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Blood Pressure Targets and Kidney and Cardiovascular Disease: Same Data but Discordant Guidelines

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Abstract

Purpose of Review: Hypertension is highly prevalent in the United States and a major risk factor for the development of cardiovascular disease. Hypertension is common in chronic kidney disease (CKD), and likely contributes to the association between CKD and cardiovascular disease. The ideal systolic blood pressure to reduce cardiovascular disease risk in individuals with CKD is controversial.

Recent Findings: Several societies have released guidelines on the treatment of hypertension in the past year, each differing in important aspects, including blood pressure targets. The release of new guidelines was largely spurred by the results of SPRINT, which suggested mortality benefit with more intensive blood pressure targets. Recent post-hoc analyses of a subgroup of ACCORD-BP participants suggest a benefit with tighter blood pressure control. However, another post-hoc analysis of ACCORD-BP participants showed worse kidney outcomes with tighter blood pressure control.

Summary: Lower target blood pressure is associated with lower mortality in CKD although longer term benefits with regards to kidney function remain unclear. Within this framework, treatment of hypertension should be tailored to each individual patient, accounting for cardiovascular disease risk, medication tolerance, and individual patient goals.

Keywords

hypertension; blood pressure; chronic kidney disease; cardiovascular disease; Systolic Blood Pressure Intervention Trial

1. Introduction

Hypertension affects 65% of people in the United States age 60 and over. Hypertension is perhaps the most important risk factor for development of cardiovascular disease (CVD), the leading cause of death in the United States. Mortality attributable to hypertension is on the rise, increasing 10.5% between 2005 and 2015 (1, 2). Hypertension is also the second leading cause of chronic kidney disease (CKD), and CKD itself, as manifest by either low glomerular filtration rate (GFR) or albuminuria, is a risk factor for cardiovascular disease(3, 4).

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Treating hypertension may both slow progression of CKD and decrease the risk of having a major cardiovascular event; accordingly, hypertension is considered a modifiable risk factor for both of these conditions. However, the optimal target blood pressure to reduce the risk of kidney disease and cardiovascular disease while not increasing the risk of adverse events, including acute kidney injury, is currently debated both in the general population and in individuals with CKD. In fact, several discordant guidelines from various organizations have been released recently, each recommending different blood pressure goals despite reviewing the same body of evidence in the literature. As clinicians, which set of guidelines should we follow? As in other populations, potential benefits of blood pressure lowering in individuals with CKD must be weighed against potential harms, including a likely greater risk of acute kidney injury, medication side-effects and burden.

This article reviews the current guidelines on blood pressure targets and blood pressure management, examining in detail key differences among these guidelines, including items specifically related to care of individuals with CKD, placing these guidelines and the current evidence into the clinical context of decision-making for individuals with CKD.

2. Current Guidelines

In 2014, the workgroup commissioned for the 8th Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 8) released an updated report on blood pressure guidelines (5). In 2003, JNC 7 had recommended treatment targets of <140/90 mm Hg in the general population and of <130/80 mm Hg in those with CKD or diabetes (6). In contrast, JNC 8 largely liberalized these goals, recommending to treat hypertension to a goal blood pressure <140/90 mm Hg in those under the age of 60 or with CKD and <150/90 mm Hg in those over the age of 60. Critically, at the time of this recommendation, the JNC 8 workgroup concluded that there was insufficient evidence to support the <140 mm Hg goal systolic pressure in older persons, while noting that future data could support this lower threshold.

The publication of JNC8 was met with considerable controversy, including a dissenting opinion authored by some workgroup members who suggested retaining the <140/90 mm Hg target in older adults with hypertension. Critically the debate centered around whether systolic BP should be below 150 mm Hg versus below 140 mm Hg. The idea of an intensive systolic BP target of below 120 mm Hg was unsupported at the time, particularly following the reporting of null results from the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial (7).

The early termination and the release of positive results from the Systolic Pressure Intervention (SPRINT) trial shook the existing paradigm, leading to re-examination of existing data in the context of the benefit seen in SPRINT with targeting an intensive systolic BP goal of <120 mm Hg as compared to a standard target systolic BP of <140 mm Hg (8). Based on the results of SPRINT and several other blood pressure trials, multiple societies updated guidelines for the treatment of hypertension, including the American College of Physicians and American Academy of Family Physicians (ACP/AAFP), the European Society of Cardiology/European Society of Hypertension (ESC/ESH), and the American

Heart Association/American College of Cardiology (AHA/ACC)(9–11). Although all three of these guidelines are based on the same body of data, they reach different conclusions.

All three guidelines focus on cardiovascular disease risk stratification. The ACP/AAFP guidelines, which focus exclusively on adults age 60 and older, define increased cardiovascular risk as including individuals with known cardiovascular disease, diabetes, older people with eGFR <45 ml/min/1.73m^2, metabolic syndrome, and older age. The AHA/ACC guidelines recommend using their pooled cohort equations, which accounts for age, sex, race, smoking status, diabetes, blood pressure, and cholesterol, to assess 10 year cardiovascular risk. The ESC/ESH guidelines assign high and very high cardiovascular risk based on CVD history, diabetes, eGFR below 60 mL/min/173m^2, 10 year CVD risk using the Systematic COronary Risk Evaluation (SCORE) system incorporating systolic BP, total cholesterol, age, smoking status, and sex ≥5%, and hypertensive LVH. The AHA/ACC and ESC/ESH guidelines also provide specific treatment goals in the setting of specific comorbid conditions like CKD, diabetes, CAD, and stroke in defining treatment goals. In contrast, although the ACP/AAFP guidelines make recommendations with regard to stroke, they state that evidence is insufficient to make recommendations for other specific chronic conditions. It is worth mentioning that all of these guidelines consider patients with CKD at high risk for CVD. An additional consideration stressed by all guidelines is that blood pressure be measured correctly; this is extensively detailed in the ACC/AHA guideline.

The ACP/AAFP guideline was released first, and specifically addresses systolic blood pressure in patients 60 years old and older; notably, this guideline states that there is insufficient evidence to address diastolic hypertension in the absence of systolic hypertension (Table 1)(9). Mirroring JNC 8, the ACP/AAFP guideline recommends a more liberal goal systolic blood pressure of <150 mm Hg for most older adults, while targeting <140 mm Hg for those at high risk for CVD or who have a history of stroke or TIA. Though they make no specific recommendations for patients with CKD, these patients would still be treated to a goal systolic BP <140 mm Hg reflecting their high CVD risk.

The AHA/ACC followed with updated guidelines in late 2017, recommending a more stringent goal blood pressure of <130/80 mm Hg for nearly all patients and reclassifying hypertension as anything above this threshold (10). Finally and most recently, the ESC/ESH released guidelines in 2018 recommending to treat to a goal blood pressure of <130/80 mm Hg if tolerated while explicitly recommending against treating to a systolic blood pressure of <120 mm Hg (11). They also recommend a less intensive goal blood pressure of 130–140/80 mm Hg in patients over the age of 65. Of note, in response to the AHA/ACC guidelines, the ACP/AAFP reiterated ongoing support of their own guidelines.

3. Key Data Supporting Hypertension Guidelines

Why do these guidelines differ so substantially and how should clinicians respond? To answer these questions, it is helpful to review recent trials that have influenced these guidelines. At the time of publication of JNC 8, only the ACCORD trial examined more versus less intensive blood pressure targets in the treatment of hypertension and met criteria for inclusion in the guideline. The ACCORD blood pressure trial, which was a subset of the

larger ACCORD trial, recruited 4733 individuals with type 2 diabetes and without significant CKD, randomizing them in a 2×2 factorial design to a goal systolic BP <120 vs goal systolic BP <140 mm Hg and to intensive versus standard glycemic control. The primary outcome was a composite of nonfatal myocardial infarction (MI), nonfatal stroke, or cardiovascular death. Over mean follow-up of 4.7 years, ACCORD showed no difference in cardiovascular events or death between individuals randomized to a standard versus intensive systolic BP target.

For the CKD population, based on the available evidence at the time, most notably the MDRD, AASK, and REIN-2 trials, the authors of the JNC 8 statement did not feel that there was sufficient evidence supporting a goal blood pressure of <130/80 mm Hg vs <140/90 mm Hg for either slowing the progression of kidney disease or reducing CVD risk. Moreover, among those with CKD, JNC 8 recommended targeting a goal blood pressure to <140/90 mm Hg only in individuals less than 70 years old, defaulting to <150/90 mm Hg in older CKD patients, citing insufficient enrollment of older individuals with CKD in clinical trials.

After the publication of the JNC 8 guidelines, two important RCTs were published that greatly influenced subsequent guidelines. These are the Systolic Blood Pressure Intervention (SPRINT) trial and the Heart Outcomes Prevention Evaluation-3 (HOPE-3) trial. SPRINT randomized non-diabetic patients over the age of 50 with hypertension and increased cardiovascular risk, prior CVD, eGFR between 20 and 60 ml/min/1.73m^2 and/or age 70+ to either a systolic blood pressure <120 mm Hg (intensive group) or <140 mmHg (standard group). The primary endpoint was a composite of MI, acute coronary syndrome, stroke, acute heart failure, or death from cardiovascular causes. The study was stopped early due to a lower risk of the composite outcome in the intensive blood pressure group. The main drivers of this composite outcome were heart failure and death from cardiovascular causes, although the risk of all cause death was also significantly lower among those randomized to the intensive blood pressure target.

Similar results were seen in the 2646 SPRINT participants with baseline eGFR <60 ml/min/1.73m^2 , although this did not achieve statistical significance (HR 0.81, CI 0.63–1.05)(12). Notably, elderly participants with CKD randomized to the intensive BP group had a lower risk of both the primary composite endpoint and mortality as compared to the standard BP group. Additionally, within the CKD cohort, there was no difference in incidence of ESRD or decrease in eGFR ≥50% from baseline, despite a greater initial decline in kidney function in the first 6 months of treatment.

In an attempt to distinguish whether the initial decline in eGFR reflected hemodynamic changes or was a true loss in kidney function, SPRINT investigators measured urinary biomarkers of both kidney damage and repair (13). Baseline values for all biomarkers were similar between the intensive and standard groups, and, despite the greater initial decline in eGFR creatinine in the intensive group, biomarkers of injury were not higher in the intensive group; in fact two of the biomarkers of injury were lower at one year in the intensive group than in the standard group. These data support the argument that the differential decline in kidney function initially experienced by the intensive group is hemodynamic.

While there was no difference in incident albuminuria between the two groups, the intensive group had a lower mean urine albumin-to-creatinine ratio during follow-up. Of concern, the intensive group did have more instances of acute kidney injury (AKI), hyperkalemia, and hypokalemia, although there was no significant difference in other adverse events such as hypotension, syncope, or falls. AKI was typically mild and resolved in most individuals(14). It is important to note that participants were only followed for 3.25 years on average before the study was discontinued; accordingly there may have been insufficient time to appreciate treatment effects with regards to long-term kidney function. Also, the CKD cohort in SPRINT had an average eGFR of 48 ml/min/1.73m^2, largely consistent with CKD stage 3; it is unknown if similar findings would be seen in more advanced CKD or in those with greater levels of albuminuria.

HOPE-3 also used a 2×2 factorial design trial, randomizing individuals with intermediate risk of cardiovascular disease to receive either placebo or candesartan 16 mg plus hydrochlorothiazide 12.5 mg as well as to receive either statin or placebo (15). The two primary endpoints were a composite of death from CVD, nonfatal MI, and nonfatal stroke and a composite of the first endpoint plus resuscitated cardiac arrest, heart failure, or revascularization. Mean blood pressure at baseline was 138.1/81.9 mm Hg. After randomization, there was a mean decrease of 10 mm Hg in systolic blood pressure in the active treatment group and 4 mm Hg in the placebo group that was maintained throughout the median follow-up of 5.9 years. Among participants with a baseline blood pressure >143.5 mm Hg, likely representing the higher cardiovascular risk participants in HOPE-3, those in the active treatment group had a lower incidence of the two primary endpoints suggesting a benefit in lowering the systolic blood pressure in patients who have a higher baseline blood pressure. In contrast, those with lower blood pressure at baseline saw no difference in the two co-primary endpoints between the candesartan/HCTZ group and the placebo group.

SPRINT showed a survival benefit by lowering systolic blood pressure to lower targets than those recommended in the JNC-8 guidelines in those with high CVD risk, and HOPE-3 showed a survival benefit in those with intermediate CVD risk and higher baseline blood pressure. Focusing on these trials, the AHA/ACC and ESC/ESH guideline recommendations of lower blood pressure targets seem reasonable in those at higher risk for CVD.

4. Other Data Informing Blood Pressure Targets in CKD

While several studies that evaluate data from AASK, MDRD, and ACCORD support lower blood pressure targets in CKD, these are post hoc analyses, often focusing on subgroups, and one should be cautious in interpreting these results due to greater risk of bias. However, useful and important information can be gained from these studies.

A recent post hoc analysis of the ACCORD trial focused specifically on the subgroup of participants randomized to the standard glycemic group, citing a higher risk of mortality in the intensive glycemia arm of the trial. In this subgroup, in contrast to the larger ACCORD blood pressure trial population, individuals randomized to the intensive BP arm had fewer CV events and lower CV mortality (HR 0.77, CI 0.63–0.95)(16). Of note, the glycemia

intervention in ACCORD was stopped early due to increased mortality in the intensive glycemia arm while the blood pressure portion of the trial continued on for the full follow-up period (17). The authors posit an interaction, such that intensive blood pressure lowering in the setting of intensive glycemic control resulted in high risk, thereby masking the benefit that would have been appreciated solely with targeting an intensive systolic blood pressure goal.

Another recent post hoc analysis of the ACCORD data examined kidney outcomes comparing intensive vs standard BP control (18). Participants were analyzed from both the ACCORD and ACCORD follow on studies and followed for a mean of 7.7 years. The primary outcome was a composite kidney outcome that was comprised of incident severely elevated urine albumin to creatinine ratio (UACR ≥300 mg/g), creatinine doubling, self-reported need for dialysis, and all-cause mortality. Secondary outcomes were the individual components of the primary outcome. The authors found a significantly higher incidence of the primary composite kidney outcome in the intensive BP target group that was seen both during the initial follow up period of ACCORD (HR 1.12, CI 1.00–1.26) and also during the post-trial follow-up period (HR 1.41, CI 1.11–1.79), with one third of participants experiencing the primary outcome. These results were driven by doubling of serum creatinine, and there was no interaction between glycemia assignment and blood pressure assignment with regards to blood pressure control or kidney outcomes. These data suggest there may be a trade-off between cardiovascular disease and kidney outcomes.

5. Summary

The management of high blood pressure has changed vastly in the past few years with the pendulum swinging initially to more liberal blood pressure targets with the 2014 publication of JNC8 and more recently swinging to more intensive blood pressure targets following the publication of SPRINT. Importantly, an update to the Kidney Disease: Improving Global Outcomes (KDIGO) blood pressure guideline and a Kidney Disease Outcomes Quality Initiative (KDOQI) commentary on the AHA/ACC guideline are both anticipated in 2019. Reviewing the current evidence, there seems to be a reduction in cardiovascular events and mortality with more intensive blood pressure control and this may be accompanied by kidney benefits, although longer term data concerning kidney effects, particularly in individuals with diabetes, are lacking. In the meantime, it seems that the best approach may be generally treating blood pressure to a goal <130/80 mm Hg in individuals with CKD, as tolerated, while accounting for other comorbid conditions, medication tolerance and patient goals that may impact individualized blood pressure targets.

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Key Points

- Current hypertension guidelines provide varying blood pressure targets, particularly for older adults
- More intensive blood pressure targets are associated with lower risk of cardiovascular disease events and mortality in individuals without diabetes, while a recently published secondary analysis of ACCORD data focusing on the subgroup randomized to normoglycemia suggests this may also be true in diabetics.
- In SPRINT, systolic blood pressure <120 mm Hg was associated with more AKI events, although these were mild and most often accompanied by full or partial recovery.
- Data on longer term kidney outcomes with regard to blood pressure targets are lacking, with the greatest uncertainty in individuals with diabetes.

Table 1.

Overview of recent blood pressure guidelines

Guideline	Year	HTN Definition	When to treat medically	Goal BP General Population	Goal BP CKD
ESC/ESH(11)	2018	***Grade 1*** 140–159	Grade 2 or 3, or Grade 1 PLUS high risk for CVD	Initial <140/90; if tolerated <130/80. Do not target <120. Age >65 target 130–140/80.	<140/90 and towards 130/80
		Grade 2 160–179			
		Grade 3 ≥180			
ACC/AHA(10)	2017	***Elevated*** 120–129/<80	Stage 2, or Stage 1 PLUS high risk for CVD	<130/80 if treating medically regardless of age or comorbidity	<130/80
		Stage 1 130–139/80–89			
		Stage 2 ≥140/90			
ACP/AAFP(9)	2017	Not explicitly defined	Systolic BP consistently > 150	Systolic BP <150; if high risk for CVD or history of stroke then systolic BP <140	Systolic BP <140
JNC 8(5)	2014	Not explicitly defined	>150/90 if age >60, >140/90 if <60, CKD, or diabetes	<150/90 if age >60, <140/90 if age <60, <140/90 age>19 if diabetes	<140/90 age 18–70
KDIGO(19)	2012	Not explicitly defined	>140/90 if no albuminuria, >130/80 if albuminuria or history of kidney transplant	Not applicable	<140/90 if non-diabetic or diabetic without albuminuria
					<130/80 if non-diabetic or diabetic with albuminuria, kidney transplant
					Tailor treatment in elderly

All blood pressure values are mm Hg. ESC/ESH, European Society of Cardiology/European Society of Hypertension; ACC/AHA, American College of Cardiology/American Heart Association; ACP/AAFP, American College of Physicians/American Association of Family Physicians; JNC, Joint National Commission; KDIGO, Kidney Disease Improving Global Outcomes; CVD, cardiovascular disease; CKD, chronic kidney disease

Table 2.

Major recent studies investigating blood pressure targets.

Study	N	CV Risk	Years of follow-up	BP Target	Key Results
ACCORD(7)	4733	High	4.7	SBP <120 vs. SBP >140	• No significant difference in CVDevents overall • Significantly less CV events/death in intensive BP-standard glycemia arm
SPRINT, Main Outcomes (8)	9361	High	3.26	SBP <120 vs. SBP >140	• Significantly less CV events and CV deaths in intensive arm
SPRINT, AKI Outcomes (14)	9361	High	3.26	SBP <120 vs. SBP >140	• AKI more frequent in intensive arm • Most AKI were stage 1 • Most had complete or partial recovery
SPRINT, CKD Cohort (12)	2646	High	3.3	SBP <120 vs. SBP >140	• Less CV events/death in intensive arm in those ≥75 • No difference in incident ESRD or decline in kidney function ≥50% • NNT at 4 years is 66
SPRINT, Tubular injury markers(13)	978	High	4	SBP <120 vs. SBP >140	• Biomarkers of injury were not higher in intensive BP group
HOPE-3(15)	12705	Intermediate	5.6	Candesartan + HCTZ vs. placebo	• Patients with higher baseline blood pressure had reduction in CV events

ACCORD, Action to Control Cardiovascular Risk in Diabetes; SPRINT, Systolic Pressure Intervention Trial; AKI, acute kidney injury; CKD, chronic kidney disease; HOPE-3, Heart Outcomes Prevention Evaluation-3

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