into groups based on renal dysfunction at baseline (CKD stage 1 or 2 vs CKD stages 3 through 5) for Supplementary Tables and based on response to CRT at 6 months. Additionally, trends over 3 groups (ie, CKD stage 1 or 2, CKD stage 3 and CKD stage 4 or 5) were statistically tested by the Cochran-Armitage trend test, the Jonckheere-Terpstra test or a linear regression model for categorical variables, non-normally distributed continuous variables and normally distributed continuous variables, respectively. Changes in renal function over time for different groups were tested using ANCOVA. Uni- and multivariable linear regression analysis was performed with log-transformed change in LVESV from baseline to 6 months as a dependent variable. Transformations were checked using multifractional polynomials. Multivariable linear regression analysis, including all variables with $P < 0.10$ in univariable analysis were constructed via backward elimination. The model was tested for collinearity and checked by plotting residuals. A propensity score was determined using linear regression with eGFR at

baseline as the dependent variable, and it includes all univariable significant ($P < 0.10$) variables. This propensity score reflects the characteristics associated with poorer renal function. The propensity score included age, sex, height, history of percutaneous coronary intervention, coronary artery bypass graft, atrial fibrillation, valvular disease, pacemaker, implantable cardiac defibrillators, upgrade to CRT, hypertension, lipidemia, diabetes, as well as etiology of HF, New York Heart Association class, dose of angiotensin converting enzyme inhibitors, beta-blockers, hydralazine, loop diuretics, use of diuretics, nitrates, digoxin, amiodarone, anticoagulants, statins, and hemoglobin (adjusted $r^2 = 0.304$). Cox proportional hazard regression analysis was performed to investigate the association of renal dysfunction with the combined endpoint. The proportional hazard assumption was checked by inspection of log-log plots and Schoenfeld residual plots. Hazard ratios were presented per SD increase of eGFR, meaning that 1 unit increase of eGFR is actually 1 SD increase. The optimal relationship between change in LVEF or LVESV (continuous variable) and the absence of mortality and admission because of HF after 1 year in patients with vs without renal dysfunction was investigated using receiver operating characteristics. The optimal cutoff point was searched for by identifying the Youden index point (sensitivity + specificity −1). A 2-tailed P value < 0.05 was considered statistically significant. All analyses were performed using R: A Language and Environment for Statistical Computing, v. 3.3.1 (R Foundation for Statistical Computing, Vienna, Austria).

Results

A total of 798 patients underwent CRT implantation between October 2008 and September 2016 and had eGFRs assessed at CRT implantation. The median eGFR at implantation was 62.8 (43.6−77.8) mL/min/1.73 m^2. At that time point, 12.4% (99) of patients were in CKD stage 1, 41.9% (334) in CKD stage 2, 33.6% (268) in CKD stage 3, 11.0% (88) in CKD stage 4, and 1.1%[9] in CKD stage 5. At the time of implant, 5 patients (0.62% of the entire cohort) were undergoing dialysis. Table 1a provides an overview of baseline characteristics for patients in CKD stage 1 or 2 (eGFR ≥ 60 mL/min/1.73 m^2), CKD stage 3 (30 ≥ eGFR < 60) vs CKD stages 4 and 5 (eGFR < 30 mL/min/1.73 m^2). In brief, patients with renal dysfunction at baseline (CKD stages 3 through 5) were older, more commonly had atrial fibrillation as well as an ischemic etiology of HF with a longer duration (all $P < 0.001$). Echocardiographic parameters at baseline, such as LVEF and LVESV at baseline were balanced in both groups. In Supplementary Table 1, baseline characteristics for CKD stages 1 and 2 vs CKD stages 3 through 5 are displayed separately.

Changes in clinical and echocardiographic parameters following CRT implantation

Compared to patients with CKD stage 1 or 2, patients with renal dysfunction at baseline (CKD stages 3 through 5) showed a smaller improvement in New York Heart Association class, LVESV and LVEF following CRT implantation (Table 1b and Supplementary Figure 1). When response was defined as LVESV decrease greater than 15%, 78.2% (68) of patients in CKD stage 1 at baseline were responders, 76.0% (231) in CKD stage 2, 64.5% (149) in CKD stage 3, 61.0% (50) in CKD stage 4, and 50.0%[4] in CKD stage 5. In Figure 1 it is shown that there was an improvement in both LVESV and LVEF in all stages of CKD, even in patients with CKD stage 4 or 5.

In patients with renal dysfunction at baseline (CKD stages 3 through 5), responders, based on LVESV decrease > 15% at 6 months, were more commonly female, more often had nonischemic HF with shorter durations and were treated with higher doses of neurohormonal blockers (Table 2) (all $P < 0.001$). In Supplementary Table 2 baseline changes in clinical and echocardiographic parameters following CRT implantation for CKD stages 1 and 2 vs CKD stages 3 through 5 are displayed. eGFR at baseline was independently associated with poorer echocardiographic response to therapy in the entire population (Supplementary Table 3). When assessed in the subgroup of patients with CKD stages 1 and 2, the eGFR was, however, not independently associated with echocardiographic response to therapy ($P = 0.910$), in contrast to patients with CKD stages 3 through 5 ($P = 0.029$). After propensity adjustment for the likelihood of having a lower eGFR at baseline, eGFR remained significantly associated with echocardiographic response to CRT in both the entire population ($P = 0.023$) as well as in patients with CKD stages 3 through 5 ($P = 0.011$).

Change in renal function over time following CRT implantation

Following CRT implantation, renal function remained unchanged in the group of patients with renal dysfunction at baseline, with a trend toward improvement (Table 1b). Supplementary Figure 2a shows the trajectory of renal function at baseline, 6 months and end of study in the various CKD-stage groups. A significantly different trajectory for patients with CKD stage 1 or 2 vs CKD stages 3 through 5 is present ($P < 0.001$); a preservation of renal function is observed for patients with CKD stages 3 through 5 following CRT implantation.

A worsening of CKD stage over 6 months was observed in 86 patients (28.1%) with CKD stage 1 or 2 at baseline, vs 16 (5.9%) patients with CKD stage 3 or 4 at baseline. On the other hand, an improvement in CKD stage was observed in 68 (24.5%) patients with renal dysfunction at baseline vs 20 (8.5%) patients with CKD stage 2 at baseline.

In patients with renal dysfunction at baseline, response to CRT (defined as a decrease in LVESV > 15%) was associated with a significantly greater improvement in eGFR at 6 months (Table 2) ($P = 0.043$) compared to nonresponders. At the end of follow-up, this difference was even more pronounced ($P = 0.013$), which is illustrated in Supplementary Figure 2b. Renal response at 6 months (defined as an increase in eGFR > 10 mL/min/1.73 m^2), however, was not significantly different in patients with or without renal dysfunction at baseline, nor in responders and nonresponders

Table 1a. Baseline Characteristics Based on the Presence of Renal Dysfunction at Implantation

	CKD stages 1, 2	CKD stage 3	CKD stages 4, 5	*P* trend
N	433	268	97	
Demographics				
Age (years)	68.9 ± 10.7	74.7 ± 8.8	77.3 ± 7.3	< 0.001
Sex (% male)	70.9 (307)	65.3 (175)	59.8 (58)	0.019
BMI (kg/m^2)	26.9 ± 4.6	26.9 ± 5.0	28.0 ± 5.1	0.096
Medical history				
Atrial fibrillation % (n)	29.2 (126)	48.1 (129)	42.3 (41)	< 0.001
Stroke % (n)	7.9 (34)	7.8 (21)	4.1 (4)	0.310
COPD % (n)	16.4 (71)	17.2 (46)	17.5 (17)	0.753
Hypertension % (n)	77.4 (335)	85.8 (230)	90.7 (88)	< 0.001
Dyslipidemia % (n)	67.9 (294)	72.0 (193)	76.3 (74)	0.072
Diabetes mellitus % (n)	24 (104)	26.9 (72)	39.2 (38)	0.006
Heart failure				
Nonischemic etiology % (n)	63.7 (275)	53.4 (143)	41.2 (40)	<0.001
Heart failure duration (months)	7.7 (1.7−61.4)	32.0 (3.9−106.1)	25.0 (2.2−75.4)	0.595
NYHA class	3 (2−3)	3 (2−3)	3(3−3)	0.011
Medication				
ACEi/ARB % (n)	86.5 (373)	85.8 (230)	69.1 (67)	0.001
Percentage target dose ACEi/ARB	50 (25−100)	50 (25−50)	25 (0−50)	<0.001
Beta-blocker % (n)	80.7 (348)	85.8 (230)	85.6 (83)	0.095
Percentage target dose BB	25 (12.5−50)	50 (25−50)	25 (12.5−50)	0.395
Mineralocorticoid antagonist % (n)	60.6 (261)	68.3 (183)	55.7 (54)	0.873
Percentage target dose MRA	25 (0−25)	25 (0−25)	25 (0−25)	0.625
Loop diuretics % (n)	37 (159)	57.1 (153)	68 (66)	< 0.001
ECG				
QRS duration (ms)	154 (130−168)	154 (134−170)	154 (132−170)	0.343
LBBB % (n)	76 (326)	76.2 (202)	68.8 (66)	0.257
Echocardiography				
LVEF (%)	30 (25−35)	30 (25−35)	30 (24.2−35)	0.280
LVESV (mL)	118.8 (84.8−162.3)	124.9 (90.4−156.4)	117.9 (87.2−164.4)	0.881
LVEDV (mL)	190 (129.5−216)	166.6 (141.3−216)	166.6 (129.5−216)	0.838
Laboratory values				
Hemoglobin (g/dL)	13.7 (12.6−14.7)	13.1 (12.1−14.3)	12.3 (11.2−13.3)	< 0.001
eGFR (mL/min/1.73m^2)	76.3 (68.5−88.0)	47.4 (40.5−53.8)	26.7 (22.0−22.9)	< 0.001
Device-related features				
CRT-defibrillator % (n)	50.6 (219)	47.8 (128)	48.5 (47)	0.536
Upgrade % (n)	17.1 (74)	28.4 (76)	35.1 (34)	< 0.001

ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; BB, beta-blocker; BMI, body mass index; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; LBBB, left bundle branch block; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; MRA, mineralocorticoid antagonist; NYHA, New York Heart Association.

Table 1b. Clinical and Echocardiographic Changes at 6 Months Based on the Presence of Renal Dysfunction at Implantation

	CKD stages 1, 2	CKD stage 3	CKD stages 4, 5	*P* trend
N	433	268	97	
Clinical				
NYHA class	1 (1−2)	2 (1−2)	2 (1−2)	< 0.001
Delta NYHA class	−1 (−2 to −1)	−1 (−1 to −0)	−1 (−1 to −0)	0.001
Laboratory values				
eGFR (mL/min/1.73 m^2)	71.8 (62.6 to −85.3)	45.6 (40.1 to −54.3)	29.6 (25.2−35.3)	< 0.001
Delta eGFR (mL/min/1.73 m^2)	0 (−14.4 to −3.0)	0 (−4.9 to −5.4)	3.7 (0.3−10.3)	< 0.001
Renal response (increase eGFR> 10 mL/min/1.73m^2 (%n))	13.4 (41)	15.8 (30)	27.9 (24)	0.003
Echocardiography				
LVESV (mL)	70.9 (53.2−104.6)	77.7 (56.9−115.2)	88.5 (64.9−137.7)	0.001
Delta LVESV (%)	−37.2 (−54.1 to −19.9)	−29.9 (−49.4 to −10)	−25.8 (−37.0 to −7.7)	< 0.001
LVESV response > 15% % (n)	76.5 (299)	64.5 (149)	60.0 (54)	< 0.001
LVEDV	118.2 (92.4−166.6)	123.8 (92.4−173.2)	147.4 (114.2−194.0)	0.090
LVEF (%)	45 (40−55)	40 (35−50)	40 (30−45)	< 0.001
Delta LVEF (%)	15 (5−25)	10 (5−20)	10 (4.2−15)	< 0.001
Therapy				
VT/VF shock % (n)	8.5 (36)	7.6 (20)	18.6 (18)	0.026
New-onset AF % (n)	26.3 (107)	29.9 (75)	36.7 (33)	0.047
Biventricular pacing (&)	100 (99−100)	100 (99−100)	100 (98.2−100)	0.518

AF, atrial fibrillation; eGFR, estimated glomerular filtration rate; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; NYHA, New York Heart Association; VT, ventricular tachycardia; VF, ventricular fibrillation.

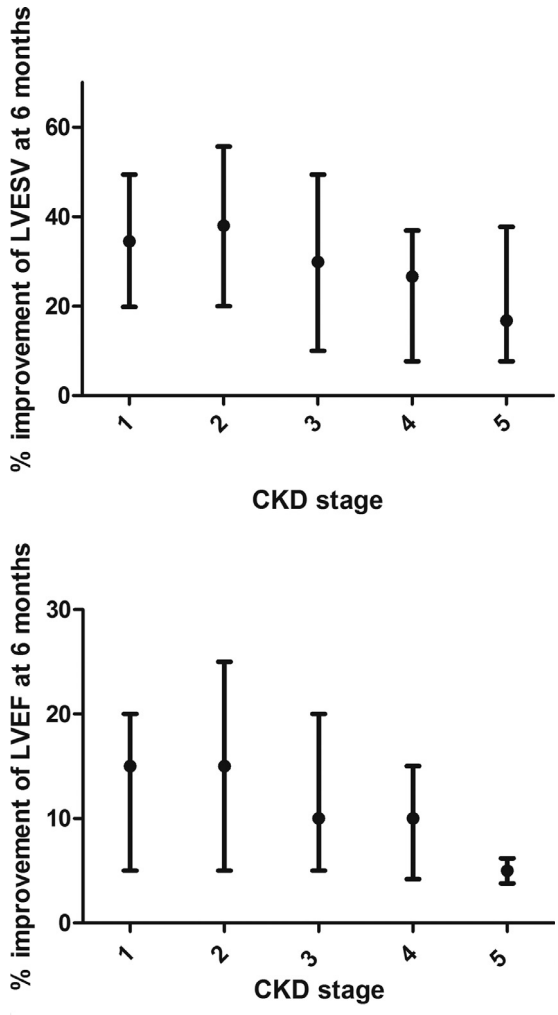

Fig. 1. Left ventricular remodeling to CRT over CKD stages based on echocardiographic parameters, median and interquartile ranges. CKD, chronic kidney disease; CRT, chronic resynchronization therapy; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume.

based on LVESV. Independent predictors of an improvement in renal function at 6 months (change in eGFR from baseline to 6 months) were the presence of a left bundle branch block (beta = 4.04, $P = 0.006$) and lower eGFR (standardized beta = −4.13, $P < 0.001$) at implantation.

Renal function and outcome following CRT implantation

During a median follow-up of 27 (13−41) months, 110 patients (13.8%) died, and 165 patients (20.1%) experienced the combined endpoint of death or hospitalization resulting from HF. A higher eGFR at baseline is associated with a significantly decreased risk of the combined endpoint (hazard ratio [HR] per SD increase: 0.60 [0.51−0.71], $P < 0.001$). After adjustment for baseline characteristics (age, sex, atrial fibrillation, hypertension, etiology and duration of heart failure, dose of angiotensin converting enzyme inhibitors, loop diuretics, and hemoglobin), higher eGFR remained independently associated with a decreased risk of the combined endpoint (HR per SD increase: 0.80 [0.67−0.96], $P = 0.013$).

To further evaluate the association between renal function, reverse remodeling and outcome, we performed receiver operating characteristics curve analysis. Using this method, we aimed to determine what amount of reverse remodeling most accurately predicted freedom from all-cause mortality or hospitalization due to HF (Figure 2). The most accurate cutoff for improvement in LVEF predicting good clinical outcome was 5.5% in patients with renal dysfunction vs 9.5% in patients with CKD stage 1 or 2 (Figure 3), suggesting a clinical benefit at a lesser degree of remodeling. Additionally, the most accurate cutoff for improvement in LVESV was −6.67% in patients with renal dysfunction vs −12.41% in patients with CKD stage 1 or 2.

When subgroups were defined based on response to CRT, responders with CKD stages 3 through 5 at baseline had outcomes similar to those of nonresponders with CKD stage 1 or 2 at baseline, in which no reverse remodeling occurred (Figure 3). Furthermore, if patients with renal dysfunction experienced an improvement in eGRF at end of follow-up, it was associated with a significantly reduced risk of all-cause mortality and of hospitalization due to HF ($P = 0.007$ compared to patients with renal dysfunction and no improvement in eGFR) (Supplementary Figure 3).

Discussion

In this large observational study of contemporary patients with HF who undergo CRT implantation, we studied the effects on renal function, reverse remodeling and clinical outcomes. Our data show that reverse remodeling following CRT is observed across all stages of CKD, yet response is more pronounced in patients without renal dysfunction. However, smaller improvements in LVEF and LVESV were already associated with a lower risk of all-cause mortality or hospitalization due to HF after 1 year for patients with CKD stages 3 through 5, compared to patients with CKD stage 1 or 2. Furthermore, a trend toward improvement in renal function following CRT was observed only in patients with more advanced stages of CKD (stages 3 through 5).

Following the publication of the landmark CRT trials, several real-world observational studies investigating the effects of renal function have been published. The main findings of these studies are that even though patients with renal dysfunction show less remodeling in response to CRT compared to patients without renal dysfunction, implantation of CRT is associated with improved outcomes.[9−11,23,24] In this study, reverse remodeling was observed across all stages of CKD, suggesting that implantation of CRT is beneficial regardless of renal function at the time of CRT implantation. In addition, previous studies have described significant reverse remodeling as an indicator of response (defined as a 15% reduction in LVESV) in 43% of patients with eGFRs < 60 mL/min/1.73 m^2 and, more specifically, in 30% of patients with CKD stage 4.[11,23] However, in our study, which describes a more contemporary real-world cohort with multidisciplinary HF care, including optimization of medical therapy, we observed higher significant reverse

Table 2. Clinical and Echocardiographic Characteristics of Responders vs Nonresponders in Patients With CKD Stages 3−5

	Nonresponders	Responders	*P* value
N	118	203	
Demographics			
Age (years)	74.5 ± 7.5	76 ± 9.1	0.116
Sex (% male)	71.2 (84)	58.6 (119)	0.033
BMI (kg/m^2)	27.3 ± 4.6	27.3 ± 5.3	0.990
Heart failure			
Nonischemic etiology % (n)	42.4 (50)	54.7 (111)	0.044
Heart failure duration (months)	46 (5.5−90.7)	15.3 (2.7−78.9)	0.029
NYHA class	3 (2−3)	3 (2−3)	0.967
Atrial fibrillation % (n)	42.4 (50)	46.3 (94)	0.571
Medication			
ACEi/ARB % (n) at baseline	78.8 (93)	84.7 (172)	0.232
Percentage target dose ACEi/ARB (%) at baseline	25 (12.1−50)	50 (25−66.7)	0.012
Percentage change ACEi/ARB from baseline to 6 months (%)	0 (0−0)	0 (0−12.5)	0.271
Beta-blocker % (n)	81.4 (96)	89.2 (181)	0.073
Percentage target dose BB (%)	25 (12.5−50)	50 (25−50)	0.006
Percentage change BB from baseline to 6 months (%)	0 (0−25)	0 (0−50)	0.350
MRA % (n)	55.9 (66)	70.4 (143)	0.012
Percentage target dose MRA (%)	25 (0−25)	25 (0−25)	0.032
Loop diuretics % (n)	70.3 (80)	57.1 (114)	0.081
Echocardiography			
LVEF (%)	30 (25−35)	30 (25−35)	0.014
LVESV (mL)	115.9 (77.1−153.5)	124.9 (94.6−156.4)	0.105
LVEDV (mL)	160 (119.6−216)	173.2 (141.3−208.5)	0.458
Laboratory values			
Hemoglobin (g/dL)	13 (11.8−14.3)	12.9 (11.9−14)	0.860
eGFR (mL/min/1.73 m^2)	40 (29.2−51.2)	42.6 (29.5−52.3)	0.217
Device related features			
CRT-defibrillator % (n)	56.8 (67)	43.8 (89)	0.034
Upgrade % (n)	37.3 (44)	25.6 (52)	0.038
Follow-up data (6 months after CRT implantation)			
Echocardiography			
LVEF (%)	32.5 (25−40)	45 (40−50)	< 0.001
Delta LVEF (%)	0 (0−5)	15 (10−20)	< 0.001
LVESV (mL)	124.9 (88.2−159.2)	68.1 (53.4−94.6)	< 0.001
Delta LVESV (%)	1.4 (−9 to 10.7)	−39 (−52.2 to 29.4)	< 0.001
LVEDV (mL)	166.6 (118.2−216)	118.2 (97.3−147.4)	< 0.001
Laboratory values			
eGFR (mL/min/1.73 m^2)	39.7 (29.6−47.7)	42.8 (35.8−51.9)	0.011
Delta eGFR (mL/min/1.73 m^2)	0 (−5.2 to 5.5)	0.8 (−1.4 to 8.1)	0.045
Renal response (increase eGFR > 10 mL/min/1.73 m^2 % (n)	17 (17)	21.7 (36)	0.442
Therapy			
VT/VF shock % (n)	21.2 (25)	6.4 (13)	< 0.001
New-onset AF % (n)	38.7 (43)	31.9 (60)	0.283
Biventricular pacing (%)	100 (98.2−100)	100 (99−100)	0.079

ACEi, angiotensin converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin receptor blocker; BMI, body mass index; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; eGFR, estimated glomerular filtration rate; LBBB, left bundle branch block; LVEF, left ventricular ejection fraction; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; NYHA, New York heart association; VT, ventricular tachycardia; VF, ventricular fibrillation.

remodeling rates for patients with renal dysfunction. For patients with CKD stage 4, significant reverse remodeling in our cohort was 61.0%, and for patients with CKD stage 5, it was 50.4%. This is in contrast to the previously mentioned studies as well as to the study by Adelstein et al, in which no echocardiographic benefit at all was observed in patients with eGFRs < 30 mL/min/1.73 m^2.[9] Furthermore, in comparison to a study of 15 patients in hemodialysis (CKD stage 5), an improvement of 3.1% in LVEF after CRT was observed, whereas in our cohort, it was 5%.[25] Patients experiencing significant reverse remodeling in our cohort generally used higher doses of guideline-recommended neurohormonal blockers. This underscores the importance of uptitration of neurohormonal blockers in patients with HF and is in line with previous studies illustrating an outcome benefit and a greater response to CRT in patients treated with higher doses of guideline-recommended therapy.[15,26] Our study confirmed that this also extends to patients with renal dysfunction.

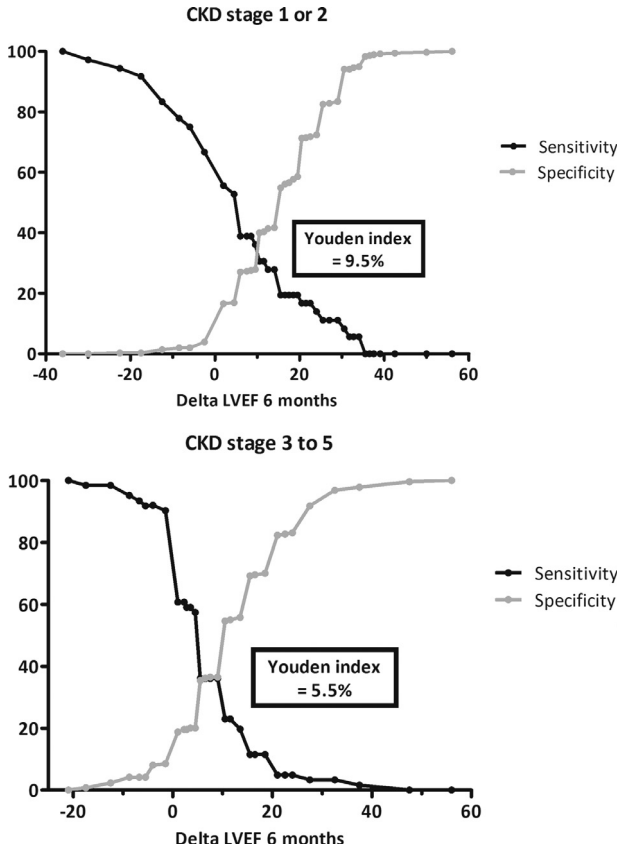

Fig. 2. Receiver operating characteristic curves for 1-year outcome, defined as all-cause mortality and HF hospitalization for improvement in LVEF at 6 months in patients with vs without renal dysfunction at baseline. CKD, chronic kidney disease; HF, heart failure; LVEF, left ventricular ejection fraction.

Several consequences of CKD, such as neurohormonal activation, inflammation and uremia, may result in myocardial fibrosis, causing a reduced left ventricular remodeling response to CRT.[27,28] In our study, we did find a significant and independent association between renal function at baseline and echocardiographic response to CRT in patients with CKD stages 3 through 5, and it remained significant after propensity adjustment. It could be hypothesized that renal function in patients with CKD stages 3 through 5 might have additional value in predicting poor response to CRT, in addition to previously defined variables.[29] However, despite the reduced reverse remodeling response (ie, less improvement of LVEF or decrease of LVESV) to CRT in patients with renal dysfunction, there is still an important clinical benefit. Importantly, our analysis indicated that patients with renal dysfunction already have improved outcomes at a lesser degree of reverse remodeling compared to patients without renal dysfunction. This is important because it is well established that the absolute risk for adverse cardiac events is higher in patients with advanced kidney disease.[30] Therefore, attaining an even modest improvement in left ventricular function will often translate into a large benefit in absolute terms. Finally, in patients with renal dysfunction at baseline and significant reverse remodeling following CRT, outcome is comparable to that of patients with normal kidney function but without echocardiographic response to CRT. Therefore, CRT implantation should be considered across the continuum of renal function. Additionally, we showed that responders to CRT with renal dysfunction used significantly higher doses of ACEi, beta-blockers an mineralocorticoid receptor antagonists, underscoring the importance of the use and uptitration of neurohormonal blockers. Even though target doses of neurohormonal blockers were not reached in most patients in our cohort, we have previously shown that uptitration of neurohormonal blockers following CRT implantation in this cohort was significantly associated with improved outcomes.[15]

We observed a response not only in terms of reverse remodeling but also a stabilization of renal function in patients with CKD stages 3 through 5 at baseline, suggesting that CRT implantation might have a positive effect on the evolution of renal function, that is, slowing (natural) renal function decline. This probably relates to improved cardiac efficacy, resulting in improved forward flow and reduced backward failure. This increase in cardiac output is associated with a reduction in neurohormonal activation, and it generates a modest blood pressure reserve, allowing an increase in the dose of neurohormonal blockers, most of which have been shown to influence beneficially the slope of renal function deterioration. Additionally, the decrease in filling pressures might have a beneficial impact on renal function because both central and abdominal venous pressures are important determinants of renal function decline.[31–33] As such, CRT might have a direct effect on renal function. In line with this, in our study, we found that patients who did exhibit significant reverse remodeling in response to CRT had more pronounced improvements in renal function (as assessed as a continuous variable). This could very well be a bidirectional effect; improved renal function might also lead to a reduction in neurohormonal activation and uremia and, as such, improve cardiac function. Following kidney transplantation, similar effects on cardiac structure and function have been described, with significant improvements in LVEF, left ventricular end-diastolic dimensions, left ventricular mass and right ventricular systolic pressure.[34] However, the improvement in renal function we observed in patients with renal dysfunction and significant reverse remodeling improvement was very small (0.8 mL/min/1.73 m^2) in responders and might not have clinical consequences. This could be due to the underlying intrinsic pathogenesis of the renal dysfunction such as nephrosclerosis, which is unlikely to respond to hemodynamic improvement.

Limitations

This was a retrospective single-center observational study without a control group, making it impossible to determine causality; therefore, it merely describes associations. Patients were enrolled over a period of 8 years, and data concerning changes in renal function between the time points studied were not available. There might be a

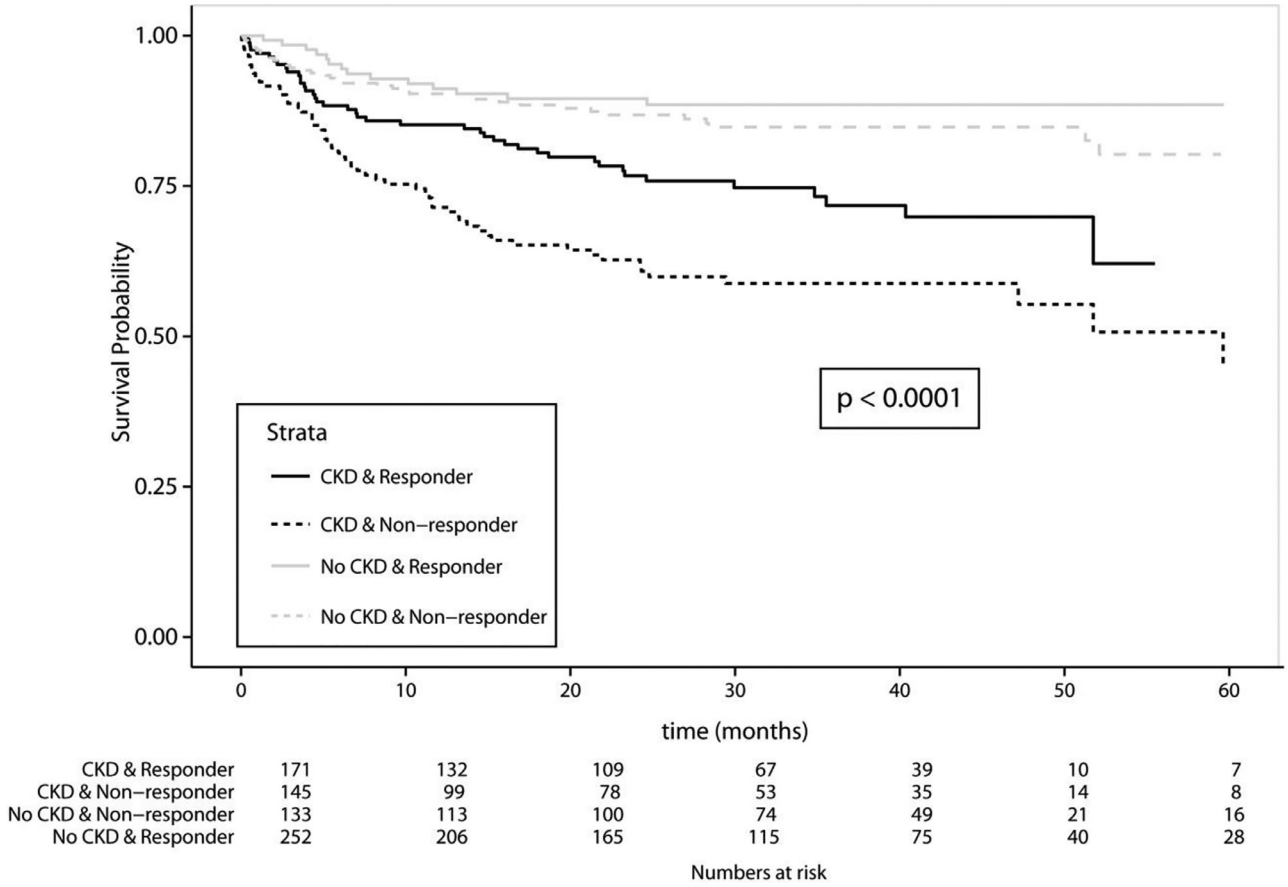

Fig. 3. Kaplan-Meier method for mortality and heart failure hospitalization for groups, based on the presence of renal dysfunction and responders to cardiac resynchronization therapy (defined as a reduction in LVESV > 15%). CKD, chronic kidney disease; CRT, cardiac resynchronization therapy; LVESV, left ventricular end-systolic volume.

selection bias; patients with severe renal dysfunction were less likely to be referred for CRT. In comparison to previous studies of this topic, this study used a large, contemporary, real-world cohort with a greater number of patients in CKD stage 4 or 5 and data about optimal medical therapy. Our study did not allow us to draw conclusions concerning the selection of patients (ie, nonresponders) and, if anything, our data suggest that CRT implantation should be considered for all patients with HF who meet the selection criteria for CRT, regardless of renal function.

Conclusions

Reverse remodeling following CRT is observed across all stages of CKD, yet response is more pronounced in patients without renal dysfunction. However, smaller improvements in LVEF and LVESV were associated with a reduction in all-cause mortality or hospitalization due to HF after 1 year for patients with CKD stages 3 through 5, compared to patients with CKD stage 1 or 2.

Disclosures

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.cardfail.2019.07.005.

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