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Calcium channel blockers for people with chronic kidney disease requiring dialysis (Review)

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[Intervention Review]

Calcium channel blockers for people with chronic kidney disease requiring dialysis

George A Mugendi[1], Florence M Mutua[2], Patrizia Natale[3,4], Tonya M Esterhuizen[5], Giovanni FM Strippoli[3,4,6]

[1]Pharmaceutics and Pharmacy Practice, School of Pharmacy, University of Nairobi, Nairobi, Kenya. [2]Department of Medical Microbiology, University of Manitoba, Winnipeg, Canada. [3]Department of Emergency and Organ Transplantation, University of Bari, Bari, Italy. [4]Sydney School of Public Health, The University of Sydney, Sydney, Australia. [5]Centre for Evidence-based Health Care, Division of Epidemiology and Biostatistics, Faculty of Medicine and Health Sciences, Stellenbosch University, Cape Town, South Africa. [6]Cochrane Kidney and Transplant, Centre for Kidney Research, The Children's Hospital at Westmead, Westmead, Australia

Contact: George A Mugendi, gendike@gmail.com.

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ABSTRACT

Background

Calcium channel blockers (CCBs) are used to manage hypertension which is highly prevalent among people with chronic kidney disease (CKD). The treatment for hypertension is particularly challenging in people undergoing dialysis.

Objectives

To assess the benefits and harms of calcium channel blockers in patients with chronic kidney disease requiring dialysis.

Search methods

We searched the Cochrane Kidney and Transplant Register of Studies to 27 April 2020 through contact with the Information Specialist using search terms relevant to this review. Studies in the Specialised Register are identified through searches of CENTRAL, MEDLINE, and EMBASE, conference proceedings, the International Clinical Trials Register (ICTRP) Search Portal and ClinicalTrials.gov.

Selection criteria

All randomised controlled trials (RCTs) and quasi-RCTs that compared any type of CCB with other CCB, different doses of the same CCB, other antihypertensives, control or placebo were included. The minimum study duration was 12 weeks.

Data collection and analysis

Two authors independently assessed study quality and extracted data. Statistical analyses were performed using a random-effects model and results expressed as risk ratio (RR), risk difference (RD) or mean difference (MD) with 95% confidence intervals (CI).

Main results

This review included 13 studies (24 reports) randomising 1459 participants treated with long-term haemodialysis. Nine studies were included in the meta-analysis (622 participants). No studies were performed in children or in those undergoing peritoneal dialysis. Overall, risk of bias was assessed as unclear to high across most domains.

Random sequence generation and allocation concealment were at low risk of bias in eight and one studies, respectively. Two studies reported low risk methods for blinding of participants and investigators, and outcome assessment was blinded in 10 studies. Three studies

were at low risk of attrition bias, eight studies were at low risk of selective reporting bias, and five studies were at low risk of other potential sources of bias. Overall, the certainty of the evidence was low to very low for all outcomes. No events were reported for cardiovascular death in any of the comparisons. Other side effects were rarely reported and studies were not designed to measure costs.

Five studies (451 randomised adults) compared dihydropyridine CCBs to placebo or no treatment. Dihydropyridine CCBs may decrease predialysis systolic (1 study, 39 participants: MD -27.00 mmHg, 95% CI -43.33 to -10.67; *low certainty evidence*) and diastolic blood pressure level (2 studies, 76 participants; MD -13.56 mmHg, 95% CI -19.65 to -7.48; I^2 = 0%, *low certainty evidence*) compared to placebo or no treatment. Dihydropyridine CCBs may make little or no difference to occurrence of intradialytic hypotension (2 studies, 287 participants; RR 0.54, 95% CI 0.25 to 1.15; I^2 = 0%, *low certainty evidence*) compared to placebo or no treatment. Other side effects were not reported.

Eight studies (1037 randomised adults) compared dihydropyridine CCBs to other antihypertensives. Dihydropyridine CCBs may make little or no difference to predialysis systolic (4 studies, 180 participants: MD 2.44 mmHg, 95% CI -3.74 to 8.62; I^2 = 0%, *low certainty evidence)* and diastolic blood pressure (4 studies, 180 participants: MD 1.49 mmHg, 95% CI -2.23 to 5.21; I^2 = 0%, *low certainty evidence)* compared to other antihypertensives. There was no evidence of a difference in the occurrence of intradialytic hypotension (1 study, 92 participants: RR 2.88, 95% CI 0.12 to 68.79; *very low certainty evidence*) between dihydropyridine CCBs to other antihypertensives. Other side effects were not reported.

Dihydropyridine CCB may make little or no difference to predialysis systolic (1 study, 40 participants: MD -4 mmHg, 95% CI -11.99 to 3.99; *low certainty evidence*) and diastolic blood pressure (1 study, 40 participants: MD -3.00 mmHg, 95% CI -7.06 to 1.06; *low certainty evidence*) compared to non-dihydropyridine CCB. There was no evidence of a difference in other side effects (1 study, 40 participants: RR 0.13, 95% CI 0.01 to 2.36; *very low certainty evidence*) between dihydropyridine CCB and non-dihydropyridine CCB. Intradialytic hypotension was not reported.

Authors' conclusions

The benefits of CCBs over other antihypertensives on predialysis blood pressure levels and intradialytic hypotension among people with CKD who required haemodialysis were uncertain. Effects of CCBs on other side effects and cardiovascular death also remain uncertain. Dihydropyridine CCBs may decrease predialysis systolic and diastolic blood pressure level compared to placebo or no treatment. No studies were identified in children or peritoneal dialysis. Available studies have not been designed to measure the effects on costs. The shortcomings of the studies were that they recruited very few participants, had few events, had very short follow-up periods, some outcomes were not reported, and the reporting of outcomes such as changes in blood pressure was not done uniformly across studies.

Well-designed RCTs, conducted in both adults and children with CKD requiring both haemodialysis and peritoneal dialysis, evaluating both dihydropyridine and non-dihydropyridine CCBs against other antihypertensives are required. Future research should be focused on outcomes relevant to patients (including death and cardiovascular disease), blood pressure changes, risk of side effects and healthcare costs to assist decision-making in clinical practice.

PLAIN LANGUAGE SUMMARY

Calcium channel blockers for people with chronic kidney disease requiring dialysis

What is the issue? People with long-term kidney disease or chronic kidney disease (CKD) often develop high blood pressure (hypertension), and those with advanced CKD need dialysis when their kidneys are no longer unable to function. Treatment for hypertension is often challenging for people with advanced CKD undergoing dialysis. Several medications are used to treat high blood pressure including calcium channel blockers (CCBs).

We wanted to find out whether the use of CCBs in people with CKD undergoing haemodialysis or peritoneal dialysis had any added benefits over other medications used to treat hypertension or placebo (no active treatment) in lowering the blood pressure, risk of death and undesired effects.

What did we do? We searched the literature up to April 2020 to identify all studies that assessed the use of CCBs in adults and children with hypertension and CKD undergoing haemodialysis or peritoneal dialysis. Each study was assessed for possible bias on several pre-determined domains. We pooled the results of studies that reported on the same outcomes for similar comparisons and reported the overall effects. We applied a system called "GRADE" to assess the quality of the evidence that we found.

What did we find? We included 13 studies randomising 1459 adults undergoing haemodialysis. We did not find any studies in children and there were no studies in patients undergoing peritoneal dialysis. Patients were randomised to CCBs, other medications used to treat hypertension, or placebo or standard care. Some studies were short-term (over few months) and heart-related complications were not assessed. The benefit of CCBs over other medications was unclear, possibly due to the small number of participants and the overall number of events. When compared to placebo or no treatment CCBs may decrease blood pressure before haemodialysis, although the quality of the evidence was low.

Conclusions The benefits of CCBs over other medications to treat hypertension could not be determined, while CCBs may lower blood pressure compared to placebo or usual care.

SUMMARY OF FINDINGS

Summary of findings 1. Dihydropyridine calcium channel blockers versus placebo/control in people with chronic kidney disease requiring dialysis

Dihydropyridine calcium channel blockers versus placebo/control in people with CKD requiring dialysis

Patient or population: people with CKD requiring dialysis
Setting: France, Germany, Japan, Russia

Intervention: dihydropyridine calcium channel blockers (amlodipine, cilnidipine or nitrendipine)
Comparison: placebo/control

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Placebo/control	Dihydropyridine calcium channel blockers			
Predialysis systolic blood pressure follow-up 3.7 months	The mean predialysis systolic blood pressure level in the dihydropyridine calcium channel blockers group was 27.00 mmHg lower (43.33 to 10.67 mmHg lower) than the placebo group [1]		-	39 (1)	⊕⊕⊖⊖ low [2,3]
Predialysis diastolic blood pressure mean follow-up 4.9 months	The mean predialysis diastolic blood pressure level in the placebo/control group ranged from 98 to 104.1 mmHg The mean predialysis diastolic blood pressure level in the placebo/control group was 13.56 mmHg lower (19.65 to 7.48 mmHg lower)		-	76 (2)	⊕⊕⊖⊖ low [3,4]
Cardiovascular death mean follow-up 3.4 months	No events [5]	No events	Not estimable	124 (3)	-
Intradialytic hypotension mean follow-up 16.4 months	122 per 1000	66 per 1000 (31 to 141)	RR 0.54 (0.25 to 1.15)	287 (2)	⊕⊕⊖⊖ low [3,6]
Other side effects	Not reported	Not reported	-	-	-

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CKD: Chronic kidney disease; **HD:** Haemodialysis; **CI:** Confidence interval; **RR:** Risk Ratio

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Studies were not designed to measure effects of dihydropyridine calcium channel blockers on predialysis systolic blood pressure level in haemodialysis
[2] Evidence certainty was downgraded by one level due to study limitations. The study had unclear risks for allocation concealment and blinding (participants and/or investigators)
[3] Evidence certainty was downgraded by one level due to the small number of participants/events (optimal Information size criterion not met)
[4] Evidence certainty was downgraded by one level due to study limitations. Some studies had unclear risk for sequence generation, all studies had unclear risks for allocation concealment and some of them were not blinded (participants and/or investigators)
[5] Cardiovascular death was reported by as a single study with zero events in both groups; studies were not designed to measure effects of dihydropyridine calcium channel blockers or placebo/control on cardiovascular death in HD
[6] Evidence certainty was downgraded by one level due to study limitations. Some studies had unclear risks for allocation concealment and were not blinded (participants and/or investigators)

Summary of findings 2. Dihydropyridine calcium channel blockers versus other antihypertensives in people with chronic kidney disease requiring dialysis

Dihydropyridine calcium channel blockers versus other antihypertensives in people with CKD requiring dialysis

Patient or population: people with CKD requiring dialysis
Setting: France, Turkey, Russia

Intervention: dihydropyridine calcium channel blockers (amlodipine or nifedipine)
Comparison: other antihypertensives (all studies reported ACEi including, enalapril, perindopril or ramipril)

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Other antihypertensives	Dihydropyridine calcium channel blockers			
Predialysis systolic blood pressure mean follow-up 10.5 months	The mean predialysis systolic blood pressure level in the other antihypertensive group ranged from 129 to 150 mmHg The mean predialysis systolic blood pressure level in the dihydropyridine calcium channel blockers group was 2.44 mmHg higher (3.74 lower to 8.62 mmHg higher)		-	180 (4)	⊕⊕⊖⊖ low [1,2]
Predialysis diastolic blood pressure	The mean predialysis diastolic blood pressure level in the other antihypertensive group ranged from 80 to 88.3 mmHg		-	180 (4)	⊕⊕⊖⊖ low [1,2]

mean follow-up 10.5 months	The mean predialysis diastolic blood pressure level in the dihydropyridine calcium channel blockers group was 1.49 mmHg higher (2.23 lower to 5.21 mmHg higher)				
Cardiovascular death mean follow-up 12 months	No events [3]	No events	Not estimable	164 (3)	-
Intradialytic hypotension follow-up 12 months	No events [4]	1/47**	RR 2.88 (0.12 to 68.79)	92 (1)	⊕⊖⊖⊖ very low [5,6]
Other side effects	Not reported	Not reported	-	-	-

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CKD: Chronic kidney disease; **HD:** Haemodialysis; **ACEi:** Angiotensin-converting enzyme inhibitors; **CI:** Confidence interval; **RR:** Risk Ratio

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

**Event rate derived from the raw data. A "per thousand" rate is non-informative in view of the scarcity of evidence and zero events in the control group.

[1] Evidence certainty was downgraded by one level due to study limitations. Some studies had unclear risk for sequence generation, all studies had unclear risks for allocation concealment and the majority of them were not blinded (participants and/or investigators)
[2] Evidence certainty was downgraded by one level due to the small number of participants/events (optimal information size criterion not met)
[3] Cardiovascular death was reported by as a single study with zero events in both groups; studies were not designed to measure cardiovascular death
[4] Occurrence of intradialytic hypotension was reported by as a single study; studies were not designed to measure the occurrence of intradialytic hypotension in HD
[5] Evidence certainty was downgraded by one level due to study limitations. The study had unclear risks for allocation concealment and was not blinded (participants and/or investigators)
[6] Evidence certainty was downgraded by two levels due to imprecision

Summary of findings 3. Dihydropyridine versus non-dihydropyridine calcium channel blockers in people with chronic kidney disease requiring dialysis

Dihydropyridine versus non-dihydropyridine calcium channel blockers in people with CKD requiring dialysis
Patient or population: people with CKD requiring dialysis

Setting: Italy

Intervention: dihydropyridine calcium channel blockers (amlodipine)

Comparison: non-dihydropyridine calcium channel blockers (verapamil)

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Non-dihydropyridine calcium channel blockers	Dihydropyridine calcium channel blockers			
Predialysis systolic blood pressure follow-up 2.8 months	The mean predialysis systolic blood pressure level in the dihydropyridine calcium channel blockers group was 4 mmHg lower (11.99 lower to 3.99 mmHg higher) than non-dihydropyridine calcium channel blockers [1]		-	40 (1)	⊕⊕⊖⊖ low [2,3]
Predialysis diastolic blood pressure follow-up 2.8 months	The mean predialysis diastolic blood pressure level in the dihydropyridine calcium channel blockers group was 3.00 mmHg lower (7.06 lower to 1.06 mmHg higher) than non-dihydropyridine calcium channel blockers [1]		-	40 (1)	⊕⊕⊖⊖ low [2,3]
Cardiovascular death follow-up 2.8 months	No events [1,3,4]	No events	Not estimable	40 (1)	-
Intradialytic hypotension	Not reported	Not reported	-	-	-
Other side effects [1,5] follow-up 2.8 months	3/19 [1]	No events**	**RR 0.13** (0.01 to 2.36)	40 (1)	⊕⊖⊖⊖ very low [2,6]

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CKD: Chronic kidney disease; **HD:** Haemodialysis; **CI:** Confidence interval; **RR:** Risk Ratio

**Event rate derived from the raw data. A "per thousand" rate is non-informative in view of the scarcity of evidence and zero events in the dihydropyridine calcium channel blocker group

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

[1] Studies not designed to measure this outcome
[2] Evidence certainty was downgraded by one level due to study limitations. The study had unclear risks for allocation concealment and was not blinded (participants and/or investigators)
[3] Evidence certainty was downgraded by one level due to the small number of participants/events (optimal information size criterion not met)
[4] Cardiovascular death was reported by as a single study with zero events in both groups
[5] Other side effects included headache reported in non-dihydropyridine calcium channel blockers group, while no events were reported in dihydropyridine calcium channel blockers group
[6] Evidence certainty was downgraded by two levels due to imprecision

BACKGROUND

CKD is a growing health concern associated with a high risk of adverse outcomes. Its global prevalence is increasing at a rate of 8% per year (Ruilope 2008). CKD aetiology differs by region, age, gender, and race. In Europe, Japan and the United States, diabetic nephropathy is the leading cause of CKD, while in the developing world, chronic glomerulonephritis and systemic hypertension are the leading causes (Ruilope 2008). Hypertension as a complication is highly prevalent in patients who have end-stage kidney disease (ESKD). In India, a population-based study determined that the crude and age-adjusted ESKD rates were 151 and 232 per million population, respectively. The number of patients requiring dialysis in India has been estimated at 55,000 with an annual growth rate of between 10% and 20% (Jha 2013).

From the 1990s, there has been an increase in CKD incidence of unknown aetiologies observed in several countries - El Salvador, Nicaragua, Costa Rica, Sri Lanka, Egypt, and India. The disease seems to have a predominance in young male farm workers and the most common aetiology was chronic tubulointerstitial nephritis (Almaguer 2014; Wanigasuriya 2014).

Studies in East Africa revealed a prevalence of hypertension ranging between 61.5% and 76% among patients with varying degrees of CKD (Maritim 2007; Rajula 2009) which illustrated the inadequacy of blood pressure control in this population. It is imperative therefore to ensure adequate blood pressure control in patients with ESKD requiring dialysis. This entails the use of appropriate antihypertensives to provide better health outcomes.

Description of the condition

CKD is defined as the progressive loss of kidney function occurring over several months to years and is characterised by gradual kidney scarring (Dipiro 2011). CKD is categorised by the level of kidney function into stages 1 to 5 as proposed by the widely-accepted United States Kidney Disease Outcomes Quality Initiative (KDOQI); staging is determined by the glomerular filtration rate (GFR) (Levey 2003).

The more recently published Kidney Disease Improving Guidelines Outcomes (KDIGO) 2012 clinical practice guidelines for the evaluation and management of CKD have a slightly different staging of CKD. They recommend that CKD be classified based on the cause, GFR category and albuminuria category (CGA). GFR categories are classified as G1, G2, G3a, G3b, G4 and G5 (Eknoyan 2013).

Data from the 1998 to 2004 National Health and Nutrition Examination Survey (NHANES) revealed a rise in CKD prevalence. Prevalence rose in people aged over 20 years from 14.5% in 1988 to 16.8% in 1994 (Onuigbo 2009). The 2003 to 2006 survey reported an increase in stage 3 CKD prevalence from 5.7% in 1988 to 8.1% in 1994 (Dipiro 2011).

Description of the intervention

CCBs are antihypertensive agents that act on both myocardial cells and blood vessels. CCBs are classified broadly as either dihydropyridine or non-dihydropyridine types. Dihydropyridine CCBs include nifedipine, which is the prototype in this group; others include amlodipine, felodipine, isradipine, nicardipine, nimodipine, nitrendipine, nisoldipine, efonipidine and cilnidipine. The non-dihydropyridine subclass includes diltiazem and verapamil which are the prototypes for the benzodiazepine and phenylalkylamine class of CCB. Gallopamil, a derivative of verapamil, is also classified as a non-dihydropyridine CCB (Hart 2008).

How the intervention might work

CCBs are vasodilators, although vasodilatory ability is not equal across all classes; the dihydropyridine CCBs are more potent than non-dihydropyridine CCBs (Sica 2005).

Both CCBs classes inhibit two types of voltage dependent channels: a high voltage activated calcium channel including P/Q, L, N, and R type channels, and low voltage activated T type channel (Hart 2008). By preferentially binding to L type channels in the vasculature, dihydropyridine CCBs cause vasodilatation and subsequent drop in blood pressure. The non-dihydropyridine CCBs bind preferentially to L type channels in the cardiac muscles, more so on the sino-atrial and atrioventricular nodes, causing negative chronotropic effects and decreasing sympathetic nervous system activity. These effects cause blood pressure to decrease (Basile 2004).

Why it is important to do this review

Most people undergoing dialysis have hypertension that is difficult to control; this contributes to increased cardiovascular morbidity and mortality (Inrig 2010; Van Buren 2012). The reported prevalence of hypertension among people on dialysis was 86% in an American cohort of 2535 clinically stable, adults on dialysis. Of these, only 30% had adequately controlled blood pressure (Agarwal 2003). Drugs used before development of ESKD may no longer provide viable options. Some drugs are dialyzable and use would result in a rise in blood pressure during dialysis (Inrig 2010; Van Buren 2012). Clinicians are faced with the challenge of choosing an appropriate therapy for controlling blood pressure for people with ESKD undergoing dialysis.

OBJECTIVES

To assess the benefits and harms of calcium channel blockers in patients with chronic kidney disease requiring dialysis.

METHODS

Criteria for considering studies for this review

Types of studies

All randomised controlled trials (RCTs) and quasi-RCTs (RCTs in which allocation to treatment was obtained by alternation, use of alternate medical records, date of birth or other predictable methods) looking at the effects of CCB on blood pressure control in patients with CKD undergoing dialysis. The minimum study duration was 12 weeks. Cross-over studies were excluded unless they had a washout period between treatments.

Types of participants

Inclusion criteria

All patients with CKD requiring dialysis (stage 5 as defined by the K/DOQI guidelines (Levey 2003) or stage G5 as defined by the KDIGO guidelines (Eknoyan 2013). We included patients who underwent either haemodialysis or peritoneal dialysis. There were no restrictions on age, gender, or race.

The participants were comorbid with hypertension as defined by the seventh report of the joint national committee on prevention, detection, evaluation and treatment of high blood pressure (JNC VII) (Chobanian 2003). Participants with or without diabetes (either type 1 or 2) were included. Patients with heart failure as classified by the New York Heart Association (NYHA) stages I to IV and angina were included.

Exclusion criteria

Kidney transplant patients and patients with CKD stages 1 to 4 and stages G1 to G4 as per the K/DOQI guidelines (Levey 2003) and KDIGO guidelines (Eknoyan 2013) respectively were excluded. Studies where follow-up was less than 12 weeks were excluded.

Types of interventions

Any type of CCB compared with other CCB, different doses of the same CCB, other antihypertensives, or placebo/control/usual treatment were included. Intervention types were to be assessed as follows.

1. CCB versus placebo/control/usual treatment
   a. Dihydropyridine CCB versus placebo/control/usual treatment
   b. Non-dihydropyridine CCB versus placebo/control/usual treatment
2. CCB versus CCB
   a. Dihydropyridine CCB versus dihydropyridine CCB
   b. Dihydropyridine CCB versus non-dihydropyridine CCB
   c. Non-dihydropyridine CCB versus non-dihydropyridine CCB
3. Different doses of CCB
   a. Dihydropyridine CCB
   b. Non-dihydropyridine CCB
4. CCB versus other antihypertensives
   a. Dihydropyridine CCB versus other antihypertensives
   b. Non-dihydropyridine CCB versus other antihypertensives

The review was amended as newer drugs that had been licensed become available. All drugs were administered orally. The dosages were those that were required for control of hypertension or appropriately adjusted dosages for reduced GFR and dialysis.

Combination preparations with other antihypertensives other than CCB were not included.

Types of outcome measures

Primary outcomes

1. Cardiovascular death
2. Predialysis blood pressure (systolic and diastolic)
3. Intradialytic hypotension.

Secondary outcomes

1. Incidence of other adverse events (e.g. reflex tachycardia, headache, constipation, bradycardia and heart block, myocardial infarction) related to the interventions
2. Cost: total healthcare costs.

Search methods for identification of studies

Electronic searches

We searched the Cochrane Kidney and Transplant Register of Studies to 27 April 2020 through contact with the Information Specialist using search terms relevant to this review. The Register contains studies identified from the following sources.

1. Monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL)
2. Weekly searches of MEDLINE OVID SP
3. Handsearching of kidney-related journals and the proceedings of major kidney conferences
4. Searching of the current year of EMBASE OVID SP
5. Weekly current awareness alerts for selected kidney and transplant journals
6. Searches of the International Clinical Trials Register (ICTRP) Search Portal and ClinicalTrials.gov

Studies contained in the Register are identified through search strategies for CENTRAL, MEDLINE, and EMBASE based on the scope of Cochrane Kidney and Transplant. Details of these strategies as well as a list of handsearched journals, conference proceedings and current awareness alerts are available in the "Specialised Register" section of information about Cochrane Kidney and Transplant.

See Appendix 1 for search terms used in strategies for this review.

Searching other resources

1. Reference lists of review articles, relevant studies, and clinical practice guidelines.
2. Letters seeking information about unpublished or incomplete studies to investigators known to be involved in previous studies.

Data collection and analysis

Selection of studies

The search strategy described was used to obtain titles and abstracts of studies that may have been relevant to the review. The titles and abstracts were screened independently by two authors, who discarded studies that were not applicable, however studies and reviews that might have included relevant data or information on trials were retained initially. Two authors independently assessed retrieved abstracts and, if necessary, the full text, of these studies to determine which studies satisfied the inclusion criteria. The two authors compared their lists and any differences were resolved by discussion and, where this failed, by arbitration by a third author.

Data extraction and management

Data extraction was carried out independently by two authors using standard data extraction forms. Studies reported in non-English language journals were translated before assessment. Where more than one publication of one study exists, reports were grouped together and the publication with the most complete data was used in the analyses. Where relevant outcomes were only published in earlier versions these data was used. Any discrepancy between published versions was highlighted. Differences in opinion on data

collection was resolved by discussion and, where this failed, by arbitration by a third author.

Assessment of risk of bias in included studies

The following items were independently assessed by two authors using the risk of bias assessment tool (Higgins 2011) (see Appendix 2).

- Was there adequate sequence generation (selection bias)?
- Was allocation adequately concealed (selection bias)?
- Was knowledge of the allocated interventions adequately prevented during the study?
  - Participants and personnel (performance bias)
  - Outcome assessors (detection bias)
- Were incomplete outcome data adequately addressed (attrition bias)?
- Were reports of the study free of suggestion of selective outcome reporting (reporting bias)?
- Was the study apparently free of other problems that could put it at a risk of bias?

Measures of treatment effect

For dichotomous outcomes (e.g. death, adverse events such as hypotension, cardiovascular death) results were expressed as risk ratio (RR) with 95% confidence intervals (CI). Where continuous scales of measurement were used to assess the effects of treatment (blood pressure), the mean difference (MD) was used, or the standardised mean difference (SMD) if different scales had been used. Studies that reported change from baseline scores were meta-analysed with studies reporting final value scores using the mean difference. In this case, if standard deviation of change was not reported, this was imputed (Higgins 2011). Studies that reported time to event of outcomes as hazard ratios and CIs were meta-analysed with studies that reported risk ratios where the proportional hazards assumption was reasonable. Otherwise, these studies were analysed as dichotomous data.

Unit of analysis issues

We did not foresee the use of non-standard design studies such as cross-over trials and cluster-RCTs would be included in the review. However, multiple arm studies were found and included. In such cases, all intervention groups that were relevant to the review were included.

Dealing with missing data

Any further information required from the original author was requested by written correspondence (e.g. emailing the corresponding author) and any relevant information obtained in this manner was included in the review. Evaluation of important numerical data such as screened, randomised patients as well as intention-to-treat (ITT), as-treated and per-protocol (PP) population was carefully performed. Attrition rates, for example drop-outs, losses to follow-up and withdrawals were investigated. Issues of missing data and imputation methods (for example, last-observation-carried-forward (LOCF)) were critically appraised (Higgins 2011).

Assessment of heterogeneity

Heterogeneity was analysed using a Chi^2 test on N-1 degrees of freedom, with an alpha of 0.05 used for statistical significance and with the I^2 test (Higgins 2003). I^2 values of 25%, 50% and 75% correspond to low, medium, and high levels of heterogeneity.

Assessment of reporting biases

If possible, funnel plots were to be used to assess for the potential existence of small study bias (Higgins 2011).

Data synthesis

Data were pooled using the random-effects model but the fixed-effect model was also used to ensure robustness of the model chosen and susceptibility to outliers.

Subgroup analysis and investigation of heterogeneity

Subgroup analyses were used to explore possible sources of heterogeneity (e.g. participants, interventions, and study quality). Heterogeneity among participants could have been related to age, gender, ethnicity/race, renal pathology, type of dialysis and co morbidities (CVD, hypertension, diabetes mellitus). Heterogeneity in treatments could have been related to prior agents used and the agent, dose, and duration of therapy. Adverse effects were tabulated and assessed with descriptive techniques, as they were likely to be different for the various agents used. Where possible, the risk difference with 95% CI was calculated for each adverse effect, either compared with no treatment or another agent.

Sensitivity analysis

We performed sensitivity analyses to explore the influence of the following factors on effect size:

- repeating the analysis excluding unpublished studies;
- repeat the analysis excluding studies with high risk of bias;
- repeating the analysis excluding any very long or large studies to establish how much they dominate the results;
- repeating the analysis excluding studies using the following filters: diagnostic criteria, language of publication, source of funding (industry versus other), country.

'Summary of findings' tables

We presented the main results of the review in 'Summary of findings' tables. These tables present key information concerning the quality of the evidence, the magnitude of the effects of the interventions examined, and the sum of the available data for the main outcomes (Schunemann 2011a). The 'Summary of findings' tables also include an overall grading of the evidence related to each of the main outcomes using the GRADE (Grades of Recommendation, Assessment, Development and Evaluation) approach (GRADE 2008). The GRADE approach defines the quality of a body of evidence as the extent to which one can be confident that an estimate of effect or association is close to the true quantity of specific interest. The quality of a body of evidence involves consideration of within-trial risk of bias (methodological quality), directness of evidence, heterogeneity, precision of effect estimates and risk of publication bias (Schunemann 2011b). We presented the following outcomes in the 'Summary of findings' tables.

- Predialysis systolic blood pressure

- Predialysis diastolic blood pressure
- Cardiovascular death
- Intradialytic hypotension
- Other side effects.

RESULTS

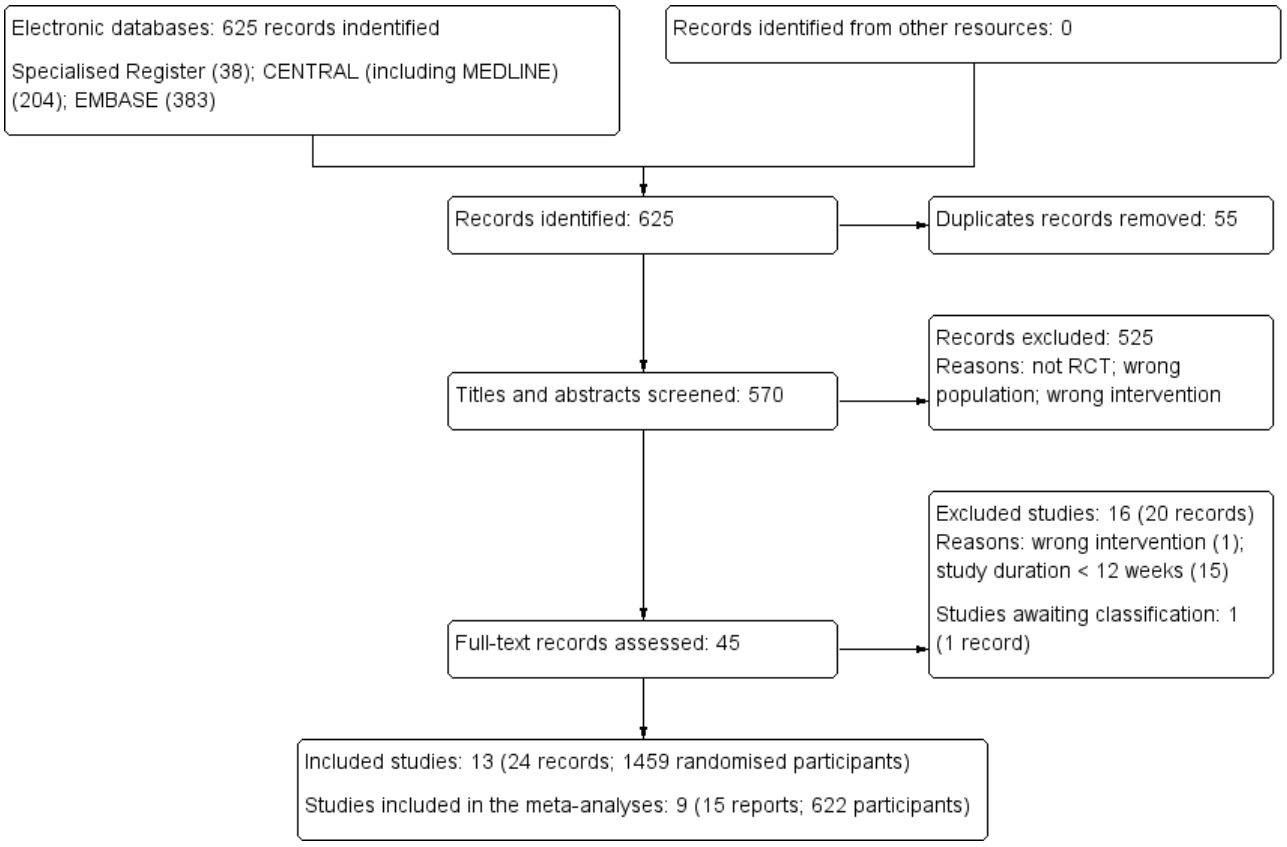
Description of studies

Results of the search

Our search identified 625 reports; 55 duplicate records were deleted. We screened 570 titles and abstracts and excluded 525 records which did not meet our inclusion criteria (not randomised, wrong population, or wrong intervention). We assessed 45 full text reports and excluded a further 20 reports (16 studies). One study (recently completed but not published) has been listed as awaiting classification (NCT01394770). We included 13 studies (24 reports) randomising 1459 participants; nine studies (15 reports; 622 participants) were included in our meta-analyses.

See Figure 1.

Figure 1. Study flow diagram



Included studies

Twelve studies evaluated dihydropyridine CCBs (Albitar 1997; Das 2003; HEART 2003; Kozlova 2006; London 1990; London 1994; LONDON 2019; Marchais 1991; Nakao 1999; Shibasaki 2002; Tepel 2008; Yilmaz 2010a), and one study (Timio 1997) compared dihydropyridine CCBs to non-dihydropyridine CCBs.

Kozlova 2006 was a four-arm study compared amlodipine either to an ACEi (perindopril), dual therapy or no intervention, while Shibasaki 2002 was a three arms study compared amlodipine either to an ACEi (enalapril) or an ARB (losartan).

Dihydropyridine CCB versus placebo or no treatment

Five studies compared dihydropyridine CCB to placebo or no treatment. London 1990 (40 participants) and Marchais 1991 (40 participants) compared nitrendipine to placebo; Tepel 2008 (251 participants) compared amlodipine to placebo; Kozlova 2006 (37 participants) compared amlodipine to no treatment; and LONDON 2019 (51 participants) compared cilnidipine to no treatment.

The outcomes assessed were predialysis systolic (London 1990) and diastolic blood pressure (Kozlova 2006; London 1990), cardiovascular death (London 1990; LONDON 2019; Marchais 1991), and intradialytic hypotension (LONDON 2019; Tepel 2008).

Dihydropyridine CCB versus non-dihydropyridine CCB

Timio 1997 (40 participants) compared dihydropyridine CCB (amlodipine) to a non-dihydropyridine CCB (verapamil).

The outcomes assessed were predialysis systolic and diastolic blood pressure, cardiovascular death, and other side effects (including headache).

Dihydropyridine CCB versus other antihypertensives

Eight studies (1037 participants) compared a dihydropyridine CCB to ACEi (including enalapril, trandolapril, perindopril and ramipril) (Albitar 1997; HEART 2003; Kozlova 2006; London 1994; Nakao 1999; Shibasaki 2002; Yilmaz 2010a) or an ARB (telmisartan or losartan) (Das 2003; Shibasaki 2002).

Outcomes reported were changes in changes in predialysis systolic and diastolic blood pressure (Albitar 1997; London 1994; Kozlova 2006; Yilmaz 2010a), cardiovascular death (Albitar 1997; London 1994; Yilmaz 2010a), and intradialytic hypotension (Yilmaz 2010a)

Das 2003 (47 participants) compared lercanidipine to ARB (telmisartan) and Shibasaki 2002 (39 participants) compared amlodipine to both enalapril and losartan, however no outcome data were extractable.

Excluded studies

We excluded 16 studies (20 reports); 15 studies did not have the required follow-up period (Aslam 2006; Atabak 2013; Cice 1997; Cice 1998; Cice 2003; EDIT 2011; Kojima 2004; Nakano 2010; Rojas-Campos 2005; Salvetti 1987; Schiffl 1991; Sherman 1990; Singhaton 2001; Soni 2000; Zuccala 1988) and one study used an inappropriate intervention (NCT02228408). See Characteristics of excluded studies.

Studies awaiting classification

NCT01394770 was registered in 2009 but never published; it was registered more than 10 years ago however its current recruitment status is listed as unknown; therefore, we have assessed it as awaiting classification.

Ongoing studies

Our search did not identify any ongoing studies.

Risk of bias in included studies

Overall, the risk of bias in the included studies are reported in Figure 2, whilst the risk of bias in each study is shown in Figure 3.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

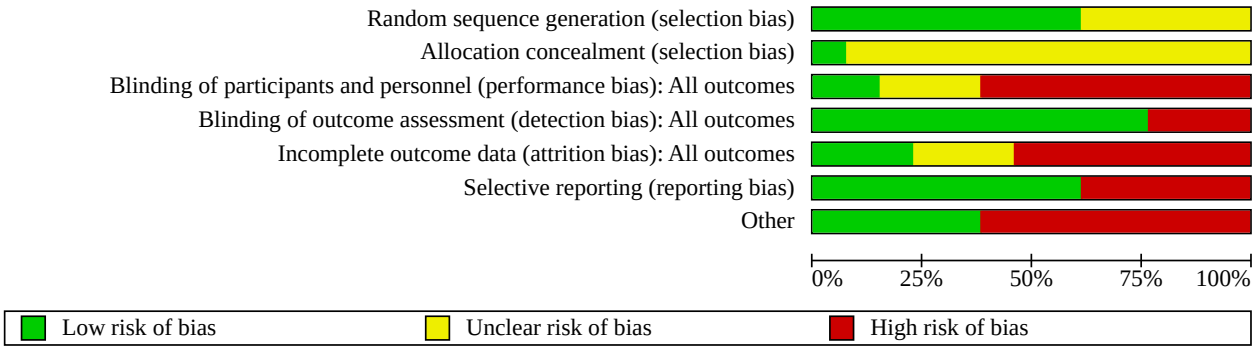
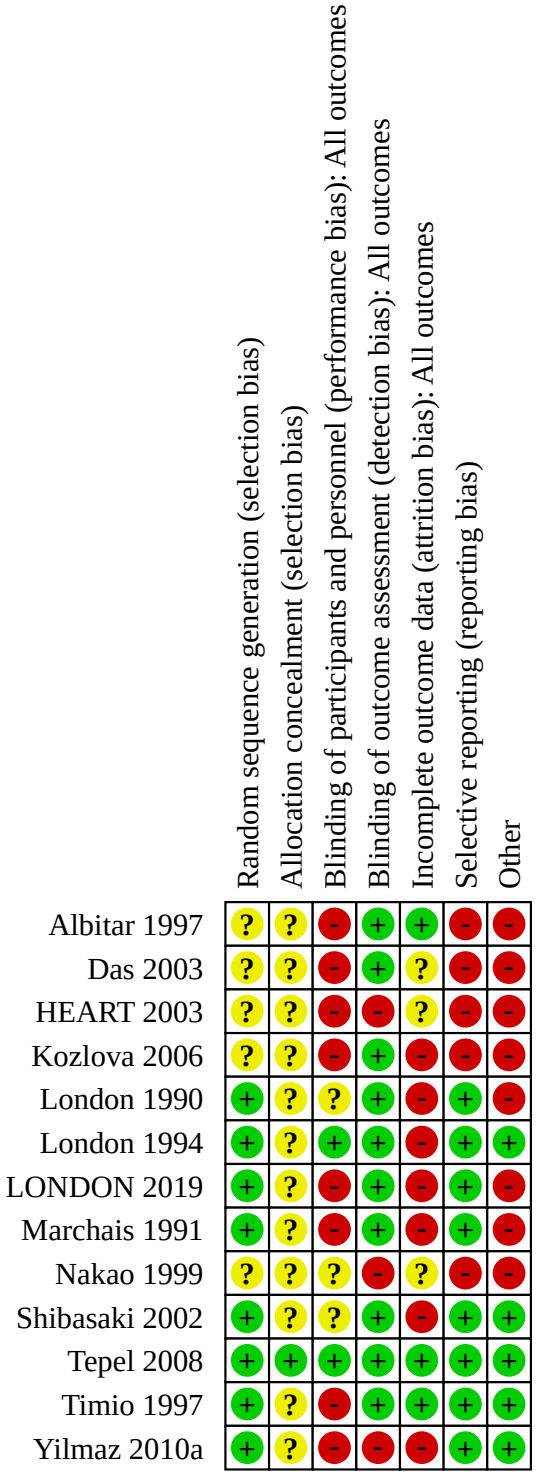


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

Random sequence generation

Eight studies were judged to be at low risk of selection bias since they reported an appropriate random sequence generation procedure (London 1990; London 1994; LONDON 2019; Marchais 1991; Shibasaki 2002; Tepel 2008; Timio 1997; Yilmaz 2010a). The remaining five studies were judged to be at unclear risk of bias (Albitar 1997; Das 2003; HEART 2003; Kozlova 2006; Nakao 1999).

Allocation concealment

Tepel 2008 was judged to be at a low risk of bias related to allocation concealment, while the remaining 12 studies were judged to be at unclear risk of bias (Albitar 1997; Das 2003; HEART 2003; Kozlova 2006; London 1990; London 1994; LONDON 2019; Marchais 1991; Nakao 1999; Shibasaki 2002; Timio 1997; Yilmaz 2010a).

Blinding

Performance bias

Two studies (London 1994; Tepel 2008) were blinded and judged to be at low risk of bias. Eight studies were not blinded and were at high risk of performance bias (Albitar 1997; Das 2003; HEART 2003; Kozlova 2006; LONDON 2019; Marchais 1991; Timio 1997; Yilmaz 2010a), while the risk of bias in three studies (London 1990; Nakao 1999; Shibasaki 2002) was judged to be uncertain.

Detection bias

Ten studies were judged to be at low risk of bias due to blinding of outcome assessors (Albitar 1997; Das 2003; Kozlova 2006; London 1990; London 1994; LONDON 2019; Marchais 1991; Shibasaki 2002; Tepel 2008; Timio 1997). There studies were adjudicated to be at high risk of detection bias (HEART 2003; Nakao 1999; Yilmaz 2010a).

Incomplete outcome data

Three studies (Albitar 1997; Tepel 2008; Timio 1997) were judged to be at low risk of attrition bias. Seven studies were considered at high risk due to incomplete outcome data (Kozlova 2006; London 1990; London 1994; LONDON 2019; Marchais 1991; Shibasaki 2002; Yilmaz 2010a). The remaining three studies were considered to be at unclear risk of bias (Das 2003; HEART 2003; Nakao 1999).

Selective reporting

Eight studies published data on all expected outcomes and were considered to be at low risk of reporting bias (London 1990; London 1994; LONDON 2019; Marchais 1991; Shibasaki 2002; Tepel 2008; Timio 1997; Yilmaz 2010a). Five studies (Albitar 1997; Das 2003; HEART 2003; Kozlova 2006; Nakao 1999) were only available as abstracts and were considered to be at high risk of bias. In addition, Kozlova 2006 failed to report some outcomes related to the control group.

Other potential sources of bias

Five studies were judged to be at low risk from other potential sources of bias (London 1994; Shibasaki 2002; Tepel 2008; Timio 1997; Yilmaz 2010a). Eight studies were assessed to be at high risk of other potential sources of bias. Three studies (London 1990; LONDON 2019, Marchais 1991) were funded by pharmaceutical companies or authors had conflict of interests, and this may have introduced some bias. Other potential sources of bias included abstract-only publications in five studies (Albitar 1997; Das 2003; HEART 2003; Kozlova 2006; Nakao 1999).

Effects of interventions

See: **Summary of findings 1** Dihydropyridine calcium channel blockers versus placebo/control in people with chronic kidney disease requiring dialysis; **Summary of findings 2** Dihydropyridine calcium channel blockers versus other antihypertensives in people with chronic kidney disease requiring dialysis; **Summary of findings 3** Dihydropyridine versus non-dihydropyridine calcium channel blockers in people with chronic kidney disease requiring dialysis

Calcium channel blockers versus placebo/control/no treatment

Five studies (Kozlova 2006; London 1990; LONDON 2019; Marchais 1991; Tepel 2008), randomising 451 adults undergoing haemodialysis, compared dihydropyridine CCBs to placebo or no treatment. The certainty of the evidence was low for all outcomes (Summary of findings 1).

Dihydropyridine CCBs may decrease predialysis systolic blood pressure level compared to placebo (Analysis 1.1 (1 study, 39 participants): MD -27.00 mmHg, 95% CI -43.33 to -10.67; *low certainty evidence*) and diastolic blood pressure level (Analysis 1.2 (2 studies, 76 participants): MD -13.56 mmHg, 95% CI -19.65 to -7.48; I^2 = 0%; *low certainty evidence*) compared to placebo or no treatment.

The effect of dihydropyridine CCBs compared to placebo or no treatment on cardiovascular death was not estimable, since no events were reported in any of the studies (Analysis 1.3: 3 studies, 124 participants).

Dihydropyridine CCBs may make little or no difference to intradialytic hypotension (Analysis 1.4: 2 studies, 287 participants): RR 0.54, 95% CI 0.25 to 1.15; I^2 = 0%;*low certainty evidence*) compared to placebo or no treatment.

Other side effects and costs were not reported by any of the included studies.

No studies compared non-dihydropyridine CCBs to placebo or control.

Calcium channel blockers versus other antihypertensives

Eight studies (Albitar 1997; Das 2003; HEART 2003; Kozlova 2006; London 1994; Nakao 1999; Shibasaki 2002; Yilmaz 2010a) randomising 1037 adults treated with haemodialysis compared dihydropyridine CCBs to other antihypertensives. Five studies (Albitar 1997; Das 2003; HEART 2003; Kozlova 2006; Nakao 1999) were abstract-only publications. Four studies (Das 2003; HEART 2003; Nakao 1999; Shibasaki 2002), while meeting our inclusion criteria, had insufficient information and were not included in the meta-analyses. The certainty of the evidence was low to very low (Summary of findings 2).

Dihydropyridine CCBs may make little or no difference to predialysis systolic (Analysis 2.1 (4 studies, 180 participants): MD 2.44 mmHg, 95% CI -3.74 to 8.62; I^2 = 0%, *low certainty evidence*) and diastolic blood pressure (Analysis 2.2 (4 studies, 180 participants):

MD 1.49 mmHg, 95% CI -2.23 to 5.21; I^2 = 0%, *low certainty evidence*) compared to other antihypertensives.

The effect of dihydropyridine CCBs compared to other antihypertensives on cardiovascular death was not estimable, since no events were reported in any of the studies (Analysis 2.3: 3 studies, 164 participants).

Yilmaz 2010a reported one case of intradialytic hypotension in the dihydropyridine CCB group (Analysis 2.4 (1 study, 92 participants): RR 2.88, 95% CI 0.12 to 68.79; *very low certainty evidence*).

Other side effects and costs were not reported by any of the included studies.

No studies compared non-dihydropyridine CCBs to other antihypertensives.

Dihydropyridine versus non-dihydropyridine calcium channel blockers

Timio 1997 compared dihydropyridine CCB to non-dihydropyridine CCB in 40 haemodialysis patients. The certainty of the evidence was low to very low (Summary of findings 3).

Timio 1997 reported may make little or no difference to predialysis systolic (Analysis 3.1 (1 study, 40 participants): MD -4.00 mmHg, 95% CI -11.99 to 3.99; *low certainty evidence*) and diastolic blood pressure level (Analysis 3.2 (1 study, 40 participants): MD -3.00 mmHg, 95% CI -7.06 to 1.06; *low certainty evidence*) between dihydropyridine and non-dihydropyridine CCB.

The effect of dihydropyridine CCB compared to non-dihydropyridine CCB on cardiovascular death was not estimable, since no events were reported in either group (Analysis 3.3: 1 study, 40 participants).

There was no evidence of a difference in other side effects (Analysis 3.4 (1 study, 40 participants): RR 0.13, 95% CI 0.01 to 2.36; *very low certainty evidence*) between dihydropyridine CCB and non-dihydropyridine CCB. Other side effects included headache.

Timio 1997 did not report intradialytic hypotension or costs.

DISCUSSION

Summary of main results

We found 13 studies that met our inclusion criteria (1459 randomised adults); five of these were available only as abstracts. Four of these studies (Das 2003; HEART 2003; Nakao 1999; Shibasaki 2002), while meeting our inclusion criteria, had insufficient information and were not included in the meta-analyses. All studies were performed in haemodialysis patients.

Random sequence generation and allocation concealment were at low risk of bias in eight and one studies, respectively. Two studies reported low risk methods for blinding of participants and investigators, and outcome assessment was blinded in 10 studies. Three studies were at low risk of attrition bias, eight studies were at low risk of selective reporting bias, and five studies were at low risk of other potential sources of bias.

Dihydropyridine CCBs may decrease predialysis systolic and diastolic blood pressure when compared to placebo or no treatment, may make little or no difference to occurrence of intradialytic hypotension, whilst the effects on cardiovascular death was uncertain.

Eight studies compared dihydropyridine CCBs with other antihypertensives. Dihydropyridine CCBs may make little or no difference to predialysis systolic and diastolic blood pressure, while the effects on cardiovascular death and occurrence of intradialytic hypotension compared to other antihypertensives were uncertain.

Dihydropyridine CCBs may make little or no difference to predialysis systolic and diastolic blood pressure, while the effects on cardiovascular death and other side effects compared to non-dihydropyridine CCBs were uncertain.

Overall completeness and applicability of evidence

This review searched for evidence supporting the use of CCBs in patients with CKD requiring dialysis. There were inadequate numbers of well conducted RCTs to answer our question conclusively.

Overall, data for carrying out the comparison between dihydropyridine CCBs and other antihypertensives came from four studies with 180 adult patients on maintenance haemodialysis (Albitar 1997; Kozlova 2006; London 1994; Yilmaz 2010a). Side effects were rarely reported (Table 1) and no studies addressed total healthcare cost. Studies done in children and in patients undergoing peritoneal dialysis were not found after an extensive literature search.

No studies compared the effect of different dihydropyridine CCBs, different non-dihydropyridine CCBs, or different doses of the same drug. No studies compared non-dihydropyridines CCBs to other antihypertensives, placebo or control.

The majority of studies included in the meta-analyses were performed in Europe; France (Albitar 1997; London 1990; London 1994; Marchais 1991), Germany (Tepel 2008), Italy (Timio 1997), Russia (Kozlova 2006), and Turkey (Yilmaz 2010a). LONDON 2019 was performed in Japan. This clearly affects the external validity of these findings, as these findings cannot be applied wholesome since clinical practice differs based on region.

The standardisation of outcomes reporting in future studies might enhance better evidence in dialysis setting. The Standardised Outcomes in Nephrology (SONG) initiative suggest that fatigue, cardiovascular disease, vascular access, and death (SONG-HD) are the core outcomes set to report in all studies in haemodialysis setting, while infection, cardiovascular disease, death, technique survival and life participation are the compulsory outcomes to assess in studies on peritoneal dialysis (SONG-PD).

Quality of the evidence

The quality of the evidence was assessed according to the recommendations of the GRADE Working Group (Higgins 2011). Overall, the quality of evidence was generally either low or very low.

Twelve studies did not report allocation concealment and most studies reported inadequate blinding of investigators and participants, attrition, and other sources of bias, reducing the certainty of treatment benefits and harms. Only Tepel 2008 was considered at low risk of bias for all domains. As many

outcomes, such as predialysis systolic and diastolic blood pressure and intradialytic hypotension, were measured using objective measures, 10 studies were at low risk of bias for outcome assessment. Heterogeneity was low across the studies included in the meta-analysis.

Potential biases in the review process

Although we applied standard Cochrane methodology, residual bias in the review process was inevitably present. It is possible that relevant but unpublished data (those studies with neutral or negative effects) may have been missed. Analysis for evidence of such publication bias was not possible due to the small number of included studies.

Four studies did not report key outcomes in a format available for meta-analysis. The included studies did not report total healthcare costs and no events were reported for cardiovascular death.

Only Timio 1997 investigated the effect of dihydropyridine versus non-dihydropyridine CCBs. Furthermore, we found no studies that involved children or people undergoing peritoneal dialysis; and 12 studies were conducted in Europe and this may limit the generalisability of our findings.

Agreements and disagreements with other studies or reviews

We found one systematic review and meta-analysis that investigated the effects of CCBs compared to ACEi or ARB in people with CKD stages 3-5 including dialysis (Lin 2017). Our Cochrane review is consistent with the findings showed in that review**,** reporting no significant differences in change in blood pressure and death between the two groups. However, differences between Lin 2017 and our updated review were related to the inclusion of patients in CKD stages 3 to 5: although the author included 21 studies, only four studies were performed in ESKD. In addition, Lin 2017 excluded studies that compared dihydropyridine CCBs to placebo, no treatment or non-dihydropyridine CCBs.

AUTHORS' CONCLUSIONS

Implications for practice

Dihydropyridine CCBs had uncertain effects on predialysis systolic and diastolic blood pressure, cardiovascular death, and occurrence of intradialytic hypotension compared to other antihypertensives. Data were provided by only a few studies with limited number of participants who experienced few events.

Dihydropyridine CCBs may reduce predialysis systolic and diastolic blood pressure levels compared to placebo or no treatment, although there was low certainty evidence; further investigation with adequately powered RCTs are needed.

Scant evidence were available to detect differences between dihydropyridine CCBs and non-dihydropyridine CCBs and no data were available to compare different doses or the efficacy of different medications from the same drug class. Other side effects were rarely reported and no studies addressed costs. No data for treatment effects in children and in peritoneal dialysis were identified.

Implications for research

Future RCTs with adequate sample size and longer follow-up are required to assess the benefits and harms of dihydropyridine and non-dihydropyridine CCBs compared to other antihypertensives, placebo or control in patients with CKD requiring dialysis. Furthermore, research in children and in patients treated with peritoneal dialysis are needed. We recommend these adequately powered prospective RCTS be undertaken. Key outcomes relevant for patients (including death and cardiovascular disease), changes in blood pressure, health care costs and side effects should be reported to assist clinical decision-making.

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REFERENCES

References to studies included in this review

Albitar 1997 *{published data only}*

Albitar S, Genin R, Fen-Chong M, Scholhn D, Serveaux MO, Chuet C. Impact of ACE inhibitors on erythropoiesis in haemodialysis (HD) populations [abstract]. *Nephrology Dialysis Transplantation* 1997;**12**(9):A190. [CENTRAL: CN-00261441]

* Albitar S, Genin R, Fen-Chong M, Serveaux MO, Chuet C. Enalapril versus nifedipine in patients on maintenance haemodialysis (HD) with erythropoietin-induced hypertension (HT) [abstract]. *Nephrology* 1997;**3**(Suppl 1):S515.

Das 2003 *{published data only}*

Das B, Mishra TK, Routray SN, Behera M. Left ventricular mass regression in patients with end-stage renal disease [abstract no: 71]. *Indian Heart Journal* 2003;**55**(5). [CENTRAL: CN-00716126]

HEART 2003 *{published data only}*

* Nakao N, Takeshi U, Atsushi T, Takada M, Kimura G. Effects of blood pressure lowering and antihypertensive drug class on cardiovascular events of hemodialysis patients results from HEmodialysis Angiotensin-inhibition Rescue Trial (HEART) [abstract no: W515]. *Nephrology Dialysis Transplantation* 2003;**18**(Suppl 4):711.

Nakao N, Usami T, Fukuda M, Yoshida A, Kimura G. Effects of blood pressure lowering and antihypertensive drug class on cardiovascular events of hemodialysis patients: results from HEmodialysis Angiotensin-inhibition Rescue Trial (HEART) [abstract no: SA-FC183]. *Journal of the American Society of Nephrology* 2003;**14**(Nov):40A. [CENTRAL: CN-00446901]

Kozlova 2006 *{published data only}*

Kozlova T, Ermolenko V, Shutov E. Effects of perindopril, amlodipine and combination of perindopril and amlodipine on left ventricular mass and diastolic function in non-diabetic haemodialysis patients with hypertension [abstract no: MP408]. *Nephrology Dialysis Transplantation* 2006;**21**(Suppl 4):iv436.

London 1990 *{published data only}*

London GM, Marchais SJ, Guerin AP, Metivier F, Safar ME, Fabiani F, et al. Salt and water retention and calcium blockade in uremia. *Circulation* 1990;**82**(1):105-13. [MEDLINE: 2364508]

London 1994 *{published data only}*

London GM, Pannier B, Guerin AP, Marchais SJ, Safar ME, Cuche JL. Cardiac hypertrophy, aortic compliance, peripheral resistance, and wave reflection in end-stage renal disease. Comparative effects of ACE inhibition and calcium channel blockade. *Circulation* 1994;**90**(6):2786-96. [MEDLINE: 7994822]

LONDON 2019 *{published data only}*

Fujimoto N, Ito T, Ishikawa E, Dohi K, Kiyohara M, Takeuchi H, et al. Effects of l/n-type calcium channel blocker cilnidipine on ambulatory blood pressure and blood pressure variability in patients with intradialytic hypertension [abstract]. *Nephrology Dialysis Transplantation* 2017;**32**(Suppl 3):iii51-iii5. [EMBASE: 617290855]

Ito T, Fujimoto N, Ishikawa E, Dohi K, Fujimoto M, Murata T, et al. The effect of an L/N-type calcium channel blocker on intradialytic blood pressure in intradialytic hypertensive patients. *Clinical & Experimental Hypertension* 2019;**41**(1):92-9. [MEDLINE: 29584458]

Ito T, Fujimoto N, Ishikawa E, Dohi K, Kiyohara M, Takeuchi H, et al. The effect of cilnidipine on intradialytic blood pressure in intradialytic hypertensive patients: A multicenter, prospective, randomized, open-label study [abstract]. *Nephrology Dialysis Transplantation* 2017;**32**(Suppl 3):iii472. [EMBASE: 617291253]

Marchais 1991 *{published data only}*

* Marchais SJ, Boussac I, Guerin AP, Delavaux G, Metivier F, London GM. Arteriosclerosis and antihypertensive response to calcium antagonists in end-stage renal failure. *Journal of Cardiovascular Pharmacology* 1991;**18 Suppl 1**:S74-8. [MEDLINE: 1723463]

Marchais SJ, Boussac I, Guerin AP, Delavaux G, Metivier F, London GM. Arteriosclerosis and antihypertensive response to calcium antagonists in end-stage renal failure. *Journal of Cardiovascular Pharmacology* 1991;**18 Suppl 5**:S14-8. [MEDLINE: 1725796]

Nakao 1999 *{published data only}*

Nakao N, Ohsaki S, Takada M, Takahashi T, Kayano T. Trandolapril compared with slow-releasing nifedipine not only reduced mortality but also improved QOL of hypertensive hemodialysis patients [abstract no: A1854]. *Journal of the American Society of Nephrology* 1999;**10**(Program & Abstracts):368A.

Shibasaki 2002 *{published data only}*

Shibasaki Y, Masaki H, Nishiue T, Matsubara H, Nishikawa M, Iwasaka T. Angiotensin II type-1 receptor antagonist losartan has greater anti-fibrotic effect than ACE inhibitor in patients with end stage renal disease [abstract]. *Nephrology Dialysis Transplantation* 2001;**16**(6):A128. [CENTRAL: CN-00447711]

Shibasaki Y, Masaki H, Nishiue T, Nishikawa M, Matsubara H, Iwasaka T. Angiotensin II type 1 receptor antagonist, losartan, causes regression of left ventricular hypertrophy in end-stage renal disease. *Nephron* 2002;**90**(3):256-61. [MEDLINE: 11867945]

Shibasaki Y, Masaki H, Nishiue T, Nishikawa M, Takahashi H, Matsubara H, et al. Angiotensin II receptor antagonist suppress left ventricular hypertrophy and fibrosis in patients with end stage renal disease [abstract]. *Journal of the American Society of Nephrology* 2001;**12**(Program & Abstracts):245A. [CENTRAL: CN-00447712]

Shibasaki Y, Nishiue T, Masaki H, Matsubara H, Iwasaka T. Angiotensin II type 1 antagonist suppress left ventricular hypertrophy and myocardial fibrosis in patient with end stage renal disease (ESRD). *Nippon Rinsho [Japanese Journal of Clinical Medicine]* 2002;**60**(10):1992-8. [MEDLINE: 12397697]

* Shibasaki Y, Nishiue T, Masaki H, Tamura K, Matsumoto N, Mori Y, et al. Impact of the angiotensin II receptor antagonist, losartan, on myocardial fibrosis in patients with end-stage

renal disease: assessment by ultrasonic integrated backscatter and biochemical markers. *Hypertension Research - Clinical & Experimental* 2005;**28**(10):787-95. [MEDLINE: 16471172]

Tepel 2008 *{published data only}*

Tepel M, Hopfenmueller W, Scholze A, Maier A, Zidek W. Effect of amlodipine on cardiovascular events in hypertensive haemodialysis patients. *Nephrology Dialysis Transplantation* 2008;**23**(11):3605-12. [MEDLINE: 18511605]

Timio 1997 *{published data only}*

Timio M, Verdura C, Lolli S, Lupparelli A. A comparative study of amlodipine and verapamil in hypertensive patients undergoing haemodialysis. *Clinical Drug Investigation* 1997;**13**(Suppl 1):73-6. [EMBASE: 27361661]

Yilmaz 2010a *{published data only}*

Yilmaz R, Altun B, Arici M, Akinci D, Ozer N, Erdem Y, et al. Effects of amlodipine and ramipril on cardiovascular system in hemodialysis patients [abstract no: PUB407]. *Journal of the American Society of Nephrology* 2005;**16**:870A.

* Yilmaz R, Altun B, Kahraman S, Ozer N, Akinci D, Turgan C. Impact of amlodipine or ramipril treatment on left ventricular mass and carotid intima-media thickness in nondiabetic hemodialysis patients. *Renal Failure* 2010;**32**(8):903-12. [MEDLINE: 20722555]

Yilmaz R, Kahraman S, Altun B, Genctoy G, Akinci D, Ozer N, et al. Effects of amlodipine and ramipril on left ventricular mass index and carotid atherosclerosis in hemodialysis patients [abstract]. In: 41st Congress. European Renal Association. European Dialysis and Transplantation Association; 2004 May 15-18; Lisbon, Portugal. 2004:352. [CENTRAL: CN-00509571]

References to studies excluded from this review

Aslam 2006 *{published data only}*

Aslam S, Santha T, Leone A, Wilcox C. Effects of amlodipine and valsartan on oxidative stress and plasma methylarginines in end-stage renal disease patients on hemodialysis. *Kidney International* 2006;**70**(12):2109-15. [MEDLINE: 17063175]

Santha T, Aslam S, Gonin J, Llach F, Umans J, Wilcox CS. The effects of valsartan and amlodipine therapy on oxidative stress and L-arginine metabolism in patients on maintenance hemodialysis: a randomized double-blind crossover study [abstract no: SA-FC092]. *Journal of the American Society of Nephrology* 2005;**16**:102A.

Atabak 2013 *{published data only}*

Atabak S, Taziki O, Argani H, Abolghasemi R, Zangneh HF, Rahmani L. Effects of oral enalapril and verapamil on dialysis adequacy and solute clearance in chronic ambulatory peritoneal dialysis. *Saudi Journal of Kidney Diseases & Transplantation* 2013;**24**(6):1170-74. [MEDLINE: 24231479]

Cice 1997 *{published data only}*

Cice G, Di Benedetto A, Tagliamonte E, Ferrara L, Sorice P, Iacono A. Effectiveness and tolerability of bisoprolol vs. nifedipine in uremic patients with ischemic cardiopathy in dialysis treatment [Efficacia e tollerabilita di bisoprololo e nifedipina in pazienti uremici con cardiopatia ischemica in trattamento dialitico]. *Cardiologia* 1997;**42**(4):397-403. [MEDLINE: 9244644]

Cice 1998 *{published data only}*

Cice G, Ferrara L, Tagliamonte E, Di Benedetto A, Iacono A. Incremental doses of diltiazem in patients with coronary artery disease in end-stage renal failure maintained on hemodialysis: which is the optimal dose? [Diltiazem a dosaggi crescenti in pazienti uremici emodializzati con cardiopatia ischemica: qual e il dosaggio ottimale?]. *Cardiologia* 1998;**43**(12):1337-43. [MEDLINE: 9988942]

Cice 2003 *{published data only}*

Cice G, Di Benedetto A, D'Andrea A, D'Isa S, Ferrara L, Russo PE, et al. Sustained-release diltiazem reduces myocardial ischemic episodes in end-stage renal disease: a double-blind, randomized, crossover, placebo-controlled trial. *Journal of the American Society of Nephrology* 2003;**14**(4):1006-11. [MEDLINE: 12660335]

EDIT 2011 *{published data only}*

Iqbal MM, Nahar N, Chowdhury AA, Ahmed S, Alam KS, Khan MF, et al. Efficacy of enalapril and sustained-release nifedipine in controlling blood pressure of patients on maintenance hemodialysis: observations from ongoing EDIT trial [abstract]. *Hemodialysis International* 2011;**15**(1):141-2. [EMBASE: 70587180]

Kojima 2004 *{published data only}*

Kojima M, Taniguchi M, Sato K, Ueda R, Dohi Y. Antihypertensive effects of long-acting calcium channel blockers on hemodialysis days--a randomized crossover trial between benidipine and nifedipine. *Nephron* 2004;**97**(2):c49-53. [MEDLINE: 15218330]

Nakano 2010 *{published data only}*

Nakano N, Ishimitsu T, Takahashi T, Inada H, Okamura A, Ohba S, et al. Effects of efonidipine, an L- and T-type calcium channel blocker, on the renin-angiotensin-aldosterone system in chronic hemodialysis patients. *International Heart Journal* 2010;**51**(3):188-92. [MEDLINE: 20558909]

NCT02228408 *{published data only}*

Charytan D. A phase IV randomized, double-blind, active-controlled, single-center study of the safety and effects on cardiac structure and function of hydralazine and isosorbide dinitrate in patients with hemodialysis dependent ESRD. www.clinicaltrials.gov/ct2/show/NCT02228408 (first received 26 August 2014).

Rojas-Campos 2005 *{published data only}*

Rojas-Campos E, Cortes-Sanabria L, Martinez-Ramirez HR, Gonzalez L, Martin-del-Campo F, Gonzalez-Ortiz M, et al. Effect of oral administration of losartan, prazosin, and verapamil on peritoneal solute transport in continuous ambulatory peritoneal dialysis patients. *Peritoneal Dialysis International* 2005;**25**(6):576-82. [MEDLINE: 16411525]

Rojas-Campos E, Martinez-Ramirez H, Cortes-Sanabria L, Camacho R, Martin-del-Campo F, Cueto-Manzano AM. Oral

verapamil increases ultrafiltration and peritoneal small solute clearance of CAPD patients [abstract no: SA-FC130]. *Journal of the American Society of Nephrology* 2005;**16**:110A. [CENTRAL: CN-00583927]

Rojas-Campos E, Martinez-Ramirez H, Cortes-Sanabria L, Zavala-Sanchez A, Camacho-Miramontes R, del Campo FM, et al. Oral verapamil increases ultrafiltration and peritoneal small solute clearance of continuous ambulatory peritoneal dialysis (CAPD) patients [abstract no: MP448]. *Nephrology Dialysis Transplantation* 2005;**20**(Suppl 5):v349.

Salvetti 1987 *{published data only}*

Salvetti A, Bozzo MV, Graziola M, Abdel-Haq B. Acute hemodynamic effect of nifedipine in hypertensives with chronic renal failure: the influence of volume status. *Journal of Cardiovascular Pharmacology* 1987;**10 Suppl 10**:S143-6. [MEDLINE: 2455118]

Schiffl 1991 *{published data only}*

Schiffl H, Strasser T. Hemodialysis-related leukotriene B4 generation and neutropenia during calcium channel blockade. *Biomaterials, Artificial Cells, & Immobilization Biotechnology* 1991;**19**(1):85-96. [MEDLINE: 1721550]

Sherman 1990 *{published data only}*

Sherman RA, Casale P, Cody R, Horton M. Effect of pre-dialysis verapamil (V) on blood pressure (BP) during hemodialysis (HD) [abstract]. *Kidney International* 1990;**37**(1):319.

Sherman RA, Casale P, Cody R, Horton MW. Effect of predialysis verapamil on intradialytic blood pressure in chronic hemodialysis patients. *American Society for Artificial Internal organs* 1990;**36**(2):67-9. [MEDLINE: 2340210]

Singhaton 2001 *{published data only}*

Singhaton S, Supaporn T, Karnchanakoon I, Supasindhu O, Choowichian P, Luwira U. Differential blood pressure between daily morning versus evening dose of amlodipine assessed by ambulatory blood pressure monitoring [abstract]. *Journal of the American Society of Nephrology* 2001;**12**(Program & Abstracts):491A.

Soni 2000 *{published data only}*

Soni JK, Brier ME, Ouseph R, Aronoff GR. Supervised antihypertensive pharmacotherapy in hemodialysis patients [abstract]. *Journal of the American Society of Nephrology* 2000;**11**(Sept):355A.

Zuccala 1988 *{published data only}*

Zuccala A, Santoro A, Ferrari G, Zucchelli P. Pathogenesis of hypertension in hemodialysis patients: a pharmacological study. *Kidney International - Supplement* 1988;**34**(25):S190-1. [MEDLINE: 3054237]

References to studies awaiting assessment

NCT01394770 *{published data only}*

Cice G. Cardiovascular events in hypertensive hemodialysed patients: aliskiren versus amlodipine. a randomized, double-blind study. www.clinicaltrials.gov/ct2/show/NCT01394770 (first received 13 July 2011).

Additional references

Agarwal 2003

Agarwal R, Nissenson AR, Batlle D, Coyne DW, Trout JR, Warnock DG. Prevalence, treatment, and control of hypertension in chronic hemodialysis patients in the United States. *American Journal of Medicine* 2003;**115**(4):291-7. [MEDLINE: 12967694]

Almaguer 2014

Almaguer M, Herrera R, Orantes CM. Chronic kidney disease of unknown etiology in agricultural communities. *MEDICC Review* 2014;**16**(2):9-15. [MEDLINE: 24878644]

Basile 2004

Basile J. The role of existing and newer calcium channel blockers in the treatment of hypertension. *Journal of Clinical Hypertension* 2004;**6**(11):621-9. [MEDLINE: 15538095]

Chobanian 2003

Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, et al. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Hypertension* 2003;**42**(6):1206-52. [MEDLINE: 14656957]

Dipiro 2011

Dipiro J, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM. Chronic kidney disease: progression - modifying therapies. In: Michael Weitz, Karen G Edmonson, editors(s). Pharmacotherapy a Pathophysiologic Approach. 8th edition. New York: McGraw Hill, 2011:767-86.

Eknoyan 2013

Eknoyan G, Lameire N, Eckardt K, Kasiske B, Wheeler D, Abboud O, et al. KDIGO 2012 clinical practice guidelines for the evaluation and management of chronic kidney disease. *Kidney International - Supplement* 2013;**3**(1):1-150. [DOI: 10.1038/kisup.2012.73]

GRADE 2008

Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008;**336**(7650):924-6. [MEDLINE: 18436948]

Hart 2008

Hart P, Bakris GL. Calcium antagonists: do they equally protect against kidney injury? *Kidney International* 2008;**73**(7):795-6. [MEDLINE: 18340349]

Higgins 2011

Higgins JP, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Inrig 2010

Inrig JK. Antihypertensive agents in hemodialysis patients: a current perspective. *Seminars in Dialysis* 2010;**23**(3):290-7. [MEDLINE: 20374548]

Jha 2013

Jha V. Current status of end-stage renal disease care in India and Pakistan. *Kidney International - Supplement* 2013;**3**(2):S157-60. [DOI: 10.1038/kisup.2013.3]

Levey 2003

Levey AS, Coresh J, Balk M, Kausz AT, Levin A, Steffes MW, et al. National Kidney Foundation practice guidelines for chronic kidney disease: evaluation, classification, and stratification. [Erratum appears in Ann Intern Med. 2003 Oct 7;139(7):605]. *Annals of Internal Medicine* 2003;**139**(2):137-47. [MEDLINE: 12859163]

Lin 2017

Lin YC, Lin JW, Wu MS, Chen KC, Peng CC, Kang YN. Effects of calcium channel blockers comparing to angiotensin-converting enzyme inhibitors and angiotensin receptor blockers in patients with hypertension and chronic kidney disease stage 3 to 5 and dialysis: A systematic review and meta-analysis. *Plos One* 2017;**12**(12):e0188975. [MEDLINE: 29240784]

Maritim 2007

Maritim M. Prevalance of peripheral arterial disease among chronic kidney disease patients at Kenyatta National Hospital [MMed Thesis]. Nairobi (Kenya): University of Nairobi, 2007.

Onuigbo 2009

Onuigbo MA. Analytical review of the evidence for renoprotection by renin-angiotensin-aldosterone system blockade in chronic kidney disease - a call for caution. *Nephron* 2009;**113**(2):c63-70. [MEDLINE: 19602900]

Rajula 2009

Rajula A. Prevalence of hypertension and adequacy of its control in chronic kidney disease patients at the renal clinic at Kenyatta National Hospital [MMed Thesis]. Nairobi (Kenya): University of Nairobi, 2009.

Ruilope 2008

Ruilope LM. Angiotensin receptor blockers: RAAS blockade and renoprotection. *Current Medical Research & Opinion* 2008;**24**(5):1285-93. [18366863]

Schunemann 2011a

Schünemann HJ, Oxman AD, Higgins JP, Vist GE, Glasziou P, Guyatt GH. Chapter 11: Presenting results and 'Summary of findings' tables. In: Higgins JP, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Schunemann 2011b

Schünemann HJ, Oxman AD, Higgins JP, Deeks JJ, Glasziou P, Guyatt GH. Chapter 12: Interpreting results and drawing conclusions. In: Higgins JP, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Sica 2005

Sica DA. Calcium channel blocker class heterogeneity; select aspects of pharmacokinetics and pharmacodynamics. *Journal of Clinical Hypertension* 2005;**7**(4 Suppl 1):21-6. [MEDLINE: 15858399]

SONG-HD

SONG Initiative. Standardised outcomes in nephrology. www.songinitiative.org/projects/song-hd/ (accessed 21 August 2020).

SONG-PD

SONG Initiative. Standardised outcomes in nephrology. www.songinitiative.org/projects/song-pd/ (accessed 21 August 2020).

Van Buren 2012

Van Buren PN, Toto R, Inrig JK. Interdialytic ambulatory blood pressure in patients with intradialytic hypertension. *Current Opinion in Nephrology & Hypertension* 2012;**21**(1):15-23. [MEDLINE: 22123207]

Wanigasuriya 2014

Wanigasuriya K. Update on uncertain etiology of chronic kidney disease in Sri Lanka's north central dry zone. *MEDICC Review* 2014;**16**(2):61-5. [MEDLINE: 24878651]

References to other published versions of this review

Mugendi 2014

Mugendi GA, Strippoli GF, Mutua FM, Esterhuizen TM. Calcium channel blockers for people with chronic kidney disease requiring dialysis. *Cochrane Database of Systematic Reviews* 2014, Issue 4. Art. No: CD011064. [DOI: 10.1002/14651858.CD011064]

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Albitar 1997

Study characteristics	
Methods	• Study design: parallel RCT

Albitar 1997 *(Continued)*

	• Duration of study: 12 months • Duration of follow-up: 12 months
Participants	• Country: France • Setting: multicentre • Inclusion criteria: patients with rHuEPO-induced hypertension • Number (analysed/randomised): treatment group (20/20); control group (20/20) • Mean age ± SD (years): not reported • Sex (M/F): not reported • Exclusion criteria: not reported
Interventions	Treatment group (dihydropyridine CCB) • Nifedipine (oral): 60 mg/day for 12 months Control group (ACEi) • Enalapril (oral): 20 mg/day for 12 months
Outcomes	• SBP assessed at baseline and at end of treatment • DBP assessed at baseline and at end of treatment • Hb assessed at baseline and at end of treatment • rHuEPO use assessed at baseline and at end of treatment • LVMI assessed at baseline and at end of treatment • Death (no death reported in the reason for attrition) assessed during the study period
Notes	• This study had 3 arms; 3rd arm was 20 non-randomised normotensive rHuEPO-dependent patients • Abstract-only publication • Funding source: not reported • It is unclear if SD or SE had been reported for BP; as these results were much lower than all other studies we decided that SE had been reported and we have converted these to SD

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised; method of randomisation was not reported. It was not possible to assess if differences between intervention groups could suggest a problem with the randomisation process
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not reported. However due to the difference between the intervention group and control group, it was possible that participants and/or investigators were aware of the treatment assignment
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Objective outcomes were assessed
Incomplete outcome data (attrition bias) All outcomes	Low risk	QUOTE: "All patients completed the study period without any intercurrent events"

Albitar 1997 *(Continued)*

Selective reporting (reporting bias)	High risk	No full-text publication identified to assess the possible selective reporting
Other	High risk	Abstract-only publication

Das 2003

Study characteristics

Methods	• Study design: not reported; patients divided into 2 groups • Duration of study: 3 months • Duration of follow-up: 3 months
Participants	• Country: India • Setting: not reported • Inclusion criteria: ESKD patients undergoing haemodialysis with hypertension having increased left ventricular mass • Number (analysed/randomised): treatment group (not reported/24); control group (not reported/23) • Mean age ± SD (years): not reported • Sex (M/F): not reported • Exclusion criteria: not reported
Interventions	Treatment group (dihydropyridine CCB) • Lercanidipine (oral): 5 to 10 mg/day for 3 months Control group (ARB) • Telmisartan (oral): 20 to 40 mg/day for 3 months
Outcomes	• LVH assessed at the beginning and at end of treatment • Change in BP assessed during the study
Notes	• Abstract-only publication • Funding source: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not reported. However due to the difference between the intervention group and control group, it was possible that participants and/or investigators were aware of the treatment assignment
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Objective outcomes were assessed

Das 2003 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Selective reporting (reporting bias)	High risk	No full-text publication identified to assess the possible selective reporting
Other	High risk	Abstract-only publication

HEART 2003

Study characteristics

Methods	• Study design: parallel RCT (two-by-two factorial design) • Duration of study: not reported • Duration of follow-up: 4.1 to 8.4 years
Participants	• Country: Japan • Setting: single centre • Inclusion criteria: HD patients (4-hour HD 3 times/week) • Number (analysed/randomised): treatment group (not reported/248); control group (not reported/250) • Mean age ± SD (years): not reported • Sex (M/F): not reported • Exclusion criteria: not reported
Interventions	Treatment group (dihydropyridine CCB) • Amlodipine (oral): 5 to 20 mg/day Control group (ACEi) • Trandolapril (oral): 0.5 to 4 mg/day
Outcomes	• Cardiovascular death assessed during the study period • Death (any cause) and morbidity assessed during the study period • Stroke assessed during the study period • Combined chronic heart failure (primary outcome, coronary revascularization, or angina with hospitalisation) assessed during the study period • Combined CVD (combined CHD, stroke, treated angina without hospitalisation, heart failure, and PVD) assessed during the study period
Notes	• Abstract-only publications • Funding source: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised method of randomisation was not reported. It was not possible to assess if differences between intervention groups could suggest a problem with the randomisation process

HEART 2003 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not reported. However due to the difference between the intervention group and control group, it was possible that participants and/or investigators were aware of the treatment assignment
Blinding of outcome assessment (detection bias) All outcomes	High risk	There was no information if an external panel adjudicated outcomes
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Selective reporting (reporting bias)	High risk	No full-text publication identified to assess the possible selective reporting
Other	High risk	Abstract-only publications

Kozlova 2006

Study characteristics	
Methods	• Study design: prospective parallel RCT • Duration of study: 6 months • Duration of follow-up: 6 months
Participants	• Country: Russia • Setting: single centre • Inclusion criteria: non-diabetic patients undergoing HD with predialysis free day BP > 140/90 mmHg, hypertension stage I-III (according with the WHO classification) • Number (analysed/randomised): treatment group 1 (16/not reported); treatment group 2 (16/not reported); control group 1 (16/not reported); control group 2 (21/not reported) • Mean age ± SD: 36.5 ± 12.7 years • Sex (M/F): 39/32 • Exclusion criteria: not reported
Interventions	Treatment group 1 (dihydropyridine CCB) • Amlodipine (oral): 5 to 10 mg/day for 6 months Treatment group 2 (dual therapy; ACEi + dihydropyridine CCB) • Perindopril (oral): 4 to 6 mg/day for 6 months • Amlodipine (oral): 5 to 10 mg/day for 6 months Control group 1 (ACEi) • Perindopril (oral): 4 to 6 mg/day for 6 months Control group 2 • No antihypertensive treatment

Kozlova 2006 *(Continued)*

Outcomes	• LVMI assessed at baseline and end of treatment • SBP assessed at baseline and end of treatment • DBP assessed at baseline and end of treatment • Ecocardiography assessed at baseline and end of treatment
Notes	• Abstract-only publication • Funding source: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised; method of randomisation was not reported. It was not possible to assess if differences between intervention groups could suggest a problem with the randomisation process
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not reported. However due to the difference between the intervention group and control group, it was possible that participants and/or investigators were aware of the treatment assignment
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Objective outcomes were assessed
Incomplete outcome data (attrition bias) All outcomes	High risk	Abstract states 71 patients included, however only 69 accounted for
Selective reporting (reporting bias)	High risk	No full-text publication identified to assess the possible selective reporting. Not all data related to the control group were reported
Other	High risk	Abstract-only publication

London 1990

Study characteristics

Methods	• Study design: double-blind, parallel RCT • Duration of study: treatment administered for 24 weeks • Duration of follow-up: 16 weeks for placebo group and 24 weeks for treatment group (only haemodynamic evaluation)
Participants	• Country: France • Setting: single centre • Inclusion criteria: patients with ESKD treated with HD 3 times/week for at least 6 months and median BP > 160/95 mmHg • Number (analysed/randomised): treatment group (20/20); control group (19/20) • Mean age ± SD (years): treatment group (57.0 ± 10.6); control group (57.4 ± 11.9) • Sex (M/F): overall (19/20); treatment group (10/10); control group (9/10)

London 1990 *(Continued)*

	• Exclusion criteria: acute MI; valvular heart disease; PVD; cerebral vascular disease; decompensated heart failure
Interventions	Treatment group (dihydropyridine CCB) • Nitrendipine (oral): 20 mg/day or twice daily after the 8th week of treatment for 24 weeks Control group • Placebo (oral): tablet once/day or twice daily after the 8th week of treatment for 24 weeks
Outcomes	• Pre- and postdialysis BP assessed at baseline, 8 and 16 weeks (only treatment group reported data at 24 weeks but due to the lack of a control group, the results were only descriptive) • Heart rate assessed at baseline, 8 and 16 weeks (only treatment group reported data at 24 weeks but due to the lack of a control group, the results were only descriptive) • Changes in pulse wave velocity and aortic diameter assessed at baseline and at 16 weeks (only treatment group reported data at 24 weeks but due to the lack of a control group, the results were only descriptive) • Changes in LVM and ejection fraction assessed at baseline and at 16 weeks (only treatment group reported data at 24 weeks but due to the lack of a control group, the results were only descriptive) • Change in body weight and blood chemistry assessed at baseline and at 16 weeks (only treatment group reported data at 24 weeks but due to the lack of a control group, the results were only descriptive) • Death (no death reported in the reason for attrition) assessed during the study period • Drop out assessed during the study period • Postdialysis hypotension assessed during the study period • Interdialytic body weight gain assessed during the study period
Notes	• Funding source: the Groupe d'Etudes de Physiopathologie de l'Insuffisance Renale (GEPIR) and Bayer Pharma

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	QUOTE: "Patients who did not respond were divided into two groups of 20, according to a randomisation list and with a balance every two patients." Study was described as randomised, method of randomisation was not reported. However, it was unlikely that differences between intervention groups could suggest a problem with the randomisation process
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"Double blind". However, insufficient information to permit judgement
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Objective outcomes were assessed
Incomplete outcome data (attrition bias) All outcomes	High risk	QUOTE: "At the 24th week, due to the lack of a control group, the results of the group of patients taking nitrendipine are only descriptive."

London 1990 *(Continued)*

		QUOTE: "One patient of the group taking placebo dropped out of the study after 4 weeks for DBP persistently higher than 114 mm Hg. Therefore, the analysis included only the remaining 19 patients."
Selective reporting (reporting bias)	Low risk	All outcomes prespecified were reported
Other	High risk	Commercial funding: Bayer Pharma

London 1994

Study characteristics	
Methods	• Study design: parallel RCT • Duration of study: 12 months • Duration of follow-up: 12 months
Participants	• Country: France • Setting: single centre • Inclusion criteria: stable HD (dialysed 3 times/week) patients whose median predialysis BP for the 6 months preceding their inclusion was > 160/95 mmHg with LVH, > 18 years • Number (analysed/randomised): treatment group (10/16), control group (14/16) • Mean age ± SD (years): treatment group (51.7 ± 15.5); control group (54.7 ± 10.1) • Sex (M/F): treatment group (7/3); control group (7/7) • Exclusion criteria: acute MI, valvular heart disease, PVD, cerebral vascular disease, decompensated heart failure
Interventions	Treatment group (dihydropyridine CCB) • Nitrendipine (oral): 20 mg orally once daily or 40 mg once daily after the 6th week of treatment for 12 months if the DBP> 95 mmHg Control group (ACEi) • Perindopril (oral): 2 mg orally administered once after each HD session or 4 mg once orally after the 6th week of treatment for 12 months if the DBP > 95 mmHg
Outcomes	• BP assessed at baseline and at 3, 6, 9, 12 months • LVM assessed at baseline and at 6 and 12 months • LV end-diastolic diameter assessed at baseline and at 6 and 12 months • Cardiac output (aortic cross-section and velocity integral) assessed at baseline and at 6 and 12 months • Stroke index assessed at baseline and at 6 and 12 months • Pulse rate assessed at baseline and at 6 and 12 months • Total peripheral resistance (cardiac output and mean BP) assessed at baseline and at 6 and 12 months • Aortic and large-artery compliance (pulse wave velocity) assessed at baseline and at 6 and 12 months • Arterial wave reflections assessed at baseline and at 6 and 12 months • Plasma renin activity, aldosterone, and plasma catecholamine level assessed at baseline and at 6 and 12 months • Death (no death reported in the reason for attrition) assessed during the study period • Change in body weight assessed during the study period • Serious adverse events assessed during the study period
Notes	• Funding source: the Groupe d'Etule de la Physiopathologie de l'Insuffisance Renale (GEPIR) and the Institut de Recherches International Serviier (IRIS)

London 1994 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	QUOTE: "After this run-in placebo period, patients were divided into two groups of 16 according to a randomisation list." Study was described as randomised, method of randomisation was not reported. However, it was unlikely that differences between intervention groups could suggest a problem with the randomisation process
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	QUOTE: "After randomisation at day 0 (baseline), patients received either 20 mg nitrendipine once daily or perindopril 2 mg after each haemodialysis session (3 times weekly). Perindopril was presented similarly to nitrendipine, i.e. in blister packs containing 7 pills (1 week of treatment). Only the pills corresponding to the day of haemodialysis contained perindopril; the other pills contained placebo." QUOTE: "Double blind"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Objective outcomes were assessed
Incomplete outcome data (attrition bias) All outcomes	High risk	QUOTE: "Thirty-two patients were included, 16 in each group. One patient of the nitrendipine group was excluded from the study after 3 weeks of treatment for noncompliance with medication schedule, and a second patient from this group had renal transplantation after 5 weeks of treatment. Six patients (4 patients on nitrendipine and 2 on perindopril) were withdrawn from the study at 6 months because of a predialysis DBP higher than 95 mmHg. The 1-year study was completed by 10 patients on nitrendipine and by 14 on perindopril."
Selective reporting (reporting bias)	Low risk	All outcomes prespecified were reported
Other	Low risk	QUOTE: "This study was supported by the Groupe d'Etude de la Physiopathologie de l'Insuffisance Renale (G.E.P.I.R.) and the Institut de Recherches International Servier (I.R.I.S.)." The study seemed to be free from other source of bias

LONDON 2019

Study characteristics

Methods	• Study design: open-label, parallel RCT • Study duration: 12 weeks • Study follow-up: 12 weeks
Participants	• Country: Japan • Setting: multicentre (3 sites) • Inclusion criteria: hospital outpatients undergoing HD 3 times/week, > 20 years; ability to provide consent; confirmation of proper fluid volume; presence of intradialytic hypertension (defined as an increase in the SBP from pre-HD to post-HD ≥ 10 mmHg) occurring in ≥ 4 of 6 consecutive HD sessions.

LONDON 2019 *(Continued)*

	"Proper fluid volume" was defined as having a post-HD blood sample with a human atrial natriuretic peptide ≤ 100 pg/mL, or a cardiothoracic ratio of ≤ 55% on a post-HD chest X-ray • Number (analysed/randomised): treatment group (25/33); control group (11/18) • Mean age ± SD (years): treatment group (69 ± 10); control group (75 ± 9.9) • Sex (M/F): overall (23/13); treatment group (16/9); control group (7/4) • Exclusion criteria: predialysis SBP ≤ 120 mmHg, severe heart failure; severe valvular heart disease; recent MI; atrial flutter/fibrillation; ventricular arrhythmia; signs of infection; active malignancy disease
Interventions	Treatment group (dihydropyridine CCB) • Cilnidipine (oral): 10 mg/day; dose level increased up to 20 mg/day in cases in which the antihypertensive effect was insufficient Control group • Control that did not receive calcium channel blockers

Outcomes	• Change in the intradialytic SBP elevation assessed at baseline and at 12 weeks
	• Change in plasma renin activity assessed during the study period
	• Change in plasma aldosterone concentration assessed during the study period
	• Change in brain natriuretic peptide assessed during the study period
	• Change in plasma norepinephrine assessed during the study period
	• Change in plasma epinephrine assessed during the study period
	• Change in dopamine during the intervention (measured post-HD in the middle of the week) assessed during the study period
	Safety outcomes
	• Potassium, measured pre-HD at the beginning of the week
	• Haemoglobin, measured pre-HD at the beginning of the week
	• Urea nitrogen, measured pre-HD at the beginning of the week
	• Creatinine, measured pre-HD at the beginning of the week
	• Uric acid, measured pre-HD at the beginning of the week
	• HDL, measured pre-HD at the beginning of the week
	• LDL, measured pre-HD at the beginning of the week
	• Triglyceride and glycoalbumin, measured pre-HD at the beginning of the week
	• Other outcomes
	  ◦ CVD assessed during the study period
	  ◦ Cancer assessed during the study period
	  ◦ Hypotension during haemodialysis assessed during the study period
	  ◦ Hypertension assessed during the study period
	  ◦ Death (no death reported in the reason for attrition) assessed during the study period

Notes	• Funding source: None. K.D. received lecture fees of equal to or more than 500,000 yen from Otsuka Pharma Inc., between 2014 and 2016. M.I. received lecture fees of more than 500,000 yen from Pfizer Japan Inc., and Daiichi Sankyo co, Mochida Pharmaceutical Co., Ltd., Bayer Yakuhin, Ltd., and Mitsubishi Tanabe Pharma Corporation between 2014 and 2016. M.I. received Departmental research grant support of equal to or more than 1,000,000 yen from Daiichi Sankyo Co. Ltd., Shionogi & Co., Ltd., Sumitomo Dainippon Pharma Co., Ltd., MSD K.K., Astellas Pharma Inc., Takeda Pharmaceutical Company Limited and Pfizer Japan Inc., Bayer Yakuhin, Ltd., Otsuka Pharma Inc., Mitsubishi Tanabe Pharma Corporation, Kowa Pharmaceutical company Ltd., Genzyme Japan co., Ltd., AstraZeneca k.k., Bristol-Myers co., Ltd., Biotronik Japan, co. Ltd., Mochida Pharmaceutical Co., Ltd., between 2014 and 2016. T.I., N.F. E.I., M.F., T.M., M.K., H.T., S.K., H.N., and T.T. had no conflict of interest to declare • Authors contacted (predialysis SBP and DBP at the end of treatment) in July 2020, but they did not reply

LONDON 2019 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	QUOTE: "A computer-generated random number sequence was determined by an individual who was not associated with this study"
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	QUOTE: "Open-label"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Objective outcomes were assessed
Incomplete outcome data (attrition bias) All outcomes	High risk	QUOTE: "Thirty-three patients were allocated to the cilnidipine group, and 18 patients to the control group. Of these, 4 patients in the cilnidipine group and 3 patients in the control group withdrew consent before the intervention. During the intervention, 4 patients in the cilnidipine and 4 in the control were excluded from the study. The full analysis set included 36 patients (cilnidipine group: n = 25, control group: n = 11)
Selective reporting (reporting bias)	Low risk	All outcomes prespecified were reported
Other	High risk	Some authors received payment from pharmaceutical companies

Marchais 1991

Study characteristics

Methods	• Study design: double-blind, placebo RCT • Study duration: 16 weeks • Study follow-up: 16 weeks
Participants	• Country: France • Setting: single centre • Inclusion criteria: patients with ESKD treated with HD for at least 6 months with median predialysis BP > 160/90 mmHg; > 18 years • Number (analysed/randomised): treatment group (20/20); control group (19/20) • Mean age ± SD (years): not reported • Sex (M/F): not reported • Exclusion criteria: acute MI (within the preceding 3 months), valvular heart disease, PVD, cerebral vascular disease, decompensated heart failure
Interventions	Treatment group (dihydropyridine CCB) • Nitrendipine (oral): 20 mg orally once daily for 2 months, then 20 mg twice daily after the 8th week of treatment for 2 months Control group

Marchais 1991 *(Continued)*

	• Placebo (oral): administered once daily for the first 2 months, then twice daily after the 8th week of treatment for 2 months
Outcomes	• Arterial pressure assessed at baseline and end of treatment • Heart rate assessed at baseline and end of treatment • Aortic calcifications assessed at baseline and end of treatment • Aortic pulse velocity assessed at baseline and end of treatment • Aortic distensibility assessed at baseline and end of treatment • Death (no death reported in the reason for attrition) assessed during the study period
Notes	• Funding source: the Groupe d'Etude de la Physiopathologie de l'Insuffisance Renale (G.E.P.I.R.). The second author (Isabelle Boussac) is affiliated to Bayer Pharma, Puteaux, France

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	QUOTE: "Patients who met the inclusion criteria after the qualification period were divided into two parallel groups of 20 patients each, according to the randomisation list." Study was described as randomised, method of randomisation was not reported. However, it was unlikely that differences between intervention groups could suggest a problem with the randomisation process
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not reported. However due to the difference between the intervention group and control group, it was possible that participants and/or investigators were aware of the treatment assignment
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Objective outcomes were assessed
Incomplete outcome data (attrition bias) All outcomes	High risk	QUOTE: "The placebo group initially had 20 subjects, but one patient dropped out of the study after 4 weeks due to the diastolic pressure being persistently > 114 mmHg"
Selective reporting (reporting bias)	Low risk	All outcomes prespecified were reported
Other	High risk	The second author is affiliated to Bayer Pharma, Puteaux, France.

Nakao 1999

Study characteristics

Methods	• Study design: double blind, parallel RCT • Study duration: 2 years • Study follow-up: 2 years
Participants	• Country: Japan • Setting: single centre

Nakao 1999 *(Continued)*

- Inclusion criteria: hypertensive patients undergoing HD 3 times/week with chronic heart failure and with the past history of at least once hospitalisation due to heart failure; at least 50 years
- Number (analysed/randomised): treatment group (not reported/98); control group (not reported/102)
- Mean age: 59.6 years
- Sex (M/F): 138/62 (data extracted from M = 69%)
- Exclusion criteria: SBP < 90 mmHg, uncontrolled hypertension, recurrent and/or recent angina attack and/or cerebral Ischaemic symptoms

Interventions	Treatment group (dihydropyridine CCB) • Slow-releasing nifedipine: 10 mg once/day tritiated to 40 mg, 4 times/day Control group (ACEi) • Trandolapril 0.25 mg titrated to 2 mg once/day
Outcomes	• Composite death or hospitalisation or both for heart failure assessed during the study period • Improvement in HRQoL (exertional ability) assessed during the study period • Death (any cause) assessed during the study period
Notes	• Abstract-only publication • Funding source: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised; method of randomisation was not reported. It was not possible to assess if differences between intervention groups could suggest a problem with the randomisation process
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	QUOTE: "Double blind". However, insufficient information to permit judgement
Blinding of outcome assessment (detection bias) All outcomes	High risk	Objective and subjective outcomes were assessed
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Selective reporting (reporting bias)	High risk	No full-text publication identified to assess the possible selective reporting
Other	High risk	Abstract-only publication

Shibasaki 2002

Study characteristics

Shibasaki 2002 *(Continued)*

Methods	• Study design: double-blind RCT • Study duration: 6 months • Study follow-up: 6 months
Participants	• Country: Japan • Setting: single centre • Inclusion criteria: maintenance HD with hypertension performed for at least 1 month; patients maintained an ideal body weight (a postdialysis weight at which all or most excess body fluid was removed, without postdialysis hypotension), SBP > 150 mmHg or DBP > 90 mmHg • Number (analysed/randomised): treatment group (13/not reported); control group 1 (13/not reported); control group 2 (13/not reported) • Mean age ± SD (years): treatment group (56.2 ± 14.1); control group 1 (57.5 ± 15.9); control group 2 (56.4 ± 12.3) • Sex (M/F): treatment group (6/7); control group 1 (7/6); control group 2 (8/5) • Exclusion criteria: history of Ischaemic heart disease; history of cerebrovascular accident; patients received an inadequate echocardiographic study for measurement of LVMI; atrial fibrillation; recurrent congestive heart failure; significant valvular heart disease; nephrotic syndrome, or a history of neoplastic disease
Interventions	Treatment group (dihydropyridine CCB) • Amlodipine (oral): 5 mg/day Control group 1 (ARB) • Losartan (oral): 50 mg/day Control group 2 (ACEi) • Enalapril (oral): 5 mg/day
Outcomes	• LVH assessed at baseline and at 6 months • Ultrasonic integrated backscatter assessed at baseline and at 6 months • Inferior vena cava index assessed at baseline and at 6 months • Interventricular septum assessed at baseline and at 6 months • LV posterior wall assessed at baseline and at 6 months • LVMI assessed at baseline and at 6 months • Relative wall thickness assessed at baseline and at 6 months • Left ventricular end-diastolic volume index assessed at baseline and at 6 months • Haematological parameters (BUN, creatinine, uric acid, Hb, iPTH, plasma angiotensin II concentration) assessed at baseline and at 6 months • Death assessed during the study period • Withdrawn from the study • MI, myocarditis and myocardial fibrosis assessed during the study period
Notes	• Funding source: in part supported by a grant-in-aid for scientific research from the Ministry of Education, Science, Sports and Culture, Japan • Authors contacted (reason for death, predialysis SBP and DBP, occurrence of intradialytic hypotension) in July 2020, but they did not reply

Risk of bias

Bias	Authors' judgement	Support for judgement

Shibasaki 2002 *(Continued)*

Random sequence generation (selection bias)	Low risk	Study was described as randomised, method of randomisation was not reported. However, it was unlikely that differences between intervention groups could suggest a problem with the randomisation process
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	QUOTE: "Double blind". However, insufficient information to permit judgement
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Objective outcomes were assessed
Incomplete outcome data (attrition bias) All outcomes	High risk	39 patients (13 per group) but 30 completed the study (30 per group)
Selective reporting (reporting bias)	Low risk	All outcomes prespecified were reported
Other	Low risk	The study seemed to be free from other source of bias

Tepel 2008

Study characteristics	
Methods	• Study design: prospective, double-blind, placebo-controlled RCT • study duration: 30 months • Study follow-up: 30 months (median follow-up was 19 months (8 to 30))
Participants	• Country: Germany • Setting: multicentre (47 centres) • Inclusion criteria: patients presently existing arterial hypertension or with a history of arterial hypertension (resting BP ≥ 140/90 mmHg or antihypertensive medication), undergoing maintenance HD for at least 3 months • Number (analysed/randomised): treatment group (123/123); control group (128/128) • Median age, IQR range (years): treatment group (60, 45 to 68); control group (62, 48 to 68) • Sex (M/F): treatment group (78/45); control group (81/47) • Exclusion criteria: persistent hypotension with SBP < 90 mmHg; history of high grade aortic stenosis; history of severe heart failure NYHA stages II and IV; acute MI in the previous 4 weeks; known allergy to amlodipine; severe disorders of liver function; pregnant or breast feeding
Interventions	Treatment group (dihydropyridine CCB) • Amlodipine (oral): 10 mg once/day for 30 months Control group • Placebo (oral): once/day for 30 months
Outcomes	• Death (any cause, including cardiovascular, sudden death, infection, cancer or other cause) assessed every 6 months during 30 months

Tepel 2008 *(Continued)*

	• Time from randomisation to first event: composite of death from any cause and cardiac events (including cardiac event including MI, need for coronary angioplasty or coronary bypass surgery, Ischaemic stroke, PVD with the need for amputation or angioplasty) assessed every 6 months during 30 months • Adverse events (including hypotension) assessed every 6 months during 30 months
Notes	• Funding source: Pfizer, Karlsruhe, Germany, authors had no conflicts of interest • Authors contacted (number of cardiovascular death) in July 2014 and July 2020, but they did not reply

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	QUOTE: "A computer-generated randomisation list was prepared centrally"
Allocation concealment (selection bias)	Low risk	QUOTE: "A computer-generated randomisation list was prepared centrally guaranteeing that in study centres patients were assigned to one of both treatment groups" QUOTE: "To ensure allocation concealment, sequentially numbered containers were used" No indication whether the containers were identical.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	QUOTE: "Double blind" Review of the protocol on clinicaltrials.gov (NCT00124969) revealed that participants and personnel were blinded.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	QUOTE: "Deaths were classified by the treating physician independently of the endpoint analysis" Review of the protocol on clinicaltrials.gov (NCT00124969) revealed that the outcome assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	QUOTE: "No patient was lost to the follow-up" (analysis was by intention-to-treat population)
Selective reporting (reporting bias)	Low risk	All outcomes prespecified were reported
Other	Low risk	QUOTE: "The study sponsor did not take part in collection, analysis or interpretation of data, or in the writing of the report." The study seemed to be free from other source of bias

Timio 1997

Study characteristics

Methods	• Study design: single-blind, parallel RCT • Study duration: 12 weeks • Study follow-up: 12 weeks
Participants	• Country: Italy • Setting: single centre • Inclusion criteria: uraemic patients undergoing HD 3 times/week with arterial hypertension (DBP between 95 and 120 mmHg)

Timio 1997 *(Continued)*

- Number (analysed/randomised): treatment group 1 (21/21); treatment group 2 (19/19)
- Mean age (SD/range) (years): overall (57.18 ± 13.4); treatment group 1 (57.4 (21 to 71)); treatment group 2 (56.9 (22 to 73))
- Sex (M/F): treatment group 1 (15/6); treatment group 2 (15/4)
- Exclusion criteria: not reported

Interventions	Treatment group 1 (dihydropyridine CCB) • Amlodipine (oral): 5 mg/day, dosage were doubled after 4 weeks if adequate BP control was not achieved (DBP < 90 mmHg) Treatment group 2 (non-dihydropyridine CCB) • Verapamil (oral): 120 mg/day, dosage were doubled after 4 weeks if adequate BP control was not achieved (DBP < 90 mmHg)

Outcomes	• BP assessed at baseline and at 4,8,12 weeks
	• Heart rate assessed at baseline and at 4,8,12 weeks
	• Change in body weight assessed at baseline and at 4,8,12 weeks
	• Chest X-ray assessed at baseline at 12 weeks
	• Electrocardiography assessed at baseline at 12 weeks
	• Ocular fundoscopy assessed at baseline at 12 weeks
	• Adverse events assessed at each visit (including hypotensive events that were asked before each dialysis session) assessed during the study period
	• Blood chemistry and haematology assessed at baseline and at 4, 12 weeks
	  ○ Red blood cells
	  ○ Hb
	  ○ ferritin
	  ○ Total proteins
	  ○ Alkaline phosphatase
	  ○ Cholesterol
	  ○ Transaminases
	  ○ Electrolytes
	• Death (no death reported in the reason for attrition) assessed during the study period

Notes	• Funding source: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Study was described as randomised; method of randomisation was not reported. However, it was unlikely that differences between intervention groups could suggest a problem with the randomisation process
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	QUOTE: "Single blind"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Objective outcomes were assessed

Timio 1997 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients completed the study
Selective reporting (reporting bias)	Low risk	All outcomes prespecified were reported
Other	Low risk	The study seemed to be free from other source of bias

Yilmaz 2010a

Study characteristics	
Methods	• Study design: parallel RCT • Study duration: 12 months • Study follow-up: 12 months
Participants	• Country: Turkey • Setting: single centre • Inclusion criteria: presence of ESKD treated with HD 3 times/week; evidence for hypertension (predialysis SBP and/or DBP > 140/90 mmHg and/or presence of an antihypertensive medication) in non-diabetic patients; ≥ 18 years • Number (analysed/randomised): treatment group (41/56); control group (43/56) • Mean age ± SD (years): treatment group (49.2 ± 13.4); control group (53.8 ± 17.6) • Sex (M/F): treatment group (27/20); control group (25/20) • Exclusion criteria: diagnosis of chronic infectious disease, coronary artery disease, MI or cerebrovascular accident in the past 12 months; known intolerance to study medication; evidence of severe hepatic disease; use of immunosuppressant or nonsteroidal anti-inflammatory drugs; congestive heart failure; presence of a malignant disease; non-compliance of the subjects; valvular heart disease; other vascular diseases; diabetic kidney disease
Interventions	Treatment group (dihydropyridine CCB) • Amlodipine (oral): 5 to 10 mg once/day in the morning for 12 months Control group (ACEi) • Ramipril (oral): 5 to 10 mg once/day in the morning for 12 months
Outcomes	• LVMI assessed at baseline, 6 and 12 months • Carotid intima-media thickness assessed at baseline, 6 and 12 months • BP assessed at baseline, 6 and 12 months • Pulse pressure assessed at baseline, 6 and 12 months • Biochemical parameters (creatinine, blood urea nitrogen, glucose, electrolytes, and albumin, erythrocyte sedimentation rate, Hb, and lipid levels) assessed every 4 weeks for 1 year • Inflammatory markers (CRP, erythrocyte sedimentation rate, white cell count) assessed every 3 months for 1 year • Serious adverse events (including withdrawal and death) assessed during the study period • Adverse events assessed during the study period • Kt/V and interdialytic weight gain assessed during the study period
Notes	• Funding source: not reported; authors declared no conflict of interest

Yilmaz 2010a *(Continued)*

- Authors contacted in July 2020, and their answer: "There was no reported cardiovascular death, the blood pressures were measured at predialysis in the study, and one intradialytic hypotension occurred"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	QUOTE: "...patients were randomly allocated to receive doses of 5 mg ramipril or 5 mg amlodipine per day. The randomisation ratio was 1:1." Study was described as randomised, method of randomisation was not reported. However, it was unlikely that differences between intervention groups could suggest a problem with the randomisation process
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not reported. However due to the difference between the intervention group and control group, it was possible that participants and/or investigators were aware of the treatment assignment
Blinding of outcome assessment (detection bias) All outcomes	High risk	The majority of outcomes assessed were objective; it was not stated if an external panel assessed adverse events
Incomplete outcome data (attrition bias) All outcomes	High risk	QUOTE: "After titration periods, 20 patients (11 from ramipril and 9 from amlodipine group) were excluded from study because these patients did not reach the target BP despite of the medication with maximum doses of ramipril or amlodipine." QUOTE: "At the end of the 12 months follow-up, 84 patients (43 patients from ramipril and 41 patients from amlodipine groups) completed the study. In ramipril group, two patients discontinued study (one because of cough, one because of hyperkalaemia); however six patients in amlodipine group did not complete protocol (one because of death, one because of hypotension, two because of transplantation, and two because of drug intolerance)."
Selective reporting (reporting bias)	Low risk	All outcomes prespecified were reported
Other	Low risk	The authors declared no conflict of interest. The study seemed to be free from other source of bias

ACEi - angiotensin converting-enzyme inhibitor; ARB - angiotensin receptor blocker; BP - blood pressure; BUN - blood urea nitrogen; CHD - chronic heart disease; CVD - cardiovascular disease; DBP - diastolic blood pressure; ESKD - end-stage kidney disease; Hb - haemoglobin; HD - haemodialysis; HDL - high-density lipoprotein; HRQoL - health-related quality of life; iPTH - intact parathyroid hormone; IQR - interquartile range; LDL - low-density lipoprotein; (LV - left ventricular; LVH - LV hypertrophy; LVM(I) - LV mass (index); M/F- male/female; MI - myocardial infarction; NYHA - New York Heart Association; PVD - peripheral vascular disease; RCT - randomised controlled trial; rHuEPO - recombinant human erythropoietin; SBP - systolic blood pressure; SD - standard deviation

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Aslam 2006	Study period less than 12 weeks (valsartan versus amlodipine)

Study	Reason for exclusion
Atabak 2013	Study period less than 12 weeks (verapamil versus enalapril)
Cice 1997	Study period less than 12 weeks (nifedipine versus bisoprolol)
Cice 1998	Study period less than 12 weeks (diltiazem versus placebo)
Cice 2003	Study period less than 12 weeks (diltiazem versus placebo)
EDIT 2011	Study period less than 12 weeks (nifedipine versus enalapril)
Kojima 2004	Study period less than 12 weeks (benidipine versus nifedipine)
Nakano 2010	Cross-over RCT comparing 2 calcium channel blockers; 12 weeks of each treatment in random order with no washout period (efonidipine versus amlodipine)
NCT02228408	Wrong interventions; compared a nitrate (Isosorbide dinitrate) with a vasodilator (hydralazine)
Rojas-Campos 2005	Cross-over RCT (verapamil versus losartan versus prazosin for less than 12 weeks)
Salvetti 1987	Study period less than 12 weeks (nifedipine versus placebo)
Schiffl 1991	Study period less than 12 weeks (nitrendipine versus placebo)
Sherman 1990	Study period less than 12 weeks (verapamil versus placebo)
Singhaton 2001	Cross-over RCT (morning versus evening administration of amlodipine for less than 12 weeks)
Soni 2000	Study period less than 12 weeks (amlodipine besylate versus telmisartan)
Zuccala 1988	Study period less than 12 weeks (captopril versus clonidine versus nifedipine)

RCT - randomised controlled trial

Characteristics of studies awaiting classification *[ordered by study ID]*

NCT01394770

Methods	Double-blind, parallel RCT
Participants	Estimated sample size: 350 Age: 10 to 80 years
Interventions	Treatment group • Amlodipine 5 mg with forced up titration to 10 mg Control group (direct renin inhibitor) • Aliskiren 150 mg for 1 month with forced up titration to 300 mg
Outcomes	Primary outcomes • Composite end-point: death (any cause); cardiac event including MI, need for coronary angioplasty or coronary bypass surgery, Ischaemic stroke Secondary outcomes

NCT01394770 *(Continued)*	• Composite end-point of: all-cause hospitalisation; new-onset heart failure, new-onset atrial fibrillation
Notes	• The study was started in 2009 but never completed. Last verified July in 2012, recruitment status was active, not recruiting. • Current recruitment status: unknown

MI - myocardial infarction; RCT - randomised controlled trial

DATA AND ANALYSES

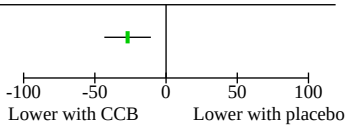
Comparison 1. Dihydropyridine calcium channel blocker versus placebo/control/usual treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Predialysis systolic blood pressure	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.2 Predialysis diastolic blood pressure	2	76	Mean Difference (IV, Random, 95% CI)	-13.56 [-19.65, -7.48]
1.3 Cardiovascular death	3	124	Risk Ratio (M-H, Random, 95% CI)	Not estimable
1.4 Intradialytic hypotension	2	287	Risk Ratio (M-H, Random, 95% CI)	0.54 [0.25, 1.15]

Analysis 1.1. Comparison 1: Dihydropyridine calcium channel blocker versus placebo/control/usual treatment, Outcome 1: Predialysis systolic blood pressure

Study or Subgroup	CCB Mean	CCB SD	CCB Total	Placebo Mean	Placebo SD	Placebo Total	Mean Difference IV, Random, 95% CI
London 1990	156	21	20	183	30	19	-27.00 [-43.33 , -10.67]

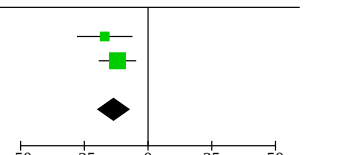
Test for subgroup differences: Not applicable



Analysis 1.2. Comparison 1: Dihydropyridine calcium channel blocker versus placebo/control/usual treatment, Outcome 2: Predialysis diastolic blood pressure

Study or Subgroup	CCB Mean	CCB SD	CCB Total	Placebo/control Mean	Placebo/control SD	Placebo/control Total	Weight	Mean Difference IV, Random, 95% CI
London 1990	81	14	20	98	20	19	31.3%	-17.00 [-27.89 , -6.11]
Kozlova 2006	92.1	8.8	16	104.1	13.9	21	68.7%	-12.00 [-19.34 , -4.66]
Total (95% CI)			**36**			**40**	**100.0%**	**-13.56 [-19.65 , -7.48]**

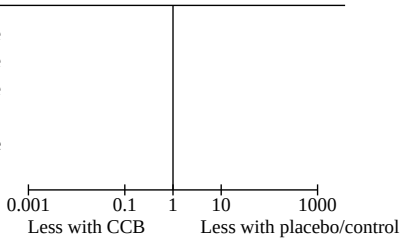
Heterogeneity: Tau² = 0.00; Chi² = 0.56, df = 1 (P = 0.46); I² = 0%
Test for overall effect: Z = 4.37 (P < 0.0001)
Test for subgroup differences: Not applicable



Analysis 1.3. Comparison 1: Dihydropyridine calcium channel blocker versus placebo/control/usual treatment, Outcome 3: Cardiovascular death

Study or Subgroup	CCB Events	CCB Total	Placebo/control Events	Placebo/control Total	Weight	Risk Ratio M-H, Random, 95% CI
Marchais 1991	0	20	0	20		Not estimable
LONDON 2019	0	29	0	15		Not estimable
London 1990	0	20	0	20		Not estimable
Total (95% CI)		**69**		**55**		**Not estimable**
Total events:	0		0			

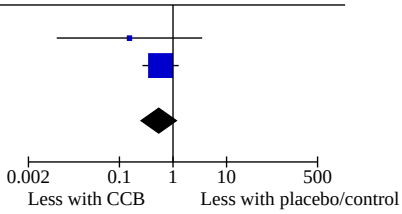
Heterogeneity: Not applicable
Test for overall effect: Not applicable
Test for subgroup differences: Not applicable



Analysis 1.4. Comparison 1: Dihydropyridine calcium channel blocker versus placebo/control/usual treatment, Outcome 4: Intradialytic hypotension

Study or Subgroup	CCB Events	CCB Total	Placebo/control Events	Placebo/control Total	Weight	Risk Ratio M-H, Random, 95% CI
LONDON 2019	0	25	1	11	5.8%	0.15 [0.01 , 3.51]
Tepel 2008	9	123	16	128	94.2%	0.59 [0.27 , 1.27]
Total (95% CI)		**148**		**139**	**100.0%**	**0.54 [0.25 , 1.15]**
Total events:	9		17			

Heterogeneity: Tau² = 0.00; Chi² = 0.66, df = 1 (P = 0.42); I² = 0%
Test for overall effect: Z = 1.59 (P = 0.11)
Test for subgroup differences: Not applicable



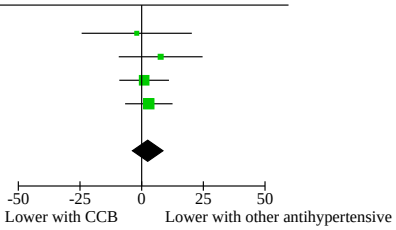
Comparison 2. Dihydropyridine calcium channel blockers versus other antihypertensives

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Predialysis systolic blood pressure	4	180	Mean Difference (IV, Random, 95% CI)	2.44 [-3.74, 8.62]
2.2 Predialysis diastolic blood pressure	4	180	Mean Difference (IV, Random, 95% CI)	1.49 [-2.23, 5.21]
2.3 Cardiovascular death	3	164	Risk Ratio (M-H, Random, 95% CI)	Not estimable
2.4 Intradialytic hypotension	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only

Analysis 2.1. Comparison 2: Dihydropyridine calcium channel blockers versus other antihypertensives, Outcome 1: Predialysis systolic blood pressure

Study or Subgroup	CCB Mean	CCB SD	CCB Total	Other antihypertensive Mean	Other antihypertensive SD	Other antihypertensive Total	Weight	Mean Difference IV, Random, 95% CI
Albitar 1997	130	31.3	20	132	40.2	20	7.7%	-2.00 [-24.33 , 20.33]
London 1994	157.7	22.8	10	150	18	14	13.2%	7.70 [-9.29 , 24.69]
Yilmaz 2010a	130	24	41	129	23	43	37.7%	1.00 [-9.06 , 11.06]
Kozlova 2006	145.8	12.4	16	142.9	15.2	16	41.4%	2.90 [-6.71 , 12.51]
Total (95% CI)			**87**			**93**	**100.0%**	**2.44 [-3.74 , 8.62]**

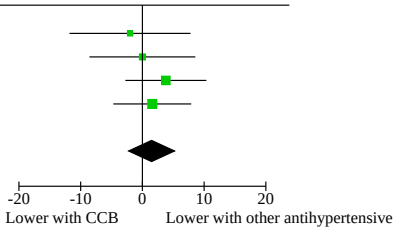
Heterogeneity: Tau² = 0.00; Chi² = 0.61, df = 3 (P = 0.89); I² = 0%
Test for overall effect: Z = 0.77 (P = 0.44)
Test for subgroup differences: Not applicable



Analysis 2.2. Comparison 2: Dihydropyridine calcium channel blockers versus other antihypertensives, Outcome 2: Predialysis diastolic blood pressure

Study or Subgroup	CCB Mean	CCB SD	CCB Total	Other antihypertensive Mean	Other antihypertensive SD	Other antihypertensive Total	Weight	Mean Difference IV, Random, 95% CI
Albitar 1997	78	17.9	20	80	13.4	20	14.4%	-2.00 [-11.80 , 7.80]
London 1994	85.7	10.1	10	85.7	11.2	14	18.8%	0.00 [-8.58 , 8.58]
Kozlova 2006	92.1	8.8	16	88.3	10.1	16	32.1%	3.80 [-2.76 , 10.36]
Yilmaz 2010a	82	15.6	41	80.4	13.8	43	34.7%	1.60 [-4.71 , 7.91]
Total (95% CI)			**87**			**93**	**100.0%**	**1.49 [-2.23 , 5.21]**

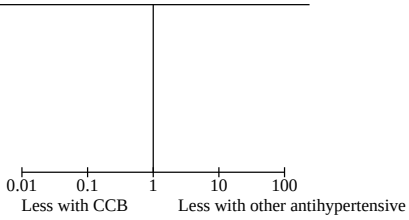
Heterogeneity: Tau² = 0.00; Chi² = 1.08, df = 3 (P = 0.78); I² = 0%
Test for overall effect: Z = 0.78 (P = 0.43)
Test for subgroup differences: Not applicable



Analysis 2.3. Comparison 2: Dihydropyridine calcium channel blockers versus other antihypertensives, Outcome 3: Cardiovascular death

Study or Subgroup	CCB Events	CCB Total	Other antihypertensive Events	Other antihypertensive Total	Weight	Risk Ratio M-H, Random, 95% CI
London 1994	0	16	0	16		Not estimable
Albitar 1997	0	20	0	20		Not estimable
Yilmaz 2010a	0	47	0	45		Not estimable
Total (95% CI)		**83**		**81**		**Not estimable**
Total events:	0		0			

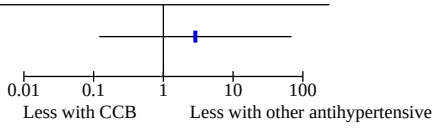
Heterogeneity: Not applicable
Test for overall effect: Not applicable
Test for subgroup differences: Not applicable



Analysis 2.4. Comparison 2: Dihydropyridine calcium channel blockers versus other antihypertensives, Outcome 4: Intradialytic hypotension

Study or Subgroup	CCB Events	CCB Total	Other antihypertensive Events	Other antihypertensive Total	Risk Ratio M-H, Random, 95% CI
Yilmaz 2010a	1	47	0	45	2.88 [0.12 , 68.79]

Test for subgroup differences: Not applicable



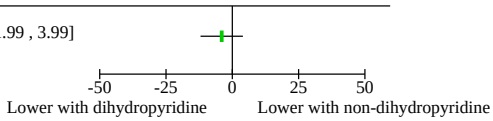
Comparison 3. Dihydropyridine versus non-dihydropyridine calcium channel blocker

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Predialysis systolic blood pressure	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
3.2 Predialysis diastolic blood pressure	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
3.3 Cardiovascular death	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.4 Other side effects	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only

Analysis 3.1. Comparison 3: Dihydropyridine versus non-dihydropyridine calcium channel blocker, Outcome 1: Predialysis systolic blood pressure

	Dihydropyridine			Non-dihydropyridine			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Random, 95% CI	IV, Random, 95% CI
Timio 1997	162	10	21	166	15	19	-4.00 [-11.99 , 3.99]	

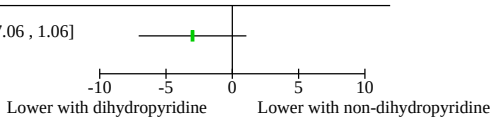
Test for subgroup differences: Not applicable



Analysis 3.2. Comparison 3: Dihydropyridine versus non-dihydropyridine calcium channel blocker, Outcome 2: Predialysis diastolic blood pressure

	Duhydropyridine			Non-dihydropyridine			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Random, 95% CI	IV, Random, 95% CI
Timio 1997	87	6	21	90	7	19	-3.00 [-7.06 , 1.06]	

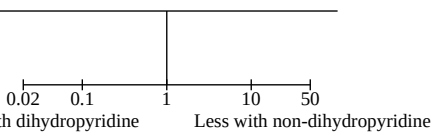
Test for subgroup differences: Not applicable



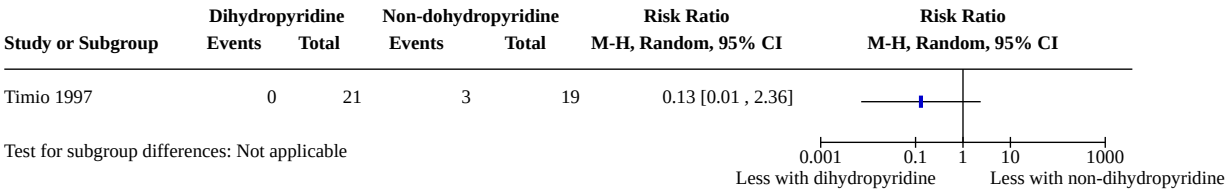
Analysis 3.3. Comparison 3: Dihydropyridine versus non-dihydropyridine calcium channel blocker, Outcome 3: Cardiovascular death

	Dihydropyridine		Non-dihydropiridine		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	M-H, Random, 95% CI	M-H, Random, 95% CI
Timio 1997	0	21	0	19	Not estimable	

Test for subgroup differences: Not applicable



Analysis 3.4. Comparison 3: Dihydropyridine versus non-dihydropyridine calcium channel blocker, Outcome 4: Other side effects



ADDITIONAL TABLES

Table 1. Table of studies reporting adverse events

Study ID	Intervention	Control	Adverse events in the intervention group	Adverse events in the control group
London 1990	Nitrendipine	Placebo	Not reported; no deaths were reported; no postdialysis hypotension was reported	Among 20 participants, the following adverse events were reported: dropped out due to DBP persistently > 114 mmHg (1). No death was reported. No postdialysis hypotension was reported
London 1994	Nitrendipine	Perindopril	Among 14 participants, the following adverse events were reported: withdrawn due to DBP > 95 mmHg (4). No deaths were reported. No serious adverse event was reported	Among 16 participants, the following adverse events were reported: withdrawn due to DBP > 95 mmHg (2). No deaths were reported. No serious adverse events were reported
LONDON 2019	Cilnidipine	Control	Among 25 participants, the following adverse events were reported: cardiogenic shock (due to acute coronary syndrome) (1), needed to decrease the dry weight more that 1% due to remarkable volume overload (3). No deaths were reported	Among 11 participants, the following adverse events were reported: colon cancer (1), hypotension (1), hypertension (1), needed to decrease the dry weight more that 1% due to remarkable volume overload (1). No deaths were reported
Marchais 1991	Nifedipine	Placebo	Not reported; no deaths were reported	Among 20 participants, the following adverse events were reported: dropped out due to DBP persistently > 114 mmHg (1). No deaths were reported
Shibasaki 2002	Amlodipine	Losartan or enalapril	Overall, of 61 participants there were: acute MI (3), myocarditis (2), death from pulmonary bleeding (1). However, no data were reported per group	Overall, of 61 participants there were: acute MI (3), myocarditis (2), death from pulmonary bleeding (1). However, no data were reported per group
Tepel 2008	Amlodipine	Placebo	Among 123 participants, the following adverse events were reported: 15 deaths. Overall, 26 sudden deaths, 7 infections, 4 cancers were record-	Among 128 participants, the following adverse events were reported: 22 deaths.

Table 1. Table of studies reporting adverse events *(Continued)*

			ed but data were not reported per group. The flow chart showed that the drug was discontinued because of adverse events in 8 participants. 18 participants reported a cardiovascular event, including MI, need for coronary angioplasty or coronary bypass surgery, Ischaemic stroke, and peripheral vascular disease with the need for amputation or angioplasty	Overall, 26 sudden deaths, 7 infections, 4 cancers were recorded but data were not reported per group. The flow chart showed that the drug was discontinued because of adverse events in 12 participants; 33 participants reported a cardiovascular event, including MI, need for coronary angioplasty or coronary bypass surgery, Ischaemic stroke, and peripheral vascular disease with the need for amputation or angioplasty
Timio 1997	Amlodipine	Verapamil	Among 21 participants, the following adverse events were reported: lower limb oedema (2), cough (2), cutaneous rash (1). No deaths were reported	Among 19 participants, the following adverse events were reported: lower limb oedema (7), headache (3). No deaths were reported
Yilmaz 2010a	Amlodipine	Ramipril	Among 47 participants, the following adverse events were reported: death (1), hypotension (1), drug intolerance (2)	Among 45 participants, the following adverse events were reported: 1 cough (1), hyperkalaemia (1) lead to the discontinuation from the study

DBP - diastolic blood pressure; MI - myocardial infarction

APPENDICES

Appendix 1. Electronic search strategies

Database	Search terms
CENTRAL	1. renal replacement therapy:ti,ab,kw 2. dialysis:ti,ab,kw 3. h*emodialysis:ti,ab,kw 4. h*emodiafiltration*:ti,ab,kw 5. h*emofiltration*:ti,ab,kw 6. (CAPD or CCPD or APD):ti,ab,kw 7. ("endstage kidney" or "endstage renal" or "end-stage kidney" or "end-stage renal"):ti,ab,kw 8. (ESKD or ESRD or ESKF or ESRF):ti,ab,kw 9. ("chronic kidney" near/2 ("stage 5" or "stage V")):ti,ab,kw 10.{or #1-#9} 11.MeSH descriptor: [Calcium Channel Blockers] explode all trees 12.amlodipine:ti,ab,kw 13.barnidipine:ti,ab,kw 14.diltiazem:ti,ab,kw 15.felodipine:ti,ab,kw 16.flunarizine:ti,ab,kw 17.gallopamil:ti,ab,kw 18.isradipine:ti,ab,kw

(Continued)

	19.lercanidipine:ti,ab,kw 20.manidipine:ti,ab,kw 21.nicardipine:ti,ab,kw 22.nifedipine:ti,ab,kw 23.nimodipine:ti,ab,kw 24.nisoldipine:ti,ab,kw 25.nitrendipine:ti,ab,kw 26.verapamil:ti,ab,kw 27.calcium channel block*:ti,ab,kw 28.(CCB or CCBs):ti,ab,kw 29.{or #11-#28} 30.{and #10, #29}
MEDLINE	1. exp Renal Dialysis/ 2. exp Hemofiltration/ 3. Kidney Failure, Chronic/ 4. dialysis.tw. 5. (haemodialysis or haemodialysis).tw. 6. (hemofiltration or haemofiltration).tw. 7. (hemodiafiltration or haemodiafiltration).tw. 8. (CAPD or CCPD or APD).tw. 9. (end-stage kidney or end-stage renal or endstage kidney or endstage renal).tw. 10.(ESKD or ESKF or ESRD or ESRF).tw. 11.(chronic kidney adj2 (stage 5 or stage V)).tw. 12.or/1-11 13.exp Calcium Channel Blockers/ 14.amlodipine.tw. 15.barnidipine.tw. 16.diltiazem.tw. 17.felodipine.tw. 18.flunarizine.tw. 19.gallopamil.tw. 20.isradipine.tw. 21.lercanidipine.tw. 22.manidipine.tw. 23.nicardipine.tw. 24.nifedipine.tw. 25.nimodipine.tw. 26.nisoldipine.tw. 27.nitrendipine.tw. 28.verapamil.tw. 29.calcium channel block*.tw. 30.(CCB or CCBs).tw. 31.or/13-30 32.and/12,31
EMBASE	1. exp Renal Replacement Therapy/ 2. (haemodialysis or haemodialysis).tw. 3. (hemofiltration or haemofiltration).tw. 4. (hemodiafiltration or haemodiafiltration).tw. 5. dialysis.tw. 6. (CAPD or CCPD or APD).tw.

(Continued)

7. Chronic Kidney Disease/
8. Kidney Failure/
9. Chronic Kidney Failure/
10.(end-stage renal or end-stage kidney or endstage renal or endstage kidney).tw.
11.(ESRF or ESKF or ESRD or ESKD).tw.
12.(chronic kidney adj2 (stage 5 or stage V)).tw.
13.or/1-12
14.exp calcium channel blocking agent/
15.calcium channel block*.tw.
16.(CCB or CCBs).tw.
17.amlodipine.tw.
18.barnidipine.tw.
19.diltiazem.tw.
20.felodipine.tw.
21.flunarizine.tw.
22.gallopamil.tw.
23.isradipine.tw.
24.lercanidipine.tw.
25.manidipine.tw.
26.nicardipine.tw.
27.nifedipine.tw.
28.nimodipine.tw.
29.nisoldipine.tw.
30.nitrendipine.tw.
31.verapamil.tw.
32.or/14-31
33.and/12,32

Appendix 2. Risk of bias assessment tool

Potential source of bias	Assessment criteria
Random sequence generation Selection bias (biased allocation to interventions) due to inadequate generation of a randomised sequence	*Low risk of bias:* Random number table; computer random number generator; coin tossing; shuffling cards or envelopes; throwing dice; drawing of lots; minimization (minimization may be implemented without a random element, and this is considered to be equivalent to being random).
	High risk of bias: Sequence generated by odd or even date of birth; date (or day) of admission; sequence generated by hospital or clinic record number; allocation by judgement of the clinician; by preference of the participant; based on the results of a laboratory test or a series of tests; by availability of the intervention.
	Unclear: Insufficient information about the sequence generation process to permit judgement.
Allocation concealment Selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment	*Low risk of bias:* Randomisation method described that would not allow investigator/participant to know or influence intervention group before eligible participant entered in the study (e.g. central allocation, including telephone, web-based, and pharmacy-controlled, randomisation; sequentially numbered drug containers of identical appearance; sequentially numbered, opaque, sealed envelopes).
	High risk of bias: Using an open random allocation schedule (e.g. a list of random numbers); assignment envelopes were used without appropriate safeguards (e.g. if envelopes were unsealed or

(Continued)

	non-opaque or not sequentially numbered); alternation or rotation; date of birth; case record number; any other explicitly unconcealed procedure.
	Unclear: Randomisation stated but no information on method used is available.
Blinding of participants and personnel Performance bias due to knowledge of the allocated interventions by participants and personnel during the study	*Low risk of bias*: No blinding or incomplete blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding; blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken.
	High risk of bias: No blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding; blinding of key study participants and personnel attempted, but likely that the blinding could have been broken, and the outcome is likely to be influenced by lack of blinding.
	Unclear: Insufficient information to permit judgement
Blinding of outcome assessment Detection bias due to knowledge of the allocated interventions by outcome assessors.	*Low risk of bias:* No blinding of outcome assessment, but the review authors judge that the outcome measurement is not likely to be influenced by lack of blinding; blinding of outcome assessment ensured, and unlikely that the blinding could have been broken.
	High risk of bias: No blinding of outcome assessment, and the outcome measurement is likely to be influenced by lack of blinding; blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome measurement is likely to be influenced by lack of blinding.
	Unclear: Insufficient information to permit judgement
Incomplete outcome data Attrition bias due to amount, nature or handling of incomplete outcome data.	*Low risk of bias:* No missing outcome data; reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias); missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate; for continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes not enough to have a clinically relevant impact on observed effect size; missing data have been imputed using appropriate methods.
	High risk of bias: Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate; for continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size; 'as-treated' analysis done with substantial departure of the intervention received from that assigned at randomisation; potentially inappropriate application of simple imputation.
	Unclear: Insufficient information to permit judgement
Selective reporting Reporting bias due to selective outcome reporting	*Low risk of bias:* The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way; the study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon).
	High risk of bias: Not all of the study's pre-specified primary outcomes have been reported; one or more primary outcomes is reported using measurements, analysis methods or subsets of the data (e.g. subscales) that were not pre-specified; one or more reported primary outcomes were not pre-specified (unless clear justification for their reporting is provided, such as an unexpected adverse effect); one or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis; the study report fails to include results for a key outcome that would be expected to have been reported for such a study.

(Continued)

	Unclear: Insufficient information to permit judgement
Other bias Bias due to problems not covered elsewhere in the table	*Low risk of bias:* The study appears to be free of other sources of bias.
	High risk of bias: Had a potential source of bias related to the specific study design used; stopped early due to some data-dependent process (including a formal-stopping rule); had extreme baseline imbalance; has been claimed to have been fraudulent; had some other problem.
	Unclear: Insufficient information to assess whether an important risk of bias exists; insufficient rationale or evidence that an identified problem will introduce bias.

HISTORY

Protocol first published: Issue 4, 2014
Review first published: Issue 10, 2020

CONTRIBUTIONS OF AUTHORS

1. Draft the protocol: GM, FM, PN, TE, GS
2. Study selection: GM, FM, PN
3. Extract data from studies: GM, FM, PN
4. Enter data into RevMan: GM, PN
5. Carry out the analysis: TE, PN
6. Interpret the analysis: GM, FM, PN, TE, GS
7. Draft the final review: GM, PN
8. Disagreement resolution: TE, GS
9. Update the review: GM, PN

DECLARATIONS OF INTEREST

- George A Mugendi: none known
- Giovanni FM Strippoli: none known
- Florence M Mutua: none known
- Patrizia Natale: none known
- Tonya M Esterhuizen: none known

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Types of interventions clarified to include studies comparing CCBs as well as different doses of CCBs. We included either dihydropyridine CCB or non-dihydropyridine CCB compared to control. Studies where follow-up was less than 12 weeks were excluded.

INDEX TERMS

Medical Subject Headings (MeSH)

Antihypertensive Agents [*therapeutic use]; Bias; Blood Pressure [drug effects]; Calcium Channel Blockers [adverse effects] [*therapeutic use]; Dihydropyridines [adverse effects] [*therapeutic use]; Hypertension [*drug therapy]; Hypotension [chemically induced]; Randomized Controlled Trials as Topic; *Renal Dialysis; Renal Insufficiency, Chronic [complications] [*therapy]

MeSH check words

Adult; Humans