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Aggressive blood pressure reduction and renin–angiotensin system blockade in chronic kidney disease: time for re-evaluation?

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Over the past decades, aggressive control of blood pressure (BP) and blockade of the renin–angiotensin–aldosterone system (RAAS) were considered the cornerstones of treatment against progression of chronic kidney disease (CKD), following important background and clinical evidence on the associations of hypertension and RAAS activation with renal injury. To this end, previous recommendations included a BP target of <130/80 mm Hg for all individuals with CKD (and possibly <125/75 mm Hg for those with proteinuria >1 g/day), as well as use of angiotensin-converting-enzyme inhibitors and angiotensin receptor blockers as first-line therapy for hypertension in all CKD patients. However, long-term extensions of relevant clinical trials support a low-BP goal only for patients with proteinuria, whereas recent cardiovascular trials questioned the benefits of low systolic BP for diabetic patients, leading to more individualized recommendations. Furthermore, our previous knowledge of the specific renoprotective properties of RAAS blockers in patients with proteinuric CKD is now extended with data on the use of these agents in patients with less advanced nephropathy and/or absence of proteinuria, deriving mostly from subanalyses of cardiovascular trials. This review discusses previous and recent clinical evidence on the issues of BP reduction and RAAS blockade by type and stage of renal damage, aiming to aid clinicians in their treatment decisions for patients with CKD.

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Chronic kidney disease (CKD) is currently recognized as an independent risk factor for cardiovascular and all-cause mortality;[1] recent data further exemplify the importance of CKD for cardiovascular complications, in relation to established risk factors, such as diabetes.[2] Therefore, prevention of CKD or retardation of disease progression in affected individuals is proposed as another strategy toward cardiovascular protection.[3] On one hand, elevated blood pressure (BP) is a major risk factor for CKD, and on the other hand, kidney injury can cause hypertension.[4–6] Observational studies suggested a strong association between high BP and the risk for renal function decline or end-stage renal disease (ESRD), whereas in various clinical trials, patients with BP below conventional thresholds showed better preservation of renal function.[4,5] Thus, in the past decade, relevant guidelines recommended a BP target of <130/80 mm Hg for all CKD patients (and possibly <125/75 mm Hg for those with proteinuria >1 g/day),[5,7–9] although evidence from trials with hard renal outcomes (that is, incidence of ESRD) randomizing patients to different BP targets was limited.[8] Recently, long-term cohort data of relevant trials supported a low-BP goal for patients with proteinuria, whereas cardiovascular trials questioned the beneficial effects of low BP for patients with diabetes,[10,11] leading to recommendations for less aggressive approaches to BP lowering in the latter.[6,12]

Angiotensin-converting-enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) are recommended as first-line therapy for hypertension in patients with CKD,[5,7–9] following evidence ranging from background studies to major renal trials in proteinuric CKD that suggested these agents to slow nephropathy progression more effectively than other antihypertensive agents.[13] However, for patients with less advanced nephropathy or absence of proteinuria, previous reports suggested inhibitors of renin–angiotensin–aldosterone system (RAAS) to confer no additional renoprotective benefit,[14,15] and recent trials showed combined RAAS blockade to increase the risk of acute renal failure and related complications.[16,17]

Overall, observations evolving over the past few years have made selection of appropriate BP targets and use of RAAS blockade a complicated issue for the average clinician. In this

review, we attempt to delineate past major studies and recent developments in these fields by analyzing available clinical evidence for the different types of individuals with CKD.

TARGET BP IN PATIENTS WITH CKD

Nondiabetic kidney disease

Two clinical trials with hard renal end points have evaluated different BP targets in patients with nondiabetic CKD: the Modification of Diet in Renal Disease (MDRD) and the African-American Study on Kidney Disease (AASK).

MDRD included two studies in patients with CKD (585 patients in study A (glomerular filtration rate (GFR) 25–55 ml/min per 1.73 m^2) and 255 in study B (GFR 13–24 ml/min per 1.73 m^2)) with the rate of change in GFR (GFR slope) as primary outcome, and a mean follow-up of 2.2 years.[18] Diabetic patients on insulin treatment were excluded by protocol; thus, only 26 patients with diabetic nephropathy participated. In a 2×2 factorial design, patients were randomized to different levels of dietary protein intake and to a usual-BP goal (mean arterial pressure <107 mm Hg for patients $\leqslant 60$ years old (roughly corresponding to $<140/90$ mm Hg) and <113 mm Hg for patients $\geqslant 61$ years old) or a low goal (mean arterial pressure <92 mm Hg for patients $\leqslant 60$ years old (corresponding to $<125/75$ mm Hg) and <98 mm Hg for patients $\geqslant 61$ years old). Neither the projected GFR decline in 3 years (10.7 vs. 11.5 ml/min per 1.73 m^2) nor the risk of ESRD and death (0.85, 95% confidence interval (CI): 0.60–1.22 for low-BP arm) differed significantly between groups.[18] However, analyses of patients by baseline proteinuria showed that higher proteinuria was associated with steeper GFR decline and that low target BP had beneficial effects on GFR slope in patients with proteinuria >0.25 g/day in study A and >1 g/day in study B (Figure 1), and the results were not substantially altered after adjustment for 10 relevant covariates.[18,19] These findings indicated that a low target BP may be beneficial in proteinuric patients and was the basis of previous recommendations for BP $<130/80$ mm Hg in patients with CKD and $<125/75$ mm Hg in patients with proteinuria >1 g/day.[5,7–9]

A patient-level meta-analysis of trials on antihypertensive treatment with or without ACEIs in predominantly non-diabetic CKD confirmed the above: in patients with proteinuria >1 g/day, levels of systolic blood pressure (SBP) between 110 and 119 mm Hg were associated with similar risk of CKD progression with levels between 120 and 129 mm Hg and significantly lower risk compared with SBP $\geqslant 130$ mm Hg; in contrast, in patients with proteinuria <1 g/day, a significant association of low BP with renoprotection was absent.[20] A subsequent analysis examined long-term outcomes considering the trial phase of MDRD (1989–1993) together with a follow-up cohort period (1993–2000) during which no specific target BP was recommended.[21] During a median follow-up of 10.7 years, low target BP was associated with a reduced risk for ESRD (adjusted hazard ratio (HR) 0.68; 95% CI: 0.57–0.82) and the composite of ESRD or death

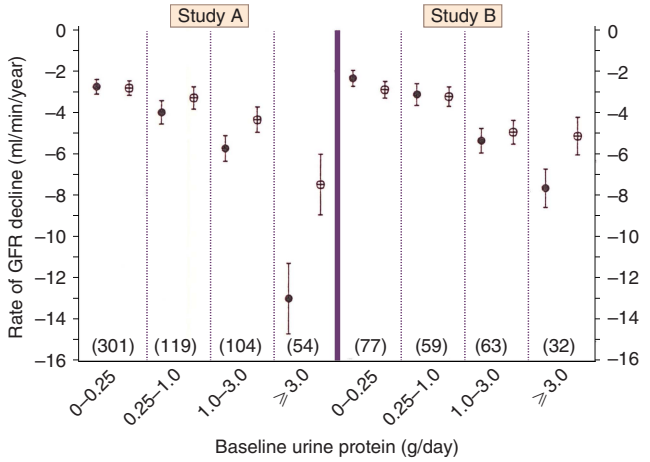

Figure 1 | Effects of different blood pressure (BP) targets on glomerular filtration rate (GFR) in the Modification of Diet in Renal Disease (MDRD) studies by baseline proteinuria. Low target BP had beneficial effects on GFR slope in patients with proteinuria >0.25 g/day in study A and >1 g/day in study B. Black circles indicate usual-BP group and white circles indicate low-BP group; numbers in parentheses reflect patients in both BP groups with at least one follow-up GFR measurement (reprinted from Peterson *et al.*[19]).

(HR 0.77; 95% CI: 0.65–0.91) as compared with usual target BP. Again, in subgroup analyses, the benefits from low target BP for ESRD and the composite end point was significant only for proteinuria >1 g/day. The *P*-value for interaction of target BP with proteinuria was 0.09 for ESRD and 0.08 for the composite outcome.[21]

AASK included 1094 African Americans with hypertensive CKD (GFR 20–65 ml/min per 1.73 m^2, mean proteinuria 0.6 g/day) randomized to goal mean arterial pressure 102–107 or $\leqslant 92$ mm Hg, and to initial treatment with metoprolol, ramipril, or amlodipine in a 3×2 factorial design. The main outcomes were GFR slope and a composite of GFR reduction $\geqslant 50\%$ (or $\geqslant 25$ ml/min per 1.73 m^2), ESRD, or death. The mean achieved BP was 128/78 mm Hg in the low-BP group and 141/85 in the usual-BP group. After a median of 3.8 years, neither GFR slope (-2.21 ± 0.17 vs. -1.95 ± 0.17 ml/min per 1.73 m^2 per year; $P=0.24$) nor the composite outcome (risk reduction for low-BP group 2%; 95% CI: -22 to 21%) differed significantly between groups.[22] After the trial phase, ~700 subjects were enrolled in an observational phase with a total follow-up of 8.8–12.2 years; target BP during the cohort phase was $<130/80$ mm Hg. A recent analysis including the two phases together showed no significant difference between the two groups in the risk of the composite outcome of doubling of serum creatinine (SCr), ESRD, or death (HR in low-BP group, 0.91; 95% CI: 0.77–1.08). However, there was a significant interaction with the baseline level of proteinuria ($P=0.02$); patients with urine protein-to-creatinine ratio of >0.22 (both measured in 24-h urine collections and expressed in mg/dl), which roughly equals a proteinuria of 320 mg/day, had lower risk of the primary outcome with intensive treatment (HR 0.73; 95% CI: 0.58–0.93; Figure 2). In those with urine