# Increase in Creatinine and Cardiovascular Risk in Patients with Systolic Dysfunction after Myocardial Infarction

Powell Jose,* Hicham Skali,* Nagesh Anavekar,† Charles Tomson,‡ Harlan M. Krumholz,§ Jean L. Rouleau,‖ Lemuel Moye,* Marc A. Pfeffer,* and Scott D. Solomon;* for the SAVE Investigators

*Cardiovascular Division, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts; †University of Melbourne, Melbourne, Australia; ‡North Bristol NHS Trust, Bristol, United Kingdom; §Section of Cardiovascular Medicine, Yale University School of Medicine, New Haven, Connecticut; and ‖University of Montreal, Quebec, Canada

**Baseline renal function is a potent independent risk factor for adverse events after acute myocardial infarction (MI). Worsening renal function (WRF) has been shown to influence outcomes in the heart failure population, but its impact on cardiovascular risk in the post-MI period has not been well defined. For assessment of the prognostic importance of WRF, 2231 patients who had left ventricular dysfunction and were enrolled in the Survival and Ventricular Enlargement (SAVE) trial were studied. Patients were randomly assigned between 3 and 16 d (average 11 d) after acute MI to receive captopril or placebo; those with a serum creatinine of >2.5 mg/dl were excluded from SAVE. WRF was defined as an increase in creatinine of >0.3 mg/dl measured from baseline to 2 wk after randomization. The predictive value of WRF on cardiovascular morbidity and mortality was examined during 42 mo of follow-up. Paired serum creatinine measurements at baseline and 2 wk were available in 1854 patients. WRF occurred in 223 (12.0%) patients and was a stronger predictor of death (hazard ratio [HR] 1.46; 95% confidence interval [CI] 1.05 to 2.02) than baseline creatinine (HR 1.31; 95% CI 1.01 to 1.70). WRF also showed an increased risk for cardiovascular death (HR 1.62; 95% CI 1.14 to 2.30) and the composite end point (HR 1.32; 95% CI 1.03 to 1.70). When stratified by treatment, 104 (5.7%) and 116 (6.4%) patients with WRF in the placebo and captopril groups had no significant association between treatment group and WRF ($P = 0.38$). The risk for death associated with WRF was HR 1.63 (95% CI 1.05 to 2.52) in the placebo group compared with HR 1.33 (95% CI 0.81 to 2.21) in the captopril group ($P = 0.49$ for interaction). WRF as early as 2 wk after MI was not uncommon (12.0%) and was associated with increased mortality in patients without renal dysfunction at baseline. Patients who received captopril did not demonstrate more WRF than patients who received placebo. Monitoring serum creatinine in patients during the first few weeks after MI may help to identify those who are at highest risk and guide effective long-term therapeutic choices.**

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Renal dysfunction is a strong independent predictor of cardiovascular outcomes and mortality in the general population (1) after myocardial infarction (MI) (2–6) and heart failure (7,8). Small increases in creatinine over a specified period, defined as worsening renal function (WRF), have been assessed in heart failure patients as an independent prognostic marker (9,10). In patients who are hospitalized for acute heart failure, WRF not only has been shown to confer additional cardiovascular risk but also has been shown to be a stronger predictor of death in patients with heart failure than the initial level of creatinine (11). Nevertheless, the prognostic value of WRF in patients after acute MI is not well defined. Furthermore, whether treatment with angiotensin-converting enzyme (ACE) inhibition in these patients is associated with WRF is unknown. We analyzed patients who were enrolled in the Survival and Ventricular Enlargement (SAVE) Trial and in whom serum creatinine was measured at baseline and at 2 wk. Our objectives were to determine the risk for all-cause and cardiovascular mortality and morbidity associated with WRF and to determine whether ACE inhibitor therapy influences this relationship.

## Materials and Methods

### *Patients*

SAVE was a randomized, double-blind, placebo-controlled trial that examined the use of the ACE inhibitor captopril in 2231 consenting patients with acute MI and left ventricular dysfunction (left ventricular ejection fraction ≤40%) (12). Patients did not have overt clinical heart failure at the time of randomization. A serum creatinine of >2.5 mg/dl was part of the exclusion criteria for SAVE. All patients received a captopril test dose of 6.25 mg; patients who developed hypotensive symptoms or ischemia after initiation of study drug ($n = 23$) were excluded from the trial. Patients were randomly assigned to receive captopril or placebo between 3 and 16 d after MI. The titration scheme involved an initial dose of 12.5 mg, which was advanced as tolerated up

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**Address correspondence to:** Dr. Scott D. Solomon, Cardiovascular Division, Brigham and Women's Hospital, 75 Francis Street, Boston, MA 02115. Phone: 617-732-7182; Fax: 617-277-4981; E-mail: ssolomon@rics.bwh.harvard.edu



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to 25 mg three times daily before discharge. During an outpatient visit approximately 2 wk later, at the discretion of site investigators, the dosage was to be doubled.

Serum creatinine was measured at baseline as well as during this visit after 2 wk. WRF was defined as an increase in creatinine of >0.3 mg/dl from baseline, which was the threshold value on the basis of receiver operator curve analyses from heart failure studies that demonstrated this increase to represent a clinically significant change in creatinine and was less likely to be due to laboratory assay variability (13).

From an initial 2231 patients, 356 patients were missing serum creatinine measurements at either baseline ($n = 31$) or 2 wk ($n = 325$), and 21 patients had a cardiovascular event occur before 2 wk, leaving for analysis 1854 randomly assigned and consenting SAVE patients who had baseline and 2-wk serum creatinine measurements and who at the first outpatient visit had no cardiovascular events. When the risk for WRF was stratified by treatment, 41 additional patients were not taking captopril because of dropout or adverse drug reactions such as hypotension and dizziness but not WRF, leaving 1813 patients who had paired samples and no cardiovascular events and were taking their assigned study medication after 2 wk. Death, cardiovascular death, and a composite outcome of death, stroke, recurrent MI, and hospitalization for congestive heart failure (CHF) were considered primary end points and were assessed during a follow-up period of 36.8 mo (95% confidence interval [CI] 36.2 to 37.5 mo) that commenced at the 2-week outpatient visit.

### *Statistical Analyses*

*T* test and $\chi^2$ tests were used to compare continuous and categorical variables between the groups. Cox proportional hazards models were used to derive univariate and multivariate estimates of risk for outcomes starting from the 2-wk visit after randomization, when the second creatinine was measured. We performed multivariable analyses using logistic and Cox regression to assess for independent predictors of WRF and the prognostic value of WRF after adjusting for known cardiovascular risk factors, including age; gender; baseline creatinine (categorized as <1.0, 1.0 to <2.0, and ≥2.0 mg/dl); left ventricular ejection fraction; previous MI; use of diuretics 24 h before MI; and a history of dyslipidemia, hypertension, diabetes, or CHF. We also examined risk according to treatment assignment to determine whether captopril modifies the relationship between WRF and cardiovascular risk. Statistical analyses were performed with STATA software, version 8.2 (Stata Corp., College Station, TX).

## Results

Patients who were excluded from this analysis because they were missing serum creatinine measurements ($n = 356$), had cardiovascular events ($n = 21$), or were not taking medication at 2 wk ($n = 41$) were older, were more likely to be female, had more hypertension, and were more frequent users of diuretics compared with those who were included in the analysis. Although there was a higher cardiovascular event rate in excluded patients, there was no significant difference in baseline creatinine, change in creatinine, or treatment assignment compared with the study cohort.

Of the 1854 patients who composed the study cohort, the change in creatinine from baseline to 2 wk was normally distributed, ranging from −1.2 to 2.8 mg/dl with a mean change in creatinine by treatment assignment of 0.05 ± 0.3 in both the placebo and captopril groups ($P = 0.9$). A total of 223 (12.0%) patient had WRF with no significant difference in time from onset of MI to enrollment into SAVE between patients with and without WRF (average 11 d after MI). Patients with WRF were older; were more likely to be female; and had a higher prevalence of diabetes, smoking, and use of diuretics but had fewer previous MI (Table 1). In the multivariate logistic regression model, only age (odds ratio [OR] 1.03; 95% CI 1.01 to 1.04)

*Table 1.* Baseline characteristics according to WRF[a]

| Characteristics | ΔCr ≤ 0.3 ($n = 1631$), 88.0% | ΔCr > 0.3 ($n = 223$), 12.0% | *P* |
|---|---|---|---|
| Age (yr) | 58.8 ± 10.6 | 60.7 ± 10.8 | 0.01 |
| Creatinine (mg/dl) | 1.20 ± 0.32 | 1.09 ± 0.35 | <0.001 |
| LVEF (%) | 31.3 ± 6.6 | 30.7 ± 6.4 | 0.20 |
| Systolic BP | 112 ± 15 | 114 ± 16 | 0.06 |
| Diastolic BP | 70 ± 10 | 70 ± 10 | 0.99 |
| Female gender | 257 (15.7) | 53 (23.8) | 0.003 |
| GFR < 60 ml/min per 1.73 $m^2$ | 549 (33.7) | 61 (27.3) | 0.06 |
| Hypertension | 677 (41.5) | 103 (46.2) | 0.18 |
| Dyslipidemia | 363 (24.0) | 47 (23.2) | 0.79 |
| Diabetes | 333 (20.4) | 62 (27.8) | 0.012 |
| Previous MI | 584 (37.6) | 63 (29.4) | 0.020 |
| History of CHF | 99 (6.1) | 9 (4.0) | 0.22 |
| Smoking | 328 (20.1) | 60 (26.9) | 0.019 |
| Medications[b] | | | |
| diuretics | 538 (34.5) | 89 (41.9) | 0.034 |
| captopril therapy | 819 (50.2) | 119 (53.4) | 0.38[c] |

[a]Data are mean ± SD or *n* (%). *t* test for continuous variables, $\chi^2$ for categorical. CHF, congestive heart failure; Cr, creatinine; LVEF, left ventricular ejection fraction; MI, myocardial infarction; WRF, worsening renal function.
[b]Sustained drug treatment within 24 h before randomization.
[c]By design.

*Table 2.* Events and risk in patients according to presence of WRF and treatment[a]

| Events | Δ Cr ≤ 0.3 ($n$ = 1631) | Δ Cr > 0.3 ($n$ = 223) | Unadjusted HR (95% CI) | Adjusted HR (95% CI)[b] | Adjusted HR by Treatment[c] (95% CI; $n$ = 1813) | |
|---|---|---|---|---|---|---|
| | | | | | Placebo ($n$ = 916) | Captopril ($n$ = 897)[d] |
| Death | 316 (19.4%) | 58 (26.0%) | 1.46 (1.10 to 1.93) | 1.46 (1.05 to 2.02) | 1.63 (1.05 to 2.52) | 1.33 (0.81 to 2.21) |
| Cardiovascular death | 260 (15.9%) | 51 (22.9%) | 1.55 (1.15 to 2.09) | 1.62 (1.14 to 2.30) | 1.74 (1.07 to 2.81) | 1.56 (0.92 to 2.63) |
| MI | 205 (12.6%) | 32 (14.3%) | 1.23 (0.84 to 1.78) | 1.04 (0.66 to 1.66) | 1.38 (0.78 to 2.47) | 0.70 (0.31 to 1.54) |
| CHF | 236 (14.5%) | 39 (17.5%) | 1.48 (1.05 to 2.07) | 1.35 (0.91 to 2.01) | 1.53 (1.08 to 2.16) | 1.20 (0.82 to 1.75) |
| Composite end point[e] | 564 (34.6%) | 94 (42.1%) | 1.41 (1.14 to 1.76) | 1.32 (1.03 to 1.70) | 1.53 (1.08 to 2.16) | 1.20 (0.82 to 1.75) |

[a]CI, confidence interval; HR, hazard ratio.
[b]Adjusted for age, gender, baseline creatinine (<1.0, 1.0 to <2.0, and ≥2.0 mg/dl), history of hypertension, history of diabetes, history of dyslipidemia, history of CHF, left ventricular ejection fraction, previous MI, use of diuretics, and treatment assignment.
[c]From the original cohort of 1854 patients, 41 who were not taking captopril at 2 wk as a result of adverse drug reactions (*e.g.*, hypotension, dizziness) were excluded for stratification of risk associated with WRF by treatment.
[d]Test for interaction: $P > 0.15$.
[e]Death, MI, CHF hospitalization, and stroke.

remained a significant predictor of WRF in this population of post-MI patients with systolic dysfunction.

Worsening renal function as early as 2 wk after acute MI was associated with a higher incidence of death and was an independent predictor of death (hazard ratio [HR] 1.46; 95% CI 1.05 to 2.02), cardiovascular death (HR 1.62; 95% CI 1.14 to 2.30), and the composite end point (HR 1.32; 95% CI 1.03 to 1.70; Table 2). The prognostic value of WRF not only remained significant after adjustment for covariates but also was a stronger predictor of cardiovascular outcomes than baseline creatinine (HR 1.31 [95% CI 1.01 to 1.70]; HR 1.21 [95% CI 0.91 to 1.61]; HR 1.15 [95% CI 0.95 to 1.39] for death, cardiovascular death, and composite end point, respectively). Although NS, there also was a higher incidence of recurrent MI and hospitalization for CHF in patients with WRF.

A total of 104 (5.7%) patient in the placebo group and 116 (6.4%) patients in the captopril group had WRF, with no difference in the rates of WRF between treatment groups ($P$ = 0.38). When stratified by treatment, the risk for death in patients with WRF was higher in the placebo group (HR 1.63; 95% CI 1.05 to 2.52) than in patients who were taking captopril at 2 wk (HR 1.33; 95% CI 0.81 to 2.21). A similar attenuation of risk was observed for the other primary end points as well as hospitalization for CHF (Table 2, Figures 1 and 2). Tests for interaction, however, were NS ($P$ = 0.49, 0.73, 0.49, and 0.37 for death, cardiovascular death, hospitalization for CHF, and the composite end point, respectively).

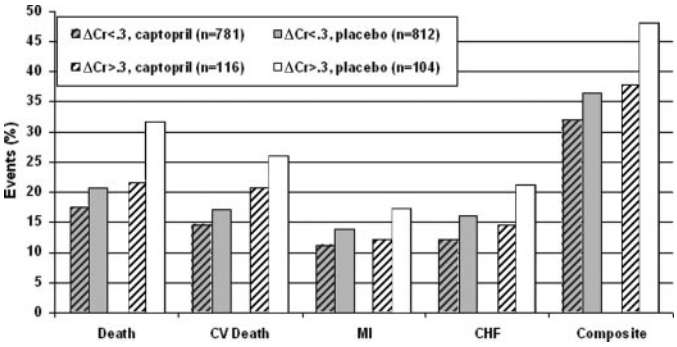


*Figure 1.* Event rate according to worsening renal function (WRF) and treatment group.

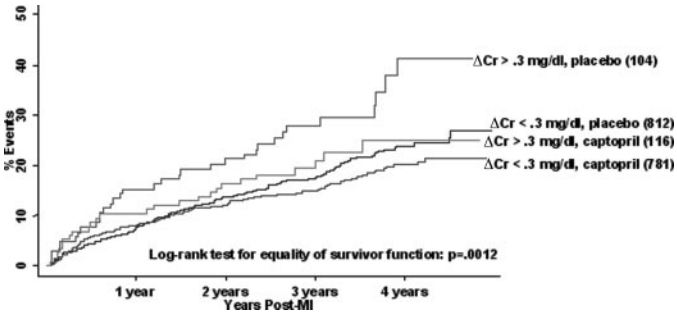


*Figure 2.* Kaplan-Meier curves for death stratified by WRF and treatment group.

## Discussion

Although baseline renal dysfunction is considered a potent cardiovascular risk factor in post-MI patients, the predictive value of WRF has not yet been addressed in this population. Because ACE inhibition can precipitate acute renal failure in the presence of severe bilateral renal artery stenosis, it is common practice to withdraw ACE inhibitors when renal function deteriorates; renal artery stenosis is a common finding among patients who undergo coronary angiography (14–18) and among those with heart failure (19). However, this policy may deprive many patients of the potential benefits of these drugs.

In this study of post-MI patients with systolic dysfunction, we observed that WRF, defined as a rise in creatinine of >0.3 mg/dl after 2 wk, was not uncommon (12.0%) and was associated with significantly increased risk for cardiovascular mortality and morbidity. The impact of WRF on outcomes persisted even after adjustment for known covariates and was a stronger predictor of events than baseline creatinine.

The majority of studies that have examined the prognostic value of reduced renal function have focused on serum creatinine values or estimated GFR at one point in time. The predictive value of WRF, however, has been less clear and has been determined primarily in patients who were hospitalized for heart failure, in which the incidence of WRF (27 and 28%) was consistently greater than in SAVE (12.0%) (9,10). More risk factors have proved predictive of WRF in the heart failure population (baseline creatinine, systolic BP, history of diabetes or CHF) than were seen in this population of post-MI patients with systolic dysfunction (age). Few trials have assessed the prognostic value of WRF in the setting of coronary artery disease. Shlipak *et al.* (20) found that WRF, defined as a change of creatinine of >0.3 mg/dl during 4 yr of follow-up, was not associated with outcome in postmenopausal women with stable coronary artery disease in the Heart and Estrogen/Progestin Replacement Study (HERS). No other study has examined the prognostic importance of WRF in the common and important setting of left ventricular dysfunction after MI.

Most clinical studies have defined WRF as an increase in creatinine of >0.3 mg/dl, a threshold that has been found in previous studies to have the highest sensitivity (81%) and specificity (62%) for predicting mortality (13). Initial analyses in our cohort (data not shown) demonstrated a similar threshold effect, with higher event rates occurring in patients with a change in creatinine of >0.3 mg/dl. Lower magnitude changes may be less clinically relevant and represent transient changes or inherent variability in creatinine measurement. However, a more linear or J-shaped association between small changes in creatinine and risk for adverse cardiovascular outcomes also has been suggested (21,22).

The decision to withdraw ACE inhibition in patients who experience elevations in serum creatinine has been controversial (23). Physicians are reluctant to continue treatment with ACE inhibitors when creatinine begins to rise because of concerns about precipitating acute renal failure (24). In proteinuric kidney disease, ACE inhibitors reduce glomerular hyperfiltration by causing efferent glomerular arteriolar vasodilation, and short-term WRF is associated with long-term stability of kidney function (25–28). However, WRF in the setting of coronary artery disease and impaired systolic function probably is more likely to be due to reduced glomerular perfusion rather than glomerular hyperfiltration in the setting of ACE inhibition and therefore may carry a different prognosis. Recent data have demonstrated the benefits of ACE inhibition in patients with advanced renal insufficiency, even when a patient's serum creatinine level continues to increase (29,30). Rapid and more extensive increases would suggest conditions such as bilateral renal artery stenosis or severe hypoperfusion, which warrant discontinuation of ACE inhibition. Butler *et al.* (31) did not find an association between WRF and ACE inhibitors in heart failure patients. Similarly, we did not observe a greater incidence of WRF in patients who received ACE inhibition in SAVE. Our data may suggest that the relationship between WRF and increased cardiovascular risk could be altered by ACE inhibitor therapy in patients after MI. Although a formal test for interaction was NS, most likely because of inadequate sample size and statistical power given the relatively small number of patients with WRF for each end point, the increased risk associated with WRF seemed consistently lower in the captopril group, raising the possibility that ACE inhibition may alter the relationship between elevation in creatinine and cardiovascular outcomes. This study has allowed for analysis of the effects of ACE inhibition on WRF and cardiovascular risk in a randomized, placebo-controlled setting. These hypothesis-generating results would argue against discontinuation of ACE inhibitor therapy after small increases in creatinine of <0.3 mg/dl.

A number of limitations of this analysis should be noted. Serum creatinine was measured 2 wk after randomization, which occurred on average 11 d after MI. The variation in time may have affected the results through either worsening or improvement of renal function. However, this variation in time not only underscores the prognostic value of WRF but also stresses the importance of repeating serum creatinine measurements from 1 to 3 wk after the acute event. The dosage of study medication (placebo or captopril) also was variable; although the study protocol did not specify that captopril should be stopped in the presence of WRF, titration regimens were left to the discretion of each patient's physician.

Patients who tolerated the initial test dosage were included regardless of whether the study medication was not titrated fully to the target dosage of 25 mg three times daily by the end of 2 wk. The majority of patients were started at 12.5 mg and titrated upward, but there were patients who started at lower dosages or were down-titrated as a result of adverse drug reactions or cardiovascular events before 2 wk, which might have influenced the predictive value of increased creatinine. We would have expected to see an average decline in GFR for patients who started captopril but did not find this in SAVE. This finding most likely was due to variation in dose titration and patients' not receiving the maximum therapeutic effect of captopril. The average change in GFR also may have been influenced by the 41 patients who dropped out of the trial as a result of adverse drug reactions from captopril. Our findings in the placebo group, however, would not have been influenced by dose titration. The results from this *post hoc* analysis were observed in post-MI patients with systolic dysfunction and cannot be extended to those with normal ventricular function. Finally, SAVE was conducted between 1988 and 1991. We cannot exclude the possibility that changes in the treatment of post-MI patients may have altered the current relation between WRF and cardiovascular risk. However, SAVE was conducted in a randomized, placebo-controlled setting and therefore allowed us to assess the true effect of ACE inhibition on cardiovascular outcomes in the setting of renal dysfunction using prospectively collected data.

## Conclusion

We have shown that in patients with acute MI and systolic dysfunction, WRF defined as an increase in creatinine of >0.3 mg/dl within the first 2 wk is not uncommon (12.0%) and when present is associated with a significant increase in risk for cardiovascular outcomes and mortality. In this population of patients with systolic dysfunction after MI, WRF was a more robust predictor of events and death than baseline serum creatinine. The risk that is associated with WRF was most prominent in patients who received placebo and seems to be attenuated in patients who receive captopril. These findings suggest that close monitoring of renal function during the first few weeks after acute MI may aid in long-term risk stratification for cardiovascular events and may argue against discontinuation of ACE inhibitor therapy after small, nonprogressive increases in creatinine.

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