Importance of Blood Pressure Control in Chronic Kidney Disease

Maura Ravera, Michela Re, Luca Deferrari, Simone Vettoretti, and Giacomo Deferrari
Division of Nephrology, Dialysis and Transplantation, Department of Internal Medicine, University of Genoa
Department of Cardio-Nephrology Azienda Ospedaliera Universitaria San Martino, Genoa, Italy

Arterial hypertension together with proteinuria is one of the most important factors associated with the progression of both diabetic and nondiabetic chronic kidney disease. In this review, the role of hypertension and proteinuria in renal disease progression, the BP target that should be achieved to slow the progression of renal damage, and the influence of baseline and current proteinuria on the renoprotective effects of antihypertensive therapy are discussed thoroughly. The interaction between the renoprotective effects of specific antihypertensive agents—mostly angiotensin-converting enzyme inhibitors and angiotensin receptor blockers—and the level of achieved BP also are evaluated. The body of evidence provided by several studies emphasizes the importance of both lowering BP and inhibiting the renin-angiotensin system as specific goals for renal and cardiovascular protection in chronic kidney disease.

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Chronic kidney disease (CKD) is a worldwide public health problem. In the United States, there is an increasing incidence and prevalence of renal failure with poor outcome and high costs and an even higher prevalence of earlier stages of CKD (approximately 80 times greater than ESRD prevalence). Moreover, CKD is associated with elevated cardiovascular morbidity and mortality (1). Therefore, strategies that are aimed at identifying, preventing, and treating CKD and its related risk factors are needed.

In the following sections, we focus on the role of hypertension and proteinuria as both independent and interdependent risk factors for renal disease progression. We also discuss BP targets that should be achieved to slow the progression of renal damage, the influence of baseline and current proteinuria on the renoprotective effects of antihypertensive therapy, and the interaction between the renoprotective action of specific antihypertensive agents—mostly angiotensin-converting enzyme inhibitors (ACE-I) and angiotensin receptor blockers (ARB)—and the level of achieved BP.

Role of Hypertension and Proteinuria on the Progression of Renal Disease

High BP can be either a cause or a consequence of CKD. High BP may develop early in the course of CKD and can be associated with adverse outcomes such as worsening renal function and development of cardiovascular disease. Hypertension is a major promoter of the decline in GFR in both diabetic and nondiabetic kidney disease (2,3). Furthermore, large, observational, prospective trials in the general population showed that hypertension is a strong independent risk factor for ESRD. A strong relationship was observed between both systolic (SBP) and diastolic BP (DBP) and ESRD, regardless of other known risk factors, in men who were recruited in the Multiple Risk Factor Intervention Trial. The relative risk (RR) for ESRD was >20-fold higher for patients with stage 4 hypertension (SBP > 210 mmHg or DBP > 120 mmHg) than for patients with optimal BP levels (SBP < 120 mmHg and DBP < 80 mmHg) (4). The recent study by the Okinawa General Health Maintenance Association confirmed these results in women as well (5).

Hypertension-related mechanisms that are involved in the progression of renal damage include the systemic BP load, the degree to which it is transmitted to the renal microvasculature (*i.e.*, renal autoregulation), and local susceptibility factors to barotrauma, which is the degree of damage for any degree of BP load. Among these last factors, proteinuria, glomerular hypertrophy, fibrogenic mediators, genetic factors, and age are the most important. Figure 1 shows the theoretical relationship between mean arterial pressure (MAP) and the changes in renal blood flow (RBF) and, hence, in the glomerular capillary pressure both in normal kidneys and in pathologic conditions (6). Under normal conditions, RBF varies very little within a broad range of systemic MAP (80 to 160 mmHg). Increases in BP within this range lead to vasoconstriction of the glomerular afferent arteriole, thereby maintaining RBF and glomerular capillary pressure constant. As a protective adaptation, chronic hypertension tends to shift the curve to the right. When MAP is >160 mmHg or when the autoregulatory mechanism is blunted as a result of renal disease, diabetes, high protein intake, dihydropyridine calcium channel blockers (CCB), we can expect an almost linear relationship between BP and capillary pressure. The increase in pressure load to the kidney vasculature results in a mechanical stretch of the glomerular capillaries and mesangial cells, which induces a repair response that is mediated by fibrogenic cytokines and angiotensin II. Repetitive injuries

Address correspondence to: Dr. Giacomo Deferrari, Division of Nephrology, Dialysis and Transplantation, Department of Internal Medicine, University of Genoa, Viale Benedetto XV 6, 16123 Genoa, Italy. Phone: +39-010-353-8959; Fax: +39-010-353-8959; E-mail: deferrar@unige.it

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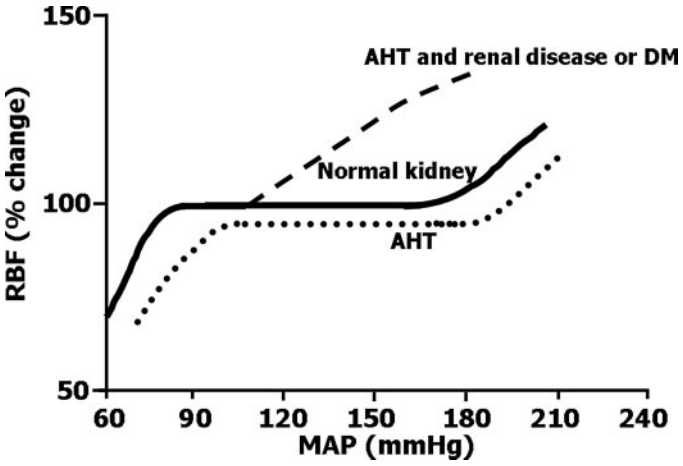

Figure 1. Relationships between renal blood flow and systemic BP (6). AHT, arterial hypertension; DM, diabetes mellitus; RBF, renal blood flow; MAP, mean arterial pressure.

and repairs can result in glomerulosclerosis, which is worsened further by local factors such as proteinuria (7).

Proteinuria is a strong, independent promoter of the progression of renal disease, as clearly demonstrated in nondiabetic renal disease by the Modification of Diet in Renal Disease study (8). Data from a secondary analysis of the Irbesartan Diabetic Nephropathy Trial (IDNT) confirmed that baseline proteinuria also is an important risk factor for renal failure in patients with type 2 diabetes and overt nephropathy. The cumulative incidence of renal failure at 3 yr was only 7.7% for patients with <1 g of proteinuria, 11.4% for those with 1 to 2 g, 22.9% for those with 2 to 4 g, 34.3% for those with 4 to 8 g, and 64.9% for those with >8 g. Doubling of proteinuria was associated with doubling of the risk for renal end point (9).

The major pathogenetic determinants of proteinuria-induced progression of renal damage are mesangial injury; the accumulation of filtered proteins in the lysosomes of proximal tubules, causing cell disruption and injury; the overexpression of proinflammatory cytokines and chemokines, growth factors, TGF-β, and endothelin by injured tubular cells and interstitium, with consequent interstitial infiltration of inflammatory cells and tubulointerstitial fibrosis; and the direct tubular toxicity of some proteins (*e.g.*, complement, oxidized LDL, IGF-I, iron species) (10). In summary, hypertension promotes the progression of renal disease by worsening glomerular injury and proteinuria, which in turn promote further glomerular and tubulointerstitial injury. As a consequence, a fall in GFR may ensue.

Impact of Changes in BP and Proteinuria on Renal Outcome

Optimal BP control is the most important target that must be achieved to prevent adverse renal outcomes in patients with CKD. A recent meta-analysis (11) of 11 randomized, controlled trials that included ACE-I arms evaluated the impact of current SBP on renal outcome in 1860 patients with nondiabetic renal disease. The lower risk for kidney disease progression was demonstrated for current SBP that ranged from 110 to 129 mmHg. Higher levels of SBP were associated with a steep increase in the RR, regardless of the drug that was used. Compared with the reference range, achieved SBP <110 mmHg was associated with increased risk, and this is consistent with the negative renal effects of reduced kidney perfusion or the presence of pre-existing cardiovascular disease (11). A study showed that in type 1 diabetes, regression or remission of the clinical evidence of diabetic nephropathy could be achieved with the combination of intensive BP control and ACE-I treatment (12). Moreover, with regard to type 1 diabetes, a meta-analysis of nine longitudinal studies that involved various antihypertensive drugs clearly showed that the achieved values of BP play an overwhelming role in determining the decline of GFR. A four-fold reduction in the decline of GFR was observed for mean BP levels <99 mmHg, regardless of the type of treatment (13). Last, in type 2 diabetes, as demonstrated by secondary analysis of the IDNT study, the risk for reaching a renal end point is reduced progressively and continuously at lower levels of the achieved SBP. An optimal renoprotective effect was demonstrated for SBP between 120 and 130 mmHg, with no further benefits below 120 mmHg (Figure 2) (14). In summary, the reduction in BP is markedly renoprotective regardless of the type of drug that is administered, in both diabetic and nondiabetic renal disease. SBP between 120 and 125 mmHg or MAP that ranged from 90 to 96 mmHg seemed to be the optimal BP target for patients with CKD.

The antiproteinuric effect of lowering BP is one of the most important mechanisms involved in the renoprotection that is induced by BP control. The Modification of Diet in Renal Disease study showed that achieving low BP, even by using non–renin-angiotensin system (RAS) acting agents, markedly reduced proteinuria during the 3 yr of follow-up (8). Although ACE-I and ARB have been shown to reduce proteinuria by 40 to 45% for similar BP reduction, proteinuria was 15 to 20% lower even in patients who were treated with different classes

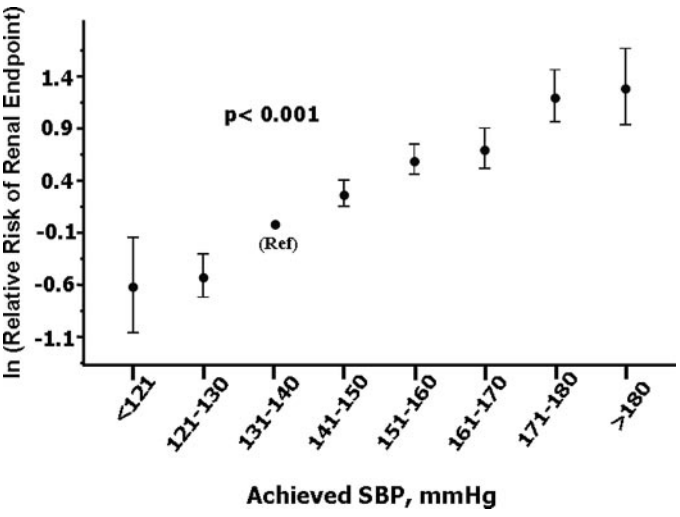

Figure 2. Impact of achieved systolic BP (SBP) on renal end point (doubling of serum creatinine or ESRD) in 1715 proteinuric patients with type 2 diabetes (14). ln, natural log.

of drugs, including CCB, provided that a reduction in BP levels was achieved (9,15).

Proteinuria changes *per se* are an important risk factor for the progression of renal disease. In type 2 diabetes, data from the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) trial showed that changes in albuminuria in the first 6 mo of therapy were roughly linearly related to the degree of long-term renal protection: every 50% reduction in albuminuria in the first 6 mo was associated with a 45% reduction in the risk for ESRD during later follow-up (16). Furthermore, a secondary analysis of the IDNT study demonstrated that the risk for renal failure was reduced by more than half (hazard ratio 0.44; $P < 0.001$) for each halving of proteinuria in the first year of the study. The cumulative incidence of adverse renal outcome (doubling of serum creatinine or ESRD) at 3 yr for patients with a >50% reduction in proteinuria was only 9.6%, whereas for those with a reduction that ranged between 0 and 50%, it was 26.2%. This compared with 34.5% for patients with up to a 50% increase in proteinuria and 38% for those with a >50% increase (9).

Moreover, the renoprotective effect of lowering BP by antihypertensive treatment is affected by baseline proteinuria and its changes (*i.e.*, current proteinuria). In nondiabetic renal disease, greater values of baseline proteinuria were associated with greater benefit of achieving lower BP (8). In patients with baseline proteinuria >3 g/d, a steeper decline in GFR becomes apparent at 92 mmHg of mean BP, whereas for proteinuria between 0.25 and 3 g/d, the decline increases at 98 mmHg. In nonproteinuric patients, lowering mean BP to <107 mmHg does not seem to confer any additional benefits in reducing the progression of renal disease (8). In the ACE Inhibition in Progressive Renal Disease meta-analysis, the relationship between current SBP and the risk for progression of renal disease markedly differed between patients with current proteinuria of 1 g/d or greater and those whose proteinuria was <1 g. In patients with higher proteinuria, the optimal SBP ranged from 110 to 119 mmHg. The adjusted risk for ESRD for these patients increased steeply, even for BP values above 120 mmHg, and was eight-fold higher for SBP values of 160 mmHg or higher. By contrast, the adjusted risk for renal failure in patients with lower levels of proteinuria increased two-fold only when SBP was 160 mmHg or greater. Last, the risk for ESRD increased when SBP was <110 mmHg, especially in proteinuric patients, therefore suggesting a J-curve behavior of the relationship between BP and the progression of renal disease (Figure 3) (11). In summary, the renoprotective effect of lower BP is actually evident in patients with higher proteinuria, thus providing additional support for recommending lower BP targets for these patients.

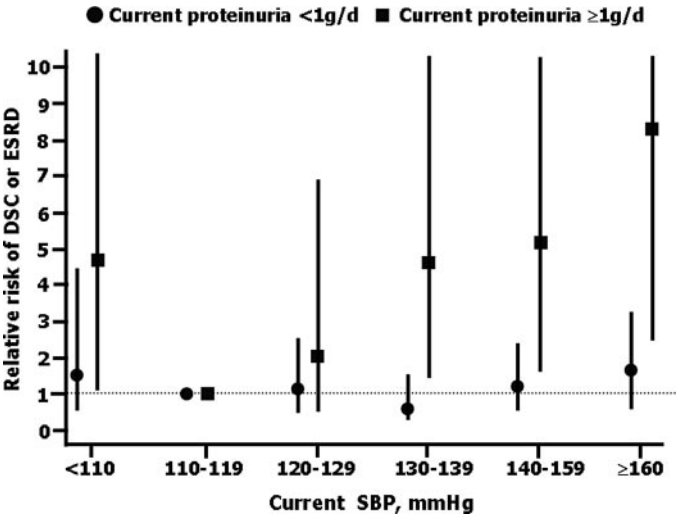

Figure 3. Nephropathy progression according to current SBP and current proteinuria (11). DSC, doubling of serum creatinine.

Role of Inhibiting RAS and Sympathetic Activity

On the basis of available studies, there is evidence showing that ACE-I or ARB are more effective in slowing the progression of renal disease than other classes of antihypertensive drugs. The ACE Inhibition in Progressive Renal Disease meta-analysis (17) of 11 randomized, controlled trials that compared the efficacy of antihypertensive regimens both with and without ACE-I in nondiabetic renal disease showed that the use of this class of drugs was associated with lower risk for both ESRD and doubling serum creatinine. In the large cohort of hypertensive, microalbuminuric patients with type 2 diabetes of the Microalbuminuria, Cardiovascular, and Renal Outcomes–Heart Outcomes Prevention Evaluation trial (18) and in two other, smaller studies (19,20), greater efficacy was demonstrated for ACE-I compared with other treatments in reducing the incidence of overt nephropathy. Furthermore, the Irbesartan in Patients with Type 2 Diabetes and Microalbuminuria study showed that treatment with the ARB irbesartan was much more effective than conventional therapy at both preventing the development of clinical proteinuria and favoring regression to normoalbuminuria in microalbuminuric patients with type 2 diabetes, despite similar BP control (21). Adding ACE-I to the conventional therapy that was administered to patients with type 1 diabetes and overt nephropathy significantly reduced both the need for replacement therapy and the mortality rate (22). As far as patients with type 2 diabetes and overt nephropathy are concerned, two studies (IDNT and RENAAL) demonstrated that ARB (irbesartan or losartan) were more effective than conventional therapy or CCB in slowing the progression of nephropathy, regardless of BP control (23,24). Moreover, secondary analysis of these two large trials demonstrated that there was some interaction between the effect of the ARB and the levels of BP that were achieved. With regard to the IDNT trial, a 33% reduction of the RR for reaching a renal end point was demonstrated for the irbesartan arm as compared with the combined amlodipine plus conventional therapy arms, regardless of the reduction of SBP. The RR for adverse renal outcomes in patients with SBP <134 mmHg was actually significantly lower in patients who were treated with irbesartan than in the other two combined groups (RR 55%, $P = 0.034$). Lower SBP and irbesartan were independent ($P = 0.61$ for interaction) and

therefore additive (Figure 4) (14). In the RENAAL study, losartan induced a 28% RR reduction of reaching a renal end point as compared with usual care, beyond what was achieved by lowering the BP. In patients with BP <140/90 mmHg, the RR further decreased to 59% (25). In summary, optimal levels of BP tended to magnify the renoprotective effects of ARB in both trials.

An overwhelming body of evidence shows that arterial hypertension in patients with CKD is associated with overactivity of the sympathetic nervous system (26–28). This activation is due to afferent stimuli that arise from the diseased kidneys and lead to increased efferent sympathetic nerve activity. Moreover, sympathetic activity is associated with poor cardiovascular outcomes, thus suggesting that reducing it might be beneficial to the patients. ACE-I and ARB are able to reduce but not to normalize sympathetic hyperactivity in patients with CKD (29). Moxonidine is a selective imidazoline-I1 receptor agonist that lowers BP by decreasing sympathetic nerve activity and thereby reducing peripheral resistance. Adding moxonidine to ARB in patients with CKD has proved to be effective at significantly reducing both MAP and sympathetic hyperactivity as compared with ARB administration alone (30). Moreover, moxonidine has a renoprotective effect that goes beyond its effect on BP. Nonhypotensive doses of moxonidine have been shown to reduce significantly glomerulosclerosis and albuminuria in subtotally nephrectomized rats (31). A total of 177 hypertensive patients that had advanced renal failure and were being treated with RAS inhibitors plus loop diuretics were given moxonidine for 6 mo as add-on therapy. This seemed to be associated with a lower decline in GFR as compared with adding nitrendipine. The renoprotective effect of moxonidine likely was independent of BP lowering, which was even more pronounced in the nitrendipine group (32). Furthermore, nonhypotensive doses of moxonidine had an anti-albuminuric effect on 15 normotensive patients who had type 1 diabetes with microalbuminuria and adequate glycemic control (33). Moreover, moxonidine may elicit beneficial adaptations in the glucose and lipid metabolism (34), thereby possibly contributing to a reduction in the global cardiovascular risk in patients with CKD.

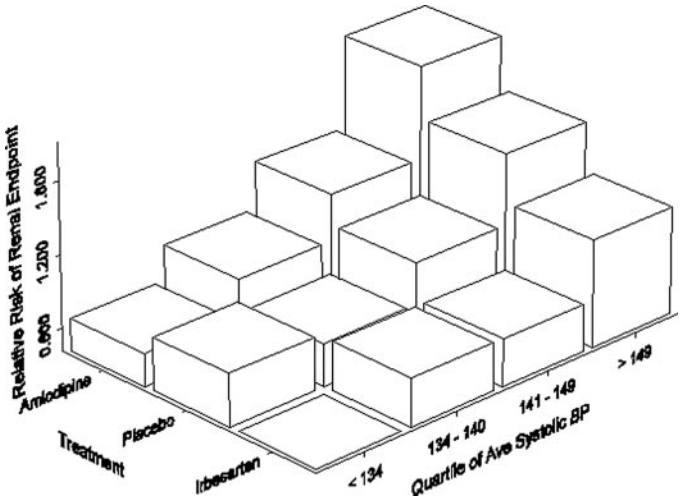

Figure 4. Renal outcomes (doubling of serum creatinine or ESRD) as a function of both achieved SBP and treatments in proteinuric patients with type 2 diabetes (14). Ave, average.

Conclusions

Consistent with these results and according to the international guidelines, BP target values <130/80 mmHg for patients with CKD and <120/75 mmHg in patients with proteinuria ≥1 g/d now are being recommended, regardless of the type of antihypertensive drug (1,35–37). Moreover, RAS-blocking agents are the standard therapy for renoprotection in patients with diabetic and nondiabetic CKD (1,35–37). Last, with regard to sympathetic hyperactivity, the use of the sympatholytic agent moxonidine in multidrug therapy seems to be a promising strategy in an attempt to achieve optimal BP levels in patients with CKD.

Furthermore, both lowering BP and inhibiting the RAS are specific goals for cardiovascular protection in CKD. A recent meta-analysis showed that lowering BP was the main target to reduce the incidence of major cardiovascular events in hypertensive patients (38). With regard to patients with type 2 diabetic nephropathy, the IDNT trial showed a linear relationship between mortality and achieved SBP that ranged between 120 and 180 mmHg or more. However, patients whose SBP was <120 mmHg had higher mortality rates, which was possibly related to pre-existing cardiovascular disease (14,39). Moreover, consistent with the data from the HOPE study, treatment with ACE-I has been shown to reduce the high cardiovascular risk in patients with mild renal insufficiency (40). However, BP control, especially SBP control, is very difficult to achieve in renal patients (14,41,42). For instance, only 30% of the patients in the IDNT trial achieved their target systolic goals, despite their using four antihypertensive agents, further confirming how difficult it is to treat these high-risk patients (14). The percentage of patients with controlled BP is much lower in the clinical practice setting (42–44).

In summary, BP levels markedly influence the renal outcomes of patients both with diabetic and with nondiabetic CKD, in particular of the proteinuric ones. Accordingly, a "goal BP– oriented management" is mandatory for reno- and cardiovascular protection. In addition, the use of RAS-blocking agents is strongly recommended owing to their renoprotective effect, which is magnified further by optimal BP control.

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