Title: Blood Pressure Lowering and Risk of Mortality in Chronic Kidney Disease: A Meta-Analysis of Randomized Controlled Trials

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Key Points

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

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

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

Abstract

Importance: Trials in hypertensive patients demonstrate that intensive blood pressure (BP) lowering reduces risk of cardiovascular disease (CVD) and all-cause mortality, but may increase 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.

Objective: We conducted a meta-analysis of Randomized controlled trials (RCTs) to determine if more intensive, compared with a less intensive, BP control is associated with reduced mortality risk in persons with CKD stages 3-5.

Data Sources: Ovid Medline, Cochrane Library, Embase, Pubmed, Science Citation Index, Google Scholar, and ClinicalTrials.gov electronic databases.

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

Data extraction and synthesis: Two reviewers 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, we contacted trial investigators and requested data within the CKD subset of their original trials.

Main outcomes and measures: All-cause mortality during the active treatment phase of each trial.

Results: We identified 30 RCTs that potentially met inclusion criteria, among which we were able to extract the CKD subset mortality data in 18 trials. Among these, there were 1293 deaths among 15,924 participants with CKD. The mean baseline systolic blood pressure (SBP) was 148±16 mm hg in both intensive and less-intensive arms. The mean SBP dropped by 16 mm Hg to 132 mm Hg in the intensive arm and by 8 mm Hg to 140 mm Hg in the less-intensive arm. More vs. less-intensive BP control resulted in 14% lower risk of all-cause mortality (Odds Ratio (OR) 0.86; 95% CI 0.76 to 0.97, p = 0.01); a finding that was without significant heterogeneity and appeared consistent across multiple subgroups including type of treatment in the comparator arm (placebo vs. less intensive BP target), length of follow-up, presence of diabetes, CKD severity, baseline systolic blood pressure (SBP), achieved SBP during the trial and degree of SBP differences across the treatment arms.

Conclusion 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.

Introduction

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 for cardiovascular disease (CVD), progression to end stage renal disease (ESRD), and all-cause mortality[3]. Hypertension is a well-known risk factor for CVD and thus 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 have addressed the optimal BP target in CKD populations [6-10], 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) and African American Study of Kidney Disease and Hypertension (AASK) failed to demonstrate benefits of BP lowering for slowing down CKD progression, and were underpowered to address CVD and mortality.[13,14]

The current Kidney Disease Improving Global Outcomes (KDIGO) BP guidelines recommend a BP goal of less than 130/80 mmHg for individuals with CKD and moderate-to-severe albuminuria and less than 140/90 mmHg for those with CKD and albuminuria <30 mg/g[7]. The Eighth Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 8) and the 2013 European Society of Hypertension/European Society of Cardiology Task Force concluded that BP target less than 140/90 mmHg for individuals with CKD, and made no distinction based on the albuminuria level.[15,16] These guidelines were published before The Systolic Blood Pressure Intervention Trial (SPRINT) was completed. The SPRINT study 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 SBP target of less than 120 mmHg as compared with less than 140 mmHg, though with a significant excess of acute kidney injury (AKI).[17] Patients with CKD

(defined as eGFR 20-59 ml/min/1.73 m^2) accounted for approximately 30% of SPRINT trial 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 control trials represent a major challenge to comprehensively address these endpoints in a meta-analysis. In contrast, mortality is similarly defined across studies, and is virtually always reported as it is an important safety signal. Mortality also provides a summary estimate of net benefits and harms of the intervention. Thus, our goal was to determine the effect of more intensive BP control on mortality among those with CKD.

Methods

Electronic searches

The Ovid MEDLINE, Cochrane Library, Embase, Pubmed, Science Citation Index, Google Scholar, and ClinicalTrials.gov electronic databases searches were completed from January 1, 1950 to June 1, 2016, with the following key words: “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 detailed database search strategy is described in the study protocol. 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 Meta-Analyses (PRISMA) statement recommendations (Table S3).[19]

Selection of Studies

Study eligibility was individually determined by two independent reviewers (RM and AN). Both open-label and double-blinded randomized controlled trials (RCT) who had adult participants with CKD, which was defined as eGFR < 60 mL/min per 1.73m^2 by either the Modification of Diet in Renal Disease (MDRD) or Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations, and had randomized participants to two defined BP targets (either BP intervention vs. placebo or no treatment, or more vs. less intensive BP control), were eligible for inclusion. 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 in dialysis patients were excluded.

Data Extraction and Quality Assessment

Demographics, co-morbid characteristics, enrollment criteria, BP control targets in each arm, mean reductions of systolic and diastolic BP, and mortality events were extracted onto standardized extraction forms. Extracted data was then verified by another researcher. For any discrepancies, both investigators met, conferred, and consensus was reached. The quality and clinical generalizability of each study was assessed according to the methods based on allocation concealment, blinding methods of participants, investigators and assessors, intention to treat analysis, percent withdrawals, and whether withdrawals were adequately described.[20]

Outcome Measures

The primary outcome was all-cause mortality during the active treatment phase of each trial.

Statistical Analysis

Mortality outcomes in each randomized BP group were pooled and weighted odds ratio (OR), comparing the lower BP arm (intensive BP) to subjects randomized to higher BP targets (less intensive or placebo), and their 95% confidence intervals (CI) were calculated using both random and fixed-effect models. The influence of individual trials on pooled effect size was assessed, and the trial was considered to have an excessive influence if, after its exclusion, the point estimate of the remaining trials was outside the confidence interval of the overall risk estimate. Heterogeneity was assessed based on I^2 test (I^2= 0-25%: no or mild heterogeneity; I^2= 25-50%: moderate heterogeneity; I^2= 50-75%: large heterogeneity; and I^2= 75-100%: extreme heterogeneity).[20] Subgroup analyses were performed stratified by type of study (drug vs. placebo vs. two defined BP target arms), study trial duration, diabetes status (yes or no), baseline SBP, the level of achieved SBP during the trial phase, and the SBP difference between the two randomized arms. Meta-regression analysis was performed to assess the relation between the SBP differences during the trial phase and mortality risk while adjusting for baseline SBP. Potential publication bias was assessed using Funnel plots. A p-value < 0.05 was considered statistically significant for all analyses including tests for heterogeneity. All statistical analyses were performed using the Comprehensive Meta-Analysis software version 2.2.064 (Biostat Inc, NJ, USA).

Results

Literature search

The initial search of the Ovid MEDLINE and Cochrane databases between January 1, 1950 and June 1, 2016 provided 4,416 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 method section. In subsequent review, 378 studies were discarded because they did not fulfill

inclusion criteria. The remaining 30 studies were reviewed in full text and identified for meta-analysis (Figure 1). Data elements from nine trials were extracted from the publications. [13,14,17,21-27] We contacted trial investigators for the remaining trials and nine provided data on number of CKD participants and deaths during the trial phase for the two BP arms for the purpose of inclusion in this meta-analysis.[28-36] Among the others, we were unable to obtain mortality data in the CKD subset from the investigators for the remaining 12 trials.[37-48] Thus, eighteen randomized trials involving 15,924 participants with CKD and complete data were included in the meta-analysis (Figure 1).

Study Characteristics

Table S1 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 fifteen trials reported adequate methods for random allocation and concealment of treatment assignment (Table S2). There were six trials that had excluded patients with insulin-dependent diabetes mellitus (IDDM)[13,22,26-28,35] whereas three trials excluded patients with all forms of diabetes.[14,17,23] Thirteen of the eighteen trials had two defined BP targets[13,14,17,22-25,31-36] and the remaining five evaluated a BP lowering intervention vs. no treatment or a placebo arm.[26-30] One trial has three defined BP targets. For the purposes of this meta-analysis, the lowest BP target group was compared to the other two groups together.[36] BP targets varied across trials (Table 1). The median (interquartile range (IQR)) baseline SBP was 143 (137-162) mm Hg in the intensive and 153 (137-163) mm Hg in the less intensive arms. The median (IQR) follow-up period was 3.6 (2.8-4.9) years. The median (IQR) difference in SBP achieved across arms among 18 adult trials was 10 (4-12) mm Hg (130 (125-141) mm hg in intensive vs. 138 (134-146) mm Hg in less-intensive arm).[13,14,17,22-36] The renal inclusion and exclusion criteria varied across trials and are described in Table S1.

BP control and risk of mortality

Figure 2 depicts the main results of the meta-analysis. In the eighteen included trials, there were 584 deaths among 7,451 participants (7.8%) in the more intensive BP arm and 709 deaths among 8,473 participants (8.4%) in the less intensive BP arm during the trial phase. Using the random-effect model, the odds ratio (OR) for death among participants with CKD randomized to the intensive BP lowering arm was 0.86 (95% CI, 0.76 to 0.97, p = 0.01) compared to the less intensive BP arm. The results were similar with the fixed-effect model. None of the individual trials have excessive influence on pooled effect size. Since we new a priori that SPRINT had found that intensive BP control improved mortality, and provides substantial power to this meta-analysis, we specifically evaluated the remaining trials excluding SPRINT in a sensitivity analysis. Results were similar in this analysis (HR 0.88, 95% CI 0.78 to 0.99, p = 0.05). There was no evidence of heterogeneity across studies (I^2 = 0.0%, p-heterogeneity = 0.77). Funnel-plot analysis revealed no evidence of publication bias based on visual inspection (Figure 3) or by performing Begg and Mazumdar rank correlation (p = 0.23) and Egger's regression (p = 0.08) tests.

Subgroup analysis

The observed effect of those randomized to the more intensive BP arm on mortality was consistent irrespective of the type of treatment in the comparator arm (placebo or less intensive BP target), median follow-up duration (< 3 years vs. ≥ 3 years), diabetic status (yes or no), CKD severity (sCR < 2.0 mg/dL or creatinine clearance < 30 ml/min vs sCR >2.0 mg/dL or creatinine clearance > 30 ml/min), baseline SBP of the entire cohort (<140 mm Hg vs. 140-160 mm Hg vs. > 160 mm Hg), or achieved SBP in the intensive lowering group (SBP <125 mmHg vs. SBP 125-135 mm Hg vs. SBP > 135 mm Hg) (Figure 4). In the trials that achieved a difference in SBP ≥ 12 mm Hg, the odds of death in the more intensive vs. less intensive arm was 0.76; trials

with differences > 6 to <12 mm Hg had an OR of 0.97; and those with differences ≤ 6 mm Hg had an OR for mortality of 1.06; formal testing for heterogeneity approached statistical significance (p=0.062). Meta-regression adjusting for baseline SBP level, showed a similar pattern trending towards greater mortality benefit in trials with greater 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= 0.19) (Figure S1).

Discussion

In this meta-analysis of eighteen randomized controlled trials among 15,924 participants with both hypertension and an eGFR < 60 ml/min/1.73m^2 randomization to more vs. less intensive BP lowering, those randomized to more intensive BP lowering had 14% lower risk of all-cause mortality. We observed a trend towards mortality benefit in studies that achieved the greatest separation in SBP between the two treatment arms especially ≥ 12 mm Hg (p=0.062). These findings add to the body of evidence which may inform public health policy, clinical guideline development, and individual patient care in patients with CKD.

A prior meta-analysis found beneficial effects in persons randomized to more intensive BP lowering on CVD events among patients with CKD (26 trials, 30 295 participants, hazard ratio (HR) 0.83; 95% CI 0.76 to 0.90).[49] CVD events are extremely important, and are the major cause of death in those with CKD. However, we evaluated all-cause mortality as it balances the competing risk of multiple clinical outcomes and because it is a “hard” outcome assessed similarly across studies. For example, if intensive BP lowering leads to higher risk of AKI and potential CKD progression but lower risk of CVD events, these outcomes could offset one another resulting in 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 multiple clinical trials evaluating intensive BP control.[17,50] Though the results from recent meta-analysis showed that intensive BP lowering was protective against kidney failure events especially in patients with CKD and proteinuria.[21] Another study in AASK and MDRD trial also showed that 5% to <20% acute decline in eGFR in intensive BP arm was not associated with a higher risk of ESRD (adjusted hazard ratio (aHR), 1.19; 95% % CI 0.84 to 1.68) and (aHR, 1.08; 95% CI, 0.84 to 1.40), respectively) were as similar changes in the less intensive group were associated with ESRD (aHR, 1.83; 95% % CI 1.30 to 2.57) and (aHR, 1.62; 95% CI, 1.25 to 2.11), respectively.[51] The results of our meta-analysis, therefore, suggest that intensive BP control may provide more benefit than harm in persons with CKD.

Approximately 30% of SPRINT study participants had CKD at baseline.[17] The primary endpoint of the SPRINT trial was a composite CVD endpoint. While the p-value for interaction for the primary CVD endpoint comparing those with and without CKD was not statistically significant (p=0.36), the effect estimate was smaller and did not reach statistical significance in the CKD subgroup (HR 0.82; 95% CI 0.63 to 1.07). Moreover, intensive BP control resulted in a higher risk of a 30% decline in eGFR among those without CKD, and more rapid loss of eGFR, and higher AKI events in SPRINT participants both with and without CKD at baseline.[17] Interestingly, in the SPRINT trial, 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 to 0.98; p= 0.04). However, the total number of death events in the SPRINT CKD subgroup were relatively low (70 deaths among 1330 individuals in intensive-BP group vs. 95 deaths among 1,336 in the standard-treatment group) and the trial excluded persons with diabetes, proteinuria greater than 1000 mg/g, and prior stroke. Whether results generalize to these other subsets, and whether the mortality benefit observed in SPRINT participants with CKD is reproducible was previously unknown. The present meta-analysis extends these findings, and provides additional

assurances in a larger study sample and across different settings. Overall, we observed little heterogeneity across studies.

We observed a trend towards the greatest mortality benefit in studies that achieved the greatest separation in SBP during the trial; a finding that did not reach statistical significance (p=0.062). These data will need to be re-evaluated 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 those with CKD. The size of the mortality reduction in CKD patients (14%) is similar to that (9% and 11%) calculated in a recent meta-analysis of all BP-lowering trials[52,53], and this suggests the benefits of BP lowering in all-cause mortality do not differ substantially in presence or absence of CKD.

The findings of this meta-analysis may have implications to both clinical practice and public health policy. In regards to public policy, the KDIGO recently announced that they have convened a panel of experts to review evidence and potentially modify their guideline recommendations regarding appropriate blood pressure targets in patients with CKD.[54] This meta-analysis may provide useful data for the upcoming guideline review. Our findings may also provide additional information for patients and healthcare providers, and may be useful to guide shared decision making about the relative risks and benefits of blood pressure lowering among those with CKD.

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 eighteen studies included in this meta-analysis, investigators from nine trials re-evaluated their data within the CKD subset and provided data specifically to support this study. Thus, this manuscript 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 outcome which has obvious clinical importance and is

similarly ascertained across studies and is therefore largely free of bias. In addition, 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 long-term follow-up[55,56], BP control often approached similar levels across treatment arms after the trial phase.[55]

Our study also has important limitations. Despite considerable efforts to contact investigators, we were not able to obtain data on mortality in persons with CKD in several prior clinical trials. These trials were therefore excluded by necessity. However, among the nineteen studies with nearly 16,000 CKD participants, we found no evidence of heterogeneity. This provides confidence, although not certainty, that results would likely have been similar with inclusion of additional studies. Next, we lacked data by strata of CKD, and therefore 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. Fourth, baseline BP, and the intensity of BP reduction in the randomized treatment arms were different across the individual trials. As such, we are not able to provide an estimate of an optimal BP target in CKD patients. We recognize that CVD events, CKD progression, AKI and ESRD events are important factors that may be in the causal pathway between more intensive BP lowering and mortality, and were not able to assess these endpoints.

Conclusions

Among trial participants with hypertension and an eGFR < 60 ml/min/1.73m^2, 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 non-significant trend towards 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 the notion that the net benefits may outweigh net harms of more intensive BP lowering in persons with CKD.

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Figure Legends

Figure 1: Title: Selection of Studies for the Meta-Analysis. Legend: None.

Figure 2: Title: Effect of Intensive Blood Pressure Lowering on Risk of Mortality in Hypertensive Trial Participants with CKD. Legend: None.

Figure 3: Title: Funnel Plot of Studies Evaluating Intensive Blood Pressure Control in Relation to Mortality among Persons with CKD. Legend: A symmetrical inverted funnel implies no publication bias. Each open circle represents individual published study.

Figure 4: Title: Effect of More Intensive Blood Pressure Lowering on Risk of Mortality in Patients with CKD, Stratified by Subgroups. Legend: None.

Figure S1: Title: Random Effects Meta-Regression Plot Depicting Risk of Mortality by Magnitude of Difference in Systolic Blood Pressure (SBP) Achieved Across Randomization Arms, Adjusting for Baseline SBP. Legend: Slope= -0.0201, 95% CI, -0.0499 to 0.0097, *P*= 0.19. The plot shows the correlation between differences in SBP (plotted as a mean value on the x-axis) and the probability of mortality (log OR) (plotted on the y-axis). Each circle represents an individual study, and the circumference of each circle is proportional to the sample size of each study. OR= odds ratio.

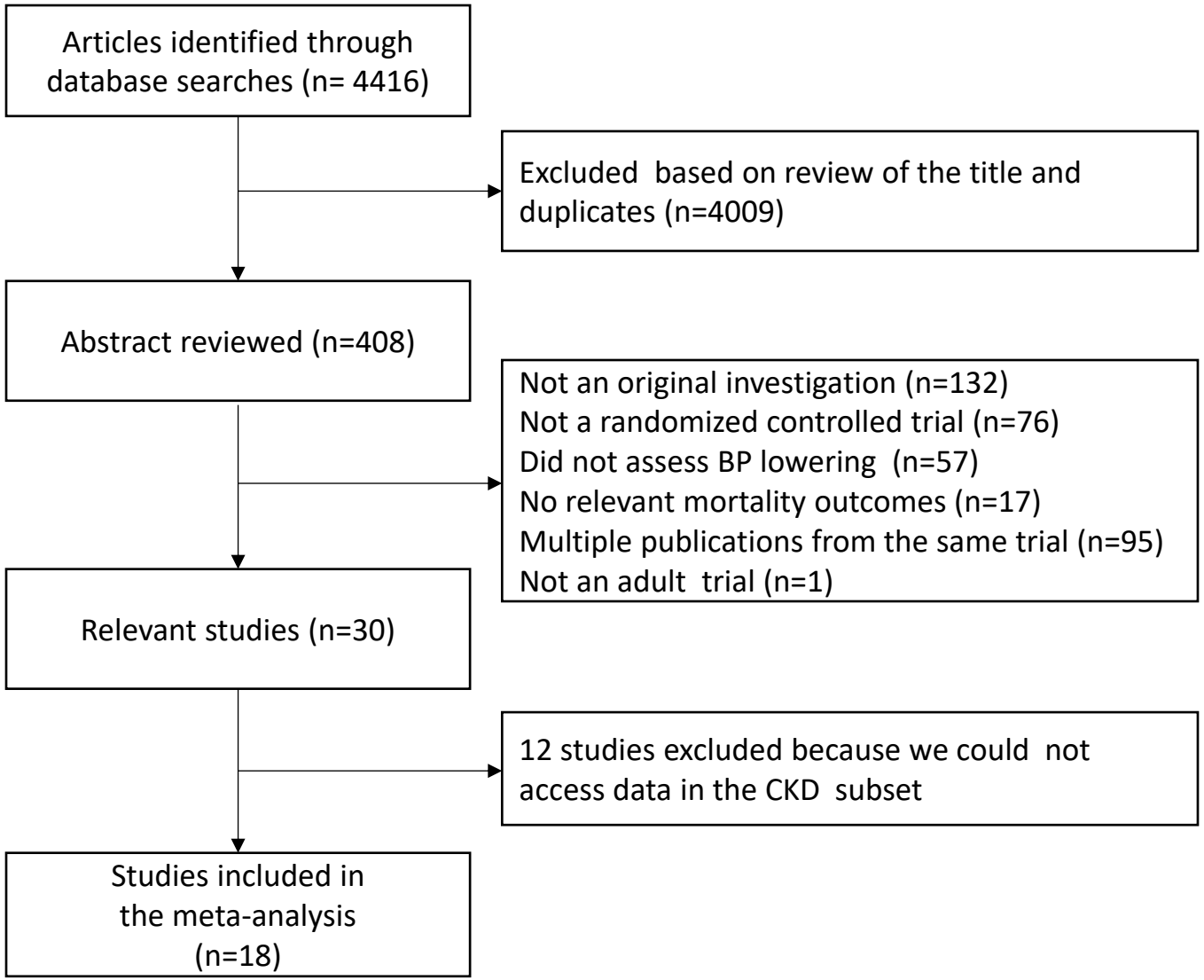
Articles identified through database searches (n= 4416)
Excluded based on review of the title and duplicates (n=4009)
Abstract reviewed (n=408)
Not an original investigation (n=132)
Not a randomized controlled trial (n=76)
Did not assess BP lowering (n=57)
No relevant mortality outcomes (n=17)
Multiple publications from the same trial (n=95)
Not an adult trial (n=1)
Relevant studies (n=30)
12 studies excluded because we could not access data in the CKD subset
Studies included in the meta-analysis (n=18)

Figure 1

Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value	More Intensive BP	Less Intensive BP
AASK (14)	0.874	0.554	1.380	-0.578	0.564	37 / 540	43 / 554
ABCD (H) (24)	0.575	0.182	1.820	-0.941	0.347	5 / 62	9 / 68
ABCD (N) (26)	1.227	0.389	3.865	0.349	0.727	6 / 57	7 / 80
ACCORD (32)	1.271	0.685	2.360	0.761	0.447	26 / 208	20 / 198
ADVANCE (27)	0.862	0.662	1.123	-1.102	0.270	117 / 1010	135 / 1023
HOT (37)	0.993	0.699	1.410	-0.039	0.969	49 / 1220	97 / 2399
HYVET (30)	0.676	0.502	0.911	-2.570	0.010	83 / 788	121 / 816
MDRD (13)	1.366	0.681	2.742	0.878	0.380	20 / 432	14 / 408
PAST-BP (34)	3.588	0.140	91.945	0.772	0.440	1 / 26	0 / 30
REIN-2 (22)	0.667	0.110	4.042	-0.441	0.659	2 / 167	3 / 168
SCHRIER (25)	0.825	0.050	13.701	-0.134	0.893	1 / 41	1 / 34
SHEP (28)	0.900	0.670	1.209	-0.700	0.484	96 / 879	103 / 859
SPRINT (17)	0.714	0.519	0.982	-2.072	0.038	70 / 1330	95 / 1316
SPS3 (35)	0.850	0.468	1.544	-0.534	0.594	24 / 216	25 / 195
SYS-EUR (29)	0.826	0.470	1.451	-0.665	0.506	26 / 242	29 / 228
TOTO (23)	2.566	0.101	64.993	0.572	0.568	1 / 42	0 / 35
UKPDS (35)	1.667	0.626	4.435	1.023	0.306	20 / 68	7 / 35
OVERALL	0.859	0.764	0.965	-2.560	0.010		

Dead/Total:
584/7451 (more-intensive) vs. 709/8473 (less-intensive)
Tau2= 0.0%; I^2 = 0.0%; df = 16; P-heterogeneity = 0.768

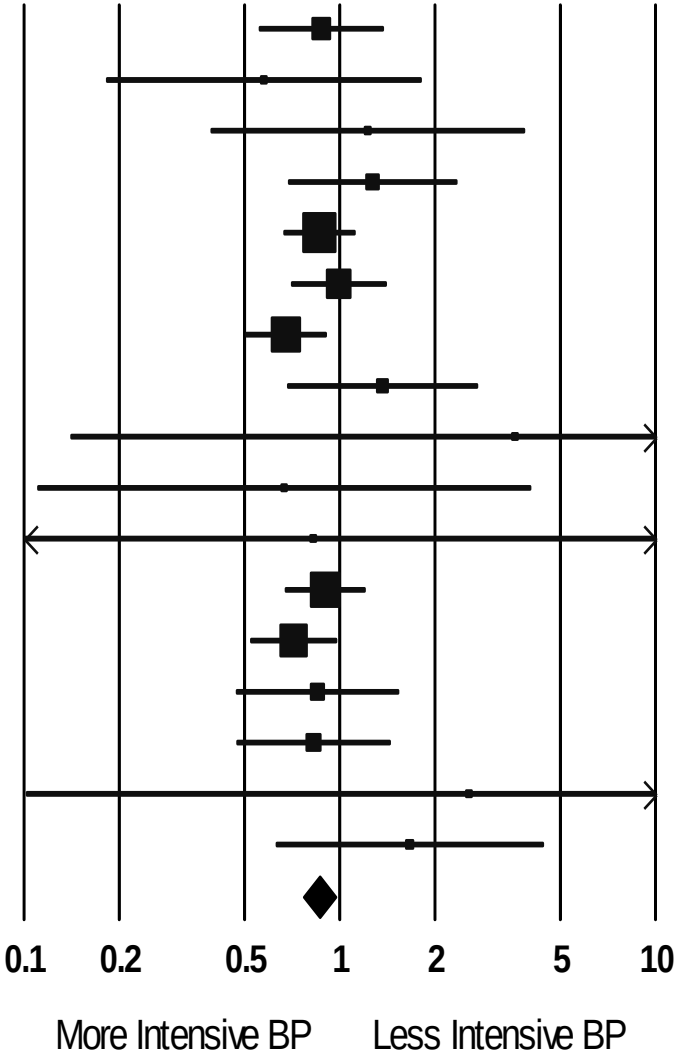

Figure 2

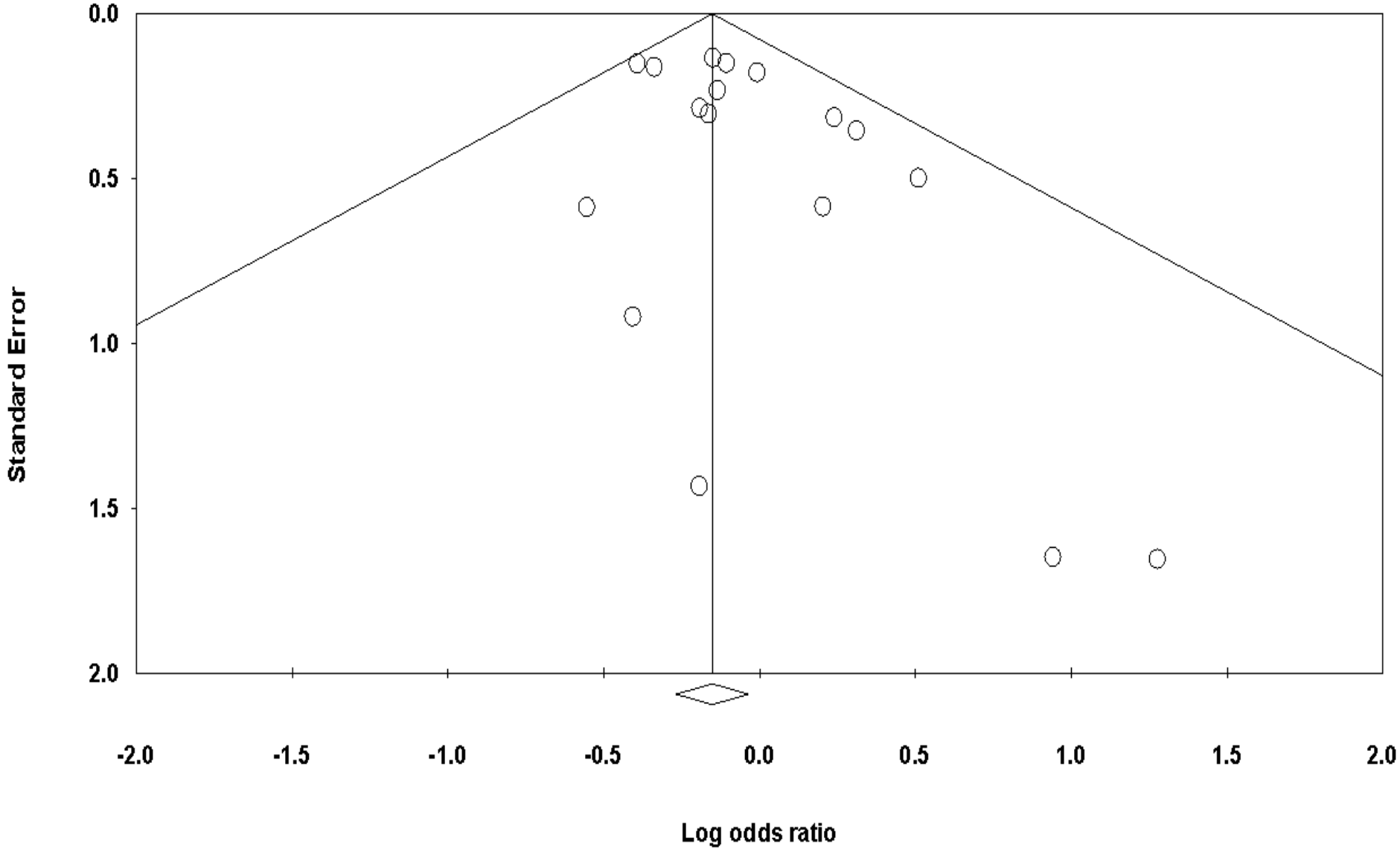
0.0
0.5
1.0
1.5
2.0
Standard Error
-2.0
-1.5
-1.0
-0.5
0.0
0.5
1.0
1.5
2.0
Log odds ratio

Figure 3

Subgroup		Number of Trials	eGFR < 60 ml/min/1.73m² (Deaths/Total)		Odds ratio	95% C.I		P-value for heterogeneity	0dds ratio (95% CI)
			More Intensive BP	Less Intensive BP					
Drug vs. Placebo		5	328/2976	395/3006	0.819	0.700	0.957	0.062	
Defined BP arms		13	256/4375	314/5467	1.020	0.860	1.209		
Follow-up	< 3 yrs	4	112/1223	153/1242	0.718	0.555	0.928	0.380	
	≥ 3 yrs	14	472/6128	556/7231	1.002	0.882	1.138		
Diabetes	yes	6	174/1428	178/1431	0.977	0.781	1.221	0.289	
	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	0.560	
	no	8	277/2468	306/2395	0.863	0.726	1.026		
Baseline SBP	< 140 mmHg	6	55/929	44/916	1.247	0.830	1.874		
	140-160 mmHg	8	275/3293	315/3225	0.842	0.710	0.997	0.138	
	> 160 mmHg	4	254/3129	350/4302	0.998	0.843	1.181		
Achieved SBP	< 125 mmHg	4	97/1602	116/1575	0.811	0.613	1.072		
	125-135 mmHg	8	96/1542	101/1538	0.945	0.708	1.261	0.368	
	> 135 mmHg	6	391/4207	492/5360	1.014	0.882	1.165		
SBP differences	≤ 6 mmHg	7	175/2550	244/3750	1.059	0.866	1.294		
	> 6 to < 12 mm Hg	7	229/2434	228/2359	0.971	0.800	1.177	0.062	
	≥ 12 mmHg	4	180/2367	237/2364	0.761	0.621	0.931		

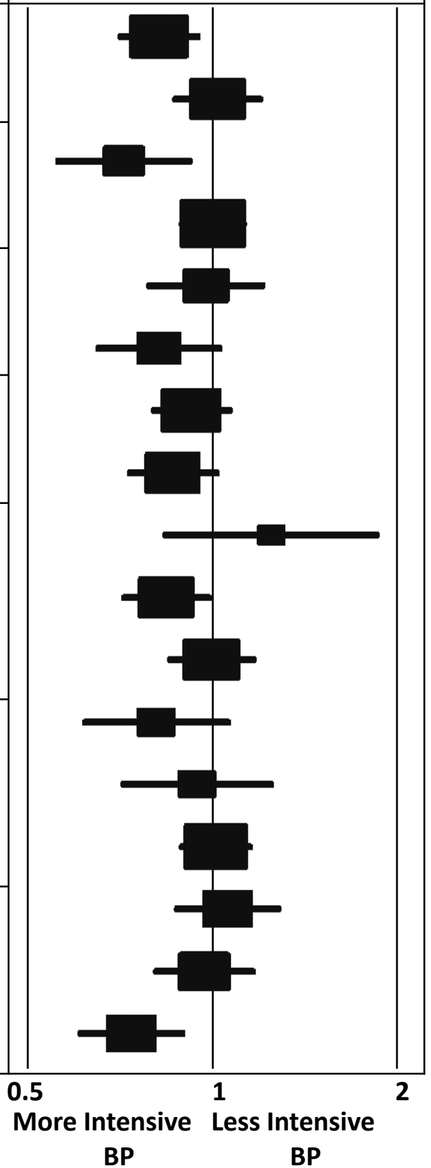

Figure 4