Published in final edited form as:

Nat Rev Nephrol. 2011 March ; 7(3): 128–130. doi:10.1038/nrneph.2010.168.

CHRONIC KIDNEY DISEASE Blood-pressure targets in chronic kidney disease

Anil K. Bidani and Karen A. Griffin

Division of Nephrology and Hypertension, Loyola University Medical Center, 2160 South First Avenue, Maywood, IL 60153, USA

Abstract

The optimal blood-pressure goals to prevent progression of chronic kidney disease (CKD) remain controversial. The results of the AASK cohort study provide additional support for more aggressive blood-pressure control (<130/90 mmHg) in proteinuric but not nonproteinuric patients with hypertensive CKD.

The recently reported results of the extended follow-up of the African American Study of Kidney Disease and Hypertension (AASK) cohort¹ address the ongoing controversy regarding the optimal blood-pressure target (<130/90 mmHg) recommended by current guidelines for patients with chronic kidney disease (CKD).^{2,3} Although observational data from multiple studies show positive and graded associations between blood pressure and risk of CKD progression, prospective randomized controlled trials in patients with CKD have failed to directly demonstrate that blood-pressure targets <130/90 mmHg further reduce CKD progression. As with the Modification of Diet in Renal Disease (MDRD) trial,⁴ the benefits of intensive blood-pressure control (target mean arterial pressure [MAP] <92 mmHg, achieved blood-pressure level 130/78 mmHg; *n* = 540) versus standard blood-pressure control (target MAP 102–107 mmHg, achieved blood-pressure level 141/86 mmHg; *n* = 554) were not seen during the trial phase of the AASK trial, which had a mean follow-up of 4.1 years.¹ At the end of the trial phase, patients were enrolled in an observational cohort study in which all patients were treated with agents that block the renin–angiotensin system (RAS) to achieve a blood-pressure level of <130/80 mmHg and followed for a total of 8.8–12.2 years; the primary clinical outcome was an observed doubling of serum creatinine level, development of end-stage renal disease (ESRD) or death.¹ Although no differences in these outcomes were reported between those who had been originally assigned to the intensive-control group and those in the standard-control group within the total AASK cohort, significant risk reductions were observed in a specified subgroup of 357 of 1,094 patients with a baseline urinary protein to creatinine ratio of >0.22 (approximate proteinuria of 300 mg per day; hazard ratio 0.73; *P* = 0.001). Although observational, these results are not unexpected and the totality of the evidence supports the use of low blood-pressure targets in proteinuric CKD, particularly when considered in the context of the known pathophysiology of CKD progression.⁵

The degree to which blood-pressure reductions are expected to reduce the risk of adverse outcomes is thought to be a function of the extent to which such outcomes depend on the exposure of the target organ to increased pressures and the ability of antihypertensive agents

to reduce such exposure. Unlike cardiovascular end points, which reflect macrovascular events and their consequences (stroke, myocardial infarction, heart failure), renal end points reflect microvascular pathology (loss of glomerular capillary filtration capacity). Although macrovascular pressures largely parallel changes in blood pressure, glomerular capillary pressure is typically isolated from variations in blood-pressure levels and is maintained at a constant level by the preglomerular (afferent arteriolar) autoregulatory responses.⁵ This protective mechanism is, in large part, responsible for the fact that <1% of the individuals with primary hypertension develop renal damage severe enough to result in ESRD. By contrast, considerable experimental and clinical evidence indicates that the loss of functional renal mass, if sufficiently severe (~75%), impairs renal autoregulation, which results in enhanced glomerular blood-pressure transmission, proteinuria, and an increased susceptibility to progressive hypertensive glomerular injury. Nevertheless, the concept that compensatory hyperfiltration in CKD states *per se* indicates the presence of pathological glomerular hypertension is probably not valid, as demonstrated by the benign renal consequences of renal transplant donation and repetitive pregnancies.⁶ Additionally, evidence indicates that CKD progression in hypertensive states might occur by mechanisms that are independent of glomerular hypertension and dependent on slowly progressive vascular pathology that results in ischemic nephron loss,⁷ particularly in some genetically susceptible groups or individuals such as African Americans.^{5,7}

Accordingly, patients with CKD likely differ in their susceptibility to renal hypertensive injury and its potential amelioration by reducing blood pressure because of differences in the underlying pathology, renal autoregulatory capacity (genetic or acquired) and/or intrinsic local tissue susceptibility (genetic or acquired). Such differences alter the threshold level of blood pressure that affects CKD progression and/or the slope of the relationship between increases in blood-pressure level and renal damage (Figure 1). The wide range of yearly decline in glomerular filtration rate observed in diabetic and nondiabetic CKD, ranging from <2 ml/min/1.73 m² in the present AASK trial to 10–30 ml/min/1.73 m² in the study of captopril by the Collaborative Study Group, support such interpretations.^{1–5} The interactions between blood pressure, proteinuria and CKD progression indicate that although proteinuria (macroalbuminuria) is clearly heterogeneous in its pathogenesis, it may nevertheless serve as a surrogate marker of increased glomerular capillary pressure and/or its responsiveness to reductions in blood pressure. Thus, it is not surprising that the benefits of lowering blood pressure were not observed in non-proteinuric or modestly proteinuric patients during the relatively short trial phases of MDRD and AASK,^{1,4} but that beneficial effects of low blood pressure were seen in children with proteinuria in the ESCAPE (Effect of Strict Blood Pressure Control and ACE Inhibition on the Progression of CRF in Pediatric Patients) trial.⁸ Unfortunately, the only trial to address this issue in adult patients with proteinuric CKD, REIN-2 (Blood-pressure control for renoprotection in patients with nondiabetic chronic renal disease), does not seem to have been optimally designed to show that reductions in blood pressure can protect against kidney disease in patients with CKD who are treated with RAS inhibitors.⁹ In addition to RAS blockade, a dihydropyridine calcium channel blocker (felodipine) was used to further decrease blood-pressure levels. This agent class is effective for macrovascular risk reduction but has been shown to impair renal autoregulation and increase the steepness of the slope of the relationship between blood pressure and glomerular injury such that the benefits of low blood pressure on proteinuria and CKD progression are largely negated.⁵

The results of the AASK trial also highlight the limitations of current management of hypertensive CKD (blood-pressure control using RAS inhibitors) at the individual patient level. Adverse renal outcomes occurred in 280 of 733 nonproteinuric patients and in an even greater proportion of at-risk proteinuric patients (136 of 181 patients in the intensive-control group versus 149 of 176 patients in the standard-control group had adverse renal outcomes).

Although genetic mechanisms (independent of angiotensin level and blood pressure) may have contributed to CKD progression to a greater extent in this African-American population than in other populations,¹ it is also likely that the achieved blood-pressure control at the individual patient level was substantially overestimated. Ambulatory blood-pressure monitoring performed at entry into the cohort phase showed masked hypertension (elevated day or night-time blood-pressure levels but controlled blood-pressure levels when measured in the clinic) to be present in 80% of patients, with 40% demonstrating reverse dipping—a night-time systolic blood pressure ~14 mmHg higher than measurements of blood pressure in the clinic.¹⁰ Moreover, the progressive decline in the average in-clinic systolic blood-pressure level and the percentage of patients with systolic blood pressure >140 mmHg during the cohort phase, with the censoring of the data of those reaching end points, is consistent with the interpretation of higher than the group average blood pressure in individuals who reached clinical end points.¹ Nevertheless, the overall disappointing results of the AASK cohort study¹ clearly demonstrate the need for additional delineation of the mechanisms responsible for CKD progression beyond casual, in-clinic blood-pressure levels and the pathogenicity of angiotensin II. Meanwhile, as we await future trials and guidelines for the CKD population, it is more than likely that the blood-pressure targets in an individual patient will still require the judgment and analysis of the risks and benefits, even if imprecise, by that individual's physician.

References

1. Appel LJ, et al. Intensive blood-pressure control in hypertensive chronic kidney disease. *N Engl J Med*. 2010; 363:918–929. [PubMed: 20818902]
2. Chobanian AV, et al. The seventh report of the Joint National Committee on prevention, detection, evaluation and treatment of high blood pressure: the JNC 7 Report. *JAMA*. 2003; 289:2560–2572. [PubMed: 12748199]
3. Lewis JB. Blood pressure control in chronic kidney disease: is less really more? *J Am Soc Nephrol*. 2010; 21:1086–1092. [PubMed: 20576804]
4. Sarnak MJ, et al. The effect of a lower target blood pressure on the progression of kidney disease: long-term follow-up of the modification of diet in renal disease study. *Ann Intern Med*. 2005; 142:342–351. [PubMed: 15738453]
5. Bidani AK, Griffin KA. Pathophysiology of hypertensive renal damage: implications for therapy. *Hypertension*. 2004; 44:595–601. [PubMed: 15452024]
6. Griffin KA, Kramer H, Bidani AK. Adverse renal consequences of obesity. *Am J Physiol*. 2008; 294:F685–F696.
7. Hill GS. Hypertensive nephrosclerosis. *Curr Opin Nephrol Hypertens*. 2008; 17:266–270. [PubMed: 18408477]
8. The ESCAPE Trial Group. Strict blood-pressure control and progression of renal failure in children. *N Engl J Med*. 2009; 361:1639–1650. [PubMed: 19846849]
9. Ruggenenti P, et al. Blood-pressure control for renoprotection in patients with non-diabetic chronic renal disease (REIN-2): multicentre, randomized controlled trial. *Lancet*. 2005; 365:939–946. [PubMed: 15766995]
10. Pogue V, et al. Disparate estimates of hypertension control from ambulatory and clinic blood pressure measurements in hypertensive kidney disease. *Hypertension*. 2009; 53:20–27. [PubMed: 19047584]

Figure 1.

Differences in underlying pathology alter the threshold level of blood pressure that affects CKD progression. The progression of CKD (doubling of serum creatinine level, development of end-stage renal disease and reduction in glomerular filtration rate) is influenced by blood-pressure levels. Moreover, the underlying pathology of patients with CKD (such as genetic susceptibility to kidney disease, severity of proteinuria and autoregulatory impairment) alters the relationship between blood-pressure level and renal damage. Abbreviation: CKD, chronic kidney disease. Permission obtained from the American Society of Nephrology © Griffin, K. A. & Bidani, A. K. *Clin. J. Am. Soc. Nephrol.* **1**, 1054–1065 (2006).