Renal Function as a Predictor of Outcome in a Broad Spectrum of Patients With Heart Failure

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Background—Decreased renal function has been found to be an independent risk factor for cardiovascular outcomes in patients with chronic heart failure (CHF) with markedly reduced left ventricular ejection fraction (LVEF). The aim of this analysis was to evaluate the prognostic importance of renal function in a broader spectrum of patients with CHF.

Methods and Results—The Candesartan in Heart Failure:Assessment of Reduction in Mortality and Morbidity (CHARM) program consisted of three component trials that enrolled patients with symptomatic CHF, based on use of ACE inhibitors and reduced (≤40%) or preserved LVEF (>40%). Entry baseline creatinine was required to be below 3.0 mg/dL (265 μmol/L). Routine baseline serum creatinine assessments were done in 2680 North American patients. An analysis of the estimated glomerular filtration rate (eGFR), using the Modification of Diet in Renal Disease equation and LVEF on risk of cardiovascular death or hospitalization for heart failure, as well as on all-cause mortality, was conducted on these 2680 patients. The proportion of patients with eGFR <60 mL/min per 1.73 m^2 was 36.0%; 42.6% for CHARM-Alternative, 33.0% for CHARM-Added, and 34.7% for CHARM-Preserved. During the median follow-up of 34.4 months (total 6493 person-years), the primary outcome of cardiovascular death or hospital admission for worsening CHF occurred in 950 of 2680 subjects. Both reduced eGFR and lower LVEF were found to be significant independent predictors of worse outcome after adjustment for major confounding baseline clinical characteristics. The risk for cardiovascular death or hospitalization for worsening CHF as well as the risk for all-cause mortality increased significantly below an eGFR of 60 mL/min per 1.73 m^2 (adjusted hazard ratio, 1.54 for 45 to 60 mL/min per 1.73 m^2 and 1.86 for <45 mL/min per 1.73 m^2 for the primary outcome, both $P<0.001$, and hazard ratio of 1.50, $P=0.006$, and 1.91, $P=0.001$, respectively, for all-cause mortality). The prognostic value of eGFR was not significantly different among the three component trials. There was no significant interaction between renal function, the effect of candesartan, and clinical outcome.

Conclusions—Impaired renal function is independently associated with heightened risk for death, cardiovascular death, and hospitalization for heart failure in patients with CHF with both preserved as well as reduced LVEF. There was no evidence that the beneficial effect of candesartan was modified by baseline eGFR. (***Circulation*. 2006;113:671-678.**)

Key Words: heart failure ■ angiotensin ■ kidney ■ risk factors ■ prognosis

Decreased renal function has consistently been found to be an independent risk factor for cardiovascular (CV) disease outcomes and all-cause mortality in a large spectrum of CV patients, including those with left ventricular systolic dysfunction and chronic heart failure (CHF).[1–12] In terms of clinical application, renal function may potentially be a stronger predictor of clinical events than left ventricular ejection fraction (LVEF).[3] However, most studies in CHF have been conducted in patients with markedly reduced LVEF, and data in patients with more preserved LV systolic function are scarce. In addition, specific data on the prognostic value of renal function in patients who are intolerant to ACE inhibitors are lacking: Given the known interactions between treatment with an ACE inhibitor and renal function,

Received August 31, 2005; revision received November 4, 2005; accepted November 23, 2005.

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Guest Editor for this article was Robert O. Bonow, MD.

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Circulation **is available at http://www.circulationaha.org** **DOI: 10.1161/CIRCULATIONAHA.105.580506**

these patients are of particular interest. Because the latter two groups form a significant proportion of the CHF population, it would be important to specifically collect and analyze data in these patients.

The Candesartan in Heart Failure:Assessment of Reduction in Mortality and Morbidity (CHARM)-Overall program was an assessment of candesartan in three distinct CHF populations; LVEF higher than 40% (CHARM-Preserved), 40% or lower and treated with an ACE inhibitor (CHARM-Added), or 40% or lower and not treated with an ACE inhibitor because of previous intolerance (CHARM-Alternative). These trials provide a unique opportunity to study prognostic properties of renal function and the interplay with renin-angiotensin-aldosterone system inhibitor therapy in a broad spectrum of patients with CHF.[13–16]

The first aim of the present analysis was to examine the prevalence of decreased renal function in the three CHARM groups and to study whether decreased renal function is as common in patients with preserved as it is in those with impaired LV systolic function. Second, we investigated the prognostic value of renal function on CV mortality and morbidity outcomes, adjusted for traditional prognostic markers, with special attention to LVEF and treatment allocation.

Methods

The rationale and details of the CHARM program have been described previously.[13] Eligible patients were women and men aged 18 years or older who had symptomatic heart failure (New York Heart Association class II–IV) for at least 4 weeks' duration. Major exclusion criteria included serum creatinine 3 mg/dL (265 μmol/L) or more, serum potassium 5.5 mmol/L (mEq/L) or more, known bilateral renal artery stenosis, symptomatic hypotension, critical aortic or mitral stenosis, recent (within 4 weeks) myocardial infarction, stroke, or open heart surgery and use of an angiotensin receptor blocker in the previous 2 weeks. Eligible consented patients were enrolled into one of three trials, done concurrently, according to LVEF higher than 40% (CHARM-Preserved, n=3023), 40% or lower and treated with an ACE inhibitor (CHARM-Added, n=2048), or 40% or lower and not treated with an ACE inhibitor because of previous intolerance (CHARM-Alternative, n=2028).[14–16] The present patient cohort was derived from the 2743 patients enrolled in North America, where baseline serum creatinine assessments were done as part of the screening process to determine eligibility, using a central laboratory. The primary outcome for each of the three component trials was CV death or unplanned admission to hospital for the management of worsening CHF and all-cause death for the overall program (n=7599), which were also used as the outcome measures in this supplementary analysis.

Renal Function

An estimated glomerular filtration rate (eGFR) at baseline was calculated in 2680 patients with sufficient data, with the use of the modified Modification of Diet in Renal Disease (MDRD) four-component equation incorporating age, race, gender, and serum creatinine level, which has been used in several large clinical trials.[9,17–19] This "simplified" MDRD formula (mL/min per 1.73m^2) is calculated according to the following equation for male subjects: $186.3\times(\text{serum creatinine})^{-1.154}\times(\text{age})^{-0.203}$. The product of this equation was multiplied by a correction factor for female subjects$\times$0.742, for black male subjects$\times$1.212, and for black female subjects$\times$1.212$\times$0.742. The eGFR was categorized into approximate quintiles using sensible cutoffs for the ease of interpretation close to cutoff points as specified by the National Kidney Disease Foundation Outcomes Quality Initiative (NKF-K/DOQI) Guidelines.[20]

Statistical Methods

Associations between baseline variables were assessed through the use of 1-way ANOVA, the Kruskal-Wallis test, and χ^2 or Fisher exact tests, when appropriate. Two-sided P values were used, taking $P<0.05$ to be significant. Both major outcomes (CV death or unplanned heart failure hospitalization; all-cause mortality) were analyzed as time to first event for this cohort of 2680 CHARM patients over the duration of the 4-year program (median follow-up, 34.4 months). Continuous variables were categorized for graphical investigation of the proportionality of hazards and estimation of crude stratum-specific rates. We used a Cox proportional hazards model to estimate hazard ratios with 95% CI. Multivariate adjustment was performed on characteristics selected a priori, including antihypertensive medications, which might confound the association of renal function with the risk of both major outcomes. Nonlinear terms were entered into the model to assess effects at the tail of the distribution, when supported by the statistical model. Inspection of the martingale residuals suggested a quadratic transformation for the continuous variable eGFR. Hence, eGFR (centered on 75 mL/min per 1.73 m^2) was entered either as a continuous variable (assuming a nonlinear effect) or as categorical variable. Age (above 60 years), heart rate, and diastolic blood pressure were entered as continuous linear variables. Age (60 years or below), the presence of ischemic CHF, diabetes, smoking, atrial fibrillation, angina, prior stroke or myocardial infarction, prior hospitalizations for CHF, LVEF, smoking status, and severity of clinical symptoms as assessed by NYHA functional class were entered as categoric variables. We also evaluated the effect of random assignment to candesartan. The final multivariable model with the use of exact quintiles of eGFR and LVEF was used to estimate quintile-specific hazard ratios and derive adjusted relative risk estimates. Finally, the robustness of the primary analysis was tested in a secondary analysis by using serum creatinine. The purpose of the latter analysis was to investigate whether the observed differences in results would hold if serum creatinine was used instead of eGFR, a more conservative scenario. All analyses were performed with Stata 8.2 (Stata Statistical Software, version 8.2, StataCorp 2004, Stata Corporation).

Results

A baseline serum creatinine measurement was missing in 61 of the 2743 patients. In 2 patients, the serum creatinine concentration recorded was >10 mg/dL, and these patients were excluded from the analysis. In the cohort of 2680 patients included in this analysis, 1087 were enrolled from CHARM-Preserved, 931 from CHARM-Added, and 662 from CHARM-Alternative.

This North American cohort had a higher body mass index and a higher rate of hypertension, CV disease, diabetes, worse clinical heart failure, and ex-smokers when compared with the other regions.

Estimated GFR and Its Association With Other Baseline Characteristics

In Table 1, baseline characteristics are shown across quintiles of eGFR at baseline. The number of comorbidities at baseline increased with decreasing eGFRs. Patients in the lowest category of eGFR had the highest rates of prior diabetes, myocardial infarction, stroke, hospitalizations for CHF, atrial fibrillation, and angina pectoris. Lower eGFR was associated with less current smokers and more treatment with diuretics, spironolactone, and vasodilators. Patients with lower eGFR were less likely to be treated with a β-blocker. There was no relation between eGFR and ACE inhibitor use, and there was no evidence for an association between LVEF and eGFR

TABLE 1. Baseline Characteristics According to eGFR Categories in 2680 Patients

	eGFR, mL/min per 1.73 m^2						
Baseline Characteristics	>90.0 (n=507)	89.9–75.0 (n=519)	74.9–60.0 (n=618)	59.9–45.0 (n=547)	<45.0 (n=419)	Total (n=2680)	*P*
Creatinine, mg/dL	0.8±0.1	0.9±0.1	1.1±0.1	1.3±0.2	1.9±0.4	1.2±0.4	<0.001
Age, y	56.7±11.3	64.2±11.2	67.1±10.4	69.2±9.6	70.6±9.5	65.3±11.6	<0.001
Men, %	70.4	68.8	69.4	64.0	58.0	66.6	<0.001
Heart rate, bpm	73.2±12.5	72.0±11.7	71.3±11.5	71.7±12.2	70.9±11.7	71.9±12.0	0.0165
Blood pressure, mm Hg							
Systolic	128.9±18.1	127.9±18.7	127.9±18.1	127.9±18.4	128.4±20.8	128.2±18.7	<0.001
Diastolic	76.4±10.7	74.9±10.8	73.6±10.1	72.1±10.4	70.2±10.6	73.6±10.7	<0.001
LVEF, %	39.1±15.4	39.0±15.6	37.9±15.1	37.8±16.3	38.9±17.0	38.5±15.8	0.500
Cause of heart failure							
Ischemic heart disease, %	55.8	64.7	70.6	71.1	76.4	67.3	<0.001
NYHA class, %							
II	43.0	37.0	38.2	33.5	27.2	36.3	<0.001
III	56.0	60.7	59.4	63.8	66.6	60.9	
IV	1.0	2.3	2.4	2.7	6.2	2.8	
Previous hospitalizations for CHF	63.6	60.3	62.1	74.8	82.3	67.8	<0.001
Previous myocardial infarction	45.9	50.5	57.0	53.9	60.1	53.2	<0.001
Diabetes mellitus							
Insulin-treated	8.5	9.8	12.0	15.2	26.5	13.7	<0.001
Non–insulin-treated	23.7	24.5	20.9	24.1	25.1	23.5	0.501
Atrial fibrillation	17.7	26.0	28.3	34.9	40.1	28.8	<0.001
Angina pectoris	56.2	63.8	65.4	62.9	67.5	62.9	0.002
Stroke	6.9	9.3	10.5	12.8	14.1	10.5	0.002
Current smoker, %	24.1	15.4	11.7	10.6	7.4	14.2	<0.001
Current treatment of heart failure							
Digitalis, %	54.4	51.3	52.3	55.3	53.2	53.4	0.691
Diuretics, %	66.4	68.0	71.5	76.8	75.1	71.4	<0.001
β-Blockers, %	60.1	56.8	54.9	53.4	50.1	55.3	0.023
Calcium antagonist, %	24.3	26.4	21.4	27.8	27.9	25.3	0.060
ACE inhibitors, %	47.3	43.4	48.2	43.1	44.4	45.5	0.287
Spironolactone, %	11.3	12.5	15.4	16.1	21.5	15.0	<0.001
Aspirin, %	57.9	60.3	60.2	54.8	54.2	57.7	0.137
Other vasodilators, %	24.3	28.5	36.3	38.9	50.8	35.0	<0.001

(P=0.5), although a greater proportion of patients with a low eGFR had a worse NYHA class.

Figure 1 shows the cumulative distribution of eGFR in CHARM-Preserved, CHARM-Added, and CHARM-Alternative. The mean eGFR in CHARM-Alternative was slightly lower than in CHARM-Added and CHARM-Preserved. The estimated mean difference in eGFR between CHARM-Added and CHARM-Alternative was 5.2 (95% CI, 2.54 to 7.87; P<0.001) and between CHARM-Preserved and CHARM-Alternative was 4.42 mL/min per 1.73 m^2 (95% CI, 1.83 to 7.00; P=0.001), respectively. Similar findings were observed when calculating cumulative distributions of serum creatinine. The proportion of patients with eGFR <60 mL/min per 1.73 m^2 was 36.0%; 42.6% for CHARM-Alternative, 33.0% for CHARM-Added, and 34.7% for CHARM-Preserved.

Estimated GFR at Baseline and Clinical Outcome

After a median follow-up of 34.4 months (range, 1 day to 45.2 months) and observation time of 6493 person-years, 950 of 2680 patients had CV death or admission to the hospital for heart failure in the time-to-event analysis, and there were 625 deaths (all-cause mortality).

Figure 2 shows that there was a stepwise increase in the cumulative incidence of CV death or admission to hospital for heart failure across successively lower quintiles of eGFR. There was a less clear separation between the curves for the higher eGFR quintiles, and the most marked differences were observed for an eGFR below 60 mL/min per 1.73 m^2. Similar patterns were observed between eGFR divided into <45.0, 45.0 to 60.0, and >60 mL/min per 1.73 m^2 and cardiovascular death or admission to hospital for heart failure stratified for preserved LVEF (Figure 3).

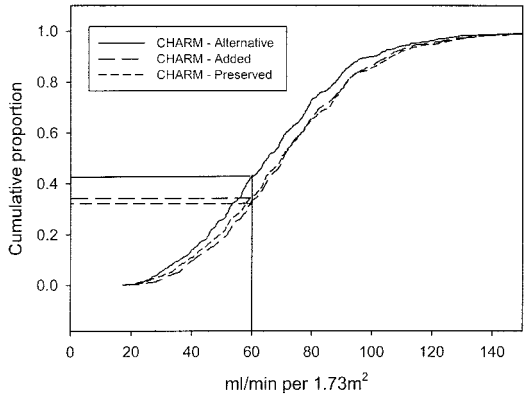

Figure 1. Cumulative distribution of eGFR in CHARM-Preserved, CHARM-Added, and CHARM-Alternative trial.

The results of multivariate modeling are displayed in Tables 2 and 3 and in Figure 4. Both a reduced eGFR and lower LVEF were found to be significant independent predictors of worse outcome after adjustment for major confounding baseline clinical characteristics. The effects of eGFR remained significant in both multivariable models ($P<0.001$). When using eGFR as a continuous variable, there was a nonlinear relation between eGFR, both in crude and adjusted analyses (Wald test for quadratic term, $P=0.001$ for both outcomes). This nonlinear effect was particularly present within the lowest eGFR quintile. Finally, the prognostic value of eGFR was compared between the three component trials, and there was no difference; that is, there was no evidence for an interaction for either outcome. There was also no interaction between eGFR and LVEF (Wald test for interaction term, $P=0.42$) or interaction between the treatment effect of candesartan and eGFR (Wald test for interaction term, $P=0.88$).

In a secondary analysis with creatinine, both increased creatinine and lower LVEF were found to be significant independent predictors of worse outcome after adjustment for major confounding baseline clinical characteristics (data not shown). In both multivariable models, there was no substantial evidence for a nonlinear effect of creatinine (Wald tests for the quadratic terms, $P=0.09$ for the primary outcome, $P=0.36$ for the secondary outcome). Finally, there was no evidence for an interaction between creatinine and LVEF (Wald test for interaction term, $P=0.57$) or for an interaction between creatinine and the effect of candesartan (Wald test for interaction term, $P=0.84$), gender, diabetes, or age.

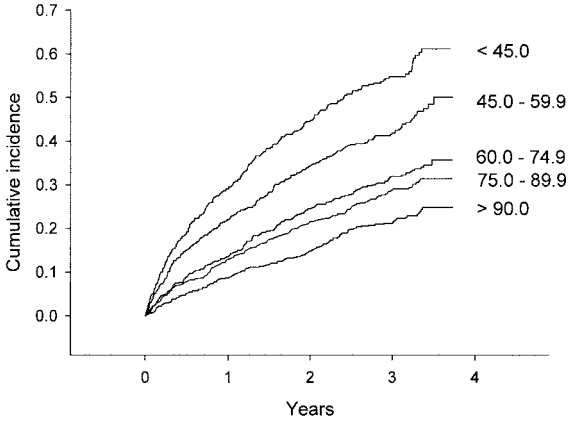

Figure 2. Kaplan-Meier plot of cumulative incidence of cardiovascular death or unplanned admission to hospital for the management of worsening CHF stratified by approximate quintiles of eGFR in mL/min per 1.73 m^2 (time in years).

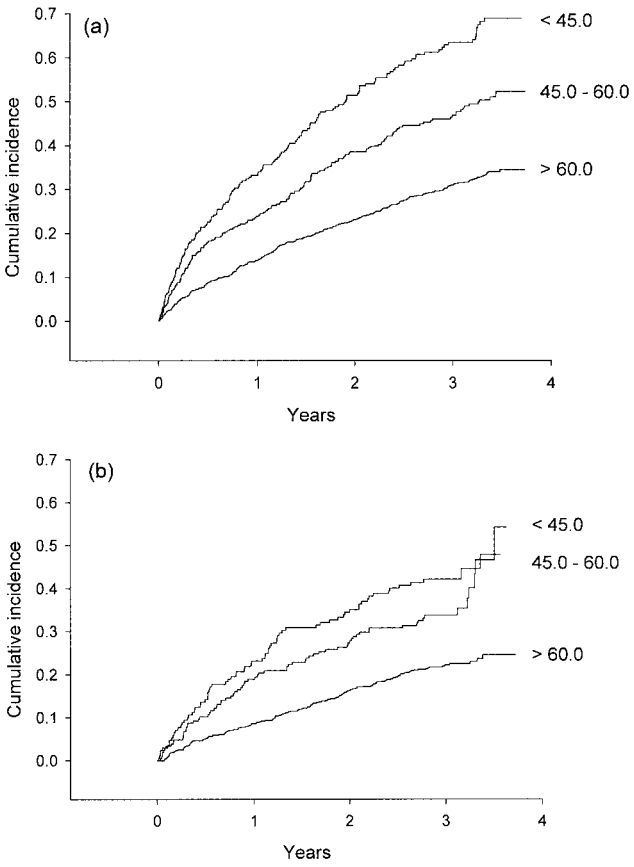

Figure 3. Kaplan-Meier plot of cumulative incidence of cardiovascular death or unplanned admission to hospital for the management of worsening CHF stratified by <45.0, 45.0 to 60.0, and >60 mL/min per 1.73 m^2 eGFR in mL/min per 1.73 m^2 in patients with (a) reduced LVEF (LVEF≤40%) (b) and preserved LV systolic function (LVEF>40%).

Discussion

The main finding of the present analysis from the CHARM program is that renal function, as reflected by eGFR through the use of the simplified MDRD formula, is strongly associated with prognosis in a broad spectrum of patients with CHF. This risk from renal insufficiency persists even after adjustment for all other known covariates, including LVEF. Moreover, no evidence for interaction was observed among renal function, treatment allocation, and primary outcome.

Renal insufficiency, as reflected by a GFR of less than 60.0 mL/min per 1.73 m^2 of body surface area, is relatively common in patients with CHF. Evidence is accumulating that renal impairment may also independently contribute to an increased CV morbidity and mortality risk in patients with CHF; this applies to patients with systolic as well as those with diastolic dysfunction.[2,3,5,6,12] The interpretation of this finding is that the presence of renal dysfunction in itself

TABLE 2. Rates of Cardiovascular Death or Unplanned Admission to Hospital for Management of Worsening CHF According to eGFR and LVEF With Crude and Adjusted Hazard Ratios for eGFR and LVEF Analyzed as Categorical and Continuous Variables

				Crude				Adjusted†			
Effect of	No. at Baseline	No. of Events	Estimated Rate (per 100 Person-Years)	Hazard Ratio	95% CI		*P*	Hazard Ratio	95% CI		*P*
eGFR											
Categorical											
90+ mL/min per 1.73 m^2	577	131	8.2	1.00	...	...	...	1.00	...	...	...
75–89.9 mL/min per 1.73 m^2	519	151	11.2	1.35	1.07	1.71	0.011	1.17	0.93	1.49	0.180
60–74.9 mL/min per 1.73 m^2	618	200	12.8	1.54	1.24	1.92	<0.001	1.24	0.98	1.56	0.070
45–59.9 mL/min per 1.73 m^2	547	237	19.8	2.34	1.89	2.90	<0.001	1.54	1.22	1.94	<0.001
<45 mL/min per 1.73 m^2	419	231	28.9	3.36	2.71	4.16	<0.001	1.86	1.47	2.36	<0.001
eGFR											
Continuous: Per decrease from 75 mL/min per 1.73 m^2											
10 mL/min per 1.73 m^2	...	...	...	1.19	1.16	1.23	<0.001	1.10	1.07	1.13	<0.001
20 mL/min per 1.73 m^2	...	...	...	1.46	1.38	1.55	<0.001	1.22	1.15	1.30	<0.001
LVEF											
Categorical*											
≥45%	1020	280	10.9	1.00	...	...	...	1.00	...	...	...
40%	255	80	12.7	1.16	0.90	1.49	0.245	1.23	0.98	1.62	0.075
35%	302	97	12.6	1.16	0.92	1.46	0.245	1.16	0.91	1.48	0.227
30%	345	129	15.3	1.40	1.13	1.72	0.002	1.35	1.08	1.69	0.007
25%	294	125	18.3	1.65	1.34	2.04	<0.001	1.54	1.23	1.94	<0.001
20%	277	134	21.4	1.93	1.57	2.38	<0.001	1.92	1.53	2.42	<0.001
15%	187	105	27.8	2.48	1.98	3.11	<0.001	2.27	1.78	2.90	<0.001
LVEF											
Per decrease of 5% in LVEF from 45%	...	...	...	1.15	1.11	1.19	<0.001	1.14	1.10	1.18	<0.001

*Categories referring to mean LVEF within that category.

†Covariates used for adjustment: allocated treatment, smoking, gender, ethnicity, age, heart rate, systolic blood pressure, diastolic blood pressure, NYHA class, medical history (diabetes, prior angina, prior stroke or myocardial infarction, prior hospitalizations for CHF), and medication (ACE inhibitors, diuretics, β-blockers, calcium channel blockers, spironolactone, other vasodilators, aspirin).

remains an important independent risk factor for CV death or heart failure hospitalization.

Our study differs from previous reports, as the CHARM program included a broad spectrum of patients with CHF with respect to both LVEF as well as use of ACE inhibitors. Within this context, it is noteworthy that although cumulative distributions of estimated renal function were slightly different in CHARM-Preserved and CHARM-Added when compared with CHARM-Alternative, the prognostic value of renal function was comparable in these CHF patient populations.

Several explanations have been proposed for the observed prognostic value of renal function in CHF. First, renal function can be seen as direct reflection of an impaired hemodynamic status that is related to the severity of the underlying (ie, cardiac) disease.[21,22] In the present study, we did not measure invasive hemodynamics. We found no interaction between eGFR and LVEF, indicating that eGFR and cardiac function had effects that were independent in terms of predicting the primary end point. Second, renal dysfunction might be a marker of general vascular disease and therefore possibly reflects severity of atherosclerosis in both kidney and heart.[23,24] Although our study cannot resolve this debate, the strong independent effect of renal function in our analysis after adjustment for numerous cardiac risk factors shows that renal function is a valuable predictive variable in evaluating outcomes, even if it probably represents partly underlying atherosclerotic or hypertensive vascular disease.

An interesting finding in the present study is the lower eGFR in CHARM-Alternative, when compared with CHARM-Added or CHARM-Preserved. This could be due to selection because a frequent reason for not using ACE inhibitors in patients with heart failure is the concern for complications attributable to worsened renal function, especially in the situation of renal insufficiency. In a post hoc analysis of Studies of Left Ventricular Dysfunction (SOLVD), initiating treatment with enalapril increased the risk of diuretic-associated renal impairment in patients with CHF.[25] However, in CHARM-Alternative, the most common reason for ACE inhibitor intolerance was cough (72%), and renal dysfunction was the reason in only 12% of the cases. It could be speculated that the lower eGFR in CHARM-Alternative might be related to the absence of the renopro-

TABLE 3. Rates of All-Cause Mortality According to eGFR and LVEF With Crude and Adjusted Hazard Ratios for eGFR and LVEF Analyzed as Categorical and Continuous Variables

				Crude				Adjusted†			
Effect of	No. at Baseline	No. of Deaths	Estimated Rate (per 100 Person-Years)	Hazard Ratio	95% CI		*P*	Hazard Ratio	95% CI		*P*
eGFR											
Categorical											
90+ mL/min per 1.73 m^2	577	77	4.5	1.00	...	...	...	1.00	...	...	...
75–89.9 mL/min per 1.73 m^2	519	92	6.1	1.38	1.02	1.87	0.037	1.13	0.83	1.54	0.432
60–74.9 mL/min per 1.73 m^2	618	126	7.1	1.59	1.20	2.11	0.001	1.14	0.85	1.54	0.378
45–59.9 mL/min per 1.73 m^2	547	159	11.0	2.48	1.89	3.26	<0.001	1.50	1.12	2.00	0.006
<45 mL/min per 1.73 m^2	419	171	16.9	3.83	2.92	5.01	<0.001	1.91	1.42	2.58	<0.001
eGFR											
Continuous: Per decrease from 75 mL/min per 1.73 m^2											
10 mL/min per 1.73 m^2	...	...	...	1.21	1.17	1.25	<0.001	1.09	1.06	1.14	<0.001
20 mL/min per 1.73 m^2	...	...	...	1.50	1.41	1.61	<0.001	1.23	1.14	1.33	<0.001
LVEF											
Categorical*											
≥45%	1020	164	5.7	1.00	...	...	...	1.00	...	...	...
40%	255	46	6.4	1.12	0.81	1.56	0.486	1.21	0.89	1.69	0.258
35%	302	66	7.6	1.33	1.00	1.77	0.051	1.32	0.98	1.78	0.070
30%	345	88	9.1	1.61	1.24	2.08	<0.001	1.56	1.19	2.06	0.002
25%	294	87	10.7	1.88	1.45	2.44	<0.001	1.82	1.38	2.42	<0.001
20%	277	96	13.0	2.28	1.77	2.93	<0.001	2.36	1.79	3.12	<0.001
15%	187	78	16.7	2.93	2.24	3.84	<0.001	2.62	1.95	3.52	<0.001
LVEF											
Per decrease of 5% in LVEF from 45%	...	...	...	1.19	1.15	1.23	<0.001	1.18	1.13	1.23	<0.001

*Categories referring to mean LVEF within that category.

†Covariates used for adjustment: allocated treatment, smoking, gender, ethnicity, age, heart rate, systolic blood pressure, diastolic blood pressure, NYHA class, medical history (diabetes, prior angina, prior stroke or myocardial infarction, prior hospitalizations for CHF), and medication (ACE inhibitors, diuretics, β-blockers, calcium channel blockers, spironolactone, other vasodilators, aspirin).

tective effects of ACE inhibition in the past. Supportive evidence is coming from experimental models and other clinical conditions.[26] Therapies directed at inhibiting AII formation and at binding to the AT_1 receptor have been shown to reduce end-organ damage in the kidneys in diabetics and hypertensives.[27–31] In CHARM-Preserved, however, only a minority of patients were taking an ACE inhibitor, so these differences in eGFR between trials probably are multifactorial and not primarily attributable to the background use of an ACE inhibitor.

In CHARM, a strong association between impaired renal function and insulin-dependent diabetes was observed, whereas the prevalence of non–insulin-dependent diabetes mellitus was equally distributed over the different ranges of renal function. This might be explained by the fact that the latter form of diabetes is at an earlier stage of progression, with fewer manifestations of microvascular and macrovascular disease complications.

One of the potential limitations of this study is that there may be unmeasured confounders that could have influenced our results. Although the observed relations between renal function and CV prognosis remained statistically significant after correction for classic risk factors, we did not account for the more recently reported confounding risk factors such as lipoproteins and hyperhomocysteinemia.[32,33] Also, renal function was estimated by the simplified MDRD equation, that is, an indirect, creatinine-based assessment of renal function. This and other equations were mainly validated in populations with moderately to severely impaired renal function. In view of the overall findings being consistent irrespective of the algebraic transformation of creatinine with and without adjustments for gender, age, and other risk factors, we believe that our results are relatively robust. However, it is not possible to extrapolate these findings to patients with more severe renal dysfunction because the trial excluded patients with baseline serum creatinine values ≥265 μmol/L (≥3 mg/dL).

Conclusions

We have shown that in a broad spectrum of patients with CHF, including those with reduced as well as preserved left ventricular systolic function and including those either receiving an ACE inhibitor or not receiving an ACE inhibitor due to intolerance, renal function, as reflected by eGFR using

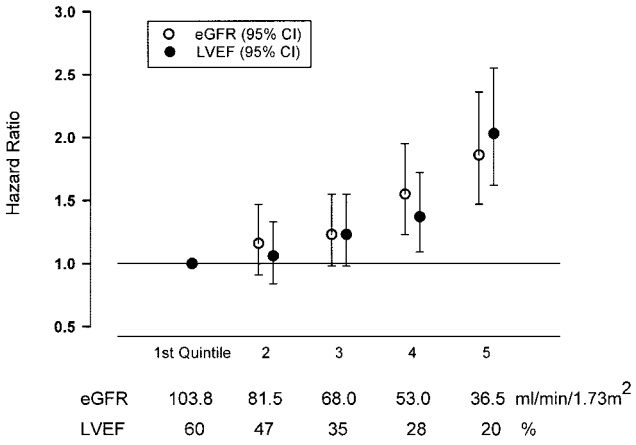

Figure 4. Multiple adjusted hazard ratios (with their 95% CI) for risk of cardiovascular death or unplanned admission to hospital for the management of worsening CHF across decreasing exact quintiles (median values presented) of both eGFR and LVEF.

the simplified MDRD formula, is strongly and independently associated with prognosis. Taking into account the renal exclusion criteria of CHARM (serum creatinine $\geq$3 mg/dL ($\geq$ 265 μmol/L), the clinical effectiveness of candesartan was evident irrespective of underlying renal function, as no statistical interaction was observed between renal function, treatment allocation, and clinical outcome.

Acknowledgments

The CHARM program was funded by AstraZeneca, which was responsible for data collection and analysis. The Executive Committee academic leadership, consisting of Drs Pfeffer, Swedberg, McMurray, Yusuf, and Granger, supervised the management of the study and were primarily responsible for the interpretation of the data, preparation, review, and approval of the manuscript. The analyses for the present study were done independently by Stuart Pocock, PhD, London School of Hygiene and Tropical Medicine, and his associate, Dorothea Nitsch, MD, MSc, both coauthors of the manuscript.

Disclosures

Drs Pfeffer, Swedberg, McMurray, Yusuf, Granger, Östergren, Pocock and Van Veldhuisen have served as consultants to or received research grants and honoraria from AstraZeneca and/or other major pharmaceutical companies. There are no relationships of interest related to the topic of the manuscript to disclose for Drs Hillege, Nitsch, Ostergren, De Zeeuw, and Cornel. Dr Michelson is an employee of AstraZeneca.

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