Are We Inhibited?

Renal Insufficiency Should Not Preclude the Use of ACE Inhibitors for Patients With Myocardial Infarction and Depressed Left Ventricular Function

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Context: Angiotensin-converting enzyme (ACE) inhibitors have been shown to decrease mortality in patients with myocardial infarction and depressed left ventricular function, but physicians may be reluctant to prescribe ACE inhibitors to patients with concomitant renal insufficiency.

Objective: To evaluate whether patients with depressed left ventricular ejection fraction following acute myocardial infarction have a similar reduction in mortality from ACE inhibitors regardless of their renal function.

Design: Retrospective cohort study using medical record data.

Setting: All nonfederal acute care hospitals.

Patients: A cohort of 20902 Medicare beneficiaries aged 65 years and older directly admitted to the hospital from February 1, 1994, through July 30, 1995, and with a documented left ventricular ejection fraction of less than 40% measured by echocardiography, radionuclide scintigraphy, or angiography following a confirmed acute myocardial infarction.

Main Outcome Measures: One-year survival for patients who received or who did not receive an ACE inhibitor at hospital discharge, stratified by the patient’s level of renal function.

Results: For the entire cohort, the receipt of an ACE inhibitor on hospital discharge was associated with greater 1-year survival (hazards ratio, 0.84; 95% confidence interval, 0.77-0.91) after adjusting for patient demographic characteristics, comorbidity, severity of illness (including left ventricular ejection fraction), and the receipt of other therapies. In stratified models, the receipt of an ACE inhibitor was associated with a 37% (16%-52%) lower mortality for patients who had poor renal function (serum creatinine level, 265 µmol/L [3 mg/dL]) and a 16% (8%-23%) lower mortality for patients who had better renal function. Use of aspirin therapy attenuated the benefit of ACE inhibitors in patients with poor renal function.

Conclusions: Moderate renal insufficiency should not be considered a contraindication to the use of ACE inhibitors in patients who have depressed left ventricular ejection fraction following myocardial infarction. Use of aspirin therapy may attenuate the benefit of ACE inhibitors in patients with high serum creatinine levels; therefore, further studies are needed to determine whether treatment with aspirin, alternative antiplatelet agents, or anticoagulation is indicated for these patients.

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SUBJECTS AND METHODS

SUBJECTS
The Cooperative Cardiovascular Project collected data from Medicare beneficiaries who were discharged from the hospital with an MI (International Classification of Diseases, Ninth Revision, Clinical Modification diagnosis code of 410). A total of 139,567 Medicare beneficiaries aged 65 years and older were directly admitted to a hospital in the United States with an acute MI between February 1, 1994, and July 30, 1995. The diagnosis was confirmed by medical record review and required either a creatine kinase-MB index above 5% or an elevated lactate dehydrogenase level with a lactate dehydrogenase-1 level greater than the lactate dehydrogenase-2 level, or by meeting 2 of the following 3 criteria: chest pain, creatine kinase level at least 2-fold greater than normal, or evidence of an acute MI confirmed by electrocardiography. We excluded patients who were transferred to another institution (n=36,747) and those who died during hospitalization (n=24,298). From this group of 78,522 patients, 20,092 had an LVEF of less than 40% as measured by echocardiography, radionuclide scintigraphy, or angiography.

MEASUREMENTS
Data collected for each patient included dates of hospitalization, demographic characteristics, comorbidities, severity of illness, electrocardiographic findings, cardiac enzyme levels, laboratory results (including serum creatinine levels), use of medications and treatment received. Data reliability, based on reabstraction of a random sample of 1078 medical records, was assessed using the k statistic; k statistics that evaluated patient receipt of medications ranged from 0.88 to 0.95.10

STATISTICAL METHODS
We used t and χ² tests to evaluate differences between patients who received ACE inhibitors at hospital discharge and those who did not, stratified by their highest serum creatinine level during hospitalization. We evaluated the effect of ACE inhibitors on 1-year survival using the Cox proportional hazards regression models, adjusting for the patient demographic characteristics, comorbidities, and severity of illness measures listed in Table 1.12 We included interaction terms related to age, sex, and race and an interaction term related to the use of aspirin and an ACE inhibitor in all models.13 We evaluated the possibility of an interaction between the effects of renal function and the receipt of ACE inhibitors on 1-year survival by including an interaction term in the model and by performing a stratified analysis based on the serum creatinine level. We also used propensity score methods to validate our results. The propensity for treatment as a function of the covariates was used to classify patients who were matched for observed characteristics but differed in treatment regimens.14 These models included over 100 covariates previously shown to influence outcomes after MI12 and produced similar results to those reported in the text.

All missing values were imputed by a “nearest neighbor” multiple imputation algorithm that imputes missing values for clusters of variables. Missing variables generally occurred in clusters. For example, if the electrocardiographic reading from one lead was missing, the values from the other leads were almost always missing; if one blood chemistry result was missing, other blood chemistry results were generally missing as well. Because the values of these variables are not independent, we imputed values by clustering using a hotdeck procedure based on approximately 50 demographic and clinical variables that were almost always present.15,16

We repeated our analyses using the serum creatinine level as a continuous variable, using varying cutoffs for a high serum creatinine level, and using the serum creatinine level from hospital admission. We also repeated our analyses when missing values were not imputed. Statistical analysis was performed using the SAS statistical package.17 All P values are 2 sided.

RESULTS

PATIENT CHARACTERISTICS
Only about one third of the patients who had poor renal function were treated with ACE inhibitors at hospital discharge, compared with about 60% of the patients who had better renal function (Table 1). Patients with a history of diabetes mellitus or congestive heart failure, and those who had congestive heart failure on hospital admission, were more likely to receive ACE inhibitors at hospital discharge. Patients who received calcium channel blockers at hospital discharge were much less likely to receive ACE inhibitors.

MORTALITY
In univariate analysis, patients with serum creatinine levels above 265 µmol/L (>3 mg/dL) had an approximately 20% lower 1-year survival compared with patients with lower serum creatinine levels (Figure 1). Use of ACE inhibitors was associated with a marked reduction in mortality for patients with higher serum creatinine levels, but had little effect on patients with lower serum creatinine levels.

In multivariate analysis, the receipt of an ACE inhibitor at hospital discharge was associated with a 37% increase in 1-year survival for patients with serum creatinine levels above 265 µmol/L (>3 mg/dL) and a 16% increase for patients with lower serum creatinine levels (Table 2). Patients with serum creatinine levels above 265 µmol/L (>3 mg/dL) who did not receive ACE inhibitors had the lowest survival rates (Figure 2). Advanced age, female sex, the presence of comorbid conditions (diabetes mellitus, dementia, or peripheral vascular disease), and increased severity of illness (congestive heart failure or conduction disturbances) all were associated with lower survival. Higher LVEF and the receipt of medications (aspirin, thrombolysis, or a β-blocker) and revascularization (percutaneous transluminal coronary angioplasty and coronary artery bypass grafting) were associated with greater 1-year survival. Analyses using a cutoff value for
Although treatment with ACE inhibitors prolongs survival in patients who have MI and depressed LVEF, many potential candidates do not receive therapy. In a study of Medicare beneficiaries with acute MI who were ideal candidates to receive ACE inhibitors, only about half of the patients received ACE inhibitor therapy on hospital discharge. We found that in similar patients who have renal insufficiency, only about one third of the patients received an ACE inhibitor.

We found no decrement in the therapeutic benefit of ACE inhibitors for patients with elevated serum creatinine levels. Rather, patients who had poor renal function had a greater increase in 1-year survival than patients who had better renal function. Although speculative, there are several explanations for these results. First, renal insufficiency was associated with a poor prognosis and may indicate more severe cardiac impairment.
angiotensin-converting enzyme inhibitors may have a greater benefit in this high-risk group. Second, patients who have renal insufficiency may have a more activated renin-angiotensin system and higher angiotensin II levels. Since ACE inhibitors decrease angiotensin II levels, their benefits may be greater in patients who have poor renal function. Finally, patients who have poor renal function may be more likely to have other disorders that benefit from ACE inhibitor therapy. Although we adjusted for the presence of diabetes mellitus or hypertension, patients who have poor renal function may have had a greater severity of these disorders.

Aspirin therapy has been shown to attenuate the beneficial effect of enalapril maleate therapy on systemic resistance and cardiac output in patients with severe heart failure, however, not every study has confirmed this finding. In a post hoc subgroup analysis of the Cooperative New Scandinavian Enalapril Survival Study II, the only trial that failed to demonstrate a benefit of ACE inhibitors for patients after MI, an apparent interaction between ACE inhibitor and aspirin use on mortality was observed. Although patients who were not treated with aspirin had a lower mortality if they were randomly assigned to receive enalapril therapy, the opposite trend was found in patients who received aspirin therapy. The same aspirin-ACE inhibitor interaction was present in the Studies of Left Ventricular Dysfunction (SOLVD) trial.

Enalapril therapy had no effect on mortality for aspirin-treated patients, but significantly reduced mortality for patients not receiving antiplatelet agents; this interaction was highly significant but needs to be interpreted cautiously because the use of aspirin therapy was not assigned randomly.

We found that the interaction among aspirin, ACE inhibitors, and mortality may be more important in patients with compromised renal function. The risks and benefits of aspirin therapy for patients with a poor LVEF after MI must be weighed for each patient. Substitution therapy with warfarin sodium or an antiplatelet agent with a different mechanism of action such as clopidogrel may be considered, especially in patients who have impaired renal function. A large international study, the Warfarin-Antiplatelet Therapy in Chronic Heart Failure (WATCH) Trial, will address this question by randomly assigning patients with heart failure to receive warfarin, aspirin, or clopidogrel therapy.

Our study has a number of limitations. First, serum creatinine measurements during hospitalization may not be reliable indicators of renal function. Since serum creatinine levels at hospital discharge were unavailable, we used the highest serum creatinine level during hospitalization to define the extent of renal insufficiency. We also performed all analyses using the serum creatinine level at hospital admission and obtained similar results. Although it is possible that the serum creatinine levels were significantly lower in some patients by the time therapy with an ACE inhibitor was begun, levels above 265 µmol/L (>3 mg/dL) are likely to identify patients with substantially compromised renal function.

Second, we did not determine whether treatment with an ACE inhibitor was begun after hospital discharge. We also lacked data on the dosage, consistency of use, and monitoring of patients receiving ACE inhibitors. However, these potential “crossover” biases would reduce the magnitude of benefit observed from receipt of an ACE inhibitor at hospital discharge.

Finally, as in all cohort studies, it is possible that unmeasured confounders resulted in the observed mortality benefit from receiving ACE inhibitors. However,

Table 2. Effect of Use of ACE inhibitors on 1-Year Mortality in 20 902 Medicare Beneficiaries With Impaired Left Ventricular Ejection Fraction After Acute Myocardial Infarction Stratified by Serum Creatinine Level

<table>
<thead>
<tr>
<th>Variable</th>
<th>Stratified Analyses</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Serum Creatinine Level &gt;270 µmol/L (&gt;3 mg/dL) (n = 1582)</td>
</tr>
<tr>
<td></td>
<td>HR 95% CI</td>
</tr>
<tr>
<td>ACE inhibitor at hospital discharge</td>
<td>0.84 (0.77-0.91)</td>
</tr>
<tr>
<td>Aspirin therapy at hospital discharge</td>
<td>0.89 (0.82-0.96)</td>
</tr>
<tr>
<td>Aspirin therapy and ACE inhibitor interaction</td>
<td>1.08 (0.97-1.20)</td>
</tr>
<tr>
<td>Serum creatinine level &gt;265 µmol/L (&gt;3 mg/dL)</td>
<td>1.34 (1.21-1.48)</td>
</tr>
</tbody>
</table>

*ACE indicates angiotensin-converting enzyme; HR, hazards ratio; CI, confidence interval; and ellipses, not applicable. All entries are adjusted for variables listed in Table 1.
patients who had poor renal function and a 16% relative risk reduction from receipt of an ACE inhibitor as compared with the simple bivariate methods increased the apparent mortality benefit of receiving ACE inhibitors compared with the simple bivariate comparisons in Figure 1. Thus, it is likely that adjusting for additional, unmeasured confounders would further increase the apparent benefits of ACE inhibitor therapy for patients with renal insufficiency.

In proving the benefit of ACE inhibitor therapy for patients who had a poor LVEF, investigators have excluded patients with renal insufficiency, presumably because of the perceived risk of treating these patients with an ACE inhibitor. However, our observational study shows that patients who had poor renal function may derive an even greater benefit from the use of ACE inhibitor therapy. Furthermore, since patients with renal insufficiency have a higher mortality than patients without renal insufficiency, the use of ACE inhibitor therapy in these patients may save more lives per patient treated. For example, assuming that patients who are not treated with an ACE inhibitor have a 50% 1-year mortality if they have poor renal function and a 30% 1-year mortality if they have better renal function, a 16% relative risk reduction from receipt of an ACE inhibitor would result in 8 lives saved for every 100 treated patients with poor renal function and approximately 5 lives saved for every 100 treated patients with better renal function.

We believe that moderate renal insufficiency should not be considered a contraindication to the use of ACE inhibitor therapy for patients who have poor LVEF following MI. However, appropriate caution should be used. Patients with renal insufficiency should receive a lower initial dose of an ACE inhibitor, undergo careful monitoring of their serum potassium and creatinine levels, and perhaps avoid using inhibitors of prostaglandin synthesis (eg, especially potent nonsteroidal anti-inflammatory drugs). An increase in the serum creatinine level of less than 30% of the baseline value can be expected with ACE inhibitor use. When the elevation in the serum creatinine level is clinically important, reducing the dose of diuretic agents is a reasonable first step if there is no fluid retention. A randomized trial for patients with renal insufficiency would help confirm our conclusion that we have been too inhibited in our use of ACE inhibitors.

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REFERENCES


**Correction**

**Error in Abstract.** In the original investigation by Blankfield et al titled “Bilateral Leg Edema, Obesity, Pulmonary Hypertension, and Obstructive Sleep Apnea,” published in the August 14/28 issue of the *ARCHIVES* (2000;160:2357-2362), an error occurred in the abstract on page 2357. The first sentence of the “Methods” section of the abstract should have read as follows: “Twenty ambulatory adults with bilateral leg edema, echocardiographic evidence of pulmonary hypertension (estimated pulmonary artery systolic pressure >30 mm Hg) without left ventricular dysfunction, and no clinically apparent pulmonary disease were enrolled from a suburban family practice and an inner-city family practice during a 3-year period.” The journal regrets the error.


**Correction**

In the article titled “Are We Inhibited? Renal Insufficiency Should Not Preclude the Use of ACE Inhibitors for Patients With Myocardial Infarction and Depressed Left Ventricular Function,” published in the September 25th issue of the ARCHIVES (2000;160:2645-2650) in the “Results” subsection of the “Abstract” on page 2645, lines 8 through 11 should have read as follows: “In stratified models, the receipt of an ACE inhibitor was associated with a 37% (16%-52%) lower mortality for patients who had poor renal function (serum creatinine level, >265 µmol/L [>3 mg/dL] and a 16% (8%-23%) lower mortality for patients who had better renal function.” The journal regrets the error.