Article

Cardiac Resynchronization Therapy in CKD: A Systematic Review


Summary
Background Cardiac resynchronization therapy (CRT) confers morbidity and mortality benefits to selected patients with heart failure. This systematic review examined effects of CRT in CKD patients (estimated GFR [eGFR] <60 ml/min per 1.73 m²).

Design, setting, participants, & measurements MEDLINE and Scopus (from 1990 to December 2012) and conference proceedings abstracts were searched for relevant observational studies and randomized controlled trials (RCTs). Studies comparing the following outcomes were included: (1) CKD patients with and without CRT and (2) CKD patients with CRT to non-CKD patients with CRT. Mortality, eGFR, and left ventricular ejection fraction data were extracted and pooled when appropriate using a random-effects model.

Results Eighteen studies (14 observational studies and 4 RCTs) were included. There was a modest improvement in eGFR with CRT among CKD patients (mean difference 2.30 ml/min per 1.73 m²; 95% confidence interval, 0.33 to 4.27). Similarly, there was a significant improvement in left ventricular ejection with CRT in CKD patients (mean difference 6.24%; 95% confidence interval, 3.46 to 9.07). Subgroup analysis of three RCTs reported lower rates of death or hospitalization for heart failure with CRT (versus other therapy) in the CKD population. Survival outcomes of CKD patients (compared with the non-CKD population) with CRT differed among observational studies and RCTs.

Conclusions CRT improves left ventricular and renal function in the CKD population with heart failure. Given the increasing use of cardiac devices, further studies examining the effects of CRT on mortality in CKD patients, particularly those with advanced kidney disease, are warranted.


Introduction
The prevalence of CKD has increased over the past decade in parallel with increasing prevalence of diabetes, hypertension, and obesity (1). CKD carries a higher cardiovascular comorbid burden including congestive heart failure (CHF), the prevalence of which is as high as 13%-20% in stage 4-5 CKD patients compared with 1%-2% in those without CKD (2-4). Reduction in nephron mass induces early cardiac fibrosis, myocardial hypertrophy, and diastolic impairment that portend an increased risk for heart failure (HF) in the CKD population (5-7). Adequate renin-angiotensin-aldosterone (RAAS) blockade with angiotensin-converting enzyme inhibitors (ACEIs), angiotensin-receptor blockers (ARBs), mineralocorticoid receptor antagonists, and β-adrenergic antagonists remains the mainstay of treatment for CHF (8). Despite their higher CHF burden, CKD patients are less likely to receive optimal treatment for CHF due to the lack of established guidelines, physician discomfort, and increased incidence of adverse events such as hyperkalemia (9–13). This is especially prevalent in patients with cardiorenal syndrome, in which protracted CHF leads to decreased renal blood flow, renal venous congestion, and CKD.

With this pharmacotherapeutic gap, it would seem intuitive to consider device therapy such as cardiac resynchronization therapy (CRT), with or without an implantable cardioverter defibrillator (ICD), in the CKD population. CRT has been proven to reduce morbidity and mortality in CHF and has been recommended as a class I indication for patients with a left ventricular ejection fraction (LVEF) ≤35%, a QRS duration ≥120 milliseconds, and New York Heart Association (NYHA) functional class III or ambulatory class IV CHF symptoms (1). A recent update amended the criteria and expanded the class I indication to include patients with milder class II HF symptoms (15). It has been shown that CRT improves cardiac structure and function through reverse remodeling in those with both systolic and diastolic CHF (16,17). However, device therapy trials have excluded patients with moderate to severe kidney disease, including those on dialysis (18–20). Because patients with kidney disease are more likely to die of cardiovascular disease than progress to ESRD, it is

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possible that there may be a higher absolute benefit in these patients (21). Therefore, we aimed to systematically review the current evidence related to CRT in the CKD population.

Materials and Methods

Study Inclusion Criteria

We considered all subset analyses of randomized controlled trials (RCTs) and observational studies (of at least 12 weeks duration) that had CRT as the primary intervention or one of the treatment arms and that did not exclude patients with a baseline estimated GFR (eGFR) <60 ml/min per 1.73 m². Studies that did not report baseline renal function or lacked a CRT arm were excluded. Studies were considered without language restrictions.

Data Sources and Search Strategy


Data Extraction

Two reviewers (N.G., S.D.N.) screened the search results according to inclusion criteria. Studies that did not meet the inclusion criteria were excluded at this stage. The same reviewers independently extracted relevant data regarding study design and setting, participant characteristics, outcome measures, and study quality from the included studies. Disagreements were resolved in consultation with an arbitrator (G.T.). In circumstances in which more than one publication of one trial existed, only the latest publication with the most complete data was included. We contacted the authors of five studies for any further information by written correspondence and any relevant information obtained (from three studies) was included in the review.

Study Quality

Study quality for full-text citations was assessed using established guidelines (22). The risk of bias among the observational studies was assessed on the basis of the following six domains: (1) study participation, (2) study attrition, (3) prognostic factor measurement, (4) outcome measurement, (5) confounding measurement, and (6) statistical analysis. These individual domains were rated as either "yes," "partly," "no," or "unclear." "Yes" categorized a low risk for bias in each individual quality domain, and "no" or "unclear" categorized studies at high risk for bias and incomplete data, respectively. The quality of RCTs was assessed using a prespecified checklist that included allocation concealment, use of intention-to-treat analyses, completeness of follow-up, and blinding of participants, investigators, and outcome assessors.

Outcome Measures

The following outcome measures were considered for inclusion: all-cause mortality, HF hospitalizations, change in renal function (eGFR or 24-hour creatinine clearance), and change in LVEF.

Statistical Analyses

Observational studies and RCT data were pooled separately. In addition, two different comparisons were made: (1) CKD patients with CRT versus CKD patients without CRT and (2) CRT in the CKD population versus CRT in the non-CKD population for both observational studies and RCTs. For dichotomous outcome measures such as mortality, we pooled only the risk estimates (hazard ratio [HR], relative risk, or odds ratio) from individual studies. Only the most adjusted risk estimates that were reported in the studies were extracted and included in the analysis. Where continuous scales of measurement were used to assess the effects of treatment (eGFR, LVEF), results were expressed using the mean difference (MD) with 95% confidence intervals (95% CIs). Data were pooled using the random-effects model because of anticipated statistical heterogeneity, but the fixed effects model was also used to ensure robustness of the model chosen and susceptibility to outliers. Heterogeneity was analyzed using a chi-squared test on $n - 1$ degrees of freedom, with $a$ of 0.05 used for statistical significance, and the $I^2$ test. Separate analysis for individual outcomes according to the stage of kidney disease was planned, but was not performed due to lack of adequate data. All analyses were undertaken in Comprehensive Meta-Analysis software (BioStat, Englewood, NJ).

Results

Search Results

The combined search of MEDLINE, Scopus, and conference proceedings identified 397 citations, 349 of which were excluded after title and abstract review (Figure 1). Forty-eight unique studies were selected for full-text review. Eighteen studies met all inclusion criteria and were included in the systematic review: 14 observational studies and 4 RCTs (11,23–39). To evaluate the effect on survival outcomes, studies were classified into the following two groups: (1) comparing outcomes in all CKD patients who had CRT versus those without CRT and (2) comparing post-CRT outcomes in patients with baseline CKD versus those without CKD. Six studies reported change in eGFR (23,24,26,32,35,36) and four studies reported change in LVEF after CRT in patients with baseline CKD (23,26,29,32) (Table 1).

Study Characteristics

Observational Studies. The observational studies had sample sizes ranging from 85 to 875 with follow-up spanning 3–36 months. Most studies reported a higher prevalence of ischemic HF (60%–65%) and diabetes. They also reported a trend toward lower prescription of β-blockers and ACEIs (80%–85%) in these patients compared with those with normal renal function at baseline. All studies except one reported eGFR using the modified Modified Diet in Renal Disease (MDRD) study equation.
Only one study included 17 patients on chronic hemodialysis (24). Table 1 summarizes the characteristics of the included studies.

**RCTs.** Data from the RCTs usually derive from secondary analysis of previously published larger studies (11,32) or subgroup analysis reported in the primary studies (30,31,33). Sample size ranged from 403 to 1820 with follow-up of 6–40 months. Most studies included patients aged >60 years and had a higher proportion of men (70–80%). The prevalence of ischemic HF varied from 38% to 66% in these trials. Boerrigter et al. compared the utilization rates of β-blockers and diuretics by baseline eGFR and noted a higher diuretic use in those with CKD (P, 0.05) and similar prescription rates of ACEIs/ARBs and β-blockers across the groups (32). Three RCTs reported survival data in patients with CRT compared with no CRT and interaction of CKD versus normal renal function in these patients (11,31,33). One study stratified outcomes by eGFR categories (32) and reported eGFR and LVEF changes in patients with and without CRT. Table 1 summarizes the characteristics of included RCTs.

### Study Quality

**Observational Studies.** Study quality varied among the individual studies and the study quality for observational studies is detailed in Table 2. Most observational (published) studies were at moderate risk of bias for study participation, attrition, and outcome measures. Prognostic factor assessment and confounding was not clear for many observational studies and likely contributed to the risk of bias. The abstracts were at high risk of bias with insufficient data regarding study attrition, confounding, and study analysis.

**RCTs.** Among the four RCTs, two trials were double blinded (32,33), one was single blinded with the end points committee unaware of treatment allocation status (31), and one was not blinded to both patients and investigators (11). All RCTs reported complete follow-up data.

**CRT versus Other Modalities in the CKD Population**

**Observational Studies.** Among observational studies, Adelstein et al. included 347 patients who had CRT plus a defibrillator (CRT-D) with baseline eGFR 30–59 ml/min per 1.73 m² (24). The survival outcomes of those with ICD alone (and who otherwise met criteria for CRT) were worse compared with patients with CRT-D (HR, 2.23; 95% CI, 1.3 to 3.7).

**RCTs.** Subgroup analysis of three RCTs reported that death or HF hospitalizations were lower with CRT in CKD patients (Table 3). Cleland et al. showed a 33% lower hazard for death or HF hospitalizations with combined CRT/medical therapy compared with medical therapy alone in CKD patients (31). Tang et al. and Goldenberg et al. showed mortality/HF benefits of CRT-D as compared with defibrillator alone in the CKD population (11,33).

**Survival in CKD Patients with CRT versus Non-CKD Patients with CRT**

**Observational Studies.** Observational studies reported inferior survival with CRT in patients with baseline CKD compared with those with normal renal function. In the pooled analysis, CRT in those with kidney disease was associated with higher death rates compared with CRT in those without CKD (n=6 studies; OR, 2.50; 95% CI, 1.64 to 3.24) (Figure 2). There was mild heterogeneity between the included studies (I²=31%). Results of the study by Van Bommel et al. could not be pooled in the analysis because eGFR was reported as a continuous measure with an adjusted HR of 0.97 (95% CI, 0.96 to 0.98) for every 1–ml/min per 1.73 m² increase in eGFR (27). Kreuz et al. reported an increased risk for mortality (HR, 1.98; 95% CI, 1.7 to 3.0) for every 0.2-mg/dl increase in serum creatinine (34).

**RCTs.** Subgroup analysis based on eGFR <60 ml/min per 1.73 m² versus ≥60 ml/min per 1.73 m² in three clinical trials showed similar benefits with death/HF hospitalizations in both groups, suggesting that there might not be differences in CRT benefits based on the presence or absence of kidney disease (Table 3).
Table 1. Characteristics of studies included in the systematic review

<table>
<thead>
<tr>
<th>First Author (Reference)</th>
<th>Year</th>
<th>Country</th>
<th>Age (yr)</th>
<th>Sample Size</th>
<th>CKD Groups (n)</th>
<th>Baseline eGFR (ml/min per 1.73 m²)</th>
<th>Baseline EF (%)</th>
<th>Follow-Up</th>
<th>Outcomes Reported</th>
</tr>
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<tbody>
<tr>
<td><strong>Observational studies</strong></td>
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<tr>
<td>Lin (23)</td>
<td>2010</td>
<td>US</td>
<td>62–77</td>
<td>482</td>
<td>140 (GFR ≥90); 303 (GFR 30–59); 39 (GFR &lt;30)</td>
<td>43.8±10.4 (CKD)</td>
<td>22±8 (CKD)</td>
<td>36.4±26.5 mo</td>
<td>Change in eGFR, LV dimensions after CRT; all-cause mortality or need for heart transplant</td>
</tr>
<tr>
<td>Adelstein (24)</td>
<td>2010</td>
<td>US</td>
<td>67 ±12 to 65±15</td>
<td>875</td>
<td>376 (GFR ≥60); 347 (GFR 30–59); 64 (GFR &lt;30)</td>
<td>60±23 (CRT-D)</td>
<td>22±7 (CRT-D)</td>
<td>34±20 mo</td>
<td>Change in eGFR; all-cause mortality (primary); composite of death, cardiac transplant, VAD (secondary)</td>
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<tr>
<td>Shalaby (25)</td>
<td>2010</td>
<td>US</td>
<td>67.3±11.3</td>
<td>330</td>
<td>121 (SCR 0.6–1.0); 108 (SCR 1.1–1.3); 101 (SCR 1.4–3.0)</td>
<td>NA</td>
<td>22.4±9.3</td>
<td>19.7±9 mo</td>
<td>Death; composite of death of HF hospitalization</td>
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<tr>
<td>Fung (26)</td>
<td>2006</td>
<td>China</td>
<td>64±12</td>
<td>85</td>
<td>85 (GFR &lt;60)</td>
<td>56.9±19.7</td>
<td>26.6±8.5</td>
<td>3 mo</td>
<td>Change in eGFR and LV function after CRT</td>
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<tr>
<td>Van Bommel (27)</td>
<td>2011</td>
<td>Netherlands</td>
<td>55–77</td>
<td>490</td>
<td>93 (GFR &gt;90); 204 (GFR 60–90); 193 (GFR &lt;60)</td>
<td>70±28</td>
<td>24±8</td>
<td>26±21 mo</td>
<td>LV remodeling at 6 mo; all-cause mortality</td>
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<tr>
<td>Bai (27)</td>
<td>2008</td>
<td>US, China, Italy</td>
<td>55–78</td>
<td>542</td>
<td>NA</td>
<td>199±8.09</td>
<td>811.6±536.7 d</td>
<td>18±9 mo</td>
<td>All-cause mortality</td>
</tr>
<tr>
<td>Verbrugge (39)</td>
<td>2012</td>
<td>Belgium</td>
<td>62–80</td>
<td>172</td>
<td>66 (GFR &lt;60)</td>
<td>NA</td>
<td>29±10</td>
<td>18±9 mo</td>
<td>All-cause mortality; HF hospitalization; LV remodeling at 6 mo</td>
</tr>
<tr>
<td>Hosoda (38)</td>
<td>2012</td>
<td>Japan</td>
<td>42–79</td>
<td>67</td>
<td>32 (GFR &lt;50); 35 (GFR ≥50)</td>
<td>50.7±21.8</td>
<td>29.4±9.9</td>
<td>30.3±22 mo</td>
<td>All-cause mortality; composite of cardiac death or HF hospitalization; change in eGFR and LV dimensions</td>
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<tr>
<td>Kreuz (34)</td>
<td>2012</td>
<td>Germany</td>
<td>56–77</td>
<td>239</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>43±30 mo</td>
<td>Risk factors for all-cause mortality after CRT-D</td>
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<td>Hyder (28)</td>
<td>2010</td>
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<td>NA</td>
<td>648</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Change in EF at 6 mo; all-cause mortality</td>
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</table>
Table 1. (Continued)

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<tr>
<th>First Author (Reference)</th>
<th>Year</th>
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<th>Age (yr)</th>
<th>Sample Size</th>
<th>CKD Groups (n)</th>
<th>Baseline eGFR (ml/min per 1.73 m²)</th>
<th>Baseline EF (%)</th>
<th>Follow-Up</th>
<th>Outcomes Reported</th>
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<tr>
<td>Rickard (29)†</td>
<td>2009</td>
<td>US</td>
<td>NA</td>
<td>19†</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
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<td>Funke (30)†</td>
<td>2010</td>
<td>US</td>
<td>66±11</td>
<td>273§</td>
<td>NA</td>
<td>34% of total</td>
<td>NA</td>
<td>NA</td>
<td>All-cause</td>
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<td>67±11</td>
<td>163§</td>
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<td>NA</td>
<td>mortality.</td>
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<td>Jeevanantham (35)†</td>
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<td>renal function.</td>
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<td>Singhal (36)†</td>
<td>2012</td>
<td>US</td>
<td>68.5±12.9</td>
<td>219§</td>
<td>53 (GFR 60–90);</td>
<td>NA</td>
<td>23.6±7</td>
<td>5 yr</td>
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<td>117 (GFR 30–59);</td>
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<td>mortality at 5 yr</td>
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<td>Boerrigter (32)</td>
<td>2008</td>
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<td>64±1</td>
<td>384</td>
<td>67 (GFR ≥90);</td>
<td>64±1</td>
<td>24±1</td>
<td>6 mo</td>
<td>Change in eGFR</td>
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<td>and LVEF after CRT</td>
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<td>155 (GFR 30–59)</td>
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<tr>
<td>Cleland (31)</td>
<td>2005</td>
<td>Europe</td>
<td>59–73</td>
<td>813</td>
<td>369 (GFR &lt;60)</td>
<td>46–73</td>
<td>21–29</td>
<td>29.4 mo</td>
<td>Death or unplanned</td>
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<td>GFR ≥60 versus &lt;60</td>
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<td>Tang (33)</td>
<td>2010</td>
<td>Canada, Europe,</td>
<td>56–76</td>
<td>1798</td>
<td>881 (GFR ≥60);</td>
<td>59.5±19.8</td>
<td>22.6±5.4</td>
<td>40 mo</td>
<td>Death from any cause</td>
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<td>Turkey, Australia</td>
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<td>781 (GFR 30–59);</td>
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<td>or HF leading to</td>
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<td>120 (GFR &lt;30)</td>
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<td>hospitalization.</td>
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<tr>
<td>Goldenberg (11)</td>
<td>2010</td>
<td>US</td>
<td>52–76</td>
<td>1820</td>
<td>NA</td>
<td>66±27</td>
<td>NA</td>
<td>2.4 yr</td>
<td>Death or risk of HF;</td>
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<td>echocardiographic response to CRT</td>
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</tbody>
</table>

eGFR, estimated GFR; EF, ejection fraction; LV, left ventricular; CRT, cardiac resynchronization therapy; CRT-D, cardiac resynchronization therapy plus defibrillator; VAD, ventricular assist device; SCr, serum creatinine; NA, not available; HF, heart failure; LVEF, left ventricular ejection fraction; ICD, implantable cardioverter defibrillator.

†All participants received CRT.
‡There were 787 patients who received CRT-D, whereas 88 received ICD alone.
§All participants received CRT-D.
¶There were 395 patients who received CRT-D, whereas 147 received CRT-P.
¶¶Included abstracts.
### Table 2. Quality assessment of the observational studies included in the systematic review

<table>
<thead>
<tr>
<th>First Author (Reference)</th>
<th>Year</th>
<th>Study Participation</th>
<th>Attrition</th>
<th>Prognostic Factor Measurement</th>
<th>Outcome Measure</th>
<th>Confounding Measurement</th>
<th>Analysis</th>
</tr>
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<tbody>
<tr>
<td>Lin (23)</td>
<td>2010</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Partly</td>
<td>Yes (adjusted variables include sex, nonischemic cardiomyopathy, LVEF, eGFR, hemoglobin, serum sodium, CKD)</td>
</tr>
<tr>
<td>Adelstein (24)</td>
<td>2010</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Partly</td>
<td>Yes (adjusted variables include age, NYHA class, LVEF, QRS interval, etiology of cardiomyopathy, CKD)</td>
</tr>
<tr>
<td>Shalaby (25)</td>
<td>2008</td>
<td>Yes</td>
<td>Unclear</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes (adjusted variables include sex, NYHA class, eGFR, LVEF, MR grade)</td>
</tr>
<tr>
<td>Fung (26)</td>
<td>2007</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Unclear</td>
</tr>
<tr>
<td>Van Bommel (27)</td>
<td>2011</td>
<td>Yes</td>
<td>Unclear</td>
<td>Yes</td>
<td>Yes</td>
<td>Partly</td>
<td>Yes (adjusted variables include sex, NYHA class, eGFR, LVEF, MR grade)</td>
</tr>
<tr>
<td>Bai (37)</td>
<td>2008</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Unclear</td>
<td>Yes (adjusted variables include age, sex, medications, Afib, DM, NYHA class, cause of cardiomyopathy, CKD)</td>
</tr>
<tr>
<td>Verbrugge (39)</td>
<td>2012</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Partly</td>
<td>Yes (adjusted variables include obesity, DM, HTN, Afib, COPD, anemia, CKD)</td>
</tr>
<tr>
<td>Hosada (38)</td>
<td>2012</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Confounding likely due to different equation for estimation of GFR</td>
</tr>
<tr>
<td>Kreuz (34)</td>
<td>2012</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Partly</td>
<td>Yes (adjusted variables include age, β-blocker use, renal function, amiodarone use, and malignant arrhythmia)</td>
</tr>
<tr>
<td>Hyder (28)</td>
<td>2010</td>
<td>Yes</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Yes</td>
<td>Unclear</td>
<td>Unclear</td>
</tr>
<tr>
<td>Rickard (29)</td>
<td>2009</td>
<td>Yes</td>
<td>Unclear</td>
<td>Yes</td>
<td>Yes</td>
<td>Unclear</td>
<td>Unclear</td>
</tr>
<tr>
<td>Funke (30)</td>
<td>2010</td>
<td>Yes</td>
<td>Unclear</td>
<td>Yes</td>
<td>Yes</td>
<td>Unclear</td>
<td>Unclear</td>
</tr>
<tr>
<td>Jeevanantham (35)</td>
<td>2011</td>
<td>Yes</td>
<td>Unclear</td>
<td>Yes</td>
<td>Yes</td>
<td>Unclear</td>
<td>Unclear</td>
</tr>
<tr>
<td>Singhal (36)</td>
<td>2012</td>
<td>Yes</td>
<td>Unclear</td>
<td>Yes</td>
<td>Yes</td>
<td>Unclear</td>
<td>Unclear</td>
</tr>
</tbody>
</table>

LVEF, left ventricular ejection fraction; eGFR, estimated GFR; NYHA, New York Heart Association; MR, mitral regurgitation; Afib, atrial fibrillation; DM, diabetes mellitus; HTN, hypertension; COPD, chronic obstructive pulmonary disease.

*These studies were presented only in abstract form and details of multivariate analysis not available.*
Effect of CRT Therapy on Renal Outcomes in Patients with Baseline CKD

There was significant improvement in eGFR with CRT in those with CKD ($n=4$ studies; MD 2.30 ml/min per 1.73 m$^2$; 95% CI, 0.33 to 4.27), with moderate heterogeneity between the studies ($I^2=56\%$) (Figure 3).

Effect of CRT on LVEF in Patients with Baseline CKD

There was significant improvement in LVEF with CRT in those with CKD ($n=3$ studies; MD 6.24%; 95% CI, 3.46 to 9.07). There was mild heterogeneity between the included studies ($I^2=26\%$) (Figure 4).

Miscellaneous Outcomes

Three studies reported symptomatic benefit with significant improvement in NYHA class and 6-minute walk test score with the use of CRT in the CKD population (29,32,39). Rickard et al. also showed a trend toward improved transplant and ventricular assist device–free survival with the use of CRT in CKD patients. Van Bommel et al. and Lin et al. reported a 6-month CRT responder status ($\geq 15\%$ decrease in LV end-systolic volume [LVESV] at 6 months) of 43% in 193 CKD patients and decreases in LV end-diastolic diameter and LV end-systolic diameter in 209 CKD patients, respectively (23,27). Adelstein et al. showed worsening of echocardiographic parameters with further LV dilation in 64 patients with severe CKD (eGFR <30 ml/min per 1.73 m$^2$) compared with those with moderate CKD (eGFR $\geq 30$ ml/min per 1.73 m$^2$) in which significant improvement was documented with CRT (24).

Discussion

Despite the higher prevalence of CKD in patients with CHF and the demonstrated benefits of CRT in non-CKD population, the beneficial effects of CRT in patients with CKD are unclear. These are attributed to the lack of high-quality data, higher costs incurred and higher overall mortality in the CKD population that may limit the efficacy of CRT. The purpose of this systematic review was to examine the available evidence on this topic; as such, we found several notable observations. Among RCTs, CRT portended a survival benefit over non-CRT modalities (medical therapy or ICD alone) in CKD patients who were eligible to receive CRT (11,31,33). Similarly, subgroup analyses of these clinical trials also showed that survival outcomes were not different between CKD and non-CKD population with CRT. However, most studies included patients with stage 3 CKD and only a limited number of stage 4 CKD patients. Observational studies comparing survival between CKD and non-CKD patients after CRT implantation showed inferior outcomes in the CKD group.

Table 3. Survival outcomes among CKD and non-CKD participants with or without CRT

<table>
<thead>
<tr>
<th>First Author Year</th>
<th>Follow-Up Duration</th>
<th>Events in CKD Group</th>
<th>HR (95% CI) for CRT versus No CRT (in CKD Group)</th>
<th>Events in Non-CKD Group</th>
<th>HR (95% CI) for CRT versus No CRT (in Non-CKD Group)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cleland (31) 2005</td>
<td>29.4 mo</td>
<td>196/369</td>
<td>0.67 (0.50 to 0.89)</td>
<td>142/370</td>
<td>0.57 (0.40 to 0.8)</td>
</tr>
<tr>
<td>Tang (33)a 2010</td>
<td>40 mo</td>
<td>407/900</td>
<td>0.71 (0.58 to 0.86)</td>
<td>250/882</td>
<td>NA</td>
</tr>
<tr>
<td>Goldenberg (11)a,b 2010</td>
<td>2.4 yr</td>
<td>NA</td>
<td>0.67 (0.50 to 0.89)</td>
<td>NA</td>
<td>0.61 (0.50 to 0.89)</td>
</tr>
</tbody>
</table>

CRT, cardiac resynchronization therapy; HR, hazard ratio; 95% CI, 95% confidence interval; NA, not available; ICD, implantable cardioverter defibrillator.

aRandomized patients to CRT plus ICD or to ICD alone
bExcluded patients with serum creatinine $>3$ mg/dl.

Figure 2. | Survival in CKD patients with CRT versus non-CKD patients with CRT (observational studies only). CRT, cardiac resynchronization therapy; 95% CI, 95% confidence interval.
Taken together, these observations suggested that despite the higher mortality risk in CKD patients, the incremental benefits of CRT are evident in this population.

The higher mortality rates and HF outcomes in CKD patients (noted in observational studies) are probably not due to a lack of ventricular response to CRT but rather due to the underlying kidney disease and its complications. Significant response to CRT (responder status) has been defined as a $\geq 15\%$ decrease in LVEVs or LV end-systolic diameter, improvement in LVEF of $\geq 3\%–5\%$, or improvement in NYHA class by $\geq 1$ in various studies. Our pooled analysis demonstrated a significant improvement in LVEF after CRT in CKD patients (Figure 4). Boerrigter et al. demonstrated a significant improvement in 6-minute walking distance and mean arterial pressure and a decrease in LV mass index and LVEVs (markers of response to CRT) in the CKD population with CRT (32). Among the CKD population, the presence of moderate CKD ($eGFR\geq 30$–59 ml/min per 1.73 m$^2$) at baseline rather than stage 4 CKD ($eGFR<15$–29 ml/min per 1.73 m$^2$) and positive response to CRT were associated with better survival. Apart from renal function per se, the associated CKD complications might explain the higher mortality despite CRT in CKD. Lin et al. attributed the difference in mortality outcomes (despite similar cardiac remodeling in CKD and non-CKD patients) to the higher prevalence of anemia in CKD (23).

Excessive activation of the RAAS and sympathetic nervous system are important pathophysiologic mechanisms that underlie progression of both CKD and CHF. RAAS activation has been shown to accelerate CKD progression by causing intraglomerular hypertension, glomerular hypertrophy, and secondary hyperfiltration injury (40). Excessive angiotensin II causes LV hypertrophy, fibrosis, and adverse ventricular remodeling. Use of RAAS blocking agents, mineralocorticoid receptor antagonists, and direct renin inhibitors confers renoprotection and ameliorates severity of HF. An increased incidence of adverse events like AKI and hyperkalemia may limit the use of RAAS blockade in patients with advanced CKD and explain the higher HF mortality in this population (13).

The underlying uremic and hyperphosphatemic milieu in CKD has an independent effect on cardiac structure and function (41). High urea levels cause accelerated coronary atherogenesis and cardiac structural alterations such as intramyocardial arteriolar wall thickening, myocardial capillary rarefaction, endothelial cell dysfunction, cardiac fibrosis, fibro elastic thickening of the aorta, and remodeling of central arteries (41–43). The lower prevalence of such mechanisms in the non-CKD population, in which CHF is induced by coronary artery disease or other mechanisms, would explain the discordance in mortality outcomes despite similar improvements in echocardiographic measures after CRT.

CRT was associated with preservation of renal function in those with moderate CKD and a modest improvement in those with mild CKD at baseline. It was also noted that patients who demonstrated an improvement in eGFR were likely to show decreased re-hospitalizations after CRT (36). Acute decompensated cardiac failure has a reciprocal effect on the kidneys, resulting in cardiorenal syndrome characterized by AKI, oliguria, and diuretic resistance (44). Acute CHF and elevated cardiac filling pressures are associated with an excess of vasoconstricting...
neurohormones like angiotensin II, NE, and endothelin and decreased responsiveness to natriuretic peptides, all of which initiate renal injury by contributing to decreased renal blood flow, renal venous congestion, excessive sodium retention and unregulated volume expansion (45). CRT ameliorates these adverse changes by improving ventricular synchrony and pump efficiency, without increasing myocardial oxygen demand. Although CRT does not have a direct effect on the kidneys, CRT responders demonstrate a subsequent decrease in sympathetic and RAAS activation, thus conferring an improvement in hemodynamics, mean arterial pressure, and renal perfusion. These improvements have also been associated with better outcomes with CRT (27,32,38).

The main strength of this systematic review is that it is based on a prespecified study protocol, which included a systematic search of MEDLINE and conference proceedings. The main limitation of this study is that it includes observational studies that may be subject to selection bias, attrition bias, and unknown confounding factors and the lack of ability to distinguish between patients with CKD and those with predominantly cardiorenal physiology. We conducted separate analyses for observational studies and RCTs in this systematic review. Furthermore, the pooled risk estimates were derived from a small number of studies and would have been more robust if there were more studies that provided relevant data in a consistent manner. We noted mild to moderate heterogeneity in the pooled analysis, but we could not explore the reasons for the heterogeneity in further analysis due to lack of adequate number of studies. eGFR data were based on serum creatinine, which might underestimate or overestimate GFR in patients with different ages and muscle mass. However, the population included in these studies had eGFR 15–59 ml/min per 1.73 m² and the MDRD equation is reliable in this setting. It is important to note that the benefits of CRT in those with ESRD (either on dialysis or those who have received a kidney transplant) have not been studied. Despite these limitations, this study summarizes the best evidence about the utility of CRT in CKD population.

In summary, the results of this study indicate that CRT might provide survival advantage in those with moderate CKD (eGFR 30–59 ml/min per 1.73 m²) and HF, along with improvement of cardiac and renal function. The outcomes of CKD patients with CRT may be inferior to those in the non-CKD population and are attributable to a higher incidence of mortality and HF hospitalizations in CKD. Future studies should include patients with advanced CKD to examine the benefits of CRT. Given the higher costs associated with CRT, additional data on the cost-effectiveness of CRT in CKD are also warranted.

Acknowledgments

We thank Marian Simonson, Cleveland Clinic Lerner School of Medicine who helped us in developing and conducting the search. We also thank Drs. Grace Lin, Evan Adelstein, and Guido Boerrigter, the authors of included studies who provided additional details to conduct these analyses.

This study was supported by a grant from the National Institutes of Health (NIH) National Center for Research Resources (NCRR) Multidisciplinary Clinical Research Career Development Program (R244990 to S.D.N.).

The contents of this manuscript are solely the responsibility of the authors and do not necessarily represent the official view of the NCRR or the NIH. Information on NCRR is available at http://www.ncrr.nih.gov/. Information on Re-Engineering the Clinical Research Enterprise can be obtained from http://nihroadmap.nih.gov/crc/default.htm.

Results of this systematic review were presented in abstract form at the Annual Meeting of the American Society of Nephrology on November 2, 2012, in San Diego, California.

Disclosures

None.

References


Received: January 22, 2013 Accepted: March 27, 2013

Published online ahead of print. Publication date available at www.cjasn.org.

This article contains supplemental material online at http://cjasn.asnjournals.org/lookup/suppl/doi:10.2215/CJN.00750113/-/DCSupplemental.
Supplemental Material

We used the following search strategy to search MEDLINE (1990- December 2012)

1 exp Renal Replacement Therapy/
2 ((renal or kidney) adj5 replacement:).tw.
3 (dialysis or hemodialysis or haemodialysis).tw.
4 (pd or capd or ccpd or apd).tw.
5 (hemodiafiltrat: or haemodiafiltrat: or hemofiltrat: or haemofiltrat:).tw.
6 ((kidney or renal) adj5 transplant:).tw.
7 renal insufficiency/ or kidney failure/ or kidney failure, chronic/ or renal insufficiency, chronic/
8 ((renal or kidney) adj5 (insufficien: or fail:)).tw.
9 kidney diseases/
10 Uremia/
11 (end stage adj5 (renal or kidney)).tw.
12 (endstage adj5 (renal or kidney)).tw.
13 (esrf or eskf or esrd or eskd).tw.
14 (chronic adj3 (kidney or renal)).tw.
15 (ckf or ckd or crf or crd).tw.
16 (uremi: or uraemi:).tw.
17 or/1-16
18 epidemiologic studies/ or exp case-control studies/ or exp cohort studies/ or cross-sectional studies/
19 exp clinical trial/
20 ((epidemiologic or case-control or cohort or longitudinal or follow-up or prospective or retrospective or cross-sectional) adj2 (study or studies)).tw.
21 cohort$1.tw.
22 (case$1 adj5 (control$ or series)).tw.
23 (clinical adj2 trial$1).tw.
24 epidemiologic methods/ or exp clinical trials as topic/
25 or/18-24
26 Cardiac Pacing, Artificial/
27 Pacemaker, Artificial/
28 (cardiac adj3 (resynchroniz: or resynchronis:)).tw.
29 (biventricular adj3 (pace: or pacing)).tw.
30 (biventricular adj3 stimulat:).tw.
31 ((multi site or multisite) adj3 (pacing or pacemaker:)).tw.
32 (heart adj3 (pacing or pacemaker:)).tw.
33 (heart adj3 (resynchroniz: or resynchronis:)).tw.
34 ((multi site or multisite) adj3 stimulat:).tw.
35 ((dual chamber or dual-chamber) adj3 (pacing or pacemaker: or stimulat:)).tw.
36 Defibrillators, Implantable/
37 Electric Countershock/
38 (cardioversion or cardioverter$1).tw.
39 defibrillat:.tw.
40 (implant: adj3 (defibrillat: or cardiover:)).tw.
41 or/26-40
42 17 and 41
43 42 and 25