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Acute Decline in Renal Function, Inflammation, and Cardiovascular Risk after an Acute Coronary Syndrome

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Background and objectives: Chronic kidney disease is associated with a higher risk of cardiovascular outcomes. The prognostic significance of worsening renal function has also been shown in various cohorts of cardiac disease; however, the predictors of worsening renal function and the contribution of inflammation remains to be established.

Design, setting, participants, & measurements: Worsening renal function was defined as a 25% or more decrease in estimated GFR (eGFR) over a 1-mo period in patients after a non-ST or ST elevation acute coronary syndromes participating in the Aggrastat-to-Zocor Trial; this occurred in 5% of the 3795 participants.

Results: A baseline C-reactive protein (CRP) in the fourth quartile was a significant predictor of developing worsening renal function (odds ratio, 2.48; 95% confidence interval, 1.49, 4.14). After adjusting for baseline CRP and eGFR, worsening renal function remained a strong multivariate predictor for the combined cardiovascular composite of CV death, recurrent myocardial infarction (MI), heart failure or stroke (hazard ratio, 1.6; 95% confidence interval, 1.1, 2.3).

Conclusions: Patients with an early decline in renal function after an acute coronary syndrome are at a significant increased risk for recurrent cardiovascular events. CRP is an independent predictor for subsequent decline in renal function and reinforces the idea that inflammation may be related to the pathophysiology of progressive renal disease.

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Impaired renal function has consistently been shown to be an independent risk factor for cardiovascular outcomes across a broad spectrum of patients including population-based studies of patients with cardiovascular disease (1,2), acute coronary syndromes (3–6), chronic heart failure with either impaired or preserved ventricular systolic function (7), and after coronary artery bypass grafting (8). Worsening renal function (WRF), defined by small increases in creatinine or decreases in GFR, has also been independently associated with adverse cardiovascular outcomes and mortality in patients after an acute MI (9), cardiac surgery (10,11), and in patients with heart failure (12–14).

Serum C-reactive protein (CRP), a marker of inflammation, has been associated with WRF in a population of nondiabetics (15), as well as in those after an MI (15,16). The predictors and prognostic significance of WRF in a cohort of patients after an

acute coronary syndrome (ACS) is not well defined. Furthermore, the contribution of inflammatory markers to WRF in this cohort is unknown. We analyzed subjects from the phase Z of the A-Z trial (Early Intensive *versus* Delayed Conservative Simvastatin Strategy in Patients with Acute Coronary Syndromes), who had both measurements of serum creatinine and thus estimates of GFR (eGFR), at baseline and 1 mo. We have previously reported that both baseline CRP and eGFR were important prognostic markers after an ACS and that the increased cardiovascular hazard associated with a reduction in eGFR was independent and additive to baseline markers of inflammation (6). The objectives of this subsequent analysis was to determine clinical factors associated with an early decline in eGFR after an ACS and second to evaluate the cardiovascular prognostic importance of an early decline in eGFR in this patient population.

Materials and Methods

Subjects

Patients studied were from phase Z of the Aggrastat to Zocor (A to Z) trial, a multicenter randomized double blind trial evaluating an early intensive simvastatin (simvastatin 40 mg/daily for 1 mo followed by 80 mg/daily) compared with delayed and less intensive simvastatin strategy (placebo for 4 mo followed by simvastatin 20 mg/daily) in patients

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stabilized after a high-risk ACS event (17). Patients were excluded from this trial if the index serum creatinine was >2.0 mg/dl ($178 \mu\text{mol/L}$) or total cholesterol >250 mg/dl (6.48 mmol/L). (Serum creatinine in mg/dl may be converted to $\mu\text{mol/L}$ by multiplying by 88.4.) Over the trial duration of 6 to 24 mo, there was a nonsignificant trend toward a reduction in the primary endpoint of cardiovascular death, MI, and readmission for an ACS in favor of the intensive statin regimen (18). There were a total of 4497 patients randomized to this trial with 4181 having measurements of both serum creatinine and CRP a mean of 4.6 d from symptom onset (median, 5 d; minimum, 2 d; maximum, 8 d). Of the 4181 subjects, 3795 had repeat measurements of serum creatinine at a mean of 32 d from the baseline measurement and were included in this analysis (median, 32 d; minimum, 22 d; maximum, 55 d).

Estimation of Renal Function

Renal impairment was assessed by an estimation of GFR using the Modification of Diet in Renal Disease equation. This is a four-component equation incorporating age, race, sex, and serum creatinine level by the following formula: estimated GFR = $186 \times (\text{serum creatinine level in mg/dl})^{-1.154} \times (\text{age in years})^{-0.203}$. The product of this formula is multiplied by a correction factor of 0.742 for women and 1.21 for African Americans (19).

For this analysis, worsening renal function was defined as a decrease in eGFR of $\geq 25\%$ compared with baseline. In sensitivity analyses, we also reanalyzed the data defining worsening renal function as an absolute increase in serum creatinine ≥ 0.3 mg/dl (20).

Statistical Analysis

Baseline characteristics between groups were compared with *t* tests or Wilcoxon rank sum tests for normally or non-normally distributed continuous variables, respectively. χ^2 tests were used for categorical variables. Because CRP levels were non-normally distributed and showed a nonlinear relationship to clinical outcomes, CRP was categorized into quartiles for all analyses. Logistic regression was used to identify univariate and multivariate predictors of a decrease of eGFR $\geq 25\%$. Covariates in these final models included age, male sex, CRP quartile, baseline eGFR as a continuous variable, total cholesterol, triglycerides, low-density lipoprotein (LDL), history of hypertension, peripheral vascular disease, diabetes, current smoking, previous MI, left ventricular (LV) dysfunction, index diagnosis, catheterization or percutaneous intervention (PCI) for index event, treatment randomization, history of diuretic use within 7 d of admission, new or increase in diuretics in the first 30 d, angiotensin converting enzyme (ACE) inhibitor use at discharge, and new ACE inhibitor use in first 30 d.

Combined cardiovascular event-free survival (freedom from cardiovascular death, recurrent MI, heart failure, or stroke) was shown with Kaplan-Meier curves and outcomes were compared with the log-rank test. Independent predictors of the cardiovascular clinical events were calculated using Cox proportional hazards modeling. All covariates that were significant in the univariate analyses and those with important clinical significance or confounding were entered into the final model. Covariates in the final model included presence of WRF, baseline eGFR, age, CRP quartiles, total cholesterol, triglycerides, LDL, sex, race, history of hypertension, history of diabetes, smoking, previous MI, LV dysfunction, index PCI, and treatment randomization.

All *P* values were two-sided and a *P* value of <0.05 was considered statistically significant. All statistical analyses were performed using STATA software, version 9.2 (Stata Corp., College Station, TX).

The authors had full access to the data and take responsibility for its integrity. All authors have read and agree to the manuscript as written.

Outcomes

The primary outcome for these analyses was a composite of cardiovascular endpoints including cardiovascular death, hospitalization for heart failure, recurrent MI, and stroke. With the exception of heart failure endpoints, all events were adjudicated by an independent blinded adjudication committee.

Results

Estimation of Renal Function

The baseline eGFR for the 4181 patients was non-normally distributed around a median of $67.8 \text{ ml/min per } 1.73 \text{ m}^2$ (range, 9.7 to $149.2 \text{ ml/min per } 1.73 \text{ m}^2$). The eGFR at 1 mo was also non-normally distributed with a median of $64.3 \text{ ml/min per } 1.73 \text{ m}^2$ (range 7.42 to $119.1 \text{ ml/min per } 1.73 \text{ m}^2$) representing a median change in eGFR of $-3.5 \text{ ml/min per } 1.73 \text{ m}^2$ over the 1-mo period. A total of 184 patients (4.9%) had an eGFR that decreased by $\geq 25\%$ from baseline over the 1-mo period.

Patients with WRF were more likely to have used diuretics within 7 d of randomization, have clinical or echocardiographic evidence of LV dysfunction, and have evidence of peripheral arterial disease. Worsening renal function was not related to differences in ACE inhibitor administration at discharge or the addition of either ACE inhibitor or diuretic within the 30-d period. In addition, the proportion of patients who had either a diagnostic coronary angiogram or PCI for the index event was not significantly greater in patients with WRF. Randomization to the early intensive statin regimen did not alter the likelihood of experiencing WRF (Tables 1 and 2).

Baseline serum CRP levels were significantly higher in the proportion of patients who developed WRF. Even after adjustment for other known predictors of WRF, the decrement in eGFR was greater across increasing quartiles of baseline CRP quartile.

Multivariable Predictors of Worsening Renal Function

Logistic regression was used to identify significant predictors of early WRF in this patient population. On multivariate analysis, age per year increase (odds ratio [OR], 1.03; 95% confidence interval [CI], 1.01, 1.05), female sex (OR, 2.37; 95% CI, 1.64, 3.42), baseline eGFR per milliliter per minute per 1.73 m^2 increase (OR, 1.06; 95% CI, 1.05, 1.08) and the fourth quartile of CRP (OR, 2.48; 95% CI, 1.49, 4.14) were significantly associated with WRF after multivariable adjustment (Figure 1).

Worsening Renal Function and Cardiovascular Outcomes

Worsening renal function 1 mo after an admission for an ACS was associated with a higher incidence of a subsequent composite cardiovascular event (adjusted hazard ratio [HR], 1.59; 95% CI, 1.10, 2.30). Although the composite CV events were more likely in the WRF group, only recurrent MI remained significant after adjustment (HR, 1.68; 95% CI, 1.01, 2.79; Table 3; Figure 2). Other significant multivariate predictors of the combined cardiovascular composite endpoint included a history of a previous MI (HR, 2.01; 95% CI, 1.61, 2.51), diabetes (HR, 1.63; 95% CI, 1.3, 2.0) or hypertension (HR, 1.41; 95% CI, 1.1, 1.7), and increased age and a baseline CRP in the third (HR, 1.38; 95% CI, 1.04, 1.8) or fourth quartile (HR, 1.5; 95% CI, 1.13,

Table 1. Baseline clinical characteristics of population based on an early decline in renal function (decline in GFR of $\geq 25\%$ over 1 mo)

Characteristic	eGFR Decrease $<25\%$ (<i>n</i> = 3611)	eGFR Decrease $\geq 25\%$ (<i>n</i> = 184)	<i>P</i>
Age (yr; mean \pm SD)	60.2 + 10.6	60.8 + 10.4	0.4
Female sex (%)	23.2	38.6	<0.001
Diuretic use within 7 days (%)	22.7	32.1	0.01
Lytics (%)	21.7	22.8	0.7
Clinical or echo evidence LV dysfunction (%)	11.2	16.9	0.02
Prior CV history			
MI (%)	16.6	15.8	0.8
CABG (%)	4.0	3.8	0.9
Diagnostic cath before			
Enrollment in Z (%)	54.9	59.8	0.2
Previous PCI (%)	4.3	5.4	0.5
PCI for index event (%)	42.1	43.7	0.7
PAD (%)	5.6	9.2	0.01
Cerebral vascular disease (%)	5.8	7.1	0.5
CHF <6 wk (%)	4.9	2.7	0.2
DM (%)	20.6	21.2	0.8
HTN (%)	49.4	56.5	0.06
Current smoking (%)	40.7	45.1	0.2
Qualifying event			
STEMI (%)	39.7	44.6	0.2
Concomitant therapies at discharge			
ASA (%)	96.7	94.6	0.1
β blocker (%)	83.5	80.4	0.3
ACE inhibitor (%)	57.9	62	0.3
Medications added b/w discharge and 30 days			
Diuretics (%)	5.5	8.2	0.1
ACE inhibitor (%)	9.1	10.3	0.6
Randomized to intensive statin group (%)	51.2	47.8	0.4

LV, left ventricle; MI, myocardial infarction; CABG, coronary artery bypass grafting; PCI, percutaneous intervention; PAD, peripheral artery disease; CHF, congestive heart failure; DM, diabetes mellitus; HTN, hypertension; STEMI, segment elevation myocardial infarction.

2.0). The prognostic value of worsening renal function remained significant even after multivariate adjustment, including baseline renal function (HR, 1.37; 95% CI, 1.04, 1.8). The analysis did not change when the definition of worsening renal function was changed to an increase in serum creatinine ≥ 0.3 mg/dl. (unadjusted HR for the combined CV endpoint, 2.21 [95% CI, 1.58, 3.11]; adjusted HR, 1.81 [95% CI, 1.25, 2.62] for the risk of a creatinine increase ≥ 0.3 mg/dl relative to those whose creatinine changed <0.3 mg/dl).

Discussion

Impaired baseline renal function is a potent independent risk factor for cardiovascular events across broad spectrums of patients (1–8). This study showed that a decline in renal function over a 1-mo period was an independent predictor of a subsequent cardiovascular event after an ACS, even after adjustment for baseline renal function. A high baseline level of serum CRP

was an important multivariate predictor of the development of worsening renal function after an ACS.

Worsening renal function has been shown to have prognostic significance in many acute settings, including acute heart failure (13,14) and in patients after cardiac surgery (10,11). The prognostic role of worsening renal function in patients has been described in patients after ST elevation MI (9), but less well defined in a broad cohort of patients with an ACS. In addition, these previous studies restricted the definition of acute kidney injury to that which occurs while patients remain in hospital. This was the first study to evaluate the prognostic impact of a decline in renal function that occurred over a longer time frame after the initial peri-infarct period.

Inherent to the discussion of the significance of worsening renal function is the lack of a standardized definition of this outcome. Many clinical studies have defined worsening renal function as an increase in serum creatinine >0.3 mg/dl

Table 2. Baseline biochemical characteristics of population based on an early decline in renal function (decline in GFR of $\geq 25\%$ over 1 mo)

Characteristic	eGFR Decrease <25% (n = 3611)	eGFR Decrease $\geq 25\%$ (n = 184)	P
Baseline creatinine (mg/dl) (median, IQR)	1.1 (1.0, 1.2)	1.0 (0.8, 1.1)	<0.001
Baseline eGFR (ml/min per 1.73 m ²) (median, IQR)	67.9 (58.8, 77.8)	78.7 (63.7, 79.8)	<0.001
Mean change in creatinine	0.02 \pm 0.2	0.48 \pm 0.5	<0.001
Mean change in eGFR	-2.06 \pm 8.6	-25.0 \pm 8.7	<0.001
Chemistry			
Total cholesterol (mg/dl) (median, IQR)	185 (74, 381)	181 (93, 276)	0.06
HDL (mg/dl) (median, IQR)	39 (33, 45)	38 (33, 46)	0.8
LDL (median, IQR)	112 (29, 320)	109 (43, 206)	0.1
Triglycerides (median, IQR)	150 (116, 199)	142 (114, 194)	0.3
CRP (mg/dl) (median, IQR)	20 (7.6, 43.3)	31 (12.5, 74.8)	<0.001
Peak CK (ratio of the upper limit of normal)	6.2 \pm 112	3.6 \pm 4.3	0.3
Peak troponin (ratio of the upper limit of normal)	267 \pm 2338	62.4 \pm 258	0.6

Serum creatinine in mg/dl may be converted to $\mu\text{mol/L}$ by multiplying by 88.4.

eGFR, estimated GFR; HDL, high-density lipoprotein; LDL, low-density lipoprotein; CRP, C reactive protein; CK, creatinine kinase.

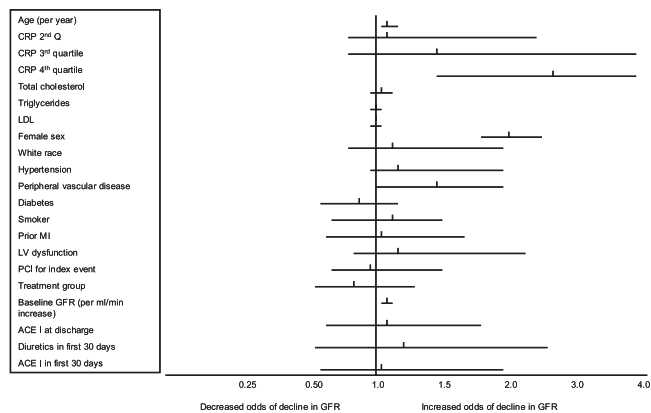


Figure 1. Multivariate predictors of worsening renal function (decline in eGFR $\geq 25\%$) over a 1-mo period.

(12,21,22), a threshold that has been found in prior studies of patients with heart failure to have the highest sensitivity (81%) and specificity (62%) for predicting mortality. However, when comparing the association of incremental rises in creatinine to increased risk for a cardiovascular event, it has been suggested that a particular threshold for worsening renal function may not exist and that there is a continuous increase in risk with the magnitude of the creatinine change (20). In addition, the precision of the creatinine determination and regression to the mean may limit the value of small changes. In this study, a 25% decline in eGFR was used to define a significant change in renal function. This definition corresponds to the “risk” category in the RIFLE (risk, injury, failure, loss, and end stage) classification (22) and has been used in previous studies evaluating the prognostic significance of an early decline in renal function (23). A change in eGFR was chosen over a change in creatinine to

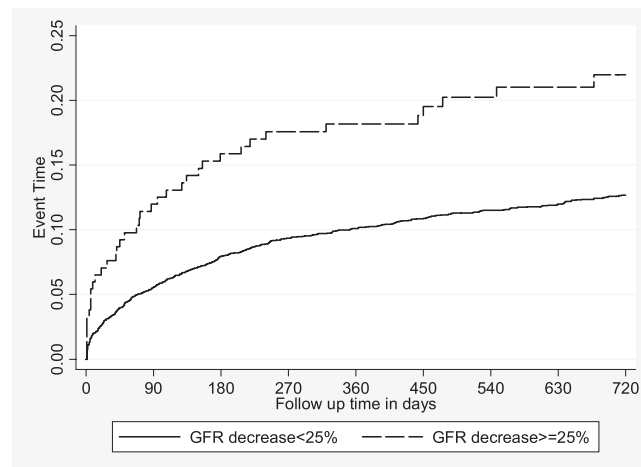


Figure 2. Kaplan-Meier estimates of the rate of death from any cause and the cardiovascular composite (CV death, recurrent MI, CHF, or stroke) endpoint according to a significant change in estimated GFR over 1 mo (Log rank, $P < 0.001$).

reflect the knowledge that eGFR is accepted as a better estimate of kidney function. The accuracy of serum creatinine as a marker of renal function is limited, because of nonlinear associations with eGFR that vary with age, gender, race, and lean body mass (23).

Worsening renal function occurred in 5% of this population after an ACS event. Advanced age, female gender, and a baseline CRP in the fourth quartile were significant independent predictors of worsening renal function; however, a higher baseline eGFR was also positively related to the development of WRF. The relationship between higher baseline eGFR and WRF may be a representation of regression toward the mean. Al-

Table 3. Hazard ratios and Kaplan-Meier event rate estimates for combined cardiovascular outcomes according to a significant decrease in GFR over 1 mo

Outcome	eGFR Decrease <25% (n = 3611)	eGFR Decrease ≥25% (n = 184)
Combined CV death/CHF/recurrent MI/stroke (%)		
Event rate (N)	12.7 (435)	22 (38)
Unadjusted (95% CI)	1.0	1.86 (1.33, 2.59)
Adjusted (95% CI)	1.0	1.59 (1.10, 2.30)
CV death (%)		
Event rate (N)	3.3 (111)	4.6 (8)
Unadjusted (95% CI)	1.0	1.46 (0.71, 2.99)
Adjusted (95% CI)	1.0	1.47 (0.70, 3.08)
CHF (%)		
Event rate (N)	3.9 (135)	7.0 (12)
Unadjusted (95% CI)	1.0	1.80 (1.00, 3.26)
Adjusted (95% CI)	1.0	1.33 (0.70, 2.52)
Recurrent MI (%)		
Event rate (N)	6.8 (234)	11.3 (20)
Unadjusted (95% CI)	1.0	1.78 (1.13, 2.81)
Adjusted (95% CI)	1.0	1.68 (1.01, 2.79)
CVA (%)		
Event rate (N)	1.4 (47)	2.8 (4)
Unadjusted (95% CI)	1.0	1.74 (0.63, 4.83)
Adjusted (95% CI)	1.0	0.80 (0.19, 3.38)

eGFR, estimated GFR; CV, cardiovascular; CHF, congestive heart failure; MI, myocardial infarction; CVA, cerebral vascular accident.

though chronic kidney disease is associated with an increased risk of acute kidney injury, the differences in the baseline eGFR between these two groups may not have been clinically significant, because both groups would have been considered to have mild chronic kidney disease based on their median eGFRs. It is also possible that, in this patient population, there were other stronger determinants of an early decline in renal function, such as the presence of acute heart failure. Although there were no significant differences in a history of heart failure (HF) between groups who did and did not develop WRF; subjects with WRF were more likely to have clinical or echocardiographic evidence of LV dysfunction or diuretic use within 7 d of admission. Serum levels of B-type natriuretic peptide have been associated with the development of HF after an ACS (24).

As all patients in this study had measurements of serum CRP done in the early phase of an acute coronary syndrome, their baseline CRP levels were significantly elevated consistent with the acute phase response. Despite these elevations, CRP levels in the fourth quartile remained a significant independent predictor for the development of worsening renal function. In addition, although measures of peak CK and troponin were significantly different among the four quartiles of CRP, the relationship was not linear, suggesting that the magnitude of CRP during the index hospitalization was not purely a reflection of the extent of myocardial necrosis. More extensive myocardial damage and HF may be associated with a decline in renal function. Renal dysfunction at baseline is an important independent risk factor in patients after an acute atherosclerotic

event. This has been shown with mild renal disease as assessed by the eGFR (3,6).

Independent of baseline renal function, this study showed that an early worsening of kidney function is an additional predictor of cardiovascular risk. It is possible that an early reduction in renal function is a marker for more advanced disease or systemic inflammation, which may predispose the patient to a recurrent cardiac event. However, the significance of an early reduction in renal function was seen in addition and independent of other traditional risk factors for recurrent cardiovascular events.

There are some limitations to this analysis that should be noted. Baseline serum creatinine was measured an average of 4.6 d after the initial ACS event and repeated ~30 d later. The variation in measurement may have affected the results through transient changes in renal function. However, this emphasizes the importance that a single measurement or a transient change in renal function still has important prognostic significance. Another important limitation is the fact that it is not possible to differentiate the component of CRP related to baseline inflammation *versus* that related to myocardial necrosis. Because extent of myocardial necrosis is a known prognostic marker, this potentially confounds the relationship between CRP and eGFR. However, the peak CK and troponin levels were not significantly different in those with and without the development of WRF. Although worsening renal function was defined based on a clinically meaningful decrease in eGFR by 25% or greater, there is not a standardized definition of this

outcome. Despite this, there was consistency in the results when repeated using a change of creatinine >0.3 mg/dl as the definition. There are also the limitations inherent to the measurement of creatinine and estimated GFR calculation (23); this may be particularly relevant given that follow-up body weight was not recorded in this study. It is possible that small changes in serum creatinine may have occurred secondary to a loss of lean muscle mass after the acute illness.

An acute decline in renal function can occur after an ACS. In the A-Z trial, this endpoint occurred in 5% of the enrolling subjects within 1 mo of randomization. The etiology of this decline is likely multifactorial; however, a high baseline CRP is an independent predictor of a subsequent decrease in estimated GFR. Our study provides support for the hypothesis that inflammation may be involved in renal dysfunction after an acute cardiac injury. Further studies are needed to clarify the relationship between an early decline in eGFR, baseline CRP, and extent of myocardial necrosis. An early decline in renal function after ACS is an independent predictor of recurrent events, independent of other traditional prognostic markers and baseline renal function. This supports the routine measurement of serum creatinine at follow-up visits.

Disclosures

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