REVIEW

Hypertension in Chronic Kidney Disease (CKD): Diagnosis, Classification, and Therapeutic Targets

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Blood pressure (BP) in the office is often recorded without standardization of the technique of measurement. When office BP measurement is performed with a research-grade methodology, it can inform better therapeutic decisions. The reference-standard method of ambulatory BP monitoring (ABPM) together with the assessment of BP in the office enables the identification of white-coat and masked hypertension, facilitating the stratification of cardiorenal risk. Compared with general population, the prevalence of resistant hypertension is 2- to 3-fold higher among patients with chronic kidney disease (CKD). The use of ABPM is mandatory in order to exclude the white-coat effect, a common cause of pseudoresistance, and confirm the diagnosis of true-resistant hypertension. After the premature termination of Systolic Blood Pressure Intervention Trial due to an impressive cardioprotective benefit of intensive BP-lowering, the 2017 American Heart Association/American College of Cardiology guideline reappraised the definition of hypertension and recommended a tighter BP target of <130/80 mm Hg for the majority of adults with a high cardiovascular risk profile, inclusive of patients with CKD. However, the benefit/risk ratio of intensive BP-lowering in particular subsets of patients with CKD (i.e., those with diabetes or more advanced CKD) continues to be debated. We explore the controversial issue of BP targets in CKD, providing a critical evaluation of the available clinical-trial evidence and guideline recommendations. We argue that the systolic BP target in CKD, if BP is measured correctly, should be <120 mm Hg.

Keywords: blood pressure; chronic kidney disease; hypertension; masked hypertension; resistant hypertension; therapeutic targets; white-coat hypertension

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DIAGNOSIS AND CLASSIFICATION OF HYPERTENSION IN CHRONIC KIDNEY DISEASE

The 2017 American Heart Association/American College of Cardiology (AHA/ACC) guideline highlights that assessment and management of hypertension should be based on standardized methods of blood pressure (BP) measurement and recommends the use of home or ambulatory BP monitoring (ABPM) for confirmation of diagnosis of hypertension and adjustment of antihypertensive treatment.[1] Similarly, the 2018 European Society of Hypertension/European Society of Cardiology (ESH/ESC) guideline recognizes the limited diagnostic accuracy of BP recordings obtained in a single office visit and recommends 2 strategies for diagnosing hypertension: repeated office visits for BP measurement or out-of-office BP monitoring.[2] An overview of BP measurement techniques and diagnostic thresholds according to the American and European guidelines is provided in Table 1.

Office BP monitoring

In Systolic Blood Pressure Intervention Trial (SPRINT),[3] a landmark trial that was prematurely terminated due to an impressive cardioprotective benefit of intensive BP-lowering in 9,361 patients with systolic BP (SBP) >130 mm Hg and high cardiovascular risk, antihypertensive treatment was guided by office BP recordings obtained with a research-grade technique to an intensive group (SBP <120 mm Hg) or a standard group (SBP <140 mm Hg). The protocol of SPRINT specified a 5-minute seated rest in a quiet room followed by 3 oscillometric BP measurements at 1-minute intervals without an observer at most sites.[3] In SPRINT Ambulatory BP ancillary study,[4] 897 SPRINT participants underwent ABPM within 3 weeks of the 27-month follow-up visit. Research-grade office SBP exhibited only a moderate correlation with daytime ambulatory SBP (Spearman coefficient: 0.56). In the intensive-treatment arm, research-grade office SBP underestimated daytime ambulatory SBP by −6.8 mm Hg with wide 95% limits of agreement (−32.7 to 19.3 mm Hg). In the standard-treatment arm, the mean difference between research-grade office and daytime ambulatory SBP was −3.3 mm Hg, but the 95% limits of agreement were once again wide (−32.3 to 24.8 mm Hg).[4]

In a diagnostic-test study enrolling 275 patients with chronic kidney disease (CKD) and office BP within the normotensive range (<140/90 mm Hg), BP was measured with the same research-grade technique that was applied in SPRINT and was compared with a single automated office

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Table 1. Techniques of BP measurement

Parameter	Routine office BP	Unattended automated office BP	Home BP	Ambulatory BP
Description	Manual or automated oscillometric measurements without specification of seated rest and with an observer in the room	Multiple automated oscillometric measurements after a 5-minute seated and without observer in the room	BP recordings obtained twice daily by the patients themselves at home typically with a validated oscillometric device	Automated BP measurements typically 3 times/hour during daytime and 2 times/hour during nighttime
Monitoring schedule	Office visit	Office visit	At least 3 and preferably 7 days	24-Hour recording on a usual day
White-coat effect	Yes	Reduced vs. routine recordings	No	No
Assessment of nighttime BP/ nocturnal dipping	No	No	No	Yes
Association with target-organ damage	Poor	Moderate	Moderate	Strong
Association with cardiovascular and kidney outcomes	Poor	Few outcome data	Superior to routine office BP	Strong
Need for patient training	No	No	Yes	Yes
Availability in daily clinical practice	Yes	Limited	Yes	Limited
Diagnostic threshold according to the 2017 AHA/ACC guideline[1]	≤130/80 mm Hg	≤130/80 mm Hg	≤130/80 mm Hg	24-Hour: ≤125/75 mm Hg Daytime: ≤130/80 mm Hg Nighttime: ≤110/65 mm Hg
Diagnostic threshold according to the 2018 ESH/ESC guideline[2]	≤140/90 mm Hg	≤135/85 mm Hg	≤135/85 mm Hg	24-Hour: ≤130/80 mm Hg Daytime: ≤135/85 mm Hg Nighttime: ≤120/70 mm Hg

Abbreviations: AHA/ACC, American Heart Association/American College of Cardiology; BP, blood pressure; ESH/ESC, European Society of Hypertension/European Society of Cardiology.

BP measurement obtained on the same day without specification of seated rest and with the presence of an observer in the room.[5] The mean difference between research-grade and routine office SBP was high and agreement between measurements was poor (mean difference: −12.7 mm Hg; 95% limits of agreement: −46.1 to 20.7).[5] Despite the common belief that office BP is typically higher than daytime ambulatory BP, research-grade office SBP underestimated daytime ambulatory SBP by −7.9 mm Hg (95% limits of agreement: −33.2 to 17.4 mm Hg). In contrast, routine office SBP overestimated daytime ambulatory SBP by 4.8 mm Hg (95% limits of agreement: −26.9 to 36.5 mm Hg).[5] Whereas SBP was related to echocardiographically documented left ventricular hypertrophy regardless of the method of measurement, the strength of the relationship was greater for ambulatory and research-grade measurements compared with routine office BP recordings.[5]

Taken together, these diagnostic-test studies indicate that in individual patients neither routine nor research-grade office BP measurements can reliably replace ABPM because of wide 95% limits of agreement. However, a standardized methodology reduces the bias inherent to routine office BP recordings.[6]

Identification of BP phenotypes with the use of out-of-office BP monitoring

The application of out-of-office BP monitoring in conjunction with measurements obtained in the office enables the identification of phenotypes of white-coat and masked hypertension, facilitating the classification of the severity of hypertension (Figure 1).[7] An estimate on the prevalence of BP phenotypes among 7,518 patients with CKD was provided by the International Database of Ambulatory BP in Renal Patients (I-DARE) collaborative group.[8] Using a threshold of <140/90 mm Hg for office BP and <130/80 mm Hg for 24-hour ambulatory BP, 1,868 patients (25%) had controlled hypertension (CH), 1,488 patients (20%) had white-coat effect (WCE), 1,239 patients (16%) had masked uncontrolled hypertension (MUCH), and 2,923 patients (39%) had sustained uncontrolled hypertension (SUCH).[8] The 4 factors associated with higher likelihood of MUCH and SUCH were male sex, diabetic status, use of ≥4 antihypertensive medications and moderate-to-severe proteinuria.[8]

The prevalence of BP phenotypes varies considerably according to the method of BP measurement and definition of hypertension.[9] In a prospective study of 333 veterans with stage 2–4 CKD who had controlled BP in the office (<140/90 mm Hg), the prevalence of MUCH was dependent on how ambulatory hypertension was defined; it was 26.7% by daytime ambulatory BP ≥135/85 mm Hg and 32.8% by 24-hour ambulatory BP ≥130/80 mm Hg, but the prevalence of MUCH was as high as 56.1% when ambulatory hypertension was defined as either daytime BP ≥135/85 mm Hg or nighttime BP ≥120/70 mm Hg.[10] When home BP monitoring was used to define hypertension (≥135/85 mm Hg), the prevalence of MUCH was found to be 50.8%.[10] The observation that the prevalence of MUCH was doubled

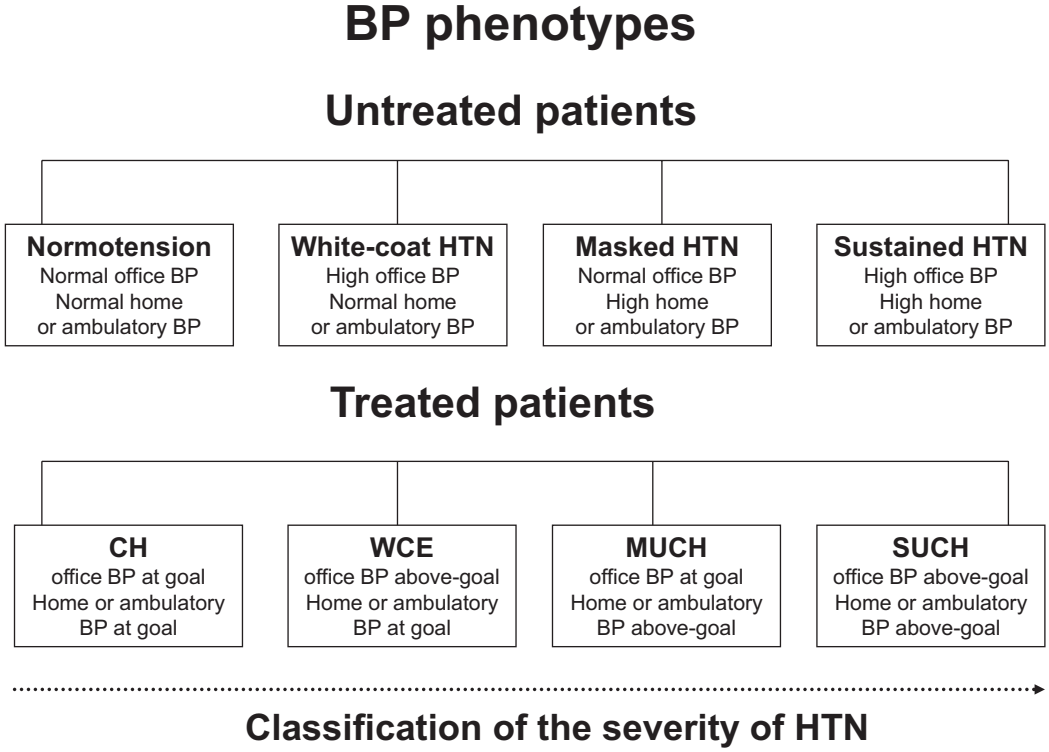

Figure 1. BP phenotypes identified with concomitant use of office and out-of-office BP monitoring in treated and untreated subjects. Abbreviations: BP, blood pressure; CH, controlled hypertension; HTN, hypertension; MUCH, masked uncontrolled hypertension; SUCH, sustained uncontrolled hypertension; WCE, white-coat effect.

when elevations in either daytime or nighttime ambulatory BP were included in the definition is not surprising. Circadian variation of BP is disrupted and isolated nocturnal hypertension is a rather common BP phenotype in the CKD setting.[11] In this cohort, nighttime BP elevation was the exclusive abnormality in nearly half of the patients.[10]

The diagnosis of MUCH is reasonably reproducible. To assess the reproducibility of MUCH diagnosis, office and out-of-office BP measurements were repeated 4 weeks apart in this study. The agreement in detection of MUCH was 75%–78% (*k* coefficient: 0.44–0.51) with the use of ABPM, but only 63% (*k* coefficient: 0.25) with home BP recordings.[10] Research-grade office SBP is a strong determinant of MUCH; the prevalence of MUCH increased with increments in office SBP, being only 2% and 17% in the 90–110 and 110–119 mm Hg subgroups, whereas it was 34% and 66% in those with office SBP of 120–129 and 130–139 mm Hg, respectively. Accordingly, the clinical suspicion of MUCH should be raised when office BP is within the prehypertensive range and confirmation of diagnosis should rely on ABPM. Surprisingly, home SBP was not superior to office SBP in diagnosing MUCH confirmed by ABPM.[10] One reason might be that home BP recordings are often taken without the same attention to detail, such as a 5-minute seated rest before the measurement.

There is an established belief that severity of hypertension goes hand-in-hand with the staging of CKD. Accumulating evidence, however, suggests that proteinuria—not estimated glomerular filtration rate (eGFR)—is the factor that is more closely associated with the severity of hypertension. In a cross-sectional analysis of 232 veterans with CKD aiming to explore the relationship of 17 risk factors for hypertension with SBP, the log of urinary protein-to-creatinine ratio (UPCR) exhibited the strongest association with SBP irrespective of how BP was measured—routine office, standardized office, home, or 24-hour ambulatory.[12] However, the strength of the relationship between UPCR and hypertension was greater when hypertension was assessed with out-of-office compared with office BP recordings. In contrast, eGFR was not an independent determinant of SBP by any technique.[12] A subsequent analysis of 336 veterans with or without CKD revealed a graded relationship of proteinuria and eGFR with mean level of 24-hour ambulatory SBP.[13] However, when both factors were inserted conjointly in the same regression model, it was proteinuria—not eGFR—the factor that remained an independent determinant of severity of hypertension. Furthermore, compared with the stage of CKD, increments in proteinuria had a more profound impact on disruption of circadian variation and the mean level of 24-hour ambulatory SBP.[13]

Among patients with CKD, a graded increment in left ventricular mass index, aortic pulse wave velocity and log of UPCR is seen with increasing severity of hypertension—from CH, MUCH, to SUCH. Whereas the association of left ventricular mass index and pulse wave velocity with BP classification status disappeared after adjustment for age, sex, race, other cardiovascular risk factors, and their treatment, the association of proteinuria with the severity of hypertension persisted.[14] If this association is causal, then renal mechanisms rather than cardiovascular target-organ damage might be more important mediators of MUCH or SUCH.

Prospective observational studies showed that among patients with CKD, increments in 24-hour, daytime, and nighttime ambulatory BP are strongly associated with higher risk of adverse cardiovascular and kidney outcomes; in contrast, office BP measurements alone are not prognostically informative.[15–17] Classification of the severity of hypertension with concomitant assessment of office and ambulatory BP facilitates the stratification of cardiorenal risk. As an example, in a prospective cohort study, 489 hypertensive CKD patients were classified into 4 phenotypes according to the achievement of office (<140/90 mm Hg) and ambulatory (daytime <135/85 and nighttime <120/70 mm Hg) BP control.[18] Over a median follow-up of 5.2 years, compared with those with CH, the risk of cardiovascular morbidity and mortality was not increased in those with WCE [hazard ratio (HR): 1.55; 95% confidence interval (CI): 0.75–3.19], but increased in those with MUCH (HR: 3.17; 95% CI: 1.50–6.69), and SUCH (HR: 2.83; 95% CI: 1.50–5.34).[18] Using CH as reference category, the risk for either end-stage kidney disease (ESKD) or death was not increased in WCE (HR: 1.24; 95% CI: 0.67–2.27), but increased in MUCH (HR: 3.59; 95% CI: 2.05–6.27) and SUCH (HR: 2.96; 95% CI: 1.83–4.78).[18] These associations persisted even after adjustment for several risk factors. Therefore, whereas WCE reflects a low-risk phenotype, the cardiorenal risk associated with MUCH is similar or even surpasses the risk of SUCH.

RESISTANT/REFRACTORY HYPERTENSION

Resistant hypertension is defined as uncontrolled BP despite the concurrent treatment with 3 antihypertensive drug classes, inclusive of a long-acting calcium channel blocker, a blocker of the renin–angiotensin–system and a diuretic, each one administered at maximum or maximally tolerated doses.[19] Patients whose BP is controlled with ≥4 antihypertensive medications are also classified as having resistant hypertension.[19]

Compared with the general population, the burden of resistant hypertension is 2- to 3-fold higher among patients with CKD.[20] In a 2019 meta-analysis of 91 studies incorporating data from a pooled sample of 3,207,901 drug-treated hypertensives, the prevalence of apparent-treatment resistant hypertension (aTRH) in the general population was estimated to be 14.7% (95% CI: 13.1%–16.3%).[21] In contrast, among patients with CKD, the prevalence of aTRH was 28.8% (95% CI: 17.5%–41.7%).[21] The prevalence of aTRH increases both with decreased eGFR and raised proteinuria. Among 10,700 drug-treated hypertensives participating in the Reasons for Geographic and Racial Differences in Stroke (REGARDS) study,[22] the prevalence of aTRH was 15.8% in the eGFR stratum of ≥60 ml/min/1.73 m^2, 24.9% in the eGFR stratum of 45–59 ml/min/1.73 m^2, and 33.4% in those with eGFR <45 ml/min/1.73 m^2. A graded increment in the prevalence of aTRH was also seen with increasing severity of proteinuria: 12.1%, 20.8%, 27.7%, and 48.3% for patients with UPCR of <10, 10–30, 30–300, and ≥300 mg/g, respectively.[22] Over a median follow-up of 6.4 years, compared with patients without aTRH at baseline, those with aTRH had 6.32-fold higher likelihood for developing ESKD (HR: 6.32; 95% CI: 4.30–9.30).[23]

Pseudoresistant hypertension is identified in patients who fulfill the above criteria of resistant hypertension, but actually have WCE confirmed by home or ABPM, or have an identifiable cause of uncontrolled BP, such as antihypertensive medication nonadherence.[20] Both the 2017 AHA/ACC and the 2018 ESH/ESC guidelines mandate the exclusion of common causes of pseudoresistance before classifying a patient as having resistant hypertension.[1,2] The prevalence and prognostic significance of true-resistant hypertension was explored in a prospective cohort study of 436 hypertensive CKD patients under nephrology care in Italy.[24] Using a threshold of 125/75 mm Hg for 24-hour ambulatory BP in conjunction with the absence or presence of resistant hypertension (defined as office BP ≥130/80 mm Hg despite adherence to ≥3 antihypertensives or treatment with ≥4 antihypertensives regardless of office BP), participants were classified into the following phenotypes: 27.1% had CH, 7.1% had WCE with resistant hypertension, 42.9% had SUCH without resistant hypertension, whereas the prevalence of true-resistant hypertension was 22.9%.[24] Compared with CH, the risk for fatal or nonfatal cardiovascular events was not increased in WCE (HR: 1.24; 95% CI: 0.55–2.78) or even SUCH (HR: 1.11; 95% CI: 0.67–1.84), but increased in those with true-resistant hypertension (HR: 1.98; 95% CI: 1.14–3.43).[24] Using those with CH as reference category, the risk for ESKD or death was not increased in WCE (HR: 1.18; 95% CI: 0.45–3.13), but increased in SUCH (HR: 2.14; 95% CI: 1.35–3.40) or true-resistant hypertension (HR: 2.66; 95% CI: 1.62–4.37).[24] Once again, ABPM enabled better stratification of cardiorenal risk, since WCE reflected a low-risk phenotype, whereas true-resistant hypertension was associated with the greatest cardiorenal risk.

Refractory hypertension represents a rare, but severe phenotype of complete antihypertensive treatment failure defined in population-based studies as above-goal BP when on ≥5 antihypertensive medications, inclusive of a diuretic.[25,26] The definition of refractory hypertension is not uniform, but the 2017 AHA/ACC guideline defines refractory hypertension as failure to control BP despite the administration of ≥5 antihypertensive medications of different classes, including a long-acting thiazide-like diuretic, such as chlorothalidone, and a mineralocorticoid receptor antagonist, such as spironolactone.[1] The prevalence and clinical correlates of refractory hypertension were assessed across 8 cycles of the National Health and Nutrition Examination Surveys (NHANES) during 1999–2014.[27] Among drug-treated hypertensives, refractory hypertension was detected in only 0.6% (95% CI: 0.5%–0.7%). Among patients with aTRH, the prevalence of refractory hypertension was 6.2% (95% CI: 5.1%–7.6%).[27] People with refractory hypertension are more likely to have diabetes, cardiovascular disease and kidney disease than drug-treated hypertensives with or without aTRH.[27] Whether refractory hypertension is associated with worse long-term clinical outcomes relative to aTRH remains to be elucidated in future studies.

BP TARGETS IN CKD

The optimal levels at which BP should be targeted when treating hypertension in CKD remains an area of controversy.[28–30] Guidelines released over the past decade provided recommendations with disparate BP targets for patients with CKD (Table 2).[1,2,31–33]

Three major trials were conducted specifically in patients with CKD aiming to compare an intensive vs. a standard BP target (Table 3). In Modification of Diet in Renal Disease (MDRD),[34] 840 predominantly nondiabetic patients with GFR of 13–55 ml/min/1.73 m^2 were randomized to a usual-protein or a low-protein diet and to a standard- or an intensive-BP target (mean BP ≤107 vs. ≤92 mm Hg) in a 2 × 2 factorial design. The rate of decline in GFR over a mean follow-up of 2.2 years did not differ between standard- and intensive-BP arms.[34] The African American Study of Kidney Disease and Hypertension (AASK) followed a 3 × 2 factorial design and randomized 1,094 black patients with hypertensive nephrosclerosis (GFR: 20–65 ml/min/1.73 m^2) to 2 levels of BP control (mean BP: 102–107 vs. ≤92 mm Hg) and to initial therapy with 3 antihypertensive drug classes (metoprolol 50–200 mg/day or ramipril 2.5–10 mg/day or amlodipine 5–10 mg/day).[35] Results were accordant with MDRD; there was no difference in GFR slope from baseline through 4 years of follow-up between intensive-treatment and standard-treatment arms. Intensive BP-lowering had no benefit on the composite outcome of ≥50 decline in

Table 2. Recommended BP targets for patients with diabetic or not-diabetic CKD across guidelines

	ESH/ESC (2018)[2]	AHA/ACG (2017)[1]	JNC8 (2014)[32]	ESH/ESC (2013)[33]	KDIGO (2012)[31]
Nondiabetic CKD					
No albuminuria	130–139/70–79	<130/80	<140/90	<140/90	<140/90
Albuminuria[a]	130–139/70–79	<130/80	<140/90	<140/90	<130/80
Diabetic CKD					
No albuminuria	130–139/70–79	<130/80	<140/90	<140/85	<140/90
Albuminuria[a]	130–139/70–79	<130/80	<140/90	<140/85	<130/80
Class/level of recommendation	1A/IIaB for the SBP/DBP target	IB for the SBP and IC for the DBP target	Expert opinion	IIa/B	IB/IID for the presence/absence of albuminuria

Abbreviations: AHA/ACG, American Heart Association/American College of Cardiology; BP, blood pressure; CKD, chronic kidney disease; DBP, diastolic blood pressure; ESH/ESC, European Society of Hypertension/European Society of Cardiology; JNC8, Eighth Joint National Committee; KDIGO, Kidney Disease Improving Global Outcomes; SBP, systolic blood pressure.

[a]Urinary albumin excretion ≥30 mg per 24 hours or equivalent.

GFR, ESKD, or death (risk reduction: 2%; 95% CI: −22% to 21%).[35] In Ramipril Efficacy in Nephropathy 2 (REIN-2),[36] 338 nondiabetic patients with proteinuric CKD (mean GFR of 34.1 ± 18.1 ml/min/1.73 m^2) were randomly assigned either to conservative (diastolic BP <90 mm Hg) or to intensified (<130/80 mm Hg) BP control. Although the primary outcome was defined as time to ESKD over a follow-up of 36 months, the trial was prematurely terminated due to futility. Over a median follow-up of 19 months, progression to ESKD was similar in the conventional and intensified BP control arms (HR: 1.00; 95% CI: 0.61–1.64).[36]

Taken together, till the completion of their randomized phase, none of these 3 trials showed an overall benefit of intensive BP-lowering on kidney outcomes. In addition, neither of these trials showed a significant improvement in cardiovascular morbidity and mortality with achievement of a tighter BP control. Another issue is the exclusion of diabetics that limits the generalizability of the results of these trials to patients with diabetic kidney disease, which comprises the largest segment of CKD and represents the most common cause of ESKD worldwide.[38]

Lower quality evidence from subgroup analyses of these trials suggested that the level of proteinuria at baseline may act as a treatment effect modifier.[39] In MDRD, there was a benefit of intensive BP-lowering on GFR slope that was greater in those with proteinuria >3 g/day, moderate in those with proteinuria 1–3 g/day and totally absent in those with proteinuria <1 g/day.[34] After the completion of the randomized phase of AASK, patients were followed in a post-trial observational cohort phase with an extended follow-up ranging from 8.8 to 12.2 years.[40] In overall analysis of both trial and cohort phases, the risk for the composite outcome of doubling of serum creatinine, ESKD or death did not differ between patients initially randomized to an intensive- vs. a standard-BP target (HR: 0.91; 95% CI: 0.77–1.08).[40] However, there was a significant interaction between the level of proteinuria at baseline and BP-treatment arm for the composite kidney outcome. In the subgroup of baseline UPCR of ≤0.22, intensive BP-lowering did not improve the composite kidney outcome (HR: 1.18; 95% CI: 0.93–1.50). Among patients with baseline UPCR >0.22, initial assignment to the intensive-BP arm was associated with 27% reduction in the composite kidney outcome (HR: 0.73; 95% CI: 0.58–0.93).[40] A long-term renoprotective benefit of intensive BP-lowering was also supported by a *post hoc* analysis of 840 MDRD participants with an extended follow-up of 10.7 years after randomization.[41] In overall analysis of both trial and cohort phases, initial randomization to the intensive-treatment arm was associated with 32% reduction in the risk of kidney failure (HR: 0.68; 95% CI: 0.57–0.82) and with 23% reduction in the composite outcome of kidney failure or death (HR: 0.77; 95% CI: 0.65–0.91).[41]

Based on the above data, the 2012 Kidney Disease Improving Global Outcomes (KDIGO) guideline differentiated the BP targets according to presence of albuminuria, recommending a more intensive goal of <130/80 mm Hg for patients with CKD and urinary albumin excretion rate of ≥30 mg/day or equivalent.[31] In contrast, the 2013 ESH/ESC guideline and eighth report of the Joint National Committee (JNC8) recommended a uniform BP target of <140/90 mm Hg regardless of the level of albuminuria.[32,33] On a closer examination, all guidelines released during 2012–2014 recognized the lack of high-quality evidence to prove that intensive BP-lowering is an effective strategy that saves lives, saves kidneys, or lowers the risk of adverse cardiovascular events. Even in the 2012 KDIGO guideline, the class of the recommendation for a lower BP goal in those with proteinuric CKD was graded as level 2 and the quality of evidence to support this guidance was rated as level D.[31] In fact, the BP goal of <130/80 mm Hg was only a suggestion based on low-quality evidence from exploratory subgroup analyses and post-trial extended follow-up observational studies that cannot demonstrate direct cause-and-effect associations.[42,43]

The effect of intensive BP-lowering on cardiovascular outcomes, all-cause mortality, and progression of CKD was

Table 3. Main randomized controlled trials comparing an intensive vs. a standardized BP target in patients with CKD

Trial	Year	Population	*N*	BP targets	Follow-up	Effect on kidney outcome
MDRD[34]	1994	Nondiabetic patients with GFR of 13–55 ml/min/1.73 m^2	844	Mean BP: ≤92 vs. ≤107 mm Hg	2.2 years (mean)	No difference between arms in the risk of ESKD or death (RR: 0.85; 95% CI: 0.60–1.22).
AASK[35]	2002	African-Americans with hypertensive CKD and GFR of 20–65 ml/min/1.73 m^2	1,094	Mean BP: <92 vs. 102–107 mm Hg	3–6.4 years	Compared with standard-treatment arm, intensive BP-lowering did not reduce the risk of >50 decline in GFR, ESKD or death (risk reduction: 2%; 95% CI: −22% to 21%).
REIN-2[36]	2005	Nondiabetic CKD patients with proteinuria >1 g/day	338	<130/80 vs. diastolic <90 mm Hg	19 months (median)	No difference between arms in the risk of progression to ESKD (HR: 1.00; 95% CI: 0.61–1.64).
SPRINT[37] (CKD subgroup)	2017	Nondiabetic patients at high cardiovascular risk with eGFR 20–60 ml/min/1.73 m^2	2,646	Systolic BP <120 vs. <140 mm Hg	3.3 years (median)	No difference between arms in the composite outcome of ≥50% decline in eGFR or ESKD (HR: 0.90; 95% CI: 0.44–1.83).

Abbreviations: AASK, African American Study of Kidney Disease and Hypertension; BP, blood pressure; CI, confidence interval; CKD, chronic kidney disease; ESKD, end-stage kidney disease; GFR, glomerular filtration rate; HR, hazard ratio; MDRD, Modification of Diet in Renal Disease; REIN-2, Ramipril Efficacy in Nephropathy 2; RR, relative risk; SPRINT, Systolic Blood Pressure Intervention Trial.

explored in a predefined subgroup analysis of 2,646 SPRINT participants with eGFR of 20–60 ml/min/1.73 m^2 at baseline.[37] Over a median follow-up of 3.3 years, compared with a standard SBP target of <140 mm Hg, intensive SBP reduction to levels <120 mm Hg resulted in a 19% reduction in the occurrence of the primary composite cardiovascular outcome (HR: 0.81; 95% CI: 0.63–1.05) and in 28% reduction in the risk of all-cause mortality (HR: 0.72; 95% CI: 0.53–0.99).[37] Treatment effects of intensive SBP reduction were not modified by the CKD status of participants at baseline (*P* values for interactions: ≥0.30). Despite the improvement in cardiovascular events and all-cause mortality, intensive BP-lowering had no benefit on progression of CKD. However, kidney failure endpoints were few. The prespecified composite outcome of >50% decline in eGFR from baseline or ESKD occurred in 15 patients in the intensive-treatment arm vs. 16 patients in the standard-treatment arm (HR: 0.90; 95% CI: 0.44–1.83).[37]

These results were interpreted as a proof of the cardioprotective benefit of intensive BP-lowering in CKD, a benefit that was not counteracted by excess risk for acceleration of eGFR decline. Based largely on the results of SPRINT,[3] the 2017 AHA/ACC guideline reappraised the definition of hypertension and recommended a tighter BP target of <130/80 mm Hg for the majority of adults with a high cardiovascular risk profile, inclusive of patients with CKD.[1] It has to be noted, however, that 1 size may not fit all patients with CKD. The results of SPRINT may not be generalizable to subgroups of patients who were originally excluded from this trial (i.e., patients with diabetic kidney disease, stage 4+ CKD or those with proteinuria >1 g/day).[37] The benefit/risk ratio of intensive BP-lowering in these subgroups remains uncertain.

Another concern is the algebraic manipulation of the intensive SBP target that was implemented in SPRINT. Taking into consideration that intensification of antihypertensive therapy in this trial was guided by a research-grade office BP measurement methodology, the 2017 AHA/ACC guideline added 10 mm Hg to the intensive SBP target of <120 mm Hg that was applied in SPRINT.[1] The 2018 ESH/ESC guideline followed an even more conservative approach, recommending that among patients with CKD, SBP should be targeted at a range of 130–139 mm Hg.[2] However, a higher or a lower algebraic adjustment for the mean difference may still be an inadequate approach to counteract the large variability among patients between research-grade and routine office BP recordings.[44] Diagnostic-test studies showed that the research-grade office SBP underestimates routine office SBP on average by −12.7 mm Hg, but the 95% limits of agreement between these measurements are wide and range from 46.1 mm Hg lower up to 20.7 mm Hg higher.[5] Accordingly, implementation of intensive BP targets in daily clinical practice may be problematic, if assessment and management of hypertension is based on routine office BP measurements. Standardization of the BP measurement methodology in the office is essential to implement SPRINT findings into practice. Whereas identification of white-coat and masked hypertension with the wider use of 24-hour ABPM might be another important step to improve BP control and clinical outcomes when managing hypertension among patients with CKD, getting the BP measurement right in the clinic is the essential first step. The SPRINT trial targeted SBP to levels <120 mm Hg in the intensive arm. If BP is measured the way it was in SPRINT, we argue that the SBP goal at least among patients with characteristics similar to that of patients who participated in SPRINT should be <120 mm Hg.

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