



# Impact of Renal Impairment on Beta-Blocker Efficacy in Patients With Heart Failure

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on behalf of the Beta-Blockers in Heart Failure Collaborative Group

## ABSTRACT

**BACKGROUND** Moderate and moderately severe renal impairment are common in patients with heart failure and reduced ejection fraction, but whether beta-blockers are effective is unclear, leading to underuse of life-saving therapy.

**OBJECTIVES** This study sought to investigate patient prognosis and the efficacy of beta-blockers according to renal function using estimated glomerular filtration rate (eGFR).

**METHODS** Analysis of 16,740 individual patients with left ventricular ejection fraction <50% from 10 double-blind, placebo-controlled trials was performed. The authors report all-cause mortality on an intention-to-treat basis, adjusted for baseline covariates and stratified by heart rhythm.

**RESULTS** Median eGFR at baseline was 63 (interquartile range: 50 to 77) ml/min/1.73 m<sup>2</sup>; 4,584 patients (27.4%) had eGFR 45 to 59 ml/min/1.73 m<sup>2</sup>, and 2,286 (13.7%) 30 to 44 ml/min/1.73 m<sup>2</sup>. Over a median follow-up of 1.3 years, eGFR was independently associated with mortality, with a 12% higher risk of death for every 10 ml/min/1.73 m<sup>2</sup> lower eGFR (95% confidence interval [CI]: 10% to 15%; p < 0.001). In 13,861 patients in sinus rhythm, beta-blockers reduced mortality versus placebo; adjusted hazard ratio (HR): 0.73 for eGFR 45 to 59 ml/min/1.73 m<sup>2</sup> (95% CI: 0.62 to 0.86; p < 0.001) and 0.71 for eGFR 30 to 44 ml/min/1.73 m<sup>2</sup> (95% CI: 0.58 to 0.87; p = 0.001). The authors observed no deterioration in renal function over time in patients with moderate or moderately severe renal impairment, no difference in adverse events comparing beta-blockers with placebo, and higher mortality in patients with worsening renal function on follow-up. Due to exclusion criteria, there were insufficient patients with severe renal dysfunction (eGFR <30 ml/min/1.73 m<sup>2</sup>) to draw conclusions. In 2,879 patients with atrial fibrillation, there was no reduction in mortality with beta-blockers at any level of eGFR.

**CONCLUSIONS** Patients with heart failure, left ventricular ejection fraction <50% and sinus rhythm should receive beta-blocker therapy even with moderate or moderately severe renal dysfunction. (J Am Coll Cardiol 2019;74: 2893-904) © 2019 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).



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## ABBREVIATIONS AND ACRONYMS

<b>AF</b>	= atrial fibrillation
<b>CI</b>	= confidence interval
<b>eGFR</b>	= estimated glomerular filtration rate
<b>HF</b>	= heart failure
<b>HFREF</b>	= heart failure with reduced ejection fraction
<b>HR</b>	= hazard ratio
<b>IPD</b>	= individual patient data
<b>LVEF</b>	= left ventricular ejection fraction
<b>NNT</b>	= number needed to treat
<b>RCT</b>	= randomized controlled trials

**H**ear failure (HF) is associated with numerous comorbidities, of which renal dysfunction is both common and of particular importance due to its impact on mortality as well as on the use of guideline-recommended therapies (1). Patients with HF have a higher incidence of renal dysfunction due to shared pathophysiological pathways and mutual risk factors. In the Swedish HF registry (2), 51% of 47,716 patients with unselected HF had an estimated glomerular filtration (eGFR) of <60 ml/min/1.73 m<sup>2</sup>, and in the CHARM (Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity) program, between 33% and 43% of patients had eGFR <60 ml/min/1.73 m<sup>2</sup> depending on HF phenotype (3). Impaired renal function is independently associated with worse outcomes; in meta-analyses of 57 studies including trials and cohorts in HF, there was a 2-fold increase in the odds of death comparing patients with and without renal dysfunction (4).

Renal impairment in HF patients also affects the prescription, dosage, maintenance, and possibly effectiveness of therapies (5,6). Although common in clinical practice, patients with renal dysfunction have often been excluded from major clinical trials, creating an evidence gap for many HF patients and a discrepancy with clinical need. Those with moderate renal dysfunction (eGFR 45 to 59 ml/min/1.73 m<sup>2</sup>) and moderately severe renal dysfunction (eGFR 30 to 44 ml/min/1.73 m<sup>2</sup>) have a higher risk of adverse

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outcomes and potentially more absolute benefit from HF therapy, but in addition have multiple comorbidities that can have an impact on clinical management. Previous analyses of beta-blockers in patients with HF and renal dysfunction suggest that efficacy may be maintained at different levels of baseline eGFR (7-10). However, the number of patients and events in these studies were limited, particularly at the more severe end of renal impairment, and hence clinicians remain uninformed about any possible interaction of treatment effect.

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We examined the effect of renal dysfunction on outcomes in patients with HF and reduced ejection fraction (HFrEF) using the totality of individual patient data (IPD) from the landmark, double-blind, randomized controlled trials (RCTs) comparing beta-blockers with placebo (11). The Beta-Blockers in Heart Failure Collaborative Group is a multinational project that has systematically harmonized clinical trial data to improve management and outcomes in patients with HF (12-15). In this study, we tested the hypothesis that compared with placebo, beta-blockers reduce mortality in patients with moderate and moderately severe renal dysfunction. Further, we looked at the prognostic impact of renal dysfunction and associated variables, and how change in renal function affects mortality.

## METHODS

The Beta-Blockers in Heart Failure Collaborative Group (Collaborative Systematic Overview of Randomised Controlled Trials of Beta-Blockers in the Treatment of Heart Failure [BB-meta-HF]) includes the lead investigators from the relevant trials, with support of the 4 pharmaceutical companies that sponsored them (AstraZeneca, GlaxoSmithKline, Merck Serono, and Menarini). This report was prepared according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) IPD guidance (16), and prospectively registered with ClinicalTrials.gov (NCT00832442) and the PROSPERO database of systematic reviews (CRD42014010012) (17).

**ELIGIBILITY AND SEARCH STRATEGY.** Detailed rationale and methods have previously been published (11-13). Placebo-controlled trials were eligible for inclusion if they recruited >300 patients, were not confounded by investigation of other treatments, had a planned follow-up of >6 months, and explicitly reported mortality as an endpoint.

Eleven trials were included that account for 95.7% of eligible participants recruited in RCTs based on a systematic review of published reports: ANZ (Australia/New Zealand Heart Failure Study) (18), BEST (Beta-Blocker Evaluation Survival Trial) (19), CAPRICORN (Carvedilol Post-Infarct Survival Control in LV Dysfunction Study) (20), CHRISTMAS (Carvedilol Hibernating Reversible Ischaemia Trial: Marker of Success Study) (21), CIBIS I (Cardiac Insufficiency Bisoprolol Study) (22), CIBIS-II (Cardiac Insufficiency Bisoprolol Study II) (23), COPENICUS (Carvedilol Prospective Randomized Cumulative Survival Study) (24), MDC (Metoprolol in Idiopathic Dilated Cardiomyopathy Study) (25), MERIT-HF

(Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure) (26), SENIORS (Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalisation in Seniors with Heart Failure) (27); and US-HF (U.S. Carvedilol Heart Failure Program) (28).

All included studies had appropriate ethical approval. Using the Cochrane Collaborations Risk of Bias Tool, we established that each trial had a low risk of bias (29).

**DATA COLLECTION AND IPD INTEGRITY.** A standardized data request form to obtain IPD from each trial has been published, along with search results and individual study demographics (11). IPD were obtained for all 11 trials identified in the systematic review, and data were extracted from original source files provided by the pharmaceutical companies and lead investigators. All data were cross-checked across different trial databases and compared with published reports. Discrepancies, inconsistencies, and incomplete data were checked against original case report forms and trial documentation to ensure IPD integrity. All 11 trial databases were then harmonized according to the standardized data request form to match patient characteristics and outcomes across all trials. Due to the small amount of missing data for relevant covariates, imputation was not performed.

**PARTICIPANTS.** For this analysis, we included patients with a baseline creatinine available and left ventricular ejection fraction (LVEF) <50% (the CIBIS I trial was excluded due to a lack of renal function data). Because we have previously identified a significant treatment interaction comparing sinus rhythm and atrial fibrillation/flutter (AF) (12), patients were stratified by heart rhythm on the baseline electrocardiogram for treatment estimates. Those with a missing electrocardiogram or paced rhythm were excluded.

**RENAL DYSFUNCTION AND RELATED VARIABLES.** Creatinine values were obtained for each enrolled patient at baseline, the interim study visit and the final follow-up visit, where available. Renal function was analyzed using eGFR calculated with the Modification of Diet in Renal Disease (MDRD) equation for nonstandardized creatinine:  $186 \times (\text{serum creatinine in mg/dl})^{-1.154} \times (\text{age})^{-0.203} \times (0.742 \text{ if female}) \times (1.21 \text{ if African/African American})$  in ml/min/1.73 m<sup>2</sup>. eGFR was categorized according to the National Kidney Foundation staging: category 1, eGFR  $\geq 90$  ml/min/1.73 m<sup>2</sup> (normal); category 2, eGFR 60 to 89 ml/min/1.73 m<sup>2</sup> (mildly decreased); category 3a, eGFR 45 to 59 ml/min/1.73 m<sup>2</sup> (mildly to moderately decreased); category 3b, eGFR 30 to

**TABLE 1** Baseline Characteristics by eGFR Category for Patients in Sinus Rhythm

	eGFR <30 ml/min/1.73 m <sup>2</sup> (n = 373)	eGFR 30-44 ml/min/1.73 m <sup>2</sup> (n = 1,825)	eGFR 45-59 ml/min/1.73 m <sup>2</sup> (n = 3,712)	eGFR 60-89 ml/min/1.73 m <sup>2</sup> (n = 6,405)	eGFR ≥90 ml/min/1.73 m <sup>2</sup> (n = 1,546)
eGFR, ml/min/1.73 m <sup>2</sup>	26 (24-28)	39 (36-42)	53 (50-57)	72 (66-79)	100 (94-109)
Age, yrs	71 (66-76)	70 (63-75)	67 (59-73)	61 (52-70)	54 (46-62)
Women	39.1	36.2	27.7	19.8	16.6
Years with HF diagnosis	4 (2-8)	4 (2-7)	3 (1-6)	2 (1-5)	2 (1-5)
Ischemic HF etiology	80.2	78.2	71.8	66.1	57.4
Prior myocardial infarction	64.8	67.4	62.4	56.0	49.4
Diabetes mellitus	43.0	31.9	24.1	22.1	23.4
NYHA functional class III/IV	80.5	71.8	67.3	60.1	70.3
LVEF, %	24 (20-31)	24 (20-31)	25 (20-32)	28 (21-33)	28 (22-33)
Heart rate, beats/min	79 (72-88)	80 (72-88)	80 (72-88)	80 (72-88)	80 (72-90)
Systolic BP, mm Hg	124 (110-140)	124 (110-140)	122 (110-138)	122 (110-138)	120 (110-137)
Diastolic BP, mm Hg	72 (65-80)	75 (68-80)	76 (70-81)	78 (70-83)	78 (70-84)
Body mass index, kg/m <sup>2</sup>	25 (23-29)	26 (23-29)	26 (24-30)	27 (24-30)	27 (24-30)
Any diuretic therapy	96.2	91.0	87.9	81.5	82.2
ACE inhibitor or ARB	92.2	93.0	95.4	95.1	95.6
Aldosterone antagonists	13.6	11.5	9.7	6.9	5.6
Digoxin	54.7	53.1	53.4	53.7	58.6

Values are median (interquartile range) or %.

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; BP = blood pressure; eGFR = estimated glomerular filtration rate; HF = heart failure; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association functional class.

44 ml/min/1.73 m<sup>2</sup> (moderately to severely decreased); and category 4 and 5 combined, eGFR <30 ml/min/1.73 m<sup>2</sup> (severely decreased or kidney failure). We pre-defined patients with eGFR 30 to 59 ml/min/1.73 m<sup>2</sup> as a group of clinical interest, and worsening renal function as 20% or greater reduction in eGFR between baseline and follow-up. When used as a continuous variable in interaction analyses, the lowest and highest 1% of eGFR values were excluded to avoid leverage of extreme results. Anemia was classified according to the World Health Organization definition (hemoglobin <13.0 g/dl in men and <12.0 g/dl in women), and proteinuria was defined as 1+ on a dipstick or ≥30 mg/dl.

**OUTCOME.** The outcome for this analysis was all-cause mortality, which included additional deaths reported after the censor date for 7 studies (18-20,24,25,27,28). There were no patients with missing vital status.

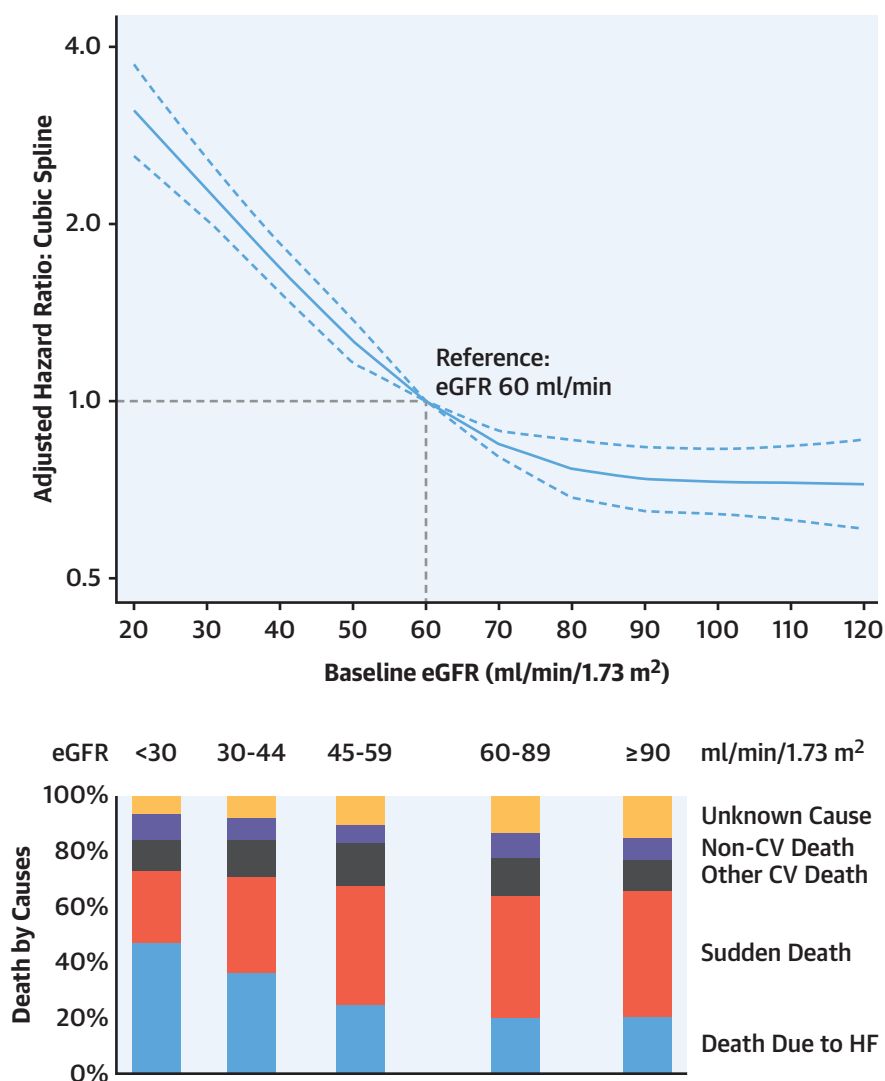
**STATISTICAL ANALYSIS.** A statistical analysis plan was generated and finalized by the Collaborative Group in advance of data analysis. Summary results are presented as percentages, or median and interquartile range (displayed as 25th to 75th quartiles). Group comparisons were made using the Kruskal Wallis nonparametric rank test. Fractional polynomials were used to find the best transformation of eGFR in adjusted analysis, including nonlinear relationships (for sinus rhythm, the best fit was the

inverse square root, and for AF the inverse squared eGFR).

All analyses of beta-blockers versus placebo followed the principle of intention to treat. Outcomes were analyzed using a Cox proportional hazards regression model stratified by study and grouped by heart rhythm and eGFR category. This is a 1-stage fixed-effects approach and assumes that all trials are estimating a common treatment effect with baseline hazards that vary across studies. Hazard ratios (HRs) and 95% confidence intervals (CIs) are presented, along with corresponding p values. We pre-specified adjustment in Cox models for baseline age, sex, LVEF, history of myocardial infarction, systolic blood pressure, heart rate, use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, and diuretic therapy. Only a minority of patients were followed for an extended period, and therefore data were censored at 1,200 days (3.3 years) from randomization.

Effect modification was assessed using p values from interaction terms fitted in the multivariable models. The interactions of continuous eGFR with mortality or beta-blocker efficacy were assessed using cubic splines in the Cox model and the Royston-Parmar flexible parametric survival model (30). There was no evidence of violation of the proportional hazards assumption in any multivariable model as determined by Schoenfeld residuals. Kaplan-Meier plots were used to graph the pooled, unadjusted data

**FIGURE 1** Prognostic Impact of Renal Dysfunction



Association of baseline renal function with all-cause mortality and cause of death. Includes patients with sinus rhythm and atrial fibrillation/flutter. CV = cardiovascular; eGFR = estimated glomerular filtration rate; HF = heart failure.

for eGFR/treatment groups, with log-rank *p* values for comparison. For worsening eGFR, analysis time began on the date of the final eGFR measurement (hence excluding any patients who had died, withdrawn consent, or were lost to follow-up before their repeat eGFR), and ends 2 years after this date.

Pre-defined sensitivity analyses in patients with eGFR 30 to 59 ml/min/1.73 m<sup>2</sup> were: 1) additional multivariable adjustment for diabetes, body mass index, New York Heart Association (NYHA) functional class (I/II vs. III/IV), and use of digoxin or aldosterone antagonists; 2) effect estimate in patients with

LVEF <35% compared with 35% to 49%; and 3) exclusion of CAPRICORN (the only post-infarct trial) and BEST (utilizing a pharmacologically distinct beta-blocker). We also performed sensitivity analyses using all available eGFR measurements for interaction analyses, rather than just the central 99%. Heterogeneity for pooled outcomes was assessed using the *I*<sup>2</sup> statistic from a fixed-effects 2-stage model. We performed post hoc analyses: 1) according to dose achieved at interim follow-up; 2) to assess the relationship between proteinuria and worsening renal function; and 3) using the CKD-EPI (Chronic Kidney

**TABLE 2 Beta-Blockers Versus Placebo According to Baseline Renal Function in Sinus Rhythm**

	eGFR				
	<30 ml/min/1.73 m <sup>2</sup>	30-44 ml/min/1.73 m <sup>2</sup>	45-59 ml/min/1.73 m <sup>2</sup>	60-89 ml/min/1.73 m <sup>2</sup>	≥90 ml/min/1.73 m <sup>2</sup>
Number of patients with complete data*	372	1,817	3,680	6,372	1,543
Number of deaths (%)	111 (29.8)	405 (22.3)	592 (16.1)	834 (13.1)	168 (10.9)
Hazard ratio for beta-blockers versus placebo	1.28	0.71	0.73	0.66	0.64
Hazard ratio 95% confidence interval	0.87 to 1.91	0.58 to 0.87	0.62 to 0.86	0.57 to 0.76	0.47 to 0.88
p value	0.35	0.001	<0.0001	<0.0001	0.006
Absolute risk reduction†	−2.4%	4.7%	4.0%	4.4%	4.7%
Absolute risk reduction 95% confidence interval	−11.7% to 6.9%	0.8% to 8.5%	1.6% to 6.5%	2.7% to 6.1%	1.5% to 7.8%
NNT/NNH	NNH 41.5	NNT 21.4	NNT 24.7	NNT 22.7	NNT 21.5

\*Including baseline adjustment variables: eGFR, age, sex, left ventricular ejection fraction, history of myocardial infarction, systolic blood pressure, heart rate, use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, and diuretic therapy. †Based on crude mortality rates for all patients.

eGFR = estimated glomerular filtration rate; NNH = number needed to harm; NNT = number needed to treat.

Disease Epidemiology Collaboration) eGFR calculator. A 2-tailed p value of 0.05 was considered statistically significant. Analyses were performed on Stata version 14.2 software (StataCorp, College Station, Texas) and R version 3.2.1 (R Core Team, Vienna, Austria).

## RESULTS

A total of 16,740 HF patients were included from 10 RCTs (Online Figure 1). Median age was 65 years (25th to 75th centiles 55 to 72 years), 23% were women, and median LVEF was 27% (21% to 33%). Baseline median eGFR was 63 ml/min/1.73 m<sup>2</sup>. A total of 1,781 patients (10.6%) had an eGFR >90 ml/min/1.73 m<sup>2</sup>, 7,641 (45.6%) 60 to 89 ml/min/1.73 m<sup>2</sup>, 4,584 (27.4%) 45 to 59 ml/min/1.73 m<sup>2</sup>, and 2,286 (13.7%) 30 to 44 ml/min/1.73 m<sup>2</sup>. Only 448 patients (2.7%) had an eGFR <30 ml/min/1.73 m<sup>2</sup>, reflecting the exclusion criteria for several trials (Online Table 1). Patients in sinus rhythm (n = 13,861) had better renal function at baseline than those with AF (n = 2,879); 64 ml/min/1.73 m<sup>2</sup> compared with 60 ml/min/1.73 m<sup>2</sup>, with 42.9% versus 48.9% of patients with eGFR <60 ml/min/1.73 m<sup>2</sup>, respectively. Other factors associated with more advanced renal dysfunction were older age and female sex, a longer duration of HF, an ischemic etiology, and concomitant diabetes (Table 1 shows data for sinus rhythm, and Online Table 2 for AF).

**IMPACT OF RENAL DYSFUNCTION ON MORTALITY IN HFREF.** During a median follow-up of 1.3 years (0.8 to 1.9 years), eGFR was associated with all-cause mortality independent of other measured prognostic variables, with a 12% increase in the hazard of death for every 10 ml/min lower eGFR (95% CI: 10% to 15%;

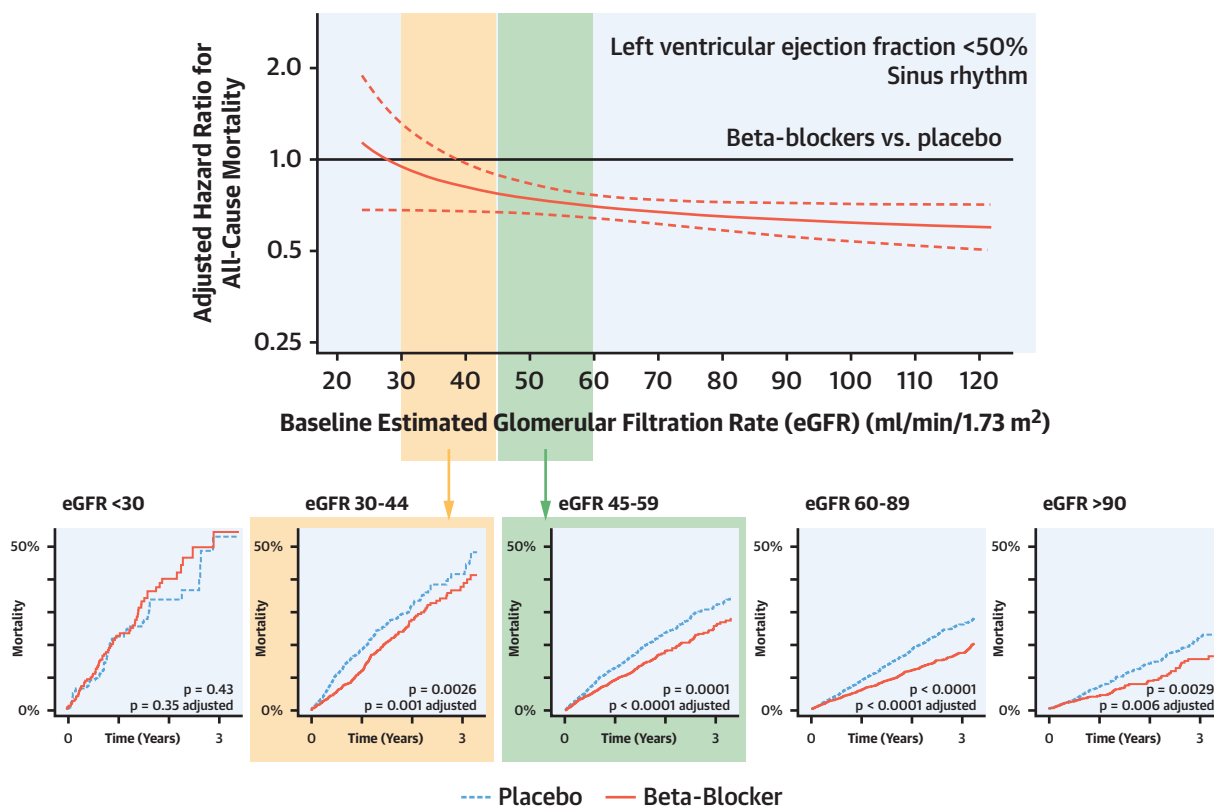
p < 0.001). Mortality was particularly high for patients with more severe renal dysfunction, and their cause of death was more often due to progressive heart failure (Figure 1, Online Table 3).

In the subset of patients with hemoglobin values, anemia was associated with higher mortality (HR: 1.35 compared with no anemia, 95% CI: 1.22 to 1.50; p < 0.001; n = 9,906). This was evident at all levels of cardiorenal dysfunction, except for patients with eGFR <30 ml/min/1.73 m<sup>2</sup> (Online Figure 2). Proteinuria at baseline was also independently associated with higher mortality (HR: 1.32 compared with no proteinuria, 95% CI: 1.02 to 1.70; p = 0.034; n = 3,081). The largest prognostic impact of proteinuria was seen in patients with eGFR ≥90 ml/min/1.73 m<sup>2</sup> (Online Figure 2); in this group, the death rate was 12.3% without proteinuria and 28.6% with proteinuria (adjusted p = 0.032).

**BETA-BLOCKER EFFICACY ACCORDING TO RENAL FUNCTION AT BASELINE.** In 13,861 patients in sinus rhythm, beta-blockers reduced mortality across all patients (HR: 0.71; 95% CI: 0.66 to 0.78; p < 0.0001), including those with moderate and moderately severe renal dysfunction (Table 2). The adjusted HR for beta-blockers versus placebo in sinus rhythm was 0.73 for eGFR 45 to 59 ml/min/1.73 m<sup>2</sup> (0.62 to 0.86; p < 0.001), and 0.71 for eGFR 30 to 44 ml/min/1.73 m<sup>2</sup> (0.58 to 0.87; p = 0.001). Absolute risk reductions and number needed to treat (NNT) to prevent 1 death were 4.0% (NNT = 25) and 4.7% (NNT = 21), respectively. There were insufficient numbers of patients with eGFR <30 ml/min/1.73 m<sup>2</sup> to be certain of any benefit or harm from beta-blocker therapy (95% CI: 0.87 to 1.91). We detected an interaction between beta-blocker efficacy and eGFR in sinus rhythm



# CENTRAL ILLUSTRATION Efficacy of Beta-Blockers According to Baseline Renal Function in Sinus Rhythm



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All-cause mortality comparing beta-blockers versus placebo in patients with sinus rhythm at baseline. **Top panel** shows a flexible parametric survival spline plot across the range of continuous renal function. Interaction  $p = 0.021$  for the central 99% of eGFR values ( $p = 0.062$  in a sensitivity analysis that includes the extremes of eGFR). **Lower panels** show Kaplan-Meier survival plots for categorical renal groups, with  $p$  values derived from log-rank tests and adjusted Cox regression (Table 2). eGFR = estimated glomerular filtration rate.

( $p = 0.021$ ), but with weak effect and only at the lowest end of the eGFR range (Central Illustration). In a sensitivity analysis that included all patients, including the extremes of eGFR, the interaction  $p$  value was 0.062.

The efficacy of beta-blockers in patients with sinus rhythm and moderate or moderately severe renal impairment was not affected by the presence of either anemia or proteinuria (interaction  $p = 0.69$  and  $p = 0.24$ ), or by LVEF or additional adjustment (Online Table 4). In 2,879 patients with AF at baseline, there was no significant reduction in mortality with beta-blockers in any category of eGFR, and no interaction of beta-blocker efficacy with continuous eGFR ( $p$  for interaction = 0.18) (Table 3, Figure 2).

**CHANGE IN RENAL FUNCTION OVER TIME, DOSE OF THERAPY, AND ADVERSE EVENTS.** Only a small drop in mean eGFR was noted overall from baseline to the last available measurement: 2.0 ml/min/1.73 m<sup>2</sup> lower eGFR after a median of 1.2 years for 7,420 surviving patients in sinus rhythm (SD  $\pm 15.2$ ). In 3,179 patients with either moderate or moderately severe renal impairment at baseline, there was an increase of 1.3 ml/min/1.73 m<sup>2</sup> (SD  $\pm 13.1$ ). We observed little difference between patients randomized to beta-blockers or placebo (Figure 3, Online Table 5).

Worsening renal function of 20% or greater during follow-up was observed in 1,342 (18.1%) of patients in sinus rhythm, and was associated with a 28% higher adjusted risk of death during the subsequent 2 years (95% CI: 9% to 49%;  $p = 0.002$ ;  $n = 4,725$ ). The

**TABLE 3 Beta-Blockers Versus Placebo According to Baseline Renal Function in AF**

	eGFR				
	<30 ml/min/1.73 m <sup>2</sup>	30-44 ml/min/1.73 m <sup>2</sup>	45-59 ml/min/1.73 m <sup>2</sup>	60-89 ml/min/1.73 m <sup>2</sup>	≥90 ml/min/1.73 m <sup>2</sup>
Number of patients with complete data*	74	458	869	1,230	235
Number of deaths (%)	24 (32.4)	137 (29.9)	172 (19.8)	207 (16.8)	36 (15.3)
Hazard ratio for beta-blockers versus placebo	0.58	0.83	1.08	0.97	0.88
Hazard ratio 95% confidence interval	0.21-1.63	0.58-1.19	0.80-1.47	0.74-1.29	0.44-1.75
p value	0.32	0.32	0.59	0.86	0.79

\*Including baseline adjustment variables: eGFR, age, sex, left ventricular ejection fraction, history of myocardial infarction, systolic blood pressure, heart rate, use of angiotensin converting enzyme inhibitors or angiotensin receptor blockers, and diuretic therapy.

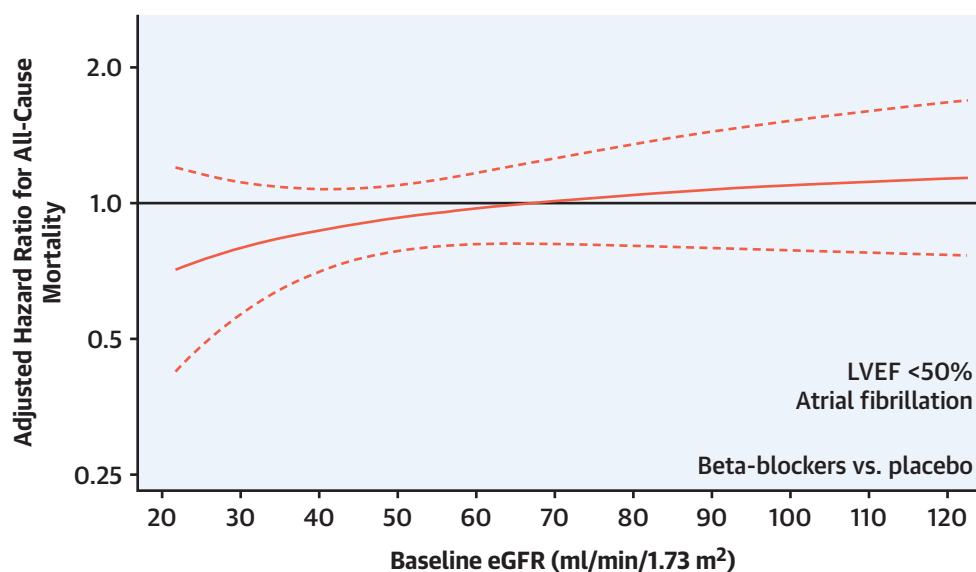
AF = atrial fibrillation; eGFR = estimated glomerular filtration rate.

corresponding mortality increase was 46% for the subset of patients with combined moderate or moderately severe renal impairment at baseline (95% CI: 14% to 87%;  $p = 0.002$ ;  $n = 2,175$ ) (Figure 3).

In patients with sinus rhythm and moderate or moderately severe renal impairment, 77% managed to reach one-half of the target dose of beta-blocker or greater (compared with 80% with eGFR 60 to 89 ml/min/1.73 m<sup>2</sup> and 84% with eGFR ≥90 ml/min/1.73 m<sup>2</sup>) (Online Table 6). These patients had substantially better prognosis than those at lower dose levels

(Online Figure 3); however, the same pattern was also seen in patients randomized to placebo. Across both sinus rhythm and AF, discontinuation of beta-blockers was similar to that seen with placebo in patients with moderate and moderately severe renal dysfunction. This was the case for all adverse events leading to therapy discontinuation, and also those specifically related to renal impairment (Online Table 7). Overall, discontinuation rates for both beta-blockers and placebo were higher in those with more advanced renal dysfunction.

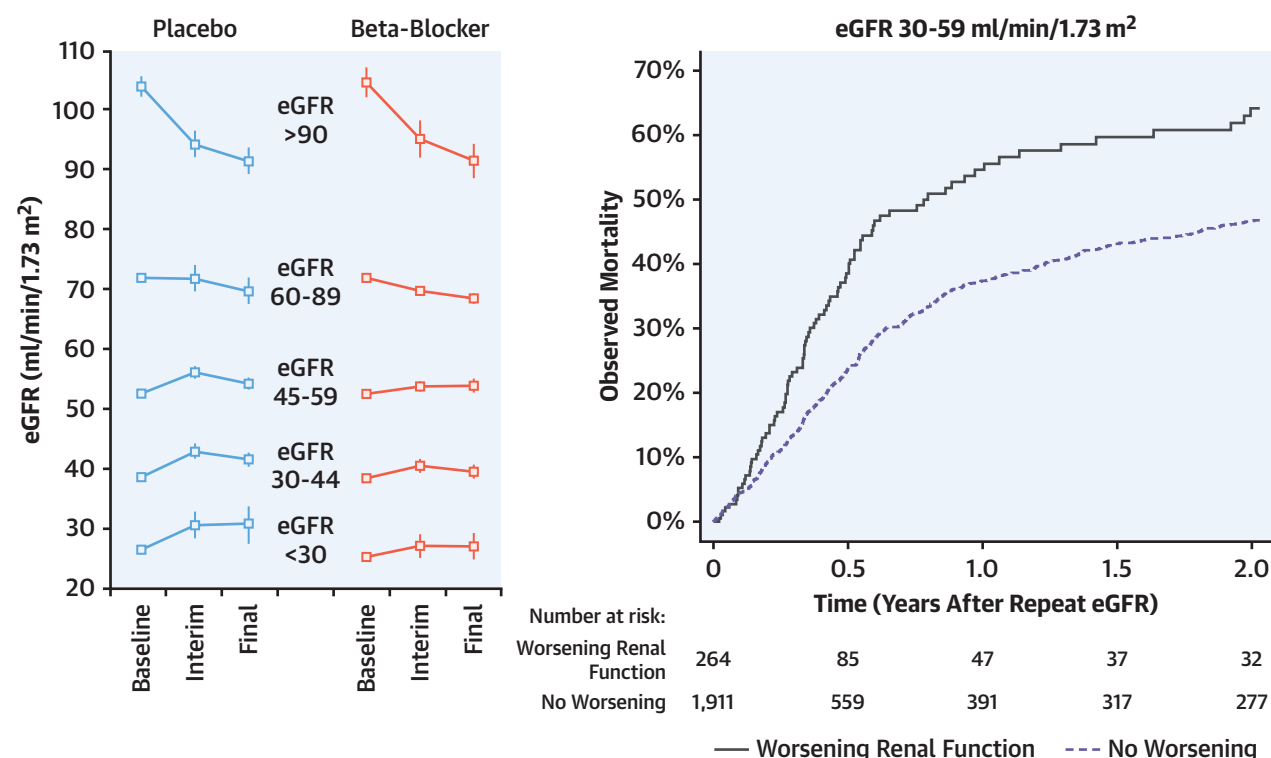
**FIGURE 2 Efficacy of Beta-Blockers According to Baseline Renal Function in AF**



All-cause mortality comparing beta-blockers versus placebo in patients with AF at baseline across the range of continuous renal function (flexible parametric survival plot). Interaction  $p = 0.18$  for the central 99% of eGFR values ( $p = 0.08$  in a sensitivity analysis that includes the extremes of eGFR). AF = atrial fibrillation; eGFR = estimated glomerular filtration rate; LVEF = left ventricular ejection fraction.



**FIGURE 3** Change in Renal Function and Impact on Mortality in Sinus Rhythm



**Left panel** shows the change in renal function in patients with sinus rhythm according to renal function groups at baseline. Mean values and 95% confidence intervals are depicted only for 5,469 patients with data available at all time-points: baseline, interim visit at a median of 0.5 years from randomization (interquartile range: 0.4 to 0.7), and final visit at a median of 1.5 years from randomization (interquartile range: 1.0 to 2.1). **Right panel** shows a Kaplan-Meier survival plot for patients in sinus rhythm with moderate or moderately severe renal impairment according to whether eGFR worsened by  $\geq 20\%$  from baseline to the last available measurement (log-rank  $p$  value  $< 0.0001$ ). Analysis time begins at the date of the last eGFR and therefore excludes patients that died or were lost to follow-up before this visit (median 1.2 years after randomization). eGFR = estimated glomerular filtration rate.

## DISCUSSION

Renal impairment is often a barrier in clinical practice for the commencement and up-titration of guideline-recommended HFrEF therapy (5,6). Most patients with HFrEF have some degree of renal impairment, yet many randomized trials have excluded those with significant renal dysfunction, leading to concerns by clinicians about efficacy and safety. Using robust and high-quality data from the landmark beta-blocker trials, we have demonstrated with sufficient sample size that beta-blockers are effective in reducing mortality in patients with HFrEF and sinus rhythm, even in those with moderately severe renal dysfunction (as low as an eGFR of 30 to 44 ml/min/1.73 m<sup>2</sup>). Despite higher rates of comorbidities, the absolute benefit in this group was similar to patients with eGFR  $> 90$  ml/min/1.73 m<sup>2</sup>. Discontinuation due to adverse events was the same for both beta-blockers

and placebo in these double-blind trials and renal function did not appear to worsen even in those with kidney dysfunction at baseline. These results suggest that renal impairment should not obstruct the prescription of beta-blockers in patients with HFrEF.

**PROGNOSTIC IMPLICATIONS OF RENAL DYSFUNCTION, ANEMIA, AND PROTEINURIA.** The prognosis for patients with HFrEF has many determinants, and renal dysfunction is a well-known contributor to adverse outcomes (4). Our data highlight the different pattern of patient prognosis according to the severity of renal dysfunction, with a complete reversal in sudden cardiac death and death due to progressive HF comparing preserved and severe renal dysfunction. Whereas anemia was associated with higher mortality across most patients (with the exception of eGFR  $< 30$  ml/min/1.73 m<sup>2</sup>, where renal replacement therapy and erythropoietin come into play [31]),

proteinuria had the most marked impact in those with preserved renal function. Proteinuria at baseline was not associated with a higher chance of worsening renal function (post hoc  $p = 0.61$ ) and so could be a useful independent marker of elevated risk (despite apparently normal renal function), or even of insufficient HF therapy (32).

#### HF TREATMENT IN PATIENTS WITH RENAL IMPAIRMENT.

Our results highlight the importance of appropriate HFrEF therapy for all patients, especially those with renal insufficiency who could benefit the most. Subgroup analyses from both the Val-HeFT (Valsartan in Heart Failure Trial) ( $N = 2,346$ ) and the RALES (Randomized Aldactone Evaluation Study;  $N = 792$ ) trials showed that the benefit of valsartan and spironolactone were consistent in patients above and below an eGFR of 60 ml/min/1.73 m<sup>2</sup> (33,34). In more recent trials, no interactions have been noted for renal impairment using this same eGFR cutoff for eplerenone ( $n = 912$ ) or sacubitril-valsartan ( $n = 3,061$ ) (35,36). However, because the median eGFR in clinical practice is often around 60 ml/min/1.73 m<sup>2</sup>, it could be argued that a more realistic cutpoint is required to reassure clinicians about the safety and efficacy of therapy. Unfortunately, data specifically in patients with moderately severe renal dysfunction are limited (37). Subgroup analysis from the MERIT-HF trial (8), as well as the CIBIS-II (10) and SENIORS (9) trials, suggested potential benefit from beta-blockers in those with eGFR <45 ml/min/1.73 m<sup>2</sup>, hence the need for this analysis that included all of these RCTs and more. HFrEF patients with severe renal dysfunction or kidney failure have largely been excluded from RCTs. One exception was a small trial in 114 dialysis patients, where carvedilol was found to improve clinical status (38). Although we have pooled data from 10 placebo-controlled trials of beta-blockers, only 448 patients (2.7%) had an eGFR <30 ml/min/1.73 m<sup>2</sup>. Event rates were high, but due to the restricted sample size, we are unable to comment on the true efficacy of beta-blockers in this patient group; new RCTs are clearly warranted to address this knowledge gap.

**WORSENING RENAL FUNCTION.** Clinicians are often concerned about the potential for worsening renal function during initiation or up-titration of HF therapy. We show that beta-blockers do not lead to any overall deterioration in renal function in those with existing impairment. The results we present on worsening renal function (not caused by initiation of renin-angiotensin-aldosterone system inhibitors) are similar to other studies showing that deterioration of function is associated with higher mortality (39).

Our data suggest that preservation of renal function may be an important management goal. However, post-randomization variables such as repeated eGFR measurement should be judged carefully even in double-blind trials, as they are prone to the same biases as observational data. Achieving target dosage remains an essential task for HF teams. We demonstrate that this is achievable for the majority of patients with renal dysfunction, even those with moderately severe impairment. However, dose is a complicated variable also affected by physician- and patient-level biases, as highlighted by the marked difference in mortality according to the placebo dose attained.

#### PATIENTS WITH HF AND CONCOMITANT ATRIAL FIBRILLATION.

We pre-specified stratification of analyses by heart rhythm due to significant interactions with beta-blocker efficacy (12) and a marked difference in the association of heart rate with mortality comparing sinus rhythm with AF (14). The lack of benefit from beta-blockers regardless of eGFR in patients with AF was therefore unsurprising. Similar to sinus rhythm, we show that renal dysfunction in patients with AF is associated with more high-risk features, but the majority of patients can reach appropriate dosage. Higher rates of renal dysfunction in AF and worse prognosis across all eGFR categories compared with sinus rhythm demonstrate the need for improved multidisciplinary management of concomitant AF and HF (40).

**STUDY STRENGTHS AND LIMITATIONS.** The current analysis uses IPD from 10 landmark, placebo-controlled trials. An extensive period of additional data collation was performed from original case report forms, including events not originally reported, with data cleaning and harmonization according to a published design (11). Each of the trials had different inclusion and exclusion criteria, although treatment effects were similar for eGFR 30 to 59 ml/min/1.73 m<sup>2</sup> even when the 2 more unique trials were excluded. Exclusion of these 2 RCTs led to no significant heterogeneity in treatment effect in the remaining studies (Online Table 4). Due to the large sample size, we were able to test the interaction of beta-blocker efficacy across the range of continuous eGFR. We confirmed nonlinearity and used fractional polynomial transformations to obtain optimal model fitting in sinus rhythm and AF. However, despite using nonlinear approaches, splines, and flexible parametric models, interaction tests have relatively low power, and we may have missed a clinically significant interaction in small subgroups. The MDRD formula was used for primary estimation of kidney function as the CKD-EPI calculation requires

standardized creatinine measurements, although we saw no difference in treatment effects in a post hoc analysis. Due to our prior findings (15), we included patients with both mid-range and reduced LVEF in the current study and demonstrated similar efficacy from beta-blockers regardless of baseline (reduced) LVEF. As discussed, any analysis of post-randomization variables (follow-up eGFR, dose, and so on) should be considered exploratory and may be affected by regression toward the mean, and selection or survivor bias. We have deliberately not addressed hospital admissions in this paper, due to concerns that kidney disease can itself influence the likelihood of a physician admitting a patient, lead to withdrawal of other heart failure therapy, and confound the association with adverse outcomes. Finally, this a retrospective analysis, and further new RCTs should be encouraged in view of the commonality of renal dysfunction in HF.

## CONCLUSIONS

Combining double-blind, individual patient-level data has provided a sufficient sample size to confirm the efficacy of beta-blockers in heart failure patients with reduced ejection fraction, sinus rhythm and renal dysfunction, including those with eGFR 30 to 44 ml/min/1.73 m<sup>2</sup>, the lowest range of eGFR tested in large placebo-controlled trials.

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## PERSPECTIVES

**COMPETENCY IN MEDICAL KNOWLEDGE:** Beta-blocker therapy reduces mortality in patients with heart failure and reduced ejection fraction in sinus rhythm, including those with moderate (eGFR 45 to 59 ml/min/1.73 m<sup>2</sup>) and moderately severe (eGFR 30 to 44 ml/min/1.73 m<sup>2</sup>) renal dysfunction.

**TRANSLATIONAL OUTLOOK:** Further research is needed in patients with atrial fibrillation, in whom beta-blockers are not associated with lower mortality rates, and those with severe renal impairment (eGFR <30 ml/min/1.73 m<sup>2</sup>), about whom there are limited data.

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**KEY WORDS** beta-blockers, heart failure, mortality, renal impairment

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**APPENDIX** For supplemental figures and tables, please see the online version of this paper.