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## Relation between Renal Dysfunction and Cardiovascular Outcomes after Myocardial Infarction

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### ABSTRACT

#### BACKGROUND

The presence of coexisting conditions has a substantial effect on the outcome of acute myocardial infarction. Renal failure is associated with one of the highest risks, but the influence of milder degrees of renal impairment is less well defined.

#### METHODS

As part of the Valsartan in Acute Myocardial Infarction Trial (VALIANT), we identified 14,527 patients with acute myocardial infarction complicated by clinical or radiologic signs of heart failure, left ventricular dysfunction, or both, and a documented serum creatinine measurement. Patients were randomly assigned to receive captopril, valsartan, or both. The glomerular filtration rate (GFR) was estimated by means of the four-component Modification of Diet in Renal Disease equation, and the patients were grouped according to their estimated GFR. We used a 70-candidate variable model to adjust and compare overall mortality and composite cardiovascular events among four GFR groups.

#### RESULTS

The distribution of estimated GFR was wide and normally shaped, with a mean ( $\pm$ SD) value of  $70\pm 21$  ml per minute per  $1.73$  m<sup>2</sup> of body-surface area. The prevalence of coexisting risk factors, prior cardiovascular disease, and a Killip class of more than I was greatest among patients with a reduced estimated GFR (less than  $45.0$  ml per minute per  $1.73$  m<sup>2</sup>), and the use of aspirin, beta-blockers, statins, or coronary-revascularization procedures was lowest in this group. The risk of death or the composite end point of death from cardiovascular causes, reinfarction, congestive heart failure, stroke, or resuscitation after cardiac arrest increased with declining estimated GFRs. Although the rate of renal events increased with declining estimated GFRs, the adverse outcomes were predominantly cardiovascular. Below  $81.0$  ml per minute per  $1.73$  m<sup>2</sup>, each reduction of the estimated GFR by 10 units was associated with a hazard ratio for death and nonfatal cardiovascular outcomes of 1.10 (95 percent confidence interval, 1.08 to 1.12), which was independent of the treatment assignment.

#### CONCLUSIONS

Even mild renal disease, as assessed by the estimated GFR, should be considered a major risk factor for cardiovascular complications after a myocardial infarction.

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**T**HE NATIONAL KIDNEY FOUNDATION defines chronic kidney disease as persistent kidney damage, as reflected by a glomerular filtration rate (GFR) of less than 60.0 ml per minute per 1.73 m<sup>2</sup> of body-surface area for more than three months.<sup>1</sup> This definition encompasses at least 11 million people in the United States, and the number is rising.<sup>2,3</sup> Community studies reveal a rising prevalence of cardiovascular disease with declining renal function.<sup>4-6</sup> Patients with end-stage renal disease, as defined by a GFR of less than 10.0 ml per minute per 1.73 m<sup>2</sup>, are at high risk for cardiovascular events, especially if they are receiving renal-replacement therapy.<sup>7</sup> More than 50 percent of deaths among patients with end-stage renal disease are due to cardiovascular events.<sup>8</sup>

The risk of subsequent cardiovascular events is higher among patients with chronic kidney disease than among persons with normal renal function.<sup>9,10</sup> The two-year mortality rate after myocardial infarction among patients with end-stage renal disease is approximately 50 percent — twice the mortality rate after myocardial infarction in the general population.<sup>11</sup> Possible explanations include higher proportions of coronary risk factors and lower use of strategies to modify cardiovascular risk.<sup>1</sup>

Limited information exists on the risks associated with lesser degrees of chronic kidney disease in patients who have had an acute myocardial infarction. The majority of what is known relates to the serum creatinine level, which is an insensitive indicator of renal function. Furthermore, the small number of studies conducted have had relatively short follow-up periods and have concentrated on fatal outcomes. Finally, only a small proportion of patients in these studies have been taking an inhibitor of the renin-angiotensin system. These drugs reduce cardiovascular risk and are nephroprotective. We evaluated the prevalence of chronic kidney disease using the estimated GFR in high-risk survivors of myocardial infarction to determine whether chronic kidney disease continues to be an independent predictor of nonfatal and fatal adverse outcomes in patients who are receiving inhibitors of the renin-angiotensin system.

## METHODS

### PATIENTS

The Valsartan in Acute Myocardial Infarction Trial (VALIANT) was a multinational, double-blind, randomized, controlled trial with three parallel treat-

ment groups that compared the efficacy and safety of long-term treatment with valsartan, captopril, and the two in combination. Eligible patients included men and women 18 years of age or older who had had an acute myocardial infarction (0.5 to 12 days previously) complicated by clinical or radiologic signs of heart failure, left ventricular systolic dysfunction, or both.<sup>12</sup> Patients with a baseline serum creatinine level of at least 2.5 mg per deciliter (221 μmol per liter) were excluded. The median duration of follow-up was 24.7 months, with a maximum of 16 visits. All patients gave their written informed consent, and the protocol was approved by the appropriate institutional review boards.

### TREATMENT

Eligible patients were randomly assigned in a 1:1:1 ratio to receive valsartan (target dose, 160 mg twice daily), captopril (target dose, 50 mg three times daily), or a combination of valsartan and captopril (target dose, 80 mg twice daily and 50 mg three times daily, respectively).<sup>12</sup>

### GFR MEASUREMENT

The GFR is considered most suitable for quantifying renal function.<sup>13</sup> Practical limitations exist in measuring GFR directly, especially in acutely ill patients. Several reliable equations incorporating clinical variables to estimate the GFR are available; we used the Modification of Diet in Renal Disease (MDRD) equation.<sup>13</sup>

### OUTCOMES

The primary end point was death from any cause.<sup>12</sup> Secondary end points included death from cardiovascular causes, congestive heart failure, recurrent myocardial infarction, resuscitation after cardiac arrest, stroke, and a composite of these.<sup>12</sup>

### STATISTICAL ANALYSIS

Patients were categorized according to the estimated GFR at baseline with the use of the four-component MDRD equation incorporating age, race, sex, and serum creatinine level<sup>13</sup>:

$$\text{estimated GFR} = 186 \times (\text{serum creatinine level} \\ \text{[in milligrams per deciliter]})^{-1.154} \\ \times (\text{age [in years]})^{-0.203}.$$

For women and blacks, the product of this equation was multiplied by a correction factor of 0.742 and 1.21, respectively.<sup>13</sup> A total of 14,527 patients had baseline creatinine values recorded a mean of 4.9 days after myocardial infarction. The distribu-

tion of the estimated GFR was divided into four categories (less than 45.0, 45.0 to 59.9, 60.0 to 74.9, and at least 75.0 ml per minute per 1.73 m<sup>2</sup>), incorporating the guidelines of the National Kidney Foundation.<sup>1</sup> Clinical outcomes included death from any cause and the cardiovascular composite end point. The estimated GFR is presented in categories for descriptive purposes but was a continuous measure in statistical tests. Baseline characteristics were analyzed with the use of Spearman's rank correlation and the Wilcoxon rank-sum test for continuous and categorical variables, respectively. Cox proportional-hazards modeling was used to compare clinical outcomes. Candidate variables included 70 baseline characteristics. For continuous variables, the Cox-model assumption of linearity between the variable and the logarithmic hazard ratio of the outcome was assessed by fitting restricted cubic splines in the model. These functions were graphically and statistically examined, and appropriate transformations were applied.<sup>14</sup> Stepwise elimination and backward selections were used to select the most parsimonious set of predictive variables. Treatment effects were then added to obtain the model reported here (see the Appendix). Kaplan–Meier estimates, stratified according to the estimated GFR, for death from any cause and the cardiovascular composite end point were determined and presented as event curves. All P values were two-sided, and a P value of less than 0.05 was considered to indicate statistical significance. Analyses were performed with the use of SAS software (version 6.0).

## RESULTS

### BASELINE CHARACTERISTICS

The baseline estimated GFR for the 14,527 patients was normally distributed (Fig. 1). The mean ( $\pm$ SD) estimated GFR was 70.2 $\pm$ 21.3 ml per minute per 1.73 m<sup>2</sup> (range, 7.6 to 139.8). A total of 5560 (38.3 percent) patients had an estimated GFR of at least 75.0 ml per minute per 1.73 m<sup>2</sup>, 4105 (28.3 percent) had an estimated GFR of 60.0 to 74.9 ml per minute per 1.73 m<sup>2</sup>, 3218 (22.2 percent) had an estimated GFR of 45.0 to 59.9 ml per minute per 1.73 m<sup>2</sup>, and 1644 (11.3 percent) had an estimated GFR of less than 45.0 ml per minute per 1.73 m<sup>2</sup>. Despite the use of a serum creatinine level of at least 2.5 mg per deciliter as an exclusion criterion, 4882 (33.6 percent) patients met the estimated GFR criteria for chronic kidney disease. The absolute

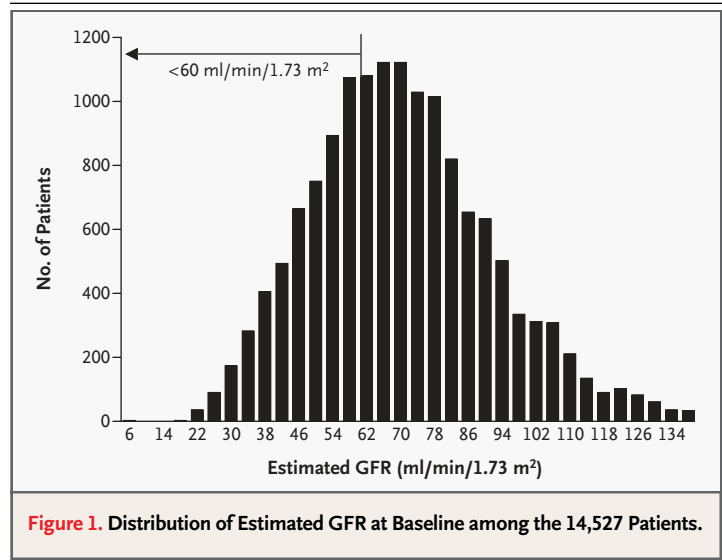


Figure 1. Distribution of Estimated GFR at Baseline among the 14,527 Patients.

difference in the mean serum creatinine level between the groups was 0.2 to 0.4 mg per deciliter (18 to 35  $\mu$ mol per liter).

The proportions of patients with coexisting conditions at baseline increased with decreasing estimated GFRs (Table 1). Patients in the lowest category of estimated GFR had the highest rates of hypertension, diabetes, prior myocardial infarction, prior congestive heart failure, and clinical evidence of left ventricular systolic dysfunction. The proportions of patients who were receiving cardiovascular pharmacotherapies (aspirin, beta-blockers, and statins) at baseline, as well as those who had undergone coronary revascularization, decreased with decreasing estimated GFRs. Although a lower estimated GFR was associated with increasing age and female sex, these variables were used in the determination of estimated GFR.

### OUTCOMES

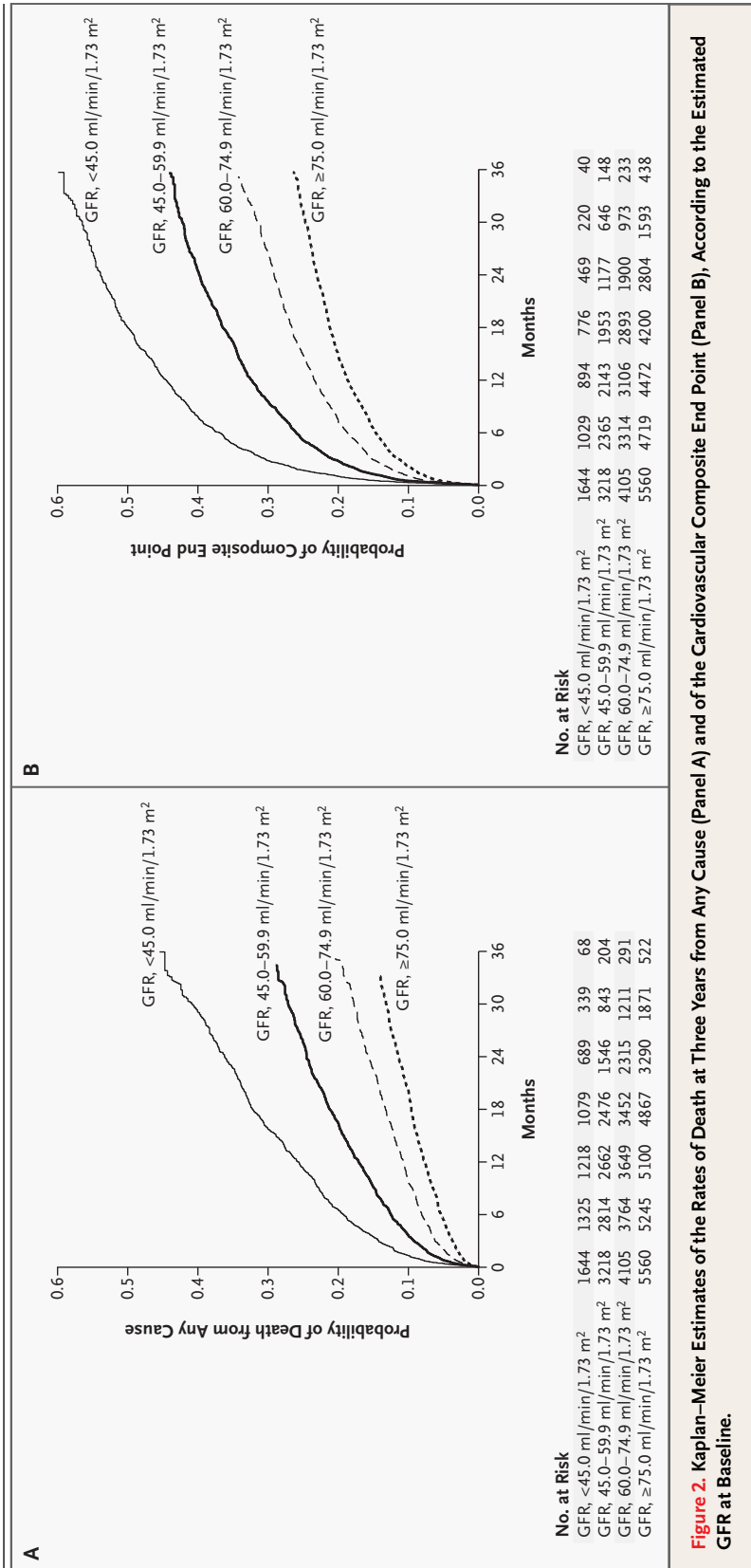
Decreasing estimated GFRs were associated with increasing mortality rates (Fig. 2A). Unadjusted Kaplan–Meier estimates of three-year mortality rates were 14.1 percent (95 percent confidence interval, 13.0 to 15.2) in the group with an estimated GFR of at least 75.0 ml per minute per 1.73 m<sup>2</sup>, 20.5 percent (95 percent confidence interval, 18.8 to 22.2) in the group with an estimated GFR of 60.0 to 74.9 ml per minute per 1.73 m<sup>2</sup>, 28.9 percent (95 percent confidence interval, 27.0 to 30.8) in the group with an estimated GFR of 45.0 to 59.9 ml per minute per 1.73 m<sup>2</sup>, and 45.5 percent (95 percent confidence interval, 42.1 to 48.9) in the group with an

**Table 1. Baseline Characteristics of the Patients According to the Estimated GFR.\***

Characteristic	GFR, <45.0 ml/min/1.73 m <sup>2</sup> (N=1644)	GFR, 45.0–59.9 ml/min/1.73 m <sup>2</sup> (N=3218)	GFR, 60.0–74.9 ml/min/1.73 m <sup>2</sup> (N=4105)	GFR, ≥75.0 ml/min/1.73 m <sup>2</sup> (N=5560)	P Value
Age (yr)	73.3±9.2	69.7±9.8	65.1±11.1	59.6±11.4	<0.001
Creatinine (mg/dl)	1.7±0.4	1.3±0.2	1.1±0.1	0.9±0.1	<0.001
Female sex (%)	56.5	41.1	28.4	19.8	<0.001
White race (%)	95.1	95.2	94.2	91.6	<0.001
Hypertension (%)	71.0	63.7	53.5	47.0	<0.001
Diabetes (%)	33.6	26.3	21.2	19.6	<0.001
Prior myocardial infarction (%)	38.0	32.0	26.3	23.8	<0.001
Prior heart failure (%)	29.3	20.1	12.3	9.4	<0.001
Killip class >I (%)	82.0	78.2	72.2	65.8	<0.001
Left ventricular systolic dysfunction (%)	79.0	76.3	75.6	77.3	0.88
Blood pressure (mm Hg)					
Systolic	126.7±18.9	125.1±17.8	122.5±16.3	120.2±15.9	<0.001
Diastolic	71.9±12.4	72.9±11.7	72.4±10.9	72.0±10.9	0.02
Medication (%)					
Aspirin	87.0	90.2	91.4	92.9	<0.001
Beta-blocker	60.7	66.0	71.9	74.7	<0.001
Statin	27.1	30.3	35.6	37.6	<0.001
ACE inhibitor	40.5	39.3	39.5	39.7	0.83
Procedure (%)†					
Cardiac catheterization	18.8	22.1	27.5	34.7	<0.001
PTCA	10.5	14.5	19.5	25.9	<0.001
CABG	0.9	1.4	1.8	3.2	<0.001

\* Plus-minus values are means ±SD. To convert values for creatinine to micromoles per liter, multiply by 88.4. ACE denotes angiotensin-converting enzyme, PTCA percutaneous transluminal coronary angioplasty, and CABG coronary-artery bypass grafting.

† The procedures took place in the interval after the myocardial infarction and before the patients were randomly assigned to a treatment group.



**Figure 2.** Kaplan–Meier Estimates of the Rates of Death at Three Years from Any Cause (Panel A) and of the Cardiovascular Composite End Point (Panel B), According to the Estimated GFR at Baseline.

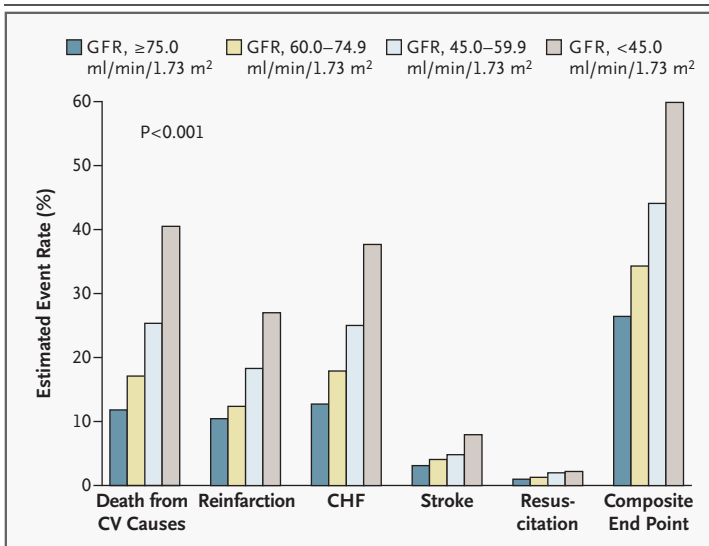
estimated GFR of less than 45.0 ml per minute per 1.73 m<sup>2</sup>.

There was a wide spectrum of risk across the categories of estimated GFR, with early divergence of the Kaplan–Meier curves for the composite end point (Fig. 2B). The composite cardiovascular end point and its individual components were more common among patients with a lower estimated GFR at baseline than among those with the highest estimated GFR ( $P < 0.001$  by the Cox model) (Fig. 3).

Using the group with an estimated GFR of at least 75.0 ml per minute per 1.73 m<sup>2</sup> as the reference group yielded unadjusted hazard ratios for death from any cause and the composite end point that increased as the degree of renal impairment increased (Table 2). In the adjusted model (the covariates used are listed in the Appendix), groups with a lower estimated GFR at baseline had worse outcomes than the reference group (Table 2). In the group with the lowest estimated GFR, the adjusted hazard ratio for adverse cardiovascular events was 1.49 (95 percent confidence interval, 1.35 to 1.65;  $P < 0.001$ ), as compared with 1.10 (95 percent confidence interval, 1.02 to 1.19) in the group with mild renal impairment (GFR, 60.0 to 74.9 ml per minute per 1.73 m<sup>2</sup>). When modeled as univariate

continuous variables (Fig. 4), a curvilinear relationship was seen between the hazard ratio and the estimated GFR, with an estimated GFR of 75.0 ml per minute per 1.73 m<sup>2</sup> used as the reference value. In the adjusted model, for baseline estimated GFR values below 81.0 ml per minute per 1.73 m<sup>2</sup>, each 10-unit decrease in the value was associated with a hazard ratio of 1.10 (95 percent confidence interval, 1.08 to 1.12;  $P < 0.001$ ) for death and nonfatal cardiovascular complications. This persisted after adjustment for treatment assignment — none of the treatments (captopril alone, valsartan alone, or combination therapy) altered the association of the baseline estimated GFR with cardiovascular outcomes.

Overall, there were few adverse renal events. Only 84 hospitalizations were attributed to renal problems, as compared with 10,394 adverse cardiovascular events. The group with the lowest estimated GFR had the highest percentage of patients with renal events that led to the discontinuation of the study drug (5.0 percent vs. 0.2 percent,  $P < 0.001$ ). Hyperkalemia requiring discontinuation of the study drug was more common in the group with the lowest estimated GFR than in the group with the highest estimated GFR (0.7 percent vs. 0.1 percent,  $P < 0.001$ ).



**Figure 3.** Kaplan–Meier Estimates of the Rates of Death at Three Years from Cardiovascular (CV) Causes, Reinfarction, Congestive Heart Failure (CHF), Stroke, Resuscitation after Cardiac Arrest, and the Composite End Point, According to the Estimated GFR at Baseline.

Data on patients with noncardiovascular events were censored. The P value is from the Cox model.

## DISCUSSION

The Joint National Committee for Detection and Treatment of Hypertension recognizes chronic kidney disease as an independent cardiovascular risk factor. We found that preexisting renal disease was a common and significant independent risk factor for adverse events in patients who had had a myocardial infarction complicated by heart failure, left ventricular systolic dysfunction, or both. Approximately one third had an estimated GFR suggestive of chronic kidney disease, a higher incidence than has been reported in previous cardiovascular trials.<sup>10,15-19</sup>

Some prior studies have used the serum creatinine level rather than the estimated GFR to detect renal dysfunction. The accuracy of the serum creatinine level as a marker of renal function is limited, owing to nonlinear associations with GFR that vary according to age, sex, race, and lean body mass.<sup>10,16,17</sup> Consequently, the National Kidney Foundation uses GFR rather than the serum creatinine level to define renal dysfunction.<sup>1,17</sup> Limitations of the use of the serum creatinine level were

**Table 2. Hazard Ratios for Death and Composite Outcomes According to the Estimated GFR and Creatinine Levels at Baseline.\***

Outcome	GFR, <45.0 ml/min/1.73 m <sup>2</sup> ; Creatinine, 1.7±0.4 mg/dl (N=1644)	GFR, 45.0–59.9 ml/min/1.73 m <sup>2</sup> ; Creatinine, 1.3±0.2 mg/dl (N=3218)	GFR, 60.0–74.9 ml/min/1.73 m <sup>2</sup> ; Creatinine, 1.1±0.1 mg/dl (N=4105)	GFR, >75.0 ml/min/1.73 m <sup>2</sup> ; Creatinine 0.9±0.1 mg/dl (N=5560)
Death (%)	45.5	28.9	20.5	14.1
Unadjusted hazard ratio (95% CI)	3.78 (3.39–4.21)	2.29 (2.07–2.53)	1.42 (1.28–1.58)	1.0†
Adjusted hazard ratio (95% CI)‡	1.70 (1.50–1.93)	1.38 (1.24–1.54)	1.14 (1.02–1.27)	1.0†
Composite end point (%)§	59.9	44.1	34.3	26.5
Unadjusted hazard ratio (95% CI)	2.94 (2.7–3.2)	1.92 (1.78–2.08)	1.33 (1.23–1.44)	1.0†
Adjusted hazard ratio (95% CI)‡	1.49 (1.35–1.65)	1.26 (1.16–1.37)	1.10 (1.02–1.19)	1.0†

\* Plus-minus values are means ±SD. Each row of hazard ratios was obtained by fitting a Cox model with the estimated GFR represented by three indicator variables. To convert values for creatinine to micromoles per liter, multiply by 88.4. CI denotes confidence interval.

† This group served as the reference group.

‡ Covariates used are listed in the Appendix.

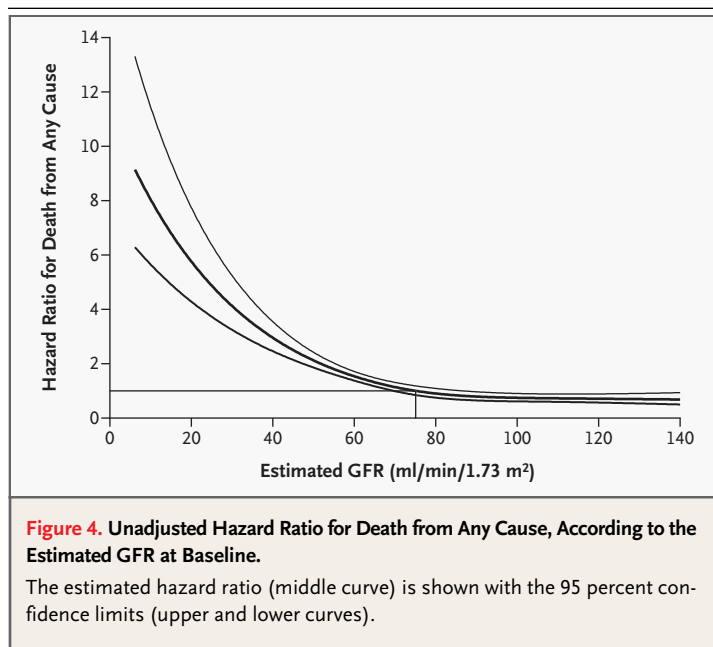
§ The composite end point consisted of death from cardiovascular causes, reinfarction, congestive heart failure, resuscitation after cardiac arrest, and stroke.

evident in our cohort, since differences in the levels between groups appeared small, whereas differences in cardiovascular risk were large. The use of estimated GFR revealed wider differences in renal function, and these differences paralleled the differences in cardiovascular risk.

Explanations for the higher frequency of renal dysfunction in our cohort than in previous cohorts include possible selection bias for patients with nearly normal renal function in other studies and an increasing incidence of chronic kidney disease. This possibility is partly accounted for by increasing rates of hypertension and diabetes mellitus.<sup>2,11</sup> As compared with other studies of patients with a recent myocardial infarction, our patients had a higher prevalence of renal dysfunction, suggesting that acute myocardial infarction complicated by left ventricular dysfunction, with or without heart failure, causes greater hemodynamic compromise and reduced renal perfusion.

We have shown not only that high-risk survivors of myocardial infarction have a high incidence of renal dysfunction, which is often missed with the use of serum creatinine measurements, but also that this dysfunction is a powerful independent predictor of fatal and nonfatal adverse cardiovascular outcomes. The presence of mild-to-moderate renal impairment after myocardial infarction increases the rate of adverse outcomes at 30 and 180 days.<sup>6,9,18–20</sup> Because previous studies used smaller cohorts and excluded patients with renal impairment, longer-term data on outcomes among patients with myocardial infarction are limited, particularly in relation to broad spectrums of renal dysfunction. Most previous studies focused on mortality, with limited information on nonfatal events. Our analysis of a cohort with a broad spectrum of renal function indicates that any short-term risk of complications and death from cardiovascular causes that is present at baseline persists in the longer term.

Three large-scale studies have examined the relationship between renal function and cardiovascular outcomes in patients with left ventricular systolic dysfunction: the Studies of Left Ventricular Dysfunction (SOLVD), Trandolapril Cardiac Evaluation (TRACE), and Survival and Ventricular Enlargement (SAVE) trials.<sup>21–23</sup> Like our trial, these trials also excluded patients with baseline serum creatinine levels of at least 2.5 mg per deciliter, and the SOLVD and SAVE studies used the MDRD equation to estimate GFR. In these studies, reduced



renal function was independently associated with an increased risk of death and cardiovascular events.<sup>21-23</sup> Despite the fact that our study differed from these studies, in that all patients received inhibitors of the renin-angiotensin system and management was more modern, we found similar associations between renal function and the risk of death and adverse cardiovascular outcomes.

The use of Framingham scores underestimates cardiovascular risk in patients with chronic kidney disease,<sup>24</sup> suggesting that other factors are also influential. After adjustment, a low estimated GFR was independently associated with an increased risk of death and complications from cardiovascular causes, reinforcing the concept that renal disease is a risk factor for cardiovascular events. Several studies have suggested that cutoff values for an estimated GFR of less than 60.0 ml per minute per 1.73 m<sup>2</sup> are predictive of adverse cardiovascular outcomes.<sup>13,24,25</sup> Our findings suggest that patients with renal impairment already have an increased risk of cardiovascular events and that this risk increases with worsening renal function.

Mechanisms by which renal dysfunction increases cardiovascular risk are under investigation. The progressive increase in cardiovascular risk with worsening estimated GFR is partly explained by factors associated with renal decline, including anemia, oxidative stress, derangements in calcium-phosphate homeostasis, inflammation, and

conditions promoting coagulation, all of which are associated with accelerated atherosclerosis and endothelial dysfunction.<sup>2-5</sup> Other nonconventional risks that progressively increase with renal decline include albuminuria, proteinuria, homocysteinemia, and elevated uric acid levels.<sup>1,4</sup>

The high prevalence of traditional coronary risk factors among patients with chronic kidney disease has been noted previously.<sup>1,4</sup> Patients with renal impairment have multiple coexisting conditions and angiographic evidence of severe and diffuse coronary artery disease.<sup>18</sup> In our cohort, the proportions of patients with hypertension and diabetes mellitus increased with worsening estimated GFR. Many coronary risk factors, particularly diabetes mellitus and hypertension, are established predictors for the progression of renal disease.<sup>4</sup> Synergism exists when conventional coronary risk factors perpetuate renal disease, and progressive renal decline increases the potency of such risk factors.

We found that older age and female sex were associated with a worsening estimated GFR. As in most studies of patients with myocardial infarction, the proportion of women was greater in the older age groups. By design, these variables reduce the estimated GFR when the MDRD equation is used, explaining the observed bias. However, several studies have documented age as a risk factor for cardiovascular and renal disease.<sup>3,5</sup>

The proportion of patients with chronic kidney disease who receive appropriate risk-factor modification and intervention is lower than in the general population, a concept termed “therapeutic nihilism.”<sup>2</sup> Many databases and registries have shown that this parallels worsening renal function.<sup>26,27</sup> Among patients with end-stage renal disease, who are known to be at extreme risk for cardiovascular events, less than 50 percent are taking a combination of aspirin, beta-blockers, angiotensin-converting-enzyme inhibitors, and statins.<sup>28,29</sup> In our study, patients in the lowest tier of renal function were the least likely to receive risk-modifying cardiovascular medications and to undergo coronary revascularization. Potential reasons include concern about worsening renal function and therapy-related toxic effects related to reduced clearance.<sup>1,16,30,31</sup> However, studies show that, when appropriately monitored, cardiovascular medications and coronary interventional strategies used in the general population can safely be administered to those with renal impairment and yield

similar benefits.<sup>24,25,32-36</sup> Our understanding of the efficacy and safety of cardiovascular medications and interventional strategies in these patients is limited, and many cardiovascular trials have excluded patients with renal disease.<sup>37</sup> Greater efforts are needed to reduce this therapeutic gap.

Blockade of the renin-angiotensin system with either angiotensin-converting-enzyme inhibitors or angiotensin-receptor blockers reduces the progression of renal disease.<sup>11,38</sup> Although dual blockade may provide more renal benefit than monotherapy, data are limited.<sup>39</sup> Whether improvements in renal function translate into improved cardiovascular risk is not clearly understood.<sup>40,41</sup> In VALIANT, all patients received effective inhibitors of the renin-angiotensin system, yet a lower baseline estimated GFR was still associated with adverse cardiovascular outcomes. Although patients with renal dysfunction are at risk for adverse cardiovascular and renal outcomes,<sup>1</sup> the predominant clinical effect of chronic kidney disease is on cardiovascular events.<sup>11</sup> The results of our study support such findings: the risk of hospitalization for renal causes increased with worsening estimated GFR, and the absolute risk was still significantly lower than the risk of cardiovascular events. In terms of cardiovascular outcomes, VALIANT documented that valsartan monotherapy had the same therapeutic benefits as captopril, and the combination increased the rate on discontinuation of treatment without further improving survival.<sup>12</sup> The absence of an interaction between treatment and the baseline estimated GFR may reflect the fact that the three approaches to the inhibition of the renin-angiotensin system have similar effects. However, this does not completely eliminate the association of baseline estimated GFR with cardiovascular outcomes. In the absence of the use of a placebo group, we cannot speak about what this effect may be.

Our study has several limitations. First, we cannot comment on the effect of the duration of renal dysfunction on the risk of adverse cardiovascular outcomes. Second, we did not address the influence of changes in renal function on risk, possibly related to therapy. Third, we could not evaluate the role of nephropathy induced by contrast medium

administered before serum creatinine was measured. Fourth, although the MDRD equation is a reliable means of estimating the GFR, it has limitations, because the serum creatinine level is influenced by nonrenal factors; the accuracy of the use of the MDRD equation for nonwhite populations other than blacks is unknown. Finally, we did not measure the rates of urinary albumin or protein excretion, factors that may drive the documented independent effect of the baseline estimated GFR on cardiovascular outcomes. Other renal-specific factors that were not included in our model may also change the influence of the estimated GFR on cardiovascular outcomes.

The presence of renal impairment that meets the criteria for chronic kidney disease is becoming common and is a significant independent risk factor for cardiovascular events among patients who have had a myocardial infarction complicated by heart failure, left ventricular systolic dysfunction, or both, as compared with patients with preserved renal function. This risk is progressive; we found that below 81.0 ml per minute per 1.73 m<sup>2</sup>, each 10-unit reduction in the baseline estimated GFR was associated with a 10 percent increase in the relative risk of death or nonfatal cardiovascular complications. The proportions of adverse renal events were still relatively small; patients have a higher risk of cardiovascular events than adverse renal outcomes. Among patients who have had a myocardial infarction, any degree of preexisting renal impairment should be considered a potent, independent, and easily identifiable risk factor for cardiovascular complications.

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Drs. Pfeffer and McMurray report having served as consultants for or having received honorariums from Novartis, AstraZeneca, Bristol-Myers Squibb, Takeda, and Merck. Dr. Maggioni reports having served as a consultant for or having received honorariums from Novartis and AstraZeneca. Drs. Califf, Solomon, Velazquez, and Rouleau report having served as consultants for or having received honorariums from Novartis. Dr. Zelenkofske is an employee of Novartis and has stock equity in the company. Dr. White reports receiving a research grant from Novartis. Dr. Pfeffer is named as a coinventor on a patent awarded to the Brigham and Women's Hospital regarding the use of inhibitors of the renin-angiotensin system in selected survivors of myocardial infarction; there is a licensing agreement between Novartis Pharmaceuticals and the Brigham and Women's Hospital that is not linked to sales.

#### APPENDIX

The following variables were used in the final multivariable models (asterisks denote terms that were kept in the final cardiovascular-events models, and daggers terms that were kept in the final mortality model):

**Continuous** — age (in years),\*† height (in centimeters), weight (in kilograms),\*† systolic blood pressure (in millimeters of mercury), diastolic blood pressure (in millimeters of mercury), heart rate (in beats per minute),\*† pulse pressure,\*† mean arterial pressure, time to randomization (in hours), and estimated GFR (in milliliters per minute per 1.73 m<sup>2</sup>)\*†; **categorical** — demographic: white race,\* sex,\* geo-

graphic region,\*† and treatment assignment\*†; coronary risk factors: presence or absence of hypertension,\* diabetes mellitus,\* dyslipidemia, and smoking (current\*† or previous\*); medical history: presence or absence of angina pectoris,\*† unstable angina,\* myocardial infarction,\*† heart failure,\*† transient ischemic attacks,\* stroke,\*† peripheral vascular disease,\*† atrial fibrillation, renal disease, pulmonary disease,\*† alcohol abuse,† cancer, hospitalizations within the prior six months,\*† angioplasty, coronary-artery bypass grafting,\* and an implantable defibrillator; procedures or events from the time of the qualifying myocardial infarction to randomization: presence or absence of coronary angiography, primary angioplasty,\*† thrombolysis,\*† angioplasty,\*† coronary-artery bypass grafting,\*† pacemaker, implantable defibrillator, intraaortic balloon pump, angina, heart failure,\*† atrial fibrillation,\*† ventricular fibrillation, ventricular tachycardia, renal insufficiency,\*† dyslipidemia,\* hypertension, and diabetes\*†; and characteristics at randomization: Killip class\*† and presence or absence of anterior myocardial infarction,\*† inferior myocardial infarction, left bundle-branch block,\*† Q waves on electrocardiograms, and radiologic evidence of heart failure.

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