Renal Function and Effectiveness of Angiotensin-Converting Enzyme Inhibitor Therapy in Patients With Chronic Stable Coronary Disease in the Prevention of Events with ACE inhibition (PEACE) Trial

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Background—Patients with reduced renal function are at increased risk for adverse cardiovascular outcomes. In the post–myocardial infarction setting, angiotensin-converting enzyme (ACE) inhibitors have been shown to be as effective in patients with impaired renal function as in those with preserved renal function.

Methods and Results—We assessed the relation between renal function and outcomes, the influence of ACE inhibition on this relation, and whether renal function modifies the effectiveness of ACE inhibition in patients with stable coronary artery disease and preserved systolic function enrolled in the Prevention of Events with ACE inhibition trial (PEACE). Patients (n=8290) were randomly assigned to receive trandolapril (target, 4 mg/d) or placebo. Clinical creatinine measures were available for 8280 patients before randomization. The estimated glomerular filtration rate (eGFR) was calculated with the 4-point Modification of Diet in Renal Disease equation. Renal function was related to outcomes, and the influence of ACE-inhibitor therapy was assessed with formal interaction modeling. The mean eGFR in PEACE was 77.6 ± 19.4, and 1355 (16.3%) patients had reduced renal function (eGFR < 60 mg·mL⁻¹·1.73 m⁻²). We observed a significant interaction between eGFR and treatment group with respect to cardiovascular and all-cause mortality (P = 0.02). Trandolapril was associated with a reduction in total mortality in patients with reduced renal function (adjusted HR, 0.73; 95% CI, 0.54 to 1.00) but not in patients with preserved renal function (adjusted HR, 0.94; 95% CI, 0.78 to 1.13).

Conclusions—Although trandolapril did not improve survival in the overall PEACE cohort, in which mean eGFR was relatively high, trandolapril reduced mortality in patients with reduced eGFR. These data suggest that reduced renal function may define a subset of patients most likely to benefit from ACE-inhibitor therapy for cardiovascular protection.

Key Words: angiotensin • coronary disease • inhibitors • kidney
has been attributed to enrollment of a lower-risk patient population in PEACE, a large majority of whom received effective concomitant therapy, such as coronary revascularization and statins, more frequently than did patients in the previous trials. There was no heterogeneity in any of the prespecified subgroups with respect to the primary outcome in PEACE.

Patients with reduced renal function are known to be at increased risk for cardiovascular events.\textsuperscript{12,13} We have previously shown in the Valsartan in Acute Myocardial Infarction (VALIANT) trial that after MI, patients with a reduced estimated glomerular filtration rate (eGFR), calculated with the use of the 4-variable Modification of Diet in Renal Disease equation that takes into account creatinine, age, sex, and race, were at significantly increased risk for all major cardiovascular events, including cardiovascular death, MI, and stroke.\textsuperscript{14} and that in the Survival And Ventricular Enlargement (SAVE) trial, ACE inhibitor therapy was associated with a trend toward greater benefit in patients with impaired renal function.\textsuperscript{15} Although we observed no difference in benefit, or the lack thereof, associated with trandolapril therapy on the primary end point of cardiovascular death, nonfatal MI, or coronary revascularization in patients enrolled in PEACE based on a serum creatinine level that was above or below the median (1.0 mg/dL), serum creatinine remains a relatively insensitive measure of renal function. We therefore investigated the influence of renal function, from the eGFR, on cardiovascular outcomes and the response to therapy with trandolapril in PEACE.

Methods

The Prevention of Events with ACE inhibition (PEACE) trial was designed to test the hypothesis that the ACE inhibitor trandolapril would reduce cardiovascular events in patients with chronic stable coronary disease.\textsuperscript{11,12} In brief, patients at least 50 years old, with stable coronary artery disease, and with normal or mildly reduced left ventricular function (left ventricular ejection fraction >40\%) were randomly assigned to treatment with the ACE inhibitor trandolapril or to placebo and followed up for a median of 4.8 years. Patients were excluded from PEACE if at the time of screening they had been hospitalized for unstable angina in the preceding 2 months, had coronary revascularization within the prior 3 months, had a planned elective coronary revascularization, or had a serum creatinine value >2.0 mg/dL (177 \textmu mol/L). A total of 8290 patients provided informed consent and were randomized. Of these, 10 patients had missing data for baseline serum creatinine and/or race, variables required to estimate GFR, and were therefore excluded, leaving 8280 patients included in this analysis. The percentage of patients assigned to trandolapril or placebo who withdrew from therapy and were not taking an open-label ACE inhibitor was 25.5\% and 8.3\%, respectively, at 3 years.

Baseline Measures

During the baseline visit with the clinic research staff, patients self-reported their cigarette smoking status, medication use, and history of hypertension, diabetes, angina, intermittent claudication, transient ischemic attack, stroke, MI, and coronary revascularization. The study documented prior MI, coronary revascularizations, ventricular function, and pharmacotherapy. Laboratory measures of serum creatinine, potassium, and total cholesterol were abstracted from recent medical records or obtained for the study from a local laboratory. The clinic research staff measured height, weight, and blood pressure according to standard clinic procedures. We estimated GFR from the local creatinine measurement from the recorded baseline serum creatinine concentration and the 4-variable Modification of Diet in Renal Disease equation\textsuperscript{16}:

\begin{align*}
\text{eGFR (mL} \cdot \text{min}^{-1} \cdot 1.73 \text{m}^2) &= 186 \times (\text{serum creatinine in } \text{mg/dL})^{-1.134} \times (\text{age in years})^{-0.203} \times (0.742 \text{ if female}) \times (1.21 \text{ if black})
\end{align*}

We categorized subjects into 4 groups based on eGFR in 15-mL increments (\(\geq 75, 60 \text{ to } 74, 45 \text{ to } 59, \text{ and } < 45\)) according to standard criteria based on the classification scheme proposed by the National Kidney Foundation’s Kidney Disease Outcomes Quality Initiative.\textsuperscript{18}

End Points

This analysis examined the following end points: total mortality; cardiovascular mortality; the PEACE primary composite outcome (cardiovascular death, nonfatal MI, coronary revascularization); and the PEACE original composite outcome (cardiovascular death or nonfatal MI).\textsuperscript{11,16} All patient-reported outcomes were new/incident outcomes and classified after critical review of the patients’ medical records by an events adjudication committee.

Statistical Analysis

We used Cox proportional-hazards models to conduct a post hoc analysis to examine the association between eGFR and cardiovascular end points. We tested for interaction between eGFR and treatment effect using a continuous model that provided the most power for interaction testing. Each model included a test of an eGFR \times treatment group interaction term. We also examined eGFR as a categorical variable to aid in the assessment of a gradient effect (<45.0; 45.0 to 59.9; 60.0 to 74.9; \(\geq 75.0\)) and to aid in the interpretation of potential interaction between eGFR and treatment group (<60.0, \(\geq 60.0\)). Cox models were also used to assess potentially confounding factors, ie, baseline factors associated with both eGFR and cardiovascular end points. The baseline covariates, chosen a priori, included age, sex, history of diabetes, history of MI, hypertension, and left ventricular ejection fraction (<0.50\%, \(\geq 50\%\)). Residual analysis was used to assess model fit. The negative-logarithm survival (cumulative hazard) function was used to test the proportional-hazards assumption. The collinearity index was used to check for intercorrelations among covariates.\textsuperscript{19} The SAS analysis system, version 8.2, was used for all analyses (SAS Institute, Inc, Cary, NC).

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

Results

The eGFR in PEACE ranged from 27 to 320 mL \(\cdot\) min\(^{-1}\) \(\cdot\) 1.73 m\(^{-2}\), with a mean of 77.6 \(\pm\) 19.4 mL \(\cdot\) min\(^{-1}\) \(\cdot\) 1.73 m\(^{-2}\) (interquartile range, 64.8 to 88.7 mL \(\cdot\) min\(^{-1}\) \(\cdot\) 1.73 m\(^{-2}\)), corresponding to a mean creatinine value of 1.03 \(\pm\) 0.22 (Figure 1). One thousand three hundred fifty-five (16.3\%) patients had a reduced
eGFR (<60 mL·min⁻¹·1.73 m²). Baseline characteristics by eGFR category are shown in Table 1. Patients with a lower eGFR were more likely to be older, female, and hypertensive and to have a history of stroke. Diabetes was more prevalent in patients with an eGFR <45 mL·min⁻¹·1.73 m². There were no trends observed with regard to left ventricular function or the use of β-blockers, aspirin, or lipid-lowering drugs. Both calcium channel blocker and diuretic use was more prevalent in patients with a lower eGFR.

We observed a significant interaction between eGFR and treatment with respect to all-cause mortality and cardiovascular mortality (P<0.02) (Figure 2). The relationship between eGFR and outcome was most marked in the placebo group (Table 2) and was attenuated in the trandolapril group.

Patients in the eGFR <45 mL·min⁻¹·1.73 m² category had the highest risk of all-cause or cardiovascular mortality, followed by patients in the eGFR 45 to 60 mL·min⁻¹·1.73 m² category. The hazard associated with worsening eGFR was considerably less apparent when additional outcomes were added to the mortality end point.

In patients with an eGFR <60 mL·min⁻¹·1.73 m², trandolapril therapy was associated with a 27% reduction in mortality (adjusted HR, 0.73; 95% CI, 0.54,1.00; P=0.05) compared with a much more modest reduction in patients

![Figure 2](http://circ.ahajournals.org/)

**Figure 2.** Kaplan-Meier estimates of the rates of death at 5 years from any cause in the placebo and trandolapril groups (eGFR <60 and eGFR ≥60).
with an eGFR $\geq 60$ (adjusted HR, 0.94; 95% CI, 0.78, 1.13; $P=0.50$; Figure 2). Similar trends were observed for cardiovascular mortality but not for the composite end points of cardiovascular death or nonfatal MI (PEACE original end point) or cardiovascular death, nonfatal MI, or revascularization (PEACE primary end point).

### Discussion

PEACE tested the hypothesis that ACE-inhibitor use in patients with preserved systolic function and stable coronary disease would reduce cardiovascular morbidity and mortality but found no difference between patients in the trandolapril and placebo groups with respect to the primary outcome of cardiovascular mortality, nonfatal MI, or revascularization. However, patients enrolled in PEACE had stable, low-risk coronary artery disease and received intensive therapy, including lipid reduction and coronary revascularization. As a consequence, the annualized rate of death was only 1.6%, similar to that of the age- and sex-matched general population. We observed that eGFR was a potent predictor of all-cause mortality and cardiovascular mortality in the low-risk PEACE patients, just as it has been shown to be in higher-risk patients after acute coronary syndromes. Moreover, we observed a significant interaction between eGFR and treatment effect in PEACE. The relation between eGFR and mortality outcome was most powerful in the placebo group and, with respect to mortality outcomes, considerably less apparent in the trandolapril group and with respect to composite end points. That serum creatinine was measured at the clinical sites and before enrollment, not in a core laboratory or with calibration, represents a limitation of this analysis. Nevertheless, these findings suggest that the relation between eGFR and outcome is substantively modified by ACE-inhibitor therapy and that patients with a reduced eGFR may be most likely to benefit from the cardiovascular protective effects of ACE inhibitors.

Increased adverse cardiovascular outcomes have been associated with worsening renal function in patients with chronic atherosclerotic disease and after MI. A variety of etiological factors have been proposed to explain the overall relation between renal function and cardiovascular risk, including nontraditional risk factors such as elevations in C-reactive protein, fibrinogen, and homocysteine. The original rationale for using ACE inhibition in patients with increased cardiovascular risk stemmed from hypotheses generated in the SAVE and Studies Of Left Ventricular Dysfunction (SOLVD) trials, which demonstrated a reduction in MI in patients treated with ACE inhibitors. A reduction in these events, in parallel with a reduction in total mortality, was also observed in the HOPE and EUROPA trials, designed specifically to test this hypothesis. PEACE, in contrast, did not report a similar benefit. The distribution of eGFR observed in the present analysis confirms that patients enrolled in PEACE were at relatively low risk, a potential explanation for the lack of benefit of ACE inhibition in PEACE, in contrast to that noted in the HOPE and
EUROPA trials. Only 16% of patients in PEACE had an eGFR < 60 mL · min⁻¹ · 1.73 m⁻², about half as many as in SAVE and the VALsartan In Acute myocardial Infarction Trial (VALIANT), which, in contrast to PEACE, enrolled patients with left ventricular dysfunction after infarction. An eGFR of 60 mL · min⁻¹ · 1.73 m⁻² is the point below which cardiovascular risk was shown to increase in these previous trials, a potential explanation for the fact that there was no apparent difference in the effect of trandolapril on the primary end point for patients with a serum creatinine value above or below the median of 1.0 mg/dL (corresponding to an eGFR of 77.6 mL · min⁻¹ · 1.73 m⁻²).

In this analysis, we observed a benefit with respect to all-cause mortality associated with trandolapril therapy in patients with an eGFR < 60 mL · min⁻¹ · 1.73 m⁻². This benefit was not observed for nonfatal end points, including nonfatal MI or stroke; for the primary PEACE composite end point (cardiovascular death, nonfatal MI, or revascularization); or for the original PEACE composite end point (cardiovascular death or nonfatal MI). The number of nonfatal MIs and strokes was relatively low in PEACE, even in the lower-eGFR groups, suggesting that this study may have simply been underpowered to show that benefit. Another explanation for this apparent paradox is that the PEACE composite end points were relatively insensitive to the effects of worsening eGFR. Indeed, the greatest trend toward benefit with trandolapril was seen for all-cause mortality, the end point that showed the steepest gradient in risk associated with decreasing eGFR (Table 2). Additionally, a treatment effect may have been diluted by the addition of the “softer” nonfatal end points, particularly revascularization, which is influenced independently by physician discretion. All-cause mortality remains the end point with the greatest overall precision.

We observed a significant interaction between eGFR and treatment effect with respect to all-cause and cardiovascular mortality, most apparent in the differential relation between eGFR and outcome in the placebo and trandolapril groups (Figure 2). The benefit of trandolapril therapy was greatest with lower eGFR. We observed a similar trend, though without a clear statistical interaction, in post-MI patients randomized to captopril or placebo in the SAVE trial. This finding from PEACE suggests that ACE-inhibitor therapy with trandolapril modifies the relation between eGFR and outcome, or alternatively, that a reduced eGFR enhances the relative efficacy of trandolapril therapy in this population. Though hypothesis generating, these results indicate that ACE inhibition may be most effective at lowering the risk in patients with a low eGFR and that low eGFR defines a population most likely to benefit from ACE-inhibitor therapy for cardiovascular protection. In contrast to the findings in SAVE, in which ACE inhibitors were as effective in patients with reduced eGFR as in those with preserved renal function, the present analysis suggests that ACE inhibitors were only effective for reducing all-cause and cardiovascular mortality in patients with reduced renal function, a finding that may be related to the relatively low-risk PEACE population. It is important to note that reduced eGFR is only one renal marker of increased cardiovascular risk. Microalbuminuria has also been shown to be a potent marker of cardiovascular risk. In PEACE, urine samples for microalbuminuria analysis were available in a subset of patients much smaller than that for whom creatinine values were available, but it will likely still provide insight on the independence of these 2 measures of risk. The recent report of ACE inhibitor benefit on renal function in nondiabetic patients with advanced chronic renal insufficiency underscores the importance of defining populations that might be most likely to benefit from pharmacological intervention.

Some limitations of this analysis should be noted. Few patients in PEACE had eGFR < 60 (16%), thus limiting our power to explore the relationship between eGFR and outcome, as well as eGFR and the effectiveness of trandolapril in this crucial range. Moreover, the even smaller number of patients in the lowest eGFR category further limits our power in this range, although point estimates for the effectiveness of trandolapril suggest that the effectiveness of trandolapril may continue to increase as eGFR decreases into this range. Nevertheless, the generalizability of these findings to the patients with severely impaired renal function is limited. Although more patients in the trandolapril group withdrew from therapy than in the placebo group, we believe that this likely resulted in an underestimation of the importance of eGFR as a modifier of trandolapril therapy.

Conclusions

We observed a significant interaction between eGFR, a measure of renal function, and treatment with the ACE inhibitor trandolapril in stable, coronary disease patients enrolled in PEACE. Trandolapril attenuated the relation between decreasing eGFR and increased all-cause and cardiovascular mortality; moreover, the effectiveness of trandolapril increased as eGFR decreased. These data help explain the lack of overall benefit in PEACE, in which mean eGFR was relatively high, suggesting a relatively low-risk patient population. Though hypothesis generating, these data further suggest that ACE inhibitors may offer the most cardiovascular protection in stable patients with reduced renal function and that renal function should be evaluated and considered when considering which low-risk patients to treat with ACE inhibition.

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Disclosures
Brigham and Women’s Hospital has been awarded patents relating to the use of inhibition of the renin-angiotensin system in selected survivors of MI. Drs Pfeffer and Braunwald are among the coinventors. Brigham and Women’s Hospital has a licensing agreement with Abbott Laboratories that is not linked to sales. All other authors report no disclosures.

References

CLINICAL PERSPECTIVE
Patients with reduced renal function are at increased risk for cardiovascular events. We explored the influence of renal function on the effectiveness of therapy with the angiotensin-converting enzyme (ACE) inhibitor trandolapril in the Prevention of Events with ACE inhibition trial (PEACE). In PEACE, patients with reduced renal function were more likely to have increased cardiovascular events, including death, myocardial infarction, stroke, or revascularization. Although overall PEACE demonstrated that trandolapril therapy was not effective in reducing cardiovascular events in patients with stable coronary disease, we observed a significant interaction between treatment with trandolapril and estimated glomerular filtration rate (eGFR). In patients with an eGFR >60 mL·min⁻¹·1.73 m⁻², there was no mortality benefit with trandolapril. In the small subset of patients (16%) with an eGFR <60 mL·min⁻¹·1.73 m⁻², trandolapril was associated with a 27% reduction in overall mortality (P=0.05). These hypothesis-generating findings help explain the apparent discrepancies between PEACE and the HOPE and EUROPA studies, in which ACE inhibitors appeared to benefit higher-risk patients, and suggest that reduced renal function may identify a subset of high-risk patients who would be most likely to benefit from an ACE inhibitor.
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