Diabetes mellitus as a compelling indication for use of renin angiotensin system blockers: systematic review and meta-analysis of randomized trials

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ABSTRACT

OBJECTIVE

To evaluate the outcomes with use of renin angiotensin system (RAS) blockers compared with other antihypertensive agents in people with diabetes.

DESIGN

Meta-analysis.

DATA SOURCES AND STUDY SELECTION

PubMed, Embase, and the Cochrane central register of controlled trials databases for randomized trials of RAS blockers versus other antihypertensive agents in people with diabetes mellitus. Outcomes were death, cardiovascular death, myocardial infarction, angina, stroke, heart failure, revascularization, and end stage renal disease.

RESULTS

The search yielded 19 randomized controlled trials that enrolled 25 414 participants with diabetes for a total of 95 910 patient years of follow-up. When compared with other antihypertensive agents, RAS blockers were associated with a similar risk of death (relative risk 0.99, 95% confidence interval 0.93 to 1.05), cardiovascular death (1.02, 0.83 to 1.24), myocardial infarction (0.87, 0.64 to 1.18), angina pectoris (0.80, 0.58 to 1.11), stroke (1.04, 0.92 to 1.17), heart failure (0.90, 0.76 to 1.07), and revascularization (0.97, 0.77 to 1.22). There was also no difference in the hard renal outcome of end stage renal disease (0.99, 0.78 to 1.28) (power of 94% to show a 23% reduction in end stage renal disease).

CONCLUSIONS

In people with diabetes, RAS blockers are not superior to other antihypertensive drug classes such as thiazides, calcium channel blockers, and β blockers at reducing the risk of hard cardiovascular and renal endpoints. These findings support the recommendations of the guidelines of the European Society of Cardiology/European Society of Hypertension and eighth Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure to also use other antihypertensive agents in people with diabetes but without kidney disease.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Various guidelines recommend renin angiotensin system (RAS) blockers as first line treatment for people with diabetes, predominantly based on placebo controlled trials done 20 years ago

However, other guidelines recommend RAS blockers on a par with other antihypertensives based on more recent trials comparing RAS blockers versus active comparators

WHAT THIS STUDY ADDS

Our study suggests that in people with diabetes, RAS blockers are similar to other antihypertensives at reducing the risk of hard cardiovascular and renal endpoints

These findings support the European Society of Cardiology/European Society of Hypertension and eighth Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure guideline recommendations

Those guidelines recommend using any antihypertensives in people with diabetes but without kidney disease

Introduction

People with diabetes are at increased risk of cardiovascular and renal events.[1] Early placebo controlled trials (such as the Heart Outcomes Prevention Evaluation and European Trial on Reduction of Cardiac Events With Perindopril in Stable Coronary Artery Disease) have shown significant benefits from use of renin angiotensin system (RAS) blockers on cardiovascular and renal events in people with diabetes, benefits touted to be independent of the drugs blood pressure lowering efficacy. As such, the 2015 American Diabetes Association guidelines recommend RAS blockers (angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs)) as first line treatment for people with diabetes and hypertension.[2] Similarly, the 2013 American Society of Hypertension/International Society of Hypertension guidelines favor RAS blockers as a first line treatment in people with diabetes.[3] The National Kidney Foundation-Kidney Disease Outcomes Quality Initiative clinical practice guidelines state in its executive summary that "Hypertensive people with diabetes and chronic kidney disease stages 1-4 should be treated with an ACE inhibitor or an ARB, usually in combination with a diuretic."[4] In contrast, the 2013 European Society of Cardiology/European Society of Hypertension guidelines[5] and the 2014 evidence based guidelines from the panel members of the eighth Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure[6] recommend any class of antihypertensive agents in people with diabetes, with a preference for RAS blockers only in the presence of proteinuria or microalbuminuria. This seemingly discordant set of recommendations begs the questions about the evidence base to support superior cardioprotective and renoprotective effects of RAS blockers in people with diabetes.

We explored whether RAS blockers are superior to other antihypertensive agents for the prevention of hard cardiovascular and renal events in people with diabetes.

Methods

Eligibility criteria

We searched PubMed, Embase, and the Cochrane central register of controlled trials until December 2015 (week 1)

for randomized controlled trials of RAS blockers (ACE inhibitor or ARB) (see supplementary table S1 for MeSH terms) in people with diabetes or impaired fasting glucose. There were no language restrictions for the search. In addition, we searched the bibliography of identified original trials, meta-analyses, and review articles to find other eligible trials ("snowball search"). Weekly reminders from PubMed kept the search up to date.

Eligible trials had to fulfill two criteria: randomized controlled trials comparing RAS blockers with other antihypertensive agents in participants with diabetes or impaired fasting glucose, and a sample size of at least 100 participants with diabetes with follow-up of at least one year (to minimize small study effect). We excluded studies conducted in cohorts with heart failure given the known efficacy of RAS blockers in this patient group. In addition, we excluded studies that had been redacted for any reason, compared ACE inhibitors with ARBs, RAS blockers with placebo, or randomized participants to an ACE inhibitor plus ARB.

Trial selection and bias assessment

Three authors (RF, BT, SB) independently assessed trial eligibility, trial bias risk, and data extraction, with disagreements resolved by consensus. The bias risk of trials was assessed using the components for randomized trials recommended by the Cochrane Collaboration[7]: allocation sequence generation, allocation concealment, and blinding of outcome assessors. For each component, we categorized trials as being at low, high, or unclear risk of bias. We considered trials with high or unclear risk of bias for any one of the above components as trials with high risk of bias.

Outcomes

Outcomes were death, cardiovascular death, myocardial infarction, angina, stroke, heart failure, revascularization, end stage renal disease, major adverse cardiovascular events, and drug withdrawal owing to adverse events.

Statistical analyses

Statistical analyses were performed using an intention to treat approach and in line with recommendations from the Cochrane Collaboration and the preferred reporting items for systematic reviews and meta-analyses statement.[7 8] We carried out analyses to compare RAS blockers (ACE inhibitor or ARB) with other agents. Subgroup analyses compared RAS blockers with each class of comparative agent (calcium channel blockers, diuretics, and β blockers). The meta-analytic summary estimates (relative risk) were calculated using the fixed effect model and the random-effects model of DerSimonian and Laird.[9] Continuity correction was used for trials with zero events. We used the I^2 statistic to assess heterogeneity—the proportion of total variation observed between the trials attributable to differences between trials rather than to sampling error (chance),[10] with an I^2 value less than 25% considered low and more than 75% high. We assessed small study effect using the Begg's and the Egger's test and by visual evaluation of the funnel plots for asymmetry.

A metaregression analysis was performed to evaluate the relation of percent of participants with nephropathy at baseline on the outcomes. We used a residual maximum likelihood to estimate the additive (between study) component of variance τ^2 for the metaregression analysis. Bootstrap analyses were performed using a Monte Carlo permutation test for metaregression, using 10 000 random permutations.[11] Sensitivity analyses were done after excluding trials that included participants with impaired fasting glucose. Analyses were performed using standard statistical software (Stata 12.1, Stata, TX),[12] with $P<0.05$ used to denote statistical significance.

Patient involvement

No patients were involved in setting the research question or the outcome measures, nor were they involved in developing plans for design or implementation of the study. No patients were asked to advise on interpretation or writing up of results. There are no plans to disseminate the results of the research to study participants or the relevant patient community.

Results

Study selection and baseline characteristics

Our search yielded 19 randomized controlled trials (see supplementary figure S1), enrolling 25 414 people with diabetes. The participants were followed for a mean of 3.8 years, totalling 95 910 patient years of follow-up. Fifteen trials compared RAS blockers with a calcium channel blocker, three with a thiazide diuretic, and two with a β blocker. In 14 trials the RAS blockers were an ACE inhibitor and in six an ARB. All trials enrolled people with type 2 diabetes. In addition, the majority of the trials (n=17) enrolled people with diabetes and hypertension.

Table 1 outlines the baseline characteristics of the included trials. In the studies that reported race/ethnicity, black people were a minority of the enrolled patients. The primary endpoint for the trials was heterogeneous (see supplementary table S2). Only three trials enrolled patients with microalbuminuria or proteinuria.

Outcomes

RAS blockers versus other antihypertensives

When compared with other antihypertensive agents, RAS blockers were associated with a similar risk of death (relative risk 0.99, 95% confidence interval 0.93 to 1.05, fig 1), cardiovascular death (1.02, 0.83 to 1.24, fig 2), myocardial infarction (0.87, 0.64 to 1.18, fig 3), angina pectoris (0.80, 0.58 to 1.11, fig 4), stroke (1.04, 0.92 to 1.17, fig 5), heart failure (0.90, 0.76 to 1.07, fig 6), and revascularization (0.97, 0.77 to 1.22, fig 7). The outcome of major adverse cardiovascular events (0.97, 0.89 to 1.06) did not differ between the two groups. In addition, there was no difference in end stage renal disease (0.99, 0.78 to 1.28, fig 8) or drug withdrawal owing to adverse effects (fig 9). The results were consistent when using a fixed effect model (figs 1-9). Heterogeneity was low to moderate, with no evidence of small study effect/publication bias (see supplementary figures S2-S10).

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Table 1 | Baseline characteristics and risk of bias assessment of included trials

Trials	Year	Sample size	Follow-up (years)	Cohort	Age (years)	Black people (%)	Risk of bias*
RAS blockers versus calcium channel blockers:							
ABCD (hypertensive)[13, 14]	1998	470	5.6	Diabetes mellitus and hypertension	58	14	+++
ABCD (normotensive)[15]	2002	354	5.3	Diabetes mellitus and normotensive	59	7	+++
ALLHAT[16, 17] (diabetes mellitus)	2002	7107	4.9	Diabetes mellitus and hypertension	67	39	+++
ALLHAT[16, 17, 18] (impaired fasting glucose)	2002	771	4.9	Impaired fasting glucose and hypertension	67	30	+++
BENEDICT[19]	2004	604	3.6	Diabetes mellitus and hypertension	62	NR	±±+
CAMELOT[20] (diabetes mellitus)	2004	233	2	Diabetes mellitus and coronary artery disease	58	NR	+++
CAMELOT[20] (impaired fasting glucose)	2004	233	2	Impaired fasting glucose and coronary artery disease	58	NR	+++
CASE-J[21, 22, 23] (diabetes mellitus)	2008	1195	3.2	Diabetes mellitus and hypertension	67	NR	+++
FACET[24]	1998	380	2.9	Diabetes mellitus and hypertension	63	NR	+±+
Fogari et al[25]	2002	205	4	Diabetes mellitus with proteinuria and hypertension	63	NR	+±±
IDNT[26, 27, 28]	2001	1146	2.6	Diabetes mellitus with nephropathy and hypertension	60	13	±++
JMIC-B[29, 30] (diabetes mellitus)	2004	372	3	Diabetes mellitus, hypertension, and coronary artery disease	64	NR	+++
J-MIND[31]	2001	436	2	Diabetes mellitus and hypertension	60	NR	++±
MITEC[32]	2009	209	2	Diabetes mellitus and hypertension	60	NR	+±+
MOSES[33, 34] (diabetes mellitus)	2005	498	2.5	Diabetes mellitus, hypertension, and cerebrovascular accident	70	NR	+++
NAGOYA HEART[35]	2012	1150	3.2	Diabetes mellitus and hypertension	63	NR	+±+
STOP-Hypertension-2[36] (diabetes mellitus)	1999	466	5	Diabetes mellitus and elderly hypertension	76	NR	±++
RAS blockers versus diuretic:							
ALLHAT[16, 17] (diabetes mellitus)	2002	9504	4.9	Diabetes mellitus and hypertension	67	39	+++
ALLHAT[16, 17, 18] (impaired fasting glucose)	2002	1035	4.9	Impaired fasting glucose and hypertension	67	30	+++
ANBP2[37, 38] (diabetes mellitus)	2003	441	4.1	Diabetes mellitus and elderly hypertension	72	NR	±++
NESTOR[39]	2003	569	1	Diabetes mellitus with microalbuminuria and hypertension	60	5	+±+
RAS blockers versus β blockers:							
UKPDS 39[40]	1998	758	8.4	Diabetes mellitus and hypertension	56	8	+++
LIFE[41, 42, 43, 44] (diabetes mellitus)	2002	1195	4.8	Diabetes mellitus and hypertension with left ventricular hypertrophy	67	12	+++

ABCD=Appropriate Blood Pressure Control in Diabetes; ALLHAT=Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial; ANBP2=Second Australian National Blood Pressure Study; BENEDICT=Bergamo Nephrologic Diabetes Complications Trial; CAMELOT=Comparison of Amlodipine vs Enalapril to Limit Occurrences of Thrombosis; CASE-J=Candesartan Antihypertensive Survival Evaluation in Japan; FACET=Fosinopril Versus Amlodipine Cardiovascular Events Randomized Trial; IDNT=Irbesartan Type II Diabetic Nephropathy Trial; JMIC-B=Japan Multicenter Investigation for Cardiovascular Diseases-B; J-MIND=Japan Multicenter Investigation of Antihypertensive Treatment for Nephropathy in Diabetics; LIFE=Losartan Intervention For Endpoint reduction; MITEC=Media Intima Thickness Evaluation with Candesartan cilexetil; MOSES=Morbidity and Mortality After Stroke, Eprosartan Compared With Nitrendipine for Secondary Prevention; NAGOYA HEART=Comparison between valsartan and amlodipine regarding morbidity and mortality in patients with hypertension and glucose intolerance; NESTOR=Natrilix SR versus Enalapril Study in Type 2 diabetic hypertensives with micrOalbuminuRia; NR=not reported; RAS-inh=Renin-Angiotensin System inhibitor; STOP-Hypertension=Swedish Trial in Old Patients with Hypertension; UKPDS=UK Prospective Diabetes Study Group.
*Represents risk of bias based on: sequence generation of allocation; allocation concealment and blinding. + represents low bias risk and ± unclear bias risk.

RAS blockers versus calcium channel blockers

When compared with calcium channel blockers, RAS blockers were associated with a similar risk of death (1.01, 0.92 to 1.10, fig 1), cardiovascular death (1.17, 0.90 to 1.50, fig 2), myocardial infarction (0.84, 0.54 to 1.30, fig 3), angina pectoris (0.69, 0.33 to 1.42, fig 4), stroke (1.08, 0.90 to 1.28, fig 5), and revascularization (1.01, 0.74 to 1.39, figs 7 and 10). However, RAS blockers were associated with a significant reduction in the risk of heart failure compared with calcium channel blockers (0.78, 0.70 to 0.88, figs 6 and 10). There was no difference in drug withdrawal owing to adverse effects (fig 9) or end stage renal disease (figs 8 and 10). Heterogeneity was low to moderate (fig 10), with no evidence of small study effect/publication bias (see supplementary figures S2-10).

RAS blockers versus thiazide diuretics

Compared with thiazide diuretics, RAS blockers were associated with a similar risk of death (0.99, 0.90 to 1.08, fig 1), cardiovascular death (0.50, 0.05 to 5.46, fig 2), and other outcomes (figs 3-9 and 11). Only three trials compared RAS blockers with diuretics and hence the confidence interval for most outcomes was wide. Heterogeneity was low to moderate (fig 11), with no evidence of small study effect/publication bias (see supplementary figures S2-10).

RAS blockers versus β blockers

Compared with β blockers, RAS blockers were associated with a similar risk of death (0.84, 0.47 to 1.51, fig 1), cardiovascular death (0.87, 0.47 to 1.60, fig 2), and other outcomes tested (figs 3-9 and 12). Only two trials compared RAS blockers with β blockers and hence the confidence interval for most outcomes was wide. Heterogeneity was high for the outcome of death but low to moderate for other outcomes (fig 12), with no evidence of small study effect/publication bias (see supplementary figures S2-10).

Influence of nephropathy

Metaregression analysis, aimed to assess the relation of percent of patients with nephropathy at baseline on the outcomes, showed no significant relation (P>0.05) for all outcomes.

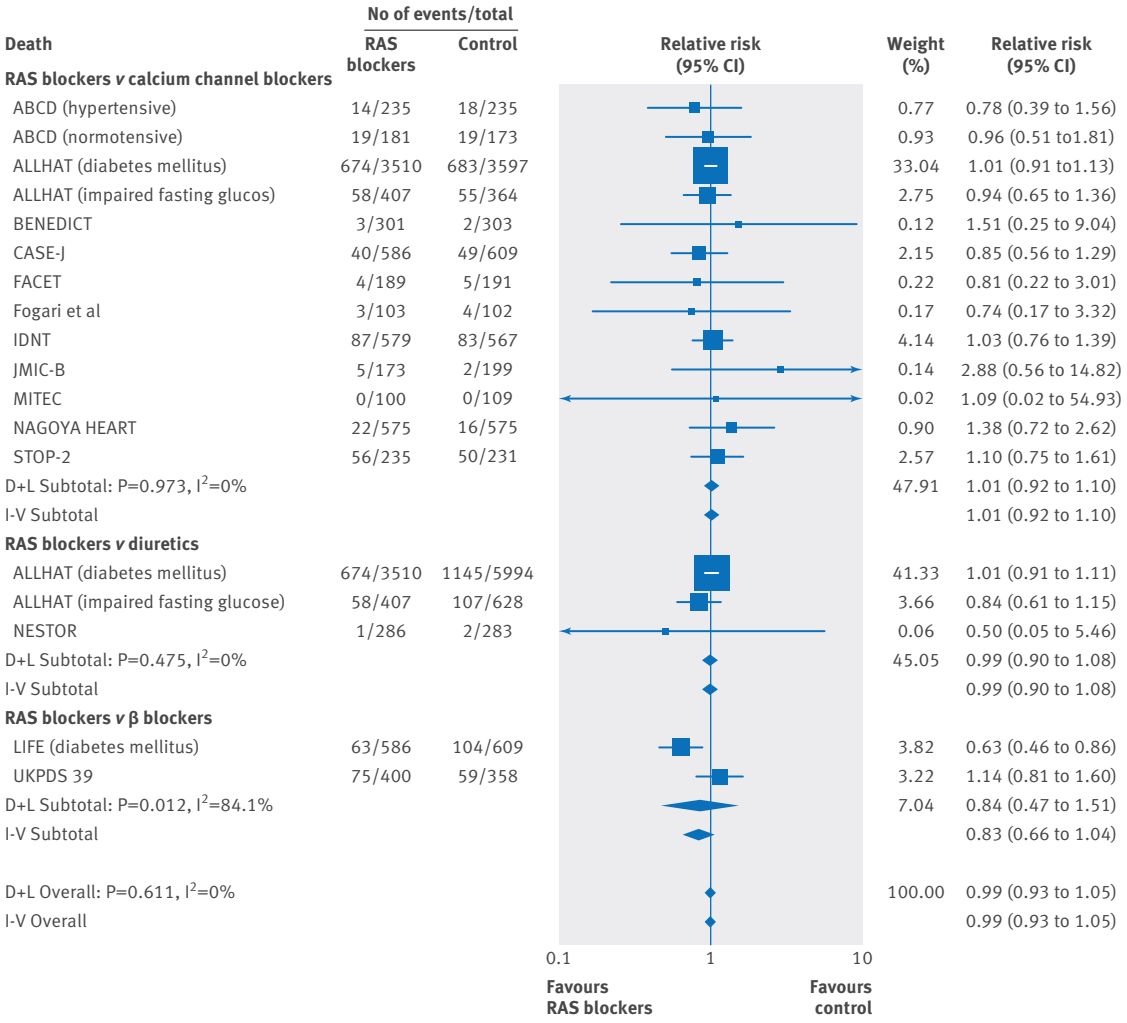

Fig 1 | Outcomes of death with renin angiotensin system (RAS) blockers compared with other antihypertensives in people with diabetes

Sensitivity analysis

Results were largely similar in sensitivity analysis excluding trials of participants with impaired fasting glucose (see supplementary table S3).

Discussion

This analysis of patients with diabetes (largely without microalbuminuria or proteinuria) with 95 910 patient years of follow-up from randomized trials failed to show a superiority of renin angiotensin system (RAS) blockade over other antihypertensive agents for reduction of cardiovascular and renal outcomes. More importantly, compared with other agents RAS blockers showed no benefit in reducing the risk of death or myocardial infarction and end stage renal disease. The results were consistent in comparisons of RAS blockers with all controls and with individual antihypertensive agents.

RAS blockers for diabetes

People with diabetes mellitus are at increased risk of hypertension, and the concomitant presence of diabetes and hypertension is associated with an exponential increase in the risk of cardiovascular, cerebrovascular, and renal events.[45] Previous trials have shown that blood pressure reduction in such patients leads to a significant reduction in cardiovascular events, emphasizing the need for aggressive management of hypertension in this cohort.[46] However, whether one antihypertensive drug class is superior to the other is controversial. Early studies of RAS blockade in patients with diabetes and microalbuminuria showed a significant "renoprotective" effect (mainly by slowing progression to clinical proteinuria) compared with placebo,[47] leading to the recommendation of RAS blockers for this indication. This recommendation was later extended to all people with diabetes. In addition, small head to head comparison trials of RAS blockers (fosinopril) versus calcium channel blockers (amlodipine) such as the Fosinopril Versus Amlodipine Cardiovascular Events Randomized Trial (380 participants) showed a significant reduction in cardiovascular events (secondary endpoint of combined outcome of myocardial infarction, stroke, or hospital admission for angina) with RAS blockers compared with calcium channel blockers.[24] However, hard endpoints of death or myocardial infarction did not differ in this trial.

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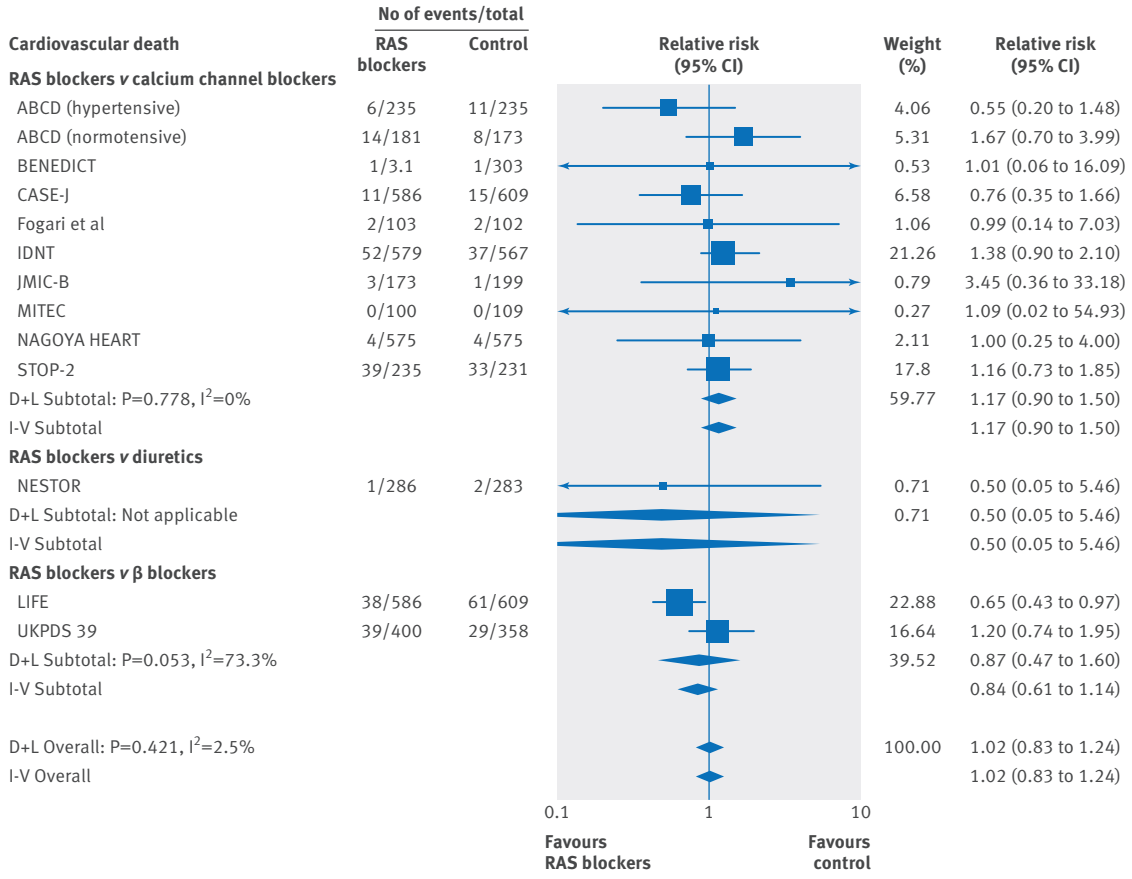

Fig 2 | Outcome of cardiovascular death with renin angiotensin system (RAS) blockers compared with other antihypertensives in people with diabetes

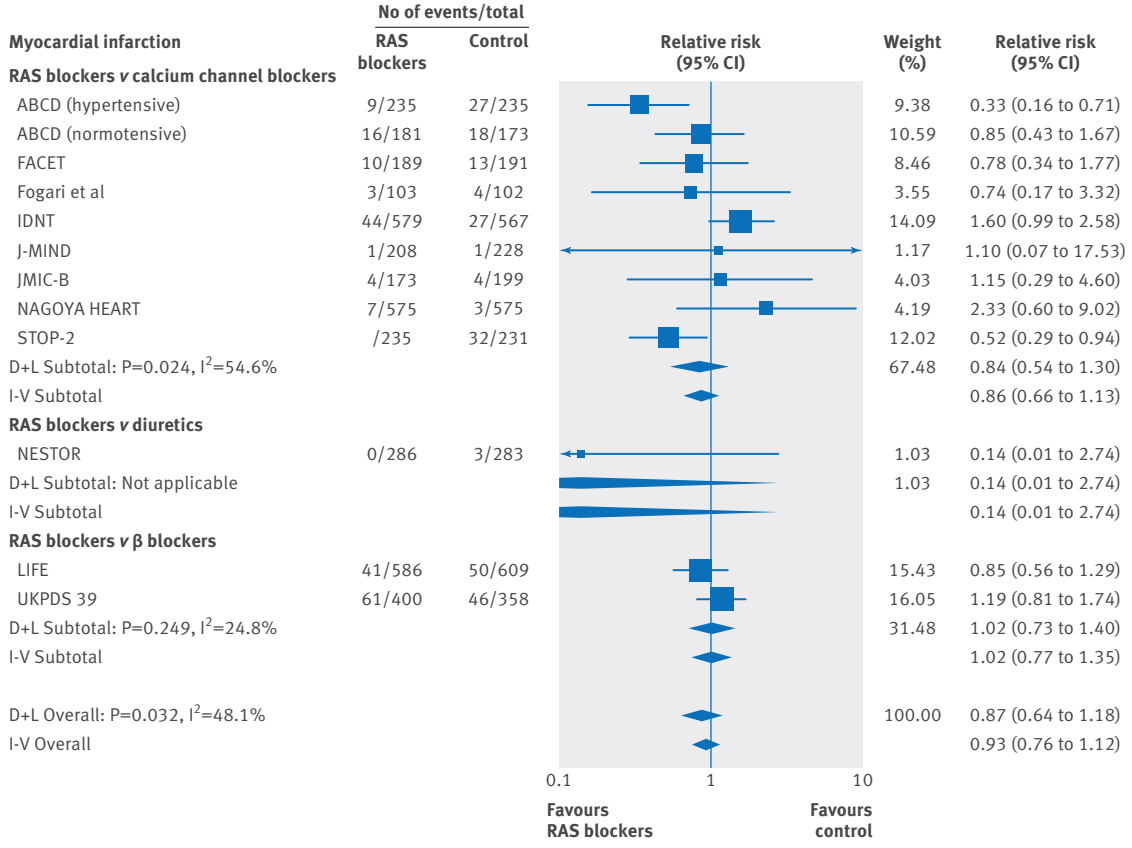

Fig 3 | Outcome of myocardial infarction with renin angiotensin system (RAS) blockers compared with other antihypertensives in people with diabetes

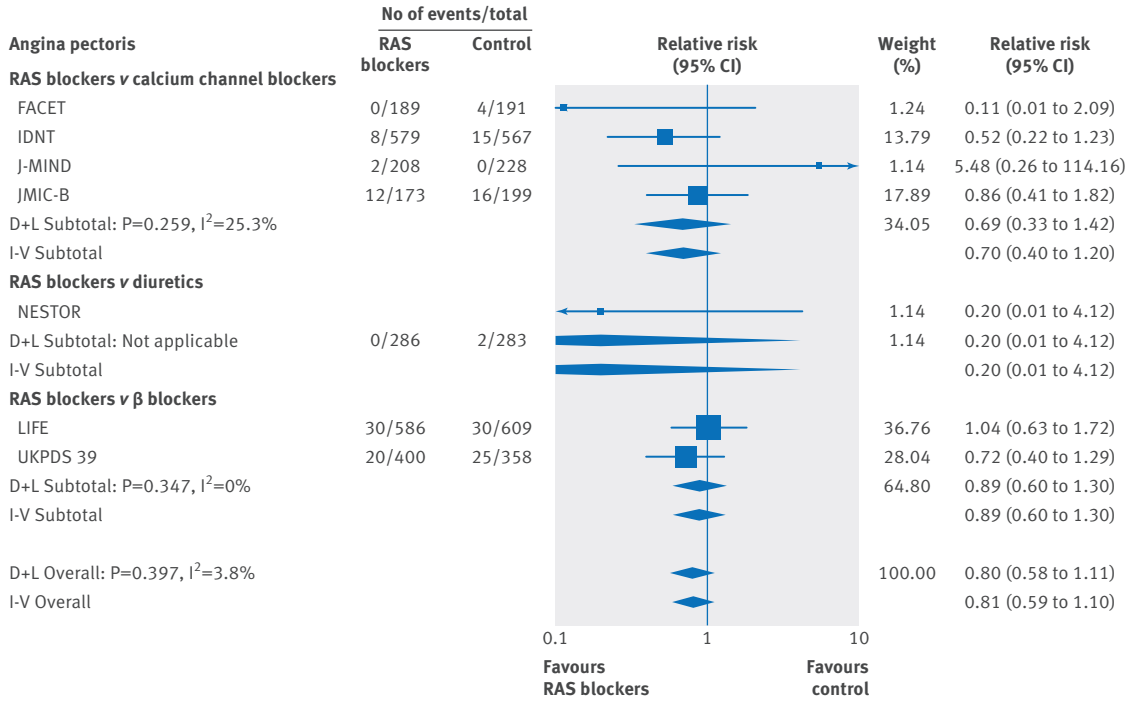

Fig 4 | Outcome of angina pectoris with renin angiotensin system (RAS) blockers compared with other antihypertensives in people with diabetes

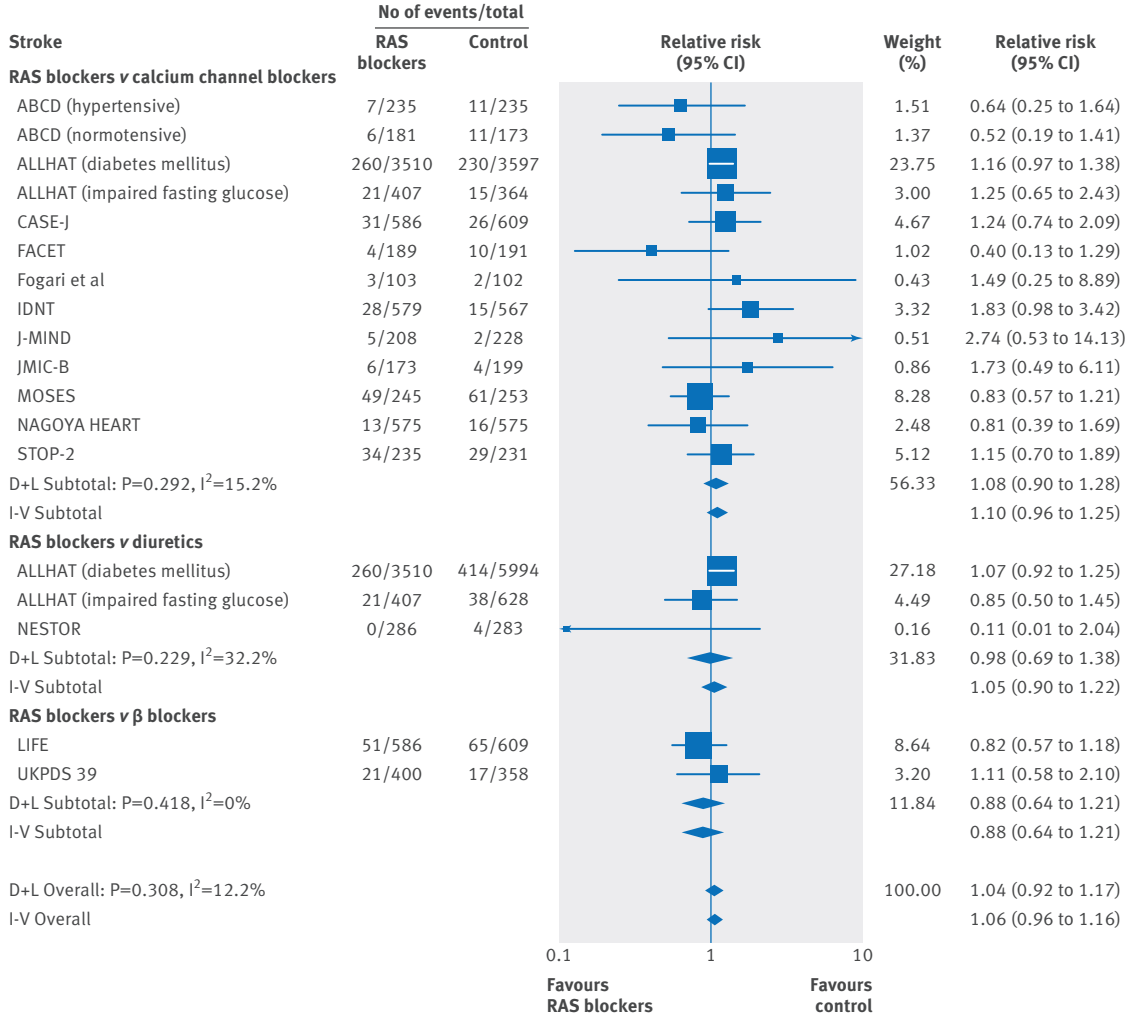

Fig 5 | Outcome of stroke with renin angiotensin system (RAS) blockers compared with other antihypertensives in people with diabetes

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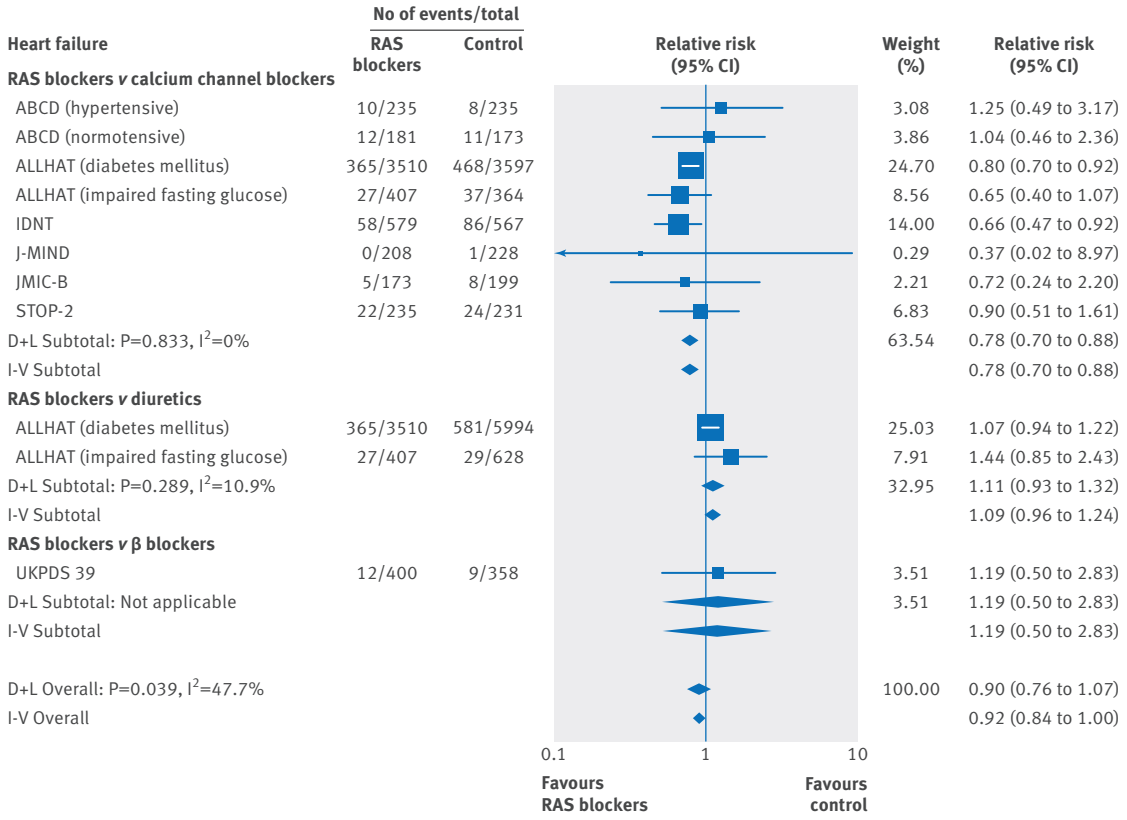

Fig 6 | Outcome of heart failure with renin angiotensin system (RAS) blockers compared with other antihypertensives in people with diabetes

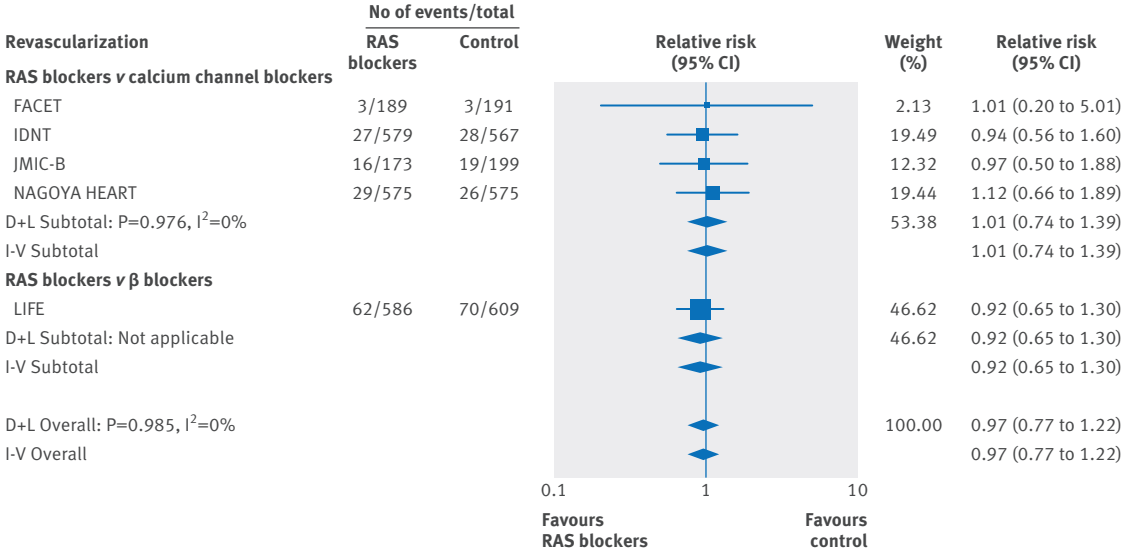

Fig 7 | Outcome of revascularization with renin angiotensin system (RAS) blockers compared with antihypertensives in people with diabetes

Subsequent guidelines, including the seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure promoted diabetes as a compelling indication for RAS blockade. The American Diabetic Association guidelines states "In people with diabetes, inhibitors of the renin-angiotensin system (RAS) may have unique advantages for initial or early treatment of hypertension." However, more recent trials have failed to show superiority of RAS blockers compared with other antihypertensive agents for hard cardiovascular outcomes.[35] In addition, studies with larger sample size (for example, the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) with 13 101 patients with diabetes) also failed to show the superiority of RAS blockers compared with other

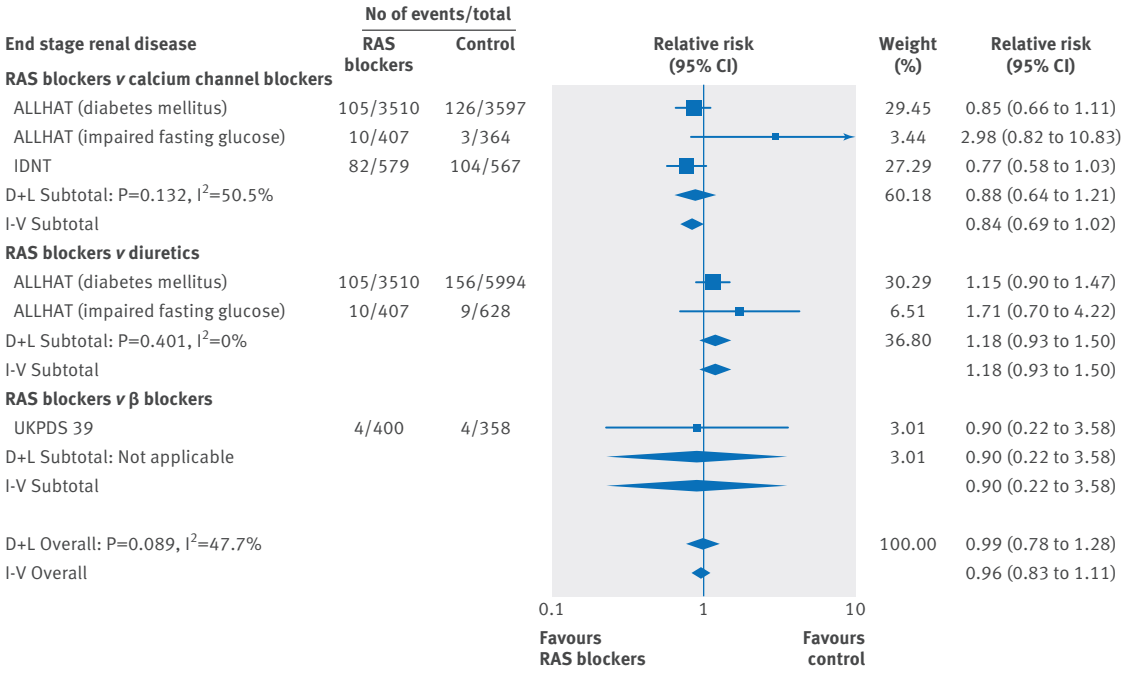

Fig 8 | Outcome of end stage renal disease with renin angiotensin system (RAS) blockers compared with other antihypertensives in people with diabetes

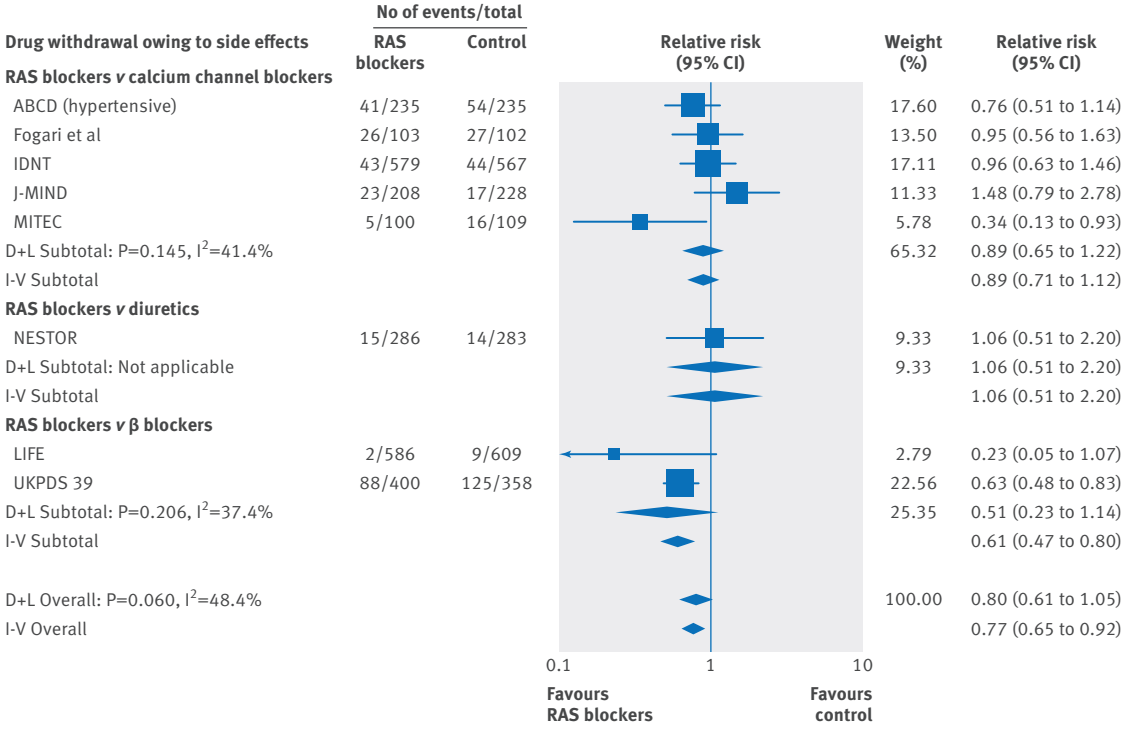

Fig 9 | Outcome of drug withdrawal owing to adverse effects with renin angiotensin system (RAS) blockers compared with other antihypertensives in people with diabetes

antihypertensive agents for cardiovascular outcomes.[18] Indeed, two decades ago one author stated about the progression of chronic kidney disease that "despite some discrepancies in experimental studies, recent controlled clinical trials show a similar slowing of progression with either ACEi [ACE inhibitor] or CCB [calcium channel blocker]."[48] Consequently opinion now diverges among various guidelines about the role of RAS blockade in people with diabetes, with some guidelines still recommending RAS blockers as preferred drugs and some relegating them to be on a par with other antihypertensive drug classes.

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Outcomes	No of studies	No of events/ No of participants: RAS blockers	No of events/ No of participants: Calcium channel blockers	I^2	Relative risk (95% CI): Random	Relative risk (95% CI): Fixed
All cause mortality	13	985/7174	986/7255	0.0	1.01 (0.92 to 1.10)	1.01 (0.92 to 1.10)
Cardiovascular mortality	10	132/3068	112/3103	0.0	1.17 (0.90 to 1.50)	1.17 (0.90 to 1.50)
Myocardial infarction	9	111/2478	129/2501	54.6	0.84 (0.54 to 1.30)	0.86 (0.66 to 1.13)
Angina	4	22/1149	35/1185	25.3	0.69 (0.33 to 1.42)	0.70 (0.40 to 1.20)
Stroke	13	467/7226	432/7324	15.2	1.08 (0.90 to 1.28)	1.10 (0.96 to 1.25)
Heart failure	8	499/5528	643/5594	0.0	0.78 (0.70 to 0.88)	0.78 (0.70 to 0.88)
Revascularization	4	75/1516	76/1532	0.0	1.01 (0.74 to 1.39)	1.01 (0.74 to 1.39)
Drug withdrawal	5	138/1225	158/1241	41.4	0.89 (0.65 to 1.22)	0.89 (0.71 to 1.12)
End stage renal disease	3	197/4496	233/4528	50.5	0.88 (0.64 to 1.21)	0.84 (0.69 to 1.02)

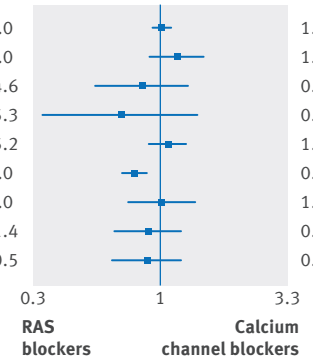

Fig 10 | Outcomes with renin angiotensin system (RAS) blockers compared with calcium channel blockers in people with diabetes

Outcomes	No of studies	No of events/ No of participants: RAS blockers	No of events/ No of participants: Diuretics	I^2	Relative risk (95% CI): Random	Relative risk (95% CI): Fixed
All cause mortality	3	733/4203	1254/6905	0.0	0.99 (0.90 to 1.08)	0.99 (0.90 to 1.08)
Cardiovascular mortality	1	1/286	2/283	NA	0.50 (0.05 to 5.46)	0.50 (0.05 to 5.46)
Myocardial infarction	1	0/286	3/283	NA	0.14 (0.01 to 2.74)	0.14 (0.01 to 2.74)
Angina	1	0/286	2/283	NA	0.20 (0.01 to 4.12)	0.20 (0.01 to 4.12)
Stroke	3	281/4203	456/6905	32.2	0.98 (0.69 to 1.38)	1.05 (0.90 to 1.22)
Heart failure	2	392/3917	610/6622	10.9	1.11 (0.93 to 1.32)	1.09 (0.96 to 1.24)
Drug withdrawal	1	15/286	14/283	NA	1.06 (0.51 to 2.20)	1.06 (0.51 to 2.20)
End stage renal disease	2	115/3917	165/6622	0.0	1.18 (0.93 to 1.50)	1.18 (0.93 to 1.50)

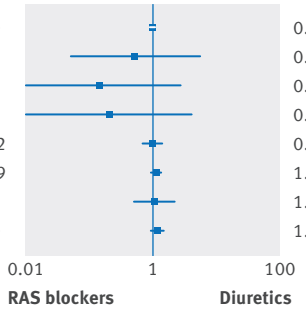

Fig 11 | Outcomes with renin angiotensin system (RAS) blockers compared with diuretics in people with diabetes

Outcomes	No of studies	No of events/ No of participants: RAS blockers	No of events/ No of participants: β blockers	I^2	Relative risk (95% CI): Random	Relative risk (95% CI): Fixed
All cause mortality	2	138/986	163/967	84.1	0.84 (0.47 to 1.51)	0.83 (0.66 to 1.04)
Cardiovascular mortality	2	77/986	90/967	73.3	0.87 (0.47 to 1.60)	0.84 (0.61 to 1.14)
Myocardial infarction	2	102/986	96/967	24.8	1.02 (0.73 to 1.40)	1.02 (0.77 to 1.35)
Angina	2	50/986	55/967	0.0	0.89 (0.60 to 1.30)	0.89 (0.60 to 1.30)
Stroke	2	72/986	82/967	0.0	0.88 (0.64 to 1.21)	0.88 (0.64 to 1.21)
Heart failure	1	12/400	9/358	NA	1.19 (0.50 to 2.83)	1.19 (0.50 to 2.83)
Revascularization	1	62/586	70/609	NA	0.92 (0.65 to 1.30)	0.92 (0.65 to 1.30)
Drug withdrawal	2	90/986	134/967	37.4	0.51 (0.23 to 1.14)	0.61 (0.47 to 0.80)
End stage renal disease	1	4/400	4/358	NA	0.90 (0.22 to 3.58)	0.90 (0.22 to 3.58)

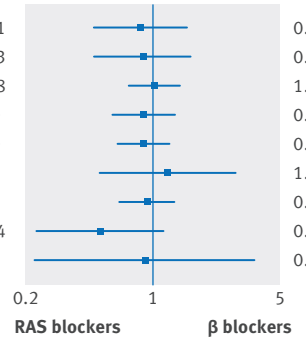

Fig 12 | Outcomes with renin angiotensin system (RAS) blockers compared with β blockers in people with diabetes

Given the controversy and the discordance in various guideline recommendations about the role of RAS blockers in people with diabetes we evaluated the comparative effectiveness of RAS blockers compared with other antihypertensive agents in people with diabetes, excluding cohorts where RAS blockers are shown to provide benefit (that is, heart failure). We also excluded placebo controlled trials since placebo is not the standard of care in such patients. The results of this study with over 95 000 patient years of follow-up from head to head randomized trials of RAS blockers versus other antihypertensive agents failed to

show a superiority of RAS blockers over other antihypertensive agents for the prevention of hard cardiovascular or renal outcomes. The notable exception in our analysis was that the RAS blockers were superior to calcium channel blockers for the prevention of heart failure. This outcome (heart failure) was mainly driven by the ALLHAT trial, the findings of which have been criticized.[49] Our findings of similar outcomes with RAS blockers compared with other antihypertensive agents therefore supports both the 2013 Society of Cardiology/European Society of Hypertension guidelines[5] and the 2014 eighth Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure[6] recommendation that any class of antihypertensive agents can be used in people with diabetes.

Diabetes with proteinuria or microalbuminuria

Both the 2013 Society of Cardiology/European Society of Hypertension guidelines[5] and the 2014 eighth Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure[6] recommend RAS blockers in the presence of proteinuria or microalbuminuria. The guideline recommendations favoring RAS blockers in those with diabetes and chronic kidney disease are driven mainly by placebo controlled trials of RAS blockers where there was a reduction in doubling of serum creatinine concentration (the Microalbuminuria, Cardiovascular, and Renal Outcomes substudy of the Heart Outcomes Prevention Evaluation study (MICRO-HOPE) and the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan study (RENAAL) and end stage renal disease (RENAAL) compared with placebo.[50 51] Casas and colleagues showed a greater benefit of RAS blockers on renal outcomes in placebo controlled trials than active comparison trials and concluded that the benefits of RAS blockers on renal outcomes probably results from a blood pressure lowering effect.[52] Palmer and colleagues, in a meta-analysis of trials enrolling patients with diabetes and kidney disease, found that no drug regimen was more effective than placebo for reducing all cause mortality.[53] However, end stage renal disease and a doubling of creatinine concentration was less likely and regression of albuminuria was more likely with ACE inhibitors or ARBs compared with placebo.[53] Limited trials have shown this superiority in active comparator trials. In the Irbesartan Type II Diabetic Nephropathy Trial (1715 patients with diabetic nephropathy) the RAS blocker irbesartan compared with the calcium channel blocker amlodipine was associated with a significant reduction in the risk of the primary composite end point (32.6%*v* 41.1%; P=0.006) of a doubling of serum creatinine concentration, the development of end stage renal disease, or death from any cause, driven by differences in doubling of serum creatinine concentration (16.9%*v* 25.4%; P<0.001), with numerically lower end stage renal disease (14.2%*v* 18.3%; P=0.07) but with no difference in death (15.0%*v* 14.6%; P>0.05).[28] Finally, Wu and colleagues in a meta-analysis of RAS blockers in patients with diabetes showed no statistically significant difference among treatments for the hard endpoint of end stage renal disease even in the placebo comparisons.[54] However, an ACE inhibitor reduced the risk of doubling of serum creatinine compared with placebo.[54] Our study excluded placebo controlled trials and failed to show a benefit for the outcome of end stage renal disease with RAS blockers compared with other antihypertensive agents. Our analysis with 17 626 patients (for the outcome of end stage renal disease) had a power of 94% to show a 23% reduction in end stage renal disease with RAS blockers compared with controls and is thus sufficiently powered to show a difference if one existed.

Limitations of this study

We used trial level data only for the analyses and hence were unable to control for differences between trials. Although a separate analysis in the cohort of patients with nephropathy is desirable, trials did not report outcomes separately for this cohort. Moreover, the definition of nephropathy was variable. In addition, most of the studies in patients with diabetes and nephropathy were placebo controlled trials and excluded in the current analysis. There were only a few trials for the RAS blocker compared with diuretics and RAS blockers compared with β blocker, and the analyses are likely underpowered. For the renal outcomes, we only evaluated end stage renal disease as an outcome as this is considered a "hard" renal endpoint. While one can argue that a doubling of serum creatinine concentration is a stringent renal endpoint, only one trial reported this outcome. Most patients with diabetes and hypertension require on an average two antihypertensive agents and thus which agent should be first may not be critical. The results were partly driven by the ALLHAT trial, given the sample size. However, this trial did not monitor urine protein.

Conclusions

This analysis of head to head comparison trials of RAS blockers versus other antihypertensive agents in people with diabetes (and largely without microalbuminuria or proteinuria) failed to show a superiority of RAS blockers compared with other antihypertensive agents for the prevention of hard outcomes. The results support the recommendation of both the 2013 European Society of Cardiology/European Society of Hypertension guidelines[5] and the 2014 eighth report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure[6] that any class of antihypertensive agents can be used in people with diabetes especially in those without renal impairment.

Contributors: SB conceived, designed, and supervised the study, carried out the statistical analysis, and drafted the manuscript. RF and BT acquired the data. All authors analyses and interpreted the data and critically revised the manuscript for important intellectual content. SB is the guarantor. He had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Ethical approval: Not required.

Data sharing: No additional data available.

Transparency: The guarantor (SB) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

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Web extra: supplementary appendix