Chronic Kidney Disease and BP Goals

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Introduction

Patients with chronic kidney disease (CKD) are at particular high risk for cardiovascular (CV) events and the rationale for treatment of hypertension in CKD is to slow ongoing renal injury and delay progression to end-stage renal disease (ESRD). Patients with CKD are more likely to have resistant hypertension and are frequently taking multiple antihypertensive agents therefore achieving the recommended blood pressure (BP) goals in this population is often therapeutically challenging. Patients with CKD are less likely to achieve BP goals and a recent NHANES analysis demonstrated that more patients with CKD have uncontrolled BP compared to non-CKD patients, even when using the higher BP targets suggested by the 2014 Adult Hypertension Management guidelines (BP < 140/90 mmHg) [1, 2]. BP goals in the CKD population are still evolving and there is no definite consensus. The 2014 guidelines [2] were based on evidence from older studies, but these guidelines may change again, targeting lower BP goals based on how data from the recently published SPRINT study is interpreted in the CKD group, representing 28% of the SPRINT cohort [3]. The majority of the current guidelines for BP goals in CKD favor a BP < 140/90 mmHg in CKD without proteinuria; however, most guidelines recommend maintaining a lower BP target for those with more severe proteinuria. This contrasts with JNC 7 [4], which recommended a BP goal of <130/80 mmHg in all patients with CKD. The recommended BP guidelines in CKD from the various guideline committees are shown in Table 39.1 and the rationale for these guidelines will be detailed below [5].

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Rationale for BP Guidelines in CKD

The 2014 Evidence-Based Guideline for the Management of High Blood Pressure in Adults (JNC 8) 2014 [1, 2] recommended a BP goal of <140/90 mmHg in CKD, regardless of level of proteinuria and presence of diabetes. They also recommended that in patients with CKD regardless of race or diabetes, initial (or add-on) treatment should include an ACEI or ARB to improve kidney outcomes. The rationale for raising the BP goal in the 2014 evidence-based guidelines was based on data obtained from three randomized, controlled trials: Modification of Diet in Renal Disease (MDRD) Study; African American Study of Kidney Disease and Hypertension (AASK) trial and the Ramipril Efficacy in Nephropathy-2 (REIN-2) trial [12–14] and subsequent meta-analyses based on the same three trials [15–18].

The MDRD study included 585 patients with a GFR of 25–55 mL/min/1.73 m^2 and 255 patients with a GFR of 13–24 mL/min/1.73 m^2. The study was a 2 × 2 factorial design and patients were randomly assigned to an intensive BP target (a mean arterial pressure (MAP) of 92 mmHg corresponding to about 125/75 mmHg) or a standard BP target (MAP of 107 mmHg or approximately 140/90 mmHg) and to 1 of 2 types of diet. The use of all antihypertensives was allowed but angiotensin converting enzyme inhibitors (ACE) ± diuretic were encouraged as first-line agents and calcium channel blockers (CCB) ± diuretics were encouraged as second line agents. Eighty-five percent of patients were white and 97% of patients had nondiabetic CKD. Diabetics requiring insulin were excluded. Achieved BP was 126/77 mmHg in the intensive BP group versus 133/80 mmHg in the standard BP group. A posttrial follow-up of 6.2 years did not show benefit of any specific BP target or antihypertensive regimen. Importantly, the death outcome was not different between the two groups, and patients who reached ESRD were excluded from the analysis. The MDRD findings were largely based on slope of change of GFR (usually halving of GFR or the development of ESRD are the typical renal outcomes), and the original

Table 39.1 BP targets and treatment recommendations in CKD

Guideline source	CKD without proteinuria[a] (mmHg)	CKD with proteinuria (mmHg)	Recommended agents
USA JNC8 [2]	<140/<90	<140/<90	ACEI or ARB
KDIGO [6]	<140/<90	<130/<80	ACEI or ARB
NICE [7]	<140/<90	<130/<80	ACEI or ARB[b]
CHEP [8]	<140/<90	<140/<90	ACEI; ARB if ACEI intolerant
ESC/ESH [9]	<140	<130	ACEI or ARB
ASH/ISH [10]	<140/<90	<140/<90[c]	ARB or ACEI
ISHIB [11]	<130/<80	<130/<80	Diuretic or CCB

[a]Proteinuria definitions vary; the authors recommend using either +1 (by dipstick); more than 500 mg protein per 24 h; or more than 200 mg albumin per 24 h (or the equivalent of these values in a spot urine determination that employs a protein-to-creatinine or albumin-to-creatinine ratio)
[b]The NICE recommendations are to use ACEI or ARB when proteinuria is present; otherwise the guidance is to follow general recommendations for BP control when proteinuria is absent
[c]ASH/ISH guidelines acknowledge that some authorities still recommend <130/<80 mmHg for CKD with proteinuria
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report did not support a benefit of more aggressive BP reduction for either halving of GFR or ESRD. A follow-up of the MDRD cohort was published in 2005, 12 years after the study finished, and concluded that those randomized to the intensive BP goal had less development of kidney outcomes compared with those in the standard BP target (62 vs. 70% requiring either dialysis initiation or transplantation), however, no BP data was available on the cohort after they completed the trial phase nor is information available indicating specifics of drug therapy in the interval [19].

The AASK trial enrolled 1094 nondiabetic black patients with hypertensive nephrosclerosis. The study had a 3 × 2 factorial design with patients being randomly assigned to an intensive (MAP < 92 mmHg) or standard (MAP 102–107 mmHg) BP target and 1 of 3 initial therapies (ramipril, metoprolol, or amlodipine). The trial allowed sequential addition of furosemide, doxazosin, clonidine, hydralazine, and minoxidil to achieve randomized BP target. The mean BP achieved was 128/78 mmHg in the intensive versus 141/85 mmHg in the standard BP groups. At a mean follow-up of 4 years, the average rate of change (as a slope) in GFR was not different between the BP groups. In the posttrial follow-up for AASK at 8–12 years, patients were treated to a BP goal of less than 130/80 mmHg and used either an ACE or an angiotensin receptor blocker (ARB) if ACE-intolerant. Target BP achieved was 131/78 versus 134/78 mmHg in the intensive versus standard BP groups. Use of ACE and ARB was similar in the both groups. There was no difference between groups in the progression of kidney disease (doubling of serum creatinine, diagnosis of ESRD, or death) in the main cohort.

REIN-2 Trial specifically enrolled 338 patients with proteinuria >1000 mg/day for 3 months. Patients with proteinuria between 1000 and 3000 mg/day were included if GFR was <45 mL/min/1.73 m^2 and patients with proteinuria >3000 mg/day were included if GFR was <70 mL/min/1.73 m^2. Type 1 diabetics were excluded. Patients were assigned to an intensive BP target of <130/80 mmHg or a standard BP target of DBP < 90 mmHg. All patients were treated with ramipril (ACE) 5 mg daily during the trial. Felodipine (dihydropyridine CCB) in the dose of 5–10 mg daily was used as add-on treatment in the intensive BP target. Antihypertensive agents other than ACE, ARB, and dihydropyridine CCB were allowed in both groups. BP achieved was 130/80 versus 134/82 mmHg in the intensive versus standard BP targets. After a median time of 19 months, no significant differences were noted in the percentage of patients who progressed to ESRD (23 vs. 20%, slightly though not significantly higher incidence in the intensive BP target group), the decline in GFR or the effects on proteinuria between the groups.

The MDRD, AASK and REIN-2 all failed to show a benefit from lower BP goals (<140/90 vs. 125–130/75–80 mmHg) in reduction of CV events, slowing progression of CKD to ESRD, and reducing mortality. The AASK trial did prospectively include proteinuria as an end point but lower BP targets did not show any benefit on slowing progression of CKD [13]. The MDRD trial; however, did show a benefit in a post hoc analysis of lower BP goals in the setting of proteinuria (more than 1 g/24 h) on the slope of glomerular filtration rate (GFR) loss [17]. There was,

however, an unequal use of ACE inhibitor treatment in the different treatment groups. A systematic review and meta-analysis of the 2272 participants of these three trials comparing lower versus higher BP targets in adults with CKD also did not show any conclusive evidence favoring a lower BP target of 125/75–130/80 versus 140/90 mmHg after a mean follow-up of 2–4 years. There was however a benefit for CKD patients with proteinuria of 300–1000 mg/day [16].

BP Goals in Diabetes

The Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial which randomized type 2 diabetics to a SBP goal of <140 versus <120 mmHg also failed to demonstrate CV protection from a lower BP target, but the rate of stroke was decreased [20]. Renal outcomes were not separately addressed in the ACCORD Trial and serum creatinine levels and estimated GFR were not improved with lower BP goals. Based on the data from MDRD, AASK and REIN, which failed to show a decrease in CV risk, mortality, and progression of CKD or to ESRD, the 2014 Evidence-Based Guideline for the Management of High Blood Pressure in Adults (JNC 8) 2014 [1] committee recommended a BP goal of <140/90 mmHg in all patients with CKD regardless of proteinuria. Although there was some data showing benefit of a lower BP in patients with proteinuria of 300–1000 mg/day, they did not recommend a lower BP goal for CKD patients with macroalbuminuria.

Current BP Guidelines in CKD

The 2012 KDIGO Clinical Practice Guideline for Management of Blood Pressure in CKD [6] was the first guideline to recommend a higher BP goal for patients with CKD. This guideline recommended a BP goal of $\leq$140/90 mmHg in CKD patients without albuminuria. They however recommended a goal BP $\leq$130/80 mmHg in CKD patients with albuminuria $\geq$30 mg/24 h. KDIGO also recommended treatment with RAAS blockade in all CKD patients with an albumin excretion rate of $\geq$30 mg/24 h.

Other guideline groups also raised the BP goals for patients with CKD including the American Diabetes Association (BP target < 140/80 mmHg) [19], Canadian Hypertension Education Program (BP target < 140/90 mmHg for CKD) [8], and European Society of Cardiology/European Society of Hypertension (SBP target < 140 mmHg for CKD) [9]. The National Institute for Health and Clinical Excellence (NICE) guideline advised initiating treatment in those with CKD at BP $\geq$ 140/90 mmHg and treating to a target of 120–139/<90 mmHg [7, 21]. The NICE guidelines also recommended drug treatment for BP $\geq$ 130/80 mmHg for albumin-to-creatinine ratio (ACR) of $\geq$70 mg/mmol and a target of 120–129/<80 mmHg).

Observational Studies in CKD

There are two recent retrospective observational studies from a national CKD database of mostly male US veterans assessing all-cause mortality in veterans with CKD. The first study compared mortality in CKD patients with a treated SBP of <120 mmHg to patients with the currently recommended SBP of <140 mmHg [22]. This study included 77,765 individuals with GFR < 60 mL/min/1.73 m^2 and uncontrolled hypertension (received $\geq$1 BP medication with evidence of a decrease in SBP). Of this cohort, 5760 patients had a treated SBP of <120 mmHg at follow-up and 72,005 patients had a treated SBP of 120–139 mmHg at follow-up. During a median follow-up of 6.0 years, 19,517 patients died (2380 deaths in SBP < 120 mmHg group (death rate of 80.9/1000 patient-years) and 17,137 deaths in SBP of 120–139 mmHg group (death rate, 41.8/1000 patient-years; $p < 0.001$). The mortality hazard ratio associated with follow-up SBP less than 120 versus 120–139 mmHg was 1.70 (95% CI 1.63–1.78). These results suggest that lower SBP levels were associated with higher all-cause mortality in patients with CKD.

The second study assessed the association of BP with death in patients with CKD [23]. They included 651,749 US Veterans with CKD and examined all possible combinations of SBP and DBP from lowest (BP = 80/40 mmHg) to highest (BP = 210/120 mmHg), in 10 mmHg increments. The study demonstrated that patients with SBP of 130–159 mmHg combined with DBP of 70–89 mmHg had the lowest adjusted mortality rates, and those in whom both SBP and DBP were concomitantly very high or very low had the highest mortality rates. Patients with moderately elevated SBP combined with DBP no <70 mmHg had consistently lower mortality rates than patients with DBP < 70 mmHg. Results were consistent in subgroups of patients with normal and elevated ACRs. Overall, the optimal BP in CKD patients in this study appeared to be 130–159/70–89 mmHg. Both these studies are retrospective observational analyses, and are at risk for confounding, but appear to indicate that a SBP <120 mmHg at least observationally is associated with an increased risk of mortality.

The Systolic BP Intervention Trial

The Systolic BP Intervention Trial (SPRINT) may finally answer the ongoing debate about what SBP goal clinicians should be targeting in certain patients with CKD [3, 24].

SPRINT is a large NIH-sponsored, multicenter, randomized, controlled intervention trial that enrolled 9361 subjects with a SBP of at least 130 mmHg. The primary goal of SPRINT was to test whether reducing SBP to a lower goal (SBP < 120 mmHg) than currently recommended (SBP < 140 mmHg) would reduce the occurrence of CV disease events defined as CV death, nonfatal heart attack, nonfatal stroke, acute coronary syndrome without heart attack, and hospitalized heart failure. Subjects enrolled were 50 years or older with SBP of 130 mmHg or higher and at least one of the following: a history of cardiovascular disease, stage 3/4 chronic kidney disease (estimated glomerular filtration rate 20–59 mL/min/1.73 m^2), an intermediate to high risk for CVD other than stroke or age $\geq$ 75 years. A subject was defined as having CVD if they had a prior myocardial infarction, percutaneous coronary intervention, coronary artery bypass grafting, carotid endarterectomy or carotid stenting, peripheral arterial disease with revascularization, acute coronary syndrome, abdominal aortic aneurysm $\geq$ 5 cm with or without repair, a coronary calcium score > 400 or left ventricular hypertrophy. A subject was defined as intermediate or high risk for CVD based on the following: Framingham Risk Score for 10-year CVD risk of 15% based on laboratory work done within the past 12 months for lipids. The primary outcome was a composite of CV events. SPRINT was terminated early after 3.26 years on a recommendation from the data safety monitoring board. The results of the SPRINT study showed a 25% reduction in the primary combined CV outcome and a 27% reduction in mortality in the group randomized to a SBP < 120 mmHg [3, 24]. This obviously has important implications for BP guidelines in this population with CKD. The baseline mean systolic and diastolic blood pressures were 139.7 and 78.1 mmHg. At 1 year, the mean SBP was 121.4 mmHg in the intensive treatment group and 136.2 mmHg in the standard-treatment group. The SPRINT study included 28% of subjects with CKD and 28% of subjects were older than 75 years, 36% were women, and 20% had prior cardiovascular disease. The sample was diverse and included 29.9% Black, 10.5% Hispanic, and 57.7% White subjects. Importantly, SPRINT *excluded* many patients with hypertension and CKD including those with a history of prior stroke, diabetes, polycystic kidney disease, any secondary cause for hypertension, GFR < 20 cc/min, >1 g of proteinuria per 24 h, glomerulonephritis treated with immunosuppressive therapy, symptomatic heart failure within last 6 months or left ventricular ejection fraction <35%, organ transplant recipients, cardiovascular event, procedure, or hospitalization for unstable angina within the last 3 months and patients <50 years of age. Although the SPRINT study will provide important information on managing systolic BP in older nondiabetic subjects with substantial CVD risk, it is important to remember that these results cannot be generalized to the other populations and to all patients with CKD.

Among participants who had CKD at baseline, a prespecified secondary analysis in SPRINT was the number of patients who developed a decrease of GFR of >50%, or end-stage renal disease (ESRD; requiring dialysis or transplantation). There were no significant differences in the intensive versus standard BP group with regards to the composite outcome of a decrease in the eGFR of 50% or more or the development of ESRD. The number of ESRD events was small in both groups (14 and 15 in the intensive group vs. the standard BP group respectively) perhaps due to early termination of the trial and a lower-than-expected decline in the eGFR. Among participants who did not have CKD at baseline, a decrease in the eGFR of $\geq$30% to a eGFR of <60 mL/min/1.73 m^2 occurred more frequently in the intensive treatment group than in the standard-treatment group (1.21 vs. 0.35%/year). This is not unexpected given the need for more intensive antihypertensive therapy in this group. With the currently available data, there is no evidence of substantial permanent kidney injury associated with the lower systolic BP goal; however, the possibility of a long-term adverse renal outcome cannot be excluded. Further more detailed subgroup analysis of CKD patients in the SPRINT study is still being performed and will incorporate longer follow-up and will likely add data to the debate of the "ideal" BP goal in CKD. A comparison of the various studies regarding intensive versus standard BP goals and CKD outcomes are summarized in Table 39.2.

BP Goals in Polycystic Kidney Disease

The HALT-PKD trial has provided some additional data on BP goals in patients with autosomal dominant polycystic kidney disease (APCKD) [25]. This study enrolled patients with hypertension and APCKD with preserved renal function in a double-blind, placebo-controlled trial, and randomly assigned 558 patients with an estimated GFR > 60 mL/min/1.73 m^2 to either a standard BP target (120/70–130/80 mmHg) or an intensive BP target (95/60–110/75 mmHg) and to either combination of ACE and ARB (lisinopril and telmisartan) or ACE plus placebo (lisinopril plus placebo). The primary outcome was the annual percentage change in the total kidney volume. The annual percentage increase in total kidney volume was significantly lower in the intensive BP group than in the standard BP group (5.6 vs. 6.6%, $p = 0.006$), without significant differences between the ACE/ARB and ACE/placebo group. The rate of change in estimated GFR was similar in the two medication groups, with a negative slope difference in the short term in the low-blood-pressure group as compared with the

Table 39.2 Comparison of studies in CKD comparing intensive versus standard BP targets

	MDRD [12]	AASK [13]	REIN-2 [14]	SPRINT [3]
Subject #	840	1094	338	2646
Cause of CKD	Nondiabetic CKD	Hypertensive nephrosclerosis	CKD excluded type 1 DM	Nondiabetic CKD
Stage CKD	3–4	3	3–4	3–4
Proteinuria inclusion	300–1000 mg/day	<300 mg/day	1000–5000 mg/day	<1000 mg/day
BP inclusion	MAP ≤ 125	DBP ≥ 90	Not specified	SBP > 130 mmHg
Baseline proteinuria	Intensive BP target: 390 mg/day Standard BP target: 310 mg/day	Intensive BP target: 0.08 g/g (0.03–0.36 g/g) Standard BP target: 0.08 g/g (0.03–0.37 g/g)	Intensive BP target: 2800 mg/day Standard BP target: 2900 mg/day	Intensive BP target: 44.1 mg/g creatinine Standard BP target: 41.1 mg/g creatinine
Target BP (mmHg)	Intensive BP target: MAP ≤ 92 (125/75) Standard BP target: MAP ≤ 107 (140/90)	Intensive BP target: MAP ≤ 92 Standard BP target: MAP ≤ 102–107	Intensive BP target: <130/80 Standard BP target: DBP <90	Intensive BP target: SBP < 120 Standard BP target: SBP 140
Achieved BP target (mmHg)	Intensive BP target: 126/77 Standard BP target: 133/80	Intensive BP target: 130/78 Standard BP target: 141/86	Intensive BP target: 130/80 Standard BP target: 134/82	Intensive BP target: SBP < 121.5 Standard BP target: SBP 134.6
Primary outcome	Rate of change in GFR	Rate of change in GFR and composite of $\geq 50\%$ (or ≥ 25 mL/min/1.73 m^2) reduction in GFR, ESRD or death	ESRD	$\geq 50\%$ change in GFR, ESRD, transplantation and incident albuminuria

CKD outcomes	MDRD trial [12]	MDRD observational follow-up [17]	AASK trial [13]	AASK observational follow-up [18]	REIN-2 trial [14]	SPRINT [3]
$\geq 50\%$ (or ≥ 25 mL/min/1.73 m^2) reduction in GFR, ESRD or death	Not stated	Not stated	Risk reduction (RR) 2% (95% CI −22 to 21%) $p = 0.85$	HR 0.91 (CI 0.77–1.08) $p = 0.27$	Not stated	HR 0.89 (CI 0.42–1.87) $p = 0.76$
Kidney failure or death	Study A: RR, not stated $p > 0.05$ Study B: RR, 0.85 (CI 0.6–1.22) $p = 0.33$	HR 0.77 (CI 0.65–0.91) $p = 0.002$	RR 12% (CI −13 to 30%) $p = 0.31$	HR 0.85 (CI 0.71–1.02) $p = 0.08$	Not stated	Not stated
50% decrease in GFR or kidney failure	Not stated	Not stated	RR 2% (CI −31 to 20%) $p = 0.87$	HR 0.95 (CI 0.78–1.15) $p = 0.59$	Not stated	HR 0.87 (CI 0.36–2.07) $p = 0.75$
Kidney failure or ESRD	HR 0.76 (CI 0.52–1.1) $p = 0.15$	HR 0.68 (CI 0.57–0.82) $p < 0.001$	RR 6% (CI −29 to 31%) $p = 0.72$	Not stated	23 versus 20% $p = 0.99$	HR 0.57 (CI. 0.19–1.54) $p = 0.27$
Incident albuminuria						HR 0.72 (CI. 0.48–1.07) $p = 0.11$

(continued)

Table 39.2 (continued)

CKD outcomes	MDRD trial [12]	MDRD observational follow-up [17]	AASK trial [13]	AASK observational follow-up [18]	REIN-2 trial [14]	SPRINT [3]
Rate of annual GFR decline, mL/min/1.73 m^2	Study A: 1.6 (CI −0.8 to 3.9) $p = 0.18$ Study B: 0.5 (CI 0.4–1.4) $p = 0.28$	Not stated	0.26 (CI −0.21 to 0.64) $p = 0.25$	Not stated	0.22 versus 0.24 $p = 0.62$	Not stated

MDRD modification of diet in renal disease, *AASK* African American Study of Kidney Disease, *REIN-2* Ramipril efficacy in nephropathy-2, *SPRINT* systolic blood pressure intervention trial, *CKD* chronic kidney disease, *DM* diabetes mellitus, *MAP* mean arterial pressure, *GFR* glomerular filtration rate, *CI* confidence interval, *RR* risk reduction; *HR* hazard ratio

standard-blood-pressure group ($p < 0.001$) and a marginally positive slope difference in the long term ($p = 0.05$). The left ventricular mass index decreased more in the intensive BP versus standard BP group (−1.17 vs. −0.57 g/m^2/year, $p < 0.001$); urinary albumin excretion was reduced by 3.77% with the intensive BP group and increased by 2.43% with the standard BP group ($p < 0.001$). Dizziness and light-headedness were more common in the intensive BP versus standard BP group (80.7 vs. 69.4%, $p = 0.002$). This study showed that a more intensive BP goal of $\leq$ 110/75 mmHg slowed the increase in total kidney volume, reduced LV mass index, and reduced urinary albumin excretion. Intensive BP control did not affect the change in eGFR. Use of single versus dual RAAS blockade did not affect outcomes.

Summary of BP Goals

In summary, there is no consensus on the ideal BP goal in CKD but most of the current BP guidelines committees currently recommend a BP goal of <140/90 mmHg for most CKD patients and some guidelines recommend a lower BP goal of <130/80 mmHg in CKD patients with proteinuria. Newer studies are now shedding light on this debate with high quality prospective data indicating that a lower BP goal may be indicated in certain populations with CKD. An even lower BP goal of $\leq$ 110/75 mmHg might be indicated in autosomal dominant PCKD patients with preserved renal function. These studies however still do not apply to a large proportion of CKD patients with diabetic nephropathy. We suggest that a BP range of 120–130 mmHg as recommended by the NICE guidelines is probably a "safe" BP goal to aim for in the interim in most patients with CKD. All the concerns are likely to be incorporated into the next set of guidelines which are likely to be revised in 2017.

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