Effect of lowering blood pressure on cardiovascular events and mortality in patients on dialysis: a systematic review and meta-analysis of randomised controlled trials

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Summary

Background **Patients undergoing dialysis have a substantially increased risk of cardiovascular mortality and morbidity. Although several trials have shown the cardiovascular benefits of lowering blood pressure in the general population, there is uncertainty about the efficacy and tolerability of reducing blood pressure in patients on dialysis. We did a systematic review and meta-analysis to assess the effect of blood pressure lowering in patients on dialysis.**

Methods **We systematically searched Medline, Embase, and the Cochrane Library database for trials reported between 1950 and November, 2008, without language restriction. We extracted a standardised dataset from randomised controlled trials of blood pressure lowering in patients on dialysis that reported cardiovascular outcomes. Meta-analysis was done with a random effects model.**

Findings **We identified eight relevant trials, which provided data for 1679 patients and 495 cardiovascular events. Weighted mean systolic blood pressure was 4·5 mm Hg lower and diastolic blood pressure 2·3 mm Hg lower in actively treated patients than in controls. Blood pressure lowering treatment was associated with lower risks of cardiovascular events (RR 0·71, 95% CI 0·55–0·92; p=0·009), all-cause mortality (RR 0·80, 0·66–0·96; p=0·014), and cardiovascular mortality (RR 0·71, 0·50–0·99; p=0·044) than control regimens. The effects seem to be consistent across a range of patient groups included in the studies.**

Interpretation **Treatment with agents that lower blood pressure should routinely be considered for individuals undergoing dialysis to reduce the very high cardiovascular morbidity and mortality rate in this population.**

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Introduction

Worldwide, many hundreds of thousands of people receive dialysis on a continuing basis because of severe and irreversible chronic kidney disease. These patients are at increased risk of cardiovascular mortality and morbidity compared with the general population.[1] Every year, between 10% and 20% of all patients on dialysis die, with around 45% of these deaths attributed to cardiovascular causes.[2]

Blood pressure is usually raised in patients receiving dialysis, possibly because the role of the kidneys in blood pressure homoeostasis is impaired; chronic volume overload and a range of other factors might also contribute to high blood pressure. Several clinical trials and meta-analyses[3–7] have shown the cardiovascular benefits of lowering blood pressure in the general population and in patients with early kidney disease; therefore, reduction of blood pressure is an attractive therapeutic target for patients on dialysis. However, the efficacy and safety of lowering blood pressure in this patient population are still uncertain. Observational studies in patients on dialysis have suggested a time-dependent association between blood pressure levels and cardiovascular outcomes, with low blood pressure being associated with higher mortality rates in the short term, but lower mortality rates in the long term. These findings probably reflect a confounding of the short-term association attributable to reverse causation.[8,9] Although most of the previous trials on blood pressure lowering have systematically excluded patients on dialysis, the first trials done in this patient population reported conflicting results.[10,11] We therefore undertook a systematic review and meta-analysis to assess the effect of treatments that reduce blood pressure in patients receiving maintenance dialysis.

Methods

Search strategy and selection criteria

We did a systematic review of the available literature in accordance with the QUORUM guidelines for the conduct of meta-analyses of intervention studies.[12] Relevant studies were identified by searches of Medline via Ovid (from 1950 up to November, 2008), Embase (from 1966 up to November, 2008), and the Cochrane Library database (Cochrane Central Register of Controlled Trials; no date restriction), with relevant text words and medical subject headings that included all spellings of antihypertensive agents, "renal dialysis", "kidney failure", and "cardiovascular disease" (see webappendix p 3 for complete search strategy). The search was limited to

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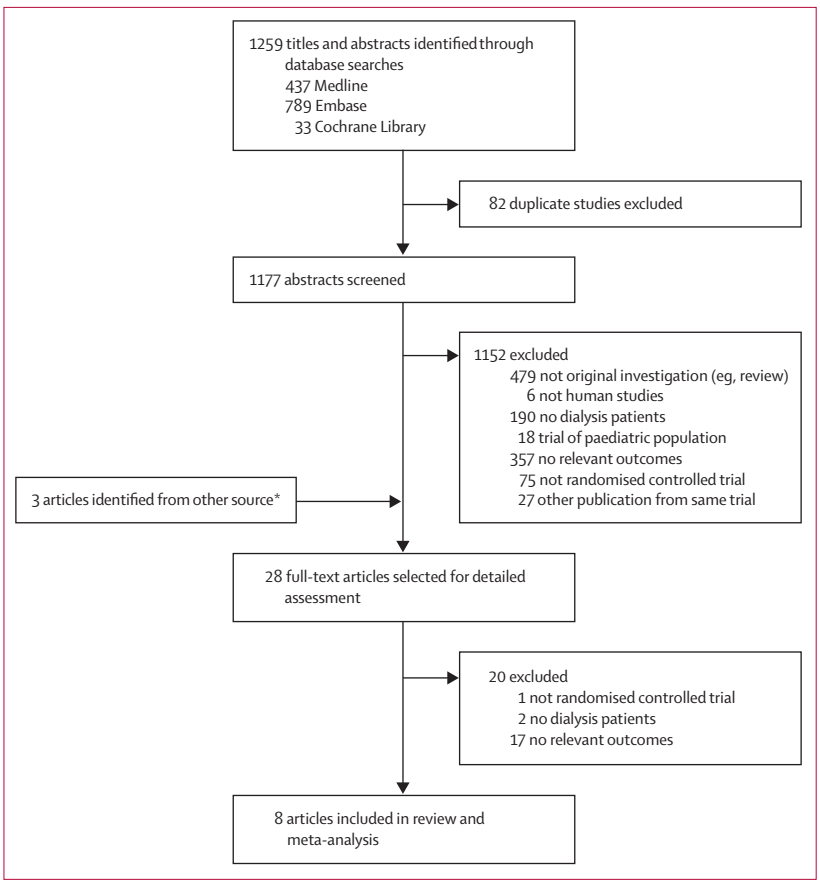

Figure 1: **Identification process for eligible studies**
*Searches on http://www.ClinicalTrials.gov.

randomised controlled trials but was without language restriction. Reference lists from identified trials and review articles were manually scanned to identify any other relevant studies. A search of the ClinicalTrials.gov website was also done to identify randomised studies that were registered as completed but not yet published. Requests for original data were made by contacting authors or principal investigators.

The literature search, data extraction, and quality assessment were done independently by two reviewers (HJLH and TN) by use of a standardised approach. All completed randomised controlled trials that assessed the effects of agents that lower blood pressure on cardiovascular outcomes in adult patients on maintenance dialysis were eligible for inclusion. Outcomes analysed were all cardiovascular events, as defined by the authors of each study, all-cause mortality, and cardiovascular mortality.

Data extraction and quality assessment

The two reviewers extracted data on patient characteristics (age, sex, systolic and diastolic blood pressure, duration on dialysis, diabetes, hypertension, and heart failure status), follow-up duration, inclusion and exclusion criteria, rates of outcome events, type and dose of blood pressure lowering agent, mean difference in systolic and diastolic blood pressure during the trial, and summary measures of effects on outcomes of blood pressure treatment. The quality of the report was judged by concealment of treatment allocation, similarity of both groups at baseline in terms of prognostic factors, eligibility criteria, blinding of outcome assessors, completeness of follow-up, and intention-to-treat analysis.[13] We also used the Jadad score to quantify study quality.[14] Any disagreement in abstracted data was resolved by a third reviewer (VP).

Statistical analysis

Individual study risk ratios (RRs) and 95% CIs were calculated before data pooling. The weighted mean blood pressure reduction was calculated by multiplying the blood pressure difference in each study by the total number of patients in each study, and then dividing by the number of studies. Summary estimates of RRs were obtained by use of a random effects model. The percentage of variability across studies attributable to heterogeneity beyond chance was estimated by use of the I^2 statistic.[15] Potential publication bias was assessed with the Egger test and represented graphically by use of Begg funnel plots of the natural log of the RR versus its standard error.[16] Potential heterogeneity in estimates of treatment effect attributable to each potential source of heterogeneity was explored by univariate meta-regression.[15] Additionally, we investigated possible sources of heterogeneity by comparing summary results obtained from subsets of studies grouped by number of events, duration of follow-up, patient status, and class of blood pressure lowering agent used. A two-sided p value of less than 0·05 was judged significant for all analyses. All statistical analyses were done with STATA, version 9.

Role of the funding source

The sponsor had no role in the study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all data in the study and had final responsibility for the decision to submit for publication.

Results

Figure 1 shows how studies were selected. Seven randomised trials that provided information on a total of 1571 patients and 495 cardiovascular events were eligible for inclusion,[10,11,17–21] and one further randomised trial in 108 patients that reported a hazard ratio with confidence intervals for cardiovascular events could also be included.[22] Six of the trials were published in peer-reviewed journals[10,11,17,19–21] and two were presented at international scientific meetings.[18,22] Most other studies identified by our search were randomised trials that provided information on intermediate clinical measures for cardiovascular disease, but no data on the outcomes as defined for our systematic review.

Table 1 summarises the characteristics of the included randomised trials. Four trials were done in Europe,[10,11,18,21] three in Japan,[19,20,22] and one in Hong Kong.[17] Of the eight trials, three assessed the effects of angiotensin-receptor blockers (ARBs),[18–20] two assessed an angiotensin-converting enzyme (ACE) inhibitor,[11,17] two a β blocker,[10,22]

	Inclusion criteria	Active treatment	Control	Design	Cardiovascular outcome	Number of patients	Men, n (%)	Age, years (mean)	Patients with diabetes, n (%)	Number of cardiovascular events
Cice et al (2003)[10]	Uraemic patients with dilated cardiomyopathy; stable weight (<2·5 kg change before enrolment)	Carvedilol 50 mg/day	Matched placebo	Randomised, placebo-controlled, double-blind trial (unblinded for second 12 months)	Myocardial infarction, cardiovascular death	114	69 (61%)	55	NR	56
Li et al (2003)[17]	Peritoneal dialysis with residual glomerular filtration rate ≥2 mL/min /1·73 m^2; blood pressure ≥120/70 mm Hg; no ACE inhibitor/ARB use for at least 6 months before enrolment	Ramipril 5 mg/day	Conventional treatment	Randomised, open-label trial	Myocardial infarction, stroke, peripheral vascular disease, cardiovascular death	60	38 (63%)	59	28 (47%)	10
Cice et al (2006)[18]	Congestive heart failure NYHA class II and III; left ventricular ejection fraction <40%	Telmisartan 80 mg/day	Matched placebo	Randomised, placebo-controlled, double-blind trial	Cardiovascular mortality	303	158 (52%)	59	98 (32%)	134
Takahashi et al (2006)[19]	≥35 years; stable interdialytic weight; post-haemodialytic cardiothoracic ratio on chest radiograph <50% in men or 35% in women	Candesartan 16–32 mg/day	Conventional treatment	Randomised, open-label, blinded endpoint trial	Myocardial infarction, unstable angina pectoris or heart failure needing hospital admission, severe arrhythmia, sudden death	80	47 (59%)	61	26 (33%)	24
Zannad et al (2006)[11]	50–80 years; haemodialysis for at least 6 months three times a week; left ventricular hypertrophy within 3 months of enrolment	Fosinopril 20 mg/day	Matched placebo	Randomised, placebo-controlled, double-blind trial	Myocardial infarction, stroke, hospital admission for heart failure, unstable angina pectoris, revascularisation, cardiac arrest, cardiovascular death	397	208 (52%)	67	124 (31%)	127
Nakao et al (2007)[22]	Haemodialysis for at least 6 months; BNP >200 pg/mL; hANP <150 pg/mL; left ventricular hypertrophy	Carvedilol 20 mg/day	Matched placebo	Randomised, open-label, placebo-controlled trial	Myocardial infarction, stroke, hospital admission for heart failure, peripheral vascular disease, arrhythmia, cardiomyopathy, sudden cardiac arrest, cardiovascular death	108	64 (59%)	60	52 (48%)	NR
Suzuki et al (2008)[20]	30–80 years; haemodialysis for at least 12 months; systolic blood pressure >160 mm Hg or >150 mm Hg if taking antihypertensive agents	Candesartan 12 mg/day, losartan 100 mg/day, or valsartan 160 mg/day	Conventional treatment	Randomised open-label trial	Myocardial infarction, stroke, CABG, percutaneous coronary intervention, congestive heart failure, cardiovascular death	366	216 (59%)	60	187 (51%)	93
Tepel et al (2008)[21]	≥18 years; haemodialysis for at least 3 months; blood pressure ≥140/90 mm Hg	Amlodipine 10 mg/day	Matched placebo	Randomised, placebo-controlled, double-blind trial	Myocardial infarction, CABG, ischaemic stroke, peripheral vascular disease needing amputation, all-cause mortality	251	159 (63%)	61	73 (29%)	51

ACE=angiotensin-converting enzyme. ARB=angiotensin-receptor blocker. BNP=brain natriuretic peptide. CABG=coronary artery bypass graft. hANP=human atrial natriuretic peptide. NR=not reported. NYHA=New York Heart Association.

Table 1: **Characteristics of studies reporting the effects of blood pressure lowering agents for prevention of cardiovascular events in patients on maintenance dialysis**

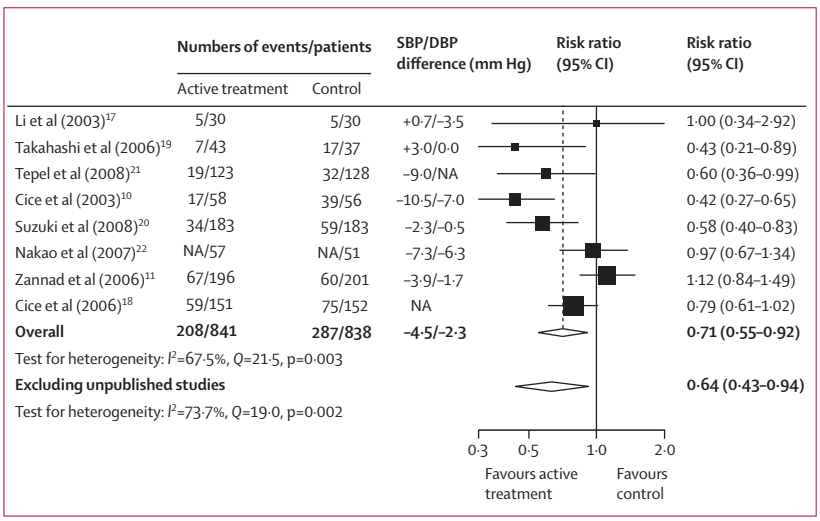

Figure 2: **Risk of cardiovascular events for blood pressure lowering treatment versus control regimens**
DBP=diastolic blood pressure. SBP=systolic blood pressure. NA=not applicable. The overall mean difference in systolic and diastolic blood pressure in the active treatment group compared with the control group is also shown. Negative values indicate lower mean follow-up blood pressure in the active treatment group.

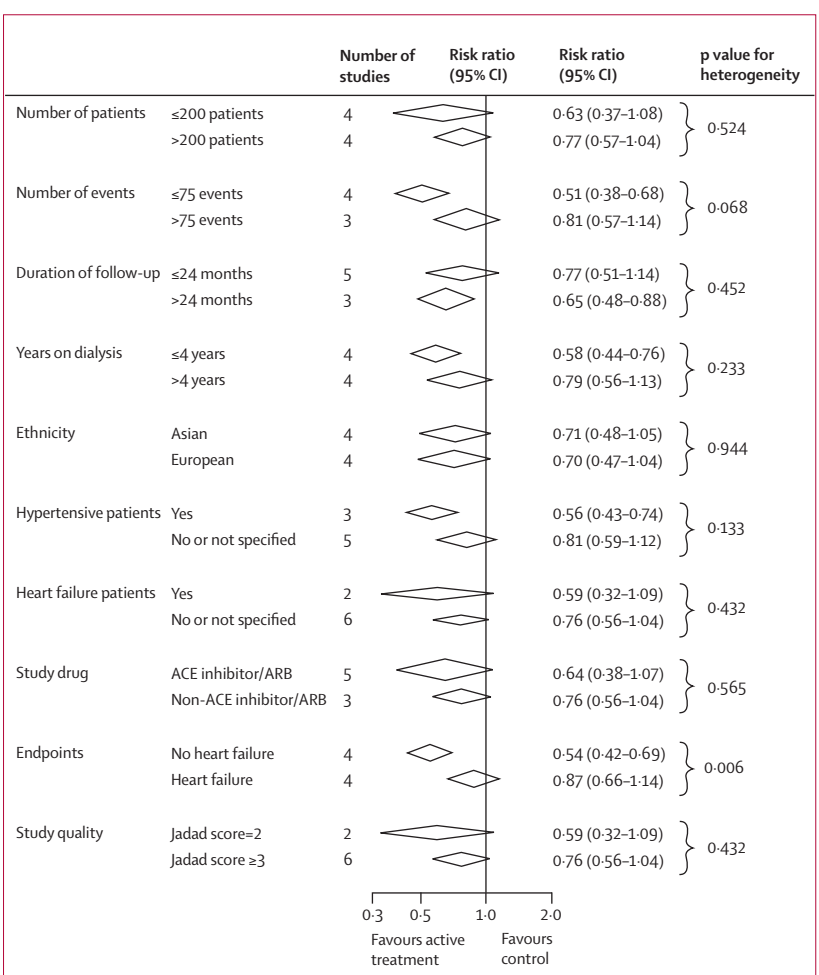

Figure 3: **Subgroup analyses for the effects of blood pressure lowering agents on cardiovascular events**
ACE=angiotensin-converting enzyme. ARB=angiotensin-receptor blocker.

and one a calcium-channel blocker.[21] The mean baseline systolic blood pressure in the contributing studies ranged from 134 mm Hg to 155 mm Hg; for diastolic blood pressure the range was 75 mm Hg to 93 mm Hg. Three studies included patients on the basis of a diagnosis of hypertension;[19–21] the other five studies enrolled patients with and without hypertension.

The components of the cardiovascular composite endpoint differed across the studies. Myocardial infarction and cardiovascular mortality were the most frequently included components, three trials included hospital admission for heart failure as an endpoint,[11,19,22] and one trial included congestive heart failure.[20] Study follow-up period ranged from 12 months to 36 months. Six trials provided information about mean follow-up blood pressure difference between treatment groups.[10,11,17,19,20,22] The weighted mean difference in blood pressure during follow-up between active and control treatment across all trials was –4·5 mm Hg for systolic and –2·3 mm Hg for diastolic blood pressure (figure 2). Quality assessment showed that few studies described concealment of allocation or blinding of outcome assessor. Two of the eight trials did not describe whether the analyses were by intention to treat (webappendix p 1).[20,22] Across all published trials the mean Jadad score was 3·1 (maximum 5).

Overall, treatment with blood pressure lowering drugs was associated with a lower risk of cardiovascular events compared with control regimens (RR 0·71, 95% CI 0·55–0·92; p=0·009; figure 2). Exclusion of the two unpublished trials did not alter the findings (RR 0·64, 0·43–0·94; p=0·022) and there was no evidence of publication bias (Egger's test p=0·287; webappendix p 2).

There was evidence of heterogeneity in the magnitude of the effect across the included studies (I^2=67·5%; p=0·003; figure 2). Figure 3 shows the results of the subgroup analyses. We identified no evidence of heterogeneity of effect in all subgroup analyses (all values for heterogeneity p>0·068) apart from when studies were divided on the basis of inclusion or exclusion of hospital admission for heart failure in the composite endpoint (p=0·006). For every trial subgroup the point estimate of effect was suggestive of benefit for this outcome. Univariate meta-regression analysis showed the presence of heterogeneity of effect by inclusion of heart failure in the composite outcome (p=0·006) and also suggested an effect of the number of events recorded in the trial (p=0·031) and the mean age of the trial participants (p=0·011). Exclusion of the trial that assessed peritoneal dialysis patients[17] did not substantially change the overall effect estimate (RR 0·70, 0·53–0·91).

Of the eight trials, seven studies (1571 patients) provided information on all-cause mortality and five studies (1240 patients) provided information on cardiovascular mortality. The risks for all-cause mortality (RR 0·80, 0·66–0·96; p=0·014) and cardiovascular mortality (RR 0·71, 0·50–0·99; p=0·044) were lower for blood pressure lowering treatments than for control regimens (figure 4).

There was no strong evidence of heterogeneity of effect size among the studies for the outcomes of all-cause mortality or cardiovascular mortality.

Two studies used an active run-in design, in which patients who did not tolerate the study drug during a preliminary phase were not randomised to treatment or placebo.[10,11] 14% and 1% of patients were excluded during the run-in periods of these trials (table 2). Five studies reported information about study treatment discontinuation rates.[10,17,18,20,21] Overall, the proportion of patients who stopped taking study medication was low and did not differ substantially between active treatment and control groups (table 2).

Discussion

Individuals undergoing dialysis are at increased risk of death and cardiovascular events but so far no treatments proven to reduce this risk have been available to patients and clinicians. Interventions such as lipid lowering,[23] dialysis prescription modification,[24] homocysteine lowering,[25–27] mineral metabolism modification,[28] and haemoglobin normalisation[29] have been assessed in randomised trials and systematic reviews, but there is no clear evidence to show that any of these approaches reduces the risk of death or major cardiovascular events. In this meta-analysis of randomised trials, we have shown that treatment with agents that lower blood pressure reduces cardiovascular morbidity and mortality in patients on maintenance dialysis. The effects are consistent with or without the presence of hypertension and other comorbidities and across a range of drug classes.

The optimum blood pressure goals for dialysis patients have not been defined. The Kidney Disease Outcomes Quality Initiative recommends a predialysis blood pressure goal of below 140/90 mm Hg.[30] The rationale for this recommendation is largely based on extrapolation of blood pressure targets from studies done in the non-dialysis population with normal renal function. Here, we found that the benefit of blood pressure lowering drugs was similar in trials that did and did not select participants on the basis of raised baseline blood pressure levels.

Drugs that lower blood pressure might increase the risk of intradialytic hypotension, and previous observational studies have suggested that this adverse event might be associated with an increased risk of all-cause mortality.[31] However, we found that blood pressure lowering was well tolerated, with few participants excluded during the active run-in phase of the two trials that used this design, and no consistent evidence of higher dropout rates in the active treatment groups than in the control groups of the studies. Additionally, the risk of death and other serious outcomes was reduced by the use of agents that lower blood pressure. Randomised controlled trials that compare the effects of different intensities of blood pressure lowering on the risk of subsequent cardiovascular outcomes in patients on dialysis would provide further insight, but until further data are available, it would seem reasonable to consider treating patients on dialysis with some form of blood pressure lowering treatment, if they are able to tolerate the drug.

This analysis is not able to separate out the effects of blood pressure lowering for specific drug classes. The results do not show any differences in cardiovascular events caused by different drug classes; however, the

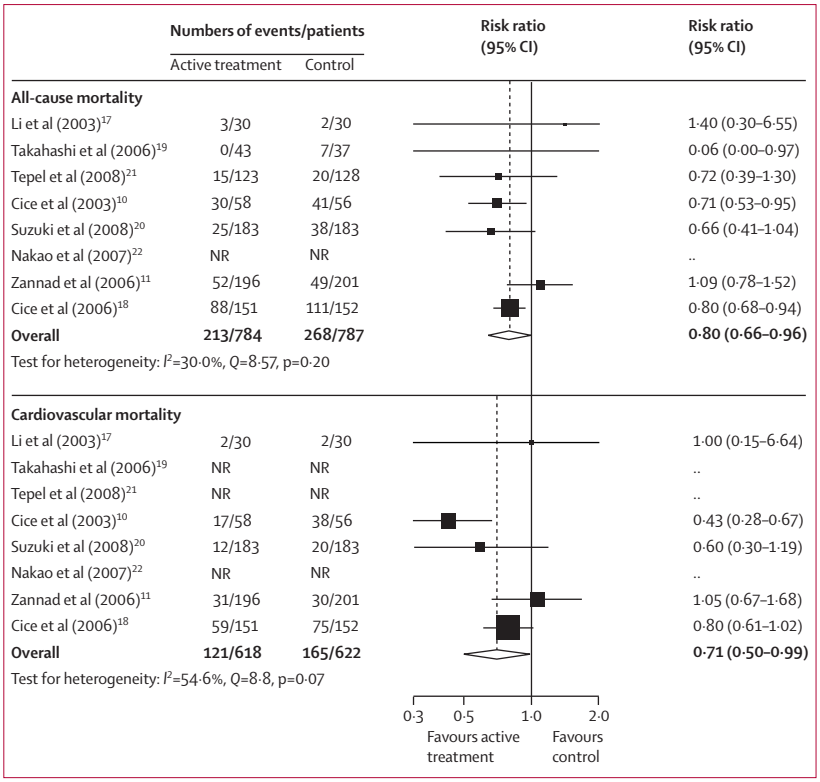

Figure 4: **Risk of all-cause mortality and cardiovascular mortality for blood pressure lowering treatment versus control regimens**
NR=not reported.

	Active agent	Active run-in*	Excluded during run-in	Patients who discontinued therapy	
				Active treatment	Control treatment
Cice et al (2003)[10]	β blocker	Yes	18/132 (14%)	11/58 (19%)	7/56 (13%)
Li et al (2003)[17]	ACE inhibitor	No	N/A	5/30 (17%)	0/30 (0%)
Cice et al (2006)[18]	ARB	No	N/A	20/151 (13%)	16/152 (11%)
Takahashi et al (2006)[19]	ARB	NR	N/A	NR	NR
Zannad et al (2006)[11]	ACE inhibitor	Yes	6/417 (1%)	NR	NR
Nakao et al (2007)[22]	β blocker	No	N/A	NR	NR
Suzuki et al (2008)[20]	ARB	No	N/A	3/183 (2%)	3/183 (2%)
Tepel et al (2008)[21]	Calcium-channel blocker	No	N/A	41/123 (33%)	43/128 (34%)

ACE=angiotensin-converting enzyme. ARB=angiotensin-receptor blocker. N/A=not applicable. NR=not reported. Data are n/N (%). *In the two studies with a preliminary run-in phase, all patients received study drug to determine before randomisation which patients were unable to tolerate the drug. Only patients who were able to tolerate the drug were randomly assigned to receive either treatment or placebo. In Zannad et al,[11] six of 417 recruited patients were excluded after the run-in period because of symptomatic hypertension. Finally, 397 patients were randomised.

Table 2: **Study treatment discontinuation rates**

statistical power to reliably compare drug classes was small. The data suggest that renin-angiotensin-system blockers, β blockers, and calcium-channel blockers are all suitable for use in patients on dialysis. Drugs such as α blockers and centrally acting agents should probably be viewed as secondary choices in the absence of randomised studies. Although the two studies of ACE inhibitors did not show beneficial effects of this treatment, it is unlikely that these agents have different effects from the other classes studied because the negative result came from a single trial and this result might have arisen by chance. Furthermore, ACE inhibitors have similar efficacy to other drug classes, especially ARBs, in the general population.[32] Head-to-head studies that compare different classes of blood pressure lowering agents have not been done in patients undergoing dialysis; however, trials in the general population have not shown markedly different effects between drug classes.[5] In the absence of further data in patients on dialysis, the choice of blood pressure lowering agents should be made on the grounds of general tolerability, side-effect profiles, and other patient variables.

Volume overload is an important contributor in the pathogenesis of high blood pressure in patients undergoing dialysis. Results from recent studies show that volume control in haemodialysis patients improves blood pressure control.[33] Since few data on the management of volume status during dialysis were provided by the trials investigated here, we were unable to assess the effect of this variable.

The blood pressure reduction achieved by patients varied widely among the trials. This variation might be related to the study population or class of drug used, but could also be the consequence of the variability in blood pressure measurement and the absence of firm criteria that define how and when to measure blood pressure. Blood pressure is very sensitive to dialysis and variations in the timing of its measurement might lead to large differences in the reading recorded. The differences in blood pressure seen in the trials included in this analysis should therefore be interpreted with some caution.

The strengths of this systematic review and meta-analysis are the rigorous methodology, the importance of the clinical question, and the magnitude of the benefits seen. The limitations include the small number and size of the studies included, the limited statistical power of methods based on tabular data to investigate sources of heterogeneity, and our inability to obtain the full results of all completed studies.

Thus, treatment with agents that lower blood pressure should routinely be considered for patients undergoing dialysis to help prevent cardiovascular events and mortality. If our data are applied to a broad population of patients on dialysis with an annual mortality rate of about 10%, we calculate that blood pressure lowering treatment could prevent two of the ten deaths expected to occur in every 100 patients per year. This absolute benefit will be greater for individuals at higher absolute risk, and is much greater than that reported for many other interventions in routine use.

Contributors

HJLH, TN, SZ, and VP were responsible for data collection, analysis, and interpretation, and manuscript preparation. DdZ, DEG, AC, MAR, and BN contributed to data interpretation. DdZ, DEG, AC, MAR, BN, MJJ, and MG contributed to critical revision of the publication. The corresponding author had full access to all data in the study and takes responsibility for the integrity of the data and accuracy of the analysis.

Conflict of interest statement

We declare that we have no conflict of interest.

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