# **Renal Insufficiency and Heart Failure** Prognostic and Therapeutic Implications From a Prospective Cohort Study

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**Background**—The prevalence, prognostic import, and impact of renal insufficiency on the benefits of ACE inhibitors and  $\beta$ -blockers in community-dwelling patients with heart failure are uncertain.

- *Methods and Results*—We analyzed data from a prospective cohort of 754 patients with heart failure who had ejection fraction, serum creatinine, and weight measured at baseline. Median age was 69 years, and 43% had an ejection fraction  $\geq$ 35%. By the Cockcroft-Gault equation, 118 patients (16%) had creatinine clearances  $\leq$ 30 mL/min and 301 (40%) had creatinine clearances between 30 and 59 mL/min. During follow-up (median 926 days), 385 patients (37%) died. Even after adjustment for all other prognostic factors, survival was significantly associated with renal function (*P*=0.002) in patients with either systolic or diastolic dysfunction; patients exhibited a 1% increase in mortality for each 1-mL/min decrease in creatinine clearance. The associations with 1-year mortality reductions were similar for ACE inhibitors (OR 0.46 [95% CI 0.26 to 0.82] versus OR 0.28 [95% CI 0.11 to 0.70]) and  $\beta$ -blockers (OR 0.40 [95% CI 0.23 to 0.70] versus OR 0.41 [95% CI 0.19 to 0.85]) in patients with creatinine clearances <60 mL/min versus  $\geq$ 60 mL/min, although these drugs were used less frequently in patients with renal insufficiency.
- *Conclusions*—Renal insufficiency is more prevalent in patients with heart failure than previously reported and is an independent prognostic factor in diastolic and systolic dysfunction. ACE inhibitors and  $\beta$ -blockers were associated with similar reductions in mortality in patients with and without renal insufficiency. (*Circulation.* 2004;109:1004-1009.)

Key Words: heart failure ■ kidney ■ prognosis

Congestive heart failure (CHF) is the fastest-growing cardiovascular diagnosis in North America; the prevalence of symptomatic disease is  $\approx 2\%$  in adults older than 45 years, the annual incidence is nearly 10 cases/1000 population in those older than 65 years, and the lifetime risk of developing CHF is estimated at 20%.<sup>1,2</sup> Despite advances in diagnosis, therapy, and prognosis over the past 2 decades, the course of heart failure in many patients continues to be one of inexorable decline.<sup>3</sup>

It is important to accurately define prognostic factors in patients with heart failure to identify high-risk individuals who require closer follow-up and more intensive intervention. It is also important to determine whether therapies proven efficacious in randomized clinical trials are effective in nontrial patients who are older and often have comorbid conditions that were exclusion criteria in the trials. Renal function is an underappreciated prognostic factor in heart failure,<sup>4</sup> and renal insufficiency is commonly viewed as a relative contraindication to some proven efficacious therapies.

Although a number of studies have reported that renal insufficiency is associated with adverse cardiovascular outcomes, particularly in patients with coronary artery disease,<sup>5–15</sup> the evidence base for patients with heart failure is less robust for 4 reasons. First, 4 of the 6 studies examining the association between renal function and outcomes in heart failure were secondary analyses of clinical trials with restricted eligibility criteria.<sup>16-21</sup> For instance, nearly all participants in these trials had left ventricular ejection fractions  $\leq$ 35% and serum creatinine levels  $\leq$ 2 mg/dL (177  $\mu$ mol/L). Moreover, in these studies, fewer than one fourth of the patients received  $\beta$ -blockers. Thus, the impact of renal insufficiency has not been elucidated adequately in a representative cohort of patients receiving contemporary therapy for CHF, especially those with abnormal serum creatinine levels or with diastolic dysfunction (who account for almost half of heart failure patients in the community).<sup>1</sup> Second, only 2 studies adjusted for concomitant hemoglobin values,<sup>18,21</sup> although anemia may well confound the relation between renal insufficiency and outcomes in these patients.<sup>22</sup> Third, the prevalence of renal insufficiency in the broader population of patients with heart failure cannot be estimated from trials with eligibility restrictions. Finally, because few patients with renal insufficiency were enrolled in the CHF trials,

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it is unclear whether ACE inhibitors and/or  $\beta$ -blockers exert similar benefits in patients with kidney disease as in those without.<sup>23</sup>

To examine the prevalence of renal insufficiency in CHF and determine whether it is independently associated with prognosis, we analyzed data from a prospective cohort of patients with heart failure followed up at a specialized clinic. In addition, we used this data set to explore whether ACE inhibitors and/or  $\beta$ -blockers had similar effects in patients with or without renal insufficiency.

#### Methods

A full description of the University of Alberta Heart Function Clinic cohort study, including the variables collected and definitions used, has been published previously.<sup>24</sup> In brief, all patients seen between September 1989 and August 2002 underwent a structured history and physical examination by a heart failure physician at the time of initial referral to the clinic to confirm the diagnosis of heart failure, and demographic, clinical, and laboratory data were collected prospectively at all follow-up visits in those patients confirmed to have heart failure (n=1042). Objective assessments of left ventricular ejection fraction were obtained in all patients within 3 months of their baseline visit. Patients were defined as having diastolic dysfunction if they had a validated diagnosis of heart failure by the Framingham criteria and their left ventricular ejection fraction was >50%.<sup>25</sup>

Vital status as of August 2002 was ascertained by review of the Alberta Vital Statistics Registry, death certificates, or review of medical records. Patients without assessment of serum creatinine or hemoglobin at baseline (n=288) were excluded from subsequent analyses (but are included in Table 1). This study was approved by the University of Alberta Clinical Research Ethics Committee.

Glomerular filtration rate at baseline was estimated with the Cockcroft-Gault equation, which has been validated in patients with a wide variety of medical diagnoses, and patients were classified into 4 groups:  $\geq$ 90, 60 to 89, 30 to 59, and <30 mL/min.<sup>26</sup> The correlation between Cockcroft-Gault creatinine clearance and glomerular filtration rate as estimated by the Modification of Diet in Renal Disease equation<sup>26</sup> was high in the cohort in the present study (*r*=0.81, *P*<0.001); creatinine clearances were used for all of the analyses reported here.

#### **Statistical Analysis**

Baseline characteristics of patients in the 4 strata specified above were compared by  $\chi^2$  test for dichotomous variables and Student's t tests for continuous variables. Crude survival curves were generated by the Kaplan-Meier method and compared with the Mantel-Haenszel log-rank test. To adjust for differences in baseline clinical characteristics and concomitant conditions/medications, multiple logistic regression analysis with the backward stepwise technique was done to examine prognostic factors for 1-year mortality, selecting all clinically important variables and other prespecified factors with P < 0.25 on bivariate analyses and accepting statistical significance at P < 0.05. All first-order interactions were tested. Logistic regression models were performed on the entire cohort, and a stratified analysis was done for systolic and diastolic dysfunction separately. Cox proportional hazards analyses were done to determine the association of serum creatinine (run as a continuous variable) with all-cause mortality (over the entire follow-up period), adjusted for age, gender, New York Heart Association (NYHA) class, concomitant medication use, and any other variables that significantly differed between patients with or without kidney disease or that predicted mortality in the multivariate model (including anemia). The proportional hazards assumption was checked with a log minus log plot. All analyses were performed with the SPSS statistical software package (version 11.5).

## Results

A total of 1042 of the 1151 patients referred to the clinic met the Framingham criteria for heart failure. The median age at baseline was 69 years, 66% were male, 66% had an ischemic cardiomyopathy, 43% had an ejection fraction  $\geq$ 35%, and 76% had NYHA class II or III symptoms at their baseline visit. The characteristics of the overall cohort are summarized in Table 1, stratified by creatinine clearance and including those patients who did not have serum creatinine or hemoglobin measured at baseline.

Renal insufficiency at baseline was common in the present cohort: only 17% of patients had creatinine clearances >90 mL/min. Patients with renal insufficiency were older, more likely to be female, had more symptomatic heart failure, were more likely to have coronary artery disease or hypertension, and were less likely to receive ACE inhibitors,  $\beta$ -blockers, or spironolactone (Table 1). The most frequently prescribed ACE inhibitors (enalapril, lisinopril, and captopril) and  $\beta$ -blockers (metoprolol, carvedilol, and bisoprolol) were the same in patients with and without reduced creatinine clearances.

During follow-up (median 926 days, interquartile range 318 to 1834 days), 385 patients (37%) died. Survival at 1, 2, and 5 years for the entire cohort was 73%, 57%, and 26%, respectively. Survival was significantly associated with creatinine clearance (log rank 27.98, P<0.0001; Figure), even after adjustment for all other factors associated with outcomes (Table 2).

On multivariate logistic regression with creatinine clearances >90 mL/min as the referent (and adjustment for age, gender, NYHA class, hemoglobin, and medications [ACE inhibitors,  $\beta$ -blockers, and aspirin]), patients with creatinine clearances <30 mL/min had an elevated risk for 1-year mortality (OR 2.48 [95% CI 1.20 to 5.12]), as did those with creatinine clearances of 30 to 59 mL/min (OR 1.70 [95% CI 0.91 to 3.20]). Results were similar in those patients with systolic (n=555) versus diastolic (n=199) dysfunction. There was no appreciable interaction between systolic/diastolic dysfunction, edema, or hemoglobin and the influence of renal insufficiency on prognosis (tests for interaction P=0.75, P=0.50, and P=0.64, respectively).

Both ACE inhibitors (OR 0.40 [95% CI 0.24 to 0.66]) and  $\beta$ -blockers (OR 0.41 [95% CI 0.27 to 0.64]) were associated with reduced 1-year mortality, even after adjustment for age, gender, NYHA class, serum creatinine, hemoglobin, and other medications. Their survival associations were similar in patients with creatinine clearances <60 mL/min (OR 0.46 [95% CI 0.26 to 0.82] for ACE inhibitors and 0.40 [95% CI 0.23 to 0.70] for  $\beta$ -blockers) and in those patients with creatinine clearances  $\geq$ 60 mL/min (OR 0.28 [95% CI 0.11 to 0.70] for ACE inhibitors and 0.41 [95% CI 0.19 to 0.85] for  $\beta$ -blockers). There was no statistically significant mortality interaction between aspirin and ACE inhibitors in the present study.

The variables entered into the Cox proportional hazards analysis and those variables that were found to be independently associated with all-cause mortality during follow-up are outlined in Table 2. When this analysis was rerun with creatinine clearance rather than serum creatinine and adjust-

	No Baseline Creatinine (n=288)	Creatinine Clearance					
		≥90 mL/min (n=129)	60 to 89 mL/min (n=206)	30 to 59 mL/min (n=301)	<30 mL/min (n=118)	P*	
Age, y	64 (14)	51 (12)	63 (11)	73 (10)	78 (11)	< 0.001	
Female	34	17	27	38	56	< 0.001	
NYHA class						< 0.001	
I	17	18	14	4	5		
II	37	42	45	34	25		
III	41	31	35	47	50		
IV	5	9	6	15	19		
Ischemic origin	57	56	68	71	80	< 0.001	
Hypertension	40	29	25	32	45	0.002	
Ejection fraction, %	32 (15)	31 (15)	33 (14)	34 (15)	39 (15)	0.005	
Systolic dysfunction	69	77	78	71	68	0.131	
Ventricular arrhythmias	17	21	19	23	14	0.156	
Atrial arrhythmias	28	23	30	37	31	0.042	
COPD	16	3	7	12	9	0.03	
Diabetes mellitus	30	23	22	22	25	0.96	
Dyslipidemia	8	8	9	7	6	0.76	
Weight, kg	80 (18)	62 (12)	71 (14)	82 (15)	96 (19)	< 0.001	
Heart rate, bpm	80 (17)	79 (15)	79 (15)	79 (16)	77 (14)	0.497	
Systolic BP, mm Hg	124 (25)	124 (23)	121 (25)	123 (25)	122 (26)	0.674	
Diastolic BP, mm Hg	74 (14)	78 (11)	76 (13)	72 (11)	70 (13)	< 0.001	
Edema present	25	18	23	28	28	0.139	
Hemoglobin, g/dL		13.9 (1.9)	13.5 (1.8)	13.0 (1.7)	12.1 (1.7)	< 0.001	
Sodium, mmol/L	139 (4)	138 (4)	139 (3)	139 (4)	139 (4)	0.228	
Electrocardiogram							
LBBB	16	30	32	36	26	0.231	
LVH	23	31	33	32	34	0.959	
Medications							
ACE inhibitors	79	92	93	84	75	< 0.001	
Angiotensin receptor blockers	6	6	5	4	3	0.422	
$\beta$ -Blockers	47	57	53	40	34	< 0.001	
Spironolactone	27	12	13	5	4	< 0.001	
Digoxin	60	62	68	68	64	0.537	
Loop diuretics	76	75	85	91	86	< 0.001	
Other vasodilators	17	10	9	10	11	0.924	
Warfarin	39	49	51	51	24	< 0.001	
Aspirin	54	67	66	74	75	0.138	
Amiodarone	11	12	17	15	12	0.541	

TABLE 1. Baseline Clinical Features of the Cohort, Stratified by Creatinine Clearance

COPD indicates chronic obstructive pulmonary disease; BP, blood pressure; LBBB, left bundle-branch block; and LVH, left ventricular hypertrophy.

Values are percents or means (SDs) unless otherwise stated.

\*Indicates P value for trend across creatinine clearance strata.

ment for all of the Table 2 covariates, it was revealed that for each 1-mL/min decrease in creatinine clearance, there was a 1% increase in mortality (P < 0.001).

## Discussion

Renal insufficiency is common in patients with heart failure, with more than half of the patients in the present

study exhibiting some impairment of kidney function. This prevalence is higher than that reported in other studies and reflects the unselected population enrolled in the present cohort study in contrast to the highly selected nature of trial participants.<sup>27</sup> The present findings are consonant with the only other study reporting on nontrial participants, in which 38% of patients admitted to the hospital with



Survival stratified by baseline creatinine clearance. Log-rank statistic=27.98 (P<0.0001).

heart failure were found to have elevated serum creatinines.<sup>21</sup> The present results confirm prior studies that have demonstrated that renal impairment is strongly associated with outcomes in heart failure patients with systolic dysfunction.<sup>16–21</sup> We have extended the evidence base by confirming the importance of renal insufficiency in heart failure patients with diastolic dysfunction and those who are receiving currently recommended therapies for CHF. Also, we have confirmed that although anemia is associated with adverse outcomes, the risks from renal insufficiency persist even after adjustment for hemoglobin (along with all other known covariates).

Why is renal insufficiency associated with poorer outcomes in patients with heart failure? Although it has been speculated that this may be attributable, at least in part, to more advanced heart failure, excess comorbidities, and/or therapeutic nihilism in patients with concomitant renal insufficiency (who are less likely to receive proven effi-

TABLE 2. Multivariate Predictors of All-Cause Mortality During Median 2.5-Year Follow-Up, by Cox Proportional Hazards Model

Variable	Р	Hazard Ratio	95% CI
Serum creatinine (per 1-µmol/L increase)	0.002	1.002	1.001–1.003
Age (per 1-year increase)	< 0.001	1.03	1.02-1.04
Female	< 0.001	0.63	0.49–0.80
NYHA class III/IV	< 0.001	1.92	1.52-2.43
$\beta$ -Blockers	< 0.001	0.57	0.45-0.72
Spironolactone	0.001	0.13	0.04-0.42
Other vasodilators	0.001	0.41	0.24-0.69
Systolic dysfunction	0.002	1.54	1.18-2.02
ACE inhibitor	0.001	0.60	0.45-0.81

Although only those variables that were statistically significant are reported in this table, other variables entered in the Cox proportional hazards analysis included ischemic origin, ejection fraction, weight, diastolic blood pressure, hemoglobin, serum sodium, presence of edema, use of loop diuretics, and history of hypertension, ventricular arrhythmias, atrial arrhythmias, or chronic obstructive pulmonary disease. cacious therapies for either the index condition or the comorbidities),<sup>28</sup> we did adjust for these factors in our analyses. It has also been speculated that patients with renal insufficiency are at higher risk for drug toxicities and thus do not obtain the same benefits from medications shown to be efficacious in the healthier patients enrolled in trials.<sup>28</sup> However, like investigators from the Cooperative Cardiovascular Project, we demonstrated similar associations between survival and the use of ACE inhibitors and  $\beta$ -blockers in patients with renal insufficiency as in those patients without renal dysfunction.29 Furthermore, subgroup analyses from the Heart Outcomes Prevention Evaluation (HOPE) and the Cardiac Insufficiency BIsoprolol Study II (CIBIS II) trial confirmed that ramipril and bisoprolol were equally efficacious and safe in patients with and without mild to moderate renal insufficiency.7,30 Studies demonstrating improvements in cardiac function after renal transplantation in patients with primary kidney disease suggest that renal insufficiency may be more than a marker for heart failure severity and instead may play a causative role in the progression of heart failure.<sup>31</sup> For example, renal insufficiency is associated with multiple changes in vascular pathobiology that may worsen cardiovascular outcomes, including abnormalities in the coagulation/fibrinolytic systems, abnormal vascular calcification (due to elevated calcium-phosphorus products), endothelial dysfunction, hyperhomocystinemia, insulin resistance, elevated levels of C-reactive protein, disruptions in the endothelin/nitric oxide balance, electrolyte perturbations predisposing to arrhythmias, and hyperactivation of the sympathetic nervous and renin-angiotensin systems.<sup>32</sup> Finally, because renal blood flow is affected proportionally to a greater extent than cardiac output in systolic failure, it is entirely plausible that creatinine clearance would be a better indicator of functional capacity than any other clinical or laboratory signs.33

There are some potential limitations with the present study. First, we used each patient's baseline weight in calculating their creatinine clearance. Although fewer than 25% of the patients in the present study were believed to be fluid overloaded on examination by experienced heart failure clinicians, it is possible that the baseline weight of some patients was higher than their true "dry" weights. This would tend to overestimate each patient's creatinine clearance. Also, calculated creatinine clearance tends to overestimate glomerular filtration rate.<sup>34</sup> However, both of these biases would work to weaken any observed association between glomerular filtration rate and cardiovascular outcomes, which suggests that if anything, the present data may underestimate the magnitude of the association between renal function and outcomes. We elected to use the Cockcroft-Gault formula because the Modification of Diet in Renal Disease equation has not yet been validated in the elderly and may not perform well in people with normal serum creatinine levels.35 Second, we were unable to adjust for unmeasured confounders (such as C-reactive protein levels, lipid profiles, or homocysteine levels) that may be important in the pathobiology of the increased risk in renal insufficiency. Additional studies are needed to carefully examine baseline differences in these factors in patients with and without renal insufficiency and the impact of therapy for these variables on subsequent clinical outcomes. Third, our cohort was derived from patients referred to our specialized heart failure clinic; as such, it does not represent an unselected population of CHF patients. However, our sample is consecutive and similar demographically and clinically to heart failure cohorts recruited in the community,<sup>1,27,36</sup> the diagnoses of heart failure and comorbidities were rigorously confirmed at baseline, left ventricular ejection fraction and serum creatinine were assessed objectively at baseline, and all clinical and laboratory data were collected prospectively during follow-up. Indeed, we believe that the data from our cohort of patients are not subject to the misclassification biases that may arise when heart failure cohorts are assembled in the community from multiple physicians and without objective assessments of left ventricular ejection fraction. Finally, we did not have any data on urinalyses or structural abnormalities of the kidneys in these patients; thus, we cannot definitively classify patients with creatinine clearances between 60 and 90 mL/min as having kidney disease or not. As such, we restricted our estimates of the prevalence of renal insufficiency and the impact of kidney disease on the effectiveness of ACE inhibitors and  $\beta$ -blockers to only those patients with estimated creatinine clearances <60 mL/min.

In summary, we found a higher prevalence of renal insufficiency in patients with heart failure than previously reported. Also, we have shown that renal insufficiency is a powerful independent prognostic factor in heart failure and that the association is similar in those patients with diastolic dysfunction and those with systolic dysfunction. Finally, we found that ACE inhibitors and  $\beta$ -blockers were associated with similar reductions in mortality in patients with and without renal insufficiency but were less often prescribed in patients with renal insufficiency. We believe that heart failure patients with renal insufficiency should be considered high risk irrespective of their functional class or other cardiovascular risk factors, and as such, every attempt should be made to maximally apply proven efficacious therapies in these patients.

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