Renal Insufficiency as an Independent Predictor of Mortality Among Women With Heart Failure

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OBJECTIVES   We sought to explore the association between renal insufficiency and mortality among women with heart failure (HF) and to evaluate this risk by the presence of preserved or depressed systolic function.

BACKGROUND   Although HF is common in older women, little is known about their risk factors for mortality.

METHODS   This prospective cohort study retrospectively analyzed data from the Heart and Estrogen/progestin Replacement Study (HERS). Of the 2,763 women in HERS, 702 had HF. Renal function was categorized as creatinine clearance (CrCl) >60 ml/min, 40 to 60 ml/min, and <40 ml/min. We used proportional hazards models to evaluate the association between renal insufficiency and mortality.

RESULTS   Over a mean 5.8 years, 228 women with HF died (32%). Renal insufficiency was strongly associated with mortality, even after adjustment for co-morbid conditions, systolic function, and medications (adjusted hazard ratio [HR] 1.53, 95% confidence interval [CI] 1.09 to 2.16 for CrCl 40 to 60 ml/min; adjusted HR 2.40, 95% CI 1.60 to 3.62 for CrCl <40 ml/min). Preserved or depressed systolic function did not modify the association between renal insufficiency and mortality risk, but the use of angiotensin-converting enzyme (ACE) inhibitors did modify this risk (ACE users: adjusted HR = 0.9, 95% CI 0.6 to 1.6; ACE nonusers: adjusted HR 2.1, 95% CI 1.3 to 3.2; p = 0.02 for interaction). Compared with other risk factors for mortality, renal insufficiency had the highest population attributable risk (27%).

CONCLUSIONS   Renal insufficiency was a major predictor of mortality among women with HF and preserved or depressed systolic function. This risk was attenuated by the use of ACE inhibitors.   (J Am Coll Cardiol 2004;44:1593–600) © 2004 by the American College of Cardiology Foundation

Heart failure (HF) is common among older women and is associated with a high rate of mortality (1,2). However, little is known about the prognostic factors associated with mortality among women with HF, partly because of the small numbers of women included in HF clinical trials (3).

In studies that included primarily men, end-stage renal disease was associated with high rates of mortality among individuals with HF (4), and even moderate degrees of renal insufficiency may increase the risk of death (5–11). Assessing the independent association between renal insufficiency and mortality in HF is challenging, however, because renal insufficiency is associated with higher rates of other cardiovascular risk factors, such as diabetes and hypertension, which may explain the elevated mortality risk.

The association between mild to moderate renal insufficiency and mortality among women with HF has not been investigated. Women with HF are known to have higher rates of diabetes and hypertension than do men with HF (12), potentially accounting for any association between renal insufficiency and mortality in this population. Additionally, women are known to have higher rates of HF with preserved systolic function than do men (13,14), and an association between renal insufficiency and mortality has not been as well studied for this type of HF.

To determine whether renal insufficiency is a predictor of mortality in women with HF, we used data from women with HF who were participants in the Heart and Estrogen/progestin Replacement Study (HERS), a randomized, controlled trial of the effects of hormone therapy on cardiovascular outcomes among women with established coronary disease.

METHODS

The HERS methods and main findings have been described (15,16). Briefly, participants were postmenopausal women with known coronary disease, as defined by a previous myocardial infarction, coronary artery bypass graft surgery, percutaneous transluminal coronary angioplasty, or angiographic evidence of ≥50% narrowing of one or more major coronary arteries. Women were excluded if they were older than 79 years of age, used hormones within three months, or had a previous hysterectomy, a coronary event within the six months before randomization, serum triglyceride levels >3.39 mmol/l (300 mg/dl), or a history of conditions that would contraindicate estrogen therapy (16). Participants were randomly assigned within clinical centers to 0.625 mg

Abbreviations and Acronyms

ACE = angiotensin-converting enzyme
CI   = confidence interval
CrCl = creatinine clearance
ECG = electrocardiogram/electrocardiographic
HERS = Heart and Estrogen/progestin Replacement
         Study
HF   = heart failure
HR   = hazard ratio
LVEF = left ventricular ejection fraction
NYHA = New York Heart Association

of conjugated equine estrogen plus 2.5 mg of medroxypro-gesterone acetate in one tablet daily (n = 1,380) or a placebo of identical appearance (n = 1,383). The institutional review boards at the coordinating center and each of the 20 HERS clinical centers approved the protocol, and all participants provided written, informed consent.

The HERS randomized, controlled trial was conducted over 4.1 years. After the conclusion of the trial, women were unblinded to treatment assignment and were observed for an additional 2.7 years, on average (HERS-II) [17]. Suspected outcome events were either reported by participants to the clinical center staff or were identified via participant interviews that were conducted every four months. Records of all hospitalizations were reviewed by an independent morbidity and mortality subcommittee that adjudicated all suspected outcome events, including hospitalizations for HF. Attributing an admission to HF was made on the basis of the judgment of these adjudicators, who considered multiple factors (clinical presentation, radiographic findings, physician diagnosis, and treatment). A hospitalization was attributed to HF if one or more of the following criteria were present in the medical record: signs and symptoms of HF, chest x-ray consistent with pulmonary edema, or treatment with intravenous diuretics.

At the baseline interview, participants provided a self-report of their medical history. On baseline physical examination, a physician assessed signs (jugular venous distention, third heart sound, significant murmurs, pulmonary rales, and peripheral edema) and symptoms (New York Heart Association [NYHA] functional classification) of HF. Women with NYHA functional class IV at the baseline interview were excluded from HERS.

Of the 2,763 women enrolled in the HERS trial, we excluded 29 who had a body mass index <18.5 kg/m². The HERS participants were included in this analysis if they had either a history of HF in their medical history or baseline interview (n = 343) or developed HF during the HERS or HERS-II follow-up period, as defined by signs and symptoms of HF on an annual visit or hospitalization for HF (n = 359). Participants were included in this analysis and contributed to follow-up data only after they met one of these eligibility criteria.

Potential predictors of mortality. Creatinine was measured from serum samples, and body mass index was calculated from height and weight measured at baseline. These were used to estimate creatinine clearance (CrCl) using the Cockcroft-Gault equation [18]. Renal function was categorized based on estimated CrCl: >60 ml/min, 40 to 60 ml/min, and <40 ml/min. These categories were modified from the National Kidney Foundation cutpoints of >60 ml/min, 30 to 60 ml/min, and <30 ml/min, because few HERS participants had CrCl <30 ml/min [19].

Demographic characteristics, behavioral risk factors, medical history, and medication use were determined by participant self-reporting on enrollment in HERS. Left ventricular hypertrophy was determined from the baseline electrocardiogram (ECG). Fasting levels of high-density lipoprotein cholesterol, lipoprotein(a), and triglycerides were measured by a central laboratory, and low-density lipoprotein cholesterol levels were calculated using the Friedewald equation [20].

Left ventricular ejection fraction (LVEF), determined from a chart review at baseline, was used to classify participants as having preserved systolic function (LVEF ≥50%) and depressed systolic function (LVEF <50%). Because echocardiography was not a required test in HERS, LVEF was unavailable in 230 of the 702 participants in this analysis.

Systolic blood pressure and NYHA functional classification were determined at each annual visit and included in some models as time-dependent co-variates. Atrial fibrillation and left bundle branch block were determined based on annual ECGs and were also handled in the models as time-dependent co-variates.

Nonfatal myocardial infarction—a primary outcome in HERS—was diagnosed using an algorithm based on ischemic symptoms, ECG abnormalities, and elevated cardiac enzymes levels [16]. For this analysis, nonfatal myocardial infarction during the observation period was included as a time-dependent predictor for all-cause mortality.

Medication use determined at four-month intervals, based on participant self-reporting, was included in our models as a time-dependent co-variate. Once a medication was initiated, we considered the participant a user of this medication, even if it was subsequently discontinued; this avoids the potential bias that occurs because medications are often discontinued during the interval preceding death.

Outcome. Death from any cause, determined by the independent morbidity and mortality committee after review of death certificates, was the outcome for this analysis. We investigated the association between potential predictors and mortality that occurred during the combined HERS and HERS-II follow-up periods.

Statistical analysis. We used multivariable proportional hazards models to determine the association between categories of renal insufficiency and all-cause mortality. The follow-up time for women with incident HF after randomization was handled using left truncation until the time of

HF diagnosis, and the baseline hazard was stratified by prevalent versus incident cases. Co-variates included in these models were baseline values for each risk factor, except the number of myocardial infarctions, atrial fibrillation, left bundle branch block, and use of medications, which were included as time-dependent co-variates. We hypothesized that the association between renal insufficiency and mortality might vary by the presence of diabetes, hypertension, systolic dysfunction, or use of angiotensin-converting enzyme (ACE) inhibitors, beta-blockers, calcium channel blockers, or digoxin. We tested for interactions between categories of renal dysfunction, and these variables and considered p < 0.1 to indicate a statistically significant interaction.

We used penalized smooth splines to model the association of creatinine clearance as a continuous (rather than categorical) predictor of mortality. We used backwards selection techniques to identify risk factors that were associated with mortality at p < 0.1. We included medications as time-dependent co-variates in all of the models, but did not interpret hazards associated with their use because of concern for confounding by indication. We repeated the models without adjustment for medications and verified that the associations were unchanged.

We estimated population-attributable risk (PAR) for each risk factor as (21):

$$PAR = p \cdot (RH - 1) / (p \cdot [RH - 1])$$

where p is the prevalence of the risk factor at baseline and RH its adjusted hazard ratio (HR) from the multivariate Cox model for all-cause mortality. We used the baseline prevalence for each risk factor identified and the hazard ratio from the multivariate Cox model to estimate attributable risk for mortality.

Most analyses were performed in SAS version 8.2 (SAS Institute, Cary, North Carolina). The penalized spline fits were implemented in R (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Of the 702 women with HF and coronary disease, 283 had CrCl 40 to 60 ml/min (40%) and 122 had CrCl <40 (17%). The mean serum creatinine values that corresponded to each of these categories was 1.0 ± 0.2 mg/dl for CrCl >60 ml/min, 1.2 ± 0.2 mg/dl for CrCl 40 to 60 ml/min, and 1.6 ± 0.5 mg/dl for CrCl <40 ml/min. Those with more severe renal dysfunction were older, more likely to have elevated systolic blood pressure, a history of coronary artery bypass grafting, and a lower body mass index, more likely to be taking diuretics and digoxin, and less likely to be taking beta-blockers (Table 1).

During 5.8 ± 1.7 years of average observation, 228 (32%) of the 702 women died. Women with CrCl >60 ml/min had an annual mortality rate of 5% compared with 7.5% for those with CrCl 40 to 60 ml/min and 14% for those with CrCl <40 ml/min (p < 0.001 for trend). We observed a

strong and graded association between the extent of renal insufficiency and mortality (Table 2). After adjusting for demographic characteristics, co-morbid conditions, LVEF, and use of medications, women with CrCl <40 ml/min had a more than twofold higher risk of death compared with those with CrCl >60 ml/min (adjusted HR 2.40, 95% CI 1.60 to 3.62). Even women with CrCl 40 to 60 ml/min still had a 50% increased risk of death compared with those with CrCl >60 ml/min (adjusted HR 1.53, 95% CI 1.09 to 2.16).

To confirm our a priori cutpoints for CrCl, we explored the mortality risk associated with renal insufficiency for each 10-ml/min increment below a CrCl of 80 ml/min. The risk of death appeared to increase at values <60 ml/min and accelerated upward below CrCl values <40 ml/min (Fig. 1). The HRs for each of these incremental decreases in CrCl are presented in Table 3.

Renal insufficiency and ventricular function. Of the 282 women with HF and documented preserved systolic function, over half had renal insufficiency: 41% with CrCl 40 to 60 ml/min and 15% with CrCl <40 ml/min. Over one-half of the 190 women with documented depressed systolic function had renal insufficiency: 35% with CrCl 40 to 60 ml/min and 23% with CrCl <40 ml/min. The association between renal function and mortality did not differ by preserved or depressed systolic function (for interaction: p = 0.38 for CrCl 40 to 60 ml/min, p = 0.23 for CrCl <40 ml/min).

Renal insufficiency and ACE inhibition. We observed a difference in the association between renal insufficiency and mortality among users and nonusers of ACE inhibitors. Women with creatinine clearance 40 to 60 ml/min using ACE inhibitors had no increased risk of death, compared with those with CrCl >60 ml/min (adjusted HR 0.9, 95% CI 0.6 to 1.6) (Table 4). By contrast, women with CrCl 40 to 60 ml/min who did not use ACE inhibitors had a twofold risk of death, compared with those with CrCl >60 ml/min (adjusted HR 2.1, 95% CI 1.3 to 3.2, p = 0.02 for interaction). The risk of death also differed among users and nonusers of ACE inhibitors with CrCl <40 ml/min (adjusted HR 1.7, 95% CI 0.9 to 3.0 for ACE users vs. HR 3.1, 95% CI 1.8 to 5.0 for nonusers; p = 0.1 for interaction).

We found no evidence that the risk of death associated with renal insufficiency varied by the presence of diabetes, elevated systolic blood pressure, or the use of beta-blockers, calcium channel blockers, or digoxin.

Other risk factors associated with mortality. Using backward selection techniques and the factors listed in Table 1, we identified nine risk factors that were significantly associated with mortality on multivariate analysis (Table 5). Women with symptoms of HF (defined as NYHA functional class III or IV) had double the mortality risk compared with those with minimal symptoms; even NYHA functional class II conferred a small but significant increased risk of mortality. Atrial fibrillation, diabetes, and depressed CrCl were also strongly associated with mortality. Multiple

Table 1. Characteristics of 702 Women With Heart Failure and Coronary Disease by Degree of Renal Insufficiency

	CrCl			
	>60 ml/min (n = 297)	40–60 ml/min (n = 283)	<40 ml/min (n = 122)	p Value for Trend
Demographic characteristics				
Age (yrs, mean ± SD)	64 ± 6	70 ± 6	72 ± 5	<0.001
Age >70 yrs	20	52	75	<0.001
Race/ethnicity				
Black	13	10	12	0.4
Other non-white race	5	4	3	
Heart failure characteristics				
New York Heart Association functional class				
II	11	12	15	0.1
III/IV	1	2	7	
Left ventricular ejection fraction				
≥50%	42	41	34	0.7
Missing	31	36	31	
Risk factors				
Number of myocardial infarctions				
1	49	48	53	0.2
>1	9	11	12	
Systolic blood pressure				
<100 mm Hg	2	1	2	0.003
>140 mm Hg	32	47	44	
Pulse >100 beats	0.3	0.7	0.8	0.5
Atrial fibrillation	2	2	5	0.1
Left bundle branch block	11	11	16	0.2
Left ventricular hypertrophy	13	15	14	0.6
History of coronary artery bypass grafting	40	48	53	0.008
History of percutaneous transluminal coronary angiography	43	35	34	0.03
Diabetes on medication	37	29	32	0.1
Little or no exercise	43	29	41	0.1
Alcohol consumption				
1–7 drinks/week	23	26	26	0.5
>7 drinks/week	3	3	2	
Smoking status				
Former smoker	50	50	48	0.09
Current smoker	15	13	9	
Body mass index				
<22 kg/m^2	1	7	16	<0.001
≥25–30 kg/m^2	29	40	42	
>30 kg/m^2	65	28	16	
Serum sodium <137 mmol/l	4	4	5	0.8
Low-density lipoprotein cholesterol >130 mg/dl	66	62	62	0.4
High-density lipoprotein cholesterol <35 mg/dl	12	11	14	0.8
Triglycerides >200 mg/dl	32	29	36	0.7
Lipoprotein (a) >25.3 mg/dl	53	54	51	0.8
Angiotensin-converting enzyme inhibitor use	40	44	48	0.1
Beta-blocker use	44	40	30	0.009
Calcium channel blocker use	61	65	71	0.04
Digoxin use	24	29	35	0.02
Diuretic use	63	64	72	0.005
Statin use	42	45	40	0.9
Aspirin use	81	79	75	0.2

CrCl = creatinine clearance.

myocardial infarctions were associated with an increased risk of death, but a single myocardial infarction was not. Compared with women who had never smoked, current smokers, but not former smokers, had an increased risk of death. Age over 70 years, depressed systolic function, and limited exercise were also independently associated with an increased risk of death.

Population-attributable risk. Of the risk factors listed in Table 5, renal insufficiency had the greatest population-attributable risk for mortality (27%) (Fig. 2). By contrast,

Table 2. Mortality Associated With Renal Insufficiency Among Women With Heart Failure and Coronary Disease

	Deaths/N*	Unadjusted HR (95% CI)	Adjusted HR for Demographic Characteristics† (95% CI)	Plus Comorbid Conditions‡ HR (95% CI)	Plus LVEF§ HR (95% CI)	Plus Medications¶ HR (95% CI)
CrCl						
>60 ml/min	69/297	1.0	1.0	1.0	1.0	1.0
40–60 ml/min	94/283	1.54 (1.13–2.11)	1.53 (1.10–2.15)	1.58 (1.13–2.22)	1.60 (1.14–2.25)	1.53 (1.09–2.16)
<40 ml/min	65/122	2.91 (2.07–4.11)	2.82 (1.90–4.18)	2.67 (1.79–3.98)	2.57 (1.72–3.84)	2.40 (1.60–3.62)

*Number dead during observation period/total number in category. †Adjusted for age in years and race/ethnicity. ‡Adjusted for age, race/ethnicity, diabetes, systolic blood pressure >140 mm Hg and number of myocardial infarctions (last variable included as a time-dependent co-variate). §Adjusted for age, race/ethnicity, diabetes, systolic blood pressure >140 mm Hg, number of myocardial infarctions, and left ventricular ejection fraction (LVEF). ¶Adjusted for age, race/ethnicity, diabetes, systolic blood pressure >140 mm Hg, number of myocardial infarctions, LVEF, and use of angiotensin-converting enzyme inhibitors, beta-blockers, aspirin, calcium channel blockers, diuretics, digoxin, and statins (medications included as time-dependent co-variates).

CI = confidence interval; CrCl = creatinine clearance; HR = hazard ratio.

atrial fibrillation, NYHA functional class III/IV, and more than one myocardial infarction were each responsible for <5% attributable risk. An LVEF was included in the model to estimate adjusted HRs, but population-attributable risk was not calculated for LVEF because of the missing values.

DISCUSSION

We found that renal insufficiency, even when mild, was independently associated with mortality among women with HF and coronary disease. This association between renal insufficiency and mortality was independent of diabetes, hypertension, and other risk factors for mortality and did not vary by the presence of preserved or depressed systolic function. There appeared to be no increased risk of mortality among women with mild renal insufficiency (CrCl 40 to 60 ml/min) who were using ACE inhibitors. We identified eight other independent risk factors for mortality among women with HF and coronary disease. Of these factors, renal insufficiency was the most common and was associated with the greatest population-attributable risk for mortality. These results highlight the importance of renal insufficiency as a prevalent and potent risk factor for death among women with HF, even among those with preserved systolic function, and raises the hypothesis that this risk could be modified by appropriate medical therapy.
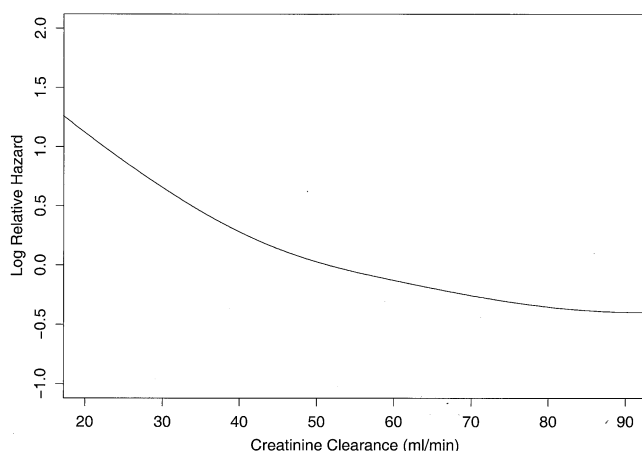
An increased risk of mortality among persons with mild to moderate renal insufficiency has previously been observed predominantly among individuals with HF with depressed systolic function (5–7,10,11,22), and many of these studies included only small numbers of women (6,7,10). Several mechanisms have been proposed to explain this increased mortality risk, including the possibilities that renal insufficiency is a marker for more severe HF, is associated with a higher burden of co-morbid illness such as diabetes, and may limit the use of effective HF medications, especially ACE inhibitors. In our analysis, we adjusted for HF severity and co-morbid illnesses and still observed an independent association between mild renal insufficiency and mortality. Additionally, in contrast to previous studies, we accounted for multiple medications used over the entire observation period and still observe the association of renal insufficiency with mortality, suggesting that these proposed mechanisms thus proposed are unlikely. Alternative explanations include the possibility that renal insufficiency may accelerate the progression of HF and thus increase the risk of mortality or that renal insufficiency may be a marker for the same underlying process causing mortality from HF (e.g., advanced microvascular disease). More animal and human studies are needed to determine the nature of the relationship between renal insufficiency and HF, and additional investigations should also focus on whether stabilization of

Figure 1. Risk of death associated with level of creatinine clearance among women with heart failure and coronary disease.

Table 3. Risk of Death Associated With 10-ml/min Increment Decreases of Creatinine Clearance Among Women With Heart Failure and Coronary Disease

	n (%)	Adjusted HR* (95% CI)	p Value
CrCl (ml/min)			
>80	118 (17)	1.0	—
71–80	76 (11)	0.9 (0.5–1.8)	0.8
61–70	103 (15)	1.0 (0.6–1.8)	0.9
51–60	144 (20)	1.5 (0.9–2.4)	0.1
41–50	139 (20)	1.6 (1.0–2.7)	0.05
31–40	91 (13)	2.0 (1.2–3.4)	0.01
≤30	31 (4)	4.7 (2.5–8.8)	<0.001

*Adjusted for age, race/ethnicity, diabetes, systolic blood pressure >140 mm Hg, number of myocardial infarctions, left ventricular ejection fraction, and use of beta-blockers, aspirin, calcium channel blockers, diuretics, digoxin, and statins.
Abbreviations as in Table 2.

Table 4. Association Between Renal Insufficiency and Mortality, Stratified by Use of Angiotensin-Converting Enzyme Inhibitors

	ACE Inhibitors (n = 460)			No ACE Inhibitors (n = 242)		
	n	Adjusted HR§ (95% CI)	p Value	n	Adjusted HR§ (95% CI)	p Value
CrCl						
>60 ml/min	183	1.0	—	114	1.0	—
40–60 ml/min*	189	0.9 (0.6–1.6)	0.8	94	2.1 (1.3–3.2)	0.001
<40 ml/min†	88	1.7 (0.9–3.0)	0.1	34	3.1 (1.8–5.0)	<0.001

*p for interaction = 0.02 for creatinine clearance 40–60 ml/min. †For interaction = 0.1 for creatinine clearance <40 ml/min. ACE inhibitor use defined as time-dependent co-variate. Participants who subsequently discontinued ACE use are defined as users. §Adjusted for age, race/ethnicity, diabetes, systolic blood pressure >140 mm Hg, number of myocardial infarctions, left ventricular ejection fraction, and use of beta-blockers, aspirin, calcium channel blockers, diuretics, digoxin, and statins.
ACE = angiotensin-converting enzyme; other abbreviations as in Table 2.

renal insufficiency may be associated with improved HF mortality.

Our study offers preliminary evidence for the beneficial effect of ACE inhibitors on mortality in the setting of mild to moderate renal insufficiency. Women with mild to moderate renal impairment (CrCl 40 to 60 ml/min) who used ACE inhibitors had a similar mortality risk to women with CrCl >60 ml/min. Currently, guidance for clinicians caring for patients who have HF and renal insufficiency is lacking, as no clinical trials have focused on treatment of these patients, and persons with renal insufficiency are poorly represented in clinical trials (23). More research in this high-risk population is needed, particularly to guide the dosing and administration of potentially beneficial medications like ACE inhibitors and other treatments, including angiotensin receptor blockers and spironolactone, as renal insufficiency worsens.

Our study included women with both preserved and depressed systolic function, and we found renal insufficiency to predict mortality independent of systolic function. Heart failure with preserved systolic function is known to be a more common presentation of HF in women (14). Currently, there are few clinical trials completed that evaluated the appropriate management of patients with HF and preserved systolic function (24). Future clinical trials of the treatment for HF with preserved systolic function should consider the prognostic importance of renal insufficiency and investigate the effectiveness of treatment strategies as renal insufficiency worsens.

We identified several other risk factors for mortality among these women with HF and coronary disease. The strong association between functional limitations due to HF symptoms and all-cause mortality highlights HF as a progressive symptomatic disorder in which patients often move through worsening stages of symptoms to death. Like others, we observed that the association between NYHA functional class and death is independent of systolic function (25–27); this observation is of particular importance in the management of women with HF because of the high prevalence of preserved systolic function. More study is necessary to determine the natural history of HF with preserved LVEF, the progression of symptoms, and the

Table 5. Adjusted Hazard Ratios Associated With Risk Factors for All-Cause Mortality Among Women With Heart Failure and Coronary Disease

	n (%)	Adjusted HR* (95% CI)	p Value
NYHA functional class† (vs. class 0 or 1)			
II	83 (12)	1.6 (1.1–2.4)	0.03
III/IV	18 (3)	2.0 (1.1–3.8)	0.03
Atrial fibrillation†	19 (3)	1.9 (1.2–3.1)	0.006
Diabetes	230 (33)	1.8 (1.3–2.4)	<0.001
CrCl <60 ml/min	405 (58)	1.6 (1.2–2.2)	0.003
Number of myocardial infarctions† (vs. no myocardial infarctions)			
1	346 (49)	0.9 (0.6–1.2)	0.35
>1	52 (8)	1.6 (1.1–2.3)	0.02
Smoking (vs. never smoked)			
Former smoker		1.0 (0.7–1.3)	0.90
Current smoker	94 (13)	1.6 (1.1–2.5)	0.02
Age >70 yrs	299 (42)	1.5 (1.1–2.0)	0.009
Left ventricular ejection fraction <50%	190 (27)	1.5 (1.1–2.2)	0.02
Little or no exercise	262 (37)	1.3 (1.0–1.8)	0.04

*Also adjusted for medications, race (African-American vs. white, HR 0.9, 95% CI 0.6–1.4, p = 0.78), and left bundle branch block (HR 1.3, 95% CI 1.0–1.8, p = 0.07). †These variables are included in the model as time-varying co-variates. The number (%) represents values at baseline for each variable.
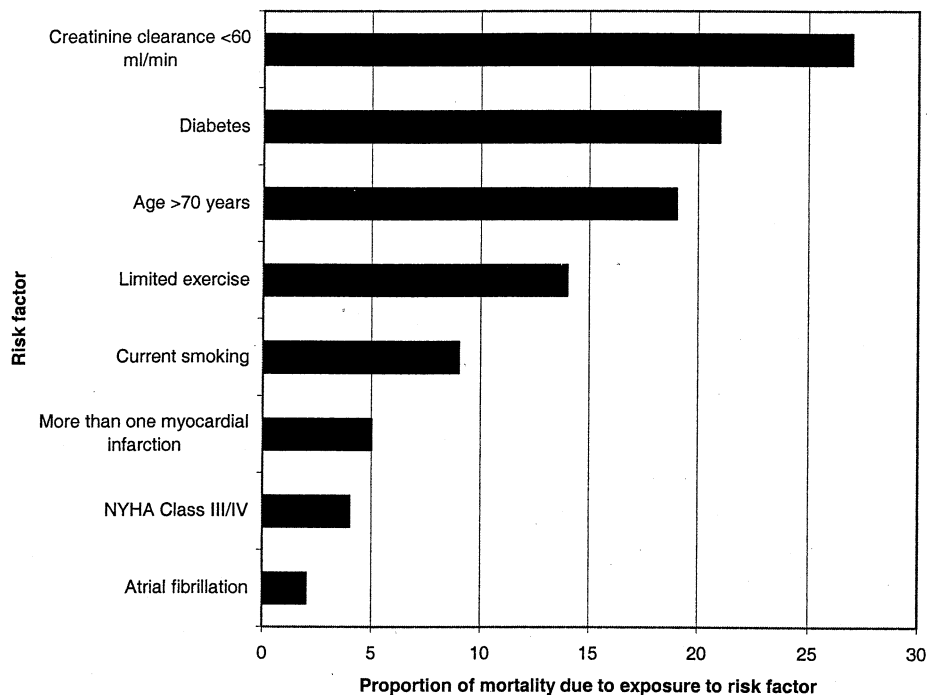NYHA = New York Heart Association; other abbreviations as in Table 2.

Figure 2. Population-attributable risk associated with risk factors for mortality among women with heart failure and coronary disease. NYHA = New York Heart Association.

identification of treatments that may improve clinical outcomes. The identification of decreased functional status is important among all patients, especially the elderly. Among patients with depressed LVEF, the identification of decreased functional status due to HF symptoms is crucial, because it should prompt the initiation of pharmacologic and perhaps nonpharmacologic therapies that have been shown to improve prognosis in symptomatic women.

Clinicians caring for women with HF must pay particular attention to the progression of renal insufficiency, as this is a common risk factor that carries important prognostic significance. Assessment of functional status is also crucial for both for guiding therapies as well as educating patients about the progressive nature of this disease. In addition to the initiation of appropriate pharmacotherapy, modifiable risk factors such as tobacco use and limited exercise should be addressed. A meta-analysis of several small trials suggests that exercise training programs can reduce mortality among patients with HF (28). Our study supports the possibility of limited exercise as an independent (and potentially modifiable) risk factor, because we observe this association independent of HF symptoms.

One limitation of this analysis is that our study was composed of women who were voluntary participants in a clinical trial. The entry criteria in HERS excluded women who were severely infirm, which likely represented the women most symptomatic with HF who would have had the greatest mortality risk. Additionally, clinical trial participants are likely to be healthier and more health conscious than typical community-dwelling women with HF. As a result of these differences, the associations that we detected

here could be somewhat biased and the attributable risk may be different in other populations. An additional limitation is that the assessment of LVEF was based on chart review at baseline, the measures of LVEF were not standardized, and a significant percentage was missing.

Conclusions. Renal insufficiency is a common and powerful predictor of mortality among women with HF. The important prognostic implications of renal insufficiency among women with HF and the dearth of information on the pathophysiology and clinical management of patients with both cardiac and renal insufficiency suggest fertile ground for future research that could lead to reductions in mortality from these common and deadly diseases.

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