RESEARCH

Blood pressure lowering and major cardiovascular events in people with and without chronic kidney disease: meta-analysis of randomised controlled trials

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Blood Pressure Lowering Treatment Trialists' Collaboration

Abstract

Objective To define the cardiovascular effects of lowering blood pressure in people with chronic kidney disease.

Design Collaborative prospective meta-analysis of randomised trials.

Data sources and eligibility Participating randomised trials of drugs to lower blood pressure compared with placebo or each other or that compare different blood pressure targets, with at least 1000 patient years of follow-up per arm.

Main outcome measures Major cardiovascular events (stroke, myocardial infarction, heart failure, or cardiovascular death) in composite and individually and all cause death.

Participants 26 trials (152 290 participants), including 30 295 individuals with reduced estimated glomerular filtration rate (eGFR), which was defined as eGFR <60 mL/min/1.73m^2.

Data extraction Individual participant data were available for 23 trials, with summary data from another three. Meta-analysis according to baseline kidney function was performed. Pooled hazard ratios per 5 mm Hg lower blood pressure were estimated with a random effects model.

Results Compared with placebo, blood pressure lowering regimens reduced the risk of major cardiovascular events by about a sixth per 5 mm Hg reduction in systolic blood pressure in individuals with (hazard ratio 0.83, 95% confidence interval 0.76 to 0.90) and without reduced eGFR (0.83, 0.79 to 0.88), with no evidence for any difference in effect (P=1.00 for homogeneity). The results were similar irrespective of whether blood pressure was reduced by regimens based on angiotensin converting enzyme inhibitors, calcium antagonists, or diuretics/β blockers. There was no evidence that the effects of different drug classes on major cardiovascular events varied between patients with different eGFR (all P>0.60 for homogeneity).

Conclusions Blood pressure lowering is an effective strategy for preventing cardiovascular events among people with moderately reduced eGFR. There is little evidence from these overviews to support the preferential choice of particular drug classes for the prevention of cardiovascular events in chronic kidney disease.

Introduction

Chronic kidney disease, most commonly defined by a reduced glomerular filtration rate (GFR) or abnormal concentrations of proteinuria, or both, is an important public health problem, affecting 10-15% of the adult general population.[1-3] It is associated with an increased risk of kidney failure and cardiovascular disease.[4-6] Individuals with early chronic kidney disease are more likely to experience a cardiovascular event than kidney failure,[7] and precise and reliable evidence about the effects of strategies to prevent cardiovascular disease in this large population of patients is of great importance.

Blood pressure is an important determinant of the risk of cardiovascular disease in the general population.[8] It is well established that interventions that lower blood pressure prevent cardiovascular events.[9 10] Blood pressure is commonly raised in individuals with chronic kidney disease,[5 6] and guidelines recommend lower blood pressure targets in this population than in people without chronic kidney disease.[11 12] Several studies have also suggested particular benefits of drug classes acting through the renin-angiotensin system for the prevention of renal complications.[13] The evidence that lowering blood pressure is beneficial for patients with chronic kidney disease as well as those without, however, remains limited, and the comparative efficacy of different regimens to lower blood pressure on the risk of cardiovascular events in patients with and without chronic kidney disease remains uncertain.[14-19]

The Blood Pressure Lowering Treatment Trialists' Collaboration[20] was established to perform a series of prospectively defined overviews of randomised trials to investigate the effects of blood pressure lowering drugs on cardiovascular morbidity and mortality, including assessments of the comparative effects of regimens between major patient subgroups. This analysis, prespecified in the original collaboration protocol,[20] quantifies the proportional benefits of blood pressure lowering, and the comparative effects of different

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classes of blood pressure lowering drugs in individuals with and without chronic kidney disease.

Methods

Data sources and study selection

Trials were eligible for inclusion in this prospective collaborative meta-analysis if they met one of the following criteria: patients were randomised to a blood pressure lowering drug/regimen or a control group (placebo or less intensive blood pressure lowering regimen) or patients were randomised between regimens based on different classes of drugs to lower blood pressure. Trials were also required to have a minimum of 1000 patient years of planned follow-up in each randomised arm and not to have presented or published their main results before finalisation of the overview protocol in July 1995.[20] The collaboration was jointly established by the principal investigators in 1995, and the inclusion criteria for the overviews[20] specified that results of trials reported only after this time could be included. In the early years of the collaboration, participants contributed aggregate trial data but, over time, agreed to provide individual patient data. New trials were identified by a range of methods including computer aided literature searches, scrutiny of abstracts and proceedings of meeting, and by inquiring among colleagues, collaborators, and the manufacturers of antihypertensive drugs. Determination of eligibility was based on a review of details of the study design and quality of the study, regardless of main results of each trial (appendix table 1). The principal investigators for eligible trials were invited to join the collaboration as they were identified. Trials for which data by kidney function had been obtained by April 2012 were included in these analyses. For this overview, data were available from 26 trials providing either individual participant data including serum creatinine concentrations (23 trials[21-44]) or summary data stratified by estimated glomerular filtration rate (tabular data from two trials[15 45] and published hazard ratios from one trial[14]). Among them, 25 trials[14 15 21-44] were included in the main analyses, while one trial[45] contributed participants only to the reduced eGFR stratum and was included in sensitivity analyses. Data regarding urinary protein excretion at baseline were available for 11 trials.[21 22 24 27-32 37 40] Two trials[15 34 39] did not provide information regarding the combined endpoint of major cardiovascular events according to chronic kidney disease status but provided data for other endpoints. The individual participant data requested included characteristics of participants recorded at screening or randomisation, selected measurements during follow-up, and details of all outcomes during the scheduled follow-up period. We used the Cochrane Collaboration's tool to assess the risk of bias.[46]

Glomerular filtration rates and proteinuria

Glomerular filtration rates were estimated with the modification of diet in renal disease formula[7]:

$$eGFR = 186.3 \times (\text{serum creatinine}/88.4)^{-1.154} \times (\text{age})^{-0.203} \times 1.210 \text{ (if black)} \times 0.742 \text{ (if female)}$$

where eGFR is in mL/min/1.73 m^2, age is in years, and serum creatinine is in μmol/L. The participants were divided into two categories of baseline eGFR ($\geq$60 mL/min/1.73 m^2 or and <60 mL/min/1.73 m^2) with established cutpoints recommended in renal guidelines.[11] Published data from two trials in which kidney function was estimated with the Cockcroft-Gault formula[14] or 125-iothalamate clearance[45] and patients were categorised as having eGFR <65 mL/min and $\geq$65 mL/min were deemed sufficiently comparable and included in the main analysis. The presence of proteinuria was defined as any of the following:

urinary albumin excretion rate s>200 μg/min or >300 mg/day, urinary albumin concentration >200 mg/L, urinary albumin creatinine ratio >300 μg/mg, or a urinary protein dipstick test result of 1+ or greater.[7] Stages of chronic kidney disease were defined according to the guidelines from the Kidney Disease Outcomes Quality Initiative (K/DOQI).[11]

Outcomes

The six outcomes were defined according to the international classification of diseases and were prespecified in the collaboration's protocol.[20] Outcomes were stroke (non-fatal stroke or death from cerebrovascular disease), coronary heart disease (non-fatal myocardial infarction or death from coronary heart disease including sudden death), heart failure (causing death or requiring admission to hospital), cardiovascular death, and total mortality. The main outcome was major cardiovascular events comprising stroke, coronary heart disease, heart failure, and cardiovascular death. Only the first event of the relevant outcome type was included in each analysis.

Treatment comparisons

The treatment comparisons tested were prespecified in the original protocol.[20] In the broad group of trials comparing an active treatment and a control, we carried out separate overviews for angiotensin converting enzyme (ACE) inhibitor based regimens versus placebo; calcium antagonist based regimens versus placebo; and more intensive versus less intensive blood pressure lowering regimens. In the broad group of trials comparing different active agents, we carried out separate overviews for ACE inhibitor based regimens versus conventional treatment (diuretics or β blocker based regimens); calcium antagonist based regimens versus conventional treatment; and ACE inhibitor based regimens versus calcium antagonist based regimens.

Data synthesis and analysis

Blood pressure reductions

The reduction in blood pressure in each trial arm was calculated as the mean of the difference between each participant's mean blood pressure during follow-up and their blood pressure at baseline. The mean difference in blood pressure between randomised groups was then calculated by subtracting the values for the two arms according to chronic kidney disease status.

Meta-analyses of subgroups according to kidney function.

To investigate the effects of active treatment compared with placebo, more intensive compared with less intensive regimens, or different drug classes on the outcomes in patients with different baseline eGFR, we performed meta-analyses according to kidney function. All the meta-analyses used a two stage approach whereby the risk estimates were first summarised in each trial and then combined.

For each trial and each outcome, we estimated the risk estimates separately for each subgroup, according to the intention to treat principle. We computed hazard ratios or odds ratios using a Cox proportional hazard regression model (20 trials providing time to event data[21 24-42 44]) or a logistic regression model (three trials in which time to event data were not available[22 23 43]) in the 23 trials for which individual patient data were available. Among the three remaining trials for which data were obtained from the investigators or published reports, we estimated the hazard ratios and variances with a Cox model for one trial[14] and

calculated the relative risks and its variances from first principles using tabular data for two trials.[15 45] Although hazard ratios, odds ratios, and relative risks are not the same, we have shown the risk estimates as hazard ratios because these risk estimates have similar values under the condition of low incidence rates of outcomes and most risk estimates in this study were hazard ratios. Additionally, we carried out sensitivity analyses to examine the impact of removing the five trials[15 22 23 43 45] in which the hazard ratios were unavailable for the risk estimates from all analyses. Pooled estimates of hazard ratios and 95% confidence intervals were calculated separately for each subgroup by a random effects model with the method of DerSimonian and Laird. The "metan" routine in Stata was used for pooled estimates. The heterogeneity in treatment effects between trials included for each comparison was estimated with Cochrane's Q and I^2. The consistency of treatment effects across the subgroups of chronic kidney disease status was tested with χ^2 tests of homogeneity. The potential for publication bias across included trials was evaluated with Begg's test and Egger's test for funnel plot asymmetry with the "metabias" routine (with P<0.10 taken as significant) and the impact of any asymmetry evaluated with the trim and fill analysis[47] with the "metatrim" routine in Stata.

Blood pressure weighted meta-analyses of subgroups according to kidney function.

For the meta-analysis weighted blood pressure reduction in the placebo controlled trials, we calculated pooled estimates per 5 mm Hg reduction in systolic blood pressure over time as

$$\exp[5*(\sum \Delta SBPi*Wi*logHRi)/\sum \Delta SBPi^2*Wi]$$

where $\Delta SBPi$ is the mean difference in systolic blood pressure over time between randomised treatment groups and $logHRi$ and Wi are natural log transformed hazard ratios of randomised treatment on each outcome and its inverse variance in trial i.[48 49] For the head to head comparisons, where much smaller differences in blood pressure were observed, we calculated similar blood pressure weighted estimates per 1 mm Hg difference between the randomised groups.

Continuous effects of eGFR

We tested for interactions between eGFR fitted as a continuous variable and the effects of treatment on the risk of cardiovascular outcomes to maximise statistical power to detect possible differences in the effects of the various regimens according to baseline eGFR. Interactions between blood pressure lowering treatment and eGFR taken as a continuous variable were investigated with Cox proportional hazard regression models or logistic regression models including study treatment, continuous eGFR values, and their interaction term. The regression coefficient for the latter term estimates the log ratio of hazard ratios for comparing treatments, which shows the effect of a unit increase in eGFR on the treatment effect. Twenty three trials contributing individual participant data were included in these analyses. The log ratios of hazard ratio were pooled with a random effects model. The pooled summary was exponentiated to arrive at the overall estimated ratio of hazard ratio for a 10 mL/min/1.73 m² decrement in eGFR for each outcome.

Meta-regression analysis according to kidney function

Meta-regression analyses were conducted to explore the association between the difference in systolic blood pressure at follow-up between randomised groups and the risk estimate for

cardiovascular events in different subgroups, where the response variable was the natural log transformed hazard ratio and the explanatory variable was the effect of treatment on blood pressure. This was investigated across trials by using random effects meta-regression models with inverse variance weighting. Analyses were carried out with the "metareg" routine in Stata. We fitted separate regression lines for each subgroup and compared the slopes of these lines to test for a differential effect of systolic blood pressure reduction on risk reduction between subgroups for each outcome by adding an interaction term between subgroup and systolic blood pressure reduction during follow-up to the model.

As trial participants could contribute only once to a given meta-analysis with regard to the comparison of active treatment versus placebo and a given meta-regression analysis, trials with randomisation to three treatment arms[21 35 38] contributed results from only two of the possible three treatment comparisons, with the control arm participants divided randomly between the two comparisons. For similar reasons, for factorial trials that included randomisation to different intensities of blood pressure lowering and randomisation to different drug treatments,[31 32 34 45] we included only the results of the randomisation to different intensities of blood pressure lowering.

All statistical analyses were conducted with SAS software for Windows, version 9.1 (SAS Institute, Cary, NC) or Stata, release 9.2 (StataCorp, College Station, TX). In every analysis a P<0.05 was taken to indicate that a result was possibly not due to chance, although each case required careful interpretation, given the large numbers of comparisons made.

Results

Characteristics of trials, patients included and follow-up blood pressure levels

Twenty five trials,[14 15 21-44] including 152 290 individuals, provided data for these analyses (tables 1, 2, and 3⇓⇓⇓). The trials involved had a low risk of bias (appendix table 1).

There were 121 995 individuals (80%) with eGFR ≥60 mL/min/1.73 m² (mean eGFR 81 (SD 17) mL/min/1.73 m²) and 30 295 individuals (20%) with eGFR <60 mL/min/1.73 m² (mean 52 (SD 7) mL/min/1.73 m²) at baseline (table 4⇓). Only 439 individuals (0.3%) had eGFR <30 mL/min/1.73 m² at baseline. Individuals with reduced eGFR tended to be older (68 *v* 63) and were more likely to be women (60% *v* 40%) (table 4). Data on urinary protein excretion were available for 37 161 individuals, mostly from trials that compared ACE inhibitor based regimens with placebo. Proteinuria was present in 2500 (7%) of these individuals, and patients with proteinuria were more likely to be men (66% *v* 55%) and tended to have a higher serum creatinine concentration at baseline (91 μmol/L *v* 86 μmol/L). The baseline characteristics of each trial included were well balanced between the randomised treatment allocations (appendix table 2). There was some evidence of publication bias (Egger's test P=0.05) across the studies (appendix fig 4). A trim and fill analysis,[47] however, did not change the pooled estimate.

Effects of active treatment compared with placebo in patients with different baseline eGFR

For major cardiovascular events, allocation to an ACE inhibitor based regimen reduced the risk of a major cardiovascular event by about a sixth (hazard ratio 0.81, 95% confidence interval 0.73 to 0.90). This reduction seemed similar irrespective of

baseline eGFR (0.81 (0.72 to 0.91) for eGFR of ≥60 mL/min/1.73m^2 *v* 0.81 (0.73 to 0.89) for eGFR of <60 mL/min/1.73m^2; P=0.99 for homogeneity; fig 1⇓). There was significant heterogeneity in treatment effect between trials for the subgroup with eGFR >60 mL/min/1.73 m^2 (Q=19.4, df=8, P=0.01, I^2=59%) but not in the subgroup with reduced GFR (see appendix fig 2). Sensitivity analyses that excluded the three trials[15 22 23] in which the hazard ratios were unavailable for the risk estimates did not make any material difference to the findings (hazard ratio 0.80 (0.68 to 0.92) for eGFR ≥60 and 0.76 (0.68 to 0.85) for eGFR<60).

Calcium antagonist based regimens likewise reduced the risk of major cardiovascular events by about a third, once again with similar effects among individuals with and without reduced eGFR (fig 1⇓). Similar findings were observed for secondary outcomes (appendix table 3).

Blood pressure weighted meta-analysis of effect of active treatment in patients with different baseline eGFR

To account for different magnitudes of reduction in blood pressure with different drug classes, we also performed a meta-analysis weighted for blood pressure reduction (fig 2⇓). A 5 mm Hg reduction in systolic blood pressure had almost identical effects on major cardiovascular events at different eGFR, with no difference between ACE inhibitor and calcium channel blocker based regimens compared with placebo (fig 2⇓). As the results for each class of drugs were similar, we undertook a pooled analysis, which showed that these regimens reduced the risk of major cardiovascular events by 17% per 5 mm Hg reduction in systolic blood pressure in both those below and above eGFR of 60 mL/min/1.73m^2 (hazard ratio 0.83 (95% confidence interval 0.76 to 0.90) and 0.83 (0.79 to 0.88), respectively). The proportional reductions in major cardiovascular events were also similar when participants were divided into three eGFR categories (≥60, 45-59, and <45 mL/min/1.73 m^2).

Net absolute effects of treatment in patients with different baseline eGFR

We investigated the absolute effects of active treatment in patients with eGFR above and below 60 mL/min/1.73m^2 on the basis of the incidence rates for major cardiovascular events in the placebo groups and the blood pressure weighted hazard ratios of active treatment. Overall, 21 major cardiovascular events were prevented for every 1000 participants treated (ACE inhibitor or calcium channel blocker based regimens) compared with placebo (number needed to treat (NNT) for preventing one event over an average of four years was 47). Although the magnitude of the relative effects of active treatment were similar across eGFR, the absolute benefit for major cardiovascular events was 50% higher at lower eGFR, with 28 events prevented for every 1000 patients with eGFR below 60 mL/min/1.73m^2 (NNT=35) compared with 19 for patients with eGFR above 60 mL/min/1.73m^2 (NNT=53).

Effects of more intensive compared with less intensive blood pressure lowering regimens in patients with different baseline eGFR

As shown in figure 3⇓, for the trials targeting different blood pressure goals there were wide confidence intervals but no evidence of heterogeneity of treatment effects on major cardiovascular events according to baseline eGFR (hazard ratio 0.87 (95% confidence interval 0.73 to 1.03) for eGFR of ≥60

mL/min/1.73m^2 *v* 1.24 (0.62 to 2.48) for eGFR of <60 mL/min/1.73m^2; P=0.33 for homogeneity). The effects of more intensive compared with less intensive regimens for secondary outcomes are shown in appendix table 4. A sensitivity analysis that included one further trial[45] that comprised only patients with reduced eGFR made little difference to the findings (1.10 (0.76 to 1.60) in patients with eGFR <60 mL/min/1.73m^2; P=0.24 for heterogeneity).

Effects of different drug classes in patients with different baseline eGFR

In the trials comparing blood pressure lowering regimens based on different drug classes, there were no clear differential effects on major cardiovascular events (fig 4⇓) between groups with different eGFR for any comparison (all P>0.6 for homogeneity). The results of the comparisons between calcium antagonist based regimens and conventional treatment after exclusion of one trial[43] in which the hazard ratios were unavailable for the risk estimates (hazard ratio 1.04 (95% confidence interval 0.98 to 1.11) for eGFR ≥60 and 1.05 (0.95 to 1.16) eGFR <60) and the results of the comparisons among different drug classes in participants with eGFR <60 after inclusion of one trial[45] that contributed patients only to the reduced eGFR stratum (1.00 (0.91 to 1.10) for ACE inhibitor *v* conventional; 1.03 (0.93 to 1.14) for calcium antagonist *v* conventional; 0.96 (0.86 to 1.08) for ACE inhibitor *v* calcium antagonist) remained substantially unchanged. The findings were also similar in the blood pressure weighted comparisons (appendix fig 3). For the secondary outcomes, there was heterogeneity in the effect of ACE inhibitor based regimens against heart failure compared with calcium antagonist based regimen by eGFR, with evidence of greater benefit for ACE inhibitors among participants with eGFR >60 (appendix table 5).

Interactions between blood pressure lowering treatment and continuous eGFR.

We found no evidence of a significant interaction between baseline eGFR and treatment effect for major cardiovascular events (all P>0.18, fig 5⇓). For the secondary outcomes, we observed just two significant interactions between eGFR and treatment among 30 comparisons, suggesting they might have arisen by chance (appendix fig 4).

Association between trial differences in blood pressure and proportional risk reductions

The association between blood pressure lowering achieved and the proportional reduction in risk of cardiovascular events achieved was similar in participants with reduced compared with normal eGFR when assessed with meta-regression. A 5 mm Hg reduction in systolic blood pressure during follow-up was associated with a relative risk reduction of 14.2% (95% confidence interval 8.6% to 19.5%) in participants with normal eGFR and 12.1% (2.9% to 20.4%) for participants with reduced eGFR for the primary outcome of major cardiovascular events (P=0.69 for homogeneity) (fig 6⇓).

Effects of active treatment compared with placebo in patients with and without proteinuria at baseline

There was no evidence of heterogeneity (P=0.84 for homogeneity) in the effect of ACE inhibitor based regimens on major cardiovascular events between individuals with (hazard ratio 0.94, 95% confidence interval 0.84 to 1.05) and without proteinuria (0.90, 0.63 to 1.29) per 5 mm Hg reduction in

systolic blood pressure, although only limited data were available (fig 7⇓). There were not enough trials with data on proteinuria to allow reliable assessment of the comparative effects of calcium antagonists, different blood pressure targets, and different drug classes in patients with and without proteinuria.

Discussion

Principal findings

These analyses, based on a large volume of data with several trials that included people who did not have hypertension, provide compelling evidence for the cardiovascular benefits of reduction in blood pressure in people with stage 1-3 chronic kidney disease. While the proportional reductions in the risk of major cardiovascular events were similar in people with and without evidence of chronic kidney disease, individuals with chronic kidney disease stood to gain much larger absolute benefits because their baseline risk was much higher. The high prevalence of chronic kidney disease in the community (10-15%) means that strategies to increase the use of blood pressure lowering treatments among this group are likely to be highly effective at reducing the burden of cardiovascular mortality and morbidity.[5][6][14][16]

Effect of different drug classes on cardiovascular events in people with chronic kidney disease

The data provided no clear evidence that any particular drug class provided greater or lesser cardiovascular protection for patients with compared with those without chronic kidney disease. This was true both for subgroup analyses done by dichotomising patients according to usual eGFR cutpoints and for the more powerful analyses done with eGFR fitted as a continuous variable. Intriguingly, the cardiovascular benefits of ACE-I and calcium channel blockers compared with placebo were virtually identical once we accounted for the small differences in blood pressure lowering achieved in analyses weighted for blood pressure reduction, although different types of calcium channel blockers were used in these analysis, including dihydropyridines (such as amlodipine and nisoldipine) and phenylalkylamines (such as verapamil). Similar findings were observed in the meta-regression analyses and in head to head comparisons that also included diuretics or β blockers. These results suggest that the cardiovascular benefits of lowering blood pressure in people with chronic kidney disease are more dependent on the blood pressure lowering effect achieved than on the agent selected. This is an observation broadly consistent with the previously reported findings across the trial populations,[9] although small benefits independent of blood pressure reduction have been reported for ACE inhibitors and coronary heart disease.[50] Additionally, a recent randomised control trial in patients with hypertension showed that treatment with benazepril plus amlodipine was superior to that with benazepril plus hydrochlorothiazide in preventing cardiovascular events, despite no clear difference in the achieved blood pressure during follow-up.[51] Several studies have also suggested that drugs acting via the renin-angiotensin system provide greater protection against renal outcomes, but we did not assess these outcomes.[13] It is therefore possible there might be additional benefits (or harms) independent of blood pressure associated with individual classes of drugs, but this analysis highlights the key role of blood pressure lowering as a driver of reduction in cardiovascular risk. Future analyses including data from completed and ongoing trials should clarify whether greater

effects on renal outcomes achieved by these drug classes in patients with proteinuria will translate into greater protection against major vascular events

Effects of intensive blood pressure lowering on cardiovascular events in chronic kidney disease

There was no clear benefit for more intensive compared with less intensive blood pressure lowering regimens in people with chronic kidney disease, although there was only limited power for these analyses and little capacity to detect whether the effects of treatment varied according to kidney function; lower blood pressure targets have, nonetheless, been suggested to improve renal outcomes in people with proteinuric chronic kidney disease,[52][53] providing some support for the earlier recommendation that blood pressure be lowered more intensively in these high risk patients. The effects of more intensive blood pressure lowering on cardiovascular outcomes in people with kidney disease remains to be demonstrated by future trials, such as the ongoing Systolic Blood Pressure Intervention Trial (SPRINT, NCT01206062).

Strengths and weaknesses

These analyses, based on more than 150 000 trial participants and 15 000 major cardiovascular events, are uniquely powerful and provide precise estimates of the effects on major cardiovascular events of the most widely used regimens to lower blood pressure in patients with and without chronic kidney disease. There are, however, several important limitations. Firstly, most participants with chronic kidney disease in this study were in stage 3a (mostly in the range of 45-60 mL/min/m^2), and few participants (0.4%) had eGFR ≤30 mL/min/1.73 m^2. As a result, the applicability of these results to populations with stage 4-5 disease is uncertain, although they are broadly consistent with a meta-analysis of blood pressure lowering in patients with severe kidney disease who were receiving dialysis.[54] Likewise, few participants had documented proteinuria and only limited numbers of events were available in this population group. Secondly, the analyses depend on the trial data that were available at the start of this study and we could not investigate some questions of interest. These include the effects on cardiovascular outcomes of regimens based on angiotensin receptor blockers and the separate evaluation of regimens based on β blockers or diuretics alone. When possible, we contacted investigators directly to request missing data or extracted data from published reports to complement available data. Therefore, while we acknowledge this is not a complete dataset, we believe selection bias in this study is minimised by the strict pre-specification of trial eligibility criteria including those related to trial size, quality, randomisation process, outcome definition, treatment comparison, and analysis as specified the published study protocol.[20] Furthermore, and in line with recommendations for reporting individual patient data meta-analyses where there are missing data,[55] we formally assessed publication bias in this study. We found some evidence of publication bias, which is likely to overestimate the pooled treatment effects, although a trim and fill analysis did not change the pooled estimate. Thirdly, we collected data based on the MDRD-GFR equation from the collaborators as the CKD-EPI equation had not yet been reported when the collaboration was first established. Indeed, it has been suggested that the CKD-EPI equation might be superior to the MDRD-GFR equation for estimating GFR in people with eGFR of ≥60 mL/min/1.73 m^2, but both equations have similar accuracy in people with eGFR of <60 mL/min/1.73 m^2.[56] As we divided into only two

categories, below and above 60 mL/min/1.73 m^2, rather than the detailed categories of eGFR, we believe this issue would be unlikely to have an important impact on the findings. Finally, uncertainty in estimation of the reduction in blood pressure in each trial will reduce the accuracy of estimation of the treatment effect of blood pressure lowering on cardiovascular risk.

Conclusions

These overviews provide clear evidence that a broad range of different blood pressure lowering regimens provide protection against cardiovascular complications in patients with and without chronic kidney disease. Specifically, blood pressure lowering per se, not the effects of a particular drug class (such as renin-angiotensin system blockade), seems to be significantly associated with lower cardiovascular risk in early stage chronic kidney disease, possibly suggesting the importance of blood pressure lowering as a driver of cardiovascular risk reduction. These findings should help to guide decision making for many physicians and their patients, given the absence of clear evidence to date supporting recommendations (for particular drug classes) to reduce the cardiovascular risk among people with early stage chronic kidney disease. As people with chronic kidney disease are at greatly increased cardiovascular risk, the benefits of blood pressure lowering in this population are large. The broader use of blood pressure lowering drugs, along with other proved treatments such as lipid lowering,[57] will both improve outcomes for affected individuals and help to reduce the escalating global burden of cardiovascular disease.

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What is already known on this topic

Blood pressure is commonly raised in people with chronic kidney disease

Guidelines recommend lower blood pressure targets in these people, though there is limited evidence that blood pressure lowering is beneficial for people with chronic kidney disease

The comparative efficacy of different classes of drug to lower blood pressure on the risk of cardiovascular events in people with chronic kidney disease also remains uncertain

What this study adds

The proportional reductions of cardiovascular complications in risk with lowered blood pressure are similar in people with and without chronic kidney disease, but people with kidney disease gain much larger absolute benefits because their baseline risk is higher

There is little evidence to support the preferential choice of particular drug classes for the prevention of cardiovascular events in people with chronic kidney disease

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Tables

Table 1| Characteristics of included double blind trials comparing active treatment for blood pressure control and placebo in patients with chronic kidney disease

Trial	Treatment comparison	No*	Entry criteria	Kidney function exclusion criteria	Follow-up (years)	Mean (SD) eGFR (mL/min/1.73m²)	No (%) with eGFR <60	No (%) with proteinuria
ACE inhibitor *v* placebo								
BENEDICT[21]	Trandolapril *v* placebo	604	HBP+DM	sCr >133 µmol/L	3.6	81 (15)	37 (6)	0 (0)†
DIAB-HYCAR[22]	Ramipril *v* placebo	4912	DM+nephropathy	sCr >150 µmol/L	3.9	77 (21)	999 (20)	1286 (26)‡
EUROPA[23]	Perindopril *v* placebo	12 218	CHD	sCr >150 µmol/L	4.2	75 (18)	1999 (17)	NA
HOPE[14]	Ramipril *v* placebo	9297	CHD, CVD, or DM + RF	None	4.5	NA	3394 (37)§	NA
PART2[24]	Ramipril *v* placebo	617	CHD or CVD	None	4.7	73 (16)	119 (19)	31 (5)¶
PROGRESS[25]	Perindopril (+/–indapamide) *v* placebo(s)	6105	Cerebrovascular disease	None	3.9	78 (24)	1172 (19)	NA
SCAT[26]	Enalapril *v* placebo	460	CHD	None	4	68 (13)	115 (26)	NA
PREVEND-IT[27]	Fosinopril *v* placebo	864	Microalbuminuria	Creatinine clearance <60% of normal age adjusted value	3.8	76 (12)	70 (8)	7 (0.8)†
ADVANCE[28]	Perindopril (+indapamide) *v* placebos	11 140	DM	None	4.3	78 (25)	2139 (19)	406 (4)**
PEACE[15]	Trandolapril *v* placebo	8290	CHD	sCr >177 µmol/L	4.8	78 (19)	1355 (16)	NA
Calcium antagonist *v* placebo								
BENEDICT[21]	Verapamil *v* placebo	605	HBP+DM +nephropathy	sCr >133 µmol/L	3.6	81 (15)	43 (7)	0 (0)†
PREVENT[29]	Amlodipine *v* placebo	825	CHD	None	3	67 (13)	249 (30)	72 (9)
SYST-EUR[30]	Nitrendipine *v* placebo	4695	HBP ≥60 years	sCr >180 µmol/L	2.6	69 (18)	1,563 (33)	109 (2)¶

ACE=angiotensin converting enzyme; CHD=coronary heart disease; CVD=cardiovascular disease; DM=diabetes mellitus; HBP=high blood pressure; sCr=serum creatinine.

*No of all randomised participants.

†Proteinuria defined as urinary albumin excretion ≥200 µg/min or ≥300 mg/day.

‡Proteinuria defined as urinary albumin concentration ≥200 mg/L.

§Mean eGFR and % of eGFR < 65 mL/min, estimated by Cockcroft-Gault formula (HOPE).

¶Proteinuria defined as dipstick test 1+ or more.

**Proteinuria defined as urinary albumin creatinine ratio ≥300 µg/mg.

Table 2| Characteristics of included trials comparing more intensive and less intensive regimens to treat raised blood pressure in patients with chronic kidney disease

Trial	Treatment comparison	No*	Trial design	Entry criteria	Kidney function exclusion criteria	Follow-up (years)	Mean (SD) eGFR (mL/min/1.73m^2)	No (%) with eGFR <60	No (%) with proteinuria
ABCD (H)[31]	DBP ≤75 mm Hg *v* ≤90 mm Hg	470	Open	HBP+DM	sCr >265 µmol/L	5.3	70 (16)	120 (26)	89 (19)†
ABCD (N)[32]	DBP 10 mm Hg below baseline *v* 80-89 mm Hg	480	Open	DM	sCr >265 µmol/L	5.3	70 (17)	137 (29)	51 (11)†
HOT[33]	DBP ≤80 mm Hg *v* ≤85 or ≤90 mm Hg	18 790	Open‡	HBP	None	3.8	75 (19)	3619 (19)	NA
UKPDS-HDS[34]	DBP < 85 mm Hg *v* <105 mm Hg	1148	Open	HBP+DM	sCr >175 µmol/L	8.4	82 (19)	103 (9)	NA
AASK[45]	MAP ≤92 mm Hg *v* 102-107 mm Hg	1094	Open	HBP+nephropathy, Afr	GFR<20 mL/min/1.73m^2	4.1	46 (13)§	1094 (100)§	NA

Afr=African American; CVD=cardiovascular disease; DB=double blind; DBP=diastolic blood pressure; DM=diabetes mellitus; HBP=high blood pressure; MAP=mean arterial pressure; sCr=serum creatinine.

*No of all randomised participants.

†Proteinuria defined as urinary albumin excretion >200 µg/min or >300 mg/day.

‡PROBE (Prospective, Randomized, Open with Blinded Endpoint evaluation) design trials.

§Mean eGFR and % of eGFR <65 mL/min, estimated by 125-iothalamate clearance (AASK).

Table 3| Characteristics of included trials comparing regimens based on different drugs to treat raised blood pressure in patients with chronic kidney disease

Trial	Treatment comparison	No*	Trial design	Entry criteria	Kidney function exclusion criteria	Follow-up (years)	Mean (SD) eGFR (mL/min/1.73m^2)	No (%) with eGFR <60	No (%) with proteinuria
ACE inhibitor *v* diuretic or β blocker									
ALLHAT[35]	Lisinopril *v* chlorthalidone	24 309	DB	HBP+RF	sCr >177 μmol/L	4.9	78 (20)	4163 (18)	NA
ANBP2[36]	Enalapril *v* hydrochlorothiazide	6083	Open†	HBP, age 65-84	sCr >221 μmol/L	4.1	68 (15)	1860 (31)	NA
CAPPP[37]	Captopril *v* β blocker or diuretic	10 985	Open†	HBP	sCr >150 μmol/L	6.1	78 (15)	1069 (10)	438 (4)‡
STOP-2[38]	Enalapril or lisinopril *v* atenolol or metoprolol or pindolol or hydrochlorothiazide + amiloride	4418	Open†	HBP, age 70-84	None	5	66 (15)	1526 (35)	NA
UKPDS-HDS[39]	Captopril *v* atenolol	758	DB	HBP+DM	sCr >175 μmol/L	8.4	83 (19)	68 (9)	NA
AASK§[45]	Ramipril *v* metoprolol	877	DB	HBP+nephropathy, Afr	GFR <20 mL/min/1.73m^2	4.1	46 (13)¶	877 (100)¶	NA
Calcium antagonist *v* diuretic or β blocker									
ALLHT[35]	Amlodipine *v* chlorthalidone	24 303	DB	HBP+ RF	sCr >177 μmol/L	4.9	78 (20)	4149 (18)	NA
ELSA[40]	Lacidipine *v* atenolol	2334	DB	HBP	None	4	80 (18)	215 (9)	11 (0.5)††
NICS-EH[41]	Nicardipine *v* trichlormethiazide	429	DB	HBP, age ≥60	None	5	90 (27)	42 (10)	NA
NORDIL[42]	Diltiazem *v* β blocker or diuretic	10 881	Open†	HBP	None	5	74 (15)	1664 (15)	NA
STOP-2[38]	Felodipine or isradipine *v* atenolol or metoprolol or pindolol or hydrochlorothiazide + amiloride	4409	Open†	HBP, age 70-84	None	5	66 (15)	1467 (33)	NA
VHAS[43]	Verapamil *v* chlorthalidone	1414	DB/Open	HBP	sCr >150 μmol/L	2	82 (24)	134 (10)	NA
AASK§[45]	amlodipine *v* metoprolol	658	DB	HBP+nephropathy, Afr	GFR <20 mL/min/1.73m^2	4.1	46 (13)¶	658 (100)¶	NA
ACE inhibitor *v* calcium antagonist									
ABCD (H)[31]	Enalapril *v* nisoldipine	470	DB	HBP+DM	sCr >265 μmol/L	5.3	70 (16)	120 (26)	89 (19)**
ABCD (N)[32]	Enalapril *v* nisoldipine	480	DB	DM	sCr >265 μmol/L	5.3	70 (17)	137 (29)	51 (11)**
ALLHAT[35]	Lisinopril *v* amlodipine	18 102	DB	HBP+CVD RF	sCr >177 μmol/L	4.9	78 (20)	3056 (18)	NA
BENEDICT[21]	Trandolapril *v* verapamil	605	DB	HBP+DM	sCr >133 μmol/L	3.6	81 (15)	36 (6)	0 (0)**
JMIC-B[44]	ACE inhibitor *v* nifedipine	1650	Open†	HBP+CHD	sCr >177 μmol/L	3	89 (27)	166 (12)	NA
STOP-2[38]	Enalapril or lisinopril *v* felodipine or isradipine	4401	Open†	HBP, age 70-84	None	5	66 (15)	1507 (34)	NA
AASK§[45]	Ramipril *v* amlodipine	653	DB	HBP+nephropathy, Afr	GFR <20 mL/min/1.73m^2	4.1	46 (13)¶	653 (100)¶	NA

ACE=angiotensin converting enzyme; Afr=African American; CHD=coronary heart disease; CVD=cardiovascular disease; DB=double blind; DM=diabetes mellitus; HBP=high blood pressure; sCr=serum creatinine.

*No of all randomised participants.

†PROBE (Prospective, Randomized, Open with Blinded Endpoint evaluation) design trials.

‡Proteinuria defined as dipstick test 1+ or more.

§AASK trial included for sensitivity analysis, because patients contributed only to reduced eGFR stratum.

¶Mean eGFR and % of eGFR <65 mL/min, estimated by 125-iothalamate clearance (AASK).

**Proteinuria defined as urinary albumin excretion ≥200 μg/min or ≥300 mg/day.

††Proteinuria was defined as urinary albumin excretion more than 500 mg/L.

Table 4| Mean baseline characteristics and follow-up differences in blood pressure between randomised groups according to different baseline glomerular filtration rate (eGFR)

Treatment comparison	No (%)*	Age (years)	Men (%)	Baseline Cr (mmol/L)	Baseline eGFR (mL/min/1.73m²)	Systolic/diastolic(mm Hg) Baseline	Systolic/diastolic(mm Hg) During follow-up
All trials†							
eGFR ≥60	121 995 (80)	63	60	83	81	156/91	141/81
eGFR <60	30 295 (20)	68	40	115	52	160/90	144/80
Active treatment v placebo†							
ACEI v placebo:							
eGFR ≥60	42 896 (79)	62	75	84	82	141/82	135/78
eGFR <60	11 399 (21)	67	55	117	52	145/82	137/77
Calcium antagonist v placebo:							
eGFR ≥60	4252 (70)	66	49	82	77	164/85	151/81
eGFR <60	1855 (30)	70	24	106	52	169/84	154/80
More intensive v less intensive regimens							
eGFR ≥60	16 687 (81)	60	58	83	81	168/104	142/83
eGFR <60	3979 (19)	65	35	114	52	170/104	143/83
Comparisons of drugs classes							
ACEI v diuretic or β blocker:							
eGFR ≥60	36 540 (81)	63	54	83	81	156/90	143/83
eGFR <60	8686 (19)	71	38	116	51	162/89	146/81
Calcium antagonist v diuretic or β blocker:							
eGFR ≥60	34 838 (82)	64	53	82	81	159/93	144/83
eGFR <60	7671 (18)	70	37	116	52	163/91	147/82
ACEI v calcium antagonist:							
eGFR ≥60	19 520 (80)	67	54	82	83	153/87	141/80
eGFR <60	5022 (20)	72	41	119	51	161/88	147/80

ACEI=angiotensin converting enzyme inhibitor.

*No of participants with available data on GFR.

†Data for age, sex, baseline SBP, baseline serum creatinine, and baseline eGFR unavailable, and same degree of blood pressure reductions during follow-up in each kidney function group were assumed in HOPE and PEACE.
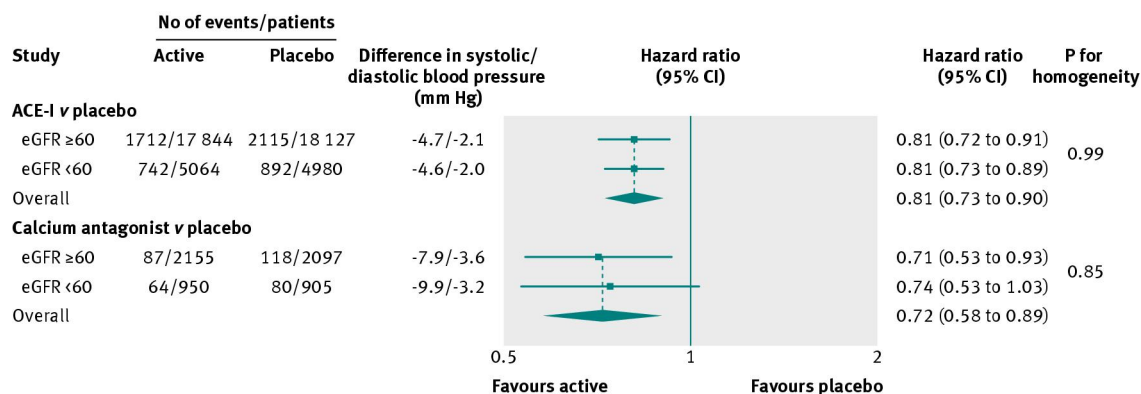
Figures

Fig 1 Effects of angiotensin converting enzyme inhibitor or calcium antagonist based regimens *v* placebo for risk of major cardiovascular events according to kidney function status. P value for homogeneity indicates consistency of effect of treatment regimen among subgroup. Overall mean difference in systolic and diastolic blood pressure during follow-up in actively treated/first listed regimens *v* control/second listed regimens, calculated by weighting difference observed in each contributing trial by number of patients in trial. Negative values indicate lower mean systolic and diastolic blood pressure during follow-up in actively treated/first listed groups than in control/second listed groups
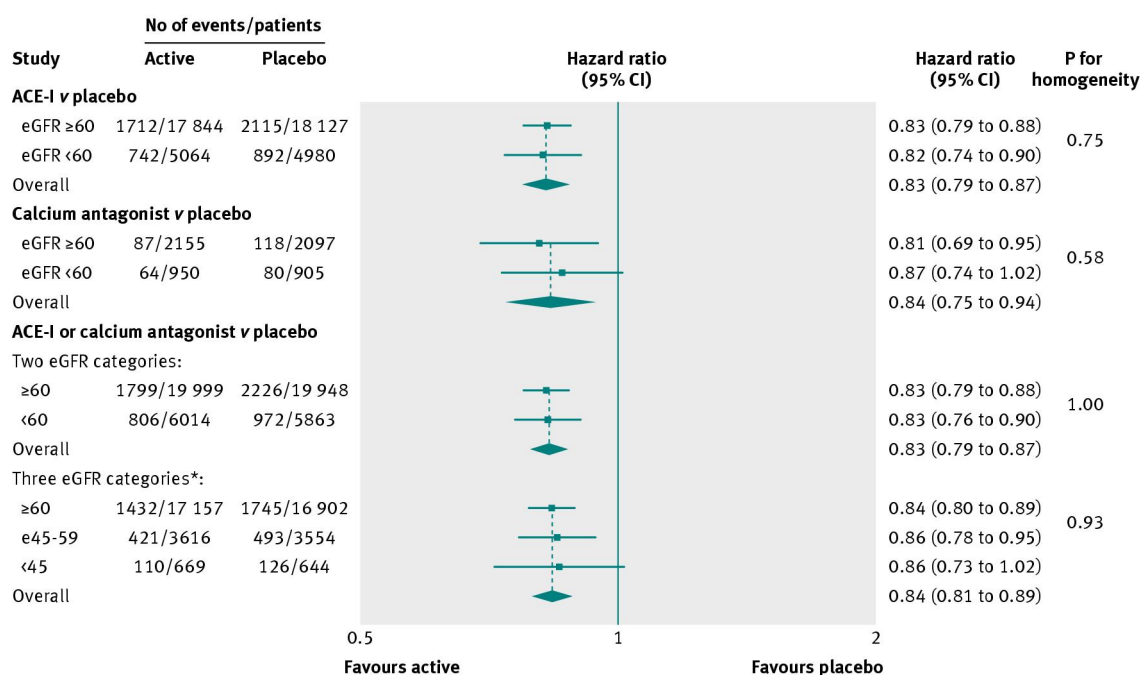
Fig 2 Effects of angiotensin converting enzyme inhibitor or calcium antagonist based regimens *v* placebo per 5 mm Hg reduction in systolic blood pressure over time on risk of major cardiovascular events according to kidney function status. Pooled estimates estimated with relative risk model weighted for blood pressure reduction. Values show relative risk per 5 mm Hg reduction in systolic blood pressure over time. *Data from HOPE trial not available for analysis of three GFR categories

	No of events/patients		Difference in systolic/ diastolic blood pressure (mm Hg)	Hazard ratio (95% CI)	Hazard ratio (95% CI)	P for homogeneity
Study	More	Less				
eGFR ≥60	200/5329	399/10 341	-3.0/-3.2		0.87 (0.73 to 1.03)	0.33
eGFR ‹60	91/1339	147/2537	-3.2/-3.2		1.24 (0.62 to 2.48)	
Overall					0.93 (0.80 to 1.07)	

0.5 — 1 — 2

Favours more   Favours less

Fig 3 Effects of more intensive v less intensive blood pressure lowering regimens for risk of major cardiovascular events according to kidney function status

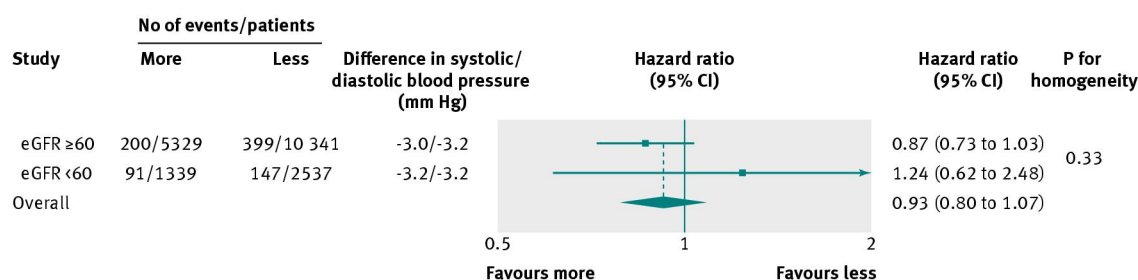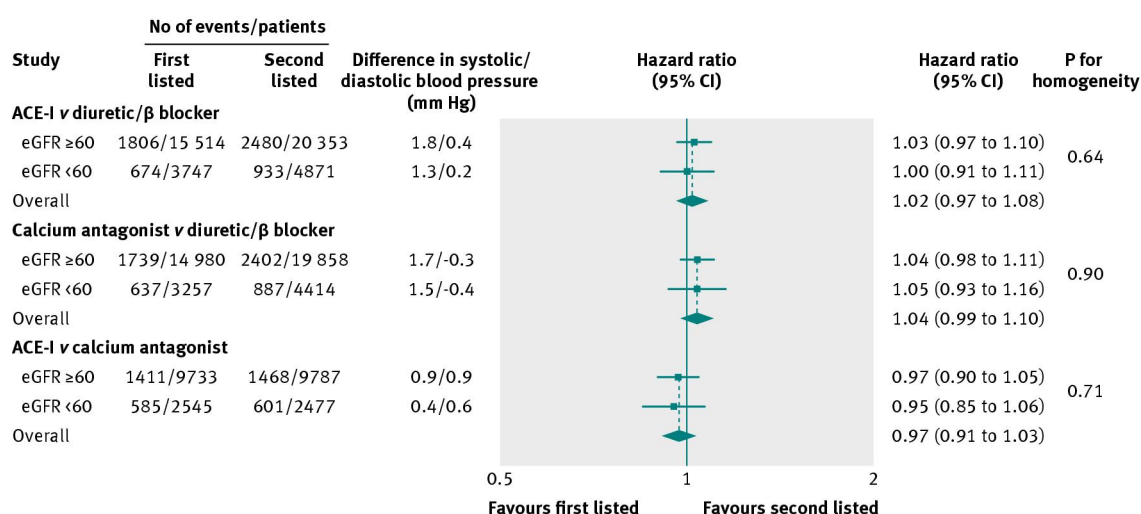|	No of events/patients		Difference in systolic/ diastolic blood pressure (mm Hg)	Hazard ratio (95% CI)	Hazard ratio (95% CI)	P for homogeneity
Study	First listed	Second listed				
ACE-I v diuretic/β blocker						
eGFR ≥60	1806/15 514	2480/20 353	1.8/0.4		1.03 (0.97 to 1.10)	0.64
eGFR ‹60	674/3747	933/4871	1.3/0.2		1.00 (0.91 to 1.11)	
Overall					1.02 (0.97 to 1.08)	
Calcium antagonist v diuretic/β blocker						
eGFR ≥60	1739/14 980	2402/19 858	1.7/-0.3		1.04 (0.98 to 1.11)	0.90
eGFR ‹60	637/3257	887/4414	1.5/-0.4		1.05 (0.93 to 1.16)	
Overall					1.04 (0.99 to 1.10)	
ACE-I v calcium antagonist						
eGFR ≥60	1411/9733	1468/9787	0.9/0.9		0.97 (0.90 to 1.05)	0.71
eGFR ‹60	585/2545	601/2477	0.4/0.6		0.95 (0.85 to 1.06)	
Overall					0.97 (0.91 to 1.03)	

0.5 — 1 — 2

Favours first listed   Favours second listed

Fig 4 Effects of blood pressure lowering regimens based on different drug classes for risk of major cardiovascular events according to kidney function status
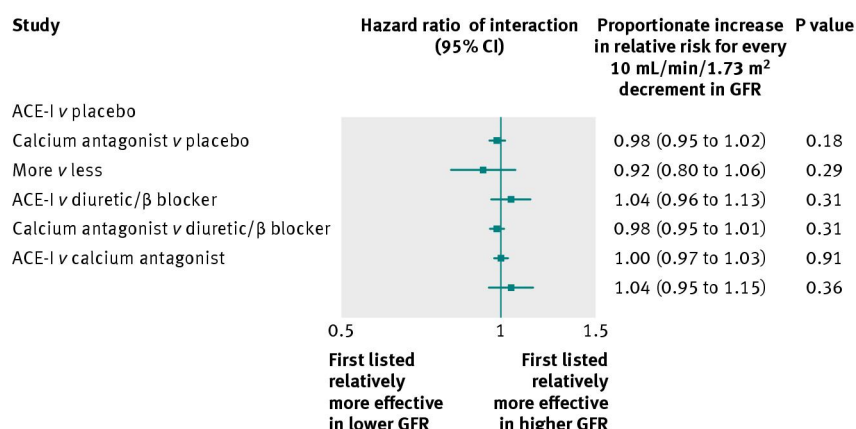
Study	Hazard ratio of interaction (95% CI)	Proportionate increase in relative risk for every 10 mL/min/1.73 m^2 decrement in GFR	P value
ACE-I v placebo		0.98 (0.95 to 1.02)	0.18
Calcium antagonist v placebo		0.92 (0.80 to 1.06)	0.29
More v less		1.04 (0.96 to 1.13)	0.31
ACE-I v diuretic/β blocker		0.98 (0.95 to 1.01)	0.31
Calcium antagonist v diuretic/β blocker		1.00 (0.97 to 1.03)	0.91
ACE-I v calcium antagonist		1.04 (0.95 to 1.15)	0.36

0.5 — 1 — 1.5

First listed relatively more effective in lower GFR   First listed relatively more effective in higher GFR

Fig 5 Proportional increase in risk ratio of treatment effect on major cardiovascular events for every 10 mL/min/1.73 m^2 decrement in eGFR
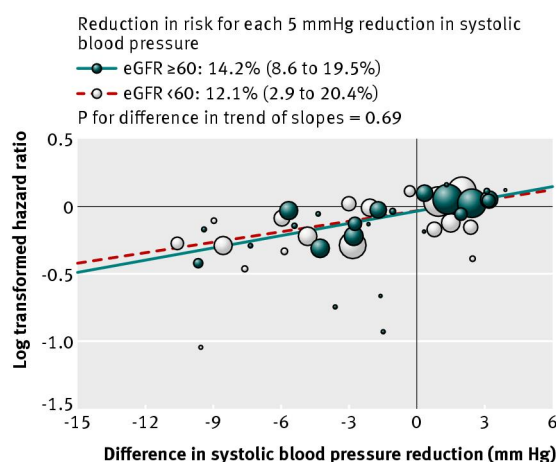
Fig 6 Associations between systolic blood pressure reduction and risk reduction for major vascular events according to kidney function status. Centre of each circle is placed at estimates of risk ratio for each trial. Area of each circle is proportional to variance of log odds ratio. Fitted lines represent summary meta-regressions for total major cardiovascular events. Intercepts were 0.96 (0.93 to 1.01) for eGFR ≥60 mL/min/1.73 m^2 and 0.97 (0.89 to 1.04) for eGFR <60 mL/min/1.73 m^2
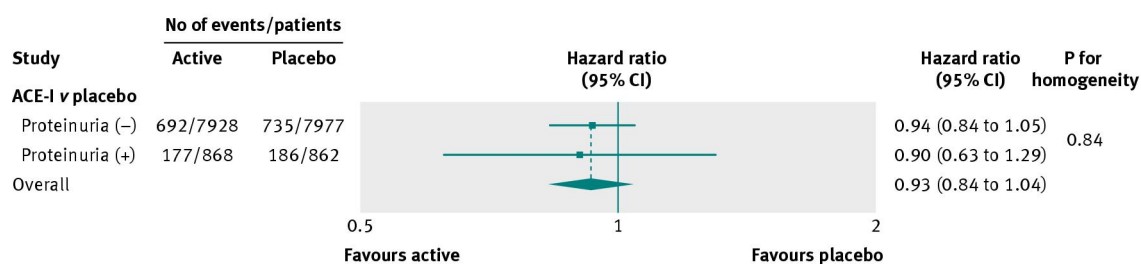

Fig 7 Effects of angiotensin converting enzyme inhibitor or calcium antagonist based regimens *v* placebo per 5 mm Hg reduction in systolic blood pressure over time on risk of major cardiovascular events according to proteinuria status