AJKD

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.

Am J Kidney Dis. ■(■):■-■. © *2015 by the National Kidney Foundation, Inc.*

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.

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 (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

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Received September 9, 2014. Accepted in revised form October 10, 2015.

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0272-6386

http://dx.doi.org/10.1053/j.ajkd.2015.10.011

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