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Do Associations With C-Reactive Protein and Extent of Coronary Artery Disease Account for the Increased Cardiovascular Risk of Renal Insufficiency?

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OBJECTIVES We sought to determine whether the association of higher C-reactive protein levels (CRP) and more extensive coronary artery disease (CAD) explains the high cardiovascular risk of renal insufficiency (RI).

BACKGROUND Renal insufficiency and renal failure (RF) have been associated with increased cardiovascular risk in several studies, and it has been suggested that this association may be due to higher CRP levels and greater extent of CAD. To what extent CRP or severity of CAD explains this risk is uncertain.

METHODS A total of 1,484 patients without myocardial infarction (MI) undergoing angiography were entered and followed for 3.0 ± 1.6 years; RI and RF were defined as estimated glomerular filtration rates (GFR) of 30 to 60 and <30 ml/min; CRP was measured by immunoassay and ≥ 1.0 mg/dl defined as elevated. A CAD score was determined by extent and severity of angiographic disease. Multivariate Cox regressions were performed using seven standard risk factors, homocysteine, GFR, CRP, and CAD score.

RESULTS Mean age was 64 years, and 67% were men; CAD was absent in 24%, mild in 11%, and severe (≥70% stenosis) in 60%; CRP and CAD scores increased with declining renal function (median CRP: 1.2, 1.4, 2.2 mg/dl, $p < 0.001$ and CAD score: 8.1, 8.7, 9.3, $p = 0.008$ for no-RI, RI, and RF). During follow-up, 208 patients (15%) died or had nonfatal MI. Unadjusted hazard ratio (HR) for death/MI was 2.3 for RI and 5.1 for RF ($p < 0.0001$). Adjustment for CRP (HR, 2.2, 4.5), CAD score (HR, 2.1, 5.1), and all other risk factors (HR, 1.7, 4.5) had minimal or modest impact on RI and RF risk; HR increased to 5.4 ($p < 0.001$) for presence of both elevated CRP and RI/RF.

CONCLUSIONS Renal insufficiency, CRP, and angiographic CAD, although correlated, are largely independent predictors of cardiovascular risk, suggesting the importance of both inflammation and as yet undefined RI-related risk factors. (J Am Coll Cardiol 2003;42:57–63) © 2003 by the American College of Cardiology Foundation

Renal insufficiency (RI) and renal failure (RF) have been associated with increased cardiovascular (CV) risk in several studies (1,2), whereas, in other studies (3,4), baseline creatinine was not predictive, possibly due to a low prevalence of coronary artery disease (CAD) at baseline. It has been suggested that RI may predict CV events due to an association with more severe CAD (5). It has also been hypothesized that RI is predictive of CV events due to the presence of an inflammatory state associated with chronic elevations of C-reactive protein (CRP) (6). Indeed, several studies have shown CRP levels to be elevated in RF, and high CRP levels in dialysis patients are predictive of future CV events (7–11). To what extent higher CRP levels and more extensive CAD in RI patients are responsible for the associated increases in CV risk has not been clearly defined.

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METHODS

Study objectives. Our principal study objectives were to determine: 1) whether RI was predictive of death or myocardial infarction (MI); 2) whether RI was associated with atherosclerotic burden and CRP, and, if so, whether the predictive value of RI would remain after multivariate adjustment; 3) whether RI is predictive of death or MI in patients without angiographic CAD; 4) whether the predictive value of CRP differs among subjects with normal renal function, RI, or RF; and 5) the magnitude of the relative risk of these factors.

Patients and follow-up. The study sample included consecutive consenting patients at a single hospital (LDS Hospital, Salt Lake City, Utah) undergoing coronary angiography between 1994 and 2000 for evaluation of symptoms suggestive of stable or unstable angina, and who had complete data recorded. Patients with acute MI (whose CRP levels are affected by an acute phase reaction) were excluded. Creatine kinase-MB, if drawn before angiography, was uniformly normal (this series was enrolled before

Abbreviations and Acronyms

ACE = angiotensin-converting enzyme
CAD = coronary artery disease
CRP = C-reactive protein
CV = cardiovascular
GFR = glomerular filtration rate
HR = hazard ratio
MDRD = Modification of Diet in Renal Disease study
MI = myocardial infarction
RF = renal failure
RI = renal insufficiency

widespread testing with troponin assays). Most subjects were residents of Utah, southwestern Idaho, or southeastern Wyoming, a population genetically representative of U.S. Caucasians. The study met approval by the hospital's institutional review board.

The risk factors used in multivariable analyses included age, sex, diabetes, smoking history (current or >10 pack years), family history of CAD, diagnosis of hypertension, diagnosis of hyperlipidemia, homocysteine (n = 1,128), glomerular filtration rate (GFR), CAD score, and CRP.

Clinical events during follow-up were determined through telephone calls and hospital records, with supplemental information from the Utah and national Social Security death registry enabling 100% probabilistic determination of vital status.

Determination of CAD severity. All angiograms were reviewed by an attending cardiologist blinded to CRP level and future outcomes, and each lesion was visually estimated for percent diameter stenosis rounded to the nearest 10%. The presence of a mild/moderate (10% to 60%) or a severe lesion (70% to 100%) in the left anterior descending, the circumflex, or the right coronary artery defined the vessel as a mild/moderately or severely affected vessel (or both).

The extent of CAD was quantified by a CAD score, which has previously been determined to be the strongest angiographic predictor of future death/MI in our database (12). The score was obtained by adding the number of distinct lesions with 10% to 60% stenosis (range, 0 to 18), the number of distinct lesions with ≥70% stenosis (range, 0 to 14), the number of major vessels with at least one moderate stenosis (range, 0 to 3), and the number of vessels with at least one severe stenosis (range, 0 to 3). The CAD score ranged from 0 to 28.

Determination of CRP. C-reactive protein was quantified by an intermediate sensitivity fluorescence polarization immunoassay (Abbott Diagnostics, Chicago, Illinois). The test is standardized to the International Federation of Clinical Chemistry International Reference Preparation for Plasma Proteins. The within-run coefficient of variation for a 1.78-mg/dl standard is 3.7%. Between-run coefficients of variation are 3.9% for a 0.74-mg/dl standard and 3.0% for a 9.08-mg/dl standard.

We chose a priori to define an elevated CRP as ≥1.0 mg/dl, a commonly used cut-point to define high-risk in the literature and our previous studies in CAD populations; this level exceeds the 98th percentile for clinically normal individuals (Abbott Laboratories).

Determination of RI and RF. We calculated a GFR on all subjects using a simplified formula (13) from the Modification of Diet in Renal Disease study (MDRD). The MDRD formula used predictors of GFR (age, gender, ethnicity, serum urea nitrogen, and albumin) and demonstrated better estimation of GFR than the Cockcroft-Gault formula or 24-h creatinine clearance. Renal insufficiency was defined a priori as a GFR <60 ml/min (which approximated the lower quartile) and renal failure as GFR < 30 ml/min.

Statistical considerations. Baseline demographic and laboratory information is presented as mean (SD) for continuous variables and frequencies for discrete variables. Comparisons among groups used analysis of variance for continuous variables and chi-square testing for discrete variables. Survival statistics were used for risk determinations. The primary outcome variable was the combination of death (all-cause) or MI. Only the first event was counted as an end point. Secondary outcome variables were death and MI alone. Cox regression analysis was used for assessment of the relative hazard of these events over time. Both univariate and multivariate analyses were performed using SPSS for Windows, version 10.0 (Chicago, Ilinois). Cox multivariate adjustments of hazard ratios used forced entry and backward conditional stepwise approaches to determine parsimonious, best-fitting models.

RESULTS

Subject population and demographics. A total of 1,484 subjects were enrolled who had angiographic and baseline demographic information, a baseline high-sensitive CRP level, and data needed to calculate GFR. Subjects were followed for up to 6.3 years (mean, 3.0 ± 1.6 years). Presentation was diagnosed as stable angina for 72% and unstable angina for 28% of subjects. Mean age was 64 years; 67% were men; 24% had no angiographic CAD, 11% had mild-moderate CAD, and 60% had severe CAD (≥70% stenosis). Baseline demographics are presented in Table 1 by renal function category. Discharge rates of medications were 43% for angiotensin-converting enzyme (ACE) inhibitors, 12% for beta-blockers, and 17% for statins, and these frequencies did not differ significantly by groups except for somewhat greater use of ACE inhibitors in RI/RF patients (Table 1).

Glomerular filtration rate correlated negatively with age (−0.33, $p < 0.001$), homocysteine (−0.18, $p < 0.001$), CRP (−0.16, $p < 0.001$), CAD score (−0.08, $p = 0.003$), diabetes (−0.05, $p = 0.04$), and hypertension (−0.05, $p = 0.05$), but the strength of the correlations was poor.

Renal function and CRP. The mean study group GFR was 73 ml/min, and the median CRP was 1.3 mg/dl; CRP

Table 1. Baseline Demographic Data

	GFR >60 (n = 1,104)	GFR 30–60 (n = 329)	GFR < 30 (n = 51)	p Value (Linearity)
Age, mean	62	70	62	< 0.001
GFR, mean (ml/min) (range)	83 (60–150)	50 (30–59.9)	17 (3.7–29.9)	< 0.001
Creatinine, mean (mg/dl) (range)	0.9 (0.5–1.4)	1.4 (0.9–2.3)	4.8 (1.7–14.4)	< 0.001
CRP, median (mg/dl)	1.2	1.4	2.2	< 0.001
Angiographic CAD present	75%	80%	76%	NS
CAD score (n = 1,126 with CAD)	8.1	8.7	9.3	0.008
Hypertension	55%	63%	71%	0.001
Hyperlipidemia	50%	45%	37%	0.02
Diabetes	17%	20%	47%	< 0.001
Glucose, mean (random, mg/dl)	118	120	147	< 0.001
Family history of CAD	36%	28%	25%	0.002
Smoker	24%	16%	10%	< 0.001
Homocysteine (n = 1,128, median)	6.7	6.8	9.7	< 0.001
ACE inhibitor at discharge	41%	50%	49%	0.004
Beta-blocker at discharge	19%	22%	17%	NS
Statin at discharge	18%	13%	12%	< 0.001
Death	7%	19%	37%	< 0.001
MI	5%	8%	8%	0.03
Death or MI (first event)	10%	23%	37%	< 0.001
Days to event or end of follow-up	1,105	1,065	707	< 0.001

Mean values unless noted otherwise in groups of normal renal function (GFR >60 ml/min), renal insufficiency (GFR 30–60 ml/min), and renal failure (GFR <30 ml/min). Diagnoses of hypertension, hyperlipidemia, family history, and diabetes are those as recorded by primary physician. Smoker represents current tobacco use or history of > 10 pack years.

ACE = angiotensin-converting enzyme; CAD = coronary artery disease; CRP = C-reactive protein; GFR = glomerular filtration rate; MI = myocardial infarction.

levels increased with declining renal function: median CRP was 1.2 mg/dl without RI, 1.4 mg/dl for RI, and 2.2 mg/dl for RF ($p < 0.001$); CRP correlated negatively with GFR (Pearson's correlation coefficient, −0.16, $p < 0.001$). Factors positively correlated with CRP levels (diabetes, 0.07, $p = 0.006$; CAD score, 0.08, $p = 0.003$; age, 0.10, $p < 0.001$) were more prevalent in patients with RI/RF, and factors negatively correlated with CRP (hyperlipidemia −0.09, $p = 0.001$) were less prevalent, partially accounting for associations of CRP and GFR.

Renal function and CAD score. The presence of angiographic CAD did not differ significantly by renal function category (Table 1). However, among patients with angiographic CAD, the extent/severity of CAD, as measured by the CAD score, increased with declining renal function: from 8.1 without RI, to 8.7 with RI, to 9.3 with RF ($p = 0.008$). The CAD score negatively correlated with GFR (−0.08, $p = 0.003$) and positively correlated with known CAD risk factors: age (0.25, $p < 0.001$), hyperlipidemia (0.25, $p < 0.001$), diabetes (0.15, $p < 0.001$), hypertension (0.14, $p < 0.001$), and family history (0.06, $p = 0.01$).

Predictive value of renal function for death or MI. During a mean follow-up of 3.0 ± 1.6 years, there were 235 events of all-cause death or nonfatal MI in 208 patients (15%). The hazard ratio (HR) for death or MI in univariate analysis was 2.3 for RI and 5.1 for RF ($p < 0.0001$); HRs for RI and RF were greater for death (3.0, 7.6, respectively) than for MI alone (1.8, 3.0) (Table 2). Although CRP significantly correlated with GFR, adjustment for CRP only slightly altered the predictive value for death/MI for RI (HR, 2.2) and RF (HR, 4.5). Similarly, adjustment for CAD score had minimal effect on the predictive value of RI (HR, 2.1) and did not alter the predictive value of RF (HR, 5.1). Homocysteine also correlated with GFR and predicted death or MI (HR, 1.3 for level >15 mg/dl, $p < 0.04$); however, adjustment for homocysteine also did not significantly alter the HR associated with RI and RF (2.1 and 6.2). Finally, after full multivariate adjustment, the HR for death or MI was only modestly affected for RI (1.7) and RF (4.5) (Table 3).

Even when the analysis was confined to patients with creatinine ≤1.5, a GFR <60 remained an independent predictor in multivariate analysis with an HR of 1.5 ($p < 0.02$). In contrast, a creatinine of 1.3 to 1.5 did not define a high-risk group (HR, 1.1; $p = 0.73$). Using mild renal

Table 2. Univariate and Bivariate (Adjusting for CRP or CAD Score) Hazard Ratios for Death and/or MI for RI or RF, and Univariate Risk Among Patients With and Without ACE inhibitors at Discharge

	RI	RF
Univariate HR for death	3.0 (2.1–4.2)	7.6 (4.5–12.6)
Univariate HR for MI	1.8 (1.1–3.0)	3.0 (1.1–8.2)
Univariate HR for death/MI	2.3 (1.7–3.1)	5.1 (3.2–8.3)
HR for death/MI adjusted for CRP	2.2 (1.7–3.0)	4.5 (2.8–7.4)
HR for death/MI adjusted for CAD score	2.1 (1.6–2.8)	5.1 (3.2–8.3)
Univariate HR for death/MI among patients discharged on ACE inhibitor	1.9 (1.3–2.9)	4.5 (2.1–9.1)
Univariate HR for death/MI among patients without ACE inhibitor at discharge	2.5 (1.7–3.8)	5.6 (2.9–10.9)

Renal failure (RF) was defined as GFR <30 and renal insufficiency (RI) as GFR 30–60 mg/dl.

HR = hazard ratio; RF = renal failure; RI = renal insufficiency. Other abbreviations as in Table 1.

Table 3. Hazard Ratio of Death or Myocardial Infarction in Multivariate Analysis

	Hazard Ratio	95% CI	p Value
Renal failure	4.5	2.7–7.3	< 0.001
Smoker	1.8	1.3–2.6	< 0.001
CAD score	1.08	1.05–1.11	< 0.001
Age (per yr)	1.03	1.02–1.05	< 0.001
Hyperlipidemia	0.53	0.39–0.73	< 0.001
Renal insufficiency	1.7	1.2–2.3	0.001
CRP >1.0 mg/dl	1.9	1.2–2.8	0.003
Diabetes	1.5	1.1–2.2	0.014
ACE inhibitor use	0.72	0.54–0.97	0.03

Renal failure was defined as GFR <30 and renal insufficiency as GFR 30–60 mg/dl. Abbreviations as in Table 1.

insufficiency as previously defined by a creatinine of 1.4 to 2.3 (1), the multivariate adjusted HR for death or MI was 1.6 ($p < 0.02$). Finally, using a creatinine of >2.5 to define renal failure, compared with a creatinine of <1.3, the multivariate adjusted HR for death or MI was 5.0 ($p < 0.001$). These findings suggest similar predictive value of creatinine and GFR once creatinine is clearly elevated above normal, whereas GFR is a stronger predictor when creatinine levels may represent either normal renal function or mild-moderate renal insufficiency (i.e., creatinine 0.9 to 1.5). If RF was defined as a GFR <40 ml/min, the HR for death/MI was modestly lower (unadjusted HR, 4.2 vs. 5.1). The HR for the RI group with a GFR of 40 to 60 ml/min was similar (unadjusted HR, 2.1 vs. 2.3).

Patients with RI or RF were more likely to be discharged on ACE inhibitors, but not beta-blockers or statins (Table 1). In multivariate analysis, the use of ACE inhibitors at discharge was associated with a reduction in the risk of death/MI (HR, 0.72, $p = 0.03$), while beta-blockers or statins were not (Table 3). In univariate analysis, the risk of death/MI was lower among patients discharged on ACE inhibitors (HR, 1.9 for RI and 4.5 for RF) compared with patients not discharged on ACE inhibitors (HR, 2.5 and 5.6, respectively) (Table 2). Similarly, the risk of death/MI was lower among patients discharged with beta-blockers (HR, 1.5 for RI, 3.0 for RF) than those without beta-blockers (HR, 2.3 and 6.9, respectively), and among patients discharged on statins (HR, 1.6 and 3.8) than those without statins (HR, 2.4 and 5.2).

Predictive value of renal function in subjects without CAD. Three hundred fifty-one patients underwent angiography for suspected cardiac disease but were found to have angiographically normal coronary arteries. The risk of incident death or MI is generally low in such patients, yet angiographically non-apparent CAD may still be present and progress or result in plaque rupture. In this group of subjects, the risk of MI was much higher in the presence of RI/RF (5.2% vs. 0.7%; multivariate HR 10.2 [1.7 to 62.3], $p = 0.01$) as was the risk of death (24.7% vs. 3.9%; multivariate HR 6.5 [3.1 to 13.7], $p < 0.001$).

Predictive value of CRP and renal function together. Elevation of CRP resulted in an HR of death/MI of 2.6 (1.7 to 3.9, $p < 0.001$). The predictive value of elevated CRP was modestly increased among patients with RI/RF (HR, 2.9; $p = 0.004$) than among patients without RI (HR, 2.1; $p = 0.003$). The combined presence of both RI/RF and elevated CRP, compared with neither, predicted a dramatic increase in risk of death or MI (HR of 5.4 (3.3 to 8.8, $p < 0.001$) (Figs. 1 and 2). These findings were not significantly

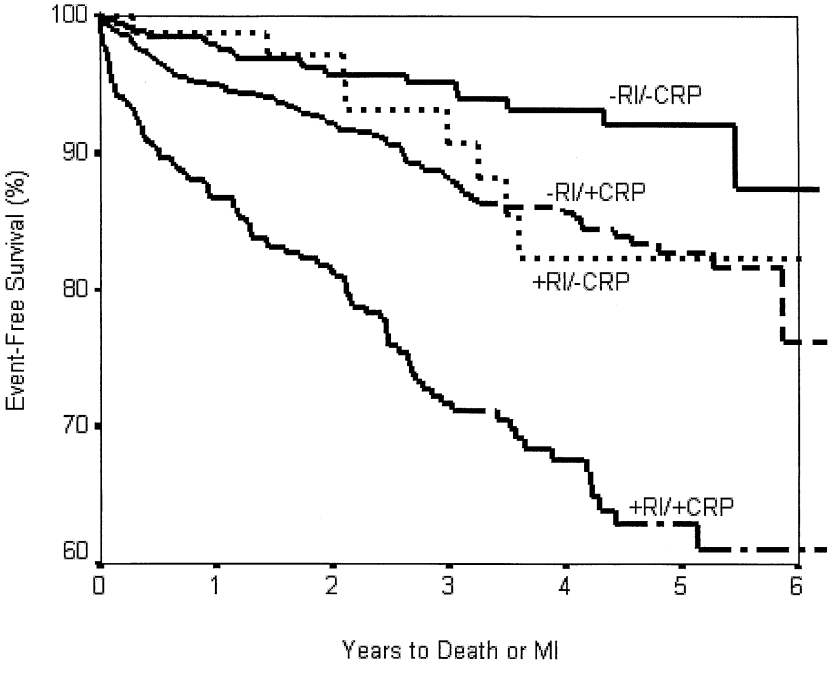

Figure 1. Kaplan-Meier event-free (first event of death or myocardial infarction [MI]) survival curves for patients with glomerular filtration rate GFR <60 mg/dl (+renal insufficiency [RI], n = 77), C-reactive protein (CRP) >1.0 mg/dl (+CRP, n = 769), both (n = 303) or neither (n = 335).

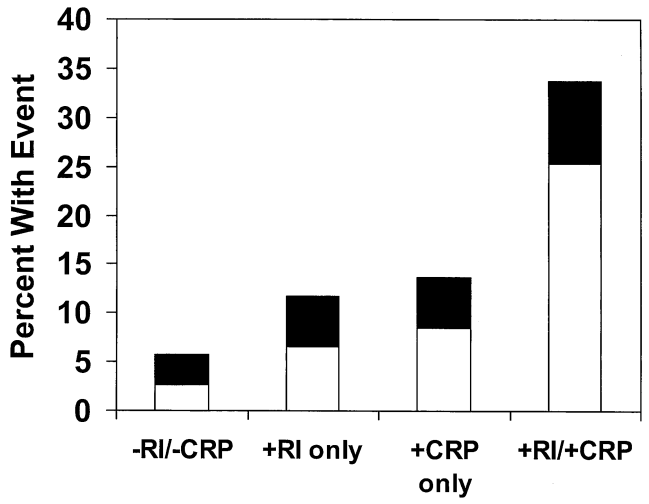

Figure 2. Absolute percentage of death or myocardial infarction (MI) among patients with glomerular filtration rate <60 mg/dl (+ renal insufficiency [RI]), C-reactive protein (CRP) >1.0 mg/dl (+CRP), both or neither, during mean follow-up of three years. **Solid bars** = MI; **open bars** = death.

altered if patients with severe RF (i.e., GFR < 20) or advanced age (i.e., age > 80) were excluded from analysis.

DISCUSSION

Study summary and perspective. In this large, well-characterized, prospectively followed cohort of subjects with suspected CAD undergoing angiography, we have demonstrated the strong associations of renal insufficiency and renal failure with incident death or MI; CRP and CAD score showed modest to moderate inverse associations with renal function and CAD score, yet adjustment for CRP, for CAD score, or for all 10 risk factors had minimal or modest impact on RI/RF risk. Specifically, the risk of RI and RF were largely independent of CRP elevation, extent of CAD, homocysteine levels, and traditional risk factors; we were able to account for only about 25% of the risk of RI/RF due to associations with confounding factors.

The use of ACE inhibitors at the time of discharge did modestly lower the associated risk of RI/RF. This is consistent with previous randomized trials showing a reduction in CV events with the use of ACE inhibitors in RI. Statins and beta-blockers did not prove to be independent predictors of protection from death/MI, possibly due to small numbers of patients on therapy.

The study does confirm that CRP levels are elevated in RI/RF, and elevated CRP was a predictor of incident events among patients with concomitant RI/RF. Importantly, HR increased impressively (to 5.4) when both elevated CRP and RI/RF were present; CRP levels may have decreased over time (due to increased utilization of lipid-lowering therapy or aspirin) or may have increased (due to the progression of CAD and CV risk factors). Changes in CRP levels over time would generally tend to weaken any association of CRP and death/MI. If the association is weakened, the associated risk of RI for death/MI due to elevation of CRP could also be weakened. However, at baseline, the correlation of RI/RF and CRP was modest in comparison with the association of CRP with future death/MI. Repeat CRP values over time would have been valuable, but is unlikely to explain the associated risk of RI. Although the presence of angiographic CAD was only slightly and nonsignificantly more frequent among patients with RI, the use of a sensitive CAD score demonstrated greater severity/extent of CAD in the setting of RI/RF. Despite this association, the predictive value of RI/RF was not accounted for by the presence of more extensive CAD. Importantly, RI/RF appear to retain independent predictive value for death or MI in both the presence and absence of angiographic CAD.

Among patients with angina who have a "normal" angiogram, the presence of RI/RF remains associated with a high risk for future MI or death. Thus, aggressive risk factor modification may be helpful in such patients.

Taken together, these study findings suggest that RI/RF, CRP, and angiographic CAD, although weakly correlated, are largely independent predictors of cardiovascular risk. Thus, in addition to inflammation and atherosclerosis, other unmeasured RI-related factors are operative in determining the excess cardiovascular risk associated with RI/RF.

Historical perspective. Prior studies have reached different conclusions on the independent predictive value of RI for cardiovascular events. In the MRFIT and TOMHS studies (4), the change in creatinine over time was predictive of future events although the baseline creatinine was not. In the Framingham Heart study (3), mild RI (creatinine 1.4 to 3.0) was not associated with cardiovascular events at 15 years of follow-up, but it was modestly associated (HR = 1.3) with all-cause mortality in men. It was concluded that RI predicted future events due to a strong association with CAD and CAD risk factors. In contrast, recent data from the Heart Outcomes and Prevention Evaluation trial showed a significant independent risk for cardiovascular events with mild RI (1), with an adjusted HR of 1.4 for cardiovascular death, MI or stroke. The Bypass Angioplasty Revascularization Investigation (BARI) trial also demonstrated an association with renal insufficiency and the risk of recurrent hospitalization, bypass surgery, and death (14).

Other recent trials have also demonstrated independent predictive values of RI for mortality. Best et al. (15) evaluated over 5,000 patients undergoing percutaneous coronary intervention and found one-year mortality to be 1.5% for GFR ≥70 ml/min, 3.6% for GFR 50 to 69 ml/min, 7.8% for GFR 30 to 49 ml/min, 18.3% for GFR < 30 ml/min, and 19.9% for patients on dialysis. The risk of future MI was also strongly correlated to renal function. Walsh et al. (16) demonstrated an adjusted HR of 2.4 for mortality among patients with elevated creatinine after MI. Wright et al. (17) demonstrated a graded risk for in-hospital mortality by renal function. The adjusted HR for death after discharge was 2.4 for mild RI, 2.2 for moderate RI, 1.9 for RF, and 5.4 for end-stage renal disease. Patients with worse

renal function were less likely to receive adjunctive and reperfusion therapy, and failure to receive these treatments was associated with an increased risk of death during follow-up. Shlipak et al. (18) analyzed over 130,000 patients with MI and demonstrated an adjusted HR for one-month mortality of 1.7 for mild RI (creatinine 1.5 to 2.4) and 2.4 for moderate RI (creatinine 2.5 to 3.9). Again, patients with RI were less likely to receive appropriate adjunctive and reperfusion therapy, which also was associated with worse outcomes.

These studies now demonstrate a consistent increase in the risk of mortality and CV complications with renal insufficiency. Some of the differences of associated risk between studies may relate, in part, to the lower sensitivity of creatinine than GFR for assessing mild renal dysfunction, definition of renal insufficiency, and differences in the studied population. Our study is consistent with these prior studies and demonstrates an increased risk of mortality and nonfatal MI with RI and RF. In addition, we have demonstrated this risk is not accounted for by the presence of more severe CAD or higher CRP levels. In contrast to prior studies, our patients had similar rates of medical therapy (ACE inhibitors, statins, and beta-blockers) among renal function groups. This may be due, in part, to a more homogenous group of selected patients, as all our patients likely had a reasonable life expectancy as indicated by the willingness to undergo cardiac catheterization. However, as with other studies, we also noted an increased HR among patients not given these medical therapies.

Potential mechanisms of RI-associated risk. A number of pathogenic mechanisms might account for the elevated cardiovascular risk associated with RI/RF, but these remain to be more clearly evaluated. These include elevated serum calcium X phosphate product (19), hyperparathyroidism (20), anemia (2), hypoalbuminemia, hyperhomocysteinemia (21,22), chronic inflammation, and uremic toxins. Asymmetric dimethylarginine, an innate inhibitor of nitric oxide synthase, is one molecule that accumulates in renal failure, possesses all the characteristics of a uremic toxin candidate, and was associated with independent risk of mortality in a recent report (23). Other uremia-related toxins likely also contribute. Consistent with these observations, our study indicates that substantial risk remains after accounting for CRP (a marker of inflammation), and homocysteine (an endothelial toxin in high doses).

Study limitations. The limitations of this study are those inherent to all prospective but non-randomized registries, including the influence on results of referral and selection bias that may be incompletely corrected despite adjustment for recognized risk factors. Our center has a low proportion of ethnic minorities, and results in these subgroups may be different. Data on long-term medication adherence and changes are not available. However, the study was large, the results robust and consistent, and adjustment for 10 covariates showed little evidence for affecting the risk of RI/RF. Also, we have only a single measurement of creatinine, which may have changed over time, especially in relation to the dye load of angiography, placing patients with RI at higher risk. The RF group as defined is a small group. Many of these patients had end-stage renal disease treated with dialysis, yet these specifics were not available. The HR of death or MI is altered somewhat with differing definitions of RF; however, our results are consistent with prior reports. Additional risk factors that may associate with RI and poor outcome (anemia, persistently elevated blood pressure, lipid levels, proteinuria) were not available for entry into multivariate analysis. Quantification of coronary angiographic findings was limited to the visual interpretation of the attending cardiologist, which is representative of "real world" practice. The cause of death was available in less than half of cases, so that our analyses relied on total rather than cause-specific (cardiovascular) death. However, among patients in whom cause of death could be determined, 75% were cardiovascular.

Conclusions. Renal insufficiency, RF, CRP, and angiographic CAD are each strong and independent predictors of future death or MI. Although RI is associated with higher CRP and more extensive CAD, these factors account for only approximately 10% of the associated risk of RI. Renal insufficiency and RF remain powerful predictors despite full adjustment for these and all standard risk factors. Jointly, high CRP and RI/RF predict a dramatic increase in death/MI risk, suggesting the importance of both inflammation and as yet undefined RI-related risk factors. These unrecognized factors provide a challenge for future research discovery efforts.

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