Outcomes of Patients With Chronic Renal Insufficiency in the Bypass Angioplasty Revascularization Investigation

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Background—Although severe chronic kidney disease (CKD) is an independent predictor of mortality among patients with coronary artery disease, the impact of mild CKD on morbidity and mortality has not been fully defined.

Methods and Results—Morbidity and mortality for the 3608 patients with multivessel coronary artery disease enrolled in the Bypass Angioplasty Revascularization Investigation randomized trial and registry were compared on the basis of the presence and absence of CKD, defined as a preprocedure serum creatinine level of >1.5 mg/dL. Seventy-six patients had CKD. Patients with renal insufficiency were older and more likely to have a history of diabetes, hypertension, and other comorbidities. Among patients undergoing PTCA, patients with CKD had a greater frequency of in-hospital death and cardiogenic shock (P<0.05 and 0.01, respectively). There was a trend toward a larger proportion of patients with CKD experiencing angina at 5 years (P=0.079). Patients with CKD had more cardiac admissions (P=0.003 and <0.0001 for patients undergoing PTCA and CABG, respectively) and a shorter time to subsequent CABG after initial revascularization than patients without CKD (P=0.01). CKD was associated with a higher risk of death at 7 years, both of all causes (relative risk 2.2, P<0.001) and of cardiac causes (relative risk 2.8, P<0.001).

Conclusions—CKD is associated with an increased risk of recurrent hospitalization, subsequent CABG, and mortality. This increased risk of death is independent of and additive to the risk associated with diabetes. (Circulation. 2002;105:2253-2258.)

Key Words: kidney ■ coronary disease ■ mortality

There are more than 300,000 patients in the United States currently receiving renal replacement therapy. Although the mortality rate for patients with end-stage renal disease (ESRD) during their first year of dialysis declined since 1988, it is still >19%, with more than one half of deaths related to cardiovascular disease. Furthermore, ESRD patients with coronary artery disease who survive myocardial infarction have an almost 60% 1-year mortality rate.

The risk associated with cardiovascular disease begins well before the onset of ESRD, ie, during the period of early chronic kidney disease (CKD). Although the population with CKD is more difficult to quantify, it numbers at least 3 million. Furthermore, patients with CKD have a greater prevalence of cardiovascular disease than the general population, and the presence of CKD is a potent predictor of mortality among patients with coronary artery disease.

Although multiple observational studies suggest that patients with concurrent coronary artery disease and CKD have greater mortality risk than patients without CKD, these patients have not been examined in the setting of a clinical trial of PTCA versus CABG. This analysis focusing on the subgroup of patients with CKD enrolled in the Bypass Angioplasty Revascularization Investigation (BARI) was therefore undertaken to explore the effect of CKD on the clinical course and survival of a cohort of patients with documented coronary artery disease.

Methods

Description of BARI
The protocol and baseline characteristics for the BARI trial have been discussed elsewhere. Patients were eligible if they had multivessel coronary artery disease, required revascularization because of angina or objective evidence of ischemia, and had not undergone and were suitable for revascularization by both CABG and PTCA. Of 4110 eligible patients, 1829 were randomized to either CABG or PTCA. Another 2010 eligible patients, who did not consent to be randomized, agreed to be followed in a registry.
A total of 3608 patients were used in this analysis: 892 randomized patients received CABG, 903 randomized patients received PTCA, 625 registry patients received CABG, and 1188 registry patients received PTCA. The primary end point was all-cause mortality. Secondary end points included myocardial infarction and subsequent revascularization.

Definition of Variables
CKD was defined as a history of serum creatinine >1.5 mg/dL. Information on this value was obtained before cardiac catheterization and recorded in the database as ≤ or >1.5 mg/dL. The trial protocol did not exclude patients on the basis of creatinine, and no patients enrolled required dialysis.

The presence of diabetes mellitus was defined by treatment with either oral hypoglycemics or insulin at baseline. Arterial emboli were defined as embolic events to an extremity or the loss of pulse that required treatment. Acute renal insufficiency after the initial revascularization procedure was defined as renal failure that required dialysis within 24 hours of revascularization. Cardiogenic shock and respiratory failure (including noncardiac pulmonary edema and adult respiratory distress syndrome) were documented in the postprocedure period. Angina included both stable (Canadian Cardiovascular Society class I through IV) and unstable angina during the prior 6 weeks. Hospital admissions were defined as “cardiac” if a cardiac procedure was performed, cardiac arrest was the reason for admission, or the hospitalization was due to a complication of a revascularization procedure.

Statistical Analysis
Clinical and demographic variables were compared for patients on the basis of the presence or absence of CKD with the Student t test or Wilcoxon rank-sum test for continuous variables and χ² or Fisher exact test for categorical variables. Proportions of patients experiencing medical complications after their initial revascularization were described for patients with and without CKD and compared by Fisher exact test. Within each treatment group, the proportion of patients experiencing angina were compared at baseline and yearly among patients with and without CKD by χ² statistics. Wilcoxon nonparametric statistics were used to compare the distribution of cardiac admissions over 5 years between patients with and without CKD, stratified on the basis of initial revascularization.

Survival curves for all-cause mortality, cardiac mortality, and subsequent CABG and PTCA were estimated by the Kaplan-Meier method and compared by log-rank test. Multivariate Cox proportional hazard regression was used to estimate the association between CKD and mortality (all-cause and cardiac). Demographic and clinical variables entered in the analysis included sex, race, age, diabetes, and revascularization strategy. Other variables tested for significance included body mass index, education, smoking at baseline, self-rated health, congestive heart failure, prior myocardial infarction, peripheral vascular disease, malignancy, any major ECG abnormality, unstable angina, stable Canadian Cardiovascular Society class III or IV angina, angina duration at least 1 year, triple-vessel disease, significant proximal left anterior descending coronary artery lesion, class C lesion, total occlusion, diffuse lesion, left/mixed dominance, left ventricular (LV) ejection fraction, and number of significant lesions. LV ejection fraction was available for 87.2% of patients. For those patients in whom LV ejection fraction data were missing, the value was estimated by a linear regression model based on demographic and clinical variables. Variables in the survival model were included in stepwise regression with P < 0.05 and 0.10 used as entry and exit criteria. After the variables were selected, interactions between CKD and treatment, diabetes, LV ejection fraction, and number of coronary artery lesions were tested with separate regression models.

All probability values are 2 sided, and all CIs are 95%. Analyses were performed with SAS version 6.12 (Cary, NC).

Results
Comparison of Baseline Comorbid Factors Between Groups With and Without CKD
Of 3608 BARI randomized and registry patients, 2.1% (76) had CKD. Patients with CKD were in general older, more likely to be black, and more likely to have diabetes, congestive heart failure, peripheral vascular disease, hypertension, and other comorbidities (Table 1). Patients with CKD also had longer duration of angina, had a greater number of significant coronary artery lesions, were more likely to have triple-vessel disease and at least 1 class C lesion, and were more likely to have abnormal LV function.

Comparison of In-Hospital Complication, Recurrent Angina, Recurrent Hospitalization, and Need for Subsequent Revascularization
In general, patients with as compared with those without CKD undergoing PTCA experienced a greater frequency of complications that included episodes of acute renal failure after their initial revascularization (Table 2). The in-hospital death rate for patients undergoing PTCA was higher for patients with than for those without CKD (6.7% versus 0.7%; P < 0.05). Similarly, the incidence of the combination of death or Q-wave myocardial infarction was significantly higher among patients undergoing PTCA with than among those without CKD (11.0% versus 3.0%; P < 0.01). In addition, PTCA patients who had CKD had significantly more episodes of cardiogenic shock (4.4% versus 0.7%; P < 0.05) and arterial emboli (4.4% versus 0.7%; P < 0.05). Patients with CKD undergoing CABG experienced complications at a rate similar to that of patients without CKD.

Among patients initially treated with CABG, there was no statistical difference between groups with and without CKD in the occurrence of angina during follow-up. Patients with CKD undergoing PTCA had a trend toward a greater frequency of angina compared with PTCA patients without CKD 5 years after initial revascularization (P = 0.079; data not shown). Patients with CKD had a greater number of cardiac hospitalizations over 5 years than did patients without CKD regardless of the initial treatment (3.64 versus 2.38 for patients with and without CKD undergoing PTCA, P = 0.003; 2.48 versus 1.77 for patients with and without CKD undergoing CABG, P = 0.001).

Time to subsequent CABG after initial revascularization differed among patients with and without CKD (P = 0.01; Figure 1). Among patients with CKD, 19.5% and 24.7% of patients required subsequent CABG surgery at 2 and 5 years after initial revascularization, respectively, compared with 12.3% and 16.2% of patients without CKD. No difference was observed between cohorts based on CKD when time to subsequent PTCA was compared. Among patients with CKD, 15.5% and 21.0% of patients required subsequent PTCA at 2 and 5 years, respectively, compared with 15.5% and 25.8% of patients without CKD (P = 0.50).

Impact of CKD and Diabetes on Survival
Seven-year all-cause mortality was markedly different for patients on the basis of both the presence and absence of CKD and of diabetes. Among patients without diabetes, mortality...
at 7 years was 39% among patients with CKD and 12% among patients without CKD (Figure 2). Mortality was higher among patients with diabetes, at 28% for patients without CKD and 67% for patients with CKD. Similar results were obtained when mortality due to cardiac causes was compared among the cohorts (Figure 3). Survival was significantly different among patients with versus those without CKD among patients both with and without diabetes (log-rank test \( P<0.001 \) for both all-cause and cardiac mortality).

In a multivariate model, CKD was associated with an increase risk of death, both of all causes (relative risk [RR] 2.31; 95% CI 1.63 to 3.28; \( P=0.001 \); Table 3) and of cardiac mortality associated with diabetes. The interactions between CKD and revascularization, diabetes (treated by either insulin or oral agents), LV function, and severity of coronary artery disease were not significant. The interaction between CKD and the presence of diabetes treated by insulin approached statistical significance (\( P=0.055 \)). In the fully adjusted model that included the interaction between the presence of CKD and diabetes treated by insulin, CKD was associated with an even greater risk of mortality among patients with (RR 3.34; 95% CI 2.11 to 6.99; \( P=0.004 \)) and among those without (RR 1.88; 95% CI 1.23 to 2.89; \( P=0.004 \)) insulin-treated diabetes.

### Discussion

Patients with mild CKD experienced a doubling of mortality compared with patients without CKD during a 7-year follow-up period after revascularization treatment for coronary atherosclerosis. Mortality risk among patients with mild CKD without diabetes was similar to that of patients with diabetes without CKD. However, when both mild CKD and diabetes were present, the mortality risk was additive at 70%
during a 7-year period. The present study provides long-term follow-up after revascularization with PTCA and CABG and demonstrates a markedly increased risk of mortality among patients with both diabetes and mild CKD. It describes the increased incidence of recurrent hospitalization and shortened time to subsequent CABG surgery for patients with CKD after initial revascularization.

These results are consistent with prior studies that suggest that even mild CKD is associated with an increased risk of in-hospital complications after PTCA and that CKD is associated with greater mortality among the general population, among patients admitted to a cardiac care unit, and after revascularization with PTCA. Although these prior studies used observational data, this is the first study to examine these relationships in the unique setting of a randomized trial. The randomized trial design obviates the indication bias imposed by the presence of CKD on choice of revascularization strategy. For this reason, the present analysis provides information critical to the assessment of the impact of CKD on outcomes in patients with cardiovascular disease.

The mechanism for the increased risk of mortality and adverse outcomes among patients with mild CKD may be related to the increased prevalence of atherosclerotic risk factors in this population. Patients with CKD have a greater risk profile, with more advanced age, congestive heart failure, hypertension, peripheral vascular disease, and chronic obstructive lung disease. Prior studies demonstrate that patients with CKD also have a higher prevalence of lipid abnormalities, hypertension, insulin resistance, and hyperhomocysteinemia. Supporting the association between CKD and accelerated atherogenesis is the increased requirement for subsequent revascularization (CABG) among patients with CKD. Accelerated atherogenesis among patients with CKD could be explained by an increased prevalence of conventional cardiovascular risk factors in this population. CKD is also a powerful risk factor for acute renal failure after coronary artery revascularization, and acute renal failure is associated with a greater risk of adverse outcomes. Although the propensity for acute renal failure may also be a marker for comorbidity, its occurrence may play a role in the mechanism of increased mortality.

Although CKD may be a marker of more severe vascular involvement from diabetes, both diabetes and CKD are independently associated with an increased mortality rate and work synergistically to increase risk of adverse outcomes. Both diabetes and CKD increase advanced glycosylation end products, which may enhance atherogenesis through the cross-linking of proteins, platelet aggregation, and lipoprotein abnormalities, resulting in cumulative vascular insults. In addition, diabetes is associated with a greater amount of asymptomatic cardiac ischemia and more aggressive development of new coronary lesions.
TABLE 3. Predictors of All-Cause Mortality to 7 Years

<table>
<thead>
<tr>
<th></th>
<th>RR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>CKD</td>
<td>2.31</td>
<td>1.63–3.28</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sex, female vs male</td>
<td>0.91</td>
<td>0.75–1.10</td>
<td>0.32</td>
</tr>
<tr>
<td>Race, black vs non-black</td>
<td>1.40</td>
<td>1.04–1.89</td>
<td>0.028</td>
</tr>
<tr>
<td>Age, y</td>
<td>1.05</td>
<td>1.04–1.06</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes mellitus*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral hypoglycemics</td>
<td>1.63</td>
<td>1.29–2.06</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Insulin</td>
<td>1.80</td>
<td>1.26–2.58</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PTCA vs CABG</td>
<td>1.04</td>
<td>0.87–1.25</td>
<td>0.67</td>
</tr>
<tr>
<td>Interaction between PTCA and insulin-treated diabetics</td>
<td>1.73</td>
<td>1.11–2.69</td>
<td>0.02</td>
</tr>
</tbody>
</table>

| Smoking history†      |      |              |       |
| Prior tobacco use     | 1.30 | 1.06–1.59    | 0.01  |
| Tobacco use at baseline| 1.82 | 1.42–2.33    | <0.001|
| Self-rated fair or poor health | 1.29 | 1.08–1.55 | 0.005 |
| Congestive heart failure | 1.87 | 1.48–2.37 | <0.001|
| Peripheral vascular disease | 1.39 | 1.15–1.69 | 0.0009|
| Hypertension          | 1.38 | 1.16–1.64    | 0.0003|
| Malignancy            | 1.73 | 1.31–2.28    | 0.0001|
| Major ECG abnormality | 1.21 | 1.02–1.44    | 0.03  |
| Left/mixed dominance  | 1.50 | 1.22–1.84    | 0.0001|
| LV ejection fraction‡ | 0.85 | 0.80–0.92    | <0.0001|
| Significant lesions, number | 1.07 | 1.01–1.14 | 0.03 |

*Compared with patients without diabetes.
†Compared with patients who have never smoked.
‡Per increase in 10%.

Because of the frequent exclusion of patients with CKD from clinical studies, limited data exist regarding the effectiveness of revascularization in this population. Among patients receiving maintenance dialysis, restenosis after PTCA has been noted to be as high as 80%. Patients with ESRD who are undergoing PTCA with coronary stents also have an increased need for repeat revascularization (35% versus 16% for patients with chronic kidney disease versus controls). Mortality after CABG among patients with ESRD is greater than among those without renal disease and may be as high as 20%. Whereas observational data suggest that outcomes after CABG versus PTCA are better for ESRD patients, no prospective studies have compared PCTA with CABG among patients with CKD. Whether this differential benefit to CABG is a step function beginning when a patient starts dialysis or is on a continuum related to worsening CKD is unclear. Thus, the optimal treatment strategy in these patients remains to be determined.

Despite demonstrating the important relationship between mild CKD and increased risk of mortality and other outcomes, these data have limitations. These results were derived from a post hoc subgroup analysis in which diabetes and CKD were not predefined subgroups. Because mild CKD was defined on the basis of 1 creatinine measurement, some values may represent variability outside the normal range caused by fluctuations in hemodynamics and may not represent true renal parenchymal disease. Furthermore, exact creatinine levels were not collected as a part of BARI.

Although this limits the ability of these data to assess the effect of CKD on outcomes as a continuum, the inclusion of patients who may be misclassified will bias these results toward the null, which strengthens this analysis. Whereas a serum creatinine of 1.5 mg/dL represents values that are only slightly greater than the upper limit of normal, it represents mild to moderate levels of CKD. When the average age for patients with CKD (64.2 years) is used, a creatinine value of 1.5 mg/dL represents a calculated clearance of 49 mL/min for a 70-kg man (42 mL/min for a woman).

Among patients with CKD, the potential for bias introduced through patient selection based on lesser comorbid conditions and the impact of this on generalizability should be noted. If such selection did occur, it would strengthen these findings by underestimating the increase in risk attributed to mild CKD. Furthermore, important mortality-reducing therapies (ie, β-blockers, ACE inhibitors, and cholesterol agents) did not significantly affect outcomes. Although these drugs may be used at lower rates among patients with CKD, the limited power and the potential for bias in terms of the patients selected for their use make assessment of their contribution to outcomes difficult to ascertain.

In summary, the present study demonstrates the increased risk of angina, recurrent hospitalization, subsequent CABG surgery, and mortality among patients with CKD and coronary artery disease despite initial revascularization therapy. These data suggest that among patients with mild CKD, treatment for atherosclerosis needs to be tailored to address the increased frequency of these events. Greater clinical awareness of the increased mortality and adverse events subsequent to revascularization among patients with mild CKD is needed to stimulate further research in the development of appropriate treatment and surveillance strategies.

References

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