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Association Between More Intensive vs Less Intensive Blood Pressure Lowering and Risk of Mortality in Chronic Kidney Disease Stages 3 to 5
A Systematic Review and Meta-analysis

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IMPORTANCE Trials in patients with hypertension have demonstrated that intensive blood pressure (BP) lowering reduces the risk of cardiovascular disease and all-cause mortality but may increase the risk of chronic kidney disease (CKD) incidence and progression. Whether intensive BP lowering is associated with a mortality benefit in patients with prevalent CKD remains unknown.

OBJECTIVES To conduct a systematic review and meta-analysis of randomized clinical trials (RCTs) to investigate if more intensive compared with less intensive BP control is associated with reduced mortality risk in persons with CKD stages 3 to 5.

DATA SOURCES Ovid MEDLINE, Cochrane Library, EMBASE, PubMed, Science Citation Index, Google Scholar, and clinicaltrials.gov electronic databases.

STUDY SELECTION All RCTs were included that compared 2 defined BP targets (either active BP treatment vs placebo or no treatment, or intensive vs less intensive BP control) and enrolled adults (≥18 years) with CKD stages 3 to 5 (estimated glomerular filtration rate <60 mL/min/1.73 m^2) exclusively or that included a CKD subgroup between January 1, 1950, and June 1, 2016.

DATA EXTRACTION AND SYNTHESIS Two of us independently evaluated study quality and extracted characteristics and mortality events among persons with CKD within the intervention phase for each trial. When outcomes within the CKD group had not previously been published, trial investigators were contacted to request data within the CKD subset of their original trials.

MAIN OUTCOME AND MEASURE All-cause mortality during the active treatment phase of each trial.

RESULTS This study identified 30 RCTs that potentially met the inclusion criteria. The CKD subset mortality data were extracted in 18 trials, among which there were 1293 deaths in 15 924 participants with CKD. The mean (SD) baseline systolic BP (SBP) was 148 (16) mm Hg in both the more intensive and less intensive arms. The mean SBP dropped by 16 mm Hg to 132 mm Hg in the more intensive arm and by 8 mm Hg to 140 mm Hg in the less intensive arm. More intensive vs less intensive BP control resulted in 14.0% lower risk of all-cause mortality (odds ratio, 0.86; 95% CI, 0.76-0.97; *P* = .01), a finding that was without significant heterogeneity and appeared consistent across multiple subgroups.

CONCLUSIONS AND RELEVANCE Randomization to more intensive BP control is associated with lower mortality risk among trial participants with hypertension and CKD. Further studies are required to define absolute BP targets for maximal benefit and minimal harm.

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Chronic kidney disease (CKD) is a major public health problem, estimated to affect 26 million Americans and 200 million individuals worldwide.[1,2] Persons with CKD are at high risk of cardiovascular disease (CVD), progression to end-stage renal disease (ESRD), and all-cause mortality.[3] Hypertension is a well-known risk factor for CVD; therefore, optimal blood pressure (BP) control is a major clinical and public health priority.[4,5] Over the past decade, several studies and clinical practice guidelines[6-10] have addressed the optimal BP target in CKD populations, yet consensus remains elusive. Observational data have demonstrated U-shaped relationships between BP and mortality risk among those with CKD.[11,12] Clinical trials testing different BP targets in CKD populations, including the Modification of Diet in Renal Disease (MDRD)[13] and the African American Study of Kidney Disease and Hypertension (AASK),[14] failed to demonstrate benefits of BP lowering for slowing down CKD progression and were underpowered to address CVD and mortality.

The current Kidney Disease: Improving Global Outcomes (KDIGO)[7] BP guidelines recommend a BP goal less than 130/80 mm Hg for individuals with CKD and moderate to severe albuminuria and less than 140/90 mm Hg for those with CKD and albuminuria less than 30 mg/g. The Eighth Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 8)[15] and the 2013 European Society of Hypertension/European Society of Cardiology Task Force[16] affirmed the BP target of less than 140/90 mm Hg for individuals with CKD and made no distinction based on the albuminuria level. These guidelines were published before the Systolic Blood Pressure Intervention Trial (SPRINT)[17] was completed. SPRINT enrolled hypertensive individuals without diabetes and with high CVD risk and found a substantially lower CVD risk and lower all-cause mortality risk in participants treated to a systolic BP (SBP) target less than 120 mm Hg compared with less than 140 mm Hg, although they found a significant excess of acute kidney injury (AKI). Patients with CKD (defined as an estimated glomerular filtration rate [eGFR] of 20-59 mL/min/1.73 m^2) accounted for approximately 30% of the SPRINT participants, and the results were similar (no statistically significant interactions) among those with CKD compared with their non-CKD counterparts. However, the trial was not specifically powered to define the risks and benefits of intensive BP control for those with CKD.

The different definitions and differential reporting of AKI, CKD progression, and CVD events from previous randomized clinical trials (RCTs) represent a major challenge to comprehensively address these end points in a meta-analysis. In contrast, mortality is similarly defined across studies and is virtually always reported because it is an important safety signal. Mortality also provides a summary estimate of the net benefits and harms of the intervention. Therefore, our objective was to conduct a systematic review and meta-analysis of RCTs to investigate if more intensive compared with less intensive BP control is associated with reduced mortality risk in persons with CKD stages 3 to 5.

Key Points

Question Does intensive blood pressure lowering decrease the risk of mortality in patients with chronic kidney disease?

Findings In this meta-analysis of 18 randomized clinical trials comprising 15 924 patients with chronic kidney disease, more intensive blood pressure lowering was associated with significantly lower risk of mortality compared with less intensive blood pressure control.

Meaning Targeting more intensive blood pressure lowering may provide a mortality benefit in persons with chronic kidney disease.

Methods

Electronic Searches

Ovid MEDLINE, Cochrane Library, EMBASE, PubMed, Science Citation Index, Google Scholar, and clinicaltrials.gov electronic database searches were completed from January 1, 1950, to June 1, 2016, with the following keywords: *randomized controlled trials*, *intensive blood pressure treatment*, *intensive blood pressure control*, *strict blood pressure treatment*, *strict blood pressure control*, *tight blood pressure treatment*, or *tight blood pressure control*.[18] The clinicaltrials.gov website was searched for randomized trials that were registered as completed but not yet published. The reference articles from each identified trial were reviewed to identify any additional relevant studies. No language restrictions were applied. The literature search was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[19] statement recommendations (eTable 1 in the Supplement).

Selection of Studies

Study eligibility was individually determined independently by 2 of us (R.M. and H.A.N.). Eligible for inclusion were both open-label and double-blinded RCTs that had adult participants (≥18 years) with CKD stages 3 to 5, which was defined as an eGFR less than 60 mL/min/1.73 m^2 by either the MDRD or Chronic Kidney Disease Epidemiology Collaboration equations and had randomized participants to 2 defined BP targets (either active BP treatment vs placebo or no treatment, or more intensive vs less intensive BP control). In some instances, identified trials included persons with CKD, but the trials had not previously published mortality events within the CKD subset. In such cases, we contacted the study investigators and requested data on the number of patients with CKD enrolled in the trial, the number in each treatment arm, and the number of deaths that occurred during the active trial phase. Studies among dialysis patients were excluded.

Data Extraction and Quality Assessment

Demographics, comorbid characteristics, enrollment criteria, BP control targets in each arm, mean reductions in SBP and diastolic BP, and mortality events were extracted onto standardized extraction forms. Extracted data were then verified by another one of us (H.A.N.). For any discrepancies, two of us (R.M. and H.A.N.) met and conferred, and consensus was

Figure 1. PRISMA Diagram of Selection of Studies for Meta-analysis
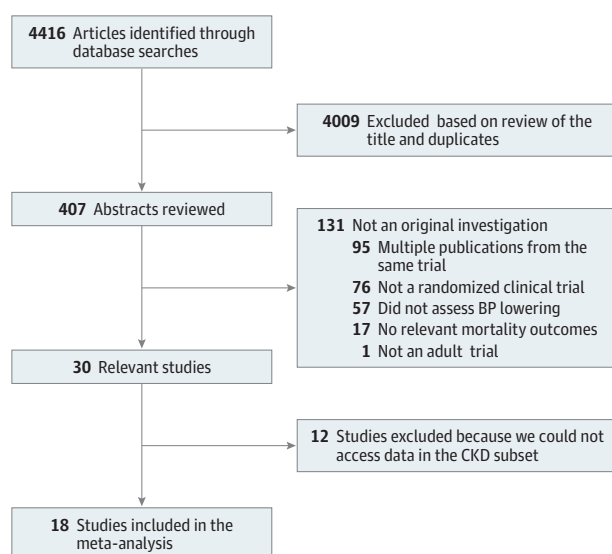
BP indicates blood pressure; CKD, chronic kidney disease; and PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

reached. The quality and clinical generalizability of each study were assessed according to the methods based on allocation concealment, masking (of participants, investigators, and assessors), intent-to-treat analysis, percentage withdrawals, and whether withdrawals were adequately described.[20]

Outcome Measures
The primary outcome was all-cause mortality. The mortality data were obtained during the active treatment phase of each trial. The mortality events that occurred during extended follow-up after the active phase of each trial were not included.

Statistical Analysis
Mortality outcomes in each randomized BP group were pooled, and weighted odds ratios (ORs) comparing the lower BP arm (intensive BP) with individuals randomized to higher BP targets (less intensive or placebo) and their 95% CIs were calculated using both random-effects and fixed-effects models. The influence of individual trials on the pooled effect size was assessed, and a trial was considered to have an excessive influence if, after its exclusion, the point estimate of the remaining trials was outside the 95% CI of the overall risk estimate. Heterogeneity was assessed based on I^2 test (I^2 of 0%-25% indicates no or mild heterogeneity, 25%-50% indicates moderate heterogeneity, 50%-75% indicates large heterogeneity, and 75%-100% indicates extreme heterogeneity).[20] Subgroup analyses were performed stratified by type of study (drug vs placebo vs 2 defined BP target arms), study trial duration, inclusion of diabetic patients (yes or no), baseline SBP, level of achieved SBP during the trial phase, and SBP difference between the 2 randomized arms. Meta-regression analysis was performed to assess the association between SBP differences during the trial phase and mortality risk while adjusting for baseline SBP. Potential publication bias was assessed using funnel plots. Two-

sided $P < .05$ was considered statistically significant for all analyses, including tests for heterogeneity. All statistical analyses were performed using a software program (Comprehensive Meta-Analysis, version 2.2.064; Biostat Inc).
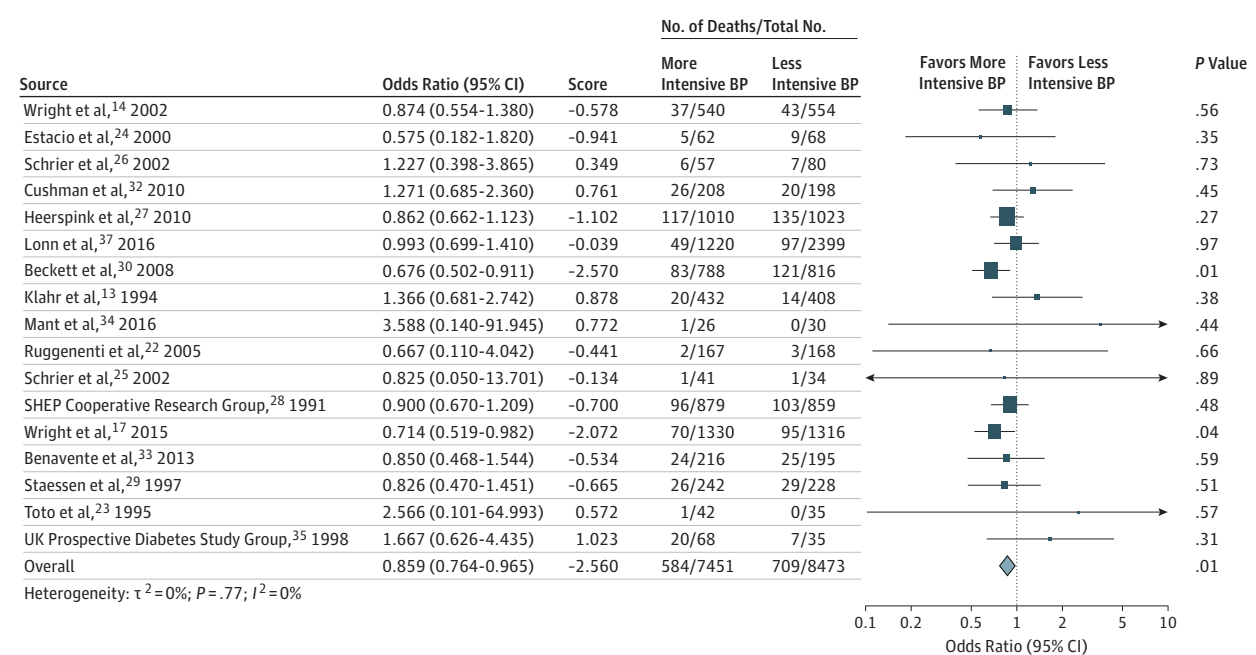
Results

Literature Search
The initial search of Ovid MEDLINE, Cochrane Library, EMBASE, PubMed, Science Citation Index, Google Scholar, and clinicaltrials.gov electronic databases between January 1, 1950, and June 1, 2016, provided 4416 citations. We reviewed abstracts and limited this search to a more detailed review of 407 abstracts of studies potentially eligible for inclusion as described in the Methods section. In subsequent review, 377 studies were excluded because they did not fulfill the inclusion criteria. The remaining 30 studies were reviewed in full text and identified for meta-analysis (**Figure 1**). Data elements from 9 trials[13,14,17,21-27] were extracted from the publications. One citation is a previous meta-analysis,[21] which was also used to abstract data. We contacted trial investigators for the remaining trials, and the authors of 9 studies[28-36] provided data on the number of participants with CKD and deaths during the trial phase for the 2 BP arms for the purpose of inclusion in this meta-analysis. We were unable to obtain mortality data in the CKD subset from the investigators for the remaining 12 trials.[37-48] Therefore, 18 RCTs involving 15 924 participants with CKD and complete data were included in the meta-analysis (Figure 1).

Study Characteristics
eTable 1 in the Supplement summarizes the main characteristics of the studies included in the meta-analysis. All trials were of good quality. Each used a parallel treatment group design, and 15 trials reported adequate methods for random allocation and concealment of treatment assignment (eTable 2 in the Supplement). Six trials[13,22,26-28,35] had excluded patients with type 1 diabetes, whereas 3 trials[14,17,23] had excluded patients with all forms of diabetes. Thirteen trials[13,14,17,22-25,31-36] among the 18 had 2 defined BP targets, and the remaining 5 trials[26-30] evaluated a BP-lowering intervention vs no treatment or a placebo arm. One trial[36] had 3 defined BP targets. For the purpose of this meta-analysis, the lowest BP target group was compared with the other 2 groups together. The BP targets varied across trials (eTable 1 in the Supplement). The mean (SD) baseline SBP was 148 (16) mm Hg in both the intensive and less intensive arms. The mean SBP decreased by 16 mm Hg to 132 mm Hg in the more intensive arms and by 8 mm Hg to 140 mm Hg in the less intensive arms. The median follow-up period was 3.6 years (interquartile range [IQR], 2.8-4.9 years). The median difference in SBP achieved across arms[13,14,17,22-36] was 10 mm Hg (IQR, 4-12 mm Hg), with a median of 130 mm Hg (IQR, 125-141 mm Hg) in the more intensive arms vs 138 mm Hg (IQR, 134-146 mm Hg) in the less intensive arms. The renal inclusion and exclusion criteria varied across trials and are summarized in eTable 1 in the Supplement.

Figure 2. Effect of Intensive Blood Pressure (BP) Lowering on Risk of Mortality in Hypertensive Trial Participants With Chronic Kidney Disease

Source	Odds Ratio (95% CI)	Score	More Intensive BP	Less Intensive BP	Favors More Intensive BP / Favors Less Intensive BP	P Value
Wright et al,[14] 2002	0.874 (0.554-1.380)	-0.578	37/540	43/554		.56
Estacio et al,[24] 2000	0.575 (0.182-1.820)	-0.941	5/62	9/68		.35
Schrier et al,[26] 2002	1.227 (0.398-3.865)	0.349	6/57	7/80		.73
Cushman et al,[32] 2010	1.271 (0.685-2.360)	0.761	26/208	20/198		.45
Heerspink et al,[27] 2010	0.862 (0.662-1.123)	-1.102	117/1010	135/1023		.27
Lonn et al,[37] 2016	0.993 (0.699-1.410)	-0.039	49/1220	97/2399		.97
Beckett et al,[30] 2008	0.676 (0.502-0.911)	-2.570	83/788	121/816		.01
Klahr et al,[13] 1994	1.366 (0.681-2.742)	0.878	20/432	14/408		.38
Mant et al,[34] 2016	3.588 (0.140-91.945)	0.772	1/26	0/30		.44
Ruggenenti et al,[22] 2005	0.667 (0.110-4.042)	-0.441	2/167	3/168		.66
Schrier et al,[25] 2002	0.825 (0.050-13.701)	-0.134	1/41	1/34		.89
SHEP Cooperative Research Group,[28] 1991	0.900 (0.670-1.209)	-0.700	96/879	103/859		.48
Wright et al,[17] 2015	0.714 (0.519-0.982)	-2.072	70/1330	95/1316		.04
Benavente et al,[33] 2013	0.850 (0.468-1.544)	-0.534	24/216	25/195		.59
Staessen et al,[29] 1997	0.826 (0.470-1.451)	-0.665	26/242	29/228		.51
Toto et al,[23] 1995	2.566 (0.101-64.993)	0.572	1/42	0/35		.57
UK Prospective Diabetes Study Group,[35] 1998	1.667 (0.626-4.435)	1.023	20/68	7/35		.31
Overall	0.859 (0.764-0.965)	-2.560	584/7451	709/8473		.01

Heterogeneity: $\tau^2 = 0\%$; $P = .77$; $I^2 = 0\%$

0.1   0.2   0.5   1   2   5   10
Odds Ratio (95% CI)

In the 18 included trials,[13,14,17,22-36] there were 584 deaths among 7451 participants in the more intensive BP arm and 709 deaths among 8473 participants in the less intensive BP arm during the trial phase. The trial by Howard et al[31] had no mortality outcomes in both BP arms (more intensive vs less intensive) and was dropped from the analysis.

BP Control and Risk of Mortality

Figure 2 shows the main results of the meta-analysis. In the 18 included trials, there were 584 deaths among 7451 participants (7.8%) in the more intensive BP arm and 709 deaths among 8473 participants (8.4%) in the less intensive BP arm during the trial phase. Using the random-effects model, the OR for death among participants with CKD randomized to the more intensive BP-lowering arm was 0.86 (95% CI, 0.76-0.97; $P = .01$) compared with the less intensive BP arm. The results were similar with the fixed-effects model. None of the individual trials had an excessive influence on the pooled effect size. There was no evidence of heterogeneity across studies ($I^2 = 0\%$, P for heterogeneity = .77). Funnel plot analysis revealed no evidence of publication bias based on visual inspection (**Figure 3**) or by performing Begg and Mazumdar rank correlation ($P = .23$) and Egger regression ($P = .08$) tests. Because we knew a priori that SPRINT had found that intensive BP control improved mortality and provided substantial statistical power to this meta-analysis, we specifically evaluated the remaining trials with the exclusion of SPRINT in a sensitivity analysis. The results were similar in this analysis (OR, 0.88; 95% CI, 0.78-0.99; $P = .05$).

Subgroup Analysis

The observed effect of those randomized to the more intensive BP arm on mortality was consistent irrespective of the following: type of treatment in the comparator arm (placebo or less intensive BP target), median follow-up duration (<3 vs ≥3 years), inclusion of diabetic patients (yes or no), CKD severity (serum creatinine level <2.0 mg/dL or creatinine clearance >30 mL/min/1.73 m² vs serum creatinine level ≥2.0 mg/dL

or creatinine clearance ≤30 mL/min/1.73 m²), baseline SBP of the entire cohort (<140 mm Hg vs 140-160 mm Hg vs >160 mm Hg), or achieved SBP in the more intensive lowering group (SBP<125 mm Hg vs SBP 125-135 mm Hg vs SBP >135 mm Hg) (**Figure 4**). (To convert creatinine level to micromoles per liter, multiply by 88.4; creatinine clearance to milliliters per second per meter squared, multiply by 0.0167.) In the trials that achieved a difference in SBP of at least 12 mm Hg, the OR of death in the more intensive vs less intensive arms was 0.76, trials with differences exceeding 6 but less than 12 mm Hg had an OR of 0.97, and those with differences of 6 mm Hg or less had an OR of 1.06; formal testing for heterogeneity resulted in a P value of .06. Meta-regression adjusting for baseline SBP level showed a similar pattern suggesting greater mortality benefit in trials with higher differences in achieved BP across treatment arms, although this finding did not reach statistical significance (slope of log OR per mm Hg difference in SBP, −0.0201; 95% CI, −0.0499 to 0.0097; $P = .19$) (eFigure in the Supplement).

Discussion

In this systematic review and meta-analysis of 18 RCTs among 15 924 participants with both hypertension and an eGFR less than 60 mL/min/1.73 m² randomized to more intensive vs less intensive BP lowering, those randomized to more intensive BP lowering had 14.0% lower risk of all-cause mortality. We observed a suggestion of a mortality benefit in studies that achieved the greatest difference in SBP between the 2

Figure 3. Studies Evaluating Intensive Blood Pressure Control Relative to Mortality Among Persons With Chronic Kidney Disease
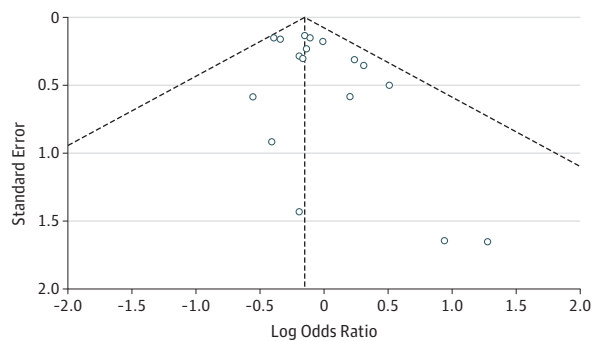
A symmetrical inverted funnel implies no publication bias. Each open circle represents an individual published study.

treatment arms (P = .06). These findings add to the body of evidence that may inform public health policy, clinical guideline development, and individual patient care in patients with CKD.

A prior meta-analysis[49] found beneficial effects in persons randomized to more intensive BP lowering on CVD events among patients with CKD (26 trials among 30 295 participants; hazard ratio [HR], 0.83; 95% CI, 0.76-0.90). Cardiovascular disease events are important and are the major cause of death in those with CKD. However, we evaluated all-cause mortality because it balances the competing risk of multiple clinical outcomes and because it is a "hard" outcome assessed similarly across studies. For example, if more intensive BP lowering leads to higher risk of AKI and CKD progression but lower risk of CVD events, these outcomes could offset one another, with no overall effect on all-cause mortality. This consideration is particularly important in persons who have CKD at baseline. Less residual kidney function may make participants with CKD particularly vulnerable to additional insults, resulting in loss of kidney function, as has been reported in clinical trials[17,50] evaluating intensive BP control. While more intensive BP control appears to acutely lower eGFR, the significance of this finding in patients with CKD remains uncertain. A recent study[51] among AASK and MDRD trial participants showed that a 5% to less than 20% acute decline in the eGFR in the intensive BP arm was not associated with higher risk of ESRD (adjusted HR [aHR], 1.19; 95% CI, 0.84-1.68 in the AASK and 1.08; 95% CI, 0.84-1.40 in the MDRD). However, a similar change in the less intensive arm was associated with ESRD (aHR, 1.83; 95% CI, 1.30-2.57 in the AASK and 1.62; 95% CI, 1.25-2.11 in the MDRD). Therefore, the results of our meta-analysis suggest that more intensive BP control may provide more benefit than harm in persons with CKD.

Approximately 30% of the SPRINT participants had CKD at baseline.[17] The primary end point of SPRINT was a composite CVD end point. While the P value for interaction for the primary CVD end point comparing those with and without CKD was not statistically significant (P = .36), the effect estimate was smaller and did not reach statistical significance in the CKD subgroup for the primary CVD end point

(HR, 0.82; 95% CI, 0.63-1.07). Moreover, intensive BP control resulted in higher risk of a 30% decline in the eGFR among those without CKD, as well as more rapid loss of the eGFR, and greater AKI events in the SPRINT participants both with and without CKD at baseline. In SPRINT, those with CKD randomized to the intensive BP-lowering arm had a statistically significant reduction in all-cause mortality (HR, 0.72; 95% CI, 0.52-0.98; P = .04). However, the total number of deaths in the SPRINT CKD subgroup was low (70 deaths among 1330 individuals in the intensive BP group vs 95 deaths among 1336 individuals in the standard treatment group), and the trial excluded persons with diabetes, proteinuria greater than 1000 mg/g, and prior stroke. It was unknown whether the results generalize to other subsets and whether the mortality benefit observed in the SPRINT participants with CKD was reproducible. The present meta-analysis extends these findings and provides additional assurance in a larger study sample and across different settings. Overall, we found little heterogeneity across studies and a similar mortality benefit in persons treated with more intensive BP lowering.
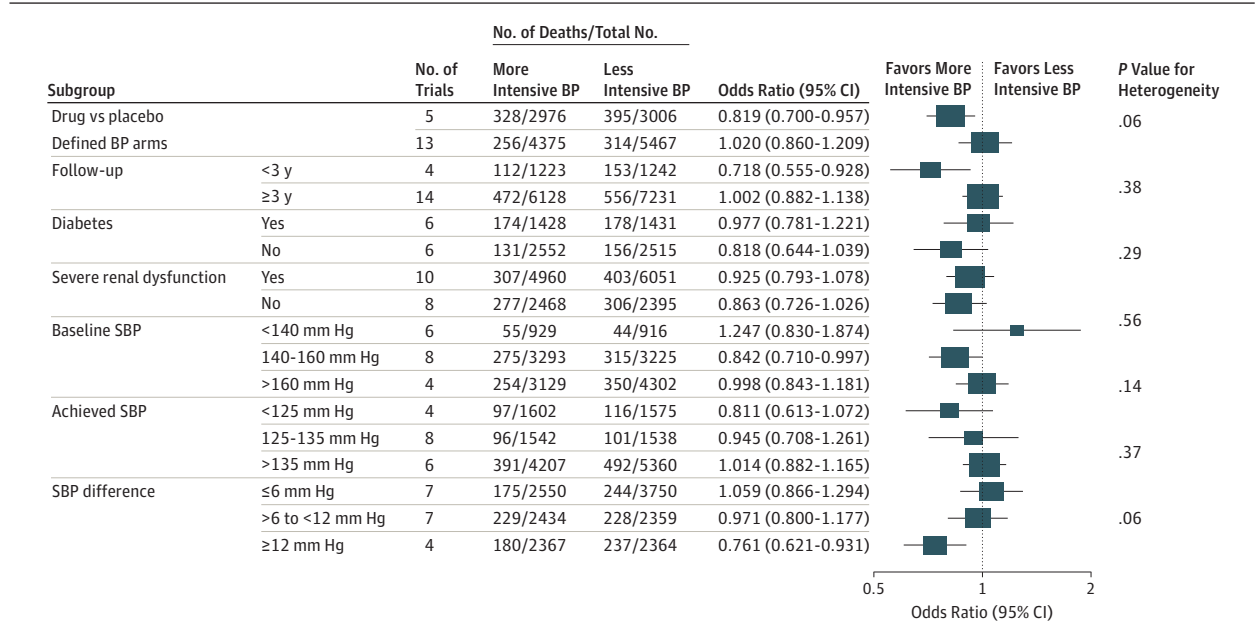
The highest mortality benefit was observed in studies that achieved the greatest difference in SBP during the trial, a result that did not reach statistical significance (P = .06 for heterogeneity).These data will need to be reevaluated when additional trials evaluating intensive BP control among those with CKD are completed. Nonetheless, this preliminary finding supports our overall conclusion that more intensive BP control may be beneficial for individuals with CKD. The size of the mortality reduction in patients with CKD (14%) is similar to the percentages (9% and 11%) calculated in recent meta-analyses[52,53] of all BP-lowering trials, and this result suggests that the benefits of BP lowering on all-cause mortality do not differ substantially in the presence or absence of CKD.

The findings of this meta-analysis may have implications to both clinical practice and public health policy. Relative to public policy, the KDIGO Blood Pressure Work Group[54] announced that they have convened a panel of experts to review evidence and potentially modify their guideline recommendations regarding appropriate BP targets in patients with CKD. The present meta-analysis may provide useful data for the upcoming guideline review. Our results may also offer additional information for patients and health care professionals and may be useful to guide shared decision making about the relative risks and benefits of BP lowering among those with CKD.

Strengths and Limitations

This study has several strengths. First, multiple high-quality, methodologically rigorous randomized trials had not previously reported differences in death rates across treatment arms in persons with prevalent CKD. Among the 18 trials included in this meta-analysis, investigators from 9 trials reevaluated their data within the CKD subset and provided data specifically to support this study. Therefore, our meta-analysis provides a substantial new evidence base about the risks and benefits of intensive BP lowering in populations with CKD. Second, we assessed mortality as a hard clinical

Figure 4. Effect of More Intensive Blood Pressure (BP) Lowering on Risk of Mortality in Patients With Chronic Kidney Disease Stratified by Subgroups

			No. of Deaths/Total No.			Favors More Intensive BP / Favors Less Intensive BP	
Subgroup		No. of Trials	More Intensive BP	Less Intensive BP	Odds Ratio (95% CI)		P Value for Heterogeneity
Drug vs placebo		5	328/2976	395/3006	0.819 (0.700-0.957)		.06
Defined BP arms		13	256/4375	314/5467	1.020 (0.860-1.209)		
Follow-up	<3 y	4	112/1223	153/1242	0.718 (0.555-0.928)		.38
	≥3 y	14	472/6128	556/7231	1.002 (0.882-1.138)		
Diabetes	Yes	6	174/1428	178/1431	0.977 (0.781-1.221)		.29
	No	6	131/2552	156/2515	0.818 (0.644-1.039)		
Severe renal dysfunction	Yes	10	307/4960	403/6051	0.925 (0.793-1.078)		.56
	No	8	277/2468	306/2395	0.863 (0.726-1.026)		
Baseline SBP	<140 mm Hg	6	55/929	44/916	1.247 (0.830-1.874)		.14
	140-160 mm Hg	8	275/3293	315/3225	0.842 (0.710-0.997)		
	>160 mm Hg	4	254/3129	350/4302	0.998 (0.843-1.181)		
Achieved SBP	<125 mm Hg	4	97/1602	116/1575	0.811 (0.613-1.072)		.37
	125-135 mm Hg	8	96/1542	101/1538	0.945 (0.708-1.261)		
	>135 mm Hg	6	391/4207	492/5360	1.014 (0.882-1.165)		
SBP difference	≤6 mm Hg	7	175/2550	244/3750	1.059 (0.866-1.294)		.06
	>6 to <12 mm Hg	7	229/2434	228/2359	0.971 (0.800-1.177)		
	≥12 mm Hg	4	180/2367	237/2364	0.761 (0.621-0.931)		

Odds Ratio (95% CI) — scale 0.5 to 2

Shown are the results among adults with estimated glomerular filtration rate less than 60 mL/min/1.73 m². Among the 18 trials, only 12 included individuals with diabetes. BP indicates blood pressure; SBP, systolic blood pressure.

outcome, which has obvious clinical importance, is similarly ascertained across studies, and is thus largely free of bias. Third, we restricted our analysis to outcomes that were assessed during the trial phase of each study only and excluded events that occurred during long-term follow-up. While there is important information obtained in such follow-up,[55,56] BP control often approached similar levels across treatment arms after the trial phase.[55]

Our study also has important limitations. First, despite considerable efforts to contact investigators, we were not able to obtain data on mortality in persons with CKD in several prior clinical trials. Therefore, these trials were excluded by necessity. Among the 18 studies with almost 16 000 participants with CKD, we found no evidence of heterogeneity. This observation provides confidence, although not certainty, that the results would likely have been similar with the inclusion of additional studies. Second, we lacked data by severity of CKD and thus could not evaluate the effect of more intensive BP lowering on mortality stratified by CKD severity. Most individuals in the included trials had CKD stage 3, and we acknowledge that the risks and benefits of more intensive BP lowering may differ in persons with more

advanced CKD. Third, baseline BP and the intensity of BP reduction in the randomized treatment arms differed across the individual trials. As such, we are not able to provide an estimate of an optimal BP target in patients with CKD. We recognize that CVD events, CKD progression, AKI, and ESRD are important factors that may be in the causal pathway between more intensive BP lowering and mortality and were not able to assess these end points.

Conclusions

Among trial participants with hypertension and an eGFR less than 60 mL/min/1.73 m², randomization to more intensive BP lowering was associated with lower risk of all-cause mortality. This finding was consistent across trials, with no evidence of heterogeneity. A nonsignificant suggestion of greater mortality benefit was observed in trials that achieved the greatest difference in SBP across arms. Although additional studies and intensive monitoring for safety are warranted, these data support that the net benefits may outweigh the net harms of more intensive BP lowering in persons with CKD.

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