Lessons Learned from Recent Hypertension Trials about Kidney Disease

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This article reviews BP trials with primary or secondary cardiovascular (CV) or renal end points. It focuses on how results of recent trials have influenced guidelines and clinical practice with specific reference to two issues: (1) Achievement of goal BP in patients with chronic kidney disease and (2) emerging data on the importance of decreasing proteinuria to prevent CV events and slow kidney disease progression. Each study is evaluated on its strengths and weaknesses as well as extrapolation of findings to the general population. The tenants of this article are that the baseline level of proteinuria and the magnitude of proteinuria reduction are important determinants of renal outcome in addition to lowering BP and should be considered in all future trials. Second, comparing trials of people with different stages of nephropathy and unknown or differing levels of proteinuria is limited in generalizing the CV or renal outcome to a more global population.

As a preamble to this article, two observations are noteworthy: First, use of antihypertensive therapy in those with stage 3 nephropathy, i.e., GFR of <60 ml/min, will not slow the rate of decline in kidney function to the same extent as in patients with normal kidney function (stage 1). Studies to address the aforementioned questions will not be performed, however, because of low event rates, relatively higher numbers of participants, and longer duration of follow-up, hence, higher cost than currently completed studies. Thus, we are faced with extrapolating from studies to clinical practice that may not be very appropriate.

Second, observations from a number of clinical studies suggest that both risk for kidney disease progression as well as CV events may be inversely related to the level of kidney function and directly related to the amount of proteinuria (macroalbuminuria), defined as >300 mg/d of protein (1–3). Thus, it is inappropriate to compare results of outcome trials in which in one case the mean GFR is <50 ml/min and in another the GFR is >80 ml/min, especially if proteinuria was not assessed. This is exemplified by comparing renal outcomes trials such as Appropriate Blood Pressure Control in Diabetes (ABCD) trial to the Irbesartan Diabetic Nephropathy Study (IDNT) or Reduction of Endpoints in NIDDM with the All Antagonist Losartan (RENAAL). Both baseline GFR and level of proteinuria were significantly different in these studies and resulted in differences in rate of progression of renal disease over a fixed period of time (4–6).

A less obvious example is seen when the results of the Antihypertensive Lipid Lowering Hypertension Trial (ALLHAT) renal outcomes post hoc analysis is compared with the ABCD trial. The ALLHAT analysis found no significant differences in the composite renal outcomes among the three treatment groups irrespective of baseline GFR or diabetes status (7). As shown in the ABCD trial, the patients in ALLHAT would not be expected to show a difference in kidney function after such a short follow-up period given that the majority of the cohort had stage 2 or better kidney function at trial initiation (4). In addition, it is difficult to appreciate fully or explain the significance of ALLHAT results because there was no measurement of proteinuria throughout the entire trial.

Proteinuria (>300 mg/d) assessment is relevant because, in contrast to ALLHAT, a post hoc analysis of the African-American Study of Kidney Disease (AASK) trial demonstrated differences in rates of renal disease progression at 5 yr on the basis of magnitude of proteinuria reduction at 6 mo after treatment initiation (8). All participants had stage 3 or greater nephropathy, and an accelerated loss of renal function was seen among those with the highest baseline levels of proteinuria. This effect was independent of baseline GFR or level of BP achieved (9). These findings are supported further by analysis of another trial in advanced kidney disease (10).

As illustrated above, differences in baseline GFR and differences in the availability of proteinuria data make comparing the results of the major trials with one another difficult (Tables 1 and 2). Among studies that did assess changes in proteinuria in the context of kidney disease progression, all studies showed that reductions in proteinuria of at least 30% correlate with better renal outcomes (5,6,11–13) (Table 1). Moreover, in one renal outcome study that assessed 24-h ambulatory BP, the effect of proteinuria reduction on outcome was independent of the level of BP reduction (14).

Trials Evaluating BP Level on Outcomes

All published guidelines clearly define goal BP as <140/90 mmHg for those without concomitant conditions and <130/80 mmHg for those with diabetes or chronic kidney disease (15–17). Although data to support the goal of <140/90 mmHg are
overwhelming, the prospective randomized trials that evaluated the hypothesis that a lower BP goal would further slow progression of chronic kidney disease or reduce CV events failed to prove the point (4,18–20).

In the Modification of Diet in Renal Disease (MDRD) trial, participants with predominantly nondiabetic kidney disease and >1 g/d proteinuria demonstrated a trend for the lower BP to decrease kidney disease progression. This is in contrast to the results of AASK and the Ramipril Efficacy In Nephropathy trial (REIN-2), which also studied patients with nondiabetic nephropathy (21,22). In both of these trials, no benefit was seen in patients who were randomly assigned to a lower BP goal on nephropathy progression. However, there are several important differences between these studies. Whereas AASK had a lower mean baseline protein excretion than REIN-2, it was appropriately powered to detect a difference in GFR decline.

### Table 1. Trials that demonstrate significant reductions in proteinuria (>300 mg/d)\(^a\)

<table>
<thead>
<tr>
<th>Trial</th>
<th>Intervention</th>
<th>Follow-Up (yr)</th>
<th>Baseline GFR (ml/min)</th>
<th>Target BP (mmHg)</th>
<th>Achieved BP (mmHg)</th>
<th>Change in Proteinuria</th>
</tr>
</thead>
<tbody>
<tr>
<td>RENAAL</td>
<td>Losartan</td>
<td>3.4</td>
<td>58</td>
<td>&lt;140/90</td>
<td>140/74</td>
<td>−35%</td>
</tr>
<tr>
<td>AASK</td>
<td>Metoprolol, Ramipril, Amlodipine</td>
<td>4</td>
<td>46</td>
<td>MAP &lt;92 in lower group and MAP 102 to 107 in usual group</td>
<td>128/78 for lower group, 141/85 for usual group</td>
<td>−14% for metoprolol, −20% for ramipril, −58% for amlodipine at 6 mo</td>
</tr>
<tr>
<td>COOPERATE</td>
<td>Trandolapril, Losartan, Combination(^b)</td>
<td>3</td>
<td>51</td>
<td>&lt;130/80</td>
<td>130.7/74.3</td>
<td>−42.1%</td>
</tr>
<tr>
<td>IDNT</td>
<td>Irbesartan, Amlodipine, Placebo</td>
<td>2.6</td>
<td>59</td>
<td>&lt;135/85</td>
<td>140/77</td>
<td>−33%</td>
</tr>
</tbody>
</table>

\(^a\)Refers to trials with >300 mg/d proteinuria at baseline. These include RENAAL, Reduction of Endpoints in NIDDM with the All Antagonist Losartan; AASK, African-American Study of Kidney Disease; COOPERATE, Combination Treatment of Angiotensin-II Receptor Blocker and Angiotensin-converting-enzyme Inhibitor in Nondiabetic Renal Disease; IDNT, Irbesartan Diabetic Nephropathy Trial; MAP, mean arterial pressure.

\(^b\)Signifies combination of trandolapril and losartan given at same dose as individually given.

### Table 2. Trials that did not measure or demonstrate reductions in proteinuria\(^a\)

<table>
<thead>
<tr>
<th>Trial</th>
<th>Intervention</th>
<th>Follow-Up (yr)</th>
<th>Baseline GFR (ml/min)</th>
<th>Target BP (mmHg)</th>
<th>Achieved BP (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABCD(^b)</td>
<td>Intensive moderate BP control</td>
<td>5.3</td>
<td>84</td>
<td>DBP of 75 versus DBP 80 to 89</td>
<td>132/78</td>
</tr>
<tr>
<td>ALLHAT(^b)</td>
<td>Chlorthalidone, Amlodipine, Lisinopril</td>
<td>4.9</td>
<td>78</td>
<td>&lt;140/90 in all groups</td>
<td>134/75</td>
</tr>
<tr>
<td>BENEDICT(^b)</td>
<td>Verapamil, Trandolapril, Combination</td>
<td>3.6</td>
<td>79(^d)</td>
<td>&lt;120/80</td>
<td>141/78</td>
</tr>
<tr>
<td>REIN-2(^c)</td>
<td>Conventional intensified BP control</td>
<td>1.6</td>
<td>35</td>
<td>DBP &lt;90 and &lt;130/80</td>
<td>134/82</td>
</tr>
</tbody>
</table>

\(^a\)ABCD, Appropriate Blood Pressure Control in Diabetes; ALLHAT, Antihypertensive Lipid Lowering Hypertension Trial; BENEDICT, Bergamo Nephrologic Diabetes Complications Trial; REIN-2, Ramipril Efficacy In Nephropathy trial (REIN-2).

\(^b\)Patients who were enrolled in these trials all had stage 2 nephropathy with microalbuminuria, if measured, or as in the case of BENEDICT no microalbuminuria. These facts, taken together with interventions that would markedly slow decline in kidney function, preclude a significant difference in renal outcome over the duration of follow-up noted in these studies.

\(^c\)Although the patients in this trial had significantly impaired kidney function, the trial followed people for only 1.6 yr. When this is considered along with the 4-mmHg difference in systolic BP between the conventional and intensive treatment groups, this trial would not have been able to detect differences in proteinuria reduction or differences in any renal outcomes.

\(^d\)Estimated by the modified Modification of Diet in Renal Disease formula.
ment groups and a 5-yr follow-up period in AASK compared with a 4.8-mmHg systolic BP difference between treatment groups and 1.6-yr follow-up in REIN-2. It is noteworthy that the subgroup in AASK (n = approximately 350) with levels of proteinuria > 300 mg/d tended to have a slower, albeit NS, decline in GFR at the lower BP level, an effect clearly seen in the small subgroup with proteinuria of > 1 g/d.

The outcomes of REIN-2 are also in contrast to the post hoc analysis of RENAAL, which showed that the subgroup that received losartan with a dihydropyridine calcium antagonist had a similar outcome to those who received losartan and other agents (23). These differences could be due to differences in the cause of kidney disease (nondiabetic versus diabetic), duration of follow-up (1.6 versus 3.4 yr), or differences in renal autoregulation between calcium antagonists, with felodipine having a relatively worse profile (24,25).

It is well known that dihydropyridine calcium channel blockers all increase GFR and do so by impairing renal autoregulation (26,27) although this increased GFR gives the mistaken impression of preserved renal function, it is at the expense of increased intraglomerular pressures and increased levels of proteinuria. These findings, taken together with other available human and animal data, suggest that patients with substantially reduced kidney function such as in REIN-2, AASK, and IDNT would not be expected to derive similar benefit to a potentially reduced kidney function such as in REIN-2, AASK, and MDRD, do show that those with advanced nephropathy and proteinuria of > 1 g/d did manifest slower declines in kidney function at BP levels < 130/80 mmHg. This was finally appreciated after almost 10 yr of follow-up in the MDRD, with similar follow-up on going in AASK (10,28).

**Proteinuria Reduction and Kidney Disease Progression**

Proteinuria, or macroalbuminuria, is a well-known independent risk marker for progressive loss of renal function (29). Although blockers of the renin-angiotensin-aldosterone (RAAS) system have been shown to be effective in preventing the progression of kidney disease, it is difficult to distinguish whether this renoprotection is due exclusively to the antihypertensive, antiproteinuric, or combined effects of these agents. For helping to address this issue, a re-analysis of some large outcome trials of people with hypertension and kidney disease were performed.

A post hoc analysis of the RENAAL data examined whether there was a relationship between (1) amount of baseline proteinuria, (2) initial reduction in proteinuria, or (3) degree of residual proteinuria on the primary end point, i.e., progression to ESRD and/or doubling of serum creatinine (30). The analysis demonstrated that baseline albuminuria was almost linearly related to renal outcome. Patients with a baseline albuminuria of ≥ 3.0 g albumin/g creatinine were found to have a 5.2-fold increased risk for reaching the primary end point and an 8.1-fold increased risk for progressing to ESRD alone, compared with the low albuminuria group (< 1.5 g/g). This analysis also found that for every 50% reduction in albuminuria in the first 6 mo after initiating treatment, there was a 36% risk reduction of the primary end point and a 45% reduction for ESRD alone at trial end. This reduction in proteinuria at 6 mo showed a linear relationship with renal outcome similar to the relationship between baseline albuminuria and renal risk, and this relationship was not related to the magnitude of BP reduction.

A post hoc analysis of another cohort with diabetic nephropathy, the IDNT, found similar results (31). In this analysis, the risk for reaching the primary end point doubled with each two-fold increase in the level of baseline proteinuria. After 1 yr of treatment, it was noted that for each 50% reduction in proteinuria, there was a > 50% reduction in the incidence of the primary end point in all of the treatment arms. Despite similar BP, a comparison of the treatment arms demonstrated that irbesartan was superior to amlodipine and placebo in both reducing the primary outcome and proteinuria. After 1 yr of treatment, 40% of the patients in the irbesartan group had a > 50% reduction in proteinuria, compared with 20% in the amlodipine group and 25% in the placebo group. After controlling for BP reduction, the authors concluded that 36% of the renoprotective effect of irbesartan is related to proteinuria reduction in the first 12 mo of therapy.

The results of a third post hoc analysis of the AASK nondiabetic cohort also support the aforementioned findings. In this analysis, baseline proteinuria and GFR predicted the rate of GFR decline. Initial change in proteinuria from baseline to 6 mo predicted subsequent development of ESRD at 5 yr, with this relationship extending to participants with baseline urinary protein levels < 300 mg/d. As in the previous studies, the change in level of proteinuria was a predictor of subsequent progression of hypertensive kidney disease at a given GFR (32).

One prospective, randomized trial in a cohort of nondiabetic patients also supports the hypothesis that early reductions in proteinuria are associated with slower declines in kidney function. The Combination Treatment of Angiotensin-II Receptor Blocker and Angiotensin-converting-enzyme Inhibitor in Non-diabetic Renal Disease (COOPERATE) trial is the only study to address adequately the role of changes in proteinuria on renal outcomes, prospectively. The study demonstrated that combining high doses of an angiotensin-converting enzyme (ACE) inhibitor and an angiotensin receptor blocker (ARB) resulted in slower progression of kidney disease, and this effect was related to a greater reduction in proteinuria rather than a reduction in BP (11). Moreover, a substudy of the main trial using 24-h ambulatory monitoring demonstrated that those with the greatest reductions in proteinuria at 6 mo had the slowest declines in GFR, an effect independent of BP level achieved (14). The notion that the combination of an ACE inhibitor and an ARB should be used only for proteinuric renal disease and not for BP reduction is supported further by the results of a
Antihypertensive Outcome Trials and Microalbuminuria

Microalbuminuria is currently defined as ≥30 and <300 mg/d protein in the urine (16). Whereas data regarding the effect of ACE inhibitors and ARB on proteinuria reduction in diabetic nephropathy are plentiful, only limited data exist regarding the use of calcium antagonists in this patient population. In people with proteinuric kidney disease, nondihydropyridine calcium antagonists reduce proteinuria (>300 mg/d) in concert with BP reduction, whereas in those with microalbuminuria (<300 mg/d), they have neutral effects (21,35,36). However, the Bergamo Nephrologic Diabetes Complications Trial (BENEDICT) was the first to assess the ability of nondihydropyridine calcium antagonist to prevent microalbuminuria in a cohort with diabetes. The trial tested the hypothesis that an ACE inhibitor together with the nondihydropyridine calcium blocker verapamil, alone or in combination, could prevent development of microalbuminuria in patients with hypertension, type 2 diabetes, and normal urinary albumin excretion (37). BENEDICT noted in 1204 hypertensive patients (defined as BP ≥130/80 mmHg or already on antihypertensive therapy) that both the combination of an ACE inhibitor with verapamil or the ACE inhibitor alone reduced development of microalbuminuria compared with placebo or verapamil alone, after a median of 3.6 yr. This study has major limitations, however. It failed to achieve BP target of 120/80 mmHg, with average systolic pressure approximately 20 mmHg higher, and had no clinical morbidity or mortality end point data.

These findings of BENEDICT may be explained, in part, by the fact that microalbuminuria is a CV risk factor that correlates with C-reactive protein (CRP) activity and not a factor that determines the presence of kidney disease (38–40). Furthermore, calcium antagonists as a class have not been shown to prevent the development of micro- or macroalbuminuria in an animal model (41–44). More information that is important will come from the ongoing second phase of this study, in which participants who developed microalbuminuria were randomly assigned again to either trandolapril alone or in combination with verapamil. The results should be available in late 2006 or early 2007.

Antihypertensive Trials, CV Outcomes, and Microalbuminuria

Whereas reductions in proteinuria (>300 mg/d) are strongly associated with slowed progression of kidney disease, reductions in microalbuminuria (>30 and <300 mg/d) correlate with decreased CV mortality (40,45,46). A recent post hoc analysis of the data from the Losartan Intervention for Endpoint Reduction in Hypertension Study (LIFE) sought to determine whether a reduction in microalbuminuria over time correlated with a decreased incidence of first occurrence of CV death, nonfatal stroke, and nonfatal myocardial infarction. More than 8000 patients with hypertension, mean age of 64 yr, and ECG-verified left ventricular hypertrophy were followed for an average of 4.8 yr. Only patients who had a morning spot urine sample for albumin to creatinine (UACR) ratio were included in the analysis. In fact, most of the participants in this trial had microalbuminuria. Participants were randomly assigned to receive either a losartan-based or an atenolol-based regimen with a target BP of <140/90 mmHg.

The analysis found that those with the highest UACR at baseline had a three- to four-fold greater risk for reaching the primary CV end point when compared with those in the lowest group (47). Moreover, the magnitude of UACR reduction at 5 yr and not the type of antihypertensive regimen used or BP achieved was an independent predictor of CV mortality reduction (47). It should be noted that the results of this trial might not be applicable to all patients with hypertension. All patients in this trial had documented left ventricular hypertrophy, and stroke was the major event that influenced the significance of the results. Thus, the results of this trial may not apply to patients who have hypertension but do not show signs of hypertensive heart disease.

A population-based prospective study of 764 participants who were aged 50 to 89 yr from a community in Denmark assessed the N-αmino terminal fragment of the pro-hormone brain natriuretic peptide (NT-proBNP) versus CRP and urinary albumin/creatinine ratio as a prognosticator of CV events over 5 yr in an older adult population. Albumin/creatinine ratios in this study were in the microalbuminuria range. This study showed that after adjustment for CV risk factors, the hazard ratio (HR) of mortality was 1.96 for NT-proBNP, 1.88 for albumin/creatinine ratio, and 1.46 for CRP. The absolute unadjusted increase in mortality was 24.5% for NT-proBNP, 19.5% for urinary albumin/creatinine ratio, and 7.8% for CRP. Elevated NT-probing levels or albumin/creatinine ratio was associated with high risk for first major CV events (nonfatal myocardial infarction, fatal coronary heart disease, unstable angina, heart failure, stroke, and transient ischemic attack) (45). This study further demonstrates that microalbuminuria is a strong predictor of CV events, better than CRP.

Conclusion

Taken together, these studies suggest that proteinuria reduction, in concert with BP reduction, is a prognostic factor for renal and CV events. Thus, proteinuria reductions of at least 35% by 6 mo to 1 yr from the start of therapy, along with a reduction in BP, predict slower progression of kidney disease and reduced CV events compared with BP reduction alone. The importance of this early effect is bolstered further by the findings in the RENAAL, IDNT, and AASK trials. Thus, it is clear that the projection made more than a decade ago that reductions in proteinuria correlated with a slowed progression of kidney disease now are supported by several clinical trials (48,49).

On the basis of the evidence of prospective, randomized trials, physicians now need to focus on achieving a BP goal of <140/90 mmHg; however, they can no longer focus only on reducing BP and assume that this intervention will lead to maximal risk reduction for their patients. Clearly, presence of
microalbuminuria or development of proteinuria heralds an enhanced risk for CV events and presence of kidney disease (16,50). On the basis of all post hoc analyses of trials, a goal BP of <130/80 mmHg clearly is warranted in those who have stage 3 or more nephropathy and also have proteinuria, especially those with >1 g/d. Thus, physicians must evaluate spot urine for albuminuria in all patients with diabetes and other evidence of hypertensive end-organ injury. A strong consideration should be given to early or initial use of antihypertensive agents such as RAAS blockers, usually in concert with diuretics, in patients with kidney disease. Moreover, those who are 20/10 mmHg above goal BP should be started on combination therapy (50). Additional strategies to reduce albuminuria maximally may include combining two agents that block the RAAS or combining ACE inhibitors with calcium channel blockers for maximal BP reduction. The Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension (ACCOMPLISH) trial is an ongoing randomized trial of approximately 12,000 hypertensive patients at high CV risk that compares an ACE inhibitor/calcium antagonist combination with an ACE inhibitor/diuretic combination in people with stages 2 and 3 nephropathy and other CV risk factors (51). It will supply further data on changes in albuminuria and CV outcomes and should add to our knowledge about the role of albuminuria and CV outcomes as well as which initial combination agents are associated with fewer events. The trial will be completed in 2007.

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