Is It the Agent or the Blood Pressure Level that Matters for Renal Protection in Chronic Nephropathies?

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Abstract. Some antihypertensive agents may be capable of reducing chronic renal insufficiency (CRI) progression because they halt some of the pathogenic mechanisms involved in renal damage. Although this effect seems to be partially independent of BP reduction, it is still unclear whether these drugs are really superior to other antihypertensive agents when the BP values recommended by the present guidelines are actually achieved. This is particularly true when considering that, in published trials, target and achieved BP values were constantly higher than those nowadays recommended. Furthermore, in the majority of these studies, patients treated with ACE-inhibitors (ACE-I) or Angiotensin II receptor antagonists (ATIIRA) achieved lower BP values than those in control groups and BP values during 24 h were not recorded. Anyway, taking into account the role of baseline and follow-up BP values, the treatment effect remained significant in almost all of the multivariate models. These findings suggest that the renoprotective effect of these agents (ACE-I, ATIIRA) is partially independent of better BP control. However, caution should be paid in attributing true biologic renoprotective properties to drugs just on the basis of statistical adjustments of BP values, although robustly performed, without being aware of what those BP values actually reflect.

Hypertension is not only an important presenting feature of renal disease and, together with proteinuria, probably a major factor contributing to progression; it is also a significant determinant of morbidity and mortality among hemodialysis patients. Effective antihypertensive therapy is therefore the most important single treatment (other than the possible treatment of primary disease) in patients affected by chronic renal insufficiency (CRI). However, it has become clear over recent years that not all antihypertensive agents are equally effective in slowing CRI progression and that some have an additional renoprotective effect that seems at least partially independent of BP reduction. However, in the majority of large trials, target and achieved BP values were constantly higher than those nowadays recommended. Moreover, the BP values were often lower in the experimental groups (ACE-inhibitors [ACE-I] or Angiotensin II receptor antagonists [ATIIRA]) compared with the control groups and BP values during 24 h were not recorded.

In this article, we would like to review the link between BP reduction and CRI progression to possibly clarify whether, at the recommended BP values, renoprotection could be equally achieved with all classes of anti-hypertensive agents, thus minimizing the clinical relevance of the benefits provided by some classes of drugs (mainly ACE-I and ATIIRA) due to mechanisms other than simply reducing BP values.

The Effect of BP Reduction on CRI Progression

Over the last decade, a number of trials have been performed to assess the degree of BP reduction needed to achieve renoprotection (1,2). The results of the Modification of Diet in Renal Disease (MDRD) Study (1) clearly showed that stricter BP control (i.e., mean arterial pressure [MAP] ≤ 92 mmHg or systolic BP [SBP]/diastolic BP [DBP] ≤ 125/75 mmHg in subjects aged ≤ 60 yr, and MAP ≤ 98 mmHg or SBP/DBP ≤ 145/75 mmHg in subjects older than 60 yr) was capable of slowing CRI progression compared with BP control that was usual for that time (i.e., MAP ≤ 107 mmHg or SBP/DBP ≤ 140/90 mmHg in subjects aged ≤ 60 yr and MAP ≤ 113 mmHg or SBP/DBP ≤ 160/90 mmHg in subjects older than 60 yr). The patients with higher levels of baseline proteinuria received greater benefits from being assigned to a low BP target.

We tried to quantify the effect of BP reduction on the rate of CRI progression by analyzing the time to end-stage renal disease (ESRD) (arbitrarily defined as a GFR of ≤ 5 ml/min) on the basis of the baseline GFR values and their rate of decline in the MDRD study and assuming the rate of CRI progression as linear and compliance and effect of treatment constant over time (which of course is not always true) (3). The results from study A showed that patients assigned to a target MAP of 92 mmHg had a decline in GFR of −3.6 ml/min per yr and −4.1 ml/min per yr, respectively (Figure 1). We estimated that such a stricter BP control could delay the time to ESRD by 1.24 yr over a period of 9.4 yr (9.43 versus 8.19 yr). In study B, only 0.43 yr could be gained with a strict BP...
The effect of tight BP control on the course of diabetic nephropathy was also investigated in 129 patients with type 1 diabetes mellitus treated with ACE-I and who had previously participated in the Angiotensin-Converting Enzyme Inhibition in Diabetic Nephropathy Study (7). Patients were randomly assigned to a MAP goal of $\leq$92 mmHg or of 100 to 107 mmHg and were followed-up for a minimum of 2 yr. Although there were no statistical differences in the rate of decline of renal function between groups, urinary protein excretion during follow-up was significantly lower in the low-BP group than in the control group (535 mg/24 h and 1723 mg/24 h, respectively; $P = 0.02$); the achievement of proteinuria remission (defined as proteinuria $< 500$ mg/24 h) was of borderline significance, that is 12 (23%) of the patients assigned to strict BP control versus 5 (11%) of those assigned to higher BP values.

**What Is the Optimal BP in Patients with Chronic Nephropathies?**

On the basis of the findings of the MDRD study, in 1995 the National High BP Education Program Working Group suggested a target BP of 130/85 mmHg in patients with renal disease (8). However, after the results of the MDRD secondary analyses (2), a lower than usual BP goal (125/75 mmHg) was recommended for patients with moderate CRI and proteinuria $> 1$ g/24 h. These recommendations are particularly important also considering that patients with CRI are considered at very high risk of developing cardiovascular disease and dying from it. More recently, the World Health Organization Guidelines for the treatment of hypertension recommended BP values of $\leq 130/85$ mmHg ($\leq 140/90$ mmHg in patients older than 60 yr) in all the patients with renal diseases (9).

**Which BP Values Have Been Actually Achieved in Large Clinical Trials?**

The majority of trials concerning the role of ACE-I on CRI progression were designed or performed before awareness of the need for a more strict BP control in CRI patients; even in more recent trials investigating the role of ATIIRA on progression of chronic nephropathies, a large proportion of patients did not achieve the recommended targets. However, this important issue has rarely been taken into account in the proper way, as suggested by the fact that the BP distribution during follow-up is usually not given, and only mean values are reported in the majority of papers. When it was reported that mean SBP during follow-up was $- 140$ mmHg, this automatically means that about half of the study population failed to reach this value.

The effect of ACE-I on progression of nondiabetic renal disease has recently been re-evaluated in the meta-analysis of patient-level data by Jafar et al. (10), including 11 randomized trials and a total of 1860 patients. Throughout the whole follow-up, mean SBP was significantly lower in the ACE-I than in the control group (139 $\pm 16$ mmHg versus 144 $\pm 16$ mmHg); the difference in mean DBP between the two groups was of lower extent (85 $\pm 7$ mmHg versus 87 $\pm 8$ mmHg) but still statistically significant ($P < 0.01$). Simply assuming a Gaussian distribution of BP values during follow-up (considering the high number of patients), we can calculate, from the characteristics of normal distributions, that 47% of patients in the ACE-I group and 60% in the control group did not achieve the target SBP of $< 140$ mmHg. If we take a minimum target of 135 mmHg for SBP in nephropathic patients, the proportion of patients who did not achieve the goal was 60% in the ACEI group and 71% in the control group. If we assume a desirable target of 130 mmHg, the proportion of failures further in-
creased: 71% in the ACE-I group, and 81% in the control group. The DBP control was better in both groups, probably reflecting that it was paid greater attention to DBP than SBP control or, more likely, that SBP control is simply more difficult to achieve. As a matter of fact, DBP during follow-up was >90 mmHg in 24% of patients in the ACE-I and in 35% of patients in the control group. Considering the current desirable targets for DBP control in chronic nephropathies, 50% of patients in the ACE-I and 60% in the control group failed to achieve DBP of <85 mmHg; 76% in the ACE-I group, and 81% in the control group could not achieve DBP of <80 mmHg.

This analysis is undoubtedly simplistic approximation, as it does not take into account the real distributions of BP data collected in the trials. However, we do think that it can reliably reflect how difficult BP control was with respect to not only the previous targets (<140/90 mmHg) but also the minimal targets advised nowadays (<135/85 mmHg or still not optimal <130/80 mmHg). The same conclusions could be drawn by the analysis of the BP distributions in the single trials.

By allowing more selective inhibition of the renin-angiotensin system at the receptor level, ATIIRA have recently come to the fore. Two large prospective randomized trials, the RENAAL and the IDNT studies, investigating the effect of ATIIRA in diabetic nephropathy, have been recently published (11,12). As their design was more recent, these trials more strictly reflect the current prevalent opinions about BP control than older trials on ACE-I. However, whereas the IDNT trial (12) assumed BP targets of <135/85 mmHg, which can be considered just sufficient, the RENAAL study (11) still assumed BP targets of <140/90 mmHg, which is certainly not a sufficient BP control for nephropathic and, particularly, diabetic patients. Moreover, the published data on BP control during follow-up were not completely informative, as only means, but not SD, were given. In our opinion, this is a limitation, as it prevents the reader from being aware of the spread of BP distribution during follow-up and of the proportion of patients above the desirable BP targets. Anyway, in the IDNT study (12), the mean BP at visits after baseline was 140/77 mmHg in the irbesartan group, 141/77 mmHg in the amlopidine group, and 144/80 mmHg in the placebo group. In the RENAAL study (11), mean BP values at the end of the study were 140/74 mmHg in the losartan group and 142/74 mmHg in the placebo group. From these partial data, we can speculate that DBP was well controlled, but SBP was >140 mmHg in at least 50% of patients in both trials.

Are All Antihypertensive Agents Equally Effective?

Although the mechanisms leading to proteinuria in chronic renal diseases are complex and not yet fully elucidated, there is a clear relationship between urinary protein excretion and BP levels. Essential hypertensive patients could have increased urinary protein excretion even in the absence of established renal damage, and this correlates with BP levels. This increase in proteinuria has been attributed to the transmission of high systemic BP to the glomeruli and, according to this hypothesis, any antihypertensive therapy is capable of decreasing proteinuria, decreasing BP values. A multivariate analysis of controlled and uncontrolled trials by Maki et al. (13) showed that each 10-mmHg reduction in BP is able to decrease proteinuria by 14% (regression coefficient, −0.14; 95% confidence interval, −0.22 to −0.06). However, there was a clear difference in the anti-proteinuric capacity of the different classes of antihypertensive drugs, with ACE-I and nondihydropyridine calcium channel blockers having the greatest capacity (13). This difference also emerges from the results of a meta-analysis by Weidmann et al. (14) concerning the anti-proteinuric ability of different antihypertensive agents in diabetic nephropathy. Despite similar degrees of BP reduction, proteinuria tended to decrease more with ACE-I (average of 45%) than with conventional therapy (average of 23%) or calcium channel blockers other than nifedipine (an average of 35%). However, after a decrease in mean BP of approximately 20 mmHg, the anti-proteinuric effect of all of the different drugs becomes the same.

In addition to their anti-proteinuric effect, some agents may be capable of reducing CRI progression because they halt some of the pathogenetic mechanisms involved in glomerular and tubulointerstitial renal damage. Indeed, several clinical trials have shown that drugs blocking the renin-angiotensin system are more effective in reducing CRI progression compared with other antihypertensive drugs (11,12,15–18). However, none of these studies has completely answered the key questions: (1) to what extent the renoprotective effect of ACE-I/ATIIRA is independent of BP reduction; and (2) whether these classes of drugs are really superior to other antihypertensive agents when present recommended BP values are actually achieved. Furthermore, the majority of the studies have been criticized because SBP and DBP values achieved with ACE-I were lower than those obtained during standard antihypertensive therapy and because BP values during 24 h were not measured.

In the Angiotensin-Converting-Enzyme Inhibition in Progressive Renal Insufficiency (AIPRI) Study, the patients randomized to benazepril had a lower decline in GFR (−3.38 ml/min per yr) than those randomized to placebo (−4.95 ml/min per yr), leading to an estimated delay in the need of renal replacement therapy of 3.85 yr over a period of 11.3 yr (11.32 versus 7.47) (3). However, benazepril treatment led to lower BP values than control treatment (i.e., traditional antihypertensive therapy not including ACE-I) during follow-up. The mean DBP decreased by 3.5 to 5 mmHg in the benazepril group, and increased by 0.2 to 1.5 mmHg in the control group; the mean SBP decreased by 4.5 to 8.0 mmHg in the benazepril group and increased by 1.0 to 3.7 mmHg in the control group (16). After adjusting for changes in DBP, the overall risk reduction for progression of renal disease in the benazepril group was still significant. However, according to the trial design, no correction for SBP, both at baseline and during follow-up, was performed.

With the aim of better clarifying the relationship between BP control and the effect of ACE-I, we have performed a secondary analysis of the AIPRI data, by taking into account the effects of both SBP and DBP at baseline and during follow-up on the risk of developing the primary composite end point (i.e.,...
doubling of baseline serum creatinine or the need for dialysis or transplantation). Table 1 reports the effect of treatment with ACE-I versus control treatment on renal outcome, adjusted for the effect of the other significant variables at Cox multivariate analysis. Proteinuria values at baseline and throughout follow-up were the main factors related to the renal outcomes: each g/d greater levels of proteinuria at baseline was associated with an increase of 39% in the relative risk for the primary end point; similarly, each g/d greater levels of proteinuria during follow-up was associated with an increase in the relative risk of 35%. As expected, lower renal function at baseline was an independent predictor of reaching the primary end point. DBP at baseline (relative risk increase of 6% for each mmHg increase) and SBP changes from baseline throughout follow-up were independently related to the primary end points. When all of these co-variates have been considered, a trend toward independent renoprotection by ACE-I was still present, but without statistical significance (relative risk reduction, 20%; \( P = 0.39 \)).

This can be estimated as the “pure” effect of benazepril, after adjusting the analysis for BP at baseline and during follow-up. These results could mean that, after proper statistical adjustments, the specific renoprotection by ACE-I in the AIPRI Study is no longer confirmed. However, the reduction in SBP from baseline during follow-up was significantly associated with the reduction in proteinuria levels (\( P = 0.013 \)), which in turn were heavily related with renal outcome, and the reduction in proteinuria was significantly higher in the benazepril than in the control group throughout the BP range (Figure 2). It is worth noting that the regression lines of the control and benazepril groups were parallel (\( P = 0.326 \)) and significantly different (\( P < 0.001 \)), which means that the anti-proteinuric effect of ACE-I was independent of the BP control achieved. This is in contrast with the results of the meta-analysis by Weidmann et al. (14). Our findings could be explained by assuming that the crude renoprotection by ACE-I was at least partially due to a selective anti-proteinuric effect and independent of BP control. In conclusion, the AIPRI data showed that: (1) an imbalance in both SBP and DBP was present during follow-up between the ACE-I and the control group; (2) only DBP adjustments were made in the primary analysis (16); and (3) when adjusting for SBP values as well, the net effect of ACE-I on renal outcome decreased and could possibly be explained by its effect on proteinuria.

In the already quoted meta-analysis by Jafar et al., comparing the efficacy of antihypertensive regimens including ACE-I with antihypertensive regimens not including ACE-I in non-diabetic renal disease (10), the patients in the ACE-I group had a greater decrease in mean SBP and DBP throughout follow-up (by 4.5 mmHg and 2.3 mmHg, respectively). However, after adjustment for changes in BP during follow-up, the treatment effect remained significant in multivariate models. These findings suggest that the renoprotective effect is partially independent of better BP control.

Anyway, in accordance with Jafar et al. (10), it is worth noting that, when dealing with fluctuating time-dependent co-variates, such as BP, both related to outcome and to treatment, any measurement error in BP would inevitably weaken the impact of BP values on outcomes and automatically increases the magnitude of the effect attributed to the treatment (namely ACE-I). This effect could be particularly true considering that 24-h BP control was not foreseen in any of the trials.

As already mentioned, the RENAAL (11) and IDNT (12) studies have recently highlighted that blocking the effects of angiotensin II through ATIIRA is renoprotective in patients with type 2 diabetes. As in the majority of trials with ACE-I in the setting of CRI, time-averaged differences in the BP between the losartan and placebo groups were observed in the RENAAL study during the first 2 yr of follow-up; later on, they were no longer present (10). Anyway, the reduction in the risk of reaching the primary composite end point of doubling baseline serum creatinine, need of dialysis or transplantation, or death remained essentially unchanged after adjustment for BP (16% and 15%, respectively) (11). In the IDNT study, similar BP control was reported in the two groups throughout follow-up (12). After correction for MAP during follow-up, the results were similar, suggesting that the better renal outcomes observed in patients treated with irbesartan could not be simply explained by a more effective control of systemic BP (12). Altogether, these findings may indicate that the effects of ATIIRA per se largely exceed those of BP difference.

However, we would like to stress that in the RENAAL and IDNT trials, as well as in all of the previous trials investigating the effect of the inhibition of the renin-angiotensin system on renal outcome decreased and could possibly be explained by its effect on proteinuria.

Table 1. Relative risks (RR) for composite end point (doubling of serum creatinine or end-stage renal disease) obtained from Cox regression analysis of AIPRI individual data

<table>
<thead>
<tr>
<th>Variables</th>
<th>RR</th>
<th>95% CI for RR</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment with ACE-I versus placebo</td>
<td>0.796</td>
<td>0.473 – 1.340</td>
<td>0.39</td>
</tr>
<tr>
<td>Stratum (CrCl &lt; 45 ml/min versus ≥ 45 ml/min)</td>
<td>2.359</td>
<td>1.441 – 3.860</td>
<td>0.001</td>
</tr>
<tr>
<td>Baseline proteinuria (each g/d increase)</td>
<td>1.389</td>
<td>1.299 – 1.486</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Baseline diastolic BP * (each mmHg increase)</td>
<td>1.061</td>
<td>1.031 – 1.091</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Systolic BP change (each mmHg increase)</td>
<td>1.027</td>
<td>1.008 – 1.047</td>
<td>0.005</td>
</tr>
<tr>
<td>Proteinuria change (each g/d increase)</td>
<td>1.347</td>
<td>1.185 – 1.531</td>
<td>&lt;0.001</td>
</tr>
</tbody>
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ACE-I, ACE-inhibitors; CrCl, creatinine clearance.
We also think that future publications should pay more attention to the distributions of BP values actually achieved, both at baseline and throughout the study follow-up, providing both central and variability parameters.

References


CRI progression, no data were available on 24-h BP control, which reflects the actual BP control much better than sporadic BP measurements. This is not a negligible shortcoming of all studies published so far. Considering that BP values were usually collected 24 h after drug administration, when treatment effect is nearly exhausted, this could not have allowed the detection of larger differences in BP values among treatment groups occurring in the next few hours after drug administration. Therefore, underestimation of the real impact of BP reduction on CRI progression might have occurred, possibly enhancing the treatment effect.

Conclusions

ACE-I and ATIIIRA are effective in reducing proteinuria and preventing the progression of renal damage in patients with chronic renal diseases, and this effect seems at least partially independent of BP reduction. However, (1) it is still unclear whether this also applies at the currently recommended target BP values, as a large percentage of patients did not achieve an optimal BP control; and (2) no 24-h BP monitoring has been performed in the different studies published so far, therefore not allowing a strict evaluation of the BP control. This is particularly relevant because BP is a fluctuating time-dependent co-variate.

For these reasons, caution should be paid in attributing true biologic renoprotective properties to drugs on the basis of statistical adjustments of BP values, although robustly performed, without being aware of what those BP values actually reflect. In other words, it cannot be taken for granted, referring to multivariate analyses, that the benefits from ACE-I/ATIIIRA shown at high BP values would be actually confirmed at present lower recommended BP levels on the sole basis of the fact that renoprotective effect of these drugs persisted after statistical correction for BP values.

Figure 2. The relationship between systolic BP (SBP) and proteinuria changes during follow-up in the AIPRI study. A reduction in SBP from baseline was associated with a reduction in proteinuria ($P = 0.013$). The observation that the two regression lines for the ACE-inhibitors (ACE-I) and placebo group were parallel ($P = 0.326$) suggests an additive beneficial effect on proteinuria by benazepril compared with conventional antihypertensive therapy.


