Blood Pressure Goals in Patients with CKD
A Review of Evidence and Guidelines

Alex R. Chang, Meghan Löser, Rakesh Malhotra, and Lawrence J. Appel

Abstract
Hypertension affects the vast majority of patients with CKD and increases the risk of cardiovascular disease, ESKD, and death. Over the past decade, a number of hypertension guidelines have been published with varying recommendations for BP goals in patients with CKD. Most recently, the American College of Cardiology/American Heart Association 2017 hypertension guidelines set a BP goal of <130/80 mm Hg for patients with CKD and others at elevated cardiovascular risk. These guidelines were heavily influenced by the landmark Systolic Blood Pressure Intervention Trial (SPRINT), which documented that an intensive BP goal to a systolic BP <120 mm Hg decreased the risk of cardiovascular disease and mortality in nondiabetic adults at high cardiovascular risk, many of whom had CKD; the intensive BP goal did not retard CKD progression. It is noteworthy that SPRINT measured BP with automated devices (5-minute wait period, average of three readings) often without observers, a technique that potentially results in BP values that are lower than what is typically measured in the office. Still, results from SPRINT along with long-term follow-up data from the Modification of Diet in Renal Disease and the African American Study of Kidney Disease and Hypertension suggest that a BP goal <130/80 mm Hg will reduce mortality in patients with CKD. Unfortunately, data are more limited in patients with diabetes or stage 4–5 CKD. Increased adverse events, including electrolyte abnormalities and decreased eGFR, necessitate careful laboratory monitoring. In conclusion, a BP goal of <130/80 is a reasonable, evidence-based BP goal in patients with CKD. Implementation of this intensive BP target will require increased attention to measuring BP accurately, assessing patient preferences and concurrent medical conditions, and monitoring for adverse effects of therapy.


Introduction
Hypertension increases the risk of atherosclerotic cardiovascular disease, congestive heart failure, and ESKD, and is a leading contributor to morbidity and mortality worldwide (1). According to 2010 data from the National Health and Nutrition Examination Survey, 84% of adults with eGFR<60 ml/min per 1.73 m² had hypertension, yet only 32% had BP controlled <140/90 mm Hg (2). Over the past half century, many pivotal hypertension trials have been published. However, methods for BP measurement and evidence-based guideline development have changed over time, leading to ongoing debate on target BP goals in the general population and special populations such as patients with CKD (3–5). In 2015, the Systolic Blood Pressure Intervention Trial (SPRINT) found that targeting a systolic BP <120 mm Hg reduced the risk of cardiovascular disease and all-cause mortality in patients at elevated risk for cardiovascular disease, 28% of whom had CKD (6). However, SPRINT measured BP with automated devices (5-minute wait period, average of three readings) often unattended by observers, a technique that differs from most routine office BP measurements (7). Here, we review the practice of BP measurement, results of trials that assessed higher versus lower BP goals in patients with CKD, and hypertension treatment guidelines.

Hypertension Guidelines
The definition of hypertension and the thresholds for treatment have been continually refined as new hypertension research accumulates (Figure 1, Supplemental Table 1) (8). In 1977, the first Joint National Committee on Detection, Evaluation, and Treatment of High BP (JNC-I) report recommended antihypertensive medication treatment for patients with diastolic BP ≥105 mm Hg (9). Risk stratification by target organ damage was emphasized in JNC-V (1993) and JNC-VI (1997), with JNC-VI recommending a BP target of <130/85 for patients with nonproteinuric kidney disease and <125/75 mm Hg for proteinuric kidney disease (10,11). JNC-VII (2003) later revised the BP target to <130/80 mm Hg for all patients with CKD, defined as eGFR<60 ml/min per 1.73 m² or albuminuria ≥300 mg/d (3). Guidelines from 2012 to 2014 interpreted evidence differently and published recommendations with disparate BP goals for patients with CKD. In 2012, the Kidney Disease Improving Global Outcomes guidelines recommended...
the <130/80 mm Hg target only for those with albuminuric (albumin-to-creatinine ratio ≥ 30 mg/g) CKD (12), whereas the 2013 European Society of Hypertension/European Society of Cardiology (ESH/ESC) and the report from the panel members appointed to JNC-8 recommended a BP target of <140/90 mm Hg for CKD, regardless of albuminuria (5,13).

In September 2015, SPRINT was halted early because of interim analyses demonstrating that the group assigned to a systolic BP goal <120 mm Hg had a 25% lower risk of cardiovascular disease and 27% lower risk of all-cause mortality than the group assigned to a systolic BP <140 mm Hg (6). Subsequently, the American College of Cardiology/American Heart Association (ACC/AHA) 2017 Hypertension guidelines redefined hypertension as BP ≥ 130/80 mm Hg and recommended antihypertensive treatment to a BP goal of <130/80 mm Hg in patients with CKD and others at increased cardiovascular risk (14). The rationale provided by the ACC/AHA guidelines committee in choosing a systolic BP target of <130 mm Hg rather than <120 mm Hg (the intensive goal in SPRINT), included concerns about applying SPRINT to a broader population and considerations related to unattended, automated BP measurements in SPRINT, which on average might be lower than routine clinic measurements. The recently published 2018 ESH/ESC guidelines recommend a target systolic BP of 130–139 mm Hg and diastolic BP of 70–79 mm Hg for patients with CKD (15).

### BP Measurement Techniques

Given the controversy over BP targets, it is important to briefly discuss BP measurement techniques, a topic that has been recently reviewed by Thomas and Drawz (16).

Methods of measuring BP were primarily developed and refined in the late 1800s and early 1900s, including a 1905 communication by Nicolai Korotkoff describing the auscultatory method (17). By 1925, BP measurements from manual observers using auscultatory devices demonstrated a direct association of systolic and diastolic BP with risk of death in analyses of data from life insurance companies (8). Although many practices continue to use manual auscultatory techniques to measure office BP, their limitations are well known, including digit preference, discrepancies of of office BP with the BpTRU device, which takes an average of five BP readings, taken at 2-minute intervals (18). Multiple of manufacturers have developed automated, oscillometric BP devices, which often include preprogrammed wait times and multiple readings to improve precision (16,19). Validation protocols for oscillometric devices have been developed by organizations such as the Association for the Advancement of Medical Instrumentation and the European Society of Hypertension; it is unclear if separate validation is required for patients with CKD or ESKD who may have increased arterial stiffness (20,21).

#### Comparisons of Different Techniques to Measure Office BP

Few studies have directly compared BP measurement approaches in routine clinical settings. In a cluster-randomized trial of 555 patients with hypertension in 67 clinics in Eastern Canada, clinics were randomized to continue using manual office BP (control) versus unattended automated office BP with the BpTRU device, which takes an initial “test” reading without a wait period, then averages the next five BP readings, taken at 2-minute intervals (19).
Randomization to automated office BP clinics was associated with 5.4 mm Hg lower systolic BP compared with control (manual BP) clinics. Unfortunately, the BpTRU device is no longer available. No similar randomized trials testing the effect of implementation of automated office BP using Omron HEM-907 with manual office BP technique exist, although limited data suggests it would similarly reduce the white-coat effect (22). Because some differences in office BP have been observed when measured at the same visit by different automated devices, clinics should use only one type of automated device (23,24).

Comparisons of Office BP and Ambulatory BP

Besides eliminating the white-coat effect, another advantage of automated office BP over manual BP is that it appears to correlate better with ambulatory BP, which is particularly relevant for patients with CKD, who are at increased risk of elevated nocturnal BP and nondipping status (25,26). In the trial by Myers et al. (19) automated office BP measured by BpTRU only slightly overestimated daytime ambulatory BP (2.3/3.3 mm Hg), whereas manual office BP considerably overestimated daytime ambulatory BP (6.5/4.3 mm Hg). In a meta-analysis of 19 studies with automated office BP measured by BpTRU and ambulatory BP monitoring, mean automated office BP did not differ significantly from daytime ambulatory BP (systolic BP −1.52 mm Hg, 95% confidence interval [95% CI], −3.29 to 0.25 mm Hg; diastolic BP 0.33 mm Hg, 95% CI, −0.97 to 1.64), although there was significant heterogeneity with study-level differences ranging from −9.7 to 9 mm Hg in mean systolic BP and −4 to 6 mm Hg in mean diastolic BP (27).

Similar data are available comparing automated office BP measured by the Omron HEM-907 XL device with ambulatory BP in a SPRINT ancillary study of 897 participants (28). In the standard arm, mean automated office BP (measured by the Omron HEM-907 XL) was 135.5/73.6 mm Hg compared with daytime ambulatory BP of 138.8/78.6 mm Hg. However, in the intensive arm, mean automated office BP was 119.7/65.9 mm Hg compared with daytime ambulatory BP of 126.5/72.0 mm Hg (28). Similarly, in a study of 275 male veterans with CKD and automated office BP (measured with the Omron HEM-907 XL) <140/90 mm Hg, mean automated office BP was 121.7/59.7 compared with daytime ambulatory BP of 129.6/71.5 mm Hg (22). Despite these apparent differences at the lower normotensive range, both automated office BP and ambulatory BP correlate more strongly with left ventricular hypertrophy than routinely measured office BP (22,29).

In summary, use of automated office BP reduces the white-coat effect and correlates better with cardiovascular and kidney risk relative to routinely measured clinic BP. Thus, if lower BP goals are targeted, it may be prudent to use automated office BP devices, although workflow redesign must be carefully considered (30). Increasing adoption of automated office BP devices is occurring in Canada. In a survey of Canadian primary care physicians, 43% reported using automated office BP to screen for hypertension, as recommended by Hypertension Canada guidelines (31,32).

What Is the Evidence for Lower BP Goals in CKD?

Three major BP trials specifically in participants with CKD (Modification of Diet in Renal Disease [MDRD] study, African-American Study of Kidney Disease and Hypertension [AASK], and the Ramipril Efficacy in Nephropathy trial 2 [REIN-2]) have been conducted. Each focused on kidney outcomes as the primary outcome; none were powered to detect differences in cardiovascular outcomes. In a meta-analysis of 18 randomized controlled trials of BP lowering in patients with stage 3–5 CKD, mean systolic BP dropped by 16–132 mm Hg in the more intensive arms and by 8–140 mm Hg in the less intensive arms (33). More intensive BP lowering reduced the risk of death by 14% (odds ratio, 0.86; 95% CI, 0.76 to 0.97). However, conclusions on specific BP goals could not be made because of heterogeneity in study designs. Data from BP trials that have included a large number of patients with CKD are shown in Table 1 (6,33–41).

The first large, randomized, controlled trial to evaluate a lower BP target in CKD was the MDRD study, which randomized 840 adults with non-diabetic CKD to a mean arterial pressure (MAP) of <92 mm Hg (approximately 125/75) or to a standard goal (102–107 mm Hg, approximately 135/85–140/90) (Table 1) (35). The primary outcome was rate of GFR decline. Overall, intensive BP lowering had no significant effect on CKD progression, although the rate of GFR decline varied by baseline proteinuria. Among participants with proteinuria >1 g/d, participants randomized to the intensive arm experienced slower GFR decline than those in the standard BP arm; no benefit with intensive BP lowering was seen in those with proteinuria <1 g/d (42). This interaction was significant in eGFR 25–55 ml/min per 1.73 m² (n = 585) and eGFR 13–24 ml/min per 1.73 m² (n = 255) subgroups. A limitation of the MDRD study is the potential for confounding of BP goal with angiotensin-converting enzyme inhibitor use (51% of intensive arm participants, 32% of standard arm participants). After the MDRD study, the AASK and REIN-2 trials were published in 2002 and 2005, respectively; the primary analyses of these trials found no evidence that intensive BP lowering to goals <130/80 decreased the risk of CKD progression (34,37) (Table 1). It is important to emphasize that all of these trials were very short in duration, with an average of just 1.3–3.8 years of active treatment.

In AASK, 1094 black participants with CKD (mean GFR 46 ml/min per 1.73 m²) attributed to hypertension were randomized to an intensive BP lowering goal (MAP <92 mm Hg) versus standard goal (MAP 102–107 mm Hg) (Table 1). After completion of the main trial, there was a cohort phase to examine long-term effects of intensive BP lowering (43). At the onset of the AASK cohort phase, all participants were switched to ramipril and a BP goal <140/90 mm Hg; the BP goal was later reduced to <130/80 mm Hg in 2004 because of the JNC-7 guidelines. Over long-term follow-up, participants randomized to intensive BP lowering did not have a decreased risk of the primary composite outcome (doubling of creatinine, ESKD, or death; hazard ratio [HR], 0.91; 95% CI: 0.77–1.08). However, there was a significant interaction by baseline proteinuria. Among those with baseline protein-to-creatinine ratio ≥0.22 g/g, randomization to the intensive BP...
Table 1. Kidney, cardiovascular, and mortality outcomes in randomized BP trials with at least 300 patients with CKD

<table>
<thead>
<tr>
<th>Study, Year, BP Method (Ref)</th>
<th>Intervention, Follow-Up Time</th>
<th>Study Population with CKD</th>
<th>Inclusion/Exclusion Criteria</th>
<th>Baseline BP, mm Hg</th>
<th>Achieved Systolic BP Difference, mm Hg</th>
<th>Kidney Outcomes for CKD Subgroup, More versus Less Intensive BP Lowering</th>
<th>CVD or Death Outcomes for CKD Subgroup, More versus Less Intensive BP Lowering</th>
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<tbody>
<tr>
<td><strong>Trials with a subset of participants with CKD</strong></td>
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<td>SHEF, 1991, random zero sphygmomanometer (33,65)</td>
<td>Drug versus placebo, mean 4.5 yr</td>
<td>1735/4766 (75%) with eGFR ≥60</td>
<td>Age ≥60 yr with elevated systolic HTN (systolic BP 160–219, diastolic BP ≥90 mm Hg); Exclusion: major CVD, &quot;established diabetes dyslipidemia&quot;</td>
<td>170/77</td>
<td>142 versus 153</td>
<td>Not reported</td>
<td>All-cause death OR, 0.90 (95% CI: 0.67–1.23)</td>
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<td>Syst-Eur, 1997, method not specified (33,39)</td>
<td>Drug(s) versus placebo, median 2.0 yr</td>
<td>470/4695 (10%) with eGFR ≥60</td>
<td>Age ≥60 yr with isolated systolic HTN and CrCl≥2.0 mg/dl; Exclusion: hypertension, nitrates, CHF, recent stroke/MI, severe CVD or non-CVD</td>
<td>174/86</td>
<td>151 versus 161</td>
<td>Not reported</td>
<td>All-cause death OR, 0.83 (95% CI: 0.47–1.45)</td>
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<td>HOT, 1998, oscillometric visomat OZ (33,62)</td>
<td>Diastolic BP ≥80 versus diastolic BP ≤80 or ≤90 mm Hg, mean 3.8 yr</td>
<td>3619/18,790 (19%) with eGFR ≥60</td>
<td>Age 50–80 yr with HTN-diastolic BP 100–115 mm Hg and CrCl&lt;3 mg/dl</td>
<td>170/105</td>
<td>139 versus 142</td>
<td>Not reported</td>
<td>All-cause death OR, 0.89 (95% CI: 0.70–1.1)</td>
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<td>HSYET, 2008, mercury sphygmomanometer or validated automated devices (33,63)</td>
<td>Drug versus placebo, median 1.8 yr</td>
<td>1604/804 (42%) with eGFR ≥60</td>
<td>Age ≥60 yr with systolic BP ≥160 mm Hg and CrCl&lt;1.7 mg/dl</td>
<td>173/91</td>
<td>143 versus 158</td>
<td>Not reported</td>
<td>All-cause death OR, 0.68 (95% CI: 0.30–0.91)</td>
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<td>JATO-2006, unspecified sphygmomanometer (54)</td>
<td>Systolic BP &lt;140 versus 140–159, mean 2.0 yr</td>
<td>2499/4148 (57%) with eGFR ≥60</td>
<td>Age ≥65–85 yr with systolic BP ≥160 mm Hg and CrCl&lt;1.5 mg/dl</td>
<td>172/89</td>
<td>136 versus 146</td>
<td>Not reported</td>
<td>Doubling of creatinine or ESKD; HR, 0.64 (95% CI: 0.21–1.97)</td>
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<td>ADVANCE, 2010, automated device (Omnicon HEM-705CP) (50)</td>
<td>Drug versus placebo, mean 4.3 yr</td>
<td>4515/11,140 (41%) with CrCl ≥60 stage 1–2, 2035 stage 1–2, 2035 stage 1–2</td>
<td>Age ≥55 yr with T1DM and major CVD or ≥1 CVD risk factor; Exclusion: definite indication for long-term insulin therapy</td>
<td>Stage 1–2 CKD 146/82</td>
<td>Stage 1–2 CKD 138 versus 142</td>
<td>Composite kidney outcome (imminent macroalbuminuria, doubling of creatinine, ESKD, or kidney death)</td>
<td>Stage CKD 1–2 composite CVD HR, 0.87 (95% CI: 0.69–1.12); all-cause death HR, 0.87 (95% CI: 0.67–1.12)</td>
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<td>ACCORD, 2010, automated device (Omnicon HEM-907) (48)</td>
<td>Systolic BP &lt;120 versus systolic BP ≤120 or ≤140, mean 4.7 yr</td>
<td>1726/4733 (65%) with CrCl ≥60 stage 1–2, 401 stage 1–2</td>
<td>Age ≥40 yr with T1DM and CrCl≥1.5 mg/dl; Exclusion: BMI&gt;45 kg/m², other serious illness</td>
<td>142/76</td>
<td>122 versus 134</td>
<td>Not reported</td>
<td>Composite CVD HR, 0.84 (95% CI: 0.67–1.11); all-cause death HR, 0.86 (95% CI: 0.63–1.16)</td>
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<td>SPS3, 2013, automated device (Colin 8000C) (33,60)</td>
<td>Systolic BP &lt;130 versus systolic BP ≥130–140, median 3.6 yr</td>
<td>411/2916 (14%)</td>
<td>Age ≥30 yr with recent lacunar stroke and CrCl≥60; Exclusion: cardiogenic shock, isolateral arterial stenosis ≥50%, evidence of previous cortical stroke, moderate to severe disability</td>
<td>143/78</td>
<td>137 versus 126</td>
<td>Not reported</td>
<td>All-cause death HR, 0.85 (95% CI: 0.47–1.54)</td>
</tr>
<tr>
<td>SPRINT 2015, automated device (Omnicon HEM-907) (48)</td>
<td>Systolic BP &lt;120 versus systolic BP ±120 or ≤140, median 3.3 yr</td>
<td>2646/5061 (25%) with CrCl ≥60</td>
<td>Age ≥50 yr at elevated CVD risk with systolic BP ≥130–140; Exclusion: diabetes, AF, CKD, prior stroke, symptomatic CHF, LVH≥2+</td>
<td>140/78</td>
<td>123 versus 135</td>
<td>50% eGFR decline or ESKD/HR 0.90 (95% CI: 0.78–1.02); 40% GFR decline HR 1.35 (95% CI: 1.01–1.83); 30% eGFR decline HR 2.03 (95% CI: 1.42–2.91)</td>
<td>Composite CVD HR, 0.81 (95% CI: 0.63–1.05); all-cause death HR, 0.72 (95% CI: 0.53–0.99)</td>
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<td><strong>CVD trials (trial phase only)</strong></td>
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<tr>
<td>MDRD, 1994, random zero sphygmomanometer (51)</td>
<td>MAP&lt;90 versus MAP≥107, mean 2.5 yr</td>
<td>840 with predominantly nondiabetic CKD (61.4–2.7 mm Hg for men and Cr≥2.0 mg/dl for women)</td>
<td>Age ≥60 yr with isolated systolic HTN (systolic BP 140–180, mean 2.6 mm Hg); Exclusion: diabetes requiring insulin, class III IV CHF</td>
<td>131/80</td>
<td>126 versus 134</td>
<td>No difference in mean GFR slope overall, but suggested MAP&lt;90 target beneficial for those with proteinuria ≥1 g/d</td>
<td>All-cause death OR, 1.37 (95% CI: 0.68–2.74)</td>
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<tr>
<td>AASK, 2002, random zero sphygmomanometer (54)</td>
<td>MAP ≥92 versus MAP&lt;95 mm Hg, median 3.8 yr</td>
<td>1094 (100%) black adults with CKD attributed to HTN and GFR 20–65</td>
<td>Age 14–70 yr with diabetes requiring insulin, class III IV CHF</td>
<td>151/96</td>
<td>130 versus 141</td>
<td>No difference in mean GFR slope or clinical composite kidney outcome (50% GFR decline, ESKD, or death)</td>
<td>All-cause death OR, 0.87 (95% CI: 0.55–1.38)</td>
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</tbody>
</table>
Table 1. (Continued)

<table>
<thead>
<tr>
<th>Study, Year, BP Method (Ref)</th>
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<tr>
<td>REIN-2, 2005, unspoolled sphygmomanometer (57)</td>
<td>Diastolic BP &lt;90 with felodipine versus BP $\geq$ 130/80, median 1.3 yr</td>
<td>335 adults with proteinuria and eGFR &lt;60</td>
<td>Age 18-70 yr: Exclusion: immunosuppression treatment, severe uncontrolled HTN, recent MI or CVA, renovascular disease</td>
<td>137/84</td>
<td>130 versus 134</td>
<td>ESKD HR, 1.00 (95% CI: 0.61–1.64)</td>
<td>All-cause death OR, 0.87 (95% CI: 0.51–1.46)</td>
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<td>HALT-PKD, 2014, automated home BP device (LotisBeta) (71)</td>
<td>BP 95/6–110/75 versus BP 120/70–130/80, mean 5.7 yr</td>
<td>558 hypertensive (BP $\geq$130/80) adults 18-49 yr with ADPKD and eGFR $\geq$ 60</td>
<td>Exclusion: kidney vascular disease, kidney disease other than ADPKD</td>
<td>Home BP 124/83</td>
<td>Home systolic BP difference: 13.4</td>
<td>Annualized change in kidney volume: 3.6% versus 7.6% (P=0.006), eGFR 2.9 versus 3.0, P=0.6, albuminuria 1.3% versus 2.4% (P&lt;0.001)</td>
<td>Decreased left ventricular mass index (1.17 versus 1.57 g/m2 per yr; P&lt;0.003) All-cause death 2 in intensive arm, 0 in control arm</td>
</tr>
</tbody>
</table>

CKD trials (extended observational follow-up) (41)

| AASK, 2010, random zero sphygmomanometer (43) | MAP $\leq$92 versus MAP 102–107, range 8.8–12.2 yr from trial start | 1054 Black, non-diabetic adults with HTN and GFR 20–65 | Exclusion: diastolic BP $\geq$ 95 mmHg, CKD-stage other than HTN, clinical CHF | 151/96 | During trial: 130 versus 141 | CKD progression: doubling creatinine, ESKD, or death: overall, HR 0.61 (95% CI: 0.77–1.08) | Not reported |

| AASK, 2017, random zero sphygmomanometer (44) | MAP $\geq$92 versus MAP 102–107, median 14.4 yr from trial start | 1067 Black, non-diabetic adults with HTN and GFR 20–65 | Exclusion: Diastolic BP $\geq$ 95 mmHg, CKD-stage other than HTN, clinical CHF | 151/96 | During trial: 130 versus 141 | ESKD: unadjusted HR, 0.92 (95% CI: 0.75–1.12) Adjusted HR, 0.95 (95% CI: 0.78–1.16) | All-cause death: unadjusted HR, 0.91 (95% CI: 0.77–1.10), adjusted HR, 0.91 (95% CI: 0.68–1.26) |

| MDRED, 2017, random zero sphygmomanometer (44) | MAP $\geq$92 versus MAP 107–107, median 19.3 yr from trial start | 840 adults 18–70 yr with predominantly non-diabetic CKD (6:1 4–7 for men and Cr 1–2 mg/dl, women) | Exclusion: diabetes requiring insulin, class III–V CHF | Before trial: 131/80 | Before trial: 136 versus 134 | ESKD: unadjusted HR, 0.86 (95% CI: 0.73–1.00) | All-cause death: unadjusted HR, 0.92 (95% CI: 0.68–1.26). Adjusted HR, 0.81 (95% CI: 0.66–1.00) |

MDRED 9 months after trial completion: difference of 8 mmHg |

SHEP, The Systolic Hypertension in Europe trial; HTN, hypertension; CVD, cardiovascular disease; OR, odds ratio; Syst-Eur, The Systolic Hypertension in Europe trial; Cr, creatinine; CHF, congestive heart failure; MI, myocardial infarction; HOT, The Hypertension Optimal Treatment study; HYVET, The Hypertension in the Very Elderly Trial; JATOS, The Japanese Trial to Assess Optimal Systolic BP in Elderly Hypertensive Patients; HR, hazard ratio; ADVANCE, The Action in Diabetes and Vascular Disease: Preterax and Diamicron Controlled Evaluation trial; T2DM, type 2 diabetes mellitus; ACCORD, Action to Control Cardiovascular Risk in Type 2 Diabetes; SP3, The Secondary Prevention of Small Subcortical Strokes trial; BMI, body mass index; SPRINT, Systolic Blood Pressure Intervention Trial; ADPKD, autosomal dominant polycystic kidney disease; LVEF, left ventricular ejection fraction; MDRD, Modification of Diet in Renal Disease; MAP, mean arterial pressure; AASK, African-American Study of Kidney Disease and Hypertension; REIN-2, Ramipril Efficacy in Nephropathy trial 2; CVA, cerebrovascular accident; HALT-PKD, Halt Progression of Polycystic Kidney Disease; PCR, protein-creatinine ratio; Ref, reference.

Arm during the trial phase was associated with reduced risk of the primary outcome (HR, 0.73; 95% CI, 0.58 to 0.93), whereas no benefit for intensive BP control was observed in patients with protein-to-creatinine ratio <0.22 g/g (HR, 1.18; 95% CI, 0.93 to 1.50). A combined analysis of MDRD study and AASK long-term follow-up data suggested that participants who were randomized to intensive BP lowering tended to be at decreased risk of ESKD (HR, 0.88; 95% CI, 0.78 to 1.00) and death (HR, 0.87; 95% CI, 0.76 to 0.99) (44).

Data on the effects of a lower BP goal on outcomes in patients with CKD attributed to diabetes are sparse. The Action to Control Cardiovascular Risk in Type 2 Diabetes (ACCORD) trial examined the effect of more intensive versus usual BP goal (systolic BP <120 mm Hg versus <140 mm Hg) on the risk of cardiovascular disease (nonsynaptic myocardial infarction, nonfetal stroke, or cardiovascular death) in 4733 participants with type 2 diabetes; 1325 (28%) had stage 1–2 CKD and 401 (8%) had stage 3 CKD (36). Intensive BP lowering did not significantly reduce the risk of the primary cardiovascular outcome (HR, 0.88; 95% CI, 0.73 to 1.06), but did reduce the risk of stroke, a secondary outcome, by 41%. However, the ACCORD trial was underpowered as the annualized cardiovascular event rate was far lower than expected (2.1% versus expected 4%). In the subgroup of 1726 adults with CKD, the HR for the primary cardiovascular outcome was 0.86 (95% CI, 0.67 to 1.11) (Table 1) (45).

In 2015, the results of SPRINT were published (6). Briefly, SPRINT randomized 9361 adults $\geq$50 years with systolic BP 130–180 mm Hg and elevated cardiovascular risk to goal systolic BP $<120$ versus $<140$ mm Hg. Patients with diabetes, stroke, heart failure, proteinuria $>1$ g/d, polycystic kidney disease, eGFR <20 ml/min per 1.73 m2, and ESKD were excluded. Intensive BP lowering reduced the risk of cardiovascular disease by 25% and all-cause mortality by 27%.
Concerns of Intensive BP Lowering

Although SPRINT suggests that intensive BP lowering may reduce risk of cardiovascular disease and death in non-diabetic adults with CKD, there are several caveats. SPRINT reported increased risks of adverse events ranging from AKI, eGFR decline ≥30%, hypokalemia, hypotension, and hypotension (6). Intensive BP lowering did not increase the risk of orthostatic hypotension or injurious falls. Regarding kidney outcomes, intensive BP lowering resulted in significantly increased risk of incident CKD, defined as eGFR decline ≥30% to eGFR < 60 ml/min per 1.73 m² in SPRINT (absolute risk difference, 2.5%; 95% CI, 1.8% to 3.2%) and to a greater degree in the ACCORD trial (absolute risk difference, 5.9%; 95% CI, 4.3% to 7.5%) (49). In SPRINT, intensive BP lowering also increased risk of eGFR decline ≥30% in the CKD subgroup (HR, 2.03; 95% CI, 1.42 to 2.91), but had no effect on eGFR decline ≥50% or ESKD (HR, 0.87; 95% CI, 0.36 to 2.07), although the trial was underpowered for the latter outcome (Table 1) (46). The occurrence of benefits (i.e., reduced cardiovascular disease and improved survival) concurrent with some adverse outcomes highlights the importance of shared decision-making when clinicians propose an intensive BP goal to their patients.

The clinical significance of GFR decline associated with intensive BP lowering is unclear. In a pooled analysis of the AASK and MDRD trials, the association of acute eGFR decline and mortality differed by BP goal (50). In the intensive arm, a 5%–20% acute eGFR decline was associated with lower mortality and a ≥20% eGFR decline was not associated with risk of death. By comparison, in the standard arm, a 5%–20% acute eGFR decline was not associated with risk of death and a ≥20% eGFR decline was associated with an increased risk of death. Data from SPRINT also provides some reassurance, as the majority of AKI events appear to have been mild and reversible (51). In a random sample of SPRINT participants with baseline eGFR < 60 ml/min per 1.73 m², tubule injury biomarkers were measured at baseline, year 1, and year 4 (52). None of the eight biomarkers of tubule injury were higher in the intensive BP arm despite decreased eGFR, and two markers (β2-microglobulin, α1-microglobulin) were actually lower in the intensive BP arm. These findings suggest that reductions in eGFR that occur during intensive BP lowering may largely reflect hemodynamic effects rather than kidney injury.

The other major concern with intensive BP lowering in clinical practice is the issue of generalizability of trial findings. In SPRINT, several types of patients were excluded: patients with standing BP <110 mm Hg, nursing home patients, poorly compliant patients, transplant patients, and those with known secondary causes of hypertension. Indeed, the average number of medications needed during follow-up in patients with CKD was only 2.9 in the intensive group and 2.0 in the standard group, suggesting potentially better medication adherence than is typically observed. In a nationally representative Irish study, participants meeting SPRINT inclusion criteria had rates of injurious falls and syncope five-fold higher than what was observed in SPRINT (53). Another criticism of SPRINT is that unlike prior randomized trials, automated office BP was measured unattended at some clinical sites. However, site-level observer attendance appeared to have little effect on BP measurement or outcomes in SPRINT (7). Probably the bigger concern is that proper BP technique used in research efficacy trials, regardless of modality, is not often achieved in clinical practice. Further, monitoring for electrolyte disturbances and AKI may be less frequent in clinical practice compared with clinical trials (19,54). Lastly, SPRINT included few participants with stage 4–5 CKD, and data in support for intensive BP lowering in patients with CKD attributed to diabetes is limited.

Conclusions

A BP goal of <130/80 is a reasonable, evidence-based BP goal in patients with CKD, and current evidence suggests that lowering BP to <130/80 mm Hg reduces future mortality risk. In contrast, intensive BP lowering on risk of ESKD is uncertain, in part because trials have been short in duration and because acute hemodynamic effects lead to a reduction in GFR. Still, in patients with proteinuric CKD, a lower BP goal appears to reduce CKD progression. Implementation of an intensive BP goal will require increased attention to measuring BP accurately, assessing patient preferences and comorbidities, shared decision-making, and monitoring for adverse effects of therapy.

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Disclosures

None.

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Supplemental Material

Supplemental Table 1. Treatment thresholds for initiating BP medications.

References


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