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What Are Optimal Blood Pressure Targets for Patients with Hypertension and Chronic Kidney Disease?

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Abstract

To maximize the risk benefit ratio of blood pressure control in people with chronic kidney diseases (CKD), a number of guidelines provide recommendations on optimal BP targets in CKD. This review examines these guidelines, their supporting evidence base and generalizability and limitations of current standards of care. Over the years, the BP targets are liberalized. They now focus on the usual BP target of <140/90 mmHg. In the elderly, where guidelines call for a target of <150/90 mmHg in the general population, the recommendations provide room

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for the clinician to tailor therapy. Among those with albuminuria of >300 mg/g creatinine low quality evidence suggests targeting BP to <130/90 mmHg. Individualization of BP lowering is key based on comorbid conditions, response to treatment and level of kidney function. Consideration of out of clinic BP monitoring either implemented by home BP recordings or ambulatory BP measurements may enhance BP control.

Introduction

Hypertension is a major public health problem affecting almost a third of US population [1]. Worldwide, high blood pressure is one of the 5 leading risk factors for global burden of disease. More than 60% patients of CKD have hypertension [1]. Control of blood pressure in CKD subjects is an important strategy to reduce the burden of cardiovascular disease, the progression of CKD, development of ESRD and mortality. The Prospective Studies Collaboration showed an increase in vascular risk in population starting with pressures as low as 115/75 and the risk doubled with each 20/10 mm Hg rise in BP [2]. Although the data in CKD are less clear, the relative magnitude of cardiovascular protection in CKD is believed to be similar. Furthermore, an independent association exists between albuminuria and both CVD and progression of CKD. Albuminuria is known to act as a risk multiplier for CVD in CKD patients [3]. Blood pressure reduction has been shown to be associated with reduction in albuminuria and progression of CKD.

In order to maximize the risk benefit ratio of blood pressure control in CKD subjects, a number of guidelines provide recommendations on optimal BP targets in CKD. This review examines these guidelines, their supporting evidence base and generalizability and limitations of current standards of care. The scope of this review is restricted to non dialysis-dependent CKD; kidney transplant recipients are also excluded.

Key Studies exploring the BP target in CKD

Over the last few years many guidelines on BP control in CKD and accompanying commentaries have been published. With respect to high quality evidence, three prospective randomized multicenter trials and three meta-analyses have specifically examined how far BP should be lowered among patients with CKD. These trials were the Modification of Diet in Renal Disease (MDRD) study [4], the African American Study of Kidney Disease (AASK) study [5] and the BP control for Renoprotection in Patients with Nondiabetic Chronic Renal Disease (REIN-2) trial [6]. Table 1 provides a summary of these studies.

Modification of Diet in Renal Disease Study

The MDRD study was the first prospective randomized controlled trial examining the effect of different BP targets on renal outcomes [4]. The study had a 2 x 2 factorial design. The two factors examined were dietary protein restriction and BP control; each factor had two levels.

Furthermore, the baseline level of glomerular filtration rate (GFR) was used as a stratification variable. Thus, study 1 used a higher level of GFR and study 2 a lower level. Accordingly, in study 1, 585 patients with GFRs of 25–55ml/min/1.73m2 of body surface area were randomly assigned to a usual- protein diet or a low-protein diet and to a usual or a low BP group. Within each factor, mean arterial pressure was targeted to be <92 mmHg (low BP group) or <107 mmHg (usual BP group). In study 2, 255 patients with GFRs of 13–24 ml/ min/1.73m2 were randomly assigned to the low-protein diet or a very-low-protein diet with a keto acid-amino acid supplement, and a usual or a low BP group. Renal function in this trial was measured using ^{125}I iothalamate clearance. It is to be noted that diabetic nephropathy was the underlying renal disease in only 3% of patients. Furthermore, BP target was not systolic or diastolic BP values and the mean arterial pressure of lower and usual BP arm would roughly correspond to BP of 125/75 mmHg and 140/90 mmHg respectively. The projected mean decline in the GFR at 3 years did not differ significantly between the BP groups. As compared with the usual BP group, the low BP group had a more rapid decline in the GFR during the first 4 months after randomization and a slower decline thereafter.

However, in post hoc analysis a significant interaction between BP target and baseline proteinuria on renal function decline was noted [7]. Thus, low BP treatment goal showing greater benefit in those with proteinuria exceeding 3g per day at baseline, moderate in those with proteinuria between 1 and 3g per day, and no benefit in those with proteinuria of less than 1g per day [7]. These post hoc analysis findings led to the

recommendation by the K-DOQI and the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC 6) of a BP goal of less than 125/75mmHg among CKD patients with > 1 g/day proteinuria which were later taken off from the more recent guidelines [8] due to concerns about the strength of the data to justify a recommendation.

Post hoc analysis suggested that a lower BP target might be more effective in preventing renal disease progression in black versus white patients [9] and that blacks have higher nocturnal BP and may benefit from greater nocturnal BP lowering [10]. Furthermore, a follow up analysis of the MDRD cohort for 7 years revealed fewer ESRD or combined ESRD and death events in the more aggressive BP lowering group [11]. The post hoc or observational nature of these data does not allow firm conclusions regarding their applicability to the care of patients with hypertension and CKD.

The use of mean arterial pressure to target BP therapy has been questioned. Mean arterial pressure is not the measure of BP control used in practice or a benchmark in standard guidelines. Further, the very nature of its derivation (diastolic pressure + one third of pulse pressure) allows for a wide range of systolic blood pressures for any given value of mean arterial pressure. As illustrated by Lewis, the low-mean arterial pressure group had a wide range of systolic pressure, approximately 98 to 154 mmHg. Achieving systolic blood pressure in this range is a very different intervention than targeting all patients' BP to <130 mmHg systolic.

Blood pressure control for Renoprotection In Nondiabetic Chronic Renal Disease (REIN-2)

The REIN-2 trial assessed the effect of intensified versus conventional BP control on progression to ESRD [6]. Participants had non-diabetic proteinuric nephropathies receiving background treatment with the ACE inhibitor ramipril (2.5–5 mg/day). They were randomly assigned to either conventional (diastolic <90mmHg; n=169) or intensified (systolic/diastolic <130/80mmHg; n=169) BP control. To achieve the intensified BP level, patients received add-on therapy with the dihydropyridine calcium-channel blocker felodipine (5–10 mg/day). Although the primary outcome measure was time to ESRD over 36 months' follow-up the study was terminated early for futility with a conclusion that among patients with nondiabetic proteinuric nephropathies receiving background ACE- inhibitor therapy, no additional benefit from further BP reduction by felodipine could be shown. In effect, over a median follow-up of 19 months, 38/167 (23%) and 34/168 (20%) subjects in intervention and control arm progressed to ESRD [hazard ratio 1.00 (95% CI 0.61–1.64); P=0.99].

African American Study of Kidney Disease (AASK)

The AASK compared the effects of two levels of BP control and three antihypertensive drug classes on GFR decline in hypertension in a 3 x 2 factorial trial design [12]. The 3 factors were the initial open-label drug therapies: the ACE-inhibitor ramipril, the beta-blocker metoprolol, or the dihydropyridine calcium- channel blocker amlodipine. Within each

factor, participants were randomly assigned to one of two mean arterial pressure goals as in the MDRD study. Importantly, subjects with proteinuria of greater than 2.5 g/g creatinine and type 1 and type 2 diabetes were excluded. Three primary treatment comparisons were specified: lower versus usual BP goal; ramipril versus metoprolol; and amlodipine versus metoprolol.

Achieved BP averaged (SD) 128/78 (12/8) mmHg in the lower BP group and 141/85 (12/7) mmHg in the usual BP group. The mean (SE) GFR slope from baseline through 4 years did not differ significantly between the lower BP group and the usual BP group. The rates of the clinical composite outcome (table 1) [risk reduction for lower BP group=2%; 95% confidence interval (CI) -22 to +21%; P=0.85) were no different. A sub-analysis did not find a difference in outcome between two BP targets in subjects with urinary protein > 0.22 per gm creatinine. Thus, no additional benefit of slowing progression of hypertensive nephrosclerosis was observed with the lower BP goal. A subsequent study on the observation cohort reported that the lower BP group with proteinuria > 0.22 per gm creatinine experienced a lower (hazard ratio 0.73, p=0.01) composite endpoint occurrence [13].

None of these three landmark randomized controlled trials revealed any significant improvement in cardiovascular disease outcomes in relation to intensive vs. usual BP control. The AASK investigators acknowledged that the trial was not powered to detect differences in the rate of myocardial infarction, stroke, or death.

In contrast to above, a meta-analysis suggests that BP control reduces CVD outcomes in CKD. A meta-analysis of RCTs by the Blood Pressure Lowering Treatment Trialists' Collaboration that comprised 26 trials (152,290 participants), had 30,295 individuals with eGFR <60 mL/min/1.73m2 [14]. The results showed that compared with placebo, blood pressure lowering regimens reduced the risk of major cardiovascular events by about 17% per 5 mm Hg reduction in systolic blood pressure in individuals with (hazard ratio 0.83, 95% CI 0.76 to 0.90) and without reduced eGFR (0.83, CI 0.79 to 0.88). The report did not identify any clear benefit for more intensive compared with less intensive blood pressure lowering regimens in people with CKD, although there was only limited power for this analysis.

Similarly, the absence of diabetics from key studies is a major limitation. Diabetes comprises the largest segment of CKD but AASK and REIN 2 excluded these people and MDRD had just 3%. Therefore, there are no adequately powered studies on diabetic CKD targeting intensive vs conventional BP control.

Meta analyses of BP targets in CKD

The subject of intensive blood pressure lowering in CKD has been a part of three meta-analyses as well. Table 2 summarizes the key aspects of these meta-analyses

Upadhyay et al included studies after 2001 only and thus had the three key trials and associated sub-group, post hoc analyses and observation cohort data studies included for analysis [15]. While the primary result was negative, lower-quality evidence suggested that a lower BP target

might be beneficial in subgroups with proteinuria greater than 300 to 1000 mg/d. It was also noted that participants in the low target groups needed more antihypertensive medications and had a slightly higher rate of adverse events.

In another meta-analysis that was limited to patients with CKD but included several observational follow up cohorts such as from the AASK study [13] Lv et al [16] showed a benefit of intensive blood pressure lowering and more so among patients with proteinuria. There was no clear benefit of aggressive BP lowering on the risk of cardiovascular events or death. However, given that the observational cohorts were included in the analyses, a cause and effect relationship is difficult to establish [16].

Evolution of BP targets in CKD

Among people with hypertension with little cardiovascular disease at baseline, meta-analyses of randomized trials indicate that patients who achieve lower BP have fewer cardiovascular events; no J curve was evident [2]. A J-curve is however reported for achieved BP in CKD with an observed increased risk for stroke, cardiovascular morbidity and mortality [17-19]. No such J-curve is noted for renal protection [20]. Over time, it has become increasingly clear that a distinction needs to be made between achieved BP and targeted BP. Achieved BP may reflect severity of disease, coexisting illness, adherence to medications and lifestyle modifications, factors beyond what may be studied in a randomized trial. Target BP can only be examined in a randomized trial and results of these trials can inform practice.

Perhaps this is best illustrated by an analysis of the AASK study [21]. Intention-to-treat analyses showed no evidence of a BP effect on either the rate of decline in glomerular filtration rate or the clinical composite outcome. In contrast, the achieved BP analyses showed that each 10-mm Hg increment in mean follow-up achieved mean arterial pressure was associated with a 0.35 mL/min per 1.73 m^2 (p=0.01) faster mean glomerular filtration rate decline and a 17% (p=0.006) increased risk of the clinical composite outcome. Even within a randomized trial, analyses based on achieved BP lead to markedly different inferences than traditional intention-to-treat analyses.

Current guidelines on blood pressure targets in CKD

Over time, the recommended BP targets in CKD have risen. This is because the more recent guidelines have come to rely more on RCTs with primary outcomes as BP targets unlike the earlier guidelines that based guidance on observational studies, post hoc analyses and sub group analyses of RCTs. The latter usually provide a lower quality of evidence. For example, observational studies can only evaluate the achieved BP and associate them with outcomes. They fall short in informing on what the BP targets should be. Eventually, the randomized controlled trials targeting BP values are able to inform clinical practice.

We will discuss the newest guidelines by KDIGO in some detail. The KDIGO guidelines use the Grades of Recommendation Assessment, Development, and Evaluation (GRADE) methodology for grading the quality of evidence and strength of recommendations. Broadly

speaking, each guideline has both strength of recommendation and quality of evidence to support it.

1. The strength of recommendation is graded as Level 1, Level 2, or Not Graded. Level 1 guideline is a recommendation, whereas level 2 is a suggestion. Level 1 guidelines have several implications for clinicians, policy makers, and patients. For clinicians, the implication of Level 1 guideline is that most patients should receive the recommended course of action. For policy makers this level of evidence can be evaluated to become a performance measure. For patients, most individuals would want the recommended course of action and only a small proportion would not.
2. The quality of evidence to support a guideline is rated. The quality is rated as A if high, B if moderate, C if low, and D if very low quality of evidence is present to support the guideline.

No guidelines received the venerated rating of IA. In fact, there is no statement that is supported by high quality evidence (grade A).

The KDIGO guidelines recommend with BP goal of ≤140/90 mmHg for anyone with no albuminuria whether they have diabetes mellitus or not and give it its best strength of recommendation and highest quality of evidence (Level 1B)

Goal BP of <130/80 mmHg was a recommendation for all people with CKD in the earlier guidelines. For people with albuminuria >30 mg/24h, now the goal BP of ≤130/80 mmHg for diabetic CKD receives Grade 2D. Among those with non-diabetic CKD, goal BP of ≤130/80 gets a grade of

2D if albuminuria is 30-300 mg/24h and 2C if albuminuria is >300 mg/24h. In other words, the goal BP is a suggestion based on low to very low quality evidence. These grades are appropriate because randomized trial data are lacking to support these recommendations.

Specifically for patients with diabetes and CKD, RCTs that examine the BP to which treatment should be targeted to are conspicuously lacking. The three key trials mentioned earlier either did not have diabetics or had only a small proportion of them in the study.

Is there an evidence-based lower limit for BP reduction? The expert group convened by KDIGO concluded, “we are left without a lowest BP target”. Should a reduction in albuminuria be a target for treatment with agents that modify BP? There have been no RCTs assessing hard renal or CV outcomes, in which patients have been randomized to different targets of urinary albumin excretion irrespective of BP so at present the answer is no.

BP and CKD in the elderly

With the demographic shift increasing the proportion of elderly subjects in population, this group is rapidly increasing in size. The term ‘elderly’ is used for persons >65 years of age whereas ‘very elderly’ is reserved for persons >80 years of age. Hypertension management in this group of patients is challenging because of vascular disease, autonomic dysfunction, difficult to control systolic hypertension, polypharmacy and

drug interactions, cognitive effects of antihypertensive therapy, post-prandial hypotension, and orthostatic hypotension.

A Cochrane review of 15 trials with 24,055 participants aged 60 years or more who had moderate to severe hypertension demonstrated relative risk reduction in all-cause mortality by 10%, and cardiovascular morbidity and cardiovascular mortality by 28% [22]. In the very elderly, reduction in cardiovascular morbidity and mortality was 25%, but no effect on all-cause mortality was seen. The JNC 8 recommends BP target <150/90 mmHg in those older than 60 years [23]

Given that there are limited randomized trial evidence in this population with CKD, the KDIGO guidelines for elderly suggest to "tailor BP treatment regimens in elderly patients with CKD by carefully considering age, co-morbidities and other therapies, with gradual escalation of treatment and close attention to adverse events related to BP treatment, including electrolyte disorders, acute deterioration in kidney function, orthostatic hypotension and drug side effects." [24] This guideline was not graded.

Individualizing antihypertensive therapy

Given the complexity and heterogeneity of CKD, the lack of evidence in many important subgroups of patients, "one size fits all" may not work for all. Even while being treated with antihypertensive drugs, the importance of lifestyle advice requires emphasis. These include guidance of dietary sodium restriction, weight loss, regular physical activity, moderation of alcohol intake, and tobacco avoidance. Even though not tested in CKD, BP control through these life-style modifications may provide benefits over the long term.

Guidelines propose that clinicians individualize therapy. For example, the KDIGO guidelines state: individualize BP targets and agents according to age, co-existent cardiovascular disease and other co-morbidities, risk of progression of CKD, presence or absence of retinopathy (in CKD patients with diabetes) and tolerance of treatment. They exhort us to inquire about postural dizziness and check for postural hypotension regularly when treating CKD patients with BP-lowering drugs. Neither of these guidelines are graded, but form the basis of good clinical practice.

Evaluation of BP can be challenging. The clinic BP has been the benchmark for most studies; the entities of white coat hypertension and "masked hypertension" require special attention. Whereas, 20-25% of the patients may have a white coat effect, it is now estimated that 25% of people with CKD who have seemingly normal BP in the clinic have masked hypertension. Emerging data supports the notion that masked hypertension is associated with increased cardiovascular events and progression to dialysis [25]. Ambulatory blood pressure monitoring is required to disclose the presence of these conditions. However, home BP monitoring may be more practical in management of these patients day-to-day and may improve therapeutic inertia [26].

Conclusion and Future Directions

The current best evidence for BP control in CKD favors less aggressive BP targets for people with CKD without proteinuria than for those with proteinuria. At present, there are few data to support that a BP goal of less than 130/80 mmHg saves lives, saves kidneys or reduces

cardiovascular events. Need for more research in special populations is needed such as in the elderly, very elderly, those with nephrotic albuminuria, those with diabetic kidney disease, and those with advanced atherosclerotic cardiovascular disease.

The ongoing Systolic Blood Pressure Intervention Trial (SPRINT) holds promise in resolving some of these questions [27]. This is a multicenter, randomized, controlled trial that compares two strategies for treating systolic blood pressure: one targets the standard target of <140 mm Hg, and the other targets a more intensive target of <120 mm Hg. The recruitment has specifically targeted three subgroups: participants with chronic kidney disease (estimated glomerular filtration rate <60 mL/min/1.73 m^2), participants with a history of cardiovascular disease, and participants 75 years of age or older. Of the 9361 people recruited 2648 have CKD. It is hoped that this study will provide more guidance particularly for systolic BP management in CKD and other high-risk subjects.

Compliance with Ethics Guidelines

Conflict of Interest

Gopesh K. Modi declares that he has no conflict of interest. Conflicts of Interest are disclosed by Rajiv Agarwal in the ICJME form.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

Table: 1

Randomized trials of BP targets in CKD

	MDRD (1994) [4]	REIN-2 (2005) [6]	AASK (2002) [12]	
N studied	840	338	1094	
BP Targets Low vs. usual	MAP < 92 vs < 107 MAP < 98 vs < 113 (Age > 61 yr)	<130/80 vs DBP < 90	MAP < 92 vs MAP 102-107	
Primary Outcome	Rate of change of GFR	ESRD	Composite of 50% reduction in GFR, ESRD and death	
Follow up	2.2 yr (mean)	19 mths (median)	3 – 6.4 yr (range)	
Primary Result	No difference between groups	No difference	No difference	

MDRD:

AASK:

REIN-2:

MAP: Mean arterial pressure

DBP: Diastolic blood pressure

Table 2: Meta analyses on effect of intensive BP control in CKD

	Upadhyay et al (2011) [15]	Lv et al (2012) [28]	Lv et al (2013) [16]
Number of studies	8 studies from 3 trials* between 2001-2011	15 studies between 1950-2011	11 studies; between 1950-2011
Number of participants	2272	37348 (CKD 2734 subjects)	9287
BP targets	125/75-130/80 vs 140/90	Identified an average of 7.5/4.5-mmHg BP difference between groups.	Varying targets in various studies
Outcome(s)	Death, ESRD, cardiovascular events, change in kidney function, number of antihypertensive agents, and adverse events.	Effect on vascular, renal and ocular outcomes	Composite of doubling of serum creatinine and 50% fall in GFR or ESRD

Primary result	No added benefit of lower BP	11% (CI 1-21%) reduction in cardiovascular events, 11% (CI 3-18%) reduction in ESRD	Intensive BP lowering reduced the composite outcome risk (hazard ratio [HR] 0.82, [CI] 0.68–0.98) and end-stage kidney disease (HR 0.79, 95% CI 0.67– 0.93)

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