Journal of the American College of Cardiology
© 2004 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 44, No. 8, 2004
ISSN 0735-1097/04/$30.00
doi:10.1016/j.jacc.2004.06.072

The Association Among Renal Insufficiency, Pharmacotherapy, and Outcomes in 6,427 Patients With Heart Failure and Coronary Artery Disease

Justin Ezekowitz, MB, BCH, MSC,* Finlay A. McAlister, MD, MSC,† Karin H. Humphries, MBA, DSC,‡ Colleen M. Norris, PHD,§ Marcello Tonelli, MD, MSC,‖ William A. Ghali, MD, MPH,¶ Merril L. Knudtson, MD,# for the APPROACH Investigators

Edmonton, Vancouver, and Calgary, Canada

OBJECTIVES This study was designed to examine the use of cardiovascular medications and outcomes in patients with heart failure (HF) and renal dysfunction.

BACKGROUND Renal insufficiency is associated with poorer outcomes in patients with HF, but the mechanisms are uncertain. In particular, the degree of therapeutic nihilism in these patients, and whether it is appropriate, is unclear.

METHODS This was a prospective cohort study with a one-year follow-up.

RESULTS In 6,427 patients with cardiologist-diagnosed HF and angiographically proven coronary artery disease (mean age 69 years; 65% men; one-year mortality, 10%), 39% had creatinine clearances <60 ml/min. Patients with renal insufficiency were less likely to be prescribed angiotensin-converting enzyme (ACE) inhibitors, beta-blockers, statins, or aspirin (all $p < 0.001$). However, users of aspirin (odds ratio [OR] 0.69, 95% confidence interval [CI] 0.57 to 0.85), statins (OR 0.79, 95% CI 0.64 to 0.97), and beta-blockers (OR 0.75, 95% CI 0.62 to 0.90) were less likely to die in the subsequent 12 months than nonusers, irrespective of renal function (all OR adjusted for covariates including atherosclerotic burden and ejection fraction). Although ACE inhibitor users with creatinine clearances ≥60 ml/min had lower 12-month mortality (OR 0.72, 95% CI 0.48 to 0.99), ACE inhibitor users with clearances <60 ml/min did not (OR 1.21, 95% CI 0.97 to 1.51).

CONCLUSIONS Renal insufficiency is common in patients with HF and coronary artery disease, and these patients have more advanced coronary atherosclerosis. Patients with renal insufficiency are less likely to be prescribed efficacious therapies, but have better outcomes if they receive these medications. (J Am Coll Cardiol 2004;44:1587–92) © 2004 by the American College of Cardiology Foundation

Renal insufficiency is common in patients with heart failure (HF) and is an adverse prognostic factor (1–7). Theories advocating increased risk when HF and renal disease coexist include a higher burden of comorbidities, increased toxicities from diagnostic procedures or therapies, accelerated atherosclerosis, or less use of proven efficacious therapies in patients with both conditions (8). Of note, this last explanation rests upon the assumption that trial-proven therapies (such as angiotensin-converting enzyme [ACE] inhibitors, beta-blockers, aspirin, and statins in HF patients with coronary disease) will improve outcomes even in patients with renal insufficiency. However, until trials that include patients with anything more than mild renal insufficiency are conducted, this assumption remains largely untested, and we must rely on observational studies to estimate the effectiveness and safety of therapies in these patients (9). Few such studies have been published and, of those that have, all but one (our previous study of 754 patients with HF from one center) (1) focused exclusively on patients with acute coronary syndromes (10–15). Thus, we designed this study to examine the use of cardiovascular medications and outcomes in patients with HF, coronary disease, and concomitant renal insufficiency.

METHODS

We combined data from the Alberta Provincial Program for Outcome Assessment in Coronary Heart Disease and the British Columbia Cardiac Registry; these prospective cohort studies compile data from all patients undergoing coronary angiography in Alberta and British Columbia (two Canadian provinces with a total population of 7.25 million in 2002). A

From the Divisions of *Cardiology, †General Internal Medicine, and ‖Nephrology, University of Alberta, Edmonton, Canada; ‡Division of Cardiology, University of British Columbia, Vancouver, Canada; §Faculty of Nursing, University of Alberta, Edmonton, Canada; and the Divisions of ¶General Internal Medicine and #Cardiology, University of Calgary, Calgary, Canada. Drs. McAlister, Tonelli, and Ghali are supported by the Alberta Heritage Foundation for Medical Research; Dr. McAlister is also supported by the Canadian Institutes of Health Research. Ms. Humphries is supported by the Michael Smith Foundation and Dr. Ghali is also supported by a Canada Research Chair. The Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease (APPROACH) Initiative is supported by the Weston Foundation, Merck Frosst Canada Inc., Guidant Corporation, Boston Scientific Ltd., Hoffman-La Roche Ltd., and Johnson and Johnson Inc.-Cordis.

Manuscript received March 1, 2004; revised manuscript received June 15, 2004, accepted June 22, 2004.

JACC Vol. 44, No. 8, 2004
October 19, 2004:1587–92

Abbreviations and Acronyms

ACE = angiotensin-converting enzyme
CAD = coronary artery disease
CI = confidence interval
HF = heart failure
LV = left ventricular
OR = odds ratio

full description of these datasets (including the variables collected and definitions used) has been published previously (16).

We restricted this analysis to patients with a diagnosis of HF assigned by their attending cardiologist before undergoing angiography who subsequently had coronary artery disease (CAD) (defined as >50% stenosis in at least one vessel) proven on angiography. Glomerular filtration rate was estimated using the previously validated Cockcroft-Gault formula with pre-catheterization serum creatinines, and patients were stratified into three groups: creatinine clearance ≥60 ml/min, 30 to 59 ml/min, and <30 ml/min (17).

Statistical analysis. Baseline characteristics of the study patients (classified into the three renal function strata) and their prescribed medications were compared by chi-square tests for dichotomous variables and analysis of variance for continuous variables. One-year crude mortality rates were calculated for patients who were/were not prescribed ACE inhibitors, aspirin, beta-blockers, and statins. To adjust for differences in baseline clinical characteristics and concomitant medication use, multiple logistic regression analysis with the backward stepwise selection technique was done to examine prognostic factors for one-year mortality, selecting all clinically important variables and other prespecified factors with $p < 0.25$ on bivariate analyses and a prevalence of at least 1%, and accepting statistical significance at $p < 0.05$. All first-order interactions were tested for statistical and clinical significance in the multivariate model (statistical significance was defined as $p < 0.05$; clinical significance was defined a priori as interaction ratios of ≥1.25 or ≤0.80) (18). An interaction ratio compares the effects of a treatment in the presence and absence of the other treatment: interaction ratios above 1.0 indicate synergy and interaction ratios below 1.0 indicate antagonism (18). Those factors that were independently associated with mortality in the entire cohort were included in logistic regression models (and, in a sensitivity analysis, Cox proportional hazards models) for each of the renal function strata to determine the associations of ACE inhibitors, beta-blockers, aspirin, and statins with mortality in each stratum.

RESULTS

The study cohort consisted of 6,427 patients with cardiologist-diagnosed HF and angiographically proven CAD: 47% of angiograms were done electively and 53% were done for acute coronary syndromes. Mean age was 69 years, and 10% of patients were older than 80 years at baseline (Table 1).

Three percent of the patients had end-stage renal disease requiring dialysis, and 39% had creatinine clearances <60 ml/min. One-year mortality was 10%, with higher death rates in women (14% vs. 8% in men, $p < 0.0001$) and older patients (6% in patients <65 years, 13% in those aged 65 to 80 years, and 22% in those >80, $p < 0.0001$). There was also a clear gradient in mortality across renal function strata: 5% in those with creatinine clearance ≥60 ml/min, 15% in those with clearances of 30 to 59 ml/min, and 28% in those with clearances <30 ml/min ($p < 0.001$). There were also gradients in medication use, with lower prescription rates for ACE inhibitors, beta-blockers, statins, and aspirin with more advanced renal insufficiency (Table 1). Patients with more advanced renal insufficiency had more comorbidities, greater coronary atherosclerotic burden, and lower ejection fractions (Table 1).

The crude mortality rates were significantly lower for users of beta-blockers, statins, and aspirin than for nonusers, irrespective of renal function (Figs. 1 and 2). The ACE inhibitors were associated with improved survival in patients with creatinine clearances ≥60 ml/min (Fig. 1), but not in those patients with clearances <60 ml/min (Fig. 2).

The multivariate predictors of one-year mortality are outlined in Table 2. Analyses of the Wald statistics revealed that the two most powerful prognostic factors were age and creatinine clearance; indeed, renal function was a stronger predictor of outcomes in this cohort of patients with ischemic HF than was coronary anatomy (Wald statistic 53 vs. 34). The one-year mortality risk increased by 0.2% for every μmol/l increase in serum creatinine.

Analyses adjusted for the variables in Table 2 (with the exception of serum creatinine) confirmed that use of beta-blockers, ACE inhibitors, statins, and aspirin were all associated with statistically significant better one-year survival in patients with HF, CAD, and a creatinine clearance ≥60 ml/min (Table 3). However, although statins and aspirin were also associated with improved survival in those patients with creatinine clearances of <60 ml/min (and beta-blockers were associated with a trend towards a survival benefit [odds ratio (OR) 0.85, 95% confidence interval (CI) 0.68 to 1.07]), ACE inhibitors were not (mortality OR 1.21, 95% CI 0.97 to 1.51). Although the interaction between ACE inhibitors and aspirin was not significant in the entire cohort ($p = 0.13$), there was a strong trend for a negative interaction on survival in those patients with creatinine clearance <60 ml/min that met our a priori definition of clinical significance ($p = 0.09$, OR for interaction term 0.56, 95% CI 0.28 to 1.11). There were no significant interactions between any of the other medications of interest, degree of renal function, and mortality.

The Cox proportional hazards analyses (adjusting for the variables in Table 2) confirmed the findings from our logistic regression analyses (Table 3).

Table 1. Characteristics of Patients With Cardiologist-Assigned Diagnosis of Heart Failure and Coronary Artery Disease Proven on Angiography

	Entire Cohort (n = 6,427)	Creatinine Clearance			p Value for Comparisons Across Renal Function Strata
		≥60 ml/min (n = 3,914)	30 to 59 ml/min (n = 2,047)	<30 ml/min (n = 466)	
Mean age (SD)	69 (11)	63 (10)	74 (8)	73 (11)	<0.001
Men, no. (%)	4,205 (65%)	2,874 (73%)	1,134 (55%)	197 (42%)	<0.001
Comorbidities					
Hypertension	2,487 (39%)	1,323 (34%)	894 (44%)	270 (58%)	<0.001
Hyperlipidemia	2,399 (37%)	1,491 (38%)	728 (36%)	180 (39%)	0.08
Diabetes mellitus	1,322 (21%)	717 (18%)	442 (22%)	163 (35%)	<0.001
Peripheral vascular disease	669 (10%)	302 (8%)	268 (13%)	99 (21%)	<0.001
Cerebrovascular disease	516 (8%)	224 (6%)	209 (10%)	83 (18%)	<0.001
Current smoker	861 (13%)	618 (16%)	197 (10%)	46 (10%)	<0.001
COPD	869 (14%)	423 (11%)	340 (17%)	106 (23%)	<0.001
Malignancy	309 (5%)	133 (3%)	136 (7%)	40 (9%)	<0.001
Prior myocardial infarct	2,168 (34%)	1,192 (30%)	767 (37%)	209 (45%)	<0.001
Prior CABG	572 (9%)	290 (7%)	219 (11%)	63 (14%)	<0.001
Prior PCI	117 (2%)	55 (1%)	47 (2%)	15 (3%)	0.009
Medications					
Aspirin	4,706 (73%)	2,946 (75%)	1,446 (71%)	314 (67%)	<0.001
ACE inhibitor or ARB	3,698 (58%)	2,228 (56%)	1,228 (60%)	242 (52%)	0.006
Beta-blocker	3,628 (56%)	2,287 (58%)	1,099 (54%)	242 (52%)	<0.001
Statin	2,545 (40%)	1,669 (43%)	716 (35%)	160 (34%)	<0.001
Thienopyridine	1,634 (25%)	1,062 (27%)	477 (23%)	95 (20%)	<0.001
Long-acting nitrates	2,458 (38%)	1,346 (35%)	891 (44%)	221 (47%)	<0.001
Warfarin	1,880 (29%)	1,119 (29%)	612 (30%)	149 (32%)	<0.001
Calcium channel blocker	1,419 (22%)	777 (20%)	497 (24%)	145 (31%)	<0.001
Coronary anatomy					
1-vessel disease	1,965 (31%)	1,331 (34%)	529 (26%)	105 (23%)	<0.001
2-vessel disease	967 (15%)	604 (15%)	304 (15%)	59 (13%)	0.27
3-vessel disease	1,434 (22%)	844 (22%)	466 (23%)	124 (27%)	0.04
Proximal left anterior descending involvement	1,335 (21%)	755 (19%)	465 (23%)	115 (25%)	<0.001
Left main disease	726 (11%)	380 (10%)	283 (14%)	63 (14%)	<0.001
Myocardium at risk, mean % (SD)	55% (33%)	52% (32%)	57% (33%)	59% (32%)	<0.001
LVEF, mean (SD)	37 (18)	39 (15)	36 (19)	28 (24)	<0.001

Data are presented as frequency (% of column total) unless otherwise stated.

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; CABG = coronary artery bypass graft; COPD = chronic obstructive pulmonary disease; LVEF = left ventricular ejection fraction; PCI = percutaneous coronary intervention.

DISCUSSION

This study provides data on four key questions about the interplay among renal dysfunction, ischemic HF, and cardiovascular pharmacotherapeutics.

First, we found that 39% of patients with HF and CAD had creatinine clearances <60 ml/min, corresponding to at least moderate renal insufficiency. This prevalence is consistent with the 38% reported in a retrospective cohort study of 665 patients with HF admitted to community hospitals in a single American state (7) and is substantially higher than that reported in the major HF trials (2).

Second, we confirmed the findings from multiple other studies that, even after adjusting for the higher burden of comorbidities, renal dysfunction is a powerful independent risk factor for mortality in patients with HF (1–7). However, because we had data on coronary anatomy and ejection fractions, we were able to extend the current evidence base in demonstrating that the adverse prognostic influence of renal dysfunction is independent of atherosclerotic burden and left ventricular (LV) systolic function. Thus, of the multiple theories offered to explain the excess risks in cardiac patients with renal disease (8), our data cast doubt on suppositions that this is merely due to comorbidities, more advanced coronary atherosclerosis, or poorer LV function in renal patients.

Third, we have confirmed in a large and heterogeneous sample of patients with ischemic HF that prescription rates for ACE inhibitors, beta-blockers, statins, and aspirin are inversely related to renal function. The underuse of medications in subgroups of patients excluded from the relevant trials is a common finding in health services research, and again serves to emphasize the importance of observational studies in determining whether these prescribing patterns are appropriate.

To that end, the fourth important finding from our study is the association between medications and outcomes that we demonstrated in patients with varying degrees of renal function (all results adjusted for covariates). First, we found

JACC Vol. 44, No. 8, 2004
October 19, 2004:1587–92

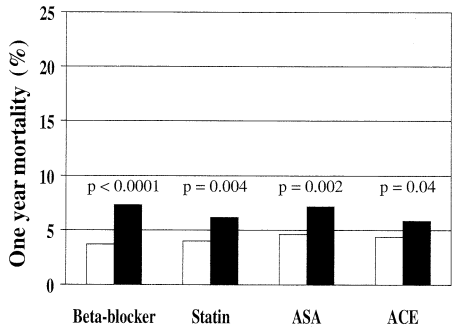

Figure 1. Crude one-year mortality rates in 3,914 patients with cardiologist-assigned diagnosis of heart failure, coronary artery disease proven by angiography, and creatinine clearance ≥60 ml/min. p values are for each pairwise comparison (i.e., crude mortality rates in users vs. nonusers for each of the medications of interest). **White bars** = user; **black bars** = nonuser. ACE = angiotensin-converting enzyme inhibitor; ASA = aspirin.

that aspirin use is associated with an approximately 25% lower mortality rate in patients with ischemic HF irrespective of renal function; this is similar to the survival benefits observed in patients at high risk for cardiovascular events, the vast majority of whom had normal renal function (19). Second, we found that statin users had lower mortality rates than nonusers in all three renal function strata; this echoes a subgroup analysis from the Cholesterol and Recurrent Events Trial (20). Third, consistent with the results of systolic HF trials, we found that in patients with creatinine clearance ≥60 ml/min, beta-blocker users had 46% fewer deaths than nonusers (21). We also found that beta-blocker users with creatinine clearances between 30 and 59 ml/min had better outcomes, echoing the results of subgroup analyses from the Cardiac Insufficiency Bisoprolol Study (CIBIS) II and the Cooperative Cardiovascular Project (22,23). In our cohort, there were too few events in patients with creatinine clearances <30 ml/min to make any definitive conclusions, although others have reported that beta-blockers are associated with significant survival benefits after acute myocardial infarction in patients with dialysis-dependent end-stage renal disease (10,11).

Finally, we found that, in patients with creatinine clearances ≥60 ml/min, ACE inhibitor users had lower one-year mortality rates: the 28% relative reduction we found is consistent with the data from the ACE inhibitor trials (24). However, we did not find lower death rates with ACE inhibitor use in patients with creatinine clearances <60 ml/min. Although this appears to be contrary to reports from the Cooperative Cardiovascular Project and the Heart Outcomes Prevention Evaluation (HOPE) study (23,25), we believe the explanation may lie in a possible negative interaction between aspirin and ACE inhibitors in patients with renal insufficiency (which has been reported in other cohorts) (13,26). Indeed, aspirin in the dose prescribed in our cohort (325 mg daily) does inhibit renal prostacyclin production and endothelial cyclooxygenase and thus may increase vascular tone and LV filling pressures (27,28); although this may have little effect in patients with preserved renal function, these mechanisms may well attenuate some of the benefits of ACE inhibitors in patients with decreased renal perfusion. Although a systematic review of six large ACE inhibitor trials reported a nonsignificant negative interaction between ACE inhibitors and aspirin ($p = 0.07$), the trials included in that systematic review included very few patients with serum creatinine >175 μmol/l (24). On the other hand, our study and the others reporting a negative interaction (13,26) included patients with moderate or severe renal insufficiency, many of whom were treated with lower doses of ACE inhibitors and higher doses of aspirin than employed in the meta-analyzed trials (28). Although the Warfarin and Antiplatelet Therapy in Chronic Heart failure (WATCH) trial reported excess HF

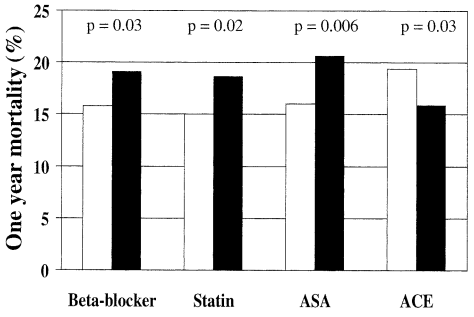

Figure 2. Crude one-year mortality rates in 2,513 patients with cardiologist-assigned diagnosis of heart failure, coronary artery disease proven by angiography, and creatinine clearance <60 ml/min. The p values are for each pairwise comparison (i.e., crude mortality rates in users vs. nonusers for each of the medications of interest). **White bars** = user; **black bars** = nonuser. Abbreviations as in Figure 1.

Table 2. Multivariate Predictors of One-Year Mortality

Variable	p Value	Odds Ratio (95% Confidence Interval)
Age (per yr)	<0.001	1.05 (1.04–1.06)
Creatinine clearance	<0.001	
<30 ml/min		3.19 (2.16–4.72)
30–59 ml/min		1.49 (1.11–2.00)
≥60 ml/min		Referent
Catheterization findings	<0.001	
Single-vessel disease		Referent
Two-vessel disease		1.22 (0.86–1.74)
Proximal left anterior descending lesion		1.71 (1.25–2.34)
Three-vessel disease		1.85 (1.36–2.52)
Left main lesion		2.36 (1.69–3.30)
Diabetes mellitus	<0.001	1.64 (1.34–2.01)
COPD	0.003	1.41 (1.12–1.76)
Peripheral vascular disease	0.01	1.38 (1.08–1.78)
Male gender	0.002	1.50 (1.16–1.93)
Aspirin	<0.001	0.69 (0.57–0.85)
Beta-blockers	0.002	0.75 (0.62–0.90)
Statins	0.02	0.79 (0.64–0.97)
ACE inhibitors	0.78	0.97 (0.81–1.16)

The variables included in the first step of these multivariate analyses were: age, gender, creatinine clearance, pulmonary disease, cerebrovascular disease, diabetes mellitus, hyperlipidemia, malignancy, smoking status, prior coronary artery bypass surgery, prior myocardial infarction, prior percutaneous intravascular revascularization, peripheral vascular disease, ACE inhibitor, beta-blocker, aspirin, calcium channel blocker, thienopyridine, and cardiac catheterization results.
Abbreviations as in Table 1.

Table 3. Adjusted All-Cause Mortality Risks With Prescribed Medications

		Creatinine Clearance		
	Entire Cohort	**≥60 ml/min**	**30–59 ml/min**	**<30 ml/min**
Beta-blockers				
OR (95% CI)	0.75 (0.62–0.90)	0.54 (0.39–0.75)	0.75 (0.57–0.98)	1.21 (0.76–1.93)
HR (95% CI)	0.76 (0.67–0.85)	0.61 (0.50–0.75)	0.82 (0.68–0.97)	0.97 (0.74–1.27)
ACE inhibitors				
OR (95% CI)	0.97 (0.81–1.16)	0.72 (0.48–0.99)	1.15 (0.88–1.49)	1.10 (0.69–1.73)
HR (95% CI)	0.95 (0.85–1.06)	0.78 (0.65–0.95)	0.95 (0.80–1.14)	1.23 (0.94–1.61)
Aspirin				
OR (95% CI)	0.69 (0.57–0.85)	0.63 (0.45–0.89)	0.75 (0.56–0.99)	0.76 (0.46–1.25)
HR (95% CI)	0.78 (0.69–0.89)	0.71 (0.58–0.87)	0.81 (0.67–0.98)	0.84 (0.64–1.11)
Statins				
OR (95% CI)	0.79 (0.64–0.97)	0.73 (0.52–1.01)	0.81 (0.60–1.10)	0.96 (0.57–1.63)
HR (95% CI)	0.84 (0.74–0.95)	0.84 (0.69–1.03)	0.86 (0.71–1.04)	0.85 (0.63–1.13)

Odds ratios (OR) are the results of the logistic regression analyses; hazards ratios (HR) are the results of the Cox proportional hazards analyses. The covariates for both sets of analyses are those listed in Table 2 (except for creatinine).

ACE = angiotensin-converting enzyme; CI = confidence interval.

hospitalizations in aspirin-treated patients (88% of whom were taking ACE inhibitors), there were too few patients with moderate or severe renal insufficiency to definitively answer the ACE inhibitor-aspirin interaction question. Until further trials are done, observational studies with rigorous adjustment for measured covariates remain the best evidence that can be brought to bear on this question.

Although our study reports on a large, well-categorized, consecutively enrolled, and heterogeneous cohort with ischemic cardiomyopathy who are similar to HF cohorts recruited in population-based studies (29), we acknowledge that these patients are likely healthier than other ischemic cardiomyopathy patients who were not referred for angiography. Indeed, the 10% one-year mortality in this cohort is substantially lower than the 29% we found in a population-based cohort of patients with HF from the same locale (30). However, we believe this selection bias does not affect analyses of the association among renal function, medication use, and outcomes. There are some other limitations to our study. For one, we only have prescribing data at baseline. However, any medication changes or noncompliance would bias our study towards the null hypothesis (by clouding any associations between prescribed medications and outcomes). Second, we relied on baseline serum creatinine to calculate each patient's creatinine clearance, which might have either underestimated (in those with elevated creatinine due to acute hemodynamic disturbances) or overestimated (in those with progressive renal failure due to contrast-induced nephropathy) kidney function during follow-up. However, this would also have introduced a null bias into our study, leading to an underestimation of the magnitude of the association between renal function and outcomes. Third, we do not have any data on unmeasured confounders such as biomarkers (parathyroid hormone, C-reactive protein, and so on); studies examining changes in these levels and subsequent clinical outcomes are clearly needed in patients with/without renal insufficiency. Fourth, although the Modification of Diet in Renal Disease (MDRD) equation is gaining popularity for the estimation of renal function, we used the Cockcroft-Gault equation in this study because it has been validated in the elderly and it performs better than the MDRD equation in subjects with normal serum creatinine, who made up nearly two-thirds of our cohort (31). Fifth, given the reported associations between anemia and poor outcome in patients with HF (30), it is unfortunate that we did not have hemoglobin data for these patients. However, we have previously shown in a cohort of 754 patients followed at a specialized clinic that renal insufficiency is an independent prognostic factor even after adjusting for hemoglobin values (1).

In conclusion, we found that renal insufficiency is common in patients with HF and CAD, and that it is a powerful and independent prognostic factor (even after adjusting for baseline differences in atherosclerotic burden and LV systolic function). We also demonstrated that ACE inhibitors, beta-blockers, statins, and aspirin were prescribed less often for patients with more advanced renal insufficiency, but that users of aspirin, statins, and beta-blockers had better survival rates than nonusers across the full spectrum of renal function. However, whereas ACE inhibitor users with creatinine clearances ≥60 ml/min had better survival rates, ACE inhibitors were not associated with reduced mortality in patients with creatinine clearances <60 ml/min. This apparent lack of benefit from ACE inhibitors in patients with moderate to severe renal insufficiency may be due to a clinically significant negative interaction between ACE inhibitors and aspirin in patients with reduced renal perfusion; however, this hypothesis needs to be tested in other datasets.

Acknowledgments

We thank the physicians, nurses, and technicians in the cardiac catheterization laboratories at the Holy Cross Hospital in Calgary; the Royal Alexandra Hospital and University of Alberta Hospital in Edmonton; and the St. Paul's, Vancouver General, Royal Columbian, Royal Jubilee,

Kelowna, and Lion's Gate Hospitals in British Columbia for their efforts in data collection for the APPROACH and BC Cardiac Registries.

Reprint requests and correspondence: Dr. Finlay A. McAlister, 2E3.24 WMC, University of Alberta Hospital, 8440 112th Street, Edmonton, Alberta, Canada T6G 2R7. E-mail: Finlay.McAlister@ualberta.ca.

REFERENCES

1. McAlister FA, Ezekowitz J, Tonelli MR, Armstrong PW. Renal insufficiency and heart failure: prognostic and therapeutic implications from a prospective cohort study. Circulation 2004;109:1004–9.
2. Dries DL, Exner DV, Domanski MJ, Greenberg B, Stevenson LW. The prognostic implications of renal insufficiency in asymptomatic and symptomatic patients with left ventricular systolic dysfunction. J Am Coll Cardiol 2000;35:681–9.
3. Hillege HL, Girbes AR, de Kam PJ, et al. Renal function, neurohormonal activation, and survival in patients with chronic heart failure. Circulation 2000;102:203–10.
4. Al-Ahmad A, Rand WM, Manjunath G, et al. Reduced kidney function and anemia as risk factors for mortality in patients with left ventricular dysfunction. J Am Coll Cardiol 2001;38:955–62.
5. Mahon NG, Blackstone EH, Francis GS, Starling RC, Young JB, Lauer MS. The prognostic value of estimated creatinine clearance alongside functional capacity in ambulatory patients with chronic congestive heart failure. J Am Coll Cardiol 2002;40:1106–13.
6. Kearney MT, Fox KA, Lee AJ, et al. Predicting death due to progressive heart failure in patients with mild-to-moderate chronic heart failure. J Am Coll Cardiol 2002;40:1801–8.
7. McClellan WM, Flanders WD, Langston RD, Jurkovitz C, Presley R. Anemia and renal insufficiency are independent risk factors for death among patients with congestive heart failure admitted to community hospitals: a population-based study. J Am Soc Nephrol 2002;13:1928–36.
8. McCullough PA. Cardiorenal risk: an important clinical intersection. Rev Cardiovasc Med 2002;3:71–6.
9. Shlipak MG. Heart failure pharmacotherapy in patients with renal insufficiency. Ann Intern Med 2003;138:917–24.
10. McCullough PA, Sandberg KR, Borzak S, Hudson MP, Garg M, Manley HJ. Benefits of aspirin and beta-blockade after myocardial infarction in patients with chronic kidney disease. Am Heart J 2002;144:226–32.
11. Berger AK, Duval S, Krumholz HM. Aspirin, beta-blocker, and angiotensin-converting enzyme inhibitor therapy in patients with end-stage renal disease and an acute myocardial infarction. J Am Coll Cardiol 2003;42:201–8.
12. Shlipak MG, Heidenreich PA, Noguchi H, Chertow GM, Browner WS, McClellan MB. Association of renal insufficiency with treatment and outcomes after myocardial infarction in elderly patients. Ann Intern Med 2002;137:555–62.
13. Frances CD, Noguchi H, Massie BM, Browner WS, McClellan M. Are we inhibited? Renal insufficiency should not preclude the use of ACE inhibitors for patients with myocardial infarction and depressed left ventricular function. Arch Intern Med 2000;160:2645–50.
14. Wright RS, Reeder GS, Herzog CA, et al. Acute myocardial infarction and renal dysfunction: a high risk combination. Ann Intern Med 2002;137:563–70.
15. Freeman RV, Mehta RH, Al Badr W, Cooper JV, Kline-Rogers E, Eagle KA. Influence of concurrent renal dysfunction on outcomes of patients with acute coronary syndromes and implications of the use of glycoprotein IIb/IIIa inhibitors. J Am Coll Cardiol 2003;41:718–24.
16. Ghali WA, Faris PD, Galbraith PD, et al., for the APPROACH Investigators. Sex differences in access to coronary revascularization after cardiac catheterization. Ann Intern Med 2002;136:723–32.
17. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976;16:31–41.
18. McAlister FA, Straus SE, Sackett DL, Altman DG. Analysis and reporting of factorial trials. A systematic review. JAMA 2003;289:2545–53.
19. Antiplatelet Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction and stroke in high risk patients. BMJ 2002;324:71–86.
20. Tonelli M, Moyé L, Sacks F, Kiberd B, Curhan G. Pravastatin for secondary prevention of cardiovascular events in mild chronic renal insufficiency. Ann Intern Med 2003;138:98–104.
21. Brophy JM, Joseph L, Rouleau JL. Beta-blockers in congestive heart failure. A Bayesian meta-analysis. Ann Intern Med 2001;134:550–60.
22. Erdmann E, Lechat P, Verkenne P, et al. Results from post-hoc analyses of the CIBIS II trial: effect of bisoprolol in high-risk patient groups with chronic heart failure. Eur J Heart Fail 2001;3:469–79.
23. Shlipak MG, Browner WS, Noguchi H, Massie B, Frances CD, McClellan M. Comparison of the effects of angiotensin converting-enzyme inhibitors and beta-blockers on survival in elderly patients with reduced left ventricular function after myocardial infarction. Am J Med 2001;110:425–33.
24. Teo KK, Yusuf S, Pfeffer M, et al., for the ACE Inhibitors Collaborative Group. Effects of long-term treatment with angiotensin converting enzyme inhibitors in the presence or absence of aspirin: a systematic review. Lancet 2002;360:1037–43.
25. Mann JFE, Gerstein HC, Pogue J, Bosch J, Yusuf S, for the HOPE Investigators. Renal insufficiency as a predictor of cardiovascular outcomes and the impact of ramipril: the HOPE randomized trial. Ann Intern Med 2001;134:629–36.
26. Nguyen KN, Aurnes I, Kjekshus J. Interaction between enalapril and aspirin on mortality after acute myocardial infarction: subgroup analysis of the Cooperative New Scandinavian Enalapril Survival Study II (CONSENSUS II). Am J Cardiol 1997;79:115–9.
27. Meune C, Mahe I, Mourad JJ, et al. Aspirin alters arterial function in patients with chronic heart failure treated with ACE inhibitors: a dose-mediated deleterious effect. Eur J Heart Failure 2003;5:271–9.
28. Meune C, Mahe I, Mouradd JJ, et al. Interaction between angiotensin-converting enzyme inhibitors and aspirin: a review. Eur J Clin Pharmacol 2000;56:609–20.
29. Krum H, Gilbert RE. Demographics and concomitant disorders in heart failure. Lancet 2003;362:147–58.
30. Ezekowitz JA, McAlister FA, Armstrong PW. Anemia is common in heart failure and is associated with poor outcomes: insights from a cohort of 12,065 patients with new onset heart failure. Circulation 2003;107:223–5.
31. Bostom AG, Kronenberg F, Ritz E. Predictive performance of renal function equations for patients with chronic kidney disease and normal serum creatinine levels. J Am Soc Nephrol 2002;13:2140–4.

APPENDIX

The members of the APPROACH Steering Committee include Dr. William Hui (Chair), Dr. Merril Knudtson, Dr. William Ghali, Dr. Stephen Archer, Dr. Michael Curtis, Dr. Michelle Graham, Dr. Arvind Koshal, Dr. Andrew Maitland, Dr. Brent Mitchell, Dr. Ross Tsuyuki, Diane Galbraith, Colleen Norris, and Karen Sutherland.