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Original Investigation

Renin-Angiotensin System Inhibitors and Kidney and Cardiovascular Outcomes in Patients With CKD: A Bayesian Network Meta-analysis of Randomized Clinical Trials

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Background: There is much uncertainty regarding the relative effects of angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs) in populations with chronic kidney disease (CKD).

Study Design: Systematic review and Bayesian network meta-analysis.

Setting & Population: Patients with CKD treated with renin-angiotensin system (RAS) inhibitors.

Selection Criteria for Studies: Randomized trials in patients with CKD treated with RAS inhibitors.

Predictor: ACE inhibitors and ARBs compared to each other and to placebo and active controls.

Outcome: Primary outcome was kidney failure; secondary outcomes were major cardiovascular events, all-cause death.

Results: 119 randomized controlled trials (n = 64,768) were included. ACE inhibitors and ARBs reduced the odds of kidney failure by 39% and 30% (ORs of 0.61 [95% credible interval, 0.47-0.79] and 0.70 [95% credible interval, 0.52-0.89]), respectively, compared to placebo, and by 35% and 25% (ORs of 0.65 [95% credible interval, 0.51-0.80] and 0.75 [95% credible interval, 0.54-0.97]), respectively, compared with other active controls, whereas other active controls did not show evidence of a significant effect on kidney failure. Both ACE inhibitors and ARBs produced odds reductions for major cardiovascular events (ORs of 0.82 [95% credible interval, 0.71-0.92] and 0.76 [95% credible interval, 0.62-0.89], respectively) versus placebo. Comparisons did not show significant effects on risk for cardiovascular death. ACE inhibitors but not ARBs significantly reduced the odds of all-cause death versus active controls (OR, 0.72; 95% credible interval, 0.53-0.92). Compared with ARBs, ACE inhibitors were consistently associated with higher probabilities of reducing kidney failure, cardiovascular death, or all-cause death.

Limitations: Trials with RAS inhibitor therapy were included; trials with direct comparisons of other active controls with placebo were not included.

Conclusions: Use of ACE inhibitors or ARBs in people with CKD reduces the risk for kidney failure and cardiovascular events. ACE inhibitors also reduced the risk for all-cause mortality and were possibly superior to ARBs for kidney failure, cardiovascular death, and all-cause mortality in patients with CKD, suggesting that they could be the first choice for treatment in this population.

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INDEX WORDS: Angiotensin-converting enzyme (ACE) inhibitor; angiotensin II receptor blocker (ARB); renin angiotensin system (RAS) inhibition; chronic kidney disease (CKD); kidney failure; cardiovascular events; mortality; all-cause death; renal disease progression; blood pressure (BP); hypertension; comparative effectiveness; Bayesian network meta-analysis.

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Chronic kidney disease (CKD) is a major public health issue of international scope, affecting 8% to 16% of the adult population.[1] Blood pressure (BP)-lowering agents are the foundation of management strategies for slowing the progression of CKD, as well as a core aspect of strategies to reduce the risk for cardiovascular disease.[2,3] Renin-angiotensin system (RAS) inhibitors are the best-studied agents for slowing the progression of kidney disease in this population.[4-9] Clinical practice guidelines, including the recent KDIGO (Kidney Disease: Improving Global Outcomes) guideline for hypertension, have recommended that angiotensin-converting enzyme

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(ACE) inhibitors or angiotensin II receptor blockers (ARBs) should be first-line therapy for patients with CKD, especially those with proteinuria, as a result of their specific benefits for renal protection.[10] In their evidence-based guideline for managing high BP, the panel members appointed to the Eighth Joint National Committee (JNC8) also recommended that initial antihypertensive treatment should include an ACE inhibitor or ARB to improve kidney outcomes in hypertensive populations with CKD.[11]

However, several questions have not been clearly answered. First, how strong and consistent is the evidence regarding any additional protective effect of RAS inhibitors over other BP-lowering agents? The presence of an additional benefit has been questioned by analyses from the large ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial), which did not show a benefit of lisinopril for reducing the risk for serum creatinine level doubling or kidney failure when compared with chlorthalidone or amlodipine in participants with CKD at baseline.[12] Second, is there a difference in the magnitude of the effect of ACE inhibitors compared with ARBs on kidney disease outcomes in patients with kidney disease, in light of the recommendations from most guideline groups that they can be used interchangeably in patients with kidney disease and the lack of evidence regarding the relative efficacy of ACE inhibitors and ARBs?[10,11,13] We therefore undertook a systematic review and Bayesian network meta-analysis to evaluate the effect of ACE inhibitors or ARBs on kidney disease and cardiovascular outcomes in individuals with CKD.

METHODS

Data Sources and Searches

We undertook a systematic review of the literature according to the approach recommended by the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement for the conduct of meta-analysis of intervention studies.[14]

Relevant studies were identified by searching the following data sources: MEDLINE (by Ovid; from 1950 to November 2014), EMBASE (from 1970 to November 2014), and the Cochrane Library database. We used the Medical Subject Headings (MeSH) and text words of randomized controlled trial, chronic kidney disease, and all spellings of known ACE inhibitors and ARBs (see Item S1, available as online supplementary material). Trials were considered without language restrictions. Reference lists from identified trials and review articles were scanned manually to identify any other relevant studies. The ClinicalTrials.gov website was also searched for randomized trials that were registered as completed but not yet published. When detailed information that was needed for the analysis was not available, we wrote to the author to request the data. The literature was searched and identified by 2 investigators (X.X. and L.L.) independently.

Study Selection

Our primary aim was to synthesize all trials with ACE inhibitors or ARBs to evaluate the effects of RAS inhibition for kidney or cardiovascular outcomes in populations with CKD; trials only comparing other active agents to each other or placebo were not included in our analysis. We selected randomized controlled trials (RCTs) with more than 20 participants with CKD in which ACE inhibitors or ARBs were given for at least 6 months (CKD was defined as glomerular filtration rate [GFR] < 60 mL/min/1.73 m^2, or elevated serum creatinine level or albuminuria with albumin excretion > 30 mg/d, or abnormalities detected by histology or dialysis). All completed RCTs that assessed the effects of ACE inhibitors or ARBs compared to each other or to placebo and/or other antihypertensive drugs in patients with CKD and that reported outcomes of kidney failure events (defined as a composite of any of the following: doubling of serum creatinine level, 50% decline in GFR, or end-stage kidney disease), and/or major cardiovascular events (defined as a composite of fatal or nonfatal myocardial infarction, stroke, and heart failure; cardiovascular death; or comparable definitions used by individual authors), and/or all-cause death, and/or drug-related adverse events (including hyperkalemia, cough, hypotension, and edema) were eligible for inclusion.

Data Extraction and Quality Assessment

Published reports were obtained for each eligible trial, and relevant information was extracted into a spreadsheet. The data sought included baseline patient characteristics (age, sex, history of diabetes mellitus, mean systolic and diastolic BPs, and albuminuria or proteinuria value), dose of drug, follow-up duration, change in BP, outcome events, and adverse events. These data were extracted from either studies conducted solely in people with kidney disease or subgroups of other trials from which data for the population with CKD at baseline could be obtained. If the required quantitative data were not provided in the relevant article from the text, we used the program g3data (www.frantz.fi/software/g3data.php) to extract numerical values from published figures. Study quality was judged by the proper conduct of randomization, concealment of treatment allocation, similarity of treatment groups at baseline, provision of a description of eligibility criteria, completeness of follow-up, and use of an intention-to-treat analysis and was quantified with the Jadad scale and Cochrane Collaboration tool for assessing the risk of bias. Data extraction and quality assessment were undertaken independently by 2 investigators (X.X. and Y.L.) using a standardized approach. Any disagreement between the 2 investigators regarding the abstracted data was adjudicated by a third reviewer (J.L.).

Data Synthesis and Statistical Analyses

WinBUGS (version 1.4.3; Medical Research Council Biostatistics Unit) and R (version 2.13.1; R Foundation for Statistical Computing) were used to perform network meta-analysis with a random-effects mixed-treatment comparisons model for multiarm trials within the Bayesian framework on the effects of kidney failure, cardiovascular outcomes, death, and adverse events[15] (Item S2). We assumed a binomial distribution for the outcome. Nodes of ACE inhibitors, ARBs, placebo, and active controls were included in the network analysis. The relative probabilities of events in the arms of a study can be parameterized in terms of the logarithm of the odds ratio (OR), and final pooled ORs and their 95% credible intervals were used to compare treatment effects for each outcome. We used noninformative priors: normal with mean 0 and variance 10,000 for mean values; uniform (0.5) for the between-study standard deviation. For each model, we generated 100,000 simulations for each of the 2 sets of different initial values, and we discarded the first 20,000 simulations as the burn-in period. Achievement of convergence was estimated using the Brooks-Gelman-Rubin statistic.[16] Convergence was reached when Rhat, the potential scale reduction factor, is close to 1 for each parameter. When multiarm trials were involved, the within-study correlation in the network was taken into account using the method suggested by Dias et al.[15] Inconsistency referring to differences between direct and various indirect effects was estimated by the loop-specific approach and node-splitting approach. It is possible to evaluate

the inconsistency when 3 treatments are connected within a closed loop. Important inconsistency threatens the validity of the results, and if present, we further explored to identify possible sources of disagreement. Inconsistent loops were identified with a significant (inconsistency factor and its 95% credible intervals that exclude 0) disagreement between direct and indirect evidence in a random-effects inconsistency model. The Bayesian *P* value was calculated by the node-splitting method, which separated evidence on a particular comparison into direct and indirect evidence.[17,18] We ranked treatment strategies for each outcome by the surface under the cumulative ranking curve (SUCRA) probabilities and the posterior probabilities; SUCRA would be 100% when a treatment is certain to be the best and 0 when a treatment is certain to be the worst, and higher posterior probabilities in each simulation indicates the higher chance of being the best treatment regimen.[19]

We performed sensitivity analyses by exclusion of trials with sample size less than 100, published before the year 2000, and lower study quality. For the continuous measurement of BP, we used the weighted mean difference between groups. To explore potential heterogeneity, multiple-treatment meta-regression analysis and subgroup analyses were done to estimate the effect of baseline average age, systolic BP, estimated GFR, serum creatinine level, systolic BP reduction, follow-up period, and presence or absence of diabetic nephropathy and were incorporated into the network meta-analysis. As a whole, traditional pairwise meta-analysis was conducted by Stata 13 (StataCorp LP) with studies that reported at least 1 end point event to estimate the assumed consistency. We calculated the log(OR) for each outcome for each individual study before pooling, and effect size was reported with ORs and 95% confidence intervals in the binary meta-analysis.

RESULTS

Description of Included Studies

Our literature search returned 9,036 results yielding 7,972 potentially relevant articles. Of these articles, we reviewed the full text of 435 reports, from which we identified 119 relevant RCTs (Fig 1). These RCTs involved a total of 64,768 participants with CKD; 85 studies reported kidney failure events, among which 51 studies reported at least 1 kidney failure event (for a total of 4,372 kidney failure events), whereas the incidence of kidney failure was zero in the other 34 studies. In addition, there were 13 trials solely including patients with end-stage renal disease, who could not develop this renal end point. A total of 10,412 major cardiovascular events were reported from 94 studies, among which 60 studies reported at least 1 cardiovascular event. There were 5,864 deaths, including 3,178 cardiovascular deaths, reported from 104 studies, with 62 trials reporting more than 1 death.

The quality of the included RCTs was estimated using the Cochrane Collaboration tool for assessing the risk of bias; low versus high risk of bias is indicated for each study in Table S1. Table 1 summarizes characteristics of the included studies. There were 34 trials that compared ACE inhibitors to placebo,[4-6,20-50] 7 studies that compared ARBs to placebo,[7,51-56] 38 studies that compared ACE inhibitors with active controls,[12,57-93] and 13 studies that compared ARBs with active controls.[94-106] One study compared either ACE inhibitors or ARBs to active control,[107] and 1 study compared ACE inhibitors with any antihypertensive treatment.[108] There were 8 studies that compared ACE inhibitors with ARBs[109-116] and 9 studies that compared dual blockade to monotherapy.[52,117-124] Eight 3-arm studies were included.[8,125-132] Sample size ranged from 20 to 8,561, and 11 studies were post hoc analyses of larger trials. Mean age of participants in all studies was 62.9 years, available direct comparisons of ACE inhibitors versus ARBs were with younger patients than studies with other controls, and mean follow-up was 3.6 years. Fifty-four trials with 30,054 patients solely recruited participants with diabetic nephropathy, 30 studies (n = 5,786) recruited participants with nondiabetic nephropathy, and 13 studies (n = 2,247) recruited patients undergoing dialysis (Table S2).

Kidney Outcomes

Data regarding the effects of ACE inhibitors compared with placebo or active agents on kidney failure events were available from 55 trials with 17,926 patients, among whom 1,464 events were observed.[6,12,24,25,27-30,32-46,48-50,58-62,64,66-76,79-82,84-88,90-92] Twelve trials of ARBs compared with placebo or active controls involving 9,168 participants reported 1,760 kidney failure events.[7,8,51-53,55,95,97,99,101,103,106] Results of random-effects Bayesian network meta-analysis for kidney failure are summarized in Fig 2A. ACE inhibitors and ARBs reduced the odds of kidney failure by 39% and 30% (ORs of 0.61 [95% credible interval, 0.47-0.79] and 0.70 [95% credible interval, 0.52-0.89]), respectively, compared to placebo and by 35% and 25% (ORs of 0.65 [95% credible interval, 0.51-0.80] and 0.75 [95% credible interval, 0.54-0.97), respectively, compared with other active controls, whereas other active controls did not show evidence of a significant protective effect for kidney failure (OR, 0.92; 95% credible interval, 0.78-1.24). Although there was no statistically significant difference between ACE inhibitors and ARBs (OR, 0.89; 95% credible interval, 0.66-1.19; Fig 2A), ACE inhibitors were estimated to have an 81.1% chance of being the best for kidney protection, followed by 18.9% for ARBs. Probabilities of rankings and SUCRAs of the treatment strategies in terms of preventing kidney failure are summarized in Fig 3A and Fig S1A.

Direct and indirect estimates by the node-splitting and loop-specific method identified no significant disagreements (Table S3; Fig S2A). Point estimates from traditional binary meta-analysis were near those from Bayesian network analysis, and their credible intervals were generally overlapping (Figs 4A and S3). No important changes in efficacy hierarchies emerged in sensitivity analysis excluding studies published before 2000, trials with small sample size,

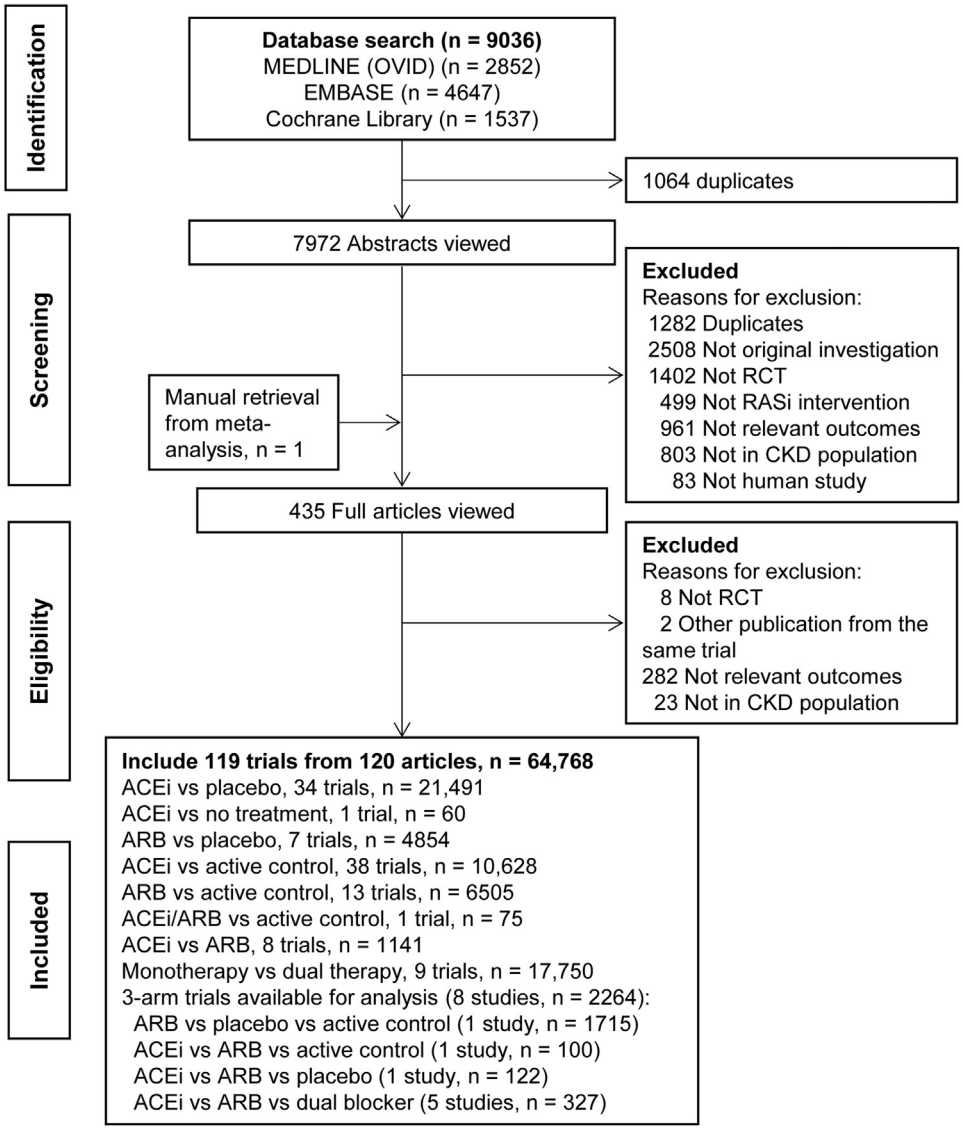

Figure 1. Identification process for eligible randomized controlled trials (RCTs). The study obtained by manual retrieval was Fried et al.[122] Detailed data for 1 trial[23] were obtained from a meta-analysis.[138] There were 8 three-arm studies included. Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CKD, chronic kidney disease; RASi, renin-angiotensin system inhibitor.

and those with lower quality (Table S4); subgroup analyses according to categories of baseline systolic BP, length of follow-up, and estimated GFR, as well as presence/absence of diabetic nephropathy (Table S5); or meta-regression of age, systolic BP reduction, and baseline serum creatinine level (Table S6). Treatment with ACE inhibitors was always associated with the lowest risk for kidney failure.

Cardiovascular Events

Seventy-six studies involving 37,538 patients evaluated the effect of ACE inhibitors or ARBs compared with placebo or active agents on major cardiovascular outcomes in individuals with CKD,[4-8,12,20-41,45,49-54,56-66,68-70,72-81,83,85,86,90,92-101,104-106] among which 51 studies reported at least 1 cardiovascular event.

Compared to placebo, both ACE inhibitors and ARBs reduced the odds of cardiovascular events (ORs of 0.82 [95% credible interval, 0.71-0.92] and 0.76 [95% credible interval, 0.62-0.89], respectively; Fig 2B). However, neither ACE inhibitors (OR, 0.94; 95% credible interval, 0.75-1.12) nor ARBs (OR, 0.86; 95% credible interval, 0.70-1.03) demonstrated a significant benefit for cardiovascular protection compared with active controls. In addition, there were no statistically significant differences between ACE inhibitors and ARBs (OR, 1.09; 95% credible interval, 0.91-1.31). Ranking curves indicated that ARBs

Table 1. Characteristics of Studies in Meta-analysis

Group	Mean Age, y	Mean Follow-up, y	No. of Trials and Participants	No. of Trials (Percentage of Patients), by Type				No. of Trials by CKD Definition[a]	No. of Trials by Proteinuria Class[b]
				DN Only	Mixed	Non-DN	Dialysis		
All trials	62.9	3.6	119 (n = 64,768)	54 (46.4)	35 (44.7)	30 (8.9)	13 (3.5)	GFR < 60: 29; proteinuria: 60; other: 30	A3: 50; A2: 21; A3: 5
ACEi vs placebo	62.4	4.0	34 (n = 21,491)	18 (51.8)	11 (45.1)	5 (3.1)	3 (2.2)	GFR < 60: 8; proteinuria: 22; other: 4	A3: 9; A2: 14; A3: 2
ARB vs placebo	62.2	3.3	7 (n = 4,854)	4 (65.6)	2 (32.2)	1 (2.2)	1 (1.7)	GFR < 60: 2; proteinuria: 5; other: 0	A3: 2; A2: 3; A1: 0
ACEi vs active control	63.2	3.7	38 (n = 10,628)	16 (19.1)	7 (58.8)	15 (22.9)	3 (2.4)	GFR < 60: 8; proteinuria: 17; other: 13	A3: 23; A2: 8; A1: 1
ARB vs active control	64.6	3.1	13 (n = 6,505)	3 (4.6)	4 (88.9)	3 (3.3)	3 (14.1)	GFR < 60: 6; proteinuria: 3; other: 4	A3: 1; A2: 3; A1: 0
ACEi vs ARB	49.6	4.0	8 (n = 1,141)	3 (33.0)	2 (36.8)	3 (30.1)	1 (5.3)	GFR < 60: 2; proteinuria: 3; other: 3	A3: 5; A2: 3; A1: 0
Dual blockade vs monotherapy	64.5	3.4	9 (n = 17,750)	4 (60.1)	2 (33.5)	2 (5.9)	1 (1.9)	GFR < 60: 2; proteinuria: 4; other: 3	A3: 4; A2: 2; A1: 2
3-arm study[c]	58.7	2.5	9 (n = 2,264)	6 (95.4)	0 (0)	2 (4.6)	1 (4.4)	GFR < 60: 1; proteinuria: 6; other: 1	A3: 4; A2: 2; A1: 0

Note: The only study of ACEi/ARBs versus active control is not shown in the table. ACEi versus ARB studies included in the table are trials of only 2 arms of ACEi and ARB. One trial (Mimura et al,[107] 2008) with the intervention of either ACEi or ARB and 1 trial (Li et al,[108] 2014) that compared ACEi to no treatment were included in row 1 and were not included in other rows.

Abbreviations and definitions: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blockers; CKD, chronic kidney disease; DN, diabetic nephropathy; GFR, glomerular filtration rate (in mL/min/1.73 m^2); KDIGO, Kidney Disease: Improving Global Outcomes.

[a]Proteinuria is by KDIGO definition; "other" category comprises high serum creatinine level, biopsy, or other.

[b]A1 to A3 are according to the KDIGO definition: A3 is severely increased; A2 is moderately increased; A1 is normal to mildly increased.

[c]Represents 8 three-arm studies that were included (1 trial for ARB vs placebo vs active control, 1 for ACEi vs ARB vs active control, 1 for ACEi vs ARB vs placebo, and 5 with ACEi vs ARB vs dual blocker).

had a 79.2% and ACE inhibitors had an 18.0% chance of being the first- and the second-ranked choice for preventing cardiovascular events, among all therapy regimens (Figs 3B and S1B). Similar ORs and overlapped credible/confidence intervals were shown between network meta-analysis and traditional meta-analysis (Fig 4B). No significant disagreement between direct and indirect estimates was detected (Table S3; Fig S2B).

For cardiovascular death, all active treatments showed no significant differences compared to placebo in the network (ORs of 0.88 [95% credible interval, 0.72-1.09], 1.12 [95% credible interval, 0.80-1.58], and 1.19 [95% credible interval, 0.81-1.72] for ACE inhibitors, ARBs, and active controls, respectively; Fig 2C), and ACE inhibitors achieved significant odds reduction compared with placebo and active controls in traditional meta-analysis (Fig 4C); the ranking of treatment strategies based on probability of protective effects by Bayesian network meta-analysis also suggested that ACE inhibitors had the greatest probability (82.0%) of being the best treatment (Fig 3C) following the assumption of consistency (Fig S2C). Detailed results for the outcomes of major cardiovascular events, heart failure, myocardial infarction, stroke, and cardiovascular death from traditional binary meta-analysis summarized in Fig S4A to E were consistent with those from the network analysis. There was no significant difference between dual blockade of RAS inhibitors and monotherapy on the outcome of cardiovascular events (Fig S5A).

All-Cause Death

All-cause death events were reported in 54 studies: 2,299 events were available from 40 studies of ACE inhibitors compared with placebo or active controls (n = 20,517),[4-6,20-24,26-28,30,32,34-36,38-41,48,50,57,60,62,64-66,68,69,72-77,79,81,82,93] and

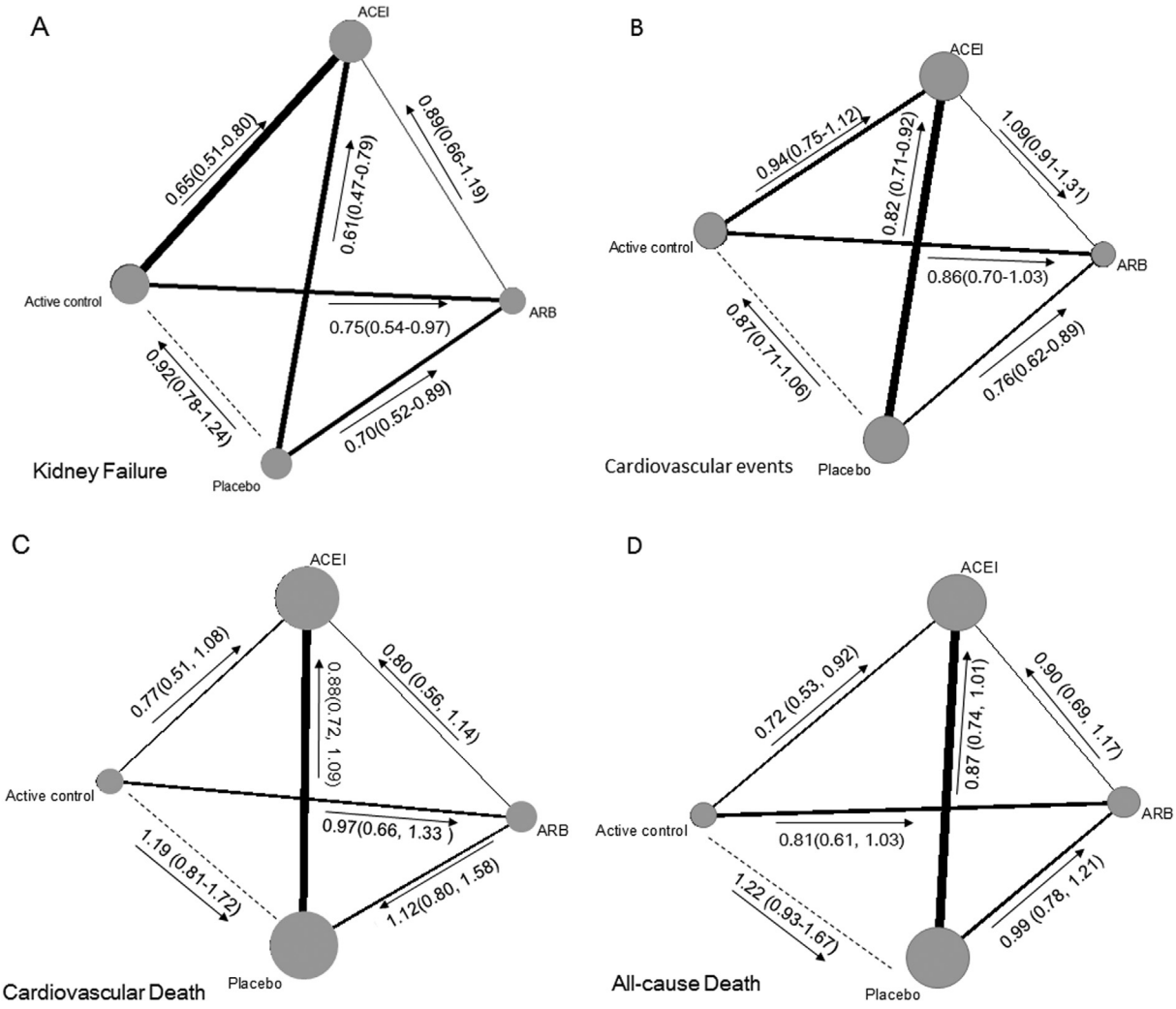

Figure 2. Network of eligible treatment comparisons for (A) kidney failure, (B) cardiovascular events, (C) cardiovascular death, and (D) all-cause mortality. The Bayesian network meta-analysis was performed with 100,000 iterations, with the first 20,000 discarded. The arrowhead points to nodes of antihypertensive treatment with lower risk from Bayesian network analysis, results of direct comparison were presented as summary odds ratio (95% credible interval). Circle size reflects the number of participants and the line width reflects the number of direct comparisons. Dotted line between 2 circles indicates that there was no direct comparison between the 2 treatments. Trials that have an arm of incorporated angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB) were not included in the network analysis for the overlap with single nodes of ACEi or ARB.

1,050 events were available from 13 trials of ARBs compared with placebo or active control (n = 9,750).[7,8,51,52,56,95,96,98,100,104,106,107,125]

Among all treatment regimens, only ACE inhibitors achieved a significant odds reduction compared with active controls (OR, 0.72; 95% credible interval, 0.53-0.92; Figs 2D and 4D). No significant difference was found among the other comparisons. Results of the Bayesian network meta-analysis for all-cause death also indicated that ACE inhibitors with 81.9% had the highest probability of being superior, followed by 15.5% of ARBs in patients with CKD (Figs 3D and S1D). The node-splitting and loop-specific approach showed no significant inconsistency within networks (Table S3; Fig S2D). Treatment with dual blockade of RAS inhibitors also did not show a significant odds reduction for all-cause death compared to monotherapy (Fig S5B).

Adverse Events

We analyzed several major drug-related adverse outcomes reported from 99 RCTs. Overall, there were 86 trials that we evaluated that reported at least 1 adverse event (Table 2). Compared with placebo, ACE inhibitors and ARBs increased the odds of hyperkalemia (ORs of 2.16 [95% credible interval, 1.24-3.68] and 1.89 [95% credible interval, 1.02-3.03], respectively). ACE inhibitors also increased the odds of cough (OR, 6.39; 95% credible interval, 2.31-15.49). No statistically significant increase in

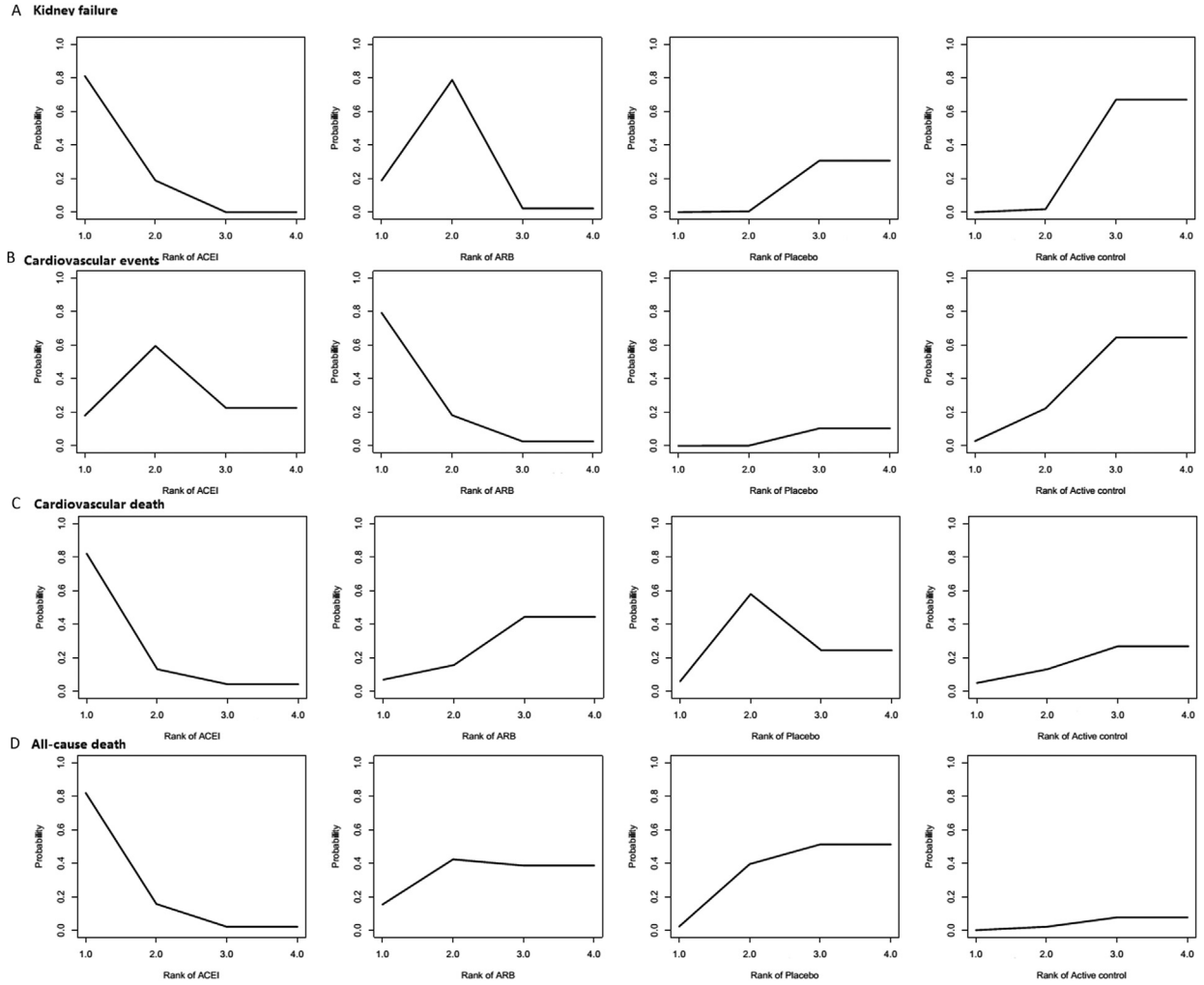

Figure 3. Rank probability curves for kidney failure, cardiovascular events, cardiovascular death, and all-cause death. Distribution of probabilities for each treatment being ranked at different positions for each outcome. Abbreviations and definitions: ACEI, angiotensin-converting-enzyme inhibitor; Active control, other active antihypertensive drugs; exclusion, ACEI and ARB; ARB, angiotensin II receptor blocker.

odds of hypotension and edema were found with all RAS inhibitor strategies compared to placebo. Inconsistency between direct and indirect estimates was evaluated for each event, and no significant discrepancy was identified (Fig S6).

DISCUSSION

ACE inhibitors and ARBs have been recommended and used widely and interchangeably in patients with CKD.[1] In this large quantitative systematic review and network meta-analysis comprising more than 100 trials and 60,000 individuals, we have demonstrated that ACE inhibitors are the most likely of all therapy regimens to produce benefits in terms of kidney failure, cardiovascular death, and all-cause death in individuals with CKD. Although ARBs also demonstrated evidence of benefit for kidney protection, the Bayesian approach suggested that ACE inhibitors had the greatest likelihood of benefit and may therefore be the preferred approach for BP lowering in patients with kidney disease.

In addition, we found that the use of either ACE inhibitors or ARBs confers cardiovascular protection in this population. No significant difference in odds reduction was found when comparing ACE inhibitors with ARBs, but ARBs showed a higher probability of being beneficial for cardiovascular events.

ACE inhibitors and ARBs have been recommended in an interchangeable fashion in most guidelines for the treatment of people with kidney disease.[10,11] The available data, summarized in this review, suggest that the benefits of ACE inhibitors in terms of kidney protection and mortality are greater than those of ARBs. The explanation for this difference could be due to different actions of ACE inhibitors and ARBs on the RAS pathway. For

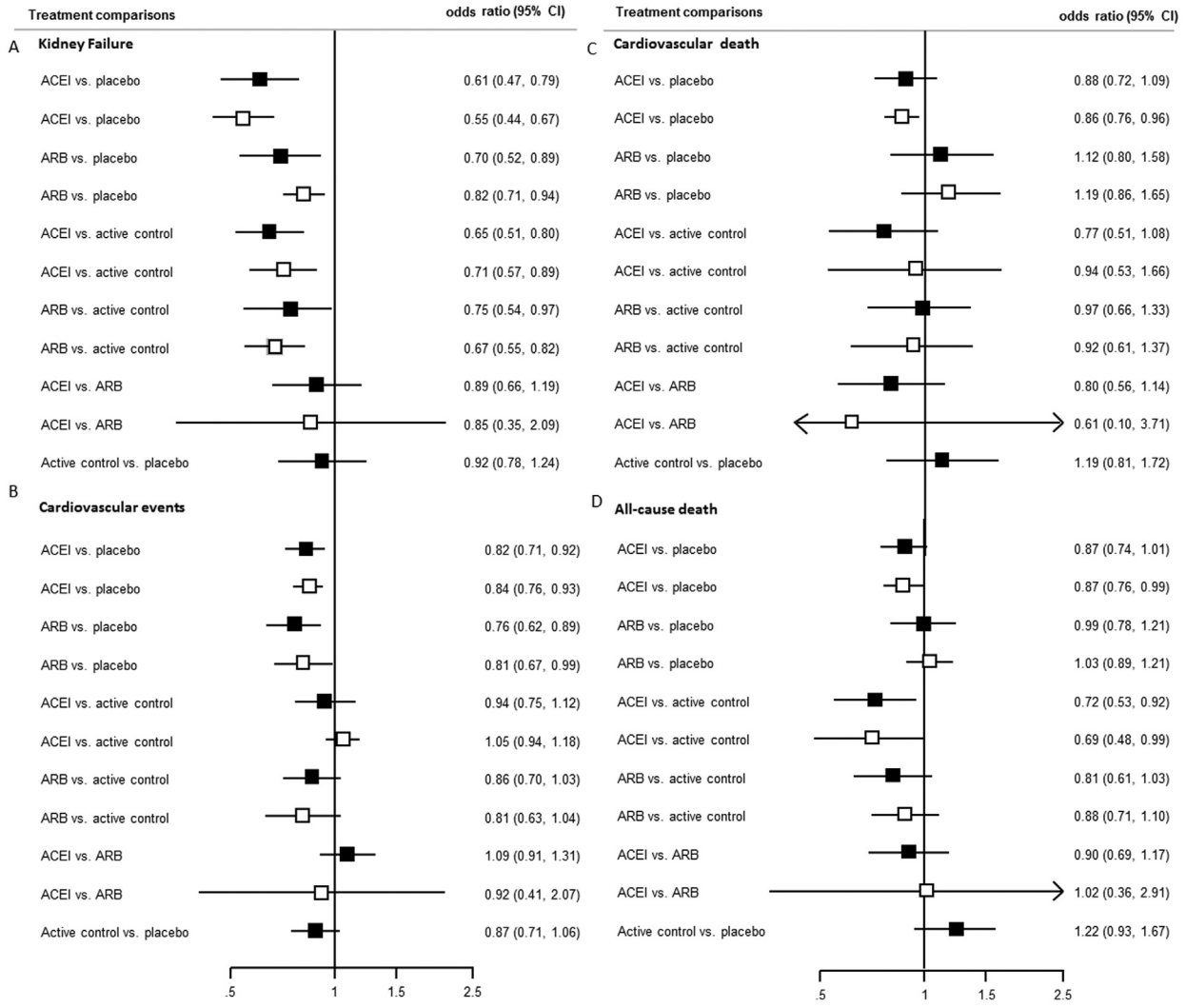

Figure 4. Forest plot of results from both the Bayesian network meta-analysis (solid squares; CI, credible interval) and traditional meta-analysis (open squares; CI, confidence interval) for outcomes of kidney failure, cardiovascular events, cardiovascular death, and all-cause death. The result of active control versus placebo from traditional pairwise meta-analysis was not provided as limited head-to head trials of active control versus placebo included in the analysis. Abbreviations and definitions: ACEI, angiotensin-converting-enzyme inhibitor; Active control, other active antihypertensive drugs; exclusion, ACEI and ARB; ARB, angiotensin II receptor blocker.

example, the inhibition of bradykinin degradation by ACE inhibitors (but not ARBs) has been suggested to improve endothelial function. In contrast, ARBs act by selective blockade of the angiotensin II type 1 (AT_1) receptor, leaving the action of AT_2 unopposed, which in turn could potentially promote vascular growth, inflammation, and fibrosis. A lesser benefit from ARBs on cardiovascular or kidney outcomes has been suggested in previous studies.[133] In trials conducted among people with hypertension or cardiovascular disease, ACE inhibitors have been observed to produce a BP-independent reduction in risk for coronary heart disease, but a similar effect has not been seen for ARBs.[134] A meta-analysis of 20 trials (158,998 patients) demonstrated that ACE inhibitors reduce the risk for death in individuals with hypertension, whereas ARBs do not.[135] In populations with diabetes mellitus, network meta-analysis has suggested that the renoprotective effects of using ACE inhibitors are superior to those of ARBs.[136] In the present study, we also found that ACE inhibitors ranked first for the likelihood of odds reduction for cardiovascular mortality and all-cause mortality in people with CKD (although the differences between these 2 classes were not statistically significant in the network meta-analysis). Thus, the present study provides additional evidence to support the viewpoint that the available data regarding the benefits of ACE inhibitors may be stronger than those for ARBs or other classes of agents, as indicated by the smallest odds compared to placebo and consistent top ranking for odds reduction of kidney failure, cardiovascular death, and all-cause death in CKD populations.

Table 2. Adverse Effects of Treatment Strategies Compared to Placebo

Treatment Strategy	Hyperkalemia; Reported in 43 Trials	Rank[a]	Cough; Reported in 68 Trials	Rank[a]	Angioedema/Edema; Reported in 26 Trials	Rank[a]	Hypotension; Reported in 29 Trials	Rank[a]
ACEi	2.16 (1.24-3.68)[b]	4	6.39 (2.31-15.49)[b]	4	47.88 (0.08-69.48)	2	1.44 (0.81-1.63)	4
ARB	1.89 (1.02-3.03)[b]	3	0.56 (0.10-1.74)	1	72.7 (0.12-217.2)	3	1.40 (0.69-1.63)	3
Active control[c]	0.64 (0.27-1.18)	1	0.61 (0.13-1.63)	2	194.02 (0.67-709.13)	4	1.23 (0.52-2.44)	2
Placebo	1.00 (reference)	2	1.00 (reference)	3	1.00 (reference)	1	1.00 (reference)	1

Note: Unless otherwise noted, values are given as odds ratio (95% credible interval).

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; SUCRA, surface under the cumulative ranking curve.

[a]Based on SUCRA probabilities; SUCRA would be 100% when treatment is certain to be the best and 0 when treatment is certain to be the worst.

[b]Statistically significant results.

[c]Represents indirect comparison.

In this study, we mainly evaluated the effects of RAS inhibitors on kidney or cardiovascular protection. Trials with comparisons between other BP-lowering agents or placebo were thus not included, which limits the strength of the conclusions of the network analysis. However, results of indirect comparisons of other antihypertensive agents and placebo (Fig 2) from this network analysis were consistent with direct comparisons from head-to-head trials summarized in other published meta-analyses.[136,137] Other BP-lowering agents were combined as 1 node with a similar overall effect in our network analysis, an approach that is supported by 2 previous systematic reviews in which no significant differences among diuretics, calcium channel blockers, or β-blockers were found for death or kidney or cardiovascular outcomes in patients with kidney disease or diabetes.[136,137]

This meta-analysis benefits from the large volume of data that was able to be included and the rigorous methodology used. However, our study has limitations. First, as with most overviews, potential reporting bias due to some trials not reporting both kidney disease and cardiovascular outcomes is a limitation. Some trials included in this study were post hoc analyses in subgroups of patients with kidney disease. Although 119 trials were included in this study, only 85 studies reported kidney failure events and 94 reported cardiovascular events. Reporting bias also could not be excluded for adverse events. Thus, potential reporting bias might influence the final results. Second, it is possible that heterogeneity between different ACE inhibitors or ARBs exists, so that different agents within classes might not have the same risk-benefit ratio in patients with CKD. Third, in 2 large studies (Ongoing Telmisartan Alone and in Combination With Ramipril Global Endpoint Trial [ONTARGET] and Aliskiren Trial in Type 2 Diabetes Using Cardio-Renal Endpoints [ALTITUDE]) with separate arms for ACE inhibitors or ARBs, details regarding numbers of events for each RAS inhibitor class were unavailable, so monotherapy and dual RAS blockade were not included in the network meta-analysis for bias and overlap. The observed differential effect of ACE inhibitors versus ARBs should therefore be interpreted with some caution.

Our network meta-analysis provides evidence that ACE inhibitors are most likely to reduce the risk for kidney failure, cardiovascular events, and death in people with CKD and have superiority over ARBs and other classes of BP-lowering agents on renoprotective effects, as well as protection against death in the CKD population, suggesting that these agents may be preferable in patients with CKD.

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Contributions: Research idea and study design: JL, HZ; data acquisition: XX, YL, XL, NZ; data analysis/interpretation: XX, YL; statistical analysis: XX, YL, LL, WH, TN, VP; supervision or mentorship: JL, HZ. HW died following initial submission of the manuscript; JL and HZ affirm that she contributed to data acquisition and vouch for her coauthorship status; all other authors approved the final author list. Except as noted, each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved. JL and HZ take responsibility that this study has been reported honestly, accurately, and transparently; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

Peer Review: Evaluated by 2 external peer reviewers, a Statistical Editor, a Co-Editor, and the Editor-in-Chief.

SUPPLEMENTARY MATERIAL

Table S1: Quality assessment for included trials.

Table S2: Baseline characteristics according to randomized treatment.

Table S3: Assessment of inconsistency between direct and indirect evidence.

Table S4: Sensitivity analyses for primary outcome of kidney failure for each treatment vs placebo.

Table S5: Subgroup analysis for primary outcome of kidney failure for each treatment vs placebo in Bayesian framework.

Table S6: Metaregression for primary outcome of kidney failure for each treatment vs placebo in Bayesian framework.

Figure S1: Ranking of treatment strategies based on probability of protective effects on outcomes of kidney failure, CV events, CV death, and all-cause death.

Figure S2: Results of consistency test for kidney failure, CV event, CV mortality, and all-cause death.

Figure S3: Effect of treatments on kidney failure in traditional meta-analysis.

Figure S4: Effect of ACE inhibitors or ARBs vs placebo or other active agents on CV events and all-cause death.

Figure S5: Effect of dual blockade vs monotherapy on CV events and all-cause death.

Figure S6: Plot of inconsistency estimates with their 95% CIs on adverse events.

Item S1: Search strategy.

Item S2: WinBUGS code for Bayesian meta-analysis with random effects mixed treatment comparisons model.

Note: The supplementary material accompanying this article (http://dx.doi.org/10.1053/j.ajkd.2015.10.011) is available at www.ajkd.org

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