Kidney International, Vol. 67, Supplement 93 (2005), pp. S15–S19

Is it the agent or the blood pressure level that matters for renal and vascular protection in chronic nephropathies?

Francesco Locatelli, Lucia Del Vecchio, Pietro Pozzoni, Marco D'Amico,[1] and Simeone Andrulli

Department of Nephrology and Dialysis, Ospedale A. Manzoni, Lecco, Italy

Is it the agent or the blood pressure level that matters for renal and vascular protection in chronic nephropathies? Over the recent years, it has been clearly documented that hypertension and proteinuria are the major factors responsible for progression of chronic kidney disease (CKD). Therefore, a target BP of at least 130/80 mm Hg has been suggested in order to reduce the rate of progression and cardiovascular mortality. Some antihypertensive agents, such as ACE inhibitors (ACEIs), angiotensin II receptor blockers (ARBs), and perhaps calcium channel blockers (CCBs), may also be capable of reducing CKD progression because they halt some of the pathogenetic mechanisms involved in renal damage, some of which is unrelated to reduction of proteinuria, per se. Although this specific effect seemed to be partially independent of blood pressure reduction, it remains controversial whether these drugs are really superior to other antihypertensive agents when blood pressure values recommended by guidelines are achieved. This issue is still a matter of debate because in published trials, target and achieved blood pressure values were constantly higher than those recommended today. Nevertheless, available findings seem to indicate that the renoprotective effect of these agents is at least partially independent of a better BP control. The only way to definitely solve this issue would be a new randomized trial. However, the clinical relevance of this trial is debatable, considering that we need all the drugs available to reach these recommended BP values.

Hypertension is not only an important presenting feature of chronic kidney disease (CKD), but together with proteinuria, it is also a major factor contributing to its progression. As a consequence, effective antihypertensive therapy is the cornerstone of treatment in CKD patients, apart from treatment, if possible, of the primary disease. Besides this, it is now well established that some antihypertensive drugs have additional renoprotective effects that seem to be at least partially independent of blood pressure (BP) reduction. However, in the majority of large trials, target and achieved BP values were constantly higher than those recommended today. Moreover, the BP values were often lower in the experimental groups [ACE inhibitors (ACEIs) or angiotensin II receptor blockers (ARBs)] compared with the control groups. Given these considerations, it is a matter of debate whether these agents would still be superior to other antihypertensive agents when recommended BP values were really achieved.

Hypertension and chronic kidney disease progression

A number of retrospective longitudinal [1, 2, 3] and cross-sectional [4] studies have provided data showing that the higher the BP, the faster the progression of renal disease. The results of the largest study, which included almost 7000 patients, indicated that the worsening in renal function correlated with BP values even within the normotensive range [4]; another study found that this observation was more evident for systolic (SBP) than for diastolic blood pressure (DBP) [5].

It seems that the rate of progression is a continuous function of mean arterial pressure (MAP), which implies that renal protection is a continuous function of BP down to the low end of the normal range. Locatelli et al [6, 7] found that the patients with rapid progression, or those who reached an end point (doubling of baseline serum creatinine or need for dialysis), had significantly higher baseline BP values than patients with slow progression. However, this relationship was not confirmed by a multivariate regression analysis [6]. Other studies failed to show a significant relationship between the progression of CKD and BP values during the course of the disease [8, 9].

In recent years, particular attention has been paid to the deleterious effects of SBP on kidney function. Jafar et al reported a meta-analysis [10] assessing the effect of ACEIs on the progression of nondiabetic renal disease on 1860 patients. In a secondary analysis [11] of this data they found that both baseline and follow-up values of SBP and DBP, together with proteinuria, were significantly

[1]Dr. D'Amico's present address is the Department of Nephrology and Dialysis, Ospedale S. Anna, Como, Italy.

Key words: hypertension, chronic kidney disease, proteinuria.

related to CKD progression. In the multivariable analysis, however, DBP was not confirmed as an independent risk factor. Interestingly enough, the graphic plot of the relative risks of progression according to SBP values had a U shape, with the lowest risk for kidney disease progression at SBP levels of between 110 and 129 mm Hg. The relationship between BP and risk for CKD progression differed according to proteinuria: in patients with higher levels of proteinuria during follow-up, the optimal current SBP seemed to be 110 to 119 mm Hg, whereas in patients with lower levels of proteinuria, the risk for kidney disease progression remained relatively constant over a wide range of SBP (110-160 mm Hg), increasing only for lower or higher values.

Similar findings were obtained in a post-hoc analysis of the RENAAL study [12]: the risk of having a renal outcome was significantly increased at all SBP levels >140 mm Hg at baseline. It was nearly doubled at SBP levels ≥160 mm Hg compared to the reference values of <130 mm Hg. The values of DBP at baseline were not significantly related to the risk of having a renal end point. Interestingly enough, baseline pulse pressure (PP) seems of greater importance (a PP of ≥70 mm Hg increased the risk of all renal end points, including ESRD or death). As underlined by the authors [12], this suggests that increased PP values are associated with reduced intrarenal autoregulation, and possibly to a loss of the kidney's ability to adjust to changes in systemic blood pressure.

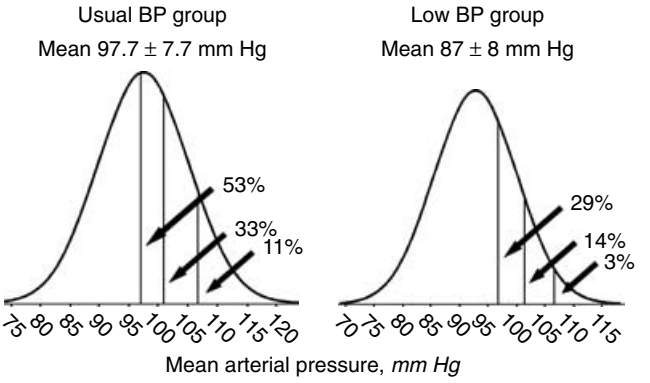

Fig. 1. MAP distribution during follow-up in the low and usual blood pressure groups of the MDRD study [18]. This estimate has been obtained assuming a Gaussian distribution of BP values during follow-up (considering the high number of patients). We then calculated from the characteristics of normal distributions the percentage of patients with MAP values higher than the threshold of 97 mm Hg (equivalent to 130/80 mm Hg), 101 mm Hg (equivalent to 135/85 mm Hg), and 107 mm Hg (equivalent to 140/90 mm Hg), respectively.

Blood pressure reduction and progression of CKD

Over the last decade, a number of trials have been performed to assess the degree of BP reduction needed to achieve renoprotection. The Modification of Diet in Renal Disease (MDRD) study [13] was the first large, randomized trial performed on this topic. The 840 patients with CKD were stratified into 2 groups according to baseline renal function, and were randomized to 2 different levels of dietary protein intake. In addition, the patients were also randomized to usual BP control (MAP ≤107 mm Hg in subjects aged ≤60 years, or ≤113 mm Hg in subjects older than 60 years) or stricter BP control (MAP ≤92 mm Hg in subjects aged ≤60 years, or ≤98 mm Hg in subjects older than 60 years) [13]. In study A (baseline GFR 25-55 mL/min), the mean decline in GFR was faster in the first 4 months of follow-up, and slower thereafter in the strict group than in the group with usual BP control, while in patients with more advanced CKD (study B: baseline GFR 13-24 mL/min), the decline of GFR was linear, and did not differ significantly between the 2 BP groups. The patients with higher levels of baseline proteinuria received greater benefits from being assigned to a low BP target. According to an estimate [14], a stricter BP control could delay the time to ESRD by 1.24 years over a period of 9.4 years. In study B, only 0.43 years could be gained with a strict BP control, for a mean projected period of 3.6 years. It is worth noting that the effects of BP control in the MDRD study [13] may have been partly confounded by an imbalance in the proportion of patients receiving ACEIs in the 2 groups (54% of the patients in the low BP group, but only by 34% in the usual BP group). In addition, a large percentage of patients did not reach the recommended BP target. We have estimated that more than half of the patients in the usual BP group had DBP >95 mm Hg; this percentage was reduced to only 30% in the group randomized to the strict BP control (Fig. 1).

The role of BP control in CKD progression has also been studied in diabetic patients. The UK Prospective Diabetes Study (UKPDS) was a randomized controlled trial aimed at evaluating whether "tight BP control" (SBP/DBP <150/85 mm Hg) was able to prevent macrovascular and microvascular complications in patients with type 2 diabetes compared with "less tight control" (SBP/DBP <180/105 mm Hg) [15]. After 9 years of follow-up, the patients assigned to "tight BP control" had a 37% reduction in their relative risk of developing microvascular end points compared with those assigned to "less tight BP control." However, these BP values are much higher than those recommended today. The effect on renal disease–related end points was less convincing than that on the combined microvascular end points, probably because the former were only infrequent, since patients were included in the study very early in the course of diabetes. More recently, the results of the African American Study of Kidney Disease and Hypertension (AASK) study have been published [16]. This study was designed to assess the impact of 2 BP goals (102 to 107 mm Hg and ≤92 mm Hg, respectively) and 3