Progression Risk, Urinary Protein Excretion, and Treatment Effects of Angiotensin-Converting Enzyme Inhibitors in Nondiabetic Kidney Disease

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It is unclear whether patients with nondiabetic kidney disease benefit from angiotensin-converting enzyme inhibitor (ACEI) therapy when they are at low risk for disease progression or when they have low urinary protein excretion. With the use of a combined database from 11 randomized, clinical trials (n = 1860), a Cox proportional hazards model, based on known predictors of risk and the composite outcome kidney failure or creatinine doubling, was developed and used to stratify patients into equal-sized quartiles of risk. Outcome risk and treatment effect were examined across various risk strata. Use of this risk model for targeting ACEI therapy was also compared with a strategy based on urinary protein excretion alone. Control patients in the highest quartile of predicted risk had an annualized outcome rate of 28.7%, whereas control patients in the lowest quartile of predicted risk had an annualized outcome rate of 0.4%. Despite the extreme variation in risk, there was no variation in the degree of benefit of ACEI therapy (P = 0.93 for the treatment × risk interaction). Significant interaction was detected between baseline urine protein and ACEI therapy (P = 0.003). When patients were stratified according to their baseline urinary protein excretion, among the subgroup of patients with proteinuria ≥500 mg/d, significant treatment effect was seen across all patients with a measurable outcome risk, including those at relatively low risk (1.7% annualized risk for progression). However, there was no benefit of ACEI therapy among patients with proteinuria <500 mg/d, even among higher risk patients (control outcome rate 19.7%). Patients with nondiabetic kidney disease vary considerably in their risk for disease progression, but the treatment effect of ACEI does not vary across risk strata. Patients with proteinuria <500 mg/d do not seem to benefit, even when at relatively high risk for progression.


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here is increasing awareness that patients who are enrolled in clinical trials can vary substantially in terms of their outcome risk (1–4) and that this variation may be more extreme in meta-analyses of individual patient data (5). When outcome risk varies substantially among trial enrollees, the overall treatment effects that are seen in the trial might obscure clinically important treatment-effect heterogeneity that is unlikely to be detected by conventional subgroup analysis but that is likely to be detected with risk-stratified analyses (2–4).

Chronic kidney disease (CKD) is a major public health problem. Data from the Third National Health and Nutrition Examination Survey (NHANES III; 1999 to 2000) suggest that approximately 12% of the US population aged ≥20 yr may have CKD (6). Adverse outcomes of CKD include loss of kidney function, sometimes leading to kidney failure, and cardiovascular disease (7,8).

A pooled analysis of individual patient data from 11 randomized, controlled trials (9–19) revealed strong and consistent effects of angiotensin-converting enzyme inhibitors (ACEI) in slowing the progression of nondiabetic kidney disease, although the treatment effect was modified by the degree of urinary protein excretion, with benefit increasing in patients with greater proteinuria (20–22). Our objective was to use a risk model to examine the variation in the risk for progression of kidney disease at baseline among patients who were included in this individual patient data meta-analysis (IPDMA) and to test whether a risk-stratified analysis demonstrates previously undiscovered variation in the treatment effect of ACEI in preventing progression of kidney disease. Our hypothesis was that many patients who are enrolled in clinical trials are at very low risk for progression even in the absence of therapy and are therefore unlikely to benefit from treatment.
Materials and Methods
For this analysis, we used the pooled individual patient data from nine published and two unpublished randomized trials that tested ACEI therapy in patients with nondiabetic nephropathy (n = 1860). Descriptions of the inclusion and exclusion criteria, of search strategies used to identify the studies, of the study and patient characteristics of the included randomized trials, and of the methods that were used to pool the studies were previously described (20,23). Briefly, the database was compiled over 4 yr starting in 1997 and included patients who were enrolled between March 1986 and April 1996. In each of these studies, patients were randomly assigned to antihypertensive regimens either with or without ACEI. The ACEI included captopril, enalapril, cilazapril, benazepril, and ramipril. Antihypertensive medications were used in both treatment groups to achieve a target BP <140/90 mmHg in all studies. All patients were followed at least once every 3 mo for the first year and at least once every 6 mo thereafter. The primary outcome for the pooled analysis was “kidney disease progression,” defined as a combined end point of a two-fold increase (doubling) in serum creatinine concentration from baseline values or development of kidney failure, defined as the onset of long-term dialysis therapy. The database was not updated, so the results of this analysis could be compared with previously reported results (20–23).

Assessing Heterogeneity of Outcome Risk
To assess baseline risk heterogeneity, we used a simple algorithm that has been proposed for this purpose (1). Briefly, based in part on previous modeling (20–22), we developed a Cox proportional hazard model using the primary outcome (kidney disease progression) as the dependent variable and previously identified risk factors for this outcome (exclusive of ACEI therapy or treatment assignment), using patients in both the treatment and the control condition. This risk model was then used to categorize patients in the data set into equal-sized quartiles on the basis of predicted risk. In addition to computing the observed rates of the outcomes in each risk quartile, we computed the observed odds of having the event of interest (kidney disease progression) in the lowest and highest quartiles of predicted risk after 1 yr in patients who were randomly assigned to the control group. We then calculated the following heterogeneity metrics (1), based on outcomes in patients who were assigned to the control group: (1) Extreme quartile odds ratio (EQuOR): calculated as the ratio of the odds of the event in the upper quartile to the odds in the lower quartile; and (2) extreme quartile rate ratio (EQuRR): This is the rate ratio for the event of interest in the group of patients in the upper quartile of predicted risk as compared with the group of patients in the lower quartile of predicted risk estimated from a Cox model that considers only the patients of the two extreme quartiles (5).

Assessing Heterogeneity of Treatment Effect
In addition to examining the heterogeneity of the outcome risk, we tested for treatment-effect differences in high-risk versus low-risk patients by testing for an interaction between risk for progression and treatment effect, to test whether patients at high risk for progression are more or less likely to benefit than those at lower risk for progression. We did this in two ways: (1) Using the patient-specific hazard of progression (calculated by the Cox model) as a linear term, which we considered our primary analysis, and (2) using quartile of risk as an ordinal variable, as our secondary analysis.

Because a previous treatment × urinary protein excretion interaction had already been identified, indicating that ACEI therapy is more effective in patients with higher urinary protein excretion, we performed similar risk-stratified analyses on subgroups with urinary protein excretion ≥500 versus <500 mg/d. For each proteinuria strata, we used the same risk model that was used to stratify the overall sample, which included the degree of proteinuria as a predictor.

Results
The baseline characteristics of our study sample are shown in Table 1. As previously reported, of the 1860 patients in the study sample, 311 (16.8%) experienced marked or severe kidney disease progression (doubling of baseline serum creatinine concentration or kidney failure): 124 (13.2%) in the ACEI group and 187 (20.5%) in the control group (P = 0.001). A total of 176 (9.5%) developed kidney failure: 70 (7.4%) in the ACEI group and 106 (11.6%) in the control group (P = 0.002).

Table 1. Baseline patient characteristicsa

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Control Group (n = 919; 49.4%)</th>
<th>ACEI Group (n = 941; 50.6%)</th>
<th>All (N = 1860)</th>
<th>P Value (χ² or T Test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women (% [n])</td>
<td>34.7 (319)</td>
<td>34.6 (326)</td>
<td>34.7 (645)</td>
<td>0.976</td>
</tr>
<tr>
<td>Age (yr; mean ± SD)</td>
<td>52.0 ± 12.7</td>
<td>51.9 ± 13.2</td>
<td>51.9 ± 12.9</td>
<td>0.824</td>
</tr>
<tr>
<td>Race (% [n])</td>
<td>6.5 (54)</td>
<td>6.4 (60)</td>
<td>6.1 (114)</td>
<td>0.653</td>
</tr>
<tr>
<td>Hypertension (present)</td>
<td>92.1 (886)</td>
<td>91.6 (881)</td>
<td>91.9 (1746)</td>
<td>0.722</td>
</tr>
<tr>
<td>Baseline plasma creatinine (mg/dl; mean ± SD)</td>
<td>2.3 ± 1.2</td>
<td>2.3 ± 1.2</td>
<td>2.3 ± 1.2</td>
<td>0.889</td>
</tr>
<tr>
<td>Baseline SBP (mmHg; mean ± SD)</td>
<td>149.6 ± 22.1</td>
<td>149.2 ± 22.0</td>
<td>149.4 ± 22.0</td>
<td>0.734</td>
</tr>
<tr>
<td>Baseline DBP (mmHg; mean ± SD)</td>
<td>91.7 ± 11.0</td>
<td>91.3 ± 11.3</td>
<td>91.5 ± 11.1</td>
<td>0.524</td>
</tr>
<tr>
<td>Baseline urinary protein excretion (g/d; mean ± SD)</td>
<td>1.8 ± 2.1</td>
<td>1.8 ± 2.5</td>
<td>1.8 ± 2.3</td>
<td>0.637</td>
</tr>
<tr>
<td>Follow-up time (d; mean ± SD)</td>
<td>777.4 ± 409.5</td>
<td>786.8 ± 416.0</td>
<td>782.2 ± 412.7</td>
<td>0.624</td>
</tr>
<tr>
<td>Cause of kidney disease (% [n])</td>
<td></td>
<td></td>
<td></td>
<td>0.860</td>
</tr>
<tr>
<td>polycystic kidney disease</td>
<td>8.1 (74)</td>
<td>7.2 (68)</td>
<td>7.6 (142)</td>
<td></td>
</tr>
<tr>
<td>glomerular diseases</td>
<td>32.8 (301)</td>
<td>32.9 (310)</td>
<td>32.9 (611)</td>
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</tr>
<tr>
<td>hypertensive nephrosclerosis</td>
<td>33.6 (309)</td>
<td>32.4 (305)</td>
<td>33.0 (614)</td>
<td></td>
</tr>
<tr>
<td>tubulointerstitial diseases</td>
<td>11.5 (106)</td>
<td>12.0 (113)</td>
<td>11.8 (219)</td>
<td></td>
</tr>
<tr>
<td>other</td>
<td>14.0 (129)</td>
<td>15.4 (145)</td>
<td>14.7 (274)</td>
<td></td>
</tr>
</tbody>
</table>

aACEI, angiotensin-converting enzyme inhibitor; DBP, diastolic BP; SBP, systolic BP.
Risk Model
The risk model included the following baseline variables: Age (log-transformed), gender, serum creatinine, urinary protein excretion, and systolic BP (Table 2). Model discrimination was good with an area under the receiver operator characteristic curve of 0.83, and the Hosmer-Lemeshow test indicated good calibration ($P = 0.33$).

Heterogeneity of Outcome Risk
Quartiles of predicted risk are shown in Figure 1, according to treatment assignment. Among patients who were assigned to the control group, the outcome rate in the lowest risk quartile was 0.4%, whereas the rate in the highest risk quartile was 28.7%. This yields an EQuOR of 105 (odds in highest risk quartile 0.40; odds in lowest quartile 0.004) and an extreme quartile risk ratio EQuRR of 71, indicating extreme heterogeneity of outcome. Patient characteristics in these quartiles of risk are shown in Table 3.

Heterogeneity of Treatment Effect
Despite the extreme variation of outcome risk in high- versus low-risk patients, the treatment effect across risk groups did not show variation across risk, either when risk was treated as a continuous variable ($P = 0.93$) or when risk quartile × treatment was examined ($P = 0.80$). This is consistent with Figure 1, which shows roughly similar treatment effects across all four quartiles. However, given the heterogeneity in outcome risk, there is considerable variation in the absolute benefits of therapy across risk strata; the number needed to treat (NNT) for 1 yr to prevent progression of disease in one patient in the low-risk group is 454, whereas this NNT is only 11 in the high-risk group. Consistent with our previous reports, significant interaction was detected between the presence or absence of urinary protein excretion ≥500 mg/d and treatment effect on the outcome risk (interaction $P = 0.003$), indicating greater benefit in those with greater proteinuria (21).

Stratification by the Presence of Proteinuria ≥500 mg/d
When patients were stratified by the presence or absence of urinary protein excretion ≥500 mg/d, outcomes remained heterogeneous even within each of these strata (Figure 2). Among patients with proteinuria above this level, the EQuRR was 19 and the EQuOR was 129. Because there were no poor outcomes among the lowest risk quartile among control patients with proteinuria <500 mg/d, the EQuOR and EQuRR were undefined.

Among the 61% of patients with proteinuria ≥500 mg/d, a substantial treatment effect was seen across all patients with a measurable outcome risk, including those at relatively low risk (1.7% annualized risk of progression). Conversely, among the 39% of patients with proteinuria <500 mg/d, no treatment benefit was found, even among patients with a relatively high risk for kidney disease progression (19.7% annualized risk of progression in the control group of the highest risk quartile).

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**Figure 1.** Risk-stratified outcome rates (doubling of baseline plasma creatinine or kidney failure with need for dialysis). This graph depicts outcome rates in equal-sized quartiles of predicted risk on the basis of the multivariable model, from low-risk patients (quartile 1) to high-risk patients (quartile 4), in patients randomly assigned to control therapy (□) and angiotensin-converting enzyme inhibitor (ACEI) therapy (■).

**Figure 2.** Risk-stratified outcome rates (doubling of baseline serum creatinine or kidney failure) in patients with and without urinary protein excretion ≥500 mg/d. These graphs depict the outcome rates in equal-sized quartiles of predicted risk on the basis of the multivariable model, from low-risk patients (quartile 1) to high-risk patients (quartile 4), in patients who were randomly assigned to control therapy (□) and ACEI therapy (■). (Top) Patients with urinary protein excretion ≥500 mg/d. (Bottom) Patients with urinary protein excretion <500 mg/d.
No risk \times treatment heterogeneity was seen within the proteinuria strata \((P = 0.29\) for those with proteinuria \(\geq 500\) mg/d; \(P = 0.08\) for those with proteinuria <500 mg/d). Within the strata of patients with proteinuria \(\geq 500\) mg/d, the NNT ranged from 58 in the low-risk group to nine in the high-risk group (Tables 2 and 3).

**Discussion**

Our analysis demonstrates that the patients who were included in the IPDMA of 11 trials that tested ACEI therapy in patients with nondiabetic kidney disease varied considerably in their baseline risk for kidney disease progression. The risk for progression in that quartile of patients at highest risk was approximately 70-fold the risk in the lowest quartile, corresponding to a variation in average probability of kidney disease progression in 1 yr from 28.7 to only 0.4% when treated with antihypertensive agents other than ACEI. Our analysis demonstrates that the treatment effect of ACEI therapy is consistent across all risk categories. However, despite the consistency of effects on the odds ratio scale, the heterogeneity of progression risk suggests heterogeneity of treatment effect on the absolute scale, with progressively less benefit as risk decreases. Given the extremely low risk for progression in the lowest quartile of risk, near-identical outcomes to population-wide therapy could be achieved by treating just the highest risk three-fourths of patients (Figure 1).

The model also revealed considerable heterogeneity of outcome risk in patients both with and without \(\geq 500\) mg/d proteinuria. Indeed, for patients with urine protein excretion <500 mg/d, because there were no outcomes in the lowest risk quartile, the extreme quartile rate ratio was undefined. For patients with urinary protein excretion \(\geq 500\) mg/d, the outcome rate for those at high risk was 19-fold higher than those at low risk.

To our knowledge, only one previous study examined the degree of heterogeneity of baseline risk in a IPDMA (5). That analysis included eight clinical trials (1792 patients, 2947 yr of follow-up) on the efficacy of high-dosage acyclovir in HIV infection and found a >100-fold difference in the risk for the outcome in the lowest compared with the highest risk quartiles. Our study results are consistent with their conclusions that meta-analysis may be a study design with extreme heterogeneity of the baseline risks compared with single studies. Indeed, using the same heterogeneity metrics, we found similarly high degrees of heterogeneity, because there were no outcomes in the lowest quartile.

However, despite the wide range in outcome risk, the treatment effect of ACEI was homogeneous on the relative risk scale across patients at different risk within each of the protein strata. Within the category of patients with proteinuria above this threshold, the beneficial effect of ACEI seems to be very strong and consistent across all categories of risk, even those at lowest risk. Patients with proteinuria below this threshold, however, do not seem to benefit. This is true even for patients who, on the basis of older age, higher serum creatinine, and higher systolic BP, are at considerable progression risk. Indeed, in the sample of patients who were included in these trials, targeting ACEI therapy to the 61% of patients with proteinuria \(\geq 500\) mg/d would lead to slightly better outcomes than population-wide therapy.

Our analysis confirms previous analyses of this database that demonstrated that the beneficial effect of ACEI is stronger in patients with greater proteinuria at the onset of therapy and that the greater degree of benefit is related to the antiproteinuric effects of ACEI (17,20–22,24). However, it was unclear from these previous analyses whether patients with lower urine protein excretion obtained benefit from ACE inhibition or the absence of an effect was an artifact of the low outcome rate in the subgroup with less proteinuria. Our analysis shows that even among the subgroup of patients who have urine protein excretion <500 mg/d and are at relatively high risk for disease progression, ACEI therapy does not have any advantage in preventing kidney disease progression compared with other antihypertensive regimens. This suggests that proteinuria is a specific marker of risk that is modified by ACEI therapy versus other antihypertensive agents, whereas the other baseline risk factors (including age, BP, and serum creatinine) identify risk that is not specifically modifiable with ACEI therapy versus other antihypertensive agents.

The ratio of protein to creatinine concentration in spot urine samples has been shown to correlate well with 24-h urine protein excretion (25). Based in part on previously reported results from our database, recent guidelines recommend measurement of spot urine total protein to creatinine ratio in all patients with CKD, and use of ACEI or angiotensin receptor blockers is recommended in patients who have nondiabetic kidney disease and spot urine total protein to creatinine ratio >200 mg/g to slow progression of CKD (26). More recently, the development and application of a kidney risk score in patients with CKD for predicting progression was proposed by some (27). Our findings suggest that once proteinuria is taken into account, further scoring does not offer incremental value in the decision to initiate ACEI therapy for nondiabetic CKD.

Several recent studies have called into question the efficacy of

**Table 2. Risk model predicting the risk for kidney disease progression**

<table>
<thead>
<tr>
<th>Variable</th>
<th>HR (95% CI)</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>0.86 (0.67 to 1.10)</td>
<td>0.222</td>
</tr>
<tr>
<td>Serum creatinine (reciprocal, for each 1-SD increase)</td>
<td>0.14 (0.11 to 0.18)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Age (log transformed, for each 1-SD increase)</td>
<td>0.77 (0.68 to 0.86)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Baseline SBP (for each 10-mmHg increase)</td>
<td>1.14 (1.09 to 1.20)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Baseline urinary protein excretion (g/d)</td>
<td>1.10 (1.07 to 1.14)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

*CI, confidence interval; HR, hazard ratio.*
ACEI compared with other antihypertensive agents in slowing the progression of kidney disease (28,29), most notably the Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), (30,31) which failed to demonstrate the superiority of the ACEI lisinopril over other antihypertensive agents in CKD (32). The heterogeneous benefits of ACEI on kidney disease progression according to the level of proteinuria has been invoked as an explanation for the results of ALLHAT (30,31), whose design features favored inclusion of lower risk patients with CKD (presumably with a low prevalence of proteinuria). Indeed, the annualized risk for progression in ALLHAT was <0.5%, placing them in our lowest risk quartile. From Figure 2 of our analysis, it becomes apparent that the small degree of absolute benefit to such low-risk patients that is expected to accrue even when they have significant proteinuria (approximately 0.2% per year) can easily be obscured by statistical fluctuations among low-proteinuria patients—particularly when patients with low proteinuria predominated in the ALLHAT trial. Stratifying patients by both the risk for progression and degree of protein excretion as we have done here reveals differences in the treatment effect among patient groups on both the absolute and relative risk scale simultaneously, which can be helpful in understanding the heterogeneous results across trials.

Similarly, the overall results of the meta-analysis by Casas et al. (28), which did not suggest a specific benefit of ACEI, reflect primarily the results of ALLHAT, which overwhelmed the other studies. Indeed, the subgroup analysis that included just the trials that enrolled patients without diabetes and examined the outcome of kidney disease progression are in agreement with our results. Finally, a recent study by Suissa et al. (29) showed that the incidence of kidney failure in patients with diabetes was higher among patients who were on ACEI therapy. These results are of only indirect relevance to ours, because our database contained only patients without diabetes and theirs contained only patients with diabetes. Furthermore, we advise caution in interpreting the results of Suissa et al. given the nonrandomized nature of the study and the strength of the randomized evidence for benefit for inhibitors of the rennin-angiotensin system (33–35). Thus, the previously reported results of the AIPRD Study database—that the beneficial effects of ACEI in nondiabetic nephropathy seem to be greater than expected for the differences between randomized groups in the level of BP (22) and that these effects depend on the level of proteinuria—have not been directly challenged by the recently reported studies.

There are limitations to this study. Stratification of patients was based on a risk model that was developed on the same patient database. Overfitting of the risk model can potentially overestimate the degree of outcome risk heterogeneity. However, because we used only five especially salient clinical risk variables and did not mine the database for additional variables that might have more subtle influences, we do not believe that overfitting substantially influenced our results. An additional limitation of our study is the relative racial/ethnic homogeneity of the sample, which may limit the generalizability of the results to more diverse populations. Also, it should be noted that the included studies were not themselves designed to assess the protective effects of ACEI in patients with varying degrees of baseline proteinuria, and there is a risk for false-positive effects when multiple post hoc analyses are performed. However, testing for treatment modification by level of protein excretion was a primary aim for our IPDMA (20,21).

Last, this study does not address the potential benefit of ACEI therapy in preventing cardiovascular disease, an important therapeutic goal in CKD (35,36). The studies that were included in our IPDMA were not designed to assess the effectiveness of ACEI on cardiovascular events. Studies that have examined the effects of ACEI on cardiovascular outcomes in patients with kidney disease have not been wholly consistent in determining whether these agents have specific benefits compared with other antihypertensive agents (37–39), although the results of some studies suggest that this effect, too, may be specific to or more pronounced in patients with greater proteinuria (39,40).

### Table 3. Quartiles of risk

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Quartile 1 (n = 465; 25.0%)</th>
<th>Quartile 2 (n = 465; 25.0%)</th>
<th>Quartile 3 (n = 465; 25.0%)</th>
<th>Quartile 4 (n = 465; 25.0%)</th>
<th>P (χ² or T Test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women (% [n])</td>
<td>37.2 (173)</td>
<td>29.0 (135)</td>
<td>28.8 (134)</td>
<td>43.7 (203)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Age (yr; mean ± SD)</td>
<td>46.9 ± 13.7</td>
<td>49.6 ± 12.6</td>
<td>52.9 ± 12.0</td>
<td>58.4 ± 10.3</td>
<td>0.000</td>
</tr>
<tr>
<td>Race (% [n])</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>white</td>
<td>94.0 (437)</td>
<td>94.0 (437)</td>
<td>91.6 (426)</td>
<td>95.9 (446)</td>
<td>0.057</td>
</tr>
<tr>
<td>black</td>
<td>6.0 (28)</td>
<td>6.0 (28)</td>
<td>8.4 (39)</td>
<td>4.1 (19)</td>
<td></td>
</tr>
<tr>
<td>Hypertension (present)</td>
<td>95.3 (443)</td>
<td>91.0 (423)</td>
<td>88.2 (410)</td>
<td>92.9 (432)</td>
<td>0.001</td>
</tr>
<tr>
<td>Baseline plasma creatinine (mg/dl; mean ± SD)</td>
<td>3.9 ± 1.3</td>
<td>2.4 ± 0.4</td>
<td>1.7 ± 0.2</td>
<td>1.1 ± 0.2</td>
<td>0.000</td>
</tr>
<tr>
<td>Baseline SBP (mmHg; mean ± SD)</td>
<td>151.2 ± 28.2</td>
<td>146.6 ± 20.5</td>
<td>141.2 ± 18.9</td>
<td>154.9 ± 22.5</td>
<td>0.000</td>
</tr>
<tr>
<td>Baseline DBP (mmHg; mean ± SD)</td>
<td>93.6 ± 12.2</td>
<td>90.9 ± 10.7</td>
<td>87.4 ± 9.6</td>
<td>94.0 ± 10.6</td>
<td>0.000</td>
</tr>
<tr>
<td>Baseline urinary protein excretion (g/d; mean ± SD)</td>
<td>3.1 ± 3.0</td>
<td>2.2 ± 2.2</td>
<td>1.4 ± 1.8</td>
<td>0.5 ± 1.0</td>
<td>0.000</td>
</tr>
<tr>
<td>Follow up time (d; mean ± SD)</td>
<td>633.5 ± 410.8</td>
<td>835.8 ± 417.6</td>
<td>900.5 ± 398.7</td>
<td>759.0 ± 375.2</td>
<td>0.000</td>
</tr>
<tr>
<td>Cause of kidney disease (% [n])</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>polycystic kidney disease</td>
<td>11.2 (52)</td>
<td>11.0 (51)</td>
<td>6.2 (29)</td>
<td>2.2 (10)</td>
<td>&lt;0.0001</td>
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<td>glomerular diseases</td>
<td>40.2 (187)</td>
<td>38.1 (177)</td>
<td>34.8 (162)</td>
<td>18.3 (85)</td>
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<tr>
<td>hypertensive nephrosclerosis</td>
<td>14.8 (69)</td>
<td>19.4 (90)</td>
<td>30.3 (141)</td>
<td>67.5 (314)</td>
<td></td>
</tr>
<tr>
<td>tubulointerstitial diseases</td>
<td>12.5 (58)</td>
<td>15.5 (72)</td>
<td>12.7 (59)</td>
<td>6.5 (30)</td>
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<tr>
<td>other</td>
<td>21.3 (99)</td>
<td>16.1 (75)</td>
<td>15.9 (74)</td>
<td>5.6 (26)</td>
<td></td>
</tr>
</tbody>
</table>
Conclusion

Our analysis did not provide strong support for the concept that a risk model based on age, gender, BP, serum creatinine, and proteinuria would be helpful for selecting patients who might be likely or unlikely to get additional benefit from ACEI therapy on progression of kidney disease, because, from a practical standpoint, targeting therapy can be accomplished by the measurement of urine protein excretion alone better than by the application of a full risk model. Despite a high degree of variation in the risk for disease progression, the treatment effect of ACEI in nondiabetic kidney disease seems to be independent of baseline risk. Among patients with urine protein excretion \( \geq 500 \text{ mg/d, ACEI seem to be very effective, and some benefit is apparent even in patients who have otherwise favorable characteristics and are at relatively low risk for progression. However, for patients with lower urine protein excretion, ACEI do not seem to offer protection against kidney disease progression, even among patients with unfavorable risk characteristics and a relatively higher likelihood for progression.}

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Disclosures

None.

References


