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Blood pressure parameters and morbid and mortal outcomes in non-dialysis dependent chronic kidney disease

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Abstract

Purpose of review—Observational and interventional studies provide conflicting evidence regarding optimal blood pressure (BP) control in persons with chronic kidney disease (CKD). Recent publications provide additional information to inform therapeutic decision making.

Recent findings—Targeting SBP to <120 mmHg, versus <140 mmHg, decreased cardiovascular events and all-cause mortality in persons with non-diabetic CKD. A meta-analysis of trials testing blood pressure management among non-dialysis dependent CKD patients (15,924 total patients) found more intensive therapies generally reduced mortality in all subgroups. Observational studies demonstrate that lower SBP is associated with higher mortality in CKD. A recent report suggests that this is due to death from cardiovascular and non-cardiovascular and non-malignant causes, whereas higher BP is associated with death from cardiovascular causes. The shape of association between BP and cardiovascular and non-cardiovascular events also appears to vary depending on baseline risk factors. Further, BP measurement methodology may differ importantly between observational and interventional studies.

Summary—We review and summarize observational and interventional literature relating BP parameters to key clinical outcomes in persons with CKD. Apart from the inherent differences between these study designs, the disparate findings from trials and observational studies may be due to differences in patient characteristics and BP measurement techniques.

Keywords

Systolic blood pressure; diastolic blood pressure; chronic kidney disease; mortality; observational studies

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Conflicts of interest

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Introduction

Chronic kidney disease (CKD) and hypertension are major health problems in the United States and globally (1). Treatment of hypertension is one of the few therapeutic interventions for improving outcomes in CKD. The Kidney Disease: Improving Global Outcomes (KDIGO) 2012 clinical practice guideline recommends systolic blood pressure (SBP) of 140 mmHg, and diastolic blood pressure (DBP) of 90 mmHg, in non-albuminuric CKD patients, and 130/80 mmHg in those with albuminuria (2). The 2014 report from the panel appointed to the Eighth Joint National Committee (JNC 8) recommended goal BP <140/90 mmHg among adults with CKD (3).

Additional studies examining BP and various clinical outcomes in CKD have been published over the intervening years, but ideal treatment goals are still unclear, as we have contradictory findings from experimental trials and observational studies. Experimental trials, of course, minimize bias, but this often comes at the expense of generalizability. To apply trial findings to our patients and achieve similar results, our patients must resemble in important respects the trial participants, and we must apply the same interventions and measurements. Observational studies trying to compare treatment approaches have high risk of bias, yet the studied populations and treatments are often more representative of usual practice. In this article, we review recent observational and interventional studies of BP in persons with non-dialysis CKD, focusing primarily on the outcomes mortality and incident ESRD, and attempted to reconcile the seemingly contradictory information.

Observational Studies

The observational study designs in this topic vary widely. Administrative cohorts, prospective protocol-driven cohorts, and *post hoc* analyses of randomized trials are used. Several studies are limited to those with diagnosed hypertension, or on BP lowering medications. One study used more complex cohort design to model hypertension control strategies (4).

Mortality

Table 1 summarizes key studies evaluating associations of BP parameters with all-cause mortality. A prospective study of 218 US veterans with non-dialysis CKD and mean eGFR 38 ml/min/1.73 m², nearly half with diabetes, demonstrated lowest risk of all-cause mortality with baseline SBP of 130–149 mmHg (5). Higher DBP (> 80 mmHg) was associated with lower mortality, however. A subset of 1705 persons from the Chronic Renal Insufficiency Cohort (CRIC) with eGFR <30 ml/min/1.73 m² found no association between baseline SBP and all-cause mortality, prior to starting dialysis (6).

Mortality is strongly associated with age and previous studies evaluated the relationship of BP, age, and mortality in CKD. An analysis of 21,015 persons aged >65 years with hypertension, receiving care through a managed care consortium, evaluated the relationship between SBP and mortality (7). Over 70% had CKD stage 3A at baseline, and nearly a third had diabetes. The lowest SBP category (< 120 mmHg) had the highest mortality in all age groups, with 17–41% increased risk compared to those with SBP 131–140 mmHg. Higher

SBP (>140 mmHg) was associated with higher mortality only in the 65–70 year-old group, with approximately 40% increased risk. The model adjusted for DBP, which may make the analyses more reflective of pulse pressure (PP) than of SBP *per se*. Mortality decreased with higher DBP, and did not vary by age group.

An analysis including >600,000 US veterans with CKD (mean eGFR 50 ml/min/1.73 m²) further investigated the relationship between SBP, DBP, and mortality (8). In this analysis, U-shaped associations of both SBP and DBP with mortality were observed, with the lowest risk among those with BP 130–159/70–89 mmHg. DBP <70 mmHg was also associated with higher mortality risk, in all except those with the highest SBP. A later analysis used a subset of this cohort to compare treatment to different SBP levels (4). Requirements were set for number of antihypertensives used and increases in antihypertensive therapy to try to isolate the effects of antihypertensive treatment from BP differences related to clinical circumstances and comorbidities. SBP <120 mmHg was associated with 70% higher mortality compared with SBP 120–139 mmHg. Another subset of this veteran cohort, of over 300,000 persons with incident CKD, demonstrated that the association of elevated SBP with higher mortality risk was attenuated with older age (9). These studies generally found no differences with severity of kidney disease. However, an analysis from the Chronic Renal Insufficiency Cohort Study (CRIC) limited to those with eGFR <30ml/min/1.73m² found no relationship between SBP and all-cause mortality prior to dialysis initiation (6).

It is well known that elevated BP lead to cardiovascular events, but what explains the relationship between low SBP and DBP and death in CKD? A recent report investigated this by evaluating the association of BP with cause-specific death (10). A cohort of 45,412 persons with eGFR 15–<60 ml/min/1.73 m² receiving at least one antihypertensive medication was created from the electronic health record of a major health system. The ubiquitous U-shaped association of SBP with all-cause mortality was found, with SBP <120 and 150 mmHg associated with higher mortality. On cause-specific analysis, lower SBP range (<110 mmHg) had higher cardiovascular and non-cardiovascular, non-malignancy mortality. For DBP, the relationship was different. Lower DBP levels (<60mmHg) were associated with higher all-cause and non-cardiovascular/non-malignancy mortality, and higher levels (>90 mmHg) had higher cardiovascular mortality (but lower non-CV/non-malignancy mortality). These findings help explain the previously observed U-shaped associations, and may have implications for guiding therapy, based on individual risk of various outcomes and avoidance of intensive BP lowering with certain chronic conditions.

ESRD

In the cohort study of 218 US veterans discussed above, 63 persons progressed to ESRD over 1009 person-years of follow-up (5). For ESRD, unlike mortality, SBP had linear associations: those with SBP 130–149 mmHg had nearly 4-times the risk, and 150 mmHg had 9 times the risk. An analysis of 16,129 persons with eGFR <60 ml/min/1.73 m² found similar ESRD risk among those with SBP <130 and 130–139 mmHg, but progressively increasing risk for higher SBP groups (11). DBP 90 mmHg was associated with significantly higher risk, but no difference was found among those with lower BP. PP was evaluated as well, but showed no association with outcomes in a model adjusted for SBP

(11). In the analysis of over 300,000 US veterans with incident CKD mentioned previously (9), 5161 patients progressed to ESRD. A linear association between SBP and ESRD risk was noted, with older age attenuating this relationship. No consistent associations between DBP and ESRD was found.

The exposure in most observational studies was baseline BP, but BP changes over time and could influence outcomes. Time-varying SBP was analyzed as the exposure in 3708 persons from the CRIC cohort (12). ESRD risk more than doubled for SBP 130–139 mmHg, compared to <120 mmHg. This was a much more pronounced effect than that seen when baseline SBP alone was the predictor. A secondary analysis of 1099 persons with eGFR ≥ 30 ml/min/1.73 m² taking part in a vitamin supplementation trial found the highest quartiles of SBP and DBP were associated with 20–30% increased risk (13). A combined outcome of ESRD or death was used in a *post hoc* analysis of the RENAAL trial data (which tested losartan versus placebo, and set goal BP < 140/90 among all participants), and found direct relationships between both SBP and DBP and the studied outcomes (14). *Post hoc* analysis of the Veterans Affairs Nephropathy in Diabetes (VA NEPHRON D) trial (which tested combined losartan and lisinopril, versus losartan alone, with goal BP in both arms 110–130/<80 mmHg) found combined outcome of significant eGFR decline, ESRD, or death to be significantly higher with SBP 140–149 mmHg, compared with 120–129 mmHg (15). DBP had a U-shaped association with the composite outcome.

Other Cardiovascular Outcomes

Recently, Sood et al. (16) evaluated the relationship of time-varying BP parameters with significant eGFR decline ($\geq 30\%$) in a cohort with advanced CKD, most of whom with diabetes (mean 16.8 ml/min/1.73m²). The investigators found increased eGFR decline at the extremes of SBP (<105 or >170 mmHg), and with DBP > 90mmHg. Renal function decline did not vary with PP. The association of SBP, DBP, and PP with atherosclerotic cardiovascular disease (ASCVD) events and heart failure in a subgroup of the CRIC cohort with eGFR <30 ml/min/1.73 m² found PP alone was associated with significantly higher heart failure risk, whereas higher SBP, DBP, and PP were associated with higher ASCVD risk (17). The cohort of 300,000 veterans with incident CKD mentioned in previous sections was analyzed for incident coronary heart disease (CHD) and stroke as well, and found linearly increased risk with SBP (attenuated with age), but no trend with DBP (9). In an analysis of 1099 patients with eGFR ≥ 30 ml/min/1.73 m², the highest quartile of PP, compared with the lowest, was associated with 67% higher risk of cardiovascular events (myocardial infarction, stroke, or extremity amputation) (13).

Herrington et al. recently published a post-hoc analysis of the Study of Heart and Renal Protection (SHARP) investigating the relationship between observed blood pressure parameters and cardiovascular and non-cardiovascular outcomes (18). This analysis, including persons with both non-dialysis and dialysis-dependent CKD, found that baseline cardiovascular risk influences the association between BP and cardiovascular outcomes. Among those at high cardiovascular risk (defined by clinical history of ASCVD or elevated troponin I), SBP had a U-shaped association with cardiovascular events, but in those at low cardiovascular risk (the remainder of the cohort), lower SBP was associated with lower risk.

Analyzing non-cardiovascular mortality, the U-shaped association was again observed with SBP among those at high cardiovascular risk, but among those at low risk non-cardiovascular mortality declined with higher SBP (18). DBP had a U-shaped association with cardiovascular outcomes in both groups, and no trend was observed for the relationship between DBP and non-cardiovascular mortality.

Interventional Studies

The Systolic Blood Pressure Intervention Trial (SPRINT) compared goal SBP <140 mmHg to <120 mmHg among non-diabetic persons age 50 or older with increased cardiovascular risk (19) (Table 2). Twenty-eight percent of participants had eGFR <60 ml/min/1.73 m² at baseline. A composite of cardiovascular events was the primary outcome. Renal events, including ESRD, were prespecified secondary outcomes, as were outcomes among the CKD subgroup. The trial was very well-executed but halted earlier based on the recommendation of Data Safety Monitoring Board. Intensive SBP lowering significantly reduced the primary cardiovascular outcome, with no interaction with presence of CKD (20). Several renal outcomes were assessed in the CKD subgroup, including incident ESRD, and composite outcome of ESRD and 50% eGFR reduction. The point estimates for these outcomes were lower with intensive control, but the numbers were low did not meet the prespecified significance level. Rate of eGFR decline was slightly higher in the intensive therapy group, similar to a prior trial of intensive BP control in persons with preserved renal function (20, 21). Hyperkalemia, hypokalemia, and acute kidney injury were more common with intensive therapy in the SPRINT CKD subgroup (19, 20). However, there were no differences in hypotension, syncope, injurious falls and hyponatremia between the two groups.

Few other trials have tested different BP targets and important outcomes in CKD and have been discussed in several previous reviews. The Modification of Diet in Renal Disease (MDRD) study compared MAP target 92 with 107 in a cohort with average GFR (iothalamate) 33 ml/min/1.73 m², and no difference was found in ESRD or mortality (22). A study performed in Japan evaluated 4418 persons age 65–85 years, of whom 2499 had eGFR < 60 ml/min/1.73 m² (23). SBP targets of <140 mmHg versus <160 mmHg were compared, and no differences in the primary renal or cardiovascular outcomes were seen. A small randomized trial of ramipril versus ramipril and felodipine in persons with non-diabetic proteinuric CKD achieved little BP difference in the two arms, and found no difference in ESRD incidence or mortality (24). The African American Study of Kidney Disease (AASK) trial tested two BP targets (MAP 92 mmHg, versus 102–107 mmHg) among 1094 African Americans with CKD attributed to hypertension (25). Despite marked BP separation (average of 128/78, versus 141/85), no significant difference was found in ESRD, all-cause mortality, or a composite outcome over 4 years of follow-up.

A recent meta-analysis of randomized controlled trials evaluated the effect of BP control intensity on mortality among persons with CKD stages 3–5 (26). The authors identified 18 trials testing different BP treatment intensities, including 15924 persons with CKD and 1293 deaths. The baseline SBP mean (SD) was 148 (16) mmHg, which decreased to 132 mmHg in the more intensive arm, compared to 140 mmHg in the less intensive arm (26). Higher intensity BP control reduced risk of death (odds ratio 0.86 [95% CI 0.76–0.97]), and this

appeared consistent regardless of intervention type, follow-up time, diabetes, degree of renal dysfunction, and baseline blood pressure (26).

Explaining the differences between observational studies and experimental trials

Observational studies are fairly consistent on the association of SBP with outcomes in CKD. Persons with SBP much removed from the average in either direction are more likely to die. Persons with SBP higher than the average are more likely to suffer from events that seem likely to be caused by elevated BP, such as myocardial infarction, stroke, or progression to ESRD, and cardiovascular causes of death also appear to explain much of the higher death rate with high SBP. But what is causing deaths in those with lower SBP, and what are the implications for therapeutic decision making? Two recent analyses, one evaluating cause-specific death (10), and one looking at cardiovascular and non-cardiovascular outcomes (18), are relevant to these questions. Lower SBP was associated with higher risk of both cardiovascular and non-cardiovascular death in non-dialysis CKD (10). Lower SBP was also found to be associated with higher risk of cardiovascular events only in those with preexisting disease, whereas it was associated with higher risk of non-cardiovascular mortality among the entire cohort (18). Together these results support the idea that lower SBP can be a marker for poor health in CKD, and that reverse causality may be present.

U-shaped or J-shaped associations between physiologic parameters and outcomes are common in CKD epidemiology and to a certain extent, these findings are influenced by parameter categorization (27). It is not surprising that SBP >180 mmHg, or DBP <50 mmHg, predict poor outcomes. More interesting are the findings nearer the means, where the best course of action may be unclear. In particular, should we increase antihypertensive medication dosage or add additional agents in a patient with SBP 130 mmHg, when observational studies suggest higher mortality with SBP < 120 mmHg, yet SPRINT found *reduced* mortality with that target? Which wins out, the causal strength of the randomized trial, or the unselected realism of the observational study? That depends, ultimately, on how much the patient, and the treatment, resembles the trial.

The internal validity of SPRINT is undoubted, application of the findings could prevent many deaths (28), and updated blood pressure clinical guidelines incorporating these important results are anticipated soon. However, generalizing to usual clinical practice must be done carefully. The method of BP measurement is particularly salient. A study in 275 predominantly male patients with CKD found measurements using SPRINT methodology (5 minutes seated rest in a quiet room, followed by 3 recordings at 1-minute intervals) to be 12.7 mmHg lower, on average, than the “routine” clinical measurement (29). Most observational studies used BP recorded for routine clinical practice, raising the question of how the findings would differ if the SPRINT methodology was used. The average SBP in the SPRINT CKD subgroup was 123.0 mmHg in the intensive group, and 135.3 mmHg in the standard group (20). If measured in the routine clinical method, would then the SPRINT intervention group SBP average 136 mmHg, and the standard group 148 mmHg? This could explain the differing outcomes in the observational studies. This argues for the need for

additional experiments: more pragmatic trial designs testing BP thresholds, and/or studies determining the feasibility of implementing “research-grade” BP measurement practices in real-world settings.

The observation that low SBP is associated with higher mortality in CKD may also be related in part to the generally older population included in these observational studies. Many people classified as having CKD (especially those with CKD Stage 3A), are elderly, and have significant risk of death from non-cardiovascular causes. SPRINT excluded persons with diabetes, and those with ≥ 1 g total urinary protein per 24 hour or urinary albumin ≥ 600 mg per 24 hour, or the analogous spot urine protein to creatinine ratios (19). Thus, the findings may not apply to many, as nearly 30% of the US CKD population has diabetes (30), and macroalbuminuria prevalence in the US CKD population is 6% in stage 3 and 39% in stage 4 (31). Mortality rate in the SPRINT CKD subgroup was 1.6 percent per year with intensive therapy, and 2.2 percent per year with standard therapy. Cardiovascular deaths made up 0.4 deaths per year in the intensive therapy group and 0.7 deaths per year in the standard therapy group (20). This is much lower than, for example, the death rates of 7.35 percent per year, and 29.3 percent over 3.9 years, in two of the observational cohorts (9, 10). Further, it is important to note that the Action to Control Cardiovascular Risk in Diabetes-Blood Pressure (ACCORD-BP) trial in diabetics, which assigned patients to an intensive-therapy with a SBP target <120 mmHg or a standard-therapy with a SBP target <140 mmHg, did not find benefit with intensive BP target (32).

Cost-effectiveness is an important consideration in instituting an intervention with such wide-ranging applicability as SPRINT. Simulations of applying SPRINT to appropriate patients suggest that cost per quality-adjusted life year gained would be within usually accepted limits (33, 34).

Conclusion

In summary, SPRINT trial data supports intense BP control ($<120/80$ mm Hg) in the non-diabetic CKD population, with the caveat that the trial’s BP measurement technique must be used. However, we must consider tradeoffs when making decisions with individual patients. The increased medicalization of patients’ lives with more frequent physician visits and BP checks, the pill burden, and side effects including AKI (which may have long-term impacts) are among the downsides. Patients must be provided the best available information on risks, benefits, and uncertainties, and their valuations of potential benefits versus certain costs must be taken into account. Additionally, trials are needed to test intensive BP control among patients with diabetic kidney disease and advanced CKD before similar targets can be confidently applied to them. The ultimate goal for clinical science must be to inform clinicians how best to individualize BP targets based on each person’s unique clinical circumstances and personal values.

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Key Points

1. Observational studies consistently reported U-shaped associations between systolic blood pressure and mortality in those with chronic kidney disease
2. Systolic blood pressure <110 mmHg is associated with higher risk of cardiovascular and non-cardiovascular, non-malignancy mortality.
3. Clinical trial data supports intense blood pressure control (<120/80 mm Hg) in those with non-diabetic CKD, and more generally in CKD trials more intensive blood pressure lowering results in lower mortality than less intensive therapy.
4. Application of trial data to clinical practice should include using the trials' blood pressure measurement techniques.

Table 1
Observational Studies of Blood Pressure and All-Cause Mortality and ESRD outcomes, in CKD

Author and year	Number of subjects	eGFR (ml/min/1.73m ²)	Association with All-Cause Mortality			Association with ESRD		
			SBP	DBP	SBP	DBP	SBP	DBP
Agarwal et al. 2009 (5)	218	Mean 38	J-shaped, lowest risk: 130 to 149 mmHg	Inverse	Direct	-	Direct	None
Peralta et al. 2012 (11)	16,129	Mean 48	-	-	J-shaped, lowest risk 130–139 mmHg	-	J-shaped, lowest risk 130–139 mmHg	J-shaped, lowest risk 60–74 mmHg
Kovesdy et al. 2013 (8)*	651,749	Mean 50	J-shaped, lowest risk: 130 to 159 mmHg	J-shaped, lowest risk: 70 to 89 mmHg	-	-	-	-
Kovesdy et al. 2014 (4)*	77,765	Mean 49	Higher risk for < 120, compared to 120 to 139 mmHg	-	-	-	-	-
Anderson et al. 2015 (12)	3,708	Mean 45	-	-	Direct	-	-	-
Bansal et al. 2015 (6)	1,705	< 30	None	-	-	-	-	-
Weiss et al. 2015 (7)	21,015	71.9% 45–59 28.1% < 45	Highest risk: 120 mmHg in all age groups U-shaped in youngest age group (65–70 years) only	-	-	-	-	-
Palit et al. 2015 (13)	1,099	Mean 18	J-shaped, lowest risk: >128 to 141 mmHg	J-shaped, lowest risk: >64 to 72 mmHg	Direct	-	Direct	Direct
Kovesdy et al. 2016 (9)*	300,424	Mean 48	J-shaped, lowest risk: 130 to 139 mmHg	J-shaped, lowest risk: 70 to 89 mmHg	Direct	-	Direct	None

eGFR: estimated glomerular filtration rate; SBP-systolic blood pressure; DBP-diastolic blood pressure; ESRD-end stage renal disease

* Analyses from same base cohort

Major Randomized Trials of Blood Pressure Targets and All-Cause Mortality and ESRD outcomes, in CKD

Table 2

Author and year	CKD group N (% of study)	Definition (summary) of CKD	Targeted blood pressure (mmHg)	Achieved blood pressure (mmHg)	Incident ESRD	All-cause mortality
Klahr et al. 1994 (22)	840 (100%)	CrCl < 70 (mean GFR 33 [iothalamate])	MAP 92 vs MAP 107	126/77 vs 134/81	No difference	No difference
Wright et al. 2002 (25)	1094 (100%)	eGFR 20–65 (mean GFR 46 [iothalamate])	MAP 92 vs 102–107	128/78 vs 141/85	% risk reduction: 6 (95% CI –29 to +31)	1.6% vs 1.9% (not statistically significant)
Ruggenenti et al. 2005 (24)	335 (100%)	CrCl < 70 (mean GFR 35 [iohexol])	DBP < 90, vs SBP/DBP < 130/80	130/80 vs 134/82	No difference (P = 0.99)	-
Wright et al. 2015 (19) and Cheung et al. 2017 (20)	2646 (28%)	eGFR < 60 (mean eGFR 48)	SBP < 120 vs < 140	CKD subgroup: 123/67 vs 137/74	CKD subgroup: HR 0.57 (95% CI 0.19–1.54)	CKD subgroup: HR 0.72 (95% CI 0.53 to 0.99)

ESRD: end-stage renal disease; CKD: chronic kidney disease; (e)GFR: (estimated) glomerular filtration rate (ml/min/1.73 m²); CrCl: creatinine clearance; HR: hazard ratio; CI: confidence interval