

Long-Term Outcomes With Cardiac Resynchronization Therapy in Patients With Mild Heart Failure With Moderate Renal Dysfunction

Usama A. Daimee, MD; Arthur J. Moss, MD; Yitschak Biton, MD; Scott D. Solomon, MD; Helmut U. Klein, MD; Scott McNitt, MS; Bronislava Polonsky, MS; Wojciech Zareba, MD, PhD; Ilan Goldenberg, MD; Valentina Kutiyifa, MD, PhD, FHRS, FESC

Background—We aimed to determine the impact of renal function on long-term outcomes with cardiac resynchronization therapy with defibrillator among patients with mild heart failure (HF).

Methods and Results—We stratified 1820 Multicenter Automatic Defibrillator Implantation Trial–Cardiac Resynchronization Therapy patients by QRS morphology into those with and without left bundle-branch block. Subgroups within each QRS morphology category were created based on glomerular filtration rate (GFR): GFR <60 and ≥60 mL/min per 1.73 m². Primary end point was death; secondary end points were HF/death and HF events alone during long-term follow-up. Among 1274 left bundle-branch block patients, 413 (32%) presented with GFR <60 (mean, 48.1±8.3) mL/min per 1.73 m². Relative to the 861 (68%) patients with GFR ≥60 (mean, 79.6±16.0) mL/min per 1.73 m², low-GFR patients experienced higher risk of death (hazard ratio [HR], 2.09; 95% confidence interval [CI], 1.53–2.86; *P*<0.01) and HF/death (HR, 1.46; 95% CI, 1.17–1.82; *P*<0.01). In both GFR groups, cardiac resynchronization therapy with defibrillator was associated with reduction in death (GFR <60: HR, 0.66; 95% CI, 0.44–1.00; *P*=0.05 and GFR ≥60: HR, 0.68; 95% CI, 0.44–1.05; *P*=0.08) and HF/death (GFR <60: HR, 0.49; 95% CI, 0.36–0.67; *P*<0.01 and GFR ≥60: HR, 0.50; 95% CI, 0.38–0.66; *P*<0.01). In the low-GFR group, there was greater absolute reduction in risk of death (GFR <60: 14% and GFR ≥60: 6%) and HF/death (GFR <60: 25 and GFR ≥60: 15%). Among non-left bundle-branch block patients, low GFR predicted outcomes; however, no benefit from cardiac resynchronization therapy with defibrillator was observed.

Conclusions—In patients with mild HF, moderate renal dysfunction is associated with higher risk of death and HF during long-term follow-up. Patients with left bundle-branch block, regardless of baseline renal function, derive long-term benefit from cardiac resynchronization therapy with defibrillator, with greater absolute risk reduction in death and HF among those with moderate renal dysfunction.

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Key Words: bundle-branch block ■ cardiac resynchronization therapy ■ defibrillators, implantable ■ heart failure ■ mortality ■ renal insufficiency

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.

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From the Heart Research Follow-up Program, Division of Cardiology, University of Rochester Medical Center, NY (U.A.D., A.J.M., Y.B., H.U.K., S.M., B.P., W.Z., I.G., V.K.); and Cardiovascular Division, Brigham and Women's Hospital, Harvard Medical School, Boston, MA (S.D.S.).

Correspondence to Valentina Kutiyifa, MD, PhD, FHRS, FESC, Heart Research Follow-up Program, Cardiology Division, University of Rochester Medical Center, 265 Crittenden Blvd, PO Box 653, Rochester, NY 14642. E-mail Valentina.Kutiyifa@heart.rochester.edu

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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 $\leq 30\%$, 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 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.^{18,26} 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 $GFR = 186 \times \text{creatinine}^{-1.154} \times \text{age}^{-0.203} \times (0.742 \text{ if women}) \times (1.21 \text{ if black})$. Each of the LBBB and non-LBBB patient categories was divided into 2 prespecified subgroups by GFR: GFR <60 and ≥ 60 mL/min per 1.73 m^2 . Current guidelines recommend classification of renal dysfunction as GFR <60 mL/min per 1.73 m^2 , a threshold that has previously been used extensively to assess the efficacy of CRT.^{19,21,27,28} The histogram of GFR values in MADIT-CRT is shown in Figure 1. Specific subanalysis in patients with low GFR (GFR <30 mL/min per 1.73 m^2) was not possible as there were only 16 (0.9%) patients in that group.

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 ≥ 60 mL/min per 1.73 m^2 using the χ^2 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

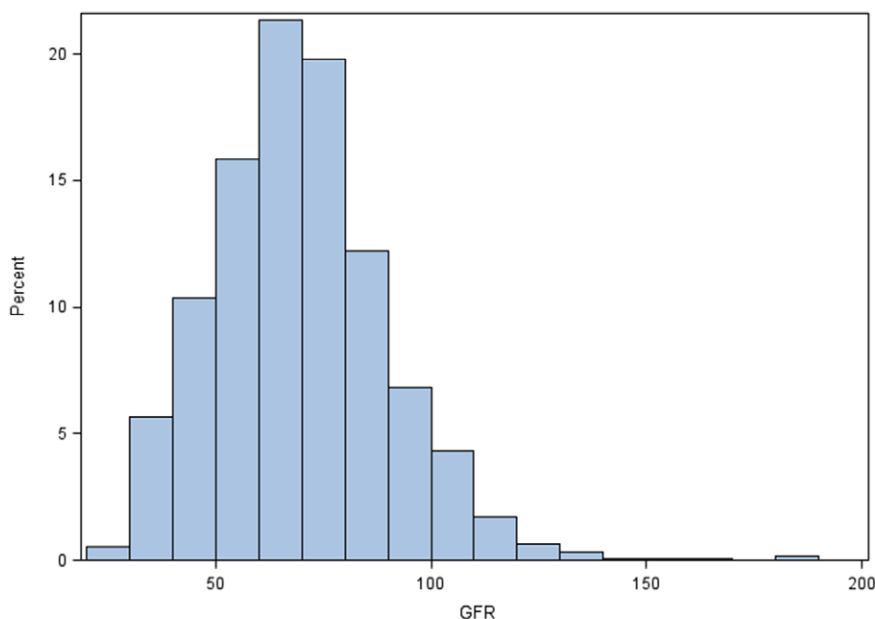


Figure 1. Distribution of glomerular filtration rate (GFR) among patients with left bundle-branch block.

Table 1. Clinical Characteristics of Left Bundle-Branch Block Patients With GFR <60 and GFR ≥60 at Baseline

| Clinical Characteristics | GFR <60 | GFR ≥60 | P Value |
|---|-----------|-----------|---------|
| No. of patients (n) | 413 | 861 | ... |
| GFR, mL/min per 1.73 m ² (mean±SD) | 48.1±8.3 | 79.6±16.0 | <0.01* |
| CRT-D assigned treatment, n (%) | 240(58) | 518(60) | 0.49 |
| Female, n (%) | 146(35) | 246(29) | 0.01* |
| Ischemic, n (%) | 209(51) | 351(41) | <0.01* |
| Worst NYHA >II (>3 mo prior), n (%) | 57(14) | 78(9) | 0.01* |
| Prior CHF hospitalization, n (%) | 190(47) | 295(35) | <0.01* |
| Prior CABG, n (%) | 117(28) | 162(19) | <0.01* |
| Diabetes mellitus, n (%) | 159(38) | 225(26) | <0.01* |
| Hypertension, n (%) | 294(72) | 508(59) | <0.01* |
| Prior myocardial infarction, n (%) | 160(40) | 244(29) | <0.01* |
| ACE inhibitor or ARB, n (%) | 389(94) | 836(97) | 0.01* |
| β-Blocker, n (%) | 378(92) | 819(95) | 0.01* |
| Diuretic, n (%) | 329(80) | 542(63) | <0.01* |
| Age at enrollment, n (%) | 68.9±9.2 | 62.0±10.9 | <0.01* |
| QRS, ms (mean±SD) | 163±19 | 163±20 | 0.79 |
| Body mass index† (mean±SD) | 28.1±5.2 | 28.7±5.2 | 0.01* |
| Blood urea nitrogen, mg/dL (mean±SD) | 28.2±10.2 | 18.2±5.8 | <0.01* |
| Creatinine, mg/dL (mean±SD) | 1.46±0.30 | 0.98±0.17 | <0.01* |
| BUN/creatinine (mean±SD) | 19.2±5.5 | 18.8±6.1 | 0.10 |
| SBP (mean±SD) | 122±18 | 123±17 | 0.07 |
| DBP (mean±SD) | 70±10 | 72±10 | <0.01* |
| LVEF, % (mean±SD) | 28.6±3.2 | 28.8±3.5 | 0.35 |
| LVEDV indexed by BSA, mL/m ² (mean±SD) | 124±27 | 127±32 | 0.24 |
| LVESV indexed by BSA, mL/m ² (mean±SD) | 89±22 | 91±26 | 0.42 |

ACE indicates angiotensin-converting enzyme; ARB, angiotensin II receptor blockers; BUN, blood urea nitrogen; BSA, body surface area; CABG, coronary artery bypass graft; CHF, congestive heart failure; CRT-D, cardiac-resynchronization therapy with defibrillator; DBP, diastolic blood pressure; GFR, glomerular filtration rate; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; NYHA, New York Heart Association; and SBP, systolic blood pressure.

*P value <0.05.

†The body mass index is the weight in kilograms divided by the square of the height in meters.

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%)

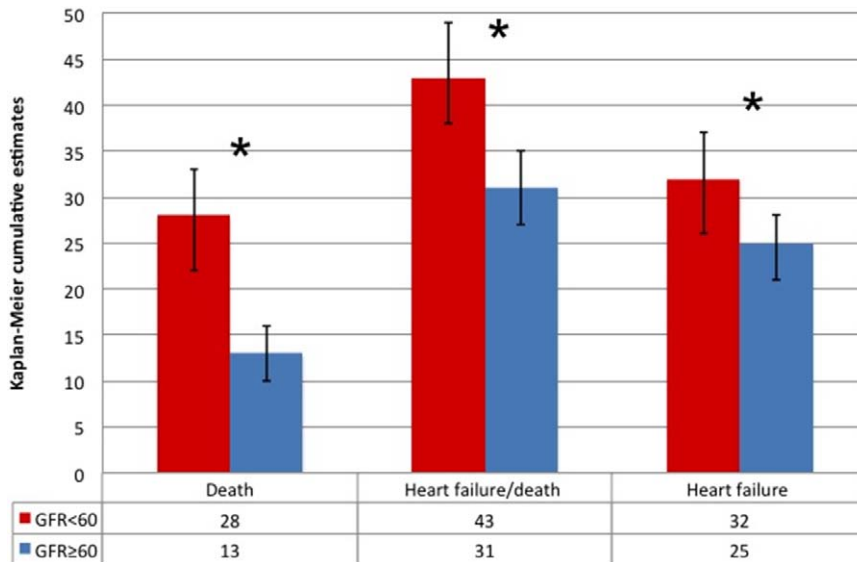


Figure 2. Kaplan–Meier estimates of the cumulative probability at 6 years of all-cause mortality, all-cause mortality or heart-failure events, and heart-failure events alone for combined sample of left bundle-branch block patients receiving cardiac resynchronization therapy with defibrillator and implantable cardioverter defibrillator-only by baseline glomerular filtration rate (GFR). * P value <0.05.

patients with GFR ≥ 60 mL/min per 1.73 m^2 (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 m^2 are presented in Table 1. Patients with GFR <60 mL/min per 1.73 m^2 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 m^2 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 m^2 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 m^2 (Figure 2).

Multivariable analysis showed that patients with GFR <60 mL/min per 1.73 m^2 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 m^2 (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 m^2 , 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

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

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 and implantable cardioverter defibrillator treatment. GFR indicates glomerular filtration rate.

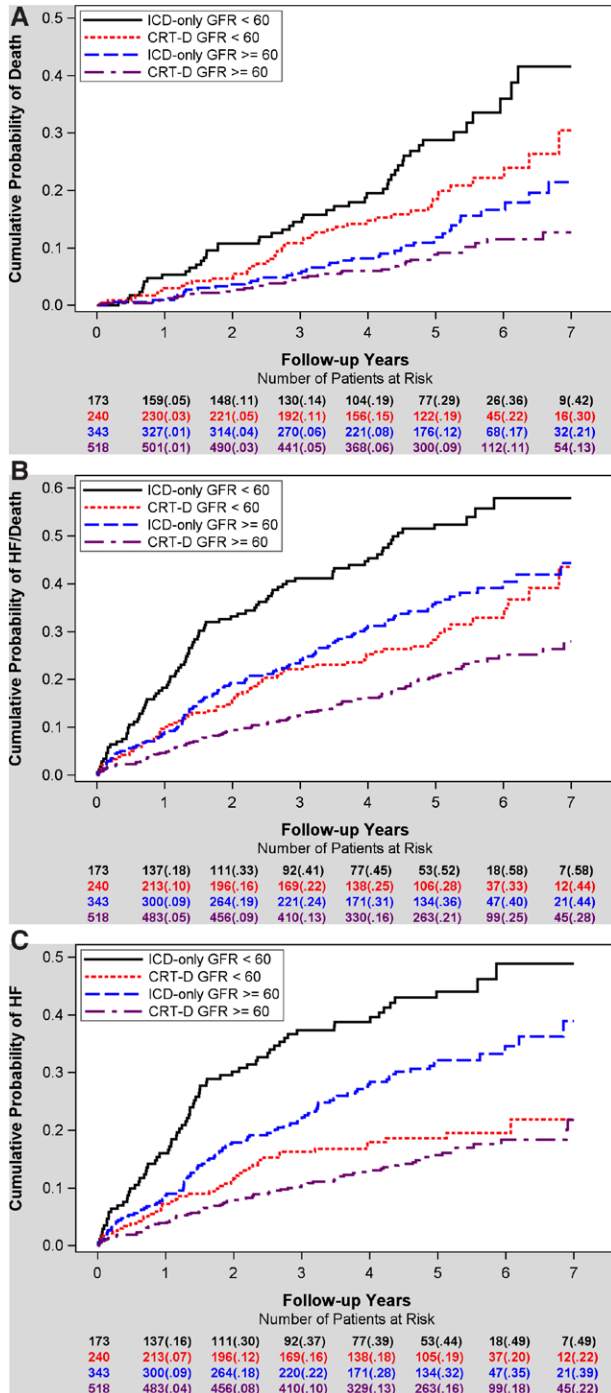


Figure 3. Kaplan-Meier estimates of the cumulative probability of (A) all-cause mortality, (B) all-cause mortality or heart-failure events, and (C) heart-failure events alone in left bundle-branch block patients receiving either cardiac resynchronization therapy with defibrillator (CRT-D) or implantable cardioverter defibrillator (ICD)-only by baseline glomerular filtration rate (GFR; data below each figure indicate numbers at risk).

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). Similarly, among LBBB patients with baseline GFR ≥ 60 mL/min per 1.73 m^2 , those treated with CRT-D experienced borderline-significant reduction in likelihood of all-cause mortality ($P=0.06$)

and significantly lower incidence of HF/death ($P<0.01$) and HF events alone ($P<0.01$; Figure 3).

Multivariable analysis confirmed that patients with baseline GFR <60 mL/min per 1.73 m^2 implanted with CRT-D experienced 34% borderline-significant decrease in risk of all-cause mortality ($P=0.05$), 51% significant reduction in the risk of HF/death ($P<0.01$), and 64% significantly lower risk of developing HF events alone ($P<0.01$) (Table 3). Consistently, among patients with GFR ≥ 60 mL/min per 1.73 m^2 , CRT-D was associated with nonsignificant 32% decrease in risk of all-cause mortality ($P=0.08$), 50% significant reduction in risk of HF/death ($P<0.01$), and 57% significantly lower risk of HF events alone ($P<0.01$; Table 3).

Importantly, when we assessed the ARR of these events in the GFR subgroups, we found that, in patients with baseline GFR <60 mL/min per 1.73 m^2 , there was an ARR of 14 percentage points (% points) for all-cause mortality, 25% points for HF/death, and 29% points for HF events alone. The ARR in the GFR ≥ 60 mL/min per 1.73 m^2 group was 6% points for all-cause mortality, 15% points for HF/death, and 17% points for HF events alone.

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 m^2 , 9 (2%) of whom had GFR <30 mL/min per 1.73 m^2 , whereas 347 (65%) presented with GFR ≥ 60 mL/min per 1.73 m^2 . During long-term follow-up, 104 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 m^2 .

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

| Variable | Hazard Ratio | 95% CI | P Value | Interaction P Value |
|---|--------------|-----------|---------|---------------------|
| End point: all-cause mortality (177 events) | | | | |
| CRT-D vs ICD in patients with GFR <60 (46 vs 46 events) | 0.66 | 0.44–1.00 | 0.05 | 0.94 |
| CRT-D vs ICD in patients with GFR ≥60 (45 vs 40 events) | 0.68 | 0.44–1.05 | 0.08 | |
| End point: all-cause mortality or heart-failure events (368 events) | | | | |
| CRT-D vs ICD in patients with GFR <60 (71 vs 84 events) | 0.49 | 0.36–0.67 | <0.01 | 0.89 |
| CRT-D vs ICD in patients with GFR ≥60 (102 vs 111 events) | 0.50 | 0.38–0.66 | <0.01 | |
| End point: heart-failure events (280 events) | | | | |
| CRT-D vs ICD in patients with GFR <60 (42 vs 67 events) | 0.36 | 0.25–0.54 | <0.01 | 0.48 |
| CRT-D vs ICD in patients with GFR ≥60 (75 vs 96 events) | 0.43 | 0.32–0.59 | <0.01 | |

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.

sex-adjusted multivariable models as suggested by experts in the field.

Furthermore, we assessed the effect of BUN alone, creatinine alone, as well as BUN/creatinine ratio on clinical outcomes during long-term follow-up, and found that GFR was the strongest predictor when compared with BUN, creatinine, and BUN/creatinine ratio. We, therefore, present our findings using GFR values.

We also evaluated the benefit of CRT-D versus ICD-only using a multivariable analysis that excluded patients with GFR <30 mL/min per 1.73 m², and we found results to be nearly identical to the total cohort.

We evaluated the effects of GFR as a continuous variable using a log-scale, and our analysis revealed similar findings. However, for easier interpretation for the clinician, we decided to report our findings based on the actual GFR values and GFR subgroups.

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.¹³ 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.^{19,20}

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,¹⁴ another report observed less improvement of left ventricular ejection fraction after CRT in the setting of renal dysfunction.²¹

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.^{1–10,19–25} 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.^{29,30} 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.³¹ 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.

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CLINICAL PERSPECTIVE

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

Usama A. Daimee, Arthur J. Moss, Yitschak Biton, Scott D. Solomon, Helmut U. Klein, Scott McNitt, Bronislava Polonsky, Wojciech Zareba, Ilan Goldenberg and Valentina Kutiyifa

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