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[Intervention Protocol]

Calcium channel blockers for people with chronic kidney disease requiring dialysis

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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

This review aims to look at the benefits and harms of CCB for people with CKD requiring dialysis.

BACKGROUND

Chronic kidney disease (CKD) is a growing health concern associated with a high risk of adverse outcomes. Its prevalence is increasing at a rate of 8% per year worldwide (Ruilope 2008). The aetiology of CKD 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 the crude and age adjusted ESKD rates were 151 and 232 per million population, respectively. The number of patients requiring dialysis in India is estimated to be 55,000 with an annual growth rate of between 10 and 20% (Jha 2013).

Data from the South African dialysis and transplant registry (SADTR) showed that hypertension was the cause of ESKD in 45.6% of 1549 patients in the year 1994 (Naicker 2003). In Kenya, studies revealed a prevalence of hypertension ranging between 61.5% and 76% among patients with varying degrees of CKD (Maritim 2007; Nadeem 2003; 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 which will guarantee better health outcomes.

Description of the condition

CKD is defined as the progressive loss of renal function occurring over several months to years and is characterized by the gradual scarring of the kidney (Dipiro 2011). CKD is categorized by the level of kidney function into stages 1 to 5 as proposed by the widely accepted United States Kidney Disease Outcomes Quality Initiative (K/DOQI); 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 the prevalence of CKD. The prevalence rose in the above 20 age group from 14.5% in the 1988 to 1994 NHANES to 16.8% in that survey (Onuigbo 2009). The more recent 2003 to 2006 survey has revealed an increase in the prevalence of stage 3 CKD from 5.7% in the 1988 to 1994 study to 8.1% (Dipiro 2011). Reliable statistics for ESKD are lacking in most African countries. It is however noted that CKD is at least three to four times more prevalent in sub-Saharan Africa than in more developed countries (Naicker 2003). The incidence and prevalence of ESKD in North Africa is higher than in the United States ranging between 34 and 200 per million (Barsoum 2003).

Description of the intervention

Calcium channel blockers (CCB) are antihypertensive agents which act on both myocardial cells as well as on blood vessels. They are classified broadly as either dihydropyridine or non-dihydropyridine types. The dihydropyridine CCB include nifedipine which is the prototype within this group. Other agents in this group are amlodipine, felodipine, isradipine, nicardipine, nimodipine, nitrendipine, nisoldipine, and efonipidine. The non-dihydropyridine subclass includes diltiazem and verapamil which are the prototypes for the benzothiazepine and phenylalkylamine class of CCB (Hart 2008). Other agents include gallopamil and bedipril.

How the intervention might work

CCB can be described as a heterogeneous group of compounds that exhibit unique structures and pharmacological properties. Their ability to lower blood pressure can be attributed to the fact that all CCB are vasodilators. This vasodilatory ability is not equal across all classes, with the dihydropyridines being more potent vasodilators than the non-dihydropyridines (Sica 2005).

The two classes of CCB 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 onto the L types of channels in the vasculature, dihydropyridine CCB cause vasodilatation with the subsequent drop in blood pressure. The non-dihydropyridine CCB on the other hand bind preferentially onto L type channels in the cardiac muscles, more so on the sino-atrial node and the atrio ventricular node, causing negative chronotropic effects and also decreasing activity of the sympathetic nervous system. These effects all cause a decrease in blood pressure (Basile 2004).

Why it is important to do this review

Most patients undergoing dialysis are usually comorbid with hypertension that is difficult to control and contributes to increased cardiovascular morbidity and mortality (Inrig 2010; Van Buren 2012). The reported prevalence of hypertension in dialysis patients was 86% in an American cohort of 2535 clinically stable, adult dialysis patients. Within that cohort, only 30% had adequately controlled blood pressure (Agarwal 2003). Drugs used prior to development of ESKD may not be a viable option thereafter. Some drugs are dialyzable and their use would result in a rise in blood pressure during dialysis (Inrig 2010; Van Buren 2012). Health care workers are therefore faced with the challenge of choosing an appropriate therapy for controlling blood pressure in ESKD patients undergoing dialysis. This choice needs to be evidence-based hence the need for this review.

OBJECTIVES

This review aims to look at the benefits and harms of CCB for people with CKD 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 should be 12 weeks.

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 will include patients who undergo either haemodialysis or peritoneal dialysis. There will be no restrictions on age, gender or race.

The participants will be 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) will be included. Patients with heart failure as classified by the New York Heart Association (NYHA) stages I to IV and angina will be 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 will be excluded.

Types of interventions

Any type of CCB compared with other antihypertensives or placebo will be included. Four intervention types will therefore be assessed as follows.

1. Dihydropyridine CCB versus placebo
2. Non-dihydropyridine CCB versus placebo
3. Dihydropyridine CCB versus other antihypertensives
4. Non-dihydropyridine CCB versus other antihypertensives.

The review will be amended as newer drugs that have been licensed become available. All drugs should be administered orally. The dosages will be those that are required for control of hypertension or appropriately adjusted dosages for reduced GFR and dialysis. Combination preparations with other antihypertensives other than CCB will not be included.

Types of outcome measures

Primary outcomes

1. Cardiovascular mortality
2. Pre-dialysis blood pressure levels
3. Occurrence of intradialytic hypotension.

Secondary outcomes

1. Incidence of other adverse events (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 will search the Cochrane Renal Group's Specialised Register through contact with the Trials Search Co-ordinator using search terms relevant to this review. The Cochrane Renal Group's Specialised 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 renal-related journals and the proceedings of major renal conferences
4. Searching of the current year of EMBASE OVID SP
5. Weekly current awareness alerts for selected renal journals
6. Searches of the International Clinical Trials Register (ICTRP) Search Portal and ClinicalTrials.gov

Studies contained in the Specialised Register are identified through search strategies for CENTRAL, MEDLINE, and EMBASE based on the scope of the Cochrane Renal Group. 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 the Cochrane Renal Group. 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 trials to investigators known to be involved in previous studies.

Data collection and analysis

Selection of studies

The search strategy described will be used to obtain titles and abstracts of studies that may be relevant to the review. The titles and abstracts will be screened independently by two authors, who will discard studies that are not applicable, however studies and reviews that might include relevant data or information on trials

will be retained initially. Two authors will independently assess retrieved abstracts and, if necessary the full text, of these studies to determine which studies satisfy the inclusion criteria. The two authors will compare their lists and any differences in opinion between the two authors will be resolved by discussion and, where this fails, by arbitration by a third author.

Data extraction and management

Data extraction will be carried out independently by two authors using standard data extraction forms. Studies reported in non-English language journals will be translated before assessment. Where more than one publication of one study exists, reports will be grouped together and the publication with the most complete data will be used in the analyses. Where relevant outcomes are only published in earlier versions these data will be used. Any discrepancy between published versions will be highlighted. Differences in opinion on data collection will be resolved by discussion and where this fails by arbitration by a third author.

Assessment of risk of bias in included studies

The following items will be 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 (detection bias)?
 - Participants and personnel
 - Outcome assessors
- Were incomplete outcome data adequately addressed (attrition bias)?
 - Are 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?

An assessment of 'low risk', 'high risk' or 'unclear risk' will be made for each of the items based on the risk of bias tool (Appendix 2). Two authors will compare the results and discuss any differences in opinion. Any disagreements will be settled by a third author.

Measures of treatment effect

For dichotomous outcomes (e.g. death, adverse events such as hypotension, cardiovascular morbidity) results will be expressed as risk ratio (RR) with 95% confidence intervals (CI). Where continuous scales of measurement are used to assess the effects of treatment (blood pressure, quality of life), the mean difference (MD) will be used, or the standardised mean difference (SMD) if different scales have been used. If some studies have reported change from baseline scores, these will be meta-analysed together

with studies reporting final value scores using the mean difference method. In this case, if standard deviations of the changes are not reported, they will be imputed as described in Chapter 16 of the Cochrane Handbook (Higgins 2011). Studies reporting time to event of outcomes as hazard ratios and confidence intervals will be meta-analysed together with studies reporting risk ratios as long as the proportional hazards assumption is reasonable. Otherwise, these studies will be analysed as dichotomous data.

Unit of analysis issues

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

Dealing with missing data

Any further information required from the original author will be requested by written correspondence (e.g. emailing the corresponding author) and any relevant information obtained in this manner will be 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 will be carefully performed. Attrition rates, for example drop-outs, losses to follow-up and withdrawals will be investigated. Issues of missing data and imputation methods (for example, last-observation-carried-forward (LOCF)) will be critically appraised (Higgins 2011).

Assessment of heterogeneity

Statistical heterogeneity will be evaluated by visually inspecting the forest plots to detect overlapping CIs, applying the Chi² test (P value < 0.10 considered statistically significant), and also by using the I² statistic where an I² of greater than 75% will be used to represent substantial heterogeneity.

Assessment of reporting biases

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

Data synthesis

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

Subgroup analysis and investigation of heterogeneity

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

Sensitivity analysis

We will perform sensitivity analyses in order 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.

ACKNOWLEDGEMENTS

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Higgins 2011

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Inrig 2010

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Jha 2013

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Levey 2003

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* Indicates the major publication for the study

APPENDICES**Appendix I. Electronic search strategies**

Database	Search terms
CENTRAL	<ol style="list-style-type: none"> 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 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

(Continued)

	<ol style="list-style-type: none">24. nisoldipine:ti,ab,kw25. nitrendipine:ti,ab,kw26. verapamil:ti,ab,kw27. calcium channel block*:ti,ab,kw28. (CCB or CCBs):ti,ab,kw29. {or #11-#28}30. {and #10, #29}
MEDLINE	<ol style="list-style-type: none">1. exp Renal Dialysis/2. exp Hemofiltration/3. Kidney Failure, Chronic/4. dialysis.tw.5. (hemodialysis 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/1-1113. 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/13-3032. and/12,31
EMBASE	<ol style="list-style-type: none">1. exp Renal Replacement Therapy/2. (hemodialysis or haemodialysis).tw.3. (hemofiltration or haemofiltration).tw.4. (hemodiafiltration or haemodiafiltration).tw.5. dialysis.tw.6. (CAPD or CCPD or APD).tw.7. Chronic Kidney Disease/8. Kidney Failure/

(Continued)

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	<i>Low risk of bias:</i> 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) <i>High risk of bias:</i> 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 <i>Unclear:</i> Insufficient information about the sequence generation process to permit judgement

(Continued)

<p>Allocation concealment Selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment</p>	<p><i>Low risk of bias:</i> 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)</p> <p><i>High risk of bias:</i> 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 non-opaque or not sequentially numbered); alternation or rotation; date of birth; case record number; any other explicitly unconcealed procedure</p> <p><i>Unclear:</i> Randomisation stated but no information on method used is available</p>
<p>Blinding of participants and personnel Performance bias due to knowledge of the allocated interventions by participants and personnel during the study</p>	<p><i>Low risk of bias:</i> 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</p> <p><i>High risk of bias:</i> 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</p> <p><i>Unclear:</i> Insufficient information to permit judgement</p>
<p>Blinding of outcome assessment Detection bias due to knowledge of the allocated interventions by outcome assessors</p>	<p><i>Low risk of bias:</i> 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</p> <p><i>High risk of bias:</i> 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</p> <p><i>Unclear:</i> Insufficient information to permit judgement</p>
<p>Incomplete outcome data Attrition bias due to amount, nature or handling of incomplete outcome data</p>	<p><i>Low risk of bias:</i> 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</p>

(Continued)

	<p>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</p> <hr/> <p><i>High risk of bias:</i> 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</p> <hr/> <p><i>Unclear:</i> Insufficient information to permit judgement</p>
<p>Selective reporting Reporting bias due to selective outcome reporting</p>	<p><i>Low risk of bias:</i> 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)</p> <hr/> <p><i>High risk of bias:</i> 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</p> <hr/> <p><i>Unclear:</i> Insufficient information to permit judgement</p>
<p>Other bias Bias due to problems not covered elsewhere in the table</p>	<p><i>Low risk of bias:</i> The study appears to be free of other sources of bias.</p>

(Continued)

	<p><i>High risk of bias:</i> 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</p>
	<p><i>Unclear:</i> Insufficient information to assess whether an important risk of bias exists; insufficient rationale or evidence that an identified problem will introduce bias</p>

CONTRIBUTIONS OF AUTHORS

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

DECLARATIONS OF INTEREST

None known.