Renal dysfunction, a frequent phenomenon in the setting of heart failure (HF), represents significant comorbidities and may lead to further deterioration of HF and worsened clinical outcomes.1–10

**Clinical Perspective on p 732**

Cardiac resynchronization therapy (CRT) has been shown to reduce the risk of death and HF events in patients with symptomatic HF, reduced left ventricular ejection fraction, and prolonged QRS complex.11–17 In patients with mild HF, CRT with implantable cardioverter-defibrillator (CRT-D) provides survival benefit during long-term follow-up.18 However, benefit from CRT-D may be limited in the presence of renal dysfunction, both in terms of survival and echocardiographic response, with results varying based on HF severity.19–25 There are limited data on the effect of CRT-D by baseline renal function during long-term follow-up. Therefore, it is unknown whether there is sustained benefit from CRT-D among those with renal dysfunction. The complex interplay between renal and cardiovascular physiology warrants closer examination of the relationship between renal function and CRT-D benefit.
The objectives of this study were (1) to assess the impact of renal function on the risk of all-cause mortality and HF events in patients receiving CRT-D or implantable cardioverter defibrillator (ICD)-only during long-term follow-up and (2) to determine the relationship between renal function and benefit from CRT-D versus ICD-only during long-term follow-up to reduce the risk of all-cause mortality and HF events.

Methods

Main Study Protocol and Treatment

The protocol and results of the Multicenter Automatic Defibrillator Implantation Trial–Cardiac Resynchronization Therapy (MADIT-CRT) trial and the long-term follow-up study have been described previously.16–18 In summary, 1820 ischemic and nonischemic cardiomyopathy patients with left ventricular ejection fraction ≤30%, QRS duration of ≥130 ms, and New York Heart Association class I or II symptoms were randomized to CRT-D versus ICD-only treatment in a 3:2 ratio. All patients received optimal medical therapy for HF consisting of β-blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers/angiotensin II inhibitors, and statins. Exclusion criteria included New York Heart Association class III or IV symptoms, coronary artery bypass graft surgery, percutaneous coronary intervention, or myocardial infarction within 90 days before enrollment; second- or third-degree heart block; chronic atrial fibrillation; and significant renal disease (blood urea nitrogen [BUN] >70 mg/dL or creatinine >3.0 mg/dL).

The 1820 patients were followed up for an average period of 2.4 years in the primary study at 110 centers in Europe/Israel and North America, initially being seen at the 1-month mark and subsequently at 3-month intervals after randomization. The duration of post-trial follow-up was a median of 5.6 years; the first phase was conducted in all 1691 surviving patients, whereas the second phase involved 854 patients at 71 centers from the United States, Canada, Europe, and Israel. Both MADIT-CRT and the post-trial follow-up studies were approved by the institutional review board, and all subjects gave informed consent.

Substudy Protocol

The present study is a retrospective analysis of the MADIT-CRT sample stratified on the basis of available data related to QRS morphology and renal function into 1274 (70%) patients with left bundle-branch block (LBBB) and 533 (29%) patients without LBBB, although it has previously been shown that patients without LBBB did not experience reduction in all-cause mortality and HF events from implantation of a CRT-D versus an ICD-only.16,18 There were 3 patients for whom LBBB data and another 10 patients for whom renal function data were not available. The analyses were performed on an intention-to-treat basis, with the initial treatment assignment applied. The cross-overs, changes in the initial treatment assignment, during long-term follow-up were rare with only 9% crossover from ICD-only to CRT-D and 5% of crossover from CRT-D to an ICD-only.18

Definitions and End Points

Glomerular filtration rate (GFR) was used to assess renal function and calculated using the formula GFR = 186 x creatinine^{-1.154} x age^{-0.203} x (0.742 if women) x (1.21 if black). Each of the LBBB and non-LBBB patient categories was divided into 2 prespecified subgroups (0.742 if women) × (1.21 if black). Each of the LBBB and non-LBBB patient categories was divided into 2 prespecified subgroups (0.742 if women) × (1.21 if black). Each of the LBBB and non-LBBB patient categories was divided into 2 prespecified subgroups. The histogram of GFR values in LBBB patient categories was divided into 2 prespecified subgroups (0.742 if women) × (1.21 if black). Each of the LBBB and non-LBBB patient categories was divided into 2 prespecified subgroups (0.742 if women) × (1.21 if black). Each of the LBBB and non-LBBB patient categories was divided into 2 prespecified subgroups (0.742 if women) × (1.21 if black). Each of the LBBB and non-LBBB patient categories was divided into 2 prespecified subgroups (0.742 if women) × (1.21 if black). Each of the LBBB and non-LBBB patient categories was divided into 2 prespecified subgroups. The histogram of GFR values in LBBB patient categories was divided into 2 prespecified subgroups.

The primary end point was all-cause mortality, whereas secondary end points consisted of the combined end point of nonfatal HF events or death (HF/death) and nonfatal HF events alone during long-term follow-up. All 3 end points were analyzed during a median follow-up period of 5.6 years. In a secondary analysis, the effect of GFR on outcomes was assessed as a continuous variable.

Physicians who were not blinded to treatment assignments determined the diagnosis of HF based on signs and symptoms consistent with congestive HF requiring diuretics in the outpatient or inpatient setting. However, adjudication of the end points was conducted by an independent mortality committee and by a HF committee unaware of treatment assignments based on prespecified criteria.

Statistical Analysis

Baseline clinical characteristics were compared between patients with baseline GFR <60 and 260 mL/min per 1.73 m2 using the χ2 test for dichotomous variables and Wilcoxon signed-rank test for continuous variables.

The cumulative probabilities of all-cause mortality, combined HF events or death, and HF events alone during long-term follow-up

Figure 1. Distribution of glomerular filtration rate (GFR) among patients with left bundle-branch block.
were displayed according to the Kaplan–Meier method by baseline GFR category and by treatment arm, with comparisons of cumulative event rates by the log-rank test.

Multivariable Cox proportional hazards regression analysis was used to assess the impact of baseline GFR by subgroups of GFR <60 and ≥60 mL/min per 1.73 m² as well as the impact of GFR as a continuous measurement on the probability of all-cause mortality, combined HF events or death, and HF events alone during long-term follow-up. Best subset selection was applied to candidate covariates, and the Cox model was adjusted for relevant clinical covariates (diabetes mellitus, ischemic cardiomyopathy, left ventricular end-systolic volume index at baseline, prior congestive heart failure hospitalization, QRS duration >150 ms, and CRT-D versus ICD-only treatment). Interaction P values for CRT-D versus ICD-only effect were computed and reported between the 2 GFR groups. We also assessed the effect of GFR on clinical outcomes using a log-scale as a sensitivity analysis.

We evaluated the absolute risk reduction (ARR) using the 6-year Kaplan–Meier event rates of all-cause mortality, combined HF events or death, and HF events alone during long-term follow-up by reporting the differences between cumulative probabilities of events in the CRT-D and ICD-only groups. We considered 6-year Kaplan–Meier cumulative probabilities to ensure sufficient numbers of patients available for follow-up for the comparison.

Although non-LBBB patients have been shown not to derive benefit from CRT-D in prior studies, we further assessed the cumulative probabilities and the risk of all-cause mortality, combined HF events or death, and HF events alone using the Kaplan–Meier survival method and multivariable Cox proportional hazards regression models among the 533 non-LBBB patients.

All statistical tests were 2-sided, and a P value of <0.05 was considered statistically significant. Analyses were performed with SAS software (version 9.4, SAS Institute, Cary, NC).

### Results

#### Baseline Clinical Characteristics of LBBB Patients

Among the 1274 patients with LBBB, a total of 413 (32%) presented with GFR <60 mL/min per 1.73 m² (mean, 48.1±8.3). As only 7 (2%) individuals had GFR <30 mL/min per 1.73 m², the GFR <60 mL/min per 1.73 m² group was classified as having moderate renal dysfunction. The remaining 861 (68%)
patients with GFR ≥60 mL/min per 1.73 m² (79.6±16.0) were characterized by mildly impaired-to-normal renal function.

Baseline clinical characteristics of LBBB patients with GFR <60 and ≥60 mL/min per 1.73 m² are presented in Table 1. Patients with GFR <60 mL/min per 1.73 m² were more likely to be older with comorbidities such as diabetes mellitus and hypertension and more often presented with history of ischemic cardiomyopathy, prior HF hospitalization, coronary artery bypass graft surgery, and myocardial infarction. Patients with GFR <60 mL/min per 1.73 m² were more often prescribed diuretics. The proportion of CRT-D assigned treatment was similar in both GFR subgroups.

During long-term follow-up, 177 patients (14%) died from any cause, 368 patients (30%) met the combined end point of HF/death, and 280 patients (22%) developed HF events alone.

**Baseline GFR Predicting All-Cause Mortality and HF Events in LBBB Patients**

Patients with LBBB in the GFR <60 mL/min per 1.73 m² subgroup had significantly higher cumulative probability of all-cause mortality (P<0.001), significantly increased rate of HF/death (P<0.01), and significantly greater incidence of HF events alone (P<0.01), when compared with patients with GFR >60 mL/min per 1.73 m² (Figure 2).

Multivariable analysis showed that patients with GFR <60 mL/min per 1.73 m² experienced 2-fold significantly higher risk of all-cause mortality (P<0.01), 46% significantly greater risk of HF/death (P<0.01), and 28% borderline-significant increase in risk of HF events alone (P=0.06), in comparison with patients with GFR >60 mL/min per 1.73 m² (Table 2).

Each 10-U reduction in GFR was associated with a 23% significantly greater risk of all-cause mortality (P<0.01), 12% significantly increased risk of HF/death (P<0.01), and 9% significant increase in HF events alone (P=0.01; Table 2).

**Effect of CRT-D Relative to ICD-Only on All-Cause Mortality and HF Events by Baseline GFR in LBBB Patients**

In LBBB patients with GFR <60 mL/min per 1.73 m², CRT-D was associated with significantly decreased cumulative

### Table 2. Relationship of Baseline GFR and the Risk of All-Cause Mortality, All-Cause Mortality or Heart-Failure Events, and Heart-Failure Events Alone in Patients With Left Bundle-Branch Block

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>End point: all-cause mortality (177 events)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GFR &lt;60 vs GFR ≥60 (92 vs 85 events)</td>
<td>2.09</td>
<td>1.53–2.86</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>GFR per every 10 U decrement (continuous)</td>
<td>1.23</td>
<td>1.13–1.35</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>End point: all-cause mortality or heart-failure events (368 events)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GFR &lt;60 vs GFR ≥60 (155 vs 213)</td>
<td>1.46</td>
<td>1.17–1.82</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>GFR per every 10 U decrement (continuous)</td>
<td>1.12</td>
<td>1.06–1.19</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>End point: heart-failure events (280 events)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GFR &lt;60 vs GFR ≥60 (109 vs 171)</td>
<td>1.28</td>
<td>1.00–1.66</td>
<td>0.06</td>
</tr>
<tr>
<td>GFR per every 10 U decrement (continuous)</td>
<td>1.09</td>
<td>1.02–1.16</td>
<td>0.01</td>
</tr>
</tbody>
</table>

The model is adjusted for diabetes mellitus, ischemic cardiomyopathy, left ventricular end-systolic volume index at baseline, prior congestive heart failure hospitalization, QRS duration >150 ms, age <65 years, female sex, and cardiac-resynchronization therapy with defibrillator vs implantable cardioverter defibrillator-only treatment. GFR indicates glomerular filtration rate.
probability of all-cause mortality ($P=0.02$), significantly reduced rate of HF/death ($P<0.01$), and significantly lower incidence of HF events alone ($P<0.01$; Figure 3).

Effect of Baseline GFR and CRT-D Relative to ICD-Only on Clinical Outcomes in Non-LBBB Patients
Among the 533 non-LBBB patients, there were 186 (35%) patients with GFR <60 mL/min per 1.73 m², 9 (2%) of whom had GFR <30 mL/min per 1.73 m², whereas 347 (65%) presented with GFR ≥60 mL/min per 1.73 m². During long-term follow-up, 184 patients (20%) died from any cause, 187 patients (35%) met the combined end point of HF/death, and 143 patients (27%) developed HF events alone. Patients with non-LBBB in the low-GFR group experienced significantly higher incidence ($P<0.01$) and higher risk of all-cause mortality (hazard ratio [HR], 2.08; 95% confidence interval [CI], 1.37–3.15; $P<0.01$), higher incidence ($P<0.01$) and higher risk of HF/death (HR, 1.84; 95% CI, 1.35–2.51; $P<0.01$), and higher incidence ($P<0.01$) and risk of HF events alone (HR, 2.00; 95% CI, 1.40–2.86; $P<0.01$), relative to patients in the GFR ≥60 mL/min per 1.73 m².

In both GFR subgroups among non-LBBB patients, CRT-D relative to ICD-only was not associated with significant reduction in the risk of all-cause mortality (GFR <60: HR, 1.33; 95% CI, 0.76–2.32; $P=0.32$ and GFR ≥60: HR, 1.09; 95% CI, 0.59–2.00; $P=0.79$), HF/death (GFR <60: HR, 1.30; 95% CI, 0.84–2.03; $P=0.24$ and GFR ≥60: HR, 1.08; 95% CI, 0.71–1.63; $P=0.74$), and HF events alone (GFR <60: HR, 1.18; 95% CI, 0.72–1.93; $P=0.52$ and GFR ≥60: HR, 0.99; 95% CI, 0.62–1.60; $P=0.97$) during long-term follow-up, confirming our previous results. Renal function, therefore, did not modify the effect of CRT-D on outcomes in patients with non-LBBB.

Sensitivity Analyses
We performed several sensitivity analyses to assess the robustness of our findings. Because GFR is derived using a formula that includes age and sex, we performed multivariable models both without the adjustment for age and sex and with adjustments, and our findings were essentially the same in both models. In the article, we present our findings from age- and
Table 3. Treatment Effect of CRT-D Relative to ICD-only by Baseline GFR for End Points of All-Cause Mortality, All-Cause Mortality or Heart-Failure Events, and Heart-Failure Events Alone in Patients With Left Bundle-Branch Block

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
<th>P Value</th>
<th>Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>End point: all-cause mortality (177 events)</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>CRT-D vs ICD in patients with GFR &lt;60</td>
<td>0.66</td>
<td>0.44–1.00</td>
<td>0.05</td>
<td>0.94</td>
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<tr>
<td>CRT-D vs ICD in patients with GFR ≥60</td>
<td>0.68</td>
<td>0.44–1.05</td>
<td>0.08</td>
<td></td>
</tr>
<tr>
<td>End point: all-cause mortality or heart-failure events (368 events)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRT-D vs ICD in patients with GFR &lt;60</td>
<td>0.49</td>
<td>0.36–0.67</td>
<td>&lt;0.01</td>
<td>0.89</td>
</tr>
<tr>
<td>CRT-D vs ICD in patients with GFR ≥60</td>
<td>0.50</td>
<td>0.38–0.66</td>
<td>&lt;0.01</td>
<td></td>
</tr>
<tr>
<td>End point: heart-failure events (280 events)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRT-D vs ICD in patients with GFR &lt;60</td>
<td>0.36</td>
<td>0.25–0.54</td>
<td>&lt;0.01</td>
<td>0.48</td>
</tr>
<tr>
<td>CRT-D vs ICD in patients with GFR ≥60</td>
<td>0.43</td>
<td>0.32–0.59</td>
<td>&lt;0.01</td>
<td></td>
</tr>
</tbody>
</table>

The model is adjusted for diabetes mellitus, ischemic cardiomyopathy, left ventricular end-systolic volume index at baseline, prior congestive heart failure hospitalization, QRS duration >150 ms, age >65 years, and female sex. CI indicates confidence interval; CRT-D, cardiac resynchronization therapy with defibrillator; GFR, glomerular filtration rate; and ICD, implantable cardioverter defibrillator.

Discussion

In the present study, we report that among patients with mild HF, moderate renal dysfunction was associated with a higher risk of all-cause mortality and HF events during long-term follow-up relative to those with mildly impaired-to-normal renal function. Furthermore, we revealed that LBBB patients both with mildly impaired-to-normal renal function and moderate renal dysfunction derive similar benefit from CRT-D during long-term follow-up with reductions in all-cause mortality and HF events. Importantly, patients with moderate renal dysfunction in our study experienced higher ARR of death and HF events.

Our results have important clinical implications for patients with moderate renal dysfunction who are shown in this study to derive sustained benefit during long-term follow-up from CRT-D with greater ARRs in adverse outcomes. These findings are encouraging for patients with moderate renal dysfunction to be considered for implantation of a CRT-D.

Prior studies of patients with moderate-to-severe HF reported ambiguous results regarding the impact of renal dysfunction on the benefit from CRT. In a subgroup analysis of the Cardiac Resynchronization-Heart Failure (CARE-HF) trial, the effect of CRT on the end point of all-cause mortality was similar in those with or without reduced renal function. Other studies suggest that patients with renal dysfunction derive less echocardiographic improvement from CRT and that those with severe renal dysfunction may represent advanced disease states that do not benefit from CRT.

There is even less clarity about the impact of renal dysfunction on clinical outcome among patients with mild-to-moderate HF receiving CRT. Although 1 study indicated similar reduction in death and HF hospitalizations among those with or without renal dysfunction, another report observed less improvement of left ventricular ejection fraction after CRT in the setting of renal dysfunction.

Such controversy surrounding the role of implanting a CRT-D device in patients with renal dysfunction becomes particularly relevant when the intricate relationship between the heart and kidneys is considered. Cardiovascular and renal diseases have risk factors in common, and patients with HF often present with renal dysfunction. Elevated BUN as a marker of renal dysfunction has further been associated with increased mortality in HF. Although BUN/creatinine ratio facilitates evaluation of volume status and kidney perfusion among patients with HF, especially when concern for acute kidney injury is present, GFR is a more commonly established indicator of renal function in clinical practice for long-term monitoring and is unaffected by confounders such as gastrointestinal hemorrhage.

This was confirmed in our study in the sensitivity analyses, as we found that GFR was the most predictive factor of outcomes compared with BUN or creatinine or BUN/creatinine ratio.

It is not surprising that impaired renal function among New York Heart Association class I and II patients with or without LBBB is associated with poor outcomes, although the state of mild HF may itself signify a lower disease burden in comparison with more advanced HF. Even in the presence of moderate renal dysfunction, however, CRT-D in our study provided significant benefit for LBBB patients in terms of reduced overall mortality as well as fewer HF events, suggesting that improvement of cardiac function with cardiac resynchronization may reverse the adverse effects of renal dysfunction. In our study, the adjusted effect of CRT-D on mortality was similar among those with GFR <60 and ≥ 60 mL/min per 1.73 m², as demonstrated by the HRs and lack of treatment–GFR interaction between the 2 groups.

To our knowledge, the present study is the largest retrospective analysis of prospectively collected data in mildly symptomatic HF patients with and without renal dysfunction comparing CRT-D with ICD-only treatment during a long-term follow-up period. We were able to show that patients...
with HF with moderate renal dysfunction, despite their less favorable prognosis, experienced significant benefit from the reversal of cardiac function by means of CRT-D. Therefore, CRT-D implantation is suggested in patients with moderate renal dysfunction unless irreversible renal disease can be predicted.

Study Limitations
This study is a retrospective analysis of the MADIT-CRT long-term follow-up study and has the inherent bias of retrospective analyses. Patients in the GFR subgroups had differences in baseline clinical characteristics, and although we adjusted our multivariable models for potential confounders, there may have been other unmeasured confounders not taken into consideration.

Furthermore, MADIT-CRT excluded patients with creatinine >3.0 mg/dL. Therefore, we were not able to assess the effect of more severe renal dysfunction on clinical outcomes and CRT-D versus ICD-only effect. MADIT-CRT enrolled patients with mild HF, therefore our results do not elucidate the relationship between renal function and more advanced HF. Information on the underlying cause of renal dysfunction was not available; however, we assume that the majority of MADIT-CRT patients had renal dysfunction in association with HF as well as factors such as age, diabetes mellitus, and hypertension. We did not collect further laboratory data during follow-up, limiting our ability to assess the degree of renal function improvement after CRT-D implantation. Because there were fewer non-LBBB patients relative to those with LBBB in MADIT-CRT, the comparison of efficacy of CRT-D versus ICD-only by renal function in the non-LBBB and LBBB subgroups may be limited.

Conclusions
In patients with mild HF with LBBB, moderate renal dysfunction is associated with higher risk of all-cause mortality and HF events compared with those with mildly impaired-to-normal renal function. Despite the higher risk of adverse events in the low-GFR group, LBBB patients, both with mildly impaired-to-normal renal function and moderate renal dysfunction, derived benefit from CRT-D versus ICD-only treatment during long-term follow-up with similar relative reductions in risk of all-cause mortality and HF events. The ARR from CRT-D relative to ICD-only is potentially greater among LBBB patients with moderate renal dysfunction. Non-LBBB patients with lower GFR had higher risk of all-cause mortality and HF events; however, benefit from CRT-D versus ICD-only was not found in either GFR subgroup. Our results support implantation of CRT-D in patients with mild HF, low left ventricular ejection fraction, wide QRS, and LBBB ECG pattern with moderate renal dysfunction at baseline.

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Disclosures
None.

References
Cardiac resynchronization therapy (CRT) is associated with reduction in heart failure (HF) or death in patients with HF with reduced left ventricular ejection fraction and QRS prolongation. Renal dysfunction is common in patients with HF, but there are limited data on the efficacy of CRT in the setting of renal dysfunction. In this retrospective analysis of the Multicenter Automatic Defibrillator Implantation Trial–Cardiac Resynchronization Therapy (MADIT-CRT), outcomes during long-term follow-up were compared among patients receiving CRT with implantable cardioverter-defibrillator (CRT-D) versus those receiving implantable cardioverter-defibrillator-only by baseline renal function. Moderate renal dysfunction was associated with greater risk of death and HF events relative to mildly impaired-to-normal renal function. However, implantation of a CRT-D versus implantable cardioverter-defibrillator-only led to significant risk reduction of death and HF events during long-term follow-up in both patients with moderate renal dysfunction and mildly impaired-to-normal renal function. Thus, CRT-D improved outcomes among those with moderate renal dysfunction despite the higher risk of death and HF in this cohort. Our findings have important clinical implications and suggest that CRT-D implantation is an effective treatment in patients with mild HF even when presenting with moderate renal dysfunction. Implantation of a CRT-D device is thus warranted in patients with mild HF with low left ventricular ejection fraction, prolonged QRS duration, and left bundle-branch block in the setting of moderate renal dysfunction to improve long-term outcomes.
Long-Term Outcomes With Cardiac Resynchronization Therapy in Patients With Mild Heart Failure With Moderate Renal Dysfunction


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