



Universiteit
Leiden
The Netherlands

Cardiac resynchronization therapy : determinants of patient outcome and emerging indications

Bommel, R.J. van

Citation

Bommel, R. J. van. (2012, May 31). *Cardiac resynchronization therapy : determinants of patient outcome and emerging indications*. Retrieved from <https://hdl.handle.net/1887/19036>

Version: Corrected Publisher's Version

License: [Licence agreement concerning inclusion of doctoral thesis in the Institutional Repository of the University of Leiden](#)

Downloaded from: <https://hdl.handle.net/1887/19036>

Note: To cite this publication please use the final published version (if applicable).

Cover Page



Universiteit Leiden



The handle <http://hdl.handle.net/1887/19036> holds various files of this Leiden University dissertation.

Author: Bommel, Rutger Jan van

Title: Cardiac resynchronization therapy : determinants of patient outcome and emerging indications

Issue Date: 2012-05-31

Chapter 9

Impaired renal function is associated with echocardiographic nonresponse and poor prognosis after cardiac resynchronization therapy

van Bommel RJ, Mollema SA, Borleffs CJ, Bertini M, Ypenburg C, Marsan NA, Delgado V, van der Wall EE, Schalij MJ, Bax JJ

J Am Coll Cardiol 2011;57(5):549-55

ABSTRACT

Background: Renal insufficiency is highly prevalent in heart failure patients, including patients eligible for CRT, and is associated with poor prognosis. Aims of this study were to investigate the effect of renal function on left ventricular (LV) reverse remodeling and long-term outcome after cardiac resynchronization therapy (CRT), and to explore the relation between LV reverse remodeling and changes in renal function at 6 months follow-up.

Methods: The study comprised 490 patients undergoing CRT. Response to CRT was defined as a decrease in LV end-systolic volume $\geq 15\%$ at 6 months follow-up. Primary end point during long-term follow-up was all-cause mortality.

Results: At baseline, mean estimated glomerular filtration rate (eGFR) was 70 ± 28 ml/min/1.73m². At 6 months follow-up, 263 patients (54%) demonstrated response to CRT. Responders had an eGFR of 74 ± 26 ml/min/1.73m² vs. 64 ± 28 ml/min/1.73m² in non-responders ($p < 0.001$). During long-term follow-up, patients with an eGFR < 60 ml/min/1.73m² had higher mortality than patients with an eGFR of 60-90 ml/min/1.73m² or an eGFR > 90 ml/min/1.73m² ($p < 0.001$). Finally, responders to CRT had preservation of renal function (Δ eGFR -0.6), while non-responders had a slight worsening in renal function (Δ eGFR -4.7), $p < 0.05$.

Conclusions: Impaired renal function in CRT candidates is associated with non-response during 6 months follow-up. Additionally, patients with impaired renal function have worse long-term survival after CRT. Response to CRT results in preservation of renal function.

INTRODUCTION

Cardiac resynchronization therapy (CRT) is a well established treatment for patients with symptomatic heart failure, depressed left ventricular (LV) ejection fraction (LVEF) and a QRS complex ≥ 120 ms.¹ Several studies have demonstrated not only improvement in clinical symptoms, exercise capacity, quality of life and LV systolic function, but also increased survival and lower incidence of heart failure related hospital admissions in patients treated with CRT as compared to patients receiving optimal medical treatment alone.²⁻⁴

In addition to the above-mentioned beneficial effects of CRT, improvement in LV systolic function in these patients has recently been linked to a sustained improvement in systemic hemodynamics.^{5,6} One study demonstrated that patients with significant LV reverse remodeling after CRT showed an improvement in renal function and in turn, this improvement in renal function resulted in improved survival after CRT.⁶

Renal failure is common in heart failure patients and is associated with poor long-term prognosis.⁷⁻¹¹ Many of these heart failure patients are considered candidates for CRT. The beneficial effect of CRT on systemic hemodynamics (including renal function) can be a possible explanation for the increased survival that is observed in these patients.

Accordingly, aims of the current study were to: 1) investigate the effect of renal function on LV reverse remodeling and long-term outcome after CRT and 2) explore the relation between LV reverse remodeling at 6 months follow-up and changes in renal function.

METHODS

Patient population and protocol

Out of a large single-center registry including all patients referred for CRT implantation, 490 patients were included, who presented with heart failure symptoms according to NYHA class III or IV and had routinely acquired blood samples at the time of implantation available. Patients were included between 1999 and 2007. All devices were implanted according to current guidelines.¹ Before CRT device implantation, blood samples were obtained for evaluation of renal function and patients were divided into 3 sub-groups based on baseline estimated glomerular filtration rate (eGFR). All patients underwent extensive evaluation, including assessment of clinical status as well as transthoracic 2D-echocardiography before CRT implantation and at 6 months follow-up. Medication remained unchanged during the 6 months follow-up period. Response to CRT was defined as a reduction $\geq 15\%$ in left ventricular end-systolic volume (LVESV) at 6 months follow-up.^{12,13} Patients who died within

the 6 months follow-up period, or underwent heart transplantation were classified as non-responders. All cause mortality was evaluated during a mean follow-up of 26 ± 21 months.

The relation between baseline renal function and echocardiographic response at 6 months follow-up, as well as long-term prognosis after CRT was assessed in all patients. Finally, in a subset of 133 patients with routinely acquired blood samples at 6 months follow-up, the effect of CRT on renal function was evaluated.

Determination of renal function

Before CRT implantation (and at 6 months follow up in 133 patients), venous blood samples were obtained. All blood samples were analyzed at the Leiden University Medical Center, The Netherlands. Estimated GFR was calculated using the standard formula by Cockcroft and Gault and expressed in $\text{ml/min}/1.73\text{m}^2$.¹⁴ Patients were divided into 3 sub-groups according to the cut-off values proposed by the National Kidney Foundation practice guidelines: an $\text{eGFR} \geq 90 \text{ ml/min}/1.73\text{m}^2$ for normal kidney function, an $\text{eGFR} 60\text{--}90 \text{ ml/min}/1.73\text{m}^2$ for mildly decreased and an $\text{eGFR} < 60 \text{ ml/min}/1.73\text{m}^2$ for moderately to severely decreased kidney function.¹⁵

Echocardiographic evaluation

All patients underwent 2D-echocardiography in the left lateral decubitus position before CRT device implantation and at 6 months follow-up. Studies were performed using a commercially available echocardiographic system (VIVID 7, General Electric Vingmed Ultrasound, Milwaukee, USA). Images were obtained using a 3.5 MHz transducer, at a depth of 16 cm in the parasternal (long- and short-axis) and apical (2- and 4-chamber images) views. Standard 2D and color Doppler data, triggered to the QRS complex, were saved in cineloop format. A minimum of 3 consecutive beats were recorded from each view and the images were digitally stored for off-line analysis (EchoPac 7.0.0, General Electric Vingmed Ultrasound, Milwaukee, USA). LVESV, left ventricular end-diastolic volume (LVEDV) and LVEF were measured from the apical 2- and 4-chamber images, using the modified biplane Simpson's rule.¹⁶ Severity of mitral regurgitation (MR) was graded semi-quantitatively from color-flow Doppler images at the parasternal long-axis and the apical 4-chamber view and expressed as the ratio of regurgitant jet area to left atrial area.¹⁷ Response to CRT was defined as a reduction $\geq 15\%$ in LVESV after 6 months follow-up.^{12, 13}

Clinical evaluation

Clinical status of the patients was evaluated at baseline and at 6 months follow-up. Assessed parameters included: NYHA functional class, quality of life score (QoL) according to the Minnesota Living with Heart Failure questionnaire¹⁸ and distance covered in the 6-minute walk test (6 MWT).¹⁹ Outcome data were collected by chart review, device interrogation and telephone contact. Primary end point was death from any cause.

Device implantation

The LV lead was inserted transvenously via the subclavian route. A coronary sinus venogram was obtained using a balloon catheter. Next, the LV pacing lead was inserted through the coronary sinus with the help of an 8Fr guiding catheter and positioned as far as possible in the venous system, preferably in a (postero-) lateral vein. The right atrial and ventricular leads were positioned conventionally, and all leads were connected to a dual-chamber biventricular implantable cardiac device.

Statistical analysis

Continuous data are presented as mean $\pm$ SD, and dichotomous data are presented as numbers and percentages. Comparison of data between patient groups was performed using the independent-samples t test for continuous data. The χ^2 test was used to compare dichotomous data. Comparison of data within patient groups (at baseline and at 6 months follow-up) was performed with the paired-samples t test. Comparisons between more than 2 patient groups were performed using one-way analysis of variance (ANOVA) with Bonferroni post-hoc testing. Survival of patients was evaluated with the Kaplan-Meier method. The effect of renal function on survival was investigated using the Cox proportional hazards model, adjusting for age, gender, etiology of heart failure, QRS duration, NYHA functional class, use of ACE-inhibitors or AII-blockers, use of diuretics, LV volumes, LVEF and MR grade. Variables that showed a statistically significant effect at the 0.05 level on (event-free) survival in univariable analyses were entered in the multivariable Cox proportional hazards model, using a backward stepwise selection to obtain the final model. At each step, the least significant variable was discarded from the model, until all variables in the model reached a p-value below 0.25. All analyses were performed with SPSS for Windows, version 16.0 (SPSS, Chicago, IL). All statistical tests were 2-sided A p-value <0.05 was considered statistically significant.

RESULTS

Patient characteristics

A total of 490 consecutive patients were included. Optimal medical therapy was administered to all patients when tolerated, as evidenced by 90% usage of ACE-inhibitors or AII-blockers and 86% usage of diuretics. Patients had severely depressed LV function, with a mean LVEF of $24\pm 8\%$. Mean plasma creatinine level was $115\pm 43\text{ }\mu\text{mol/l}$ and mean estimated creatinine clearance was $70\pm 28\text{ ml/min/1.73m}^2$.

Response to CRT

In the overall population, improvement in both clinical and echocardiographic parameters at 6 months follow-up was observed. Mean NYHA class declined from 3.1 ± 0.3 to 2.1 ± 0.6 ($p<0.001$), QoL improved from 36 ± 17 to 25 ± 18 ($p<0.001$) and 6 MWT increased from $300\pm 106\text{ m}$ to $392\pm 124\text{ m}$ ($p<0.001$). Furthermore, a decrease in LVEDV from $227\pm 83\text{ ml}$ to $198\pm 46\text{ ml}$ ($p<0.001$), a decrease in LVESV from $172\pm 74\text{ ml}$ to $138\pm 66\text{ ml}$ ($p<0.001$) and a consequential increase in LVEF from $25\pm 8\%$ to $32\pm 10\%$ ($p<0.001$) were noted. Table 1 provides an overview of patient characteristics for CRT responders ($n = 263, 54\%$) vs. CRT non-responders ($n = 227, 46\%$). No differences between responders and non-responders existed at baseline except for a more frequently observed ischemic etiology of heart failure in non-responders ($p<0.001$). Furthermore, non-responders had higher plasma creatinine levels and lower eGFR ($p<0.001$ for both), see Table 1.

Table 1. Patient characteristics of responders and non-responders to CRT

Variable	Responders (n = 263)	Non-responders (n = 227)	p-value
Age (years)	65 ± 10	66 ± 11	0.392
Gender M / F	202 / 61	190 / 37	0.070
Ischemic etiology (n)	129 (49%)	164 (72%)	<0.001
QRS duration (ms)	159 ± 33	154 ± 31	0.130
Systolic blood pressure (mmHg)	111 ± 20	113 ± 22	0.438
Diastolic blood pressure (mmHg)	69 ± 11	70 ± 13	0.716
ACE-inhibitors/All-blocker	238 (90%)	208 (92%)	0.752
Diuretics	221 (84%)	203 (89%)	0.086
Spironolactone	122 (46%)	118 (52%)	0.239
B-blockers	185 (70%)	153 (67%)	0.494
Serum creatinine (μmol/l)	104 ± 30	127 ± 51	<0.001
eGFR (ml/min/1.73m ²)	74 ± 26	64 ± 28	<0.001
NYHA class			
Baseline	3.1 ± 0.3	3.1 ± 0.3	0.326
follow-up	1.9 ± 0.6*	2.3 ± 0.7*	<0.001
6 MWT (m)			
Baseline	308 ± 99	291 ± 113	0.112
follow-up	417 ± 108*	358 ± 136*	<0.001
QoL score			
Baseline	35 ± 16	38 ± 18	0.132
follow-up	21 ± 16*	29 ± 20*	<0.001
LVEDV (ml)			
Baseline	234 ± 86	219 ± 79	0.055
follow-up	179 ± 71*	223 ± 75	<0.001
LVESV (ml)			
Baseline	176 ± 77	167 ± 70	0.181
follow-up	116 ± 58†	167 ± 66	<0.001
LVEF (%)			
Baseline	26 ± 8	25 ± 8	0.293
follow-up	37 ± 9*	26 ± 8	<0.001
MR grade	1.5 ± 1.0	1.6 ± 1.1	0.400

6 MWT = 6 minute walking test; ACE = angiotensin-converting enzyme; eGFR = estimated glomerular filtration rate; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; LVESV = left ventricular end-systolic volume; MR = mitral regurgitation; NYHA = New York Heart Association; QoL = quality of life

*: p<0.05, follow-up vs. baseline

†: by definition, follow-up vs. baseline

Renal function and response to CRT

To evaluate renal function as an indicator for response to CRT, patients were divided into 3 sub-groups according to the National Kidney Foundation practice guidelines; patients with an eGFR <60 ml/min/1.73m² (n = 193), patients with an eGFR 60–90 ml/min/1.73m² (n = 204) and patients with an eGFR ≥90 ml/min/1.73m² (n = 93). Baseline characteristics of the 3 sub-groups are displayed in Table 2. Patients with higher eGFR tended to be younger, have a less wide QRS complex, use fewer diuretics, and have a better exercise tolerance, higher LVEF and less MR. Next, response rates in the 3 sub-groups were assessed and are displayed in Figure 1. Significantly less patients (43%) in the group with moderately to severely decreased kidney function (eGFR <60 ml/min/1.73m²) demonstrated echocardiographic response to CRT at 6 months follow-up as compared to the 2 other groups (p<0.001 for eGFR <60 ml/min/1.73m² vs. eGFR 60–90 ml/min/1.73m² and p = 0.023 for eGFR <60 ml/min/1.73m² vs. eGFR ≥90 ml/min/1.73m²). No differences in response rate were observed between the group with an eGFR ≥90 ml/min/1.73m² (58% responders) and the group with an eGFR 60–90 ml/min/1.73m² (62% responders, p = 0.609).

Table 2. Patient characteristics of the 3 eGFR sub-groups

Variable	eGFR <60 ml/ min/1.73m ² n = 193	eGFR 60–90 ml/ min/1.73m ² n = 204	eGFR ≥ 90 ml/ min/1.73m ² n = 93	p-value
Age (years)	71 ± 8	65 ± 8	56 ± 11	<0.001
Gender M / F	152 / 41	165 / 39	75 / 18	0.856
Ischemic etiology (n)	123 (64%)	121 (59%)	49 (53%)	0.200
QRS duration (ms)	161 ± 30	159 ± 33	147 ± 35	0.001
Systolic blood pressure (mmHg)	111 ± 19	112 ± 20	115 ± 23	0.387
Diastolic blood pressure (mmHg)	69 ± 12	69 ± 12	70 ± 13	0.868
ACE-inhibitors/AII-blockers	169 (88%)	189 (93%)	88 (95%)	0.084
Diuretics	176 (91%)	179 (88%)	69 (74%)	<0.001
B-blockers	129 (67%)	136 (67%)	73 (78%)	0.088
NYHA class	3.1 ± 0.3	3.1 ± 0.3	3.0 ± 0.2	0.160
6 MWT (m)	266 ± 99	308 ± 105	352 ± 98	<0.001
QoL score	37 ± 16	38 ± 18	33 ± 18	0.091
LVEDV (ml)	218 ± 77	235 ± 92	229 ± 72	0.127
LVESV (ml)	168 ± 71	177 ± 80	170 ± 64	0.423
LVEF (%)	24 ± 8	26 ± 8	27 ± 8	0.022
MR grade	1.7 ± 1.1	1.5 ± 1.1	1.1 ± 0.8	<0.001

Abbreviations as in Table 1

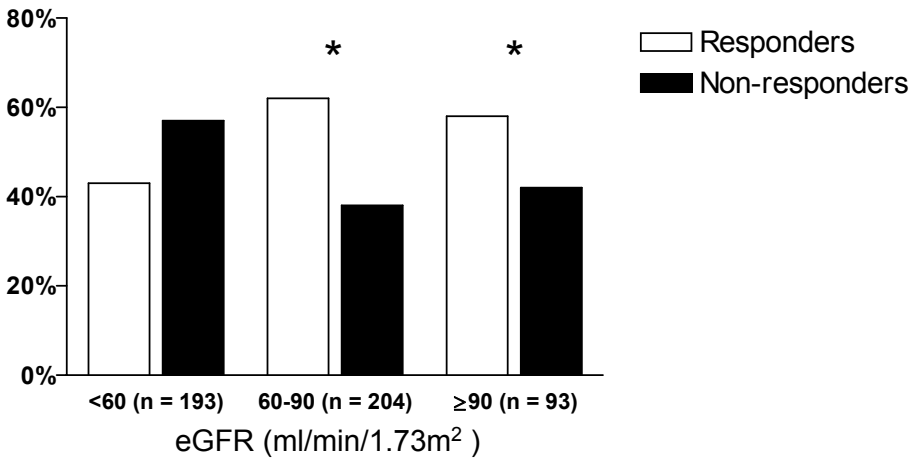
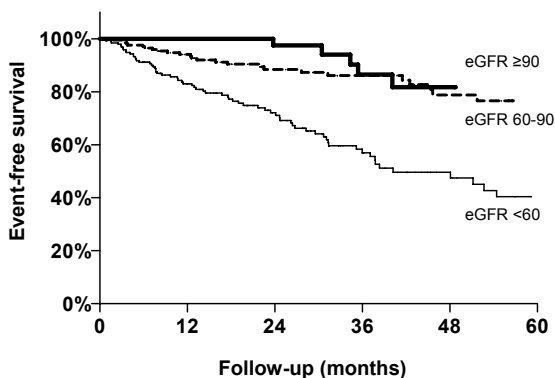


Figure 1. Differences in response to CRT between the 3 sub-groups. * $p < 0.05$ (Bonferroni corrected for 3 comparisons), percentage responders vs. $\text{eGFR} < 60 \text{ ml/min/1.73m}^2$.

Renal function and long-term prognosis after CRT

Renal function was also investigated in relation to mortality after CRT. At the end of the follow-up period (mean: 26 ± 21 months), 106 patients (22%) had died. Survival between the 3 patient sub-groups ($\text{eGFR} < 60 \text{ ml/min/1.73m}^2$, $\text{eGFR} 60\text{--}90 \text{ ml/min/1.73m}^2$ and $\text{eGFR} \geq 90 \text{ ml/min/1.73m}^2$) was compared using Kaplan-Meier curves. Patients with an $\text{eGFR} < 60 \text{ ml/min/1.73m}^2$ had a significantly worse survival as compared to the other 2 groups ($p < 0.001$ vs. $\text{eGFR} 60\text{--}90 \text{ ml/min/1.73m}^2$ and $p < 0.001$ vs. $\text{eGFR} \geq 90 \text{ ml/min/1.73m}^2$). On the contrary, survival was comparable between the $\text{eGFR} \geq 90 \text{ ml/min/1.73m}^2$ and $\text{eGFR} 60\text{--}90 \text{ ml/min/1.73m}^2$ sub-groups ($p = 0.138$), see Figure 2.

Finally, eGFR was tested as an independent predictor for mortality using a Cox proportional hazards model, adjusting for age, gender, etiology of heart failure, QRS duration, NYHA functional class, use of ACE-inhibitors or AII-blockers, use of diuretics, LV volumes, LVEF and MR grade. Estimated GFR remained a very strong predictor of survival after CRT, with a corrected hazard ratio (HR) of 0.97 (95% C.I. 0.96 – 0.98, $p < 0.001$) for every 1 ml/min/1.73m^2 increase in baseline eGFR , see Table 3.



Patients at risk

eGFR ≥ 90 ml/min/1.73m ²	93	59	38	23	10	9
eGFR 60-90 ml/min/1.73m ²	204	139	85	63	37	30
eGFR <60 ml/min/1.73m ²	193	123	76	42	23	15

Figure 2. Kaplan-Meier survival curves for time to all-cause mortality in patients with an eGFR ≥ 90 ml/min/1.73m², an eGFR 60-90 ml/min/1.73m² and an eGFR <60 ml/min/1.73m².

$p < 0.001$, overall comparison between the 3 groups.

$p = 0.138^*$, eGFR ≥ 90 ml/min/1.73m² vs. eGFR 60-90 ml/min/1.73m².

$p < 0.001^*$, eGFR 60-90 ml/min/1.73m² vs. eGFR <60 ml/min/1.73m².

$p < 0.001^*$, eGFR ≥ 90 ml/min/1.73m² vs. eGFR <60 ml/min/1.73m².

* p -values Bonferroni corrected for 3 comparisons.

Table 3. Uni- and multivariable Cox proportional hazards models for time to all-cause mortality

	Univariable		Multivariable	
	HR (95%-C.I.)	p -value	HR (95%-C.I.)	p -value
Age (years)	1.04 (1.02-1.06)	<0.001		
Male gender	1.79 (1.02-3.14)	0.043	2.34 (1.30-4.22)	0.005
Ischemic HF	1.69 (1.13-2.54)	0.011		
QRS (ms)	1.00 (0.99-1.01)	0.939		
NYHA class	2.25 (1.38-3.68)	0.001	1.72 (1.02-2.89)	0.041
Diuretics	2.15 (1.05-4.42)	0.038		
ACE-inhibitors/All-blockers	0.75 (0.41-1.36)	0.342		
eGFR (ml/min/1.73m ²)	0.97 (0.96-0.98)	<0.001	0.97 (0.96-0.98)	<0.001
LVESV (ml)	1.00 (1.00-1.01)	0.034		
LVEDV (ml)	1.00 (1.00-1.00)	0.124		
LVEF (%)	0.96 (0.94-0.99)	0.004	0.98 (0.96-1.01)	0.213
MR grade	1.45 (1.23-1.72)	<0.001	1.31 (1.10-1.57)	0.003

C.I. = confidence interval, rest of abbreviations as in Table 1

Changes in renal function after CRT

In a subset of 133 patients with routinely acquired blood samples at 6 months follow-up, the effect of CRT on evolution of renal function was assessed. In this subset of patients, a slight deterioration of renal function at 6 months follow-up was noted (eGFR 71 ml/min/1.73m² at baseline vs. eGFR 69 ml/min/1.73m² at follow-up, $p = 0.012$). Patients who did not respond to CRT showed deterioration of renal function over the 6 months follow-up period (Δ eGFR -4.7 ml/min/1.73m² for baseline vs. follow-up, $p = 0.001$) while in CRT responders, renal function remained stable at 6 months follow-up (Δ eGFR -0.6 ml/min/1.73m² for baseline vs. follow-up, $p = 0.659$). Changes in eGFR between responders and non-responders differed significantly (Δ eGFR -4.7 for non-responders vs. Δ eGFR -0.6 for responders, $p < 0.05$), see Figure 3.

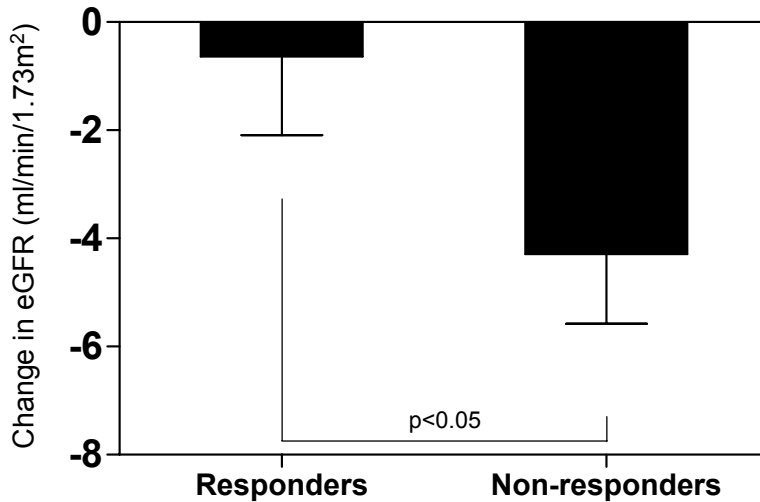


Figure 3. Change in eGFR from baseline to 6 months follow-up, responders vs. non-responders to CRT.

DISCUSSION

The findings of the current study can be summarized as follows: heart failure patients with moderately or severely decreased renal function show lower response to CRT as compared to patients with normal or mildly decreased renal function. Additionally, patients with severely decreased renal function have worse long-term prognosis after CRT. Finally, patients who demonstrate significant LV reverse remodeling after CRT (reduction in LVESV $\geq 15\%$ at 6 months follow-up) have preservation of renal function, while patients who do not exhibit significant LV reverse remodeling have a slight worsening in renal function after CRT.

Renal failure is highly prevalent among heart failure patients. It has been estimated that as many as 25% - 50% of patients with heart failure have impaired renal function (creatinine clearance < 60 -75 ml/min/1.73m²).^{7, 20} A retrospective analysis of the Studies of LV Dysfunction (SOLVD) trial revealed that in heart failure patients with a LVEF $\leq 35\%$, a total of 32% of patients had a eGFR < 60 ml/min/1.73m². The same analysis demonstrated a strong relation between renal function and all-cause mortality; a 10 ml/min/1.73m² lower eGFR was associated with a 1.064 (95% C.I. 1.033 – 1.096) higher risk for mortality in these patients.⁷ The currently observed hazard ratio for eGFR is fairly higher than that reported by SOLVD, but may be attributed to the fact that in the SOLVD trial, only 12% of patients were in NYHA class III or IV, vs. 100% in the present study.

Similar observations as in SOLVD were noted in another large trial, Candesartan in Heart Failure: Assessment of reduction in Mortality and Morbidity (CHARM).⁸ In this study, around 35% of the 2680 patients had an eGFR < 60 ml/min/1.73m² and this was associated with increased mortality during long-term follow-up (HR 1.50, 95% C.I. 1.15 – 2.00). The findings of these large interventional trials in heart failure patients demonstrate that renal failure is a major determinant of long-term outcome in this population.

More recently, interactions between renal function and CRT have been described. Fung et al first reported an association between impaired renal function and clinical outcome in patients treated with CRT.⁶ The authors found in a small cohort of 85 patients, that patients without reverse remodeling had a deterioration in renal function (61.9 ± 17 ml/min/1.73m² vs. 48.8 ± 13.0 ml/min/1.73m²) while patients with significant LV reverse remodeling (defined as $\geq 10\%$ reduction in LVESV) showed a slight improvement in renal function (51.7 ± 20.4 ml/min/1.73m² at baseline vs. 54.2 ± 19.1 ml/min/1.73m² at 3 months follow-up, $p < 0.001$). In addition, patients with a deterioration in renal function during follow-up had a significantly higher mortality rate than patients with preserved renal function (HR 1.96, $p < 0.01$). Surprisingly, patients who showed no significant LV reverse remodeling at 3 months follow-up had a higher baseline eGFR than patients who demonstrated $\geq 10\%$ reduction in LVESV. This is to some extent contradictory to the current findings, where CRT responders (patients who showed $\geq 15\%$ reduction in LVESV) had higher baseline eGFR than non-responders. Perhaps

the definition of response or differences in patient characteristics (overall higher baseline eGFR, larger baseline volumes in the current study) might be responsible for this discrepancy.

Another small study on the evolution of renal function during CRT showed similar results. In 33 patients undergoing CRT, Kimura et al reported that responders to CRT (patients with $>0\%$ increase in LVEF at 3 months follow-up) had an improvement in eGFR of $+3.0 \pm 3.4$ ml/min/ 1.73m^2 , while non-responders (patients with a decrease in LVEF at 3 months follow-up) had a deterioration in renal function of -11.5 ± 4.3 ml/min/ 1.73m^2 .²¹ There were no significant differences in baseline renal function between responders and non-responders. The authors concluded that response to CRT results in preservation of renal function, while non-responders had (further) deterioration, a finding similar to that in the present study.

The largest, currently available, body of evidence for the beneficial effects of CRT on renal function comes from a sub-analysis of the Multicenter InSync Randomized Clinical Evaluation (MIRACLE) study.²² In this trial, 453 patients were randomized to either CRT or control group. Patients were divided into 3 sub-groups (eGFR $30 < 60$ ml/min/ 1.73m^2 , eGFR $60 < 90$ ml/min/ 1.73m^2 and eGFR ≥ 90 ml/min/ 1.73m^2), similar to the currently constructed sub-groups. In all 3 sub-groups, the patients in the CRT group derived superior benefit to the control group with regard to decrease in LV volumes and increase in LVEF. There was however, an interesting difference in LV reverse remodeling at 6 months follow-up between the 3 sub-groups. Patients with an eGFR ≥ 90 ml/min/ 1.73m^2 had a mean reduction in LVESV of 53 ± 10 ml, patients with an eGFR $60 < 90$ ml/min/ 1.73m^2 had a mean reduction in LVESV of 40 ± 7 ml, and finally, patients with an eGFR $30 < 60$ ml/min/ 1.73m^2 had a reduction of 30 ± 9 ml. Although the authors did not test for significance of these results, this observation remains interesting and further strengthens the current observation that impaired baseline renal function results in less response (reverse remodeling) after CRT.

What the exact underlying mechanism on the observed higher response in patients with preserved renal function remains currently unclear. Theoretically, impaired renal function could be caused by an increased venous pressure,¹¹ which in turn may result in less reverse remodeling after CRT. Conversely, impaired renal function was also associated with lower LVEF and more severe MR in the present study, which in turn may have influenced CRT response. However, these assumptions cannot be confirmed by the current (or any other published) study.

Perhaps the most important question raised by the present and earlier mentioned studies,^{6, 21, 22} is through which mechanism CRT improves (or maintains) renal function in heart failure patients. Since renal function (eGFR) is strongly influenced by renal perfusion,²³ one explanation might be the fact that renal perfusion is improved by a CRT induced systemic hemodynamic benefit.⁵ In turn, this systemic hemodynamic benefit is most likely effectuated by an improvement in LV systolic function and/or reduction in MR.^{24, 25} Although this hypothesis cannot be confirmed by the current results, the mechanism is supported by recent findings reported by Mullens et al, obtained with invasive hemodynamic evaluation in CRT recipients.⁵

In this study, including 40 patients who previously underwent CRT implantation, switching OFF biventricular pacing resulted in an immediate 7% decrease in systemic systolic pressure, as well as a 22% increase in central venous pressure. Since CRT increases systemic systolic pressure and decreases central venous pressure, it is not unlikely that either of these, or an interplay between the 2, is responsible for the observed favorable effect of CRT on eGFR (and prognosis).^{5, 11}

Limitations

Since the current study represents a non-randomized observational design, we could only assess the absolute effect of CRT in the different eGFR sub-groups. The relative effect of CRT (vs. no CRT) may be similar among sub-groups, as reported by both the sub-analysis from the MIRACLE trial²² and CARE-HF.²

Also, progression of renal dysfunction as part of the natural course of disease may have been of influence. Patients with a small reduction in renal function were classified as “non-responders” but (in individual patients) may well be “responders”, since progression of disease may have been attenuated compared with natural history, and deterioration of renal function may have been more extensive in the absence of CRT.^{5, 26} The same reasoning may be applicable to LV reverse remodeling.

Conclusions

The current study provides novel insight in the effect of baseline renal function on reverse remodeling and the subsequent long-term prognosis, the effects of remodeling on changes in renal function, in the largest patient cohort described to date. Although it is known from the important sub-analysis from MIRACLE that the relative effects of CRT (as compared to controls) on LV volumes and LVEF is similar among the 3 renal function sub-groups, the current study confirms the suggestion that the absolute effect of CRT may be larger in patients with preserved renal function. In addition, these patients have a better long-term prognosis than patients with impaired renal function. The present findings may help to further determine which patient will respond after CRT, and which patient might not respond. Even though patient selection for CRT may not be altered by knowledge of pre-implantation renal function, it may help to place the individual patient in the appropriate part of the response spectrum and aid in setting of expectations.

REFERENCES

1. Strickberger SA, Conti J, Daoud EG et al. Patient selection for cardiac resynchronization therapy: from the Council on Clinical Cardiology Subcommittee on Electrocardiography and Arrhythmias and the Quality of Care and Outcomes Research Interdisciplinary Working Group, in collaboration with the Heart Rhythm Society. *Circulation* 2005;111:2146-2150.
2. 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;352:1539-1549.
3. Bristow MR, Saxon LA, Boehmer J et al. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. *N Engl J Med* 2004;350:2140-2150.
4. Abraham WT, Fisher WG, Smith AL et al. Cardiac resynchronization in chronic heart failure. *N Engl J Med* 2002;346:1845-1853.
5. Mullens W, Verga T, Grimm RA, Starling RC, Wilkoff BL, Tang WH. Persistent hemodynamic benefits of cardiac resynchronization therapy with disease progression in advanced heart failure. *J Am Coll Cardiol* 2009;53:600-607.
6. Fung JW, Szeto CC, Chan JY et al. Prognostic value of renal function in patients with cardiac resynchronization therapy. *Int J Cardiol* 2007;122:10-16.
7. Al-Ahmad A, Rand WM, Manjunath G et al. Reduced kidney function and anemia as risk factors for mortality in patients with left ventricular dysfunction. *J Am Coll Cardiol* 2001;38:955-962.
8. Hillege HL, Nitsch D, Pfeffer MA et al. Renal function as a predictor of outcome in a broad spectrum of patients with heart failure. *Circulation* 2006;113:671-678.
9. McAlister FA, Ezekowitz J, Tonelli M, Armstrong PW. Renal insufficiency and heart failure: prognostic and therapeutic implications from a prospective cohort study. *Circulation* 2004;109:1004-1009.
10. Ruilope LM, van Veldhuisen DJ, Ritz E, Lüscher TF. Renal function: the Cinderella of cardiovascular risk profile. *J Am Coll Cardiol* 2001;38:1782-1787.
11. Damman K, van D, V, Navis G, Voors AA, van Veldhuisen DJ, Hillege HL. Increased central venous pressure is associated with impaired renal function and mortality in a broad spectrum of patients with cardiovascular disease. *J Am Coll Cardiol* 2009;53:582-588.
12. Bleeker GB, Bax JJ, Fung JW et al. Clinical vs. echocardiographic parameters to assess response to cardiac resynchronization therapy. *Am J Cardiol* 2006;97:260-263.
13. Bax JJ, Bleeker GB, Marwick TH et al. Left ventricular dyssynchrony predicts response and prognosis after cardiac resynchronization therapy. *J Am Coll Cardiol* 2004;44:1834-1840.
14. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron* 1976;16:31-41.
15. Levey AS, Coresh J, Balk E et al. National Kidney Foundation practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Ann Intern Med* 2003;139:137-147.
16. Schiller NB, Shah PM, Crawford M et al. Recommendations for quantitation of the left ventricle by two-dimensional echocardiography. American Society of Echocardiography Committee on Standards, Subcommittee on Quantitation of Two-Dimensional Echocardiograms. *J Am Soc Echocardiogr* 1989;2:358-367.
17. Bonow RO, Carabello BA, Kanu C et al. ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (writing committee to revise the 1998 Guidelines for the Management of Patients With Valvular Heart Disease): developed in collaboration with the

- Society of Cardiovascular Anesthesiologists: endorsed by the Society for Cardiovascular Angiography and Interventions and the Society of Thoracic Surgeons. *Circulation* 2006;114:e84-231.
18. Rector TS, Kubo SH, Cohn JN. Validity of the Minnesota Living with Heart Failure questionnaire as a measure of therapeutic response to enalapril or placebo. *Am J Cardiol* 1993;71:1106-1107.
 19. Guyatt GH, Sullivan MJ, Thompson PJ et al. The 6-minute walk: a new measure of exercise capacity in patients with chronic heart failure. *Can Med Assoc J* 1985;132:919-923.
 20. Dries DL, Exner DV, Domanski MJ, Greenberg B, Stevenson LW. The prognostic implications of renal insufficiency in asymptomatic and symptomatic patients with left ventricular systolic dysfunction. *J Am Coll Cardiol* 2000;35:681-689.
 21. Kimura S, Ito M, Chinushi M et al. Preservation of renal function in response to cardiac resynchronization therapy. *Circ J* 2008;72:1794-1799.
 22. Boerrigter G, Costello-Boerrigter LC, Abraham WT et al. Cardiac resynchronization therapy improves renal function in human heart failure with reduced glomerular filtration rate. *J Card Fail* 2008;14:539-546.
 23. Damman K, Navis G, Smilde TD et al. Decreased cardiac output, venous congestion and the association with renal impairment in patients with cardiac dysfunction. *Eur J Heart Fail* 2007;9: 872-878.
 24. Mullens W, Tang WH, Grimm RA. Using echocardiography in cardiac resynchronization therapy. *Am Heart J* 2007;154:1011-1020.
 25. Ypenburg C, Lancellotti P, Tops LF et al. Mechanism of improvement in mitral regurgitation after cardiac resynchronization therapy. *Eur Heart J* 2008;29:757-765.
 26. Cleland JG, Tavazzi L, Daubert JC, Tageldien A, Freemantle N. Cardiac resynchronization therapy: are modern myths preventing appropriate use? *J Am Coll Cardiol* 2009;53:608-611.