Comparative efficacy and safety of blood pressure-lowering agents in adults with diabetes and kidney disease: a network meta-analysis

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Summary

Background The comparative efficacy and safety of pharmacological agents to lower blood pressure in adults with diabetes and kidney disease remains controversial. We aimed to investigate the benefits and harms of blood pressure-lowering drugs in this population of patients.

Methods We did a network meta-analysis of randomised trials from around the world comparing blood pressure-lowering agents in adults with diabetic kidney disease. Electronic databases (the Cochrane Collaboration, Medline, and Embase) were searched systematically up to January, 2014, for trials in adults with diabetes and kidney disease comparing orally administered blood pressure-lowering drugs. Primary outcomes were all-cause mortality and end-stage kidney disease. We also assessed secondary safety and cardiovascular outcomes. We did random-effects network meta-analysis to obtain estimates for primary and secondary outcomes and we presented these estimates as odds ratios or standardised mean differences with 95% CIs. We ranked the comparative effects of all drugs against placebo with surface under the cumulative ranking (SUCRA) probabilities.

Findings 157 studies comprising 43 256 participants, mostly with type 2 diabetes and chronic kidney disease, were included in the network meta-analysis. No drug regimen was more effective than placebo for reducing all-cause mortality. However, compared with placebo, end-stage renal disease was significantly less likely after dual treatment with an angiotensin-receptor blocker (ARB) and an angiotensin-converting-enzyme (ACE) inhibitor (odds ratio 0·62, 95% CI 0·43–0·90) and after ARB monotherapy (0·77, 0·65–0·92). No regimen significantly increased hyperkalaemia or acute kidney injury, although combined ACE inhibitor and ARB treatment had the lowest rank among all interventions because of borderline increases in estimated risks of these harms (odds ratio 2·69, 95% CI 0·97–7·47 for hyperkalaemia; 2·69, 0·98–7·38 for acute kidney injury).

Interpretation No blood pressure-lowering strategy prolonged survival in adults with diabetes and kidney disease. ACE inhibitors and ARBs, alone or in combination, were the most effective strategies against end-stage kidney disease. Any benefits of combined ACE inhibitor and ARB treatment need to be balanced against potential harms of hyperkalaemia and acute kidney injury.

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Introduction

Diabetes mellitus affects 3–4% of adults worldwide, with prevalence projected to double over the first three decades of the 21st century.[1] Chronic kidney disease occurs in 25–40% of patients with diabetes within 20–25 years of onset, and diabetes is now the leading cause of end-stage kidney disease,[2] accounting for nearly half of all patients treated with dialysis.[3] The combination of diabetes and kidney disease is associated with a four-fold increase in the prevalence of atherosclerotic vascular disease and death.[4] Blood pressure lowering with pharmacological agents has been central to the treatment of diabetic kidney disease for decades, and improved care—including antihypertensive treatment—has been credited with decreased prevalence of end-stage kidney disease over the past 10 years.[5]

The pharmacology of blood pressure-lowering agents is becoming increasingly complex as new drugs are introduced, but the comparative efficacy and safety of available drugs is largely unknown, mainly because of an absence of head-to-head trials.[6] In clinical practice

Panel: Search strategy and selection criteria

We searched the Cochrane Renal Group's specialised register, the Cochrane Central Register of Controlled Trials, Medline, and Embase for randomised controlled trials available up to January, 2014, without language restrictions. We also included unpublished data from trials that were part of a systematic review[6] and data for participants with diabetes and albuminuria in the ONTARGET trial.[10] We included parallel-group studies in which follow-up was at least 8 weeks, and both fixed-dose and flexible-dose studies were included in which treating investigators could titrate drug doses.

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guidelines, the equivalence of angiotensin-converting-enzyme (ACE) inhibitors and angiotensin-receptor blockers (ARBs) is assumed. Furthermore, concurrent use of these two classes of agent is not recommended, partly because concomitant salt restriction or combined treatment with other drugs has been judged equally effective and possibly safer.[7,8] Concern over the risks of acute kidney injury and hyperkalaemia with dual ACE inhibitor and ARB treatment led to premature termination of the Veterans Affairs Nephropathy in Diabetes (VA NEPHRON-D) trial[9] in adults with diabetes and proteinuria, resulting in inconclusive effects on clinical endpoints. Moreover, in the Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET),[10] the absence of a benefit of dual treatment was argued to be possibly attributable to the low proportion of patients recruited with chronic kidney disease, for whom dual treatment might be selectively effective.[11] In a network meta-analysis of blood pressure drugs in adults with diabetes, dual ACE inhibitor and ARB treatment was not investigated.[12] The aim of our study was to assess the comparative effects of all blood pressure-lowering agents in adults with diabetes and kidney disease using the technique of network meta-analysis.

Methods

Study design

We did a network meta-analysis using a frequentist model. Network meta-analysis integrates data from direct comparisons of treatments within trials and from indirect comparisons of interventions assessed against a common comparator in different trials, to compare all investigated treatments. We followed a prespecified study protocol (appendix pp 2–15) and reported the meta-analysis according to the Preferred Reporting Items of Systematic Reviews and Meta-Analyses (PRISMA) statement.[13]

See Online for appendix

Participants

We included adults aged 18 years or older who had diabetes and chronic kidney disease and were treated in clinical trials that compared any orally administered blood pressure-lowering agent (ACE inhibitor, ARB, calcium-channel blocker, β blocker, α blocker, diuretic, renin inhibitor, aldosterone antagonist, or endothelin inhibitor), alone or in combination, with a second blood pressure agent or combination, placebo, or control. We defined chronic kidney disease according to Kidney Disease Improving Global Outcomes (KDIGO) criteria.[14] We did not include participants who underwent kidney transplantation or dialysis.

Procedures

Our search strategy and selection criteria are outlined in the panel. At least two of three reviewers (SCP, EN, and MR) selected studies and extracted data independently. We assessed risk of bias in contributing studies with standard criteria.[15]

Outcomes

Primary outcomes were all-cause mortality and end-stage kidney disease (need for dialysis or kidney transplantation). Secondary cardiovascular outcomes were myocardial infarction, stroke, cardiovascular mortality, and blood pressure; additional secondary outcomes were related to kidney function (doubling of serum creatinine, regression of albuminuria, and acute kidney injury) and adverse events (hyperkalaemia [commonly defined as serum potassium >5·5 mmol/L], presyncope, cough, and peripheral oedema). We included acute kidney injury as an outcome post hoc during the data extraction phase.

Statistical analysis

We did two types of meta-analysis. First, we did standard pairwise meta-analysis with a random-effects model.[16]

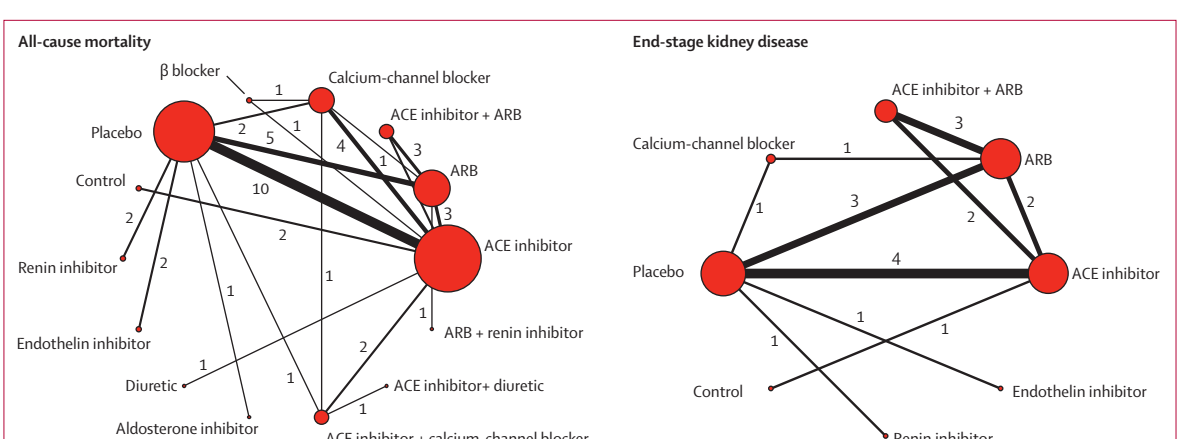


Figure 1: **Networks of treatment comparisons for primary outcomes of blood pressure-lowering agents in adults with diabetes and kidney disease**
The size of the nodes (red circles) corresponds to the number of trials of the treatments. Comparisons are linked with a line, the thickness of which corresponds to the number of trials that assessed the comparison. Numbers next to every line joining two treatments correspond to the number of studies that compared the treatments. ACE=angiotensin-converting enzyme. ARB=angiotensin-receptor blocker.

We assessed heterogeneity in these analyses with the I^2 metric.[15] Second, we did random-effects network meta-analysis,[17] assuming a common heterogeneity variable for all comparisons (the tau [τ] value). τ is the estimated SD of underlying effects of treatment across studies in a meta-analysis. We did random-effects pairwise and network meta-analyses to obtain estimates for primary and secondary outcomes, and presented these estimates as odds ratios (dichotomous outcomes) or standardised mean differences (continuous outcomes) with 95% CIs. We investigated the extent of heterogeneity in every network by comparing the magnitude of τ for the network with an empirical distribution of heterogeneity variances specific to the types of outcome and treatments being compared.[18] We applied a 0·5 zero-cell correction before meta-analysis.

Network meta-analysis assumes transitivity—ie, that one can learn about treatment A versus treatment B via treatment C.[19] We assumed that, in principle, participants fulfilling our inclusion criteria could be randomly allocated to any of the treatments being compared. Transitivity holds when all direct comparisons between treatments do not differ with respect to the distribution of effect modifiers (eg, studies comparing ACE inhibitor with placebo were similar to studies comparing ARB with placebo in terms of the level of albuminuria). Potential effect modifiers for studies in this setting included extent of albuminuria, hypertension at baseline, type 1 or type 2 diabetes, and duration of treatment follow-up.

Disagreement between direct and indirect evidence can suggest that the transitivity assumption might not hold. We assessed evidence for consistency in the networks in two ways. First, we used a loop-specific approach to investigate consistency within every closed triangular or quadratic loop in every network as the difference between direct and indirect estimates for a specific treatment comparison (inconsistency factor) in the loop.[20,21] We identified inconsistent loops as those yielding a 95% CI excluding zero. Second, we used the design-by-treatment interaction model that provides a single inference, using the χ^2 test, about the plausibility of assuming consistency throughout the entire network.[22] To investigate the generalisability of the findings, we assessed the effect of differing trial and participant characteristics on the primary outcomes in sensitivity analyses by restricting analyses to studies with the following design characteristics: type 1 or type 2 diabetes; microalbuminuria; macroalbuminuria; hypertensive participants; adequately concealed allocation; follow-up longer than 24 months; and not terminated prematurely.

To rank the treatments for an outcome, we used surface under the cumulative ranking (SUCRA) probabilities, which express as a percentage the efficacy or safety of every intervention relative to an imaginary intervention that is always the best without uncertainty.[23] Thus, large SUCRA scores might indicate a more effective or safer intervention. We did meta-analyses with Stata version 13, using the mvmeta command[24] and Stata routines described elsewhere.[25,26]

	Direct drug comparisons/ participants (n/N)	Odds ratio (95% CI)	
		Pairwise meta-analysis	Network meta-analysis
All-cause mortality			
ACE inhibitor + calcium-channel blocker	1/335	0·20 (0·01–4·17)	0·36 (0·12–1·05)
Aldosterone antagonist	1/55	0·22 (0·01–4·91)	0·28 (0·01–6·46)
ACE inhibitor + ARB	0/0	..	0·84 (0·63–1·11)
ARB	5/4443	0·91 (0·71–1·16)	0·87 (0·71–1·07)
Calcium-channel blocker	2/1333	0·89 (0·65–1·22)	0·88 (0·63–1·23)
ACE inhibitor + diuretic	0/0	..	0·72 (0·05–10·2)
ARB + renin inhibitor	0/0	..	0·86 (0·05–14·0)
ACE inhibitor	10/7938	0·85 (0·61–1·19)	0·94 (0·76–1·15)
Renin inhibitor	2/9896	0·93 (0·39–2·24)	1·05 (0·81–1·36)
Diuretic	0/0	..	1·89 (0·17–21·3)
Endothelin inhibitor	2/1699	1·55 (0·82–2·89)	1·53 (0·79–2·97)
β blocker	0/0	..	5·13 (0·81–32·4)
End-stage kidney disease			
ACE inhibitor + ARB	0/0	..	0·62 (0·43–0·90)
ACE inhibitor	4/6580	0·73 (0·47–1·14)	0·71 (0·51–1·01)
Endothelin inhibitor	1/1392	0·72 (0·44–1·16)	0·71 (0·44–1·14)
ARB	3/3227	0·81 (0·69–0·96)	0·77 (0·65–0·92)
Calcium-channel blocker	1/1136	0·87 (0·56–1·35)	1·04 (0·79–1·38)
Renin inhibitor	1/8579	1·21 (0·86–1·71)	1·21 (0·85–1·70)
Acute kidney injury			
ACE inhibitor + calcium-channel blocker	0/0	..	0·50 (0·04–7·19)
Calcium-channel blocker	0/0	..	0·89 (0·12–6·58)
ACE inhibitor	0/0	..	1·19 (0·33–4·26)
Renin inhibitor	2/9156	1·28 (0·96–1·71)	1·28 (0·95–1·70)
Endothelin inhibitor	1/89	1·82 (0·08–39·4)	1·47 (0·06–33·8)
ARB	3/748	1·58 (0·60–4·19)	1·54 (0·58–4·06)
Aldosterone antagonist	1/54	1·58 (0·53–4·68)	1·50 (0·52–4·31)
ACE inhibitor + ARB	0/0	..	2·69 (0·98–7·38)
Hyperkalaemia			
Calcium-channel blocker	1/1136	1·51 (0·25–9·06)	0·71 (0·22–2·33)
β blocker	0/0	..	0·53 (0·02–14·5)
ACE inhibitor + diuretic	0/0	..	1·11 (0·23–5·41)
Endothelin inhibitor	1/1392	1·24 (0·66–2·33)	1·24 (0·42–3·69)
Diuretic	0/0	..	1·34 (0·26–6·45)
Renin inhibitor	2/9156	1·68 (1·15–2·45)	1·83 (0·88–3·78)
ARB	2/1714	2·54 (0·94–6·86)	1·88 (0·86–4·12)
ACE inhibitor	3/480	1·63 (0·33–7·95)	1·92 (0·74–4·97)
Aldosterone antagonist	3/365	2·23 (0·81–6·13)	2·53 (0·82–7·84)
ACE inhibitor + ARB	0/0	..	2·69 (0·97–7·47)

Primary outcomes are acute mortality and end-stage kidney disease; secondary safety outcomes are acute kidney injury and hyperkalaemia. Treatments are ranked according to SUCRA values. ACE=angiotensin-converting enzyme. ARB=angiotensin-receptor blocker. SUCRA=surface under the cumulative ranking.

Table: **Pairwise and network estimates of the effects of different drug regimens compared with placebo on primary and some secondary safety outcomes**

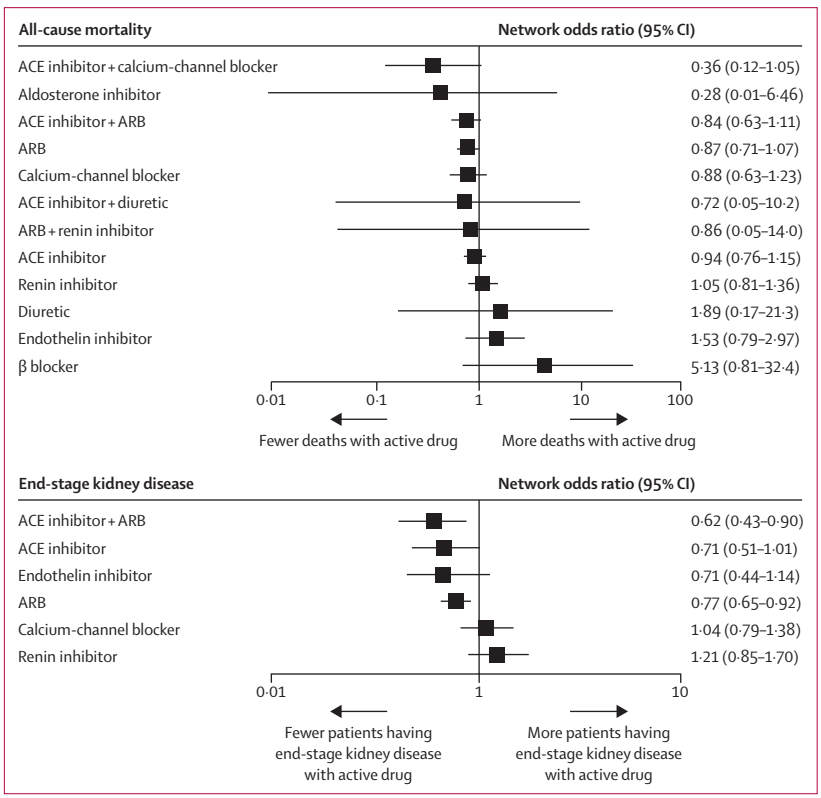


Figure 2: **Network meta-analysis of blood pressure-lowering agents compared with placebo for primary outcomes in adults with diabetes and kidney disease**
Common heterogeneity variables for all comparisons in this network meta-analysis were τ=0·10 for all-cause mortality (moderate heterogeneity) and τ≈0 for end-stage kidney disease (low heterogeneity). Treatments are ranked by SUCRA values. ACE=angiotensin-converting enzyme. ARB=angiotensin-receptor blocker. SUCRA=surface under the cumulative ranking.

Role of the funding source
The funders had no role in study design, data collection, data analysis, data interpretation, or writing of the report. SCP and GFMS had access to all data in the study and GFMS had final responsibility for the decision to submit for publication.

Results
188 studies including 45 338 adults were eligible for the systematic review, and 157 studies with data for 43 256 participants were available for network meta-analysis (appendix pp 16–36). The PRISMA[13] flowchart showing electronic searching processes is shown in the appendix (p 37). Seven drug classes alone or in combination were compared with placebo or standard treatment—ACE inhibitors, ARBs, aldosterone antagonists, β blockers, calcium-channel blockers, endothelin inhibitors, and renin inhibitors. Mean age of participants was 52·5 years (SD 12·0). 53 studies were exclusively of individuals with macroalbuminuria (9445 patients), and 102 studies were solely of people with microalbuminuria (15 576 patients). Nine studies of 17 258 participants were terminated early.

Risk of bias in studies contributing to the primary outcomes was generally low (appendix p 38). Overall, 65% of information for all-cause mortality and 89% of information for end-stage kidney disease was judged low risk. Moreover, no major tendency was noted for smaller studies to overestimate or underestimate active treatment effects on mortality, whereas data were sparse for end-stage kidney disease (appendix pp 39–40).

Networks of eligible comparisons for the primary outcomes are presented in figure 1, showing predominantly pairwise comparisons of drugs with ACE inhibitors or placebo. 19 (21%) of 90 possible pairwise treatment comparisons had direct evidence for all-cause mortality and ten (36%) of 27 possible pairwise treatment comparisons had direct evidence for end-stage kidney disease. Networks for secondary outcomes showed a similar preponderance for ACE inhibitor and placebo-controlled trials (appendix pp 41–42). For acute kidney injury, 15 (21%) of 78 possible treatment comparisons had direct evidence, whereas for hyperkalaemia, 11 (31%) of 36 possible treatment comparisons had direct evidence.

In pairwise comparisons for the primary outcomes and for acute kidney injury and hyperkalaemia, no evidence of statistical heterogeneity was seen in general (appendix pp 43–47). Analyses for blood pressure outcomes were highly heterogeneous. In the network meta-analyses, statistical heterogeneity was moderate in networks for all-cause mortality, regression of albuminuria, hyperkalaemia, cough, and peripheral oedema and was substantial in networks for systolic blood pressure and diastolic blood pressure. Treatment estimates from direct and indirect evidence in general did not show evidence of statistical inconsistency except for several loops of evidence for blood pressure outcomes (appendix pp 48–52). However, results for inconsistency were imprecise and, therefore, the possibility of inconsistency could not be excluded. Global inconsistency was not noted within any network, except for blood pressure endpoints.

Data for direct comparisons and network estimates for both primary outcomes and for the safety outcomes of hyperkalaemia and acute kidney injury are shown in the table and, for other outcomes, the appendix (pp 53–67). We ranked the comparative effects of all drugs against placebo with SUCRA probabilities.

All-cause mortality was reported in 33 studies (29 782 participants), but because data were scant for some treatments, it was difficult to draw clear conclusions. No blood pressure-lowering strategy was significantly better than placebo (figure 2). Odds ratios ranged from 0·36 (95% CI 0·12–1·05) for the highest ranked treatment strategy (ACE inhibitor combined with calcium-channel blocker) to 5·13 (0·81–32·4) for the lowest ranked agent (β blocker). End-stage kidney disease was reported in 13 studies (24 477 participants).

Dual ACE inhibitor and ARB treatment, and ARB monotherapy, was significantly better than placebo (odds ratio 0·62, 95% CI 0·43–0·90, and 0·77, 0·65–0·92, respectively), and ACE inhibitor monotherapy and endothelin inhibitors were also ranked highly (figure 2). ARB therapy alone or in combination with ACE inhibitor treatment was superior to a calcium-channel blocker or renin inhibitor (appendix pp 53–67).

Figure 3 presents estimated effects of drug regimens on secondary kidney function outcomes. Treatments were generally similar to placebo for risks of acute kidney injury (11 studies, 26 960 participants), although estimated treatment effects were very imprecise and outcome definitions were heterogeneous, including worsening kidney function, acute renal failure, and an increase in serum creatinine (appendix p 68). Dual treatment with an ACE inhibitor and an ARB was ranked lowest for acute kidney injury, based on borderline increased risk (figure 3). For prevention of serum creatinine doubling (14 studies, 20 637 participants), endothelin inhibitors, ACE inhibitor monotherapy, and ARB monotherapy were significantly better than placebo. Renin inhibitors increased the risk of serum creatinine doubling (figure 3). For regression of albuminuria (36 studies, 11 299 participants), most regimens were efficacious, with the exception of monotherapy with either a calcium-channel blocker or a diuretic (figure 3).

Figure 4 presents estimated effects of drug regimens on secondary cardiovascular and safety outcomes. ARB monotherapy was superior to placebo for prevention of myocardial infarction (18 studies, 21 471 participants), whereas the effects of other drugs were not significant or were very imprecise. Treatment estimates for stroke (15 studies, 19 878 participants; figure 4) and cardiovascular mortality (nine studies, 17 806 participants; appendix p 58) were also non-significant. No drug regimen increased the risk of hyperkalaemia (18 studies, 16 450 participants), although the combination of ACE inhibitor and ARB was ranked low because of a borderline higher risk than other strategies (figure 4). Renin inhibitors raised the risk of presyncope (33 studies, 25 929 participants). Regimens containing either an ACE inhibitor or an ARB caused cough (38 studies, 22 730 participants), whereas calcium-channel blocker monotherapy led to peripheral oedema (25 studies, 15 245 participants).

Estimated effects of drug regimens on blood pressure are shown in the appendix (pp 66–67). Point estimates indicated reductions in both systolic and diastolic blood pressure for all treatment regimens compared with placebo, with significant reductions in diastolic blood pressure with renin inhibitors, combined treatment with ACE inhibitors and calcium-channel blockers, and monotherapy with aldosterone antagonists, calcium-channel blockers, and ACE inhibitors. Dual ACE inhibitor and calcium-channel blocker treatment lowered diastolic blood pressure to a greater extent than did monotherapy with a calcium-channel blocker, ACE inhibitor, ARB, or β blocker. In general, no effects on blood pressure were noted with other treatment options.

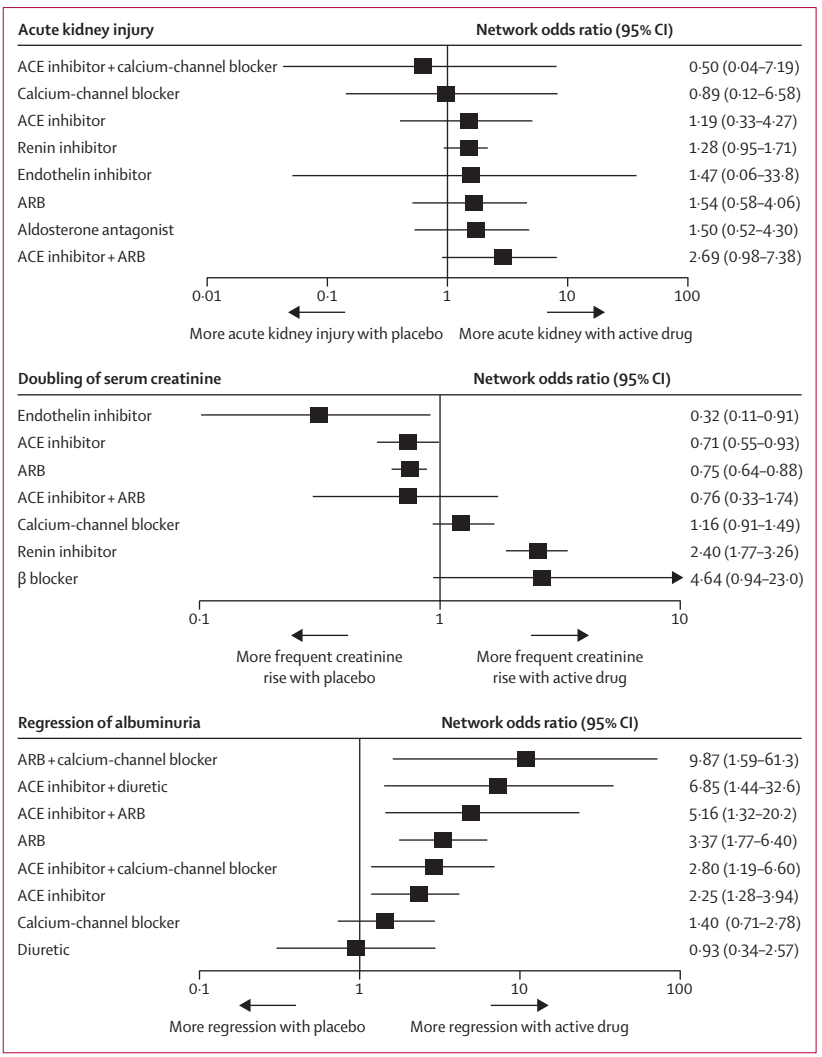
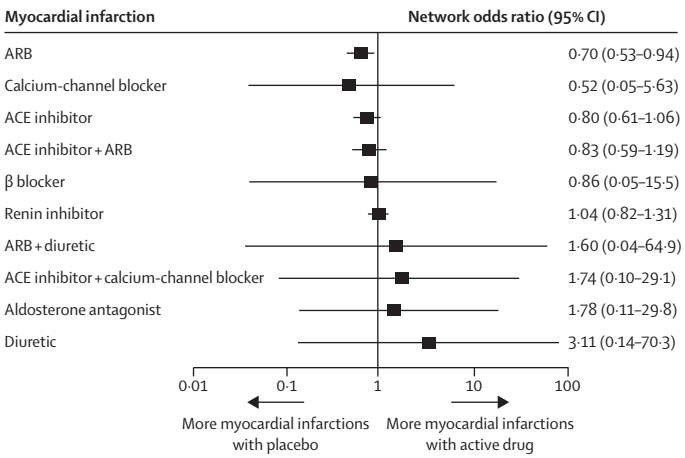


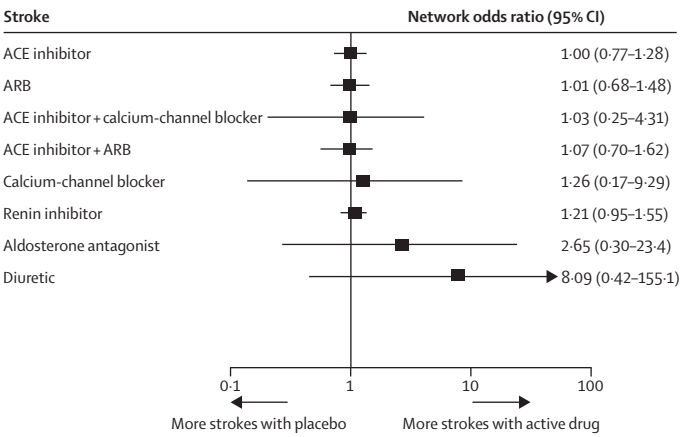
Figure 3: **Network meta-analysis of blood pressure-lowering agents compared with placebo for kidney function outcomes in adults with diabetes and kidney disease**
Common heterogeneity variables for every outcome in this network meta-analysis were τ≈0 for acute kidney injury and for doubling of serum creatinine (low heterogeneity) and τ=0·61 for regression of albuminuria (moderate heterogeneity). Treatments are ranked by SUCRA values. ACE=angiotensin-converting enzyme. ARB=angiotensin-receptor blocker. SUCRA=surface under the cumulative ranking.

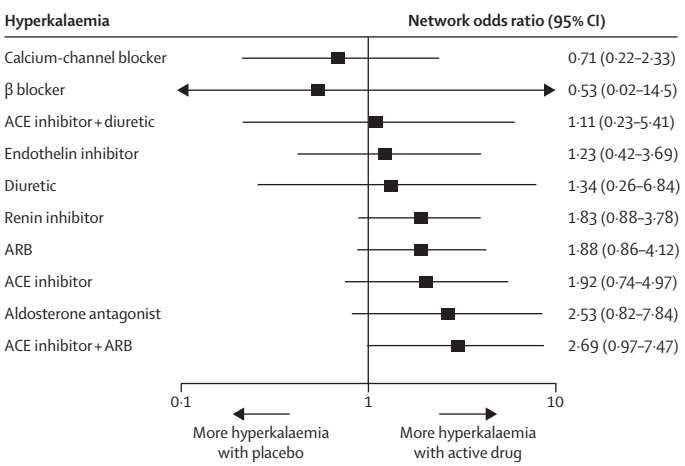
Results for all-cause mortality and end-stage kidney disease were generally robust in sensitivity analyses (appendix pp 69–72), and important changes in treatment rankings were not evident. Data for end-stage kidney disease were restricted largely to participants with macroalbuminuria and those who had type 2 diabetes.

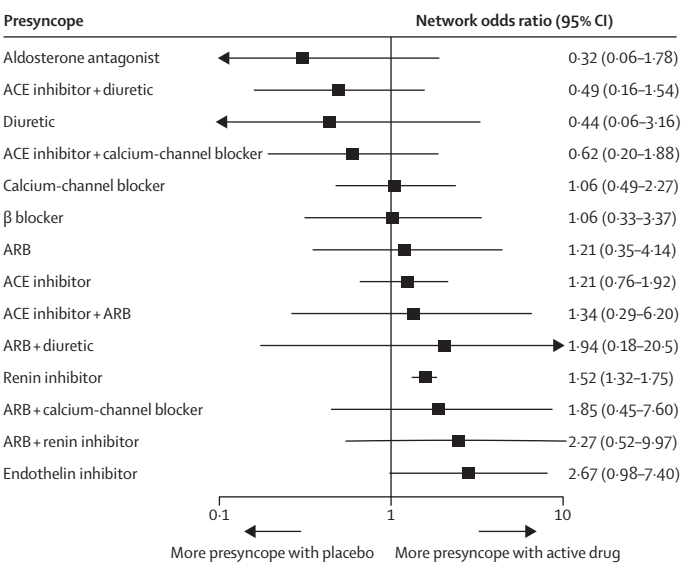
Discussion

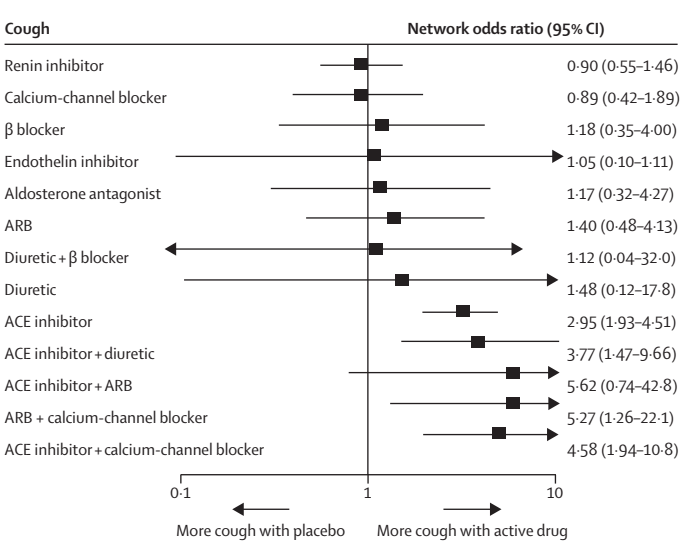
Our network meta-analysis provides unified hierarchies of evidence for all blood pressure-lowering agents in adults who have diabetes and kidney disease,

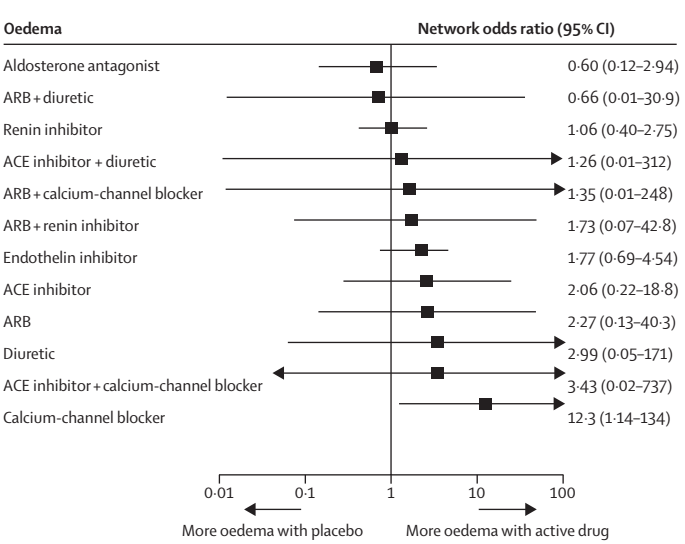

Myocardial infarction
Network odds ratio (95% CI)
ARB 0·70 (0·53–0·94)
Calcium-channel blocker 0·52 (0·05–5·63)
ACE inhibitor 0·80 (0·61–1·06)
ACE inhibitor + ARB 0·83 (0·59–1·19)
β blocker 0·86 (0·05–15·5)
Renin inhibitor 1·04 (0·82–1·31)
ARB + diuretic 1·60 (0·04–64·9)
ACE inhibitor + calcium-channel blocker 1·74 (0·10–29·1)
Aldosterone antagonist 1·78 (0·11–29·8)
Diuretic 3·11 (0·14–70·3)
0·01
0·1
1
10
100
More myocardial infarctions with placebo
More myocardial infarctions with active drug


Stroke
Network odds ratio (95% CI)
ACE inhibitor 1·00 (0·77–1·28)
ARB 1·01 (0·68–1·48)
ACE inhibitor + calcium-channel blocker 1·03 (0·25–4·31)
ACE inhibitor + ARB 1·07 (0·70–1·62)
Calcium-channel blocker 1·26 (0·17–9·29)
Renin inhibitor 1·21 (0·95–1·55)
Aldosterone antagonist 2·65 (0·30–23·4)
Diuretic 8·09 (0·42–155·1)
0·1
1
10
100
More strokes with placebo
More strokes with active drug


Hyperkalaemia
Network odds ratio (95% CI)
Calcium-channel blocker 0·71 (0·22–2·33)
β blocker 0·53 (0·02–14·5)
ACE inhibitor + diuretic 1·11 (0·23–5·41)
Endothelin inhibitor 1·23 (0·42–3·69)
Diuretic 1·34 (0·26–6·84)
Renin inhibitor 1·83 (0·88–3·78)
ARB 1·88 (0·86–4·12)
ACE inhibitor 1·92 (0·74–4·97)
Aldosterone antagonist 2·53 (0·82–7·84)
ACE inhibitor + ARB 2·69 (0·97–7·47)
0·1
1
10
More hyperkalaemia with placebo
More hyperkalaemia with active drug


Presyncope
Network odds ratio (95% CI)
Aldosterone antagonist 0·32 (0·06–1·78)
ACE inhibitor + diuretic 0·49 (0·16–1·54)
Diuretic 0·44 (0·06–3·16)
ACE inhibitor + calcium-channel blocker 0·62 (0·20–1·88)
Calcium-channel blocker 1·06 (0·49–2·27)
β blocker 1·06 (0·33–3·37)
ARB 1·21 (0·35–4·14)
ACE inhibitor 1·21 (0·76–1·92)
ACE inhibitor + ARB 1·34 (0·29–6·20)
ARB + diuretic 1·94 (0·18–20·5)
Renin inhibitor 1·52 (1·32–1·75)
ARB + calcium-channel blocker 1·85 (0·45–7·60)
ARB + renin inhibitor 2·27 (0·52–9·97)
Endothelin inhibitor 2·67 (0·98–7·40)
0·1
1
10
More presyncope with placebo
More presyncope with active drug


Cough
Network odds ratio (95% CI)
Renin inhibitor 0·90 (0·55–1·46)
Calcium-channel blocker 0·89 (0·42–1·89)
β blocker 1·18 (0·35–4·00)
Endothelin inhibitor 1·05 (0·10–1·11)
Aldosterone antagonist 1·17 (0·32–4·27)
ARB 1·40 (0·48–4·13)
Diuretic + β blocker 1·12 (0·04–32·0)
Diuretic 1·48 (0·12–17·8)
ACE inhibitor 2·95 (1·93–4·51)
ACE inhibitor + diuretic 3·77 (1·47–9·66)
ACE inhibitor + ARB 5·62 (0·74–42·8)
ARB + calcium-channel blocker 5·27 (1·26–22·1)
ACE inhibitor + calcium-channel blocker 4·58 (1·94–10·8)
0·1
1
10
More cough with placebo
More cough with active drug


Oedema
Network odds ratio (95% CI)
Aldosterone antagonist 0·60 (0·12–2·94)
ARB + diuretic 0·66 (0·01–30·9)
Renin inhibitor 1·06 (0·40–2·75)
ACE inhibitor + diuretic 1·26 (0·01–312)
ARB + calcium-channel blocker 1·35 (0·01–248)
ARB + renin inhibitor 1·73 (0·07–42·8)
Endothelin inhibitor 1·77 (0·69–4·54)
ACE inhibitor 2·06 (0·22–18·8)
ARB 2·27 (0·13–40·3)
Diuretic 2·99 (0·05–171)
ACE inhibitor + calcium-channel blocker 3·43 (0·02–737)
Calcium-channel blocker 12·3 (1·14–134)
0·01
0·1
1
10
100
More oedema with placebo
More oedema with active drug

overcoming the absence of comparative data in head-to-head trials. No blood pressure-lowering strategy was superior to placebo with respect to survival. However, ACE inhibitor and ARB treatment (alone or in combination) and endothelin inhibitors were ranked as the most effective agents for prevention of end-stage kidney disease, although only an ARB (alone or combined with an ACE inhibitor) was significantly better than placebo. The risks of drug-induced acute kidney injury and hyperkalaemia were similar for all drugs, although point estimates suggested clinically important effects on potassium and kidney function with dual ACE inhibitor and ARB treatment. Drug effects on myocardial infarction, stroke, and cardiovascular mortality were not significant for many blood pressure-lowering strategies. Effects on blood pressure did not differ by treatment regimens, consistent with the notion that pharmacological effects are independent of blood pressure lowering.

Safety endpoints were defined poorly in clinical trials, particularly acute kidney injury. Because treatment effects on safety endpoints have been used to terminate trials prematurely (eg, the VA NEPHRON-D trial),[9] greater standardisation and validation of these endpoints as predictors of patient-level outcomes such as end-stage kidney disease and mortality is needed.

Our finding that dual ACE inhibitor and ARB treatment seems effective for prevention of end-stage kidney disease challenges the 8th Joint National Committee (JNC 8) guidelines on prevention, diagnosis and management of hypertension, in which recommendations were made against combining these two treatments in this clinical setting.[8] However, our results can inform the KDIGO guidelines, which in 2012 concluded that although effects of dual blockade were promising based on treatment reductions in proteinuria, the benefits of dual treatment on clinically important renal outcomes remained unproven.[7]

Despite the potential benefits of combination treatment with an ACE inhibitor and an ARB in diabetic kidney disease, concerns about widespread adoption of this strategy are justified, because information on the balance between potential benefits (survival and end-stage kidney disease) and safety (acute kidney injury and hyperkalaemia) are scarce. In ONTARGET,[10] dual treatment with telmisartan and ramipril increased the risk of a composite endpoint of dialysis, doubling of serum creatinine, and death in high-risk patients with and without diabetes (driven mainly by an augmented need for short-term dialysis),[10] although notably the point estimate strongly favoured dual treatment within a small subgroup of patients with overt diabetic nephropathy. In the VA NEPHRON-D study,[9] ARB monotherapy was compared with combination ACE inhibitor and ARB treatment in adults with proteinuria and diabetes, but this study was terminated early because of a high prevalence of acute kidney injury and hyperkalaemia in patients receiving dual treatment, fuelling concerns about combination treatment. In our network meta-analysis, we showed that combination treatment seems to prevent end-stage kidney disease, does not increase doubling of serum creatinine, and greatly improves albuminuria, perhaps at the expense of an increased risk of acute kidney injury and hyperkalaemia. Since acute kidney injury endpoints were frequently defined poorly in trials included in our meta-analysis (with the exception of ONTARGET and the VA NEPHRON-D study), changes in kidney function reported previously could be a physiological result of haemodynamic changes due to treatment. Direct outcomes of changes in kidney function after treatment initiation remain unclear and warrant further clarification. Emerging treatments for hyperkalaemia might have favourable effects on the risk:benefit ratio of combination treatment, although this idea is speculative at present.[27–29] However, scaling up the widespread use of dual ACE inhibitor and ARB treatment to routine practice, particularly in settings with low resources and without sufficient monitoring, might alter adversely the balance of benefits towards treatment-related toxic effects.

In absolute terms, our findings suggest that giving 1000 adults with diabetes and kidney disease a combination of an ACE inhibitor and an ARB for 1 year might prevent 14 patients developing end-stage kidney disease and induce regression of albuminuria in 208 people, at the cost of 55 patients having acute kidney injury and 135 individuals developing hyperkalaemia. Treatment with an ARB alone in 1000 patients over 1 year might prevent 11 cases of end-stage kidney disease, induce regression of albuminuria in 118 people, but lead to acute kidney injury in 17 patients and hyperkalaemia in 70 individuals. Although our analysis suggests a somewhat greater efficacy of combination regimens for kidney function outcomes, treatment decisions are ultimately made after consideration of efficacy and safety. Although both acute kidney injury and hyperkalaemia are potentially dangerous, we do not know how many patients receiving treatment would need acute dialysis as a result of treatment-induced changes in the glomerular filtration rate, because of scant data. Furthermore, no evidence has shown that combination therapy has different effects

Figure 4: **Network meta-analysis of blood pressure-lowering agents compared with placebo for secondary cardiovascular and safety outcomes in adults with diabetes and kidney disease**

Common heterogeneity variables for every outcome in this network meta-analysis were τ=0 for myocardial infarction, stroke, and presyncope (low heterogeneity), τ=0·95 for hyperkalaemia (moderate heterogeneity), τ=0·24 for cough (moderate heterogeneity), and τ=0·52 for oedema (moderate heterogeneity). Treatments are ranked by SUCRA values. ACE=angiotensin-converting enzyme. ARB=angiotensin-receptor blocker. SUCRA=surface under the cumulative ranking.

on mortality or acute kidney injury when compared with ACE inhibitor or ARB monotherapy. Because few other interventions are available to slow progression of kidney disease, beyond blood pressure control, dual blockade offers a treatment strategy for carefully selected patients with diabetes in whom risks can be monitored.

Uncertainty surrounding whether ACE inhibitors, ARBs, or their combination have different effects in prevention of clinically important outcomes in adults with diabetes and kidney disease has been exacerbated by a focus on placebo-controlled trials, resulting in scant comparative data. In line with evidence supporting a favourable effect of ACE inhibitors compared with placebo,[30,31] in 1997 the 6th Joint National Committee (JNC 6) guidelines recommended use of ACE inhibitors as first-line treatment for patients with type 1 or type 2 diabetes and proteinuria.[32] In 2004, the corresponding 7th Joint National Committee (JNC 7) guidelines recommended ACE inhibitors or ARBs as equivalent for use in diabetes and kidney disease to delay deterioration of kidney function and worsening albuminuria,[33] whereas contemporaneous National Kidney Foundation guidelines recommended either monotherapy with an ACE inhibitor or ARB or a combination of these drugs in the event of persistent macroalbuminuria.[34] Findings of a pairwise meta-analysis undertaken at the time these guidelines were published indicated protection against end-stage kidney disease with ARB monotherapy and potential beneficial effects of ACE inhibitor treatment on this outcome, but understanding whether these agents or their combination had different comparative effects was precluded by standard meta-analytical capabilities.[6] Current international guidelines for management of blood pressure in chronic kidney disease[7] suggest that ACE inhibitors and ARBs are similarly effective at protecting against kidney failure. The findings of our network meta-analysis show that differing efficacy of these agents alone or in combination has not been proven for mortality and end-stage kidney disease or adverse treatment effects.

JNC 8 guidelines suggest using a combination of an ACE inhibitor or ARB with other agents (eg, a diuretic or calcium-channel blocker) within 1 month of treatment if blood pressure goals are not reached,[8] yet strong evidence for this approach is scarce in patients with diabetic kidney disease. Although ACE inhibitor or ARB treatment combined with calcium-channel blockade led to regression of albuminuria without augmentation of acute kidney injury in our analysis, effects of these drug combinations on end-stage kidney disease were not measurable because of few trials. The high SUCRA ranking of dual ACE inhibitor and calcium-channel blocker treatment for several end-points, including mortality, surrogate renal outcomes, acute kidney injury, and blood pressure control, suggests that future trials of this drug combination are needed and would strongly inform clinical practice.

Notably, in our analysis, data for many established blood pressure-lowering agents suggested little or no benefit on clinical outcomes—or actually suggested harm. Monotherapy with a calcium-channel blocker had no noticeable beneficial effects on survival, major cardiovascular events, or end-stage kidney disease. Point estimates suggested calcium-channel blockers were disadvantageous for prevention of serum creatinine doubling and regression of proteinuria, although they did not cause acute kidney injury. Accordingly, the most appropriate role for calcium-channel blockade is likely to be in conjunction with renin-angiotensin inhibition for this population of patients. β-blocker monotherapy seemed to worsen survival and accelerate kidney failure and is not likely to be appropriate as first-line treatment for diabetic kidney disease. Diuretics had no effect on survival or albuminuria and were ranked lowest for effects on myocardial infarction and stroke. Data for the effects of diuretics on end-stage kidney disease were absent.

This network meta-analysis expands information about blood pressure-lowering agents, including direct renin inhibitors and endothelin antagonists. Renin inhibitors augmented kidney failure and treatment estimates accorded with worsening end-stage kidney disease, without evidence for improved survival or diminished cardiovascular events. Although endothelin inhibitors were possibly beneficial in terms of kidney function, insufficient data relating to myocardial infarction and stroke, and a point estimate consistent with decreased survival, suggest that these agents should be used with caution until additional data are available with respect to cardiovascular outcomes. This caution is especially important bearing in mind the adverse events resulting from fluid overload that were reported when the endothelin antagonist avosentan was used in adults with diabetic nephropathy.[35]

Our study has potential limitations. First, because of scant primary data, effects of blood pressure treatment on cardiovascular events and related mortality were very uncertain, a pivotal weakness in our understanding of these drugs. The present debate about optimum treatments in diabetes and kidney disease would be assisted greatly by collection of robust data for these outcomes in future trials. Second, data for the outcome of end-stage kidney disease were restricted largely to patients who had macroalbuminuria and those with type 2 diabetes. Thus, our results might be less generalisable to adults who have microalbuminuria and individuals who have type 1 diabetes. Third, acute kidney injury was defined poorly, and scant evidence relating to this outcome does not allow us to make proper estimates of the risk–benefit ratio of blood pressure-lowering treatments in diabetic kidney disease. Fourth, few data were available from countries of

low-to-middle income. Fifth, we did not control for dose in our analyses; in most studies we included, clinicians were allowed to titrate drug doses for individual participants, which led to clinically unimportant differences in blood pressure outcomes.

In conclusion, little evidence is available that blood pressure lowering in adults with diabetes and kidney disease increases survival. Our analysis shows that ACE inhibitors and ARBs, alone or in combination, are the most effective strategies for prevention of end-stage kidney disease, and these findings can inform clinical decision making. However, we must consider the potential harms of these treatments in individual patients. Surveillance for treatment-related acute kidney injury and hyperkalaemia is important, as is better standardisation of the definitions of these adverse events and improved understanding of their outcomes, particularly in the context of future trials. Our analysis does not support the use of β blockers, calcium-channel blockers, renin inhibitors, or diuretic monotherapy in this clinical setting.

Contributors

SCP, JCC, GS, MT, and GFMS had the idea for and designed the review. SCP, EN, and MR identified and acquired reports of trials and extracted data. DM and GS provided statistical advice and input and SCP did all data analyses, checked for statistical inconsistency, and interpreted data. EN, JCC, MT, NW, MR, DCW, and GFMS contributed to data interpretation. SCP drafted the report and all other authors (DM, EN, JCC, GS, MT, NW, MR, DCW, and GFMS) critically reviewed the report.

Declaration of interests

SCP received a research grant from Canterbury Medical Research Foundation during the study and has received a research grant from Amgen Dompe outside the submitted work. MT has received honoraria for a lecture series on management of dyslipidaemia of chronic kidney disease from Merck outside the submitted work; all honoraria were donated to charity. DCW has received personal fees for consultancy and non-financial support from Amgen, Fresenius, Otsuka, Vifor Pharma, Astellas, Janssen, Sanofi, Mitsubishi, ZS Pharma, Akebia, UCB, Bristol-Myers Squibb, and Fibrogen outside the submitted work; non-financial support from Roche outside the submitted work; and personal fees for consultancy from Baxter outside the submitted work. GFMS received a research grant from Agenzia Italiana del Farmaco during the study and has received personal fees for consultancy and travel from Servier Laboratories outside the submitted work. DM, EN, JCC, GS, NW, and MR declare no competing interests.

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