Renoprotection of Optimal Antiproteinuric Doses (ROAD) Study: A Randomized Controlled Study of Benazepril and Losartan in Chronic Renal Insufficiency

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The Renoprotection of Optimal Antiproteinuric Doses (ROAD) study was performed to determine whether titration of benazepril or losartan to optimal antiproteinuric doses would safely improve the renal outcome in chronic renal insufficiency. A total of 360 patients who did not have diabetes and had proteinuria and chronic renal insufficiency were randomly assigned to four groups. Patients received open-label treatment with a conventional dosage of benazepril (10 mg/d), individual uptitration of benazepril (median 20 mg/d; range 10 to 40), a conventional dosage of losartan (50 mg/d), or individual uptitration of losartan (median 100 mg/d; range 50 to 200). Uptitration was performed to optimal antiproteinuric and tolerated dosages, and then these dosages were maintained. Median follow-up was 3.7 yr. The primary end point was time to the composite of a doubling of the serum creatinine, ESRD, or death. Secondary end points included changes in the level of proteinuria and the rate of progression of renal disease. Compared with the conventional dosages, optimal antiproteinuric dosages of benazepril and losartan that were achieved through uptitration were associated with a 51 and 53% reduction in the risk for the primary end point (P = 0.028 and 0.022, respectively). Optimal antiproteinuric dosages of benazepril and losartan, at comparable BP control, achieved a greater reduction in both proteinuria and the rate of decline in renal function compared with their conventional dosages. There was no significant difference for the overall incidence of major adverse events between groups that were given conventional and optimal dosages in both arms. It is concluded that uptitration of benazepril or losartan against proteinuria conferred further benefit on renal outcome in patients who did not have diabetes and had proteinuria and renal insufficiency.


Irreversibility of the renin-angiotensin axis with an angiotensin-converting enzyme inhibitor (ACEi) or an angiotensin II receptor blocker (ARB) slows the progression of chronic renal insufficiency in the presence or absence of diabetes (1–5). However, many patients progress to ESRD despite using an ACEi or ARB (1–5). Optimizing renin-angiotensin system (RAS) blockade to provide more effective renal protection has received considerable attention. Increasing evidence suggests that, in addition to effective BP control, proteinuria should be considered as an independent risk factor and an essential treatment target for renal protection (2,6,7). Reduction of proteinuria with RAS blockade results in protection against protein-induced renal fibrosis, which should translate into preservation of renal function in the long term (8,9). Animal studies have demonstrated that maximal renal benefit from ACEi or ARB requires higher dosages than those needed to normalize BP (10,11). Small clinical studies have shown that titrating ACEi or ARB to higher dosages is effective at reducing proteinuria (12–15), although there have been conflicting reports (16,17). Taken together, these data suggest that the recommended dosages of ACEi or ARB in current practice, which are based on their BP-lowering effect, might be inadequate to halt satisfactorily renal progression. However, most of the dosage-response studies to date looked exclusively at reductions in proteinuria but failed to evaluate hard end points as the outcome parameter. This is partly explained by the short observation period (between 8 wk and 9 mo) in these studies. Optimal antiproteinuric dosages of ACEi or ARB have not been explored thoroughly with respect to long-term renal outcomes and, importantly, tolerability and safety in patients with renal insufficiency.

Several studies have provided evidence that ARB are renoprotective in patients with type 2 diabetes (3,4,18). It is to be confirmed whether an ARB is as effective as an ACEi in retarding progression in nondiabetic nephropathy, because data from a trial that was designed primarily to compare the effects of combined therapy with ACEi and ARB to each monotherapy suggest that there is no difference in renal protection between ACEi and ARB (19).

The primary aim of this study was to evaluate whether the optimal antiproteinuric dosages of benazepril (an ACEi) or...
losartan (an ARB), as compared with their conventional dosages, can safely improve the renal outcome in patients who do not have diabetes and have proteinuria and chronic renal insufficiency. The second aim was to compare the long-term renoprotection of benazepril and losartan at their optimal antiproteinuric dosages.

Materials and Methods

Design and Patients

Renoprotection of Optimal Antiproteinuric Doses (ROAD) was a prospective, randomized, open, blinded end point (PROBE) study that was conducted at Nanfang Hospital Renal Division. An adjudicating group, whose members were unaware of patients’ treatment assignments, reviewed the data to determine which patients had reached study end points and to evaluate safety. The study protocol was approved by the Nanfang Ethics Committee, and all patients provided written informed consent. A study period of 3 yr was chosen on the basis of the results of previous trials that involved patients with non-diabetic chronic nephropathy and that suggested that a 3-yr follow-up is adequate to assess efficacy (2,5).

Between January 2002 and May 2003, consecutive patients who were aged 18 to 70 yr and had chronic kidney disease (CKD) were screened for the study at the Nanfang Hospital Renal Division, which has a catchment that includes eight cities near Guangzhou with a total population in the year 2000 of 29.8 million. Eligible patients had not received ACEi or ARB for at least 6 wk before screening and met the following inclusion criteria: A serum creatinine level of 1.5 to 5.0 mg/dl (133 to 442 μmol/L) and a creatinine clearance (20) of 20 to 70 ml/min per 1.73 m², with variations of at least 20% compared with the previous 3 mo; diagnosis of nondiabetic renal disease (as established on the basis of patient history and as a result of serum biochemical tests and renal biopsy); and persistent overt proteinuria (defined as urinary protein excretion of >1.0 g/d for ≥3 mo without evidence of urinary tract infection or overt heart failure [a New York Heart Association class of III or IV]). Exclusion criteria were an immediate need for dialysis; current treatment with corticosteroids, nonsteroidal anti-inflammatory drugs, or immunosuppressive drugs; hyper- or hypokalemia (serum potassium concentration ≥5.6 or ≤3.5 mmol/L); renovascular disease; myocardial infarction or cerebrovascular accident in the year preceding the trial; connective-tissue disease; and obstructive uropathy.

Randomization and Interventions

Eligible patients got their sequence numbers from the coordinator and were randomly allocated into four groups according to a computer-generated randomization sequence list using a blocking size of 8. The list was prepared by the Department of Biostatistics, Southern Medical University. For safety’s sake, all patients entered an 8-wk pretitration phase in which patients in groups 1 and 2 received 10 mg of benazepril (1) and those in groups 3 and 4 received 50 mg of losartan daily (21). After 4 wk of therapy with the study drugs, patients who continued to show inadequate BP control (i.e., a systolic BP [SBP] of >130 mmHg and/or a diastolic BP of >80 mmHg) had an additional antihypertensive agent (diuretic, calcium channel blocker, β blockers, centrally acting agent, or combination of these medications, excluding ACEi and ARB) added to their treatment regimen. All patients were under close observation, including weekly measurements of BP, serum creatinine, and serum potassium.

At completion of the pretitration phase, patients with stable renal function (<30% increase from inclusion baseline in serum creatinine, confirmed by at least three separate measurements) and serum potassium levels <5.6 mmol/L and without other adverse events then entered the titration period. Patients in groups 1 and 3 remained on fixed dosages of benazepril (10 mg/d) or losartan (50 mg/d), respectively. Patients in groups 2 and 4 had their dosages of benazepril or losartan uptitrated as follows: Patients in group 2 received monthly uptitration of benazepril from a starting dosage of 10 mg/d to 20, 30, and 40 mg/d. Patients in group 4 were treated with increasing dosages of losartan (from 50 to 100, 150, and 200 mg/d) with each titration period of 4 wk. BP (measured with a mercury-column sphygmomanometer in the sitting position 3 to 4 h after the administration of the study drug) was measured every week by staff who were blind to the study design and recorded as mean of three readings. Urinary protein excretion, serum creatinine, and potassium levels were measured every 2 wk during the titration period. The dosage of study drug was downtitrated to the previous level in the following circumstances: The antiproteinuric effect of the study drug had reached its plateau (i.e., urinary protein excretion did not fall by ≥10% [22] versus the previous titration period [determined by two values that were obtained 4 wk apart at same dosage; the accuracy of urine collection was confirmed by determination of specimen’s creatinine content]), or SBP decreased to <120 mmHg despite withdrawal of all additional antihypertensive medication. Patients who developed hyperkalemia (serum potassium ≥6.0 mmol/L) that was refractory to medical treatment or whose serum creatinine increased >30% versus previous values had the study drug dosage downtitrated to the previous step or withdrawn. In patients who were not responsive to uptitration (defined as <10% reduction in proteinuria from the levels at the start of titration), the study drug was uptitrated monthly to the maximum licensed dosage (benazepril 40 mg/d in group 2; losartan 200 mg/d in group 4). When still no response was observed, the dosage was decreased to the starting dosage; patients remained in the study and were included in the analyses. Patients in groups 2 and 4 were maintained on their study drug once their individual optimal antiproteinuric and tolerated dosage was achieved. Additional antihypertensive agents (as described previously) were administered or withdrawn, as required, to maintain BP control. The patients (including withdrawn cases) were followed up every month thereafter for data collection.

All patients were instructed to reduce their salt intake to approximately 5 to 7 g/d, to eat 0.5 to 0.7 protein/kg body wt per d, and to restrict their intake of foods that are rich in potassium. Dietary compliance was assessed by evaluation of 24-h urinary excretion of urea and chloride.

Outcome Variables

The primary efficacy variable was time to the first event for the composite end point: Doubling of the serum creatinine concentration, ESRD, or death. Doubling of serum creatinine concentration from the baseline value was confirmed by a second serum creatinine value that was obtained at least 4 wk after the initial doubling. ESRD was defined by the need for long-term dialysis or renal transplantation.

Secondary end points included changes in urinary protein excretion rate and the progression of renal disease as assessed by estimated GFR (eGFR) that was calculated by Modification of Diet in Renal Disease (MDRD) equation (23). To avoid the imprecision of the MDRD equation in Chinese, we also included evaluated creatinine clearance (24) to reflect the rate of decline in renal function.

Statistical Analyses

The sample size was estimated before the study with the nQuery Advisor software 5.0 (Statistical Solutions Ltd., Cork, Ireland). Our preliminary study in patients with renal insufficiency showed that the rate of the primary end point among patients who were treated with 10
mg of benazepril was approximately 33%, whereas in those who received 20 mg of benazepril, 23% reached the primary end point (25). Thus, we estimated that the optimal antiproteinuric dosage of benazepril would reduce this rate to 10%. The enrollment of 70 patients in each group of benazepril arm would provide the study with a statistical power of 80% at a two-sided significance level of 0.05.

Because no data on long-term renal effect of ARB in patients with nondiabetic nephropathy were available at the start of the study, we assumed that treatment with an optimal antiproteinuric dosage of losartan would also reduce the rate of the primary end point to 10% versus the conventional dosage. It was estimated that to give the study an 80% power to detect statistical significance, at least 70 patients in each group of the losartan arm had to complete the study.

The primary and secondary end points were analyzed according to the intention-to-treat (ITT) principle. We included data from all patients who entered active treatment. The missing data were treated using lost operation carry forward principle to satisfy ITT analysis. For further confirmation of the result, the primary end points were also analyzed by using the per-protocol principle. The Cox regression model based on the assessment of goodness-of-fit by −2 log likelihood ratio was used to determine the hazard ratio for the primary end point. The model was also adjusted by baseline variables as the covariables, which were proteinuria, eGFR, and SBP, at end point to detect their effect. The risk reduction was calculated as 100% × (1 − hazard ratio). Event curves were based on Kaplan-Meier analysis, and significance was assessed by log-rank test.

Changes in urinary protein excretion, creatinine clearance, and BP were analyzed by repeated-measures ANOVA. Multiple comparisons were conducted with LSD test when ANOVA was significant. The relationship between proteinuria reduction and the rate of the decline of renal function was analyzed by Pearson correlation. Two-tailed \( P \leq 0.05 \) were considered statistically significant. Analyses were performed with SPSS 13.0.

Results

A total of 406 patients were screened during January 2002 to May 2003, and 360 were identified for study participation and randomly assigned to the four groups (Figure 1). The baseline characteristics of the patients were similar in the four groups (Table 1). The mean age and the distribution of the primary causes of renal dysfunction across the groups were similar to those reported in the registry of the Chinese Society of Nephrology (26). The median length of follow-up was 3.7 yr (min-max, approximately 2.0 to 4.5).

Fifty patients withdrew during the pretitration phase with main cause of dry cough (30 [60%] of 50). Seventeen of them were lost to follow-up: Eight because of poor adherence (one in group 1, two in group 2, two in group 3, and three in group 4), and nine because of refusal to continue the treatment (five in group 1 and four in group 2; Figure 1). Four patients were lost to follow-up after the pretitration phase because they moved away (one in group 1 and three in group 4; Figure 1).

Primary Outcomes

In the benazepril arm, 15 of 84 patients who were treated with optimal antiproteinuric dosages (group 2) reached the primary end point, compared with 26 of 83 patients who received the conventional dosage (group 1; 17.9 versus 31.3%; \( P = 0.025 \); Figure 2A). Likewise, in the losartan arm, 13 of 84 patients who received optimal antiproteinuric dosages (group 4) reached the primary end point, as compared with 26 of 88 patients who received the conventional dosage (group 3; 15.5 versus 29.5%; \( P = 0.022 \); Figure 2A). Treatment with optimal antiproteinuric dosages of benazepril or losartan, compared

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Figure 1. Study flow diagram.
53\% (95\% CI 5.5 to 74.1) in the losartan arm (P = 0.039 in the benazepril arm and 0.035 in the losartan arm). The ITT analyses of the individual components of the primary end point indicated that the risk for doubling of serum creatinine level was 49\% lower in the benazepril arm and 50\% lower in the losartan arm among patients who received optimal antiproteinuric dosages than among those who were given the conventional dosage (P = 0.041 and P = 0.040, respectively). Use of the optimal antiproteinuric dosage of benazepril or losartan also reduced the risk for ESRD by 47\%.
(95% CI 4.2 to 72.1) in the benazepril arm and 47% (95% CI 3.6 to 76.9) in the losartan arm (P = 0.042 and P = 0.046, respectively). The per-protocol analyses of the primary end points showed similar results (Figure 2B). There was no statistically significant difference between benazepril and losartan in the overall relative risk reduction at their respective optimal antiproteinuric dosages or at conventional dosages.

Secondary Outcomes

In both the benazepril and losartan arms, there was a significantly greater reduction in the level of proteinuria among patients who were given optimal antiproteinuric dosages than conventional dosages (Figure 3A). The median of final changes from baseline in benazepril arm at 4, 12, 24, and 36 mo was 51, 50, 53, and 50% in group 2 and 37, 35, 36, and 38% in group 1 (P < 0.05). Among the patients who received losartan, the changes of urinary protein excretion at 4, 12, 24, and 36 mo were 52, 51, 52, and 53% in group 4 and 36, 36, 39, and 41% in group 3 (P < 0.05). The proteinuria reduction remained significant after adjustment for differences in the SBP (P = 0.033 and 0.034 for benazepril and losartan, respectively). There was no significant difference in proteinuria reduction between benazepril and losartan at both conventional and optimal antiproteinuric dosages.

Use of optimal antiproteinuric dosages versus conventional dosages reduced the decline in renal function by 60% in the benazepril arm (P = 0.021) and 55% in the losartan arm (P = 0.037), as assessed by creatinine clearance (Figure 3B). In addition, the optimal antiproteinuric dosage was associated with slowing in the decline of eGFR in both benazepril (P = 0.02) and losartan arms (P = 0.03; Figure 3C). There was a close correlation between the extent of the reduction in proteinuria at 3 mo and the rate of decline in the eGFR (r = −0.554, P < 0.001) and creatinine clearance at the study end (r = −0.487, P < 0.001). Changes in renal function were similar between benazepril and losartan arms at both conventional and optimal antiproteinuric doses (P > 0.05).

Dosage-Response Relationship

Optimal antiproteinuric efficacy of benazepril was obtained with a 20-mg dosage in 43 (61%) patients, 30-mg dosage in 11 (16%) patients, 40-mg dosage in three (4%) patients, and >40-mg dosage (i.e., proteinuria reduction >10% of previous level at maximum dosage of 40 mg) in three (4%) patients. The mean dosage at the end of the uptitration phase was 20.8 mg (SD 7.4). Dosage titration with losartan revealed a similar pattern. Optimal antiproteinuric efficacy was obtained with a 100-mg dosage in 48 (57%) patients, 150-mg dosage in 12 (14%) patients, 200-mg dosage in nine (11%) patients, and >200-mg dosage (i.e., proteinuria reduction >10% of previous level at maximum dosage of 200 mg) in three (4%) patients. The mean dosage at the end of the uptitration phase was 117.7 mg (SD 42.6). Four (6%) patients in group 2 and six (7%) patients in group 4 were not responsive to uptitration and were maintained on the starting dosages of the study drugs.

Uptitration was stopped in five patients before the optimal antiproteinuric dosage had been reached because of SBP >120 mmHg (two in group 2 and three in group 4). Two patients titrated back because of reversible hyperkalemia (one in group 2 and one in group 4). Five patients (three in group 2 and two in group 4) withdrew during uptitration because of adverse events.

The antihypertensive efficacy was similar within arms and between arms during the study (P > 0.05; Figure 3D). There was no statistically significant difference in SBP between patients with decline of eGFR >5 or ≤5 ml/min per 1.73 m² (Figure 3E). Urinary excretion of urea and chloride was comparable among groups during the study (Figure 3F). Classes of conventional antihypertensive drugs that were used before and during the study are listed in Table 2.
No patient died during the study period. The incidence of dry cough was significantly higher in the benazepril arm as compared with the losartan arm, but it did not seem to be dosage related (Table 3). There were no dosage-related differences between benazepril and losartan with respect to the incidence of nonfatal cardiovascular events or other adverse events. Hyperkalemia occurred in eight (4.4%) patients in the benazepril arm and eight (4.4%) patients in the losartan arm. Of these 16 patients, six were successfully treated with dietary modifications, concomitant diuretic therapy, and optimized acid-base balance. The remaining 10 patients withdrew from the study. The mean hemoglobin levels at baseline and during the study were comparable in groups. The proportion of patients who receiving recombinant human erythropoietin and the mean dosage of recombinant human erythropoietin were similar among the groups during the follow-up (data not shown).

Figure 3. Median of changes in urinary proteinuria excretion (A), median of creatinine clearance (B), estimated GFR (eGFR; C), BP in all patients (D), median of systolic BP in patients with decline of eGFR (ΔeGFR) >5 or ≤5 ml/min per 1.73 m² (E), and median of urinary excretion of urea and chloride (F).

Safety

No patient died during the study period. The incidence of dry cough was significantly higher in the benazepril arm as compared with the losartan arm, but it did not seem to be dosage related (Table 3). There were no dosage-related differences between benazepril and losartan with respect to the incidence of nonfatal cardiovascular events or other adverse events. Hyperkalemia occurred in eight (4.4%) patients in the benazepril arm and eight (4.4%) patients in the losartan arm. Of these 16 patients, six were successfully treated with dietary modifications, concomitant diuretic therapy, and optimized acid-base balance. The remaining 10 patients withdrew from the study. The mean hemoglobin levels at baseline and during the study were comparable in groups. The proportion of patients who receiving recombinant human erythropoietin and the mean dosage of recombinant human erythropoietin were similar among the groups during the follow-up (data not shown).

Discussion

The results of the ROAD study indicate that treatment with optimal antiproteinuric dosages of the ACEi benazepril or the ARB losartan, as compared with their conventional antihypertensive dosages, resulted in significant reduction in the risk for the primary end point (doubling of serum creatinine concent-
tration, ESRD, or death) in patients who did not have diabetes and had overt proteinuria and chronic renal insufficiency. The greater reduction in proteinuria and the slower decline in creatinine clearance and eGFR that were seen in the titration groups provide further evidence of the long-term renal protection that is afforded by this strategy. Although previous clinical studies have shown that titrating an ACEi or an ARB to higher dosages reduces proteinuria more effectively (27–30), to our knowledge, this is the first study to demonstrate that titration of these therapies against urinary protein excretion provides further benefit not only on proteinuria but also on a renal hard end point.

Table 2. Use of conventional antihypertensive medications

<table>
<thead>
<tr>
<th>Drug (n [%])</th>
<th>Benazepril</th>
<th>Losartan</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Group 1 (n = 90)</td>
<td>Group 2 (n = 90)</td>
</tr>
<tr>
<td>Calcium channel blocker</td>
<td></td>
<td></td>
</tr>
<tr>
<td>at baseline</td>
<td>60 (67)</td>
<td>54 (60)</td>
</tr>
<tr>
<td>during treatment</td>
<td>72 (80)</td>
<td>69 (77)</td>
</tr>
<tr>
<td>Dihydropyridine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>at baseline</td>
<td>48 (53)</td>
<td>44 (49)</td>
</tr>
<tr>
<td>during treatment</td>
<td>55 (61)</td>
<td>52 (58)</td>
</tr>
<tr>
<td>Non-dihydropyridine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>at baseline</td>
<td>12 (13)</td>
<td>10 (11)</td>
</tr>
<tr>
<td>during treatment</td>
<td>17 (19)</td>
<td>17 (19)</td>
</tr>
<tr>
<td>Diuretic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>at baseline</td>
<td>46 (51)</td>
<td>46 (51)</td>
</tr>
<tr>
<td>during treatment</td>
<td>71 (79)</td>
<td>70 (78)</td>
</tr>
<tr>
<td>β blocker</td>
<td></td>
<td></td>
</tr>
<tr>
<td>at baseline</td>
<td>43 (48)</td>
<td>44 (49)</td>
</tr>
<tr>
<td>during treatment</td>
<td>48 (53)</td>
<td>47 (52)</td>
</tr>
<tr>
<td>Centrally acting agent</td>
<td></td>
<td></td>
</tr>
<tr>
<td>at baseline</td>
<td>28 (31)</td>
<td>27 (30)</td>
</tr>
<tr>
<td>during treatment</td>
<td>34 (38)</td>
<td>28 (31)</td>
</tr>
</tbody>
</table>

Table 3. Adverse events after randomization

<table>
<thead>
<tr>
<th>Adverse Events</th>
<th>Benazepril</th>
<th>Losartan</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Group 1 (n = 90)</td>
<td>Group 2 (n = 90)</td>
</tr>
<tr>
<td>Adverse events</td>
<td></td>
<td></td>
</tr>
<tr>
<td>nonfatal cardiovascular event</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>myocardial infarction</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>heart failure</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>stroke</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Other adverse events</td>
<td></td>
<td></td>
</tr>
<tr>
<td>hyperkalemia</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>acute decline in renal function</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>dry cough</td>
<td>17</td>
<td>15</td>
</tr>
<tr>
<td>hypotension</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

BP is one of the most important predictors for renal outcome (1–7). In this study, SBP was rigorously controlled under a level of 130 mmHg but not 120 mmHg, because it has been evidenced that the risk for both renal and cardiovascular diseases starts to increase at a SBP as low as 127 mmHg (31,32). BP and the use of conventional antihypertensive drugs were comparable at baseline and during treatment in the four groups. RAS blockade reduced the risk for renal progression even when adjusted for BP. Benazepril and losartan both are long-acting RAS blockers. Although the study was not able to examine the 24-h BP, the previous studies that used the similar dosage of benazepril (20 mg/d) and losartan (approximately 50 to 100 mg/d) achieved stable control of 24-h BP (33,34). These data suggest that the additive renal protection that is conferred by
uptitration of benazepril or losartan might not be completely dependent on BP. This rationale is further supported by the data from animal studies that indicated non-BP-dependent protective effects against renal fibrosis during high-dosage therapy with ACEi or ARB (10,35).

The extent of renal dysfunction at baseline may influence the outcome (1,2). However, the baseline renal function was comparable among the four groups, and renal function was stable as evidenced by the small variations of creatinine clearance before the study. Furthermore, the decrease in the risk for renal outcome remained significant after adjustment for baseline eGFR. Therefore, we may not attribute the observed renal benefit to the difference in baseline renal dysfunction.

The median of proteinuria reduction that was observed at 3 mo of titration treatment was approximately 1.0 g/d. The Ramipril Efficacy in Nephropathy (REIN) study showed that for each 1.0-g/d reduction in proteinuria seen at 3 mo of ACEi therapy, subsequent GFR decline was slowed by 2.0 ml/min per yr (36). Consistent with the other studies (22,37), proteinuria in this cohort was further reduced by approximately 12 to 17% by increase of benazepril or losartan from its conventional dosage to higher dosages. However, this less impressive difference was associated with significant benefit in renal outcome, suggesting that proteinuria is a strong time-dependent predictor for renal progression (2) and should be reduced as much as possible. Furthermore, RAS blockade has been shown to have benefit on renal progression, which is in addition to the antiproteinuric effect (10,38).

Our study was designed to establish the optimal strategy for reducing proteinuria with RAS blockers. Considering the increasing recognition of individual differences in responsiveness and tolerability to antiproteinuric interventions (39,40), we individually titrated benazepril or losartan to its optimal antiproteinuric dosage. We found that the optimal antiproteinuric efficacy was obtained at the 20-mg dosage of benazepril or 100-mg dosage of losartan in more than half of the patients who received titration. Approximately 25% of patients needed even higher dosages of benazepril or losartan for proteinuria control. It is important, however, to note that <8% of patients were refractory to the antiproteinuric effect of benazepril or losartan. Uptitration of these drugs to the maximum licensed dosages (benazepril 40 mg, losartan 200 mg) did not seem to overcome such therapy resistance. Although it is obviously important to determine the patient factors that may be related to the response variability, this study was not appropriate to analyze these factors, because only a few patients showed therapy resistance.

Uptitration of benazepril or losartan was generally well tolerated in this study. Only 4% of patients stopped titration because of intolerability before the optimal antiproteinuric dosages were achieved. Long-term use of the optimal antiproteinuric dosages of benazepril or losartan seemed to be well tolerated in patients with chronic renal insufficiency. Dry cough was the most common adverse event in the benazepril arm, but it did not seem to be dosage related. The overall incidence of other adverse events between groups that were given conventional and titrated dosages was similar in both the benazepril and losartan arms. Five percent of patients in the titration groups experienced an increase in serum potassium levels of >6.0 mmol/L, but only six patients withdrew from the study. However, we cannot exclude the possibility that the lower rate of serious hyperkalemia in patients with higher dosages of benazepril or losartan may be related to the lower potassium intake (suggested by the lower protein intake, approximately 0.5 g/kg per d) in this cohort and the wide use of diuretics (75%) during follow-up.

This study also provided direct evidence that the long-term renoprotective effects of benazepril and losartan were remarkably similar at the optimal antiproteinuric dosages. These two classes of drugs, at comparable BP control, achieved a similar reduction in both proteinuria and the risk for the primary end point in patients who did not have diabetes and had overt proteinuria and renal insufficiency. Data from a trial that was designed primarily to compare the effects of combined ACEi and ARB treatment with each monotherapy provided indirect evidence supporting this notion (19). Given the finding that both drugs have a dosage-response relationship for renal protection, it is fair to assume that, in clinical practice, full-dosage titration of a RAS blocker aimed at optimal reduction of proteinuria might be more important than the choice of the initial drug. Combination of ACEi and ARB have been shown to be superior to either agent alone (19). However, the safety of this approach remains to be further confirmed, especially in patients with advanced CKD.

Because this was an open-label study, there is a possibility of bias in the recording of the results. However, the Prospective Randomized Open Blinded End-Point (PROBE) design is a well-accepted approach that is as rigorous as the double-blind design, at least when, as in this case, hard end points are considered (41). Although the study was of single-center design, the clinical characteristics of our cohort were similar to those reported in the registry of China. Therefore, our cohort can reflect the general status of nondiabetic CKD, at least in Chinese.

Conclusion

In patients who did not have diabetes and had overt proteinuria and chronic renal insufficiency, use of optimal antiproteinuric dosages of benazepril and losartan was associated with a significant improvement in renal outcome as compared with their conventional dosages in current clinical practice. The renoprotective effects might be comparable between the ACEi benazepril and the ARB losartan in this population.

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Disclosures

None.
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