Aldosterone Antagonists in Addition to Renin Angiotensin System Antagonists for Preventing the Progression of CKD: Editorial Summary of a Cochrane Review

Edmund Y.M. Chung and Giovanni F.M. Strippoli

Chronic kidney disease (CKD) is a public health challenge, as it has a prevalence of 11% and is the 14th-leading cause of death worldwide (12.2 deaths per 100,000 people). Since 1990, deaths from CKD have increased at a higher rate than for any other cause except for deaths from complications of HIV infection.[1] Angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) are the standard of care to delay the progression of earlier stages of CKD to kidney failure in patients with proteinuria irrespective of the primary cause of kidney disease; in addition, these agents are associated with reduction in cardiovascular risk.[2,3] Incomplete suppression of aldosterone by renin-angiotensin-aldosterone system blockade with ACEIs or ARBs (called the 'aldosterone escape phenomenon') occurs in 10%-40% of cases and is associated with worsening proteinuria in both diabetic and nondiabetic kidney disease, suggesting a role for aldosterone antagonists in preventing the progression of CKD.[4] Addition of aldosterone antagonists to ACEIs or ARBs may provide benefits (reduction of proteinuria and effects on patient-level outcomes such as kidney failure or major cardiovascular events) but also be associated with harms (hyperkalemia and acute kidney injury [AKI]).

A Cochrane systematic review of the benefits and harms of aldosterone antagonists in CKD was published in 2014.[5] This review identified 27 studies (1,549 participants) and found that nonselective aldosterone antagonists (spironolactone) combined with an ACEI or ARB (or both) significantly reduced proteinuria, had no significant effect on estimated glomerular filtration rate (eGFR), and increased the risk of hyperkalemia and gynecomastia. It found no data on patient-level outcomes (kidney failure, death, or major cardiovascular events).[5] An update of this systematic review was performed and published 6 years thereafter, when additional trials of aldosterone antagonists had been performed in people with CKD, including with new agents (the novel nonsteroidal mineralocorticoid receptor antagonists, eg, finerenone and esaxerenone) that have been developed.[6] This review included 18 new studies (4,248 participants) through January 7, 2020.[7] Studies were all randomized controlled trials and quasi-randomized controlled trials in participants with CKD stages 1 to 4, as defined by the KDOQI guideline,[8] and albuminuria or proteinuria. Treatment effects were summarized using random effects meta-analysis. Risk of bias was evaluated using the Cochrane risk-of-bias tool and the certainty of the evidence was ascertained using GRADE.[9]

Findings

A total of 44 studies (5,745 participants) were included in the review, of which 23 included participants with diabetic kidney disease and 21 included participants with nondiabetic proteinuric kidney disease (IgA nephropathy, benign nephrosclerosis, membranous nephropathy, idiopathic chronic glomerulonephritis, or heart failure with associated proteinuric kidney disease). For the comparison between aldosterone antagonists to standard care or placebo, 22 studies (1,441 participants) assessed nonselective aldosterone antagonists (spironolactone), 6 studies (925 participants) assessed selective aldosterone antagonists (eplerenone), 4 studies (2,626 participants) assessed nonsteroidal mineralocorticoid antagonists (finerenone and esaxerenone), and all studies had co-intervention with an ACEI or ARB (or both). The median study follow-up duration was 3 months and none of the studies was powered to detect patient-level outcomes including kidney failure, mortality, or major cardiovascular events. Risk of bias in the evaluated methodological domains was unclear or high risk in most studies.

Aldosterone Antagonists (Selective or Nonselective) Versus Standard Care or Placebo

Aldosterone antagonists had uncertain effects on kidney failure (2 studies, 84 participants; risk ratio [RR], 3.00 [95% CI, 0.33-27.65]; very low-certainty evidence), death (3 studies, 421 participants; RR, 0.58 [95% CI, 0.10-3.50]; low-certainty evidence), and cardiovascular events (3 studies, 1,067 participants; RR, 0.95 [95% CI, 0.26-3.56]; low-certainty evidence), with study methodological limitations and few events in the available studies. Aldosterone antagonists may reduce protein excretion (14 studies, 1,193 participants; standardized mean difference [SMD], −0.51 [95% CI, −0.82 to −0.20]; very low-certainty evidence). However, this is difficult to apply clinically, since the heterogeneous measures of proteinuria in the included studies necessitated the use of SMD, which summarizes the intervention effect in each study relative to the standard deviation observed in each study. For example, an SMD of −0.51 expresses a mean level of proteinuria half a standard deviation lower than the mean level of proteinuria in the placebo group, which cannot be translated into an absolute difference in level of proteinuria. In very low-certainty evidence, aldosterone antagonists may reduce systolic blood pressure (14 studies, 911 participants; mean difference, −4.98 [95% CI, −8.22 to

−1.75] mm Hg) but had uncertain effects on diastolic blood pressure (13 studies, 875 participants; mean difference, −1.04 [95% CI, −2.82 to 0.73] mm Hg). Aldosterone antagonists may reduce eGFR (13 studies, 1,165 participants; mean difference, −3.00 [95% CI, −5.51 to −0.49] mL/min/1.73 m^2, low-certainty evidence) in short-term data. The effects of aldosterone antagonist selectivity on proteinuria, eGFR, and blood pressure remain uncertain, as the effect of selective aldosterone antagonists or nonsteroidal mineralocorticoid antagonists on these outcomes were only reported in a single study each.

Treatment with aldosterone antagonists probably increases the risk of hyperkalemia (17 studies, 3,001 participants; RR, 2.17 [95% CI, 1.47-3.22]; moderate-certainty evidence), AKI (5 studies, 1,446 participants; RR, 1.94 [95% CI, 0.99-3.79]; moderate-certainty evidence), and gynecomastia (4 studies, 281 participants; RR, 5.14 [95% CI, 1.14-23.23]; moderate-certainty evidence). The risk of hyperkalemia and AKI were similar for nonselective aldosterone antagonists, selective aldosterone antagonists, and nonsteroidal mineralocorticoid antagonists. Gynecomastia was only reported in studies of nonselective aldosterone antagonists.

Other Comparisons

The efficacy and safety of aldosterone antagonists compared to diuretics, calcium channel blockers, ACEI alone, combination ACEI and ARB, or nitrates are uncertain owing to a limited number of studies and no reporting on kidney failure, death, or cardiovascular events for each comparison. A single study (1,066 participants) compared the nonsteroidal mineralocorticoid antagonist finerenone to the selective aldosterone antagonist eplerenone in participants with heart failure and CKD and/or diabetes mellitus. This new agent is thought to be more selective for the mineralocorticoid receptor with less binding to the androgen receptor and to have no impact on urinary potassium levels, suggesting a more potent treatment with a lower risk of hyperkalemia and gynecomastia. The composite of death, cardiovascular hospitalization, or emergency presentation for worsening chronic heart failure occurred less in the higher-dose finerenone group compared to the eplerenone group in a secondary exploratory end point, but there were no differences in the primary outcome of reduction in N-terminal pro-B-type natriuretic peptide or the incidence of hyperkalemia.[10]

Conclusions

The effects of aldosterone antagonists in addition to an ACEI or ARB on the risks of kidney failure, mortality, or major cardiovascular events in people with proteinuric CKD remain uncertain. Aldosterone antagonists may reduce proteinuria and systolic blood pressure in adults with stage 1-4 CKD but may also reduce eGFR and probably increase the risk of hyperkalemia, AKI, and gynecomastia. The available data are limited by underpowered studies with short follow-up duration and few detected events. The potential kidney and cardiovascular benefits of aldosterone antagonists when added to ACEI or ARB therapy require further high-quality studies with adequate power and follow-up to detect differences in kidney failure and major cardiovascular events. The potential harms of aldosterone antagonists may be addressed with the concurrent use of potassium-binding agents. The novel nonsteroidal mineralocorticoid antagonists (finerenone and esaxerenone) also appear promising, with the recent FIDELIO-DKD trial showing an 18% reduction in the composite outcome (kidney failure, sustained eGFR decrease of at least 40%, or death from kidney causes) with finerenone compared to placebo in addition to ACEI or ARB in participants with CKD and type 2 diabetes but with a higher incidence of hyperkalemia.[11] Secondary outcomes of FIDELIO-DKD also showed a 14% reduction in the composite of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for heart failure, and we eagerly await the results of the FIGARO-DKD trial, which is powered to assess the effect of finerenone on cardiovascular mortality in diabetic kidney disease.[11]

Article Information

Authors' Full Names and Academic Degrees: Edmund Y.M. Chung, MD, MMed (Clin Epi), and Giovanni F.M. Strippoli, MD, PhD.

Authors' Affiliations: Department of Medicine, Royal North Shore Hospital, Sydney, Australia (EYMC); Department of Emergency and Organ Transplantation, University of Bari, Bari, Italy (GFMS); Cochrane Kidney and Transplant, Centre for Kidney Research, The Children's Hospital at Westmead, Westmead, Australia (GFMS); and School of Public Health, University of Sydney, Sydney, Australia (GFMS).

Address for Correspondence: Giovanni F.M. Strippoli, MD, PhD, Department of Emergency and Organ Transplantation, University of Bari (Bari), Italy, Piazza Giulio Cesare, 70124 Bari, Italy. Email: gfmstrippoli@gmail.com

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