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Calcium channel blockers for preventing acute tubular necrosis in kidney transplant recipients (Review)

Shilliday IR, Sherif M

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[Intervention Review]

Calcium channel blockers for preventing acute tubular necrosis in kidney transplant recipients

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ABSTRACT

Background

The incidence of delayed graft function in cadaveric grafts has increased over the last few years due in part to the large demand for cadaveric kidneys necessitating the use of kidneys from marginal donors. Calcium channel blockers have the potential to reduce the incidence of post-transplant acute tubular necrosis (ATN) if given in the peri-operative period. However, there is controversy surrounding their use in this situation with no consensus as to their efficacy.

Objectives

To evaluate the benefits and harms of using calcium channel blockers in the peri-transplant period in patients at risk of ATN following cadaveric kidney transplantation.

Search methods

We searched the Cochrane Renal Group's specialised register, the Cochrane Central Register of Controlled Trials (CENTRAL, in *The Cochrane Library*) MEDLINE (from 1966) and EMBASE (from 1980). The Trials Search Coordinator was contacted to develop the search strategy.

Selection criteria

Randomised controlled trials comparing calcium channel blockers given in the peri-transplant period with controls were included. Quasi-randomised trials were excluded.

Data collection and analysis

Data was extracted and quality assessed independently by two reviewers, with differences resolved by discussion. Dichotomous outcomes are reported as risk ratio (RR) and measurements on continuous scales are reported as mean differences (MD) with 95% confidence intervals (CI).

Main results

Thirteen trials (724 participants) were suitable for inclusion. Treatment with calcium channel blockers in the peri-transplant period was associated with a significant decrease in the incidence of post-transplant ATN (RR 0.62, 95% CI 0.46 to 0.85) and delayed graft function (RR 0.55, 95% CI 0.42 to 0.73). There was no difference between control and treatment groups in graft loss, mortality, requirement for haemodialysis. There was insufficient information to comment on adverse events.

Authors' conclusions

These results suggest that calcium channel blockers given in the peri-operative period may reduce the incidence of ATN post-transplantation. The result should be treated with caution due to the heterogeneity of the trials which made comparison of studies and pooling of data difficult.

PLAIN LANGUAGE SUMMARY

Calcium channel blockers can reduce the death of tubular cells in the kidney after a transplant operation

Acute tubular necrosis (ATN) is the sudden death of tubular cells in the kidney. ATN can happen after a kidney transplant if the kidney does not receive enough oxygen. Calcium channel blockers stop calcium ions flowing into the muscle cells of the heart and blood vessels. These blockers cause the muscles to widen and relax, lowering a person's blood pressure and improving their circulation. The review of 13 studies (724 participants) found that giving calcium channel blockers during a kidney transplant operation reduces the chance of ATN after the operation. The effect of giving the blockers after the operation still needs to be investigated.

BACKGROUND

The incidence of delayed graft function in cadaveric grafts has increased over the last few years for both primary and re-grafts. In 1999 the incidence of delayed graft function in Australia was 24% for primary grafts and 42% for re-grafts (ANZDATA 2000). This high incidence is in part due to the large demand for cadaveric kidneys, which has necessitated the use of kidneys from marginal donors, and also the increase in total ischaemic time (ANZDATA 2000). Grafts with delayed function have a poorer long-term survival than grafts that function immediately, with the difference between the two appearing after the first year and reaching 10% by nine years post-transplant (ANZDATA 2000). The United States Renal Data System (USRDS) annual data report for 2006 defines delayed graft function as the need for dialysis during the first week after transplant. The rate of delayed graft function in 2004 was similar to the rate published in 1995 (21.4% and 20.9% respectively) (USRDS 2006).

After ischaemia there is a rise in intracellular calcium which has a number of detrimental effects including; a rise in intra-mitochondrial calcium concentration which uncouples oxidative phosphorylation and reduces ATP production (Wilson 1984), activation of phospholipases causing an alteration in membrane enzyme and membrane damage (Chien 1980; Matthys 1984) and free radical generation (McCord 1985). Renal vasoconstriction also occurs.

Calcium channel blockers have the potential to protect glomerular filtration rate (GFR) during renal ischaemia by several mechanisms. These include,

- Prevention of the rise in intra-mitochondrial calcium
- Prevention of re-perfusion injury
- Increased renal blood flow
- Selective dilatation of pre-glomerular vessels
- Restoration of normal autoregulation during increased sympathetic stimulation

Evidence that calcium channel blockers are beneficial if given after the ischaemic event is not forthcoming. Most patients with acute tubular necrosis (ATN) present after the ischaemic event and therefore calcium channel blockers are unlikely to improve GFR in this situation. They do, however, have the potential to reduce the incidence of post-transplant ATN if given in the peri-operative period. In reality there is controversy surrounding their use in this particular situation, with authors disagreeing as to their effectiveness in reducing the incidence of initial non-function of the graft (Donmez 1999; Harper 1996; Ladefoged 1994; Nicholson 1996). In addition, the studies use a variety of calcium channel blockers from different classes, given by different routes over different time periods. The issue is further clouded by the fact that some calcium channel blockers (especially diltiazem) may exert an immunosuppressive effect (Mandreoli 1990; McMillen 1985). Diltiazem interacts with cyclosporin and cyclosporin A pharmacokinetics and lower doses of these immunosuppressive drugs can be given to obtain therapeutic levels (Chrysostomou 1993; Morris 1998). Calcium channel blockers also minimise vasoconstrictive cyclosporin nephrotoxicity (Asberg 1997; Berg 1991).

Our aim was to review the literature and assess the effect calcium channel blockers given in the peri-transplant period had on the incidence of post-transplant ATN.

OBJECTIVES

Different calcium channel blockers clearly act in a number of ways in the transplant situation and separating out their various effects is difficult. However, we aimed to evaluate the benefits and harms of using calcium channel blockers in the peri-transplant period in patients at risk of ATN following kidney transplantation. We only looked at the effect on delayed graft function due to amelioration of ATN which all calcium channel blockers have the potential to do. We did not examine in great detail the incidence of acute rejection episodes which is a different issue, and one which is not applicable to all calcium channel blockers.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) comparing any calcium channel blocker given in the peri-transplant period with controls in patients who have had a kidney transplant. Quasi-RCTs will not be included.

Types of participants

Kidney transplant recipients of any age, sex, or race and with any type of kidney disease causing end-stage renal failure who receive a kidney transplant. Patients who had previous grafts were included. Patients receiving grafts from live donors were excluded.

Types of interventions

Any calcium channel blocker given by any route pre or immediately post-transplant to the recipient ± donor or added to the perfusate. Control patients should receive identical treatment but no calcium channel blocker.

Types of outcome measures

The outcome measures include those used by transplant registries to assess the development of ATN and subsequent graft function.

- Immediate graft function: defined as a spontaneous fall in serum creatinine of 10% within 24 hours or a spontaneous fall in serum creatinine of 10% within 25-72 hours post-transplant.
- Poor immediate graft function: no spontaneous fall in creatinine (10%) within 72 hours but no further dialysis required.
- No immediate function: no spontaneous fall (> 10%) in serum creatinine. Dialysis required within 72 hours.
- Serum creatinine at one week and one month.
- GFR at one week and one month.
- Adverse effects of therapy.
- Incidence of biopsy proven ATN.

Search methods for identification of studies

Relevant trials were initially obtained from the following sources (see Additional Table 1 - *Electronic search strategies*)

1. Cochrane Renal Group specialised register of RCTs

2. Cochrane Central Register of Controlled Trials (CENTRAL in *The Cochrane Library*) for any "New" records not yet incorporated in the specialised register
3. MEDLINE and Pre MEDLINE (from 1966) were searched using the above terms, combined with the optimally sensitive strategy for the identification of RCTs (Dickersin 1994) (see Cochrane Renal Group Module).
4. EMBASE (from 1980) was searched using terms similar to those used for MEDLINE and combined with a search strategy for the identification of RCTs (Lefebvre 1996).
5. Reference lists of nephrology textbooks, review articles and relevant trials.
6. Conference proceeding's abstracts from nephrology scientific meetings.
7. Letters seeking information about unpublished or incomplete trials to investigators known to be involved in previous trials.
8. Studies in languages other than English will be included.

Data collection and analysis

Included and excluded studies

This review was undertaken by two reviewers. Titles and abstracts identified by the search strategy described were screened independently. All potentially relevant reviews were retained and the full text of these studies examined to determine which studies satisfied the inclusion criteria. Data extraction was carried out independently by the same reviewers using standard data extraction forms. Studies reported in languages other than those familiar to the authors were translated and evaluated in the presence of a native speaker of the language. Where more than one publication of one trial existed, only the publication with the most complete data was included. Where important data was not reported, we attempted to contact the original authors to get the necessary information. Discrepancies between the reviewers were resolved by discussion.

Study quality

The quality of studies to be included was assessed independently by two reviewers without blinding to authorship or journal, using the checklist developed for the Cochrane Renal Group. Discrepancies were resolved by discussion. The quality items assessed were allocation concealment, intention-to-treat analysis, completeness to follow-up and blinding of investigators, participants,outcome assessors and data analysis.

Quality checklist

Allocation concealment

- *Adequate:* Randomisation method described that would not allow investigator/participant to know or influence intervention group before eligible participant entered in the study
- *Unclear:* Randomisation stated but no information on method used is available
- *Inadequate:* Method of randomisation used such as alternate medical record numbers or unsealed envelopes; any information in the study that indicated that investigators or participants could influence intervention group

Blinding

- *Investigators*: Yes/No/Not stated
- *Participants*: Yes/No/Not stated
- *Outcome assessor/s*: Yes/No/Not stated
- *Data analysis*: Yes/No/Not stated

The above are considered not blinded if the treatment group can be identified in >20% of participants because of the side effects of treatment.

Intention-to-treat analysis

- Yes: Specifically reported by authors that intention-to-treat analysis was undertaken and this was confirmed on study assessment.
- Yes: Not stated but confirmed upon study assessment.
- No: Not reported and lack of intention-to-treat analysis confirmed on study assessment (patients who were randomised were not included in the analysis because they did not receive the study intervention, they withdrew from the study or were not included because of protocol violation).
- No: Stated but not confirmed upon study assessment.

Completeness of follow-up

Per cent of participants excluded or lost to follow-up.

Statistical assessment

Dichotomous outcomes (need for rescue medication, rate of pain recurrence, adverse event rate) results are expressed as risk ratio (RR) with 95% confidence intervals (CI). Data was pooled using the random effects model but the fixed effect model was also analysed to ensure robustness of the model chosen and susceptibility to outliers. Where continuous scales of measurement were used to assess the effects of treatment (patient-rated pain scores, time to pain relief), the mean difference (MD) was used, or the standardised mean difference (SMD) if different scales were used. Heterogeneity was analysed using a Chi squared test on N-1 degrees of freedom, with a P of 0.05 used for statistical significance and the I^2 statistic (Higgins 2003). I^2 values of 25%, 50% and 75% correspond to low, medium and high levels of heterogeneity respectively.

Analysis was used to explore possible sources of heterogeneity (e.g. participants, treatments and study quality). Heterogeneity among participants could be related to age, stone size/site, and drug route/dose and where possible these subgroups were explored. Heterogeneity in treatments could be related to prior agent(s) used and the agent, dose and duration of therapy. Where possible, the risk difference (RD) with 95% CI was to be calculated for adverse effects.

The applicability of the results to individual patients will be determined by calculating the reduction in risk of developing ATN post-transplant in the treatment groups relative to the risk of post-transplant ATN in the groups not given calcium channel blockers.

Where sufficient RCTs were identified, an attempt was made to examine for publication bias using a funnel plot (Egger 1997).

RESULTS

Description of studies

Thirty two studies were identified from the initial search and 13 met our inclusion criteria. Four were duplicate publications. This

left nine studies with 445 participants (Frei 1987; Ladefoged 1994; Lustig 1996; Neumayer 1989; Neumayer 1992a; Neumayer 1992b; Oppenheimer 1992; Tenschert 1991; Wilkie 1994). Wilkie 1994 had three study groups and groups P (placebo) and NS (nifedipine short duration) were suitable for inclusion in the meta-analysis, and Neumayer 1992a and Neumayer 1992b reported two studies in one paper which have been treated as two separate studies in this review. A second search a year after publication of the review led to the inclusion of a tenth study (Kuypers 2004). The most recent search (January 2007) has led to the inclusion of three further studies (Dawidson 1991; Harper 1992; Morales 1990) giving a total of 724 participants in the review.

A variety of different calcium channel blockers were used;

- diltiazem (seven studies: Frei 1987; Ladefoged 1994; Neumayer 1989; Neumayer 1992a; Neumayer 1992b; Oppenheimer 1992; Tenschert 1991),
- nifedipine (three studies - all retard preparation: Harper 1992; Morales 1990; Wilkie 1994),
- verapamil (Dawidson 1991),
- gallopamil (Lustig 1996) and
- lacidipine (Kuypers 2004).

In six studies the grafts were perfused with Euro-Collins solution containing calcium channel blocker - diltiazem (Frei 1987; Ladefoged 1994; Neumayer 1989; Neumayer 1992a; Oppenheimer 1992) and gallopamil (Lustig 1996). Four study populations (Harper 1997 Kuypers 2004; Morales 1990; Wilkie 1994) received oral therapy only. One group (Neumayer 1989) only treated the donor kidney by adding diltiazem to the perfusate, recipients did not receive calcium channel blocker. Five treatment groups (recipients) were given a bolus of calcium channel blocker followed by an infusion and then oral calcium channel blocker (Frei 1987; Ladefoged 1994; Neumayer 1992a; Neumayer 1992b; Oppenheimer 1992); two study groups did not receive a bolus of diltiazem prior to the infusion (Lustig 1996; Tenschert 1991). The duration of calcium channel blocker infusion before beginning oral therapy varied between groups. One study group (Dawidson 1991) were given 10 mg verapamil into the newly anastomosed renal artery in 2.5 mg increments to avoid hypotension, followed by oral verapamil.

Immunosuppression post-transplant was not comparable between groups, although all patients in all studies were on calcineurin inhibitors. Four groups used cyclosporine and prednisolone (Frei 1987; Neumayer 1989; Neumayer 1992a; Neumayer 1992b,). One group received cyclosporine only (Oppenheimer 1992), five received cyclosporine, prednisolone and azathioprine (Dawidson 1991; Ladefoged 1994; Lustig 1996; Tenschert 1991; Wilkie 1994),one of these also received ATG (Lustig 1996) and another Minnesota antilymphocyte globulin (Dawidson 1991). One study population received cyclosporine, mycophenolate mofetil and prednisone (Kuypers 2004).

SIX studies listed exclusion criteria which included current treatment with a calcium channel blocker, cardiac conduction abnormalities, congestive cardiac failure, liver disease, age less than 18 or greater than 65 years, no consent, PRA greater than 90%, high clinical urgency, intolerant of cyclosporine or azathioprine, intolerant of calcium channel blocker, allografts from donors receiving calcium channel blocker in the seven days prior to harvesting, already on an inducer of cytochrome P450, haplotype matched living related donor, systolic BP less than 90 mm Hg, history of bleeding and pregnant females (Dawidson 1991; Frei 1987; Kuypers 2004; Neumayer 1992a; Neumayer 1992b; Wilkie 1994).

The definitions of immediate, poor and no immediate function in the protocol were based on the definitions used by the Australian and New Zealand Transplant Registry (ANZDATA 2000). In reality the definition of ATN/initial non-function varied widely between studies. One group did not supply a definition (Tenschert 1991). The other definitions were as follows:

- *Initial non-function*: need for dialysis during the first post-operative week (Frei 1987).
- Diagnosis of ATN based on the presence of oliguria and/or delayed decrease in serum creatinine, plus morphologic changes of ATN on biopsy (Lustig 1996).
- *Delayed graft function*: continued need for dialysis post-operatively, and for patients not on dialysis - a lack of decrease in the serum creatinine (Ladefoged 1994).
- *Primary graft function:* graft function without haemodialysis within the first seven days (Neumayer 1989; Neumayer 1992a; Neumayer 1992b).
- *Definition of ATN*: need for dialysis within the first week after transplant (Oppenheimer 1992).
- *Initial non-function:* requirement for dialysis in the immediate post-transplant period (Wilkie 1994).
- *Delayed graft function:* need for dialysis post-transplantation (Kuypers 2004).
- *Initial non-function*: dialysis dependency by fourth post operative day in the absence of graft rejection (Harper 1992)

The duration of follow up varied widely between studies as follows:

- Six months follow-up (Frei 1987; Oppenheimer 1992; Wilkie 1994).
- Three months follow-up (Ladefoged 1994; Lustig 1996).
- GFR reported up to day seven, follow-up for four weeks (Neumayer 1989).
- GFR reported up to day seven, total follow-up four years (Neumayer 1992a; Neumayer 1992b) .
- No duration of follow-up given (Tenschert 1991).
- Two years follow-up (Kuypers 2004).
- Creatinine reported up to day 12, follow-up from 17.1 ± 5.4 months (controls), 17.9 ± 5.8 (study group) (Dawidson 1991)

Authors were contacted for clarification of characteristics of patients and studies as well as results but no additional information was obtained.

Risk of bias in included studies

Allocation concealment

Eleven studies did not report any concealment approach. Wilkie 1994 used a computerised randomisation system which allocated a trial number and a unique treatment identifier number to each patient. Lustig 1996 used a study coordinator, who had no role in the selection and treatment of patients, to allocate the trial number.

Blinding

Four of the studies (Kuypers 2004; Ladefoged 1994; Lustig 1996; Wilkie 1994) were double-blind. Two further studies (Frei 1987; Oppenheimer 1992) did not make it clear whether blinding took place or not and the remainder of the studies were not blinded.

Intention-to-treat

The use of intention-to-treat analysis was present in five studies (Frei 1987; Harper 1997; Morales 1990; Neumayer 1992a; Neumayer 1992b).

Completeness of follow-up

Loss to follow-up is uncommon in transplant patients and only one study reports two patients lost to follow-up (Kuypers 2004).

Effects of interventions

Graft loss

Nine studies reported graft loss (Dawidson 1991; Frei 1987; Ladefoged 1994; Lustig 1996; Morales 1990; Neumayer 1992a; Neumayer 1992b; Oppenheimer 1992; Wilkie 1994). Results for Neumayer 1992a and Neumayer 1992b were given together and have been included as *analysis 01.01.01*. There was no significant difference between the use of calcium channel blockers and placebo/no treatment in the prevention of graft loss (Analysis 1.1: RR 0.76, 95% CI 0.42 to 1.39, P = 0.38; I^2 = 18.1%).

Mortality

Seven studies reported mortality (Dawidson 1991; Frei 1987; Ladefoged 1994; Lustig 1996; Morales 1990; Oppenheimer 1992; Wilkie 1994). There was no significant difference between the use of calcium channel blockers and placebo/no treatment on mortality (Analysis 1.2*:* RR 0.55, 95%CI 0.13 to 2.35, P = 0.42; I^2 = 0%).

ATN

Eight studies reported ATN post-transplant (Frei 1987; Ladefoged 1994; Lustig 1996; Morales 1990; Neumayer 1989; Neumayer 1992a; Neumayer 1992b; Oppenheimer 1992). There was a significant reduction in the number of patients with ATN post-transplant in patients treated with calcium channel blockers (Analysis 1.3*:* RR 0.62, 95% CI 0.46 to 0.85, P = 0.003; I^2 = 18.2%).

Only Lustig 1996 routinely biopsied all grafts to confirm the clinical diagnosis of ATN. Ladefoged 1994 routinely biopsied 34/39 patients comprising the study population. Frei 1987 and Oppenheimer 1992 make no mention of biopsies and the remaining five studies performed biopsies to diagnose episodes of acute rejection.

Renal function

GFR and creatinine clearance

Four studies reported GFR or creatinine clearance at days one and seven and at one, three and six months (Kuypers 2004; Ladefoged 1994; Neumayer 1989; Wilkie 1994). These measures have been included on the same plot, with the summary point turned off. There were no significant differences in GFR/creatinine clearance at any of the measured time points (Analysis 1.4). Data from one study (Dawidson 1991) has not been included in this outcome as it is not clear from the text if only data from patients with GFR > 10 mL/min has been reported. Clarification has been sought.

Serum creatinine

Nine studies reported serum creatinine levels at various time points (Dawidson 1991; Frei 1987; Harper 1997; Kuypers 2004; Ladefoged 1994; Lustig 1996; Morales 1990; Oppenheimer 1992; Tenschert 1991). There was a significant reduction in serum creatinine at day two for the calcium channel blocker group (Analysis 1.5.1: MD -248.00 µmol/L, 95%CI -441.17 to -54.83, P = 0.01). Similar significant reductions were seen at day 7 (*analysis 01.05.02*: MD -87.61 µmol/L, 95% CI -147.95 to -27.27, P = 0.004; I^2 = 0%) and day 14 (Analysis 1.5.3: MD -129.00 µmol/L, 95% CI -149.74 to -108.26, P < 0.00001). However for one, three and six months post-transplant there were no significant differences between the calcium channel blocker and the placebo/no treatment groups.

Delayed graft function

Nine studies reported delayed graft function (Dawidson 1991 Frei 1987; Harper 1997; Kuypers 2004; Morales 1990; Neumayer 1989; Neumayer 1992a; Neumayer 1992b; Wilkie 1994). There was a significant reduction in the number of patients with delayed graft function in the calcium channel blocker group (Analysis 1.6*:* RR 0.55, 95% CI 0.42 to 0.73; P = 0.00003; I^2 = 2.2%).

Requirement for haemodialysis post-operatively

Five studies reported the number of haemodialysis sessions/patient required post-operatively (Morales 1990; Neumayer 1989; Neumayer 1992a; Neumayer 1992b; Tenschert 1991). All three studies by Neumayer give the results as the mean number of dialysis sessions/patient for the whole group (i.e. those with immediate graft function are included) rather than only those with delayed graft function who required dialysis. Neumayer 1992a, two patients with delayed graft function in the diltiazem group required a total of 12 dialysis sessions between them, and in the control group with delayed graft function nine patients required a total of 78 haemodialysis sessions. The number of dialysis/patient in the remaining two studies (Morales 1990; Tenschert 1991) tended to be higher in the control groups but this did not reach statistical significance.

Adverse events

Four studies reported adverse events. Ladefoged 1994 reported one death due to cytomegalovirus (CMV) infection and one episode of life threatening sepsis in the diltiazem group. Wilkie 1994 reported two cases of headache and oedema associated with nifedipine therapy, eight cases of CMV infection, and two cases of pneumocystis pneumonia (group/s not stated). One patient in the nifedipine group also developed Epstein Barr virus-induced cerebral lymphoma and one patient in the control group had a cerebrovascular event. It is not clear whether the side effects reported in the nifedipine group occurred in different patients. Kuypers 2004 reports an extensive list of side effects although there was no significant difference in the incidence of adverse or serious adverse events between the calcium channel blocker and placebo groups. The most commonly reported side effects in this study were hypertension, constipation, oedema, diarrhoea, palpitations and tachycardia. Dawidson 1991 reported three deaths in the control group due to intestinal perforation, pneumonia and liver failure.

DISCUSSION

Very few studies have been designed specifically to look at the effect that calcium channel blockers have on the development

of ATN post-transplantation. This meta-analysis of thirteen studies showed that the use of calcium channel blockers in the peri-operative period reduced the incidence of ATN post-transplantation. However, this result should be treated with caution due to the small number and heterogeneity of trials. Immunosuppression post-transplant was not comparable between groups, although all patients were on a calcineurin inhibitor. In addition, the type and administration of the calcium channel blockers varied between studies. In seven of the studies the graft was not perfused with perfusate containing calcium channel blocker and one study (Neumayer 1989) assessed the effect of calcium channel blocker by only treating the donor kidney. The use of different types of calcium channel blockers may have affected the outcome.

Lustig 1996 did not show a significant difference between calcium channel blocker and placebo groups but, when analysed separately, the clinical course of recipients who received kidneys from donors aged greater than 50 years showed a significantly higher rate of ATN in the placebo group compared to matched calcium channel blocker recipients (91% versus 36%, $P < 0.02$). Donor age and cold ischaemic times were apparently comparable (no data provided) but the age of recipients in the treatment group was significantly lower. By three months post-transplant there was no significant difference in serum creatinine. This finding needs further investigation as the use of kidneys from older donors is becoming much more common place due to the shortage of kidneys for transplantation. If this result can be reduplicated calcium channel blockers may have a role in reducing the risk of ATN in high-risk patients receiving kidneys from older donors.

Only one study routinely performed biopsies to confirm the clinical diagnosis of ATN, and the definition of ATN differed widely between studies, which contributes to the difficulty in comparing studies and pooling data.

The small number of studies available for review is disappointing and makes it difficult to come to any definite conclusion about the effects of calcium channel blockers on ATN in the post-transplant period. Overall study quality was poor with only one study having adequate allocation concealment. Inadequate allocation concealment may over exaggerate the efficacy of the experimental treatment and meta-analysis of trials with inadequate allocation concealment can overestimate the benefits of treatment.

Exclusion of unpublished trials will result in publication bias. As unpublished trials are more likely to show no effect of treatment, publication bias will also over estimate the benefits of treatment. Funnel plot asymmetry will indicate whether or not bias is present but due to the small number of studies was not possible.

It is difficult to assess what the long-term gain of a decrease in the incidence of ATN, as patients were followed up at different time periods and for different lengths of time. It would appear from the limited data available that calcium channel blockers given in the peri-operative period have no effect on renal function at three and six months post-transplant.

AUTHORS' CONCLUSIONS

Implications for practice

Calcium channel blockers given in the peri-operative period appear to reduce the incidence of ATN post-transplantation. The result should be treated with caution due to the small number of trials available and the heterogeneity of the trials, in particular the use of different calcium channel blockers given by different routes, the different definitions of ATN/initial non-function, marked differences in the immunosuppressive regimens and different lengths of follow-up.

Implications for research

Studies designed specifically to determine the relationship between the post-operative administration of calcium channel blockers and the incidence of ATN post-transplantation are still desirable. They should also assess the long-term benefits of any reduction in ATN. Subsequent trials should include protocol biopsies.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Dawidson 1991

Methods	Randomised: yes Blinded: unknown Intention to treat: no
Participants	INCLUSION CRITERIA No history of calcium channel blocker use. TREATMENT GROUP (verapamil) Number: 30 Age: 36.4 ± 12.4 years. Cold ischaemic time: 19.3 ± 8.6 hours HLA A, B, DR mismatches: 1.0 ± 0.9 DR mismatches 1.3 ± 0.7 PRA: 15.3% ± 29.6 CONTROL GROUP Number: 29 Age: 41.1 ± 12.2 years Cold ischaemic time: 20.1 ± 8.1 hours. HLA A, B, DR mismatches: 1.0 ± 1.0 DR mismatches 1.5 ± 0.6 PRA: 20.6 ± 28.2 EXCLUSION CRITERIA Pre-op CCB use, cardiac arrythmia, no consent, failure to randomise.

Dawidson 1991 *(Continued)*

Interventions	TREATMENT GROUP Graft perfused with Euro-Collins (13) or University of Wisconsin (17). 10 mg verapamil given intra-arterially into newly anastomosed renal artery in 2.5 mg increments. Post operatively 120 mg slow release verapamil given twice daily for 14 days. CONTROL GROUP Graft perfused with Euro-Collins (14) or university of Wisconsin (15). IMMUNOSUPPRESSION Identical in both groups. Methylprednisolone 375 mg iv on the day of surgery (day 0) tapered to prednisolone 20 mg/d by day 10. Azathioprine 100 mg (day 0) and decreased to 25 mg daily for 5 days. Minnesota antilymphocyte globulin 15 mg/kg/d iv on post-op days 1 to 5. If not dialysis dependent CSA A 7 mg/kg started on day 6 and increased to 12 mg/kg on day 7. Dose adjusted according to renal function and trough level.
Outcomes	1. Number with immediate graft function 2. Number with delayed graft function 3. Serum creatinine days 1 to 12 4. GFR days 1-3, 7-9.
Notes	Definition of delayed graft function: GFR < 10 mL/min at day 7. Title of table including daily creatinine for days 1-12 indicated results are for 30 patients receiving verapamil and 29 controls. Text comments on results for day 7 and says that patients with DGF have been removed i.e. number for verapamil 26 and control 22. Only results for day 7 used as not clear how many patients have DGF on other days. Only GFR for days 7-9 included as number of patient included in days 1-3 not clear.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Frei 1987

Methods	Randomised: yes Blinded: unknown Intention-to-treat: yes
Participants	TREATMENT GROUP (diltiazem) Number: 54 Age: 41.2 ± 10 years Donor age: 33.5 ± 14 years Cold ischaemia time (hours): 26.43 ± 3.15 Warm ischaemia time (min): 7 ± 8 HLA mismatch (AB): 2.3 ± 1.1 HLA mismatch (DR): 0.4 ± 0.4 Diuresis - donor (mL/h) 383 ± 243 Donor creatinine (umol/L): 102.1 ± 48 CONTROL GROUP Number: 56 Age: 40.7 ± 12 years Donor age: 35.3 ± 12 years Cold ischaemia time (hours): 25.49 ± 3.62

Frei 1987 *(Continued)*

	Warm ischaemia time (min): 37 ± 7 HLA mismatch (AB): 2.3 ± 1 HLA mismatch (DR): 0.6 ± 0.5 Diuresis - donor (mL/h): 391 ± 307 Donor creatinine (umol/L): 91.2 ± 38 EXCLUSION CRITERIA Cardiac conduction disturbances, CCF, liver disease, age < 18 or > 65, no consent
Interventions	TREATMENT GROUP (diltiazem) Graft perfused with Euro-Collins. Diltiazem 100 mg/L added to perfusate. IV diltiazem 0.28 mg/kg 2 hours pre-op followed by an infusion of diltiazem 0.12 mg/kg/h for up to 72 hours. Then 90 mg orally bd until day 30. IMMUNOSUPPRESSION Same in both groups - prednisolone 1 mg/kg tapered to 7.5 mg daily by 3 months, CSA A 10 mg/kg/d 6 hours post-op orally in 2 divided doses. Dose adjusted - trough (RIA) 400-600 ng/mL.
Outcomes	1. Number with immediate graft function 2. Number with delayed graft function 3. GFR at 1 month
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Harper 1997

Methods	Randomised: yes Blinded: unknown Intention to treat: yes
Participants	TREATMENT GROUP (nifedipine retard) Number: 28 PRA status: 14.5%. CONTROL GROUP Number: 24 PRA status: 2.3%.
Interventions	TREATMENT GROUP (nifedipine retard) Oral nifedipine retard 10 mg three times daily for one week then 20 mg twice daily. Increased to 40 mg twice daily if necessary for BP. First dose given pre-operatively. IMMUNOSUPPRESSION Same in both groups: CSA 17 mg/kg/d reduced by 2 mg/kg/wk to maintenance of 7mg/kg/d at 6 weeks. Identical prednisolone regimens in both groups (dose not given)
Outcomes	1. Number with immediate graft function 2. Number with delayed graft function 3. Creatinine at day 14

Harper 1997 *(Continued)*

Notes	Three study groups. Groups A and B suitable for inclusion. Definition of DGF: dialysis dependence by 4th post operative day in the absence of graft rejection. No significant difference between groups in donor or recipient age, HLA mismatches, total and cold ischaemic time, anastomosis time or graft perfusion fluid. No details given.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Kuypers 2004

Methods	Randomised: yes Blinded: no Intention to treat: no
Participants	INCLUSION CRITERIA Age: 18-65 years Primary cadaveric kidney transplantation Donor age 10-65 years Written informed consent TREATMENT GROUP (lacidipine) Number: 66 Age: 46.5 ± 12.6 years Donor age: 37.9 ± 16 years Cold ischaemia time (hours): 17.42 ± 3.73 HLA mismatch: 2.48 ± 1.3 CONTROL GROUP Number: 65 Age: 48.3 ± 12.6 years Donor age: 43.5 ± 14.8 years Cold ischaemia time (hours): 17.7 ± 5.4 HLA mismatch: 2.43 ± 1.2 EXCLUSION CRITERIA Pregnancy. Women of childbearing age had to be taking adequate contraception for the duration of the study.
Interventions	TREATMENT GROUP Lacidipine 2 mg daily immediately after transplant. Dose increased at 1 and 3 weeks if diastolic BP remained elevated. Thereafter other antihypertensives (excluding CCB) were added in. Preservation fluid: University of Wisconsin (67.2%), HTK (5.2%), Euro-Collins (20.7), other (6.9%). CONTROL GROUP Preservation fluid: University of Wisconsin (58.6%), HTK (12%), Euro-Collins (19%), Other (8.6%). IMMUNOSUPPRESSION Both groups received CSA (dose adjusted to maintain trough 100-250 ng/mL), MMF 1 g twice daily, prednisone 0.5 mg/kg/d for one month, tapering to a minimum maintenance dose of 5 mg/d.
Outcomes	1. Delayed graft function 2. Rejection episodes 3. Serum creatinine 1, 3, 6, 12, 18 and 24 months 4. Creatinine clearance and GFR 1, 3, 6, 12, 18 and 24 months

Kuypers 2004 *(Continued)*

	5. Adverse events and hospitalisation
Notes	Definition of DGF: need for dialysis post transplantation. 131 enrolled, 41 patients withdrawn (adverse events 21, patient's refusal 7, investigator's decision 7, lost from follow up 2). All 131 patients evaluated in the safety analysis, 118 included in the ITT analysis. 13 excluded from ITT because of missing data.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Ladefoged 1994

Methods	Randomised: yes Double blind: yes Intention-to-treat: no
Participants	TREATMENT GROUP (diltiazem) Number: 19 Age: 42 years (range 21-64) Donor age: 45 years (range 12-64) Cold ischaemia time (hours): 22.6 (15-35) Warm ischaemia time (min): 9.0 (0-22) HLA mismatch (AB): 1.9 (0-3) HLA mismatch (DR): 0.4 (0-2) Diuresis - donor (mL/h): not reported Donor creatinine: not reported CONTROL GROUP Number: 20 Age: 45 years (range 20-64) Donor age: 41 years (range 16-61) Cold ischaemia time (hours): 23.7 (12-39) Warm ischaemia time (min): 9.6 (0-33) HLA mismatch (AB): 1.6 (0-3) HLA mismatch (DR): 0.6 (0-2) Diuresis - donor (mL/h): not reported Donor creatinine: not reported
Interventions	Grafts perfused with Euro-Collins perfusate. TREATMENT GROUP Grafts also perfused with diltiazem 20 mg/L. Recipients given diltiazem bolus 0.3 mg/kg pre-op, then infusion 3 mg/kg/24 h then 60-120 mg tid orally. CONTROL GROUP Placebo 0.3 mg/kg bolus, then infusion 3 mg/kg/24 h then 60-120 mg tid orally. IMMUNOSUPPRESSION Same in both groups - CSA, prednisolone and azathioprine.
Outcomes	1. DGF 2. Rejection 3. re-rejection

Ladefoged 1994 *(Continued)*

	4. Graft survival 5. Creatinine clearance 6. Serum creatinine
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Lustig 1996

Methods	Randomised: yes Double blind: yes Intention-to-treat: no
Participants	TREATMENT GROUP (gallopamil) Number: 23 Age: 37 ± 12 years Donor age (years): 51 ± 15 Cold ischaemia time (hours): 19 ± 5 Warm ischaemia time (min): not reported HLA mismatch: not reported Diuresis, donor (mL/h): not reported Donor creatinine mg/dL (umol/L): 1.2 ± 0.3 (106 ± 26.5) CONTROL GROUP Number: 24 Age: 35 ± 17 years Donor age (years): 42 ± 21 Cold ischaemia time (hours): 19 ± 6 Warm ischaemia time (min): not reported HLA mismatch: not reported Diuresis, donor (mL/h): not reported Donor creatinine mg/dL (umol/L): 1.2 ± 0.3 (106 ± 26.5)
Interventions	Grafts perfused with Euro-Collins solution. TREATMENT GROUP Gallopamil 12 mg/L added to perfusate. Recipient given gallopamil 0.00015 mg/min/kg infusion for 12 hours then 75 mg bd for 3 months. CONTROL GROUP Placebo 0.00015 mg/min/kg infusion for 12 hours followed by placebo 75 mg bd for 3 months. IMMUNOSUPPRESSION Same in both groups: ATG 100 mg/d for 10 days, CSA from day 5, azathioprine 2mg/kg/d from day 5, prednisolone from day 1.
Outcomes	1. Oliguric ATN. 2. Serum creatinine days 2, 7, 120. 3. Graft survival. 4. Patient survival.
Notes	DEFINITION OF ATN

Lustig 1996 *(Continued)*

	Oliguria and /or delayed decrease in serum creatinine, together with morphologic changes typical of ATN on aspiration or core biopsy.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Morales 1990

Methods	Randomised: yes Double blind: no Intention-to-treat: yes
Participants	TREATMENT GROUP (nifedipine retard) Number: 27 Recipient age: 46.8 ± 9.5 Cold ischaemic time (hours): 23.8 ± 1.9 HLA DR : Rx 1.7 ± 0.8 CONTROL GROUP Number: 27 Recipient age: 38.9 ± 13.5 Cold ischaemic time (hours): 22.6 ± 3.8 HLA DR: 1.8 ± 0.4
Interventions	TREATMENT GROUP Nifedipine retard 20 mg pre-op followed by 40 mg /day for the first 15 post-op days. CONTROL GROUP Placebo IMMUNOSUPPRESSION The same in both groups. Steroids 0.5 mg/kg/d. CSA A 10 mg/kg before surgery and at t = 24 hours, dose reduced gradually according to trough levels or side effects.
Outcomes	1. Immediate graft function 2. Acute tubular necrosis - not biopsy proven 3. Rejection episodes 4. Length of hospital stay 5. Number of haemodialysis/patient 6. Plasma creatinine
Notes	Definition of DGF

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Neumayer 1989

Methods	Randomised: yes Blinded: no Intention-to-treat: yes
Participants	TREATMENT GROUP (Diltiazem) Number: 16 Age: 46 ± 12 years Donor age: 47 ± 16 years Ischaemia time Cold ischaemia time (hours): 21 ± 4 Warm ischaemia time (min): 34 ± 4 Mismatches: 2.8 ± 0.8 Diuresis - donor (mL/h): not reported Donor creatinine: 102 ± 68 umol/L CONTROL GROUP Number: 19 Age: 48 ± 13 years Donor age: 42 ± 17 years Ischaemia time Cold ischaemia time (hours): 21 ± 4 Warm ischaemia time (min): 37 ± 9 Mismatches: 2 ± 0.9 Diuresis - donor (mL/h): not reported Donor creatinine: 141 ± 144 umol/L
Interventions	Grafts perfused with Euro-Collins solution. TREATMENT GROUP Diltiazem 20 mg/L added to perfusate of study group. Recipients not given calcium antagonist. IMMUNOSUPPRESSION CSA, steroids
Outcomes	1. Primary graft function 2. DGF 3. Haemodialysis 4. Renal perfusion 5. Rejection episodes
Notes	Results have been converted from mean ± SEM to mean ± SD. Four groups: 1. control, 2. diltiazem, 3. iloprost and 4. diltiazem plus iloprost. Data from control and diltiazem groups extracted. No exclusion criteria given.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Neumayer 1992a

Methods	Randomised: yes Blinded: no

Neumayer 1992a *(Continued)*

	Intention-to-treat: yes
Participants	TREATMENT GROUP (diltiazem) Number: 20 Age: 42 ± 4 years Donor age: 44 ± 4 years Cold ischaemia time (hours): 19 ± 0 Warm ischaemia time (min): 31 ± 0 HLA mismatch: 2.7 ± 0.4 Diuresis - donor (mL/h): 269 ± 54 Donor creatinine: 92 ± 4 umol/L CONTROL GROUP Number: 22 Age: 40 ± 5 years Donor age: 38 ± 5 years Cold ischaemia time (hours): 21 ± 0 Warm ischaemia time (min): 38 ± 0 HLA mismatch: 2.9 ± 0.5 Diuresis - donor (mL/h): 292 ± 52 Donor creatinine: 105 ±9 umol/L EXCLUSION CRITERIA No consent, systolic BP < 91 mm Hg, CCF, heart block without pacemaker, history of bleeding
Interventions	Grafts perfused with Euro-Collins solution. TREATMENT GROUP Perfusion fluid also contained diltiazem 20 mg/L. Recipient: bolus diltiazem 0.28 mg/kg then infusion 0.002 mg/min/kg for 2 days, then 60 mg bd for 396 ± 79 days. IMMUNOSUPPRESSION For both groups: CSA, prednisolone.
Outcomes	1. Primary graft function. 2. Delayed graft function 3. HD post transplant 4. Rejection episodes
Notes	Three randomised studies in one paper. Study one suitable for inclusion. Results have been converted from mean ± SEM to mean ± SD. Primary graft function defined as no HD required within the first 7 days post transplant.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Neumayer 1992b

Methods	Randomised: yes Blinded: no Intention-to-treat: yes
Participants	TREATMENT GROUP (diltiazem) Number: 10

Neumayer 1992b *(Continued)*

	Age: 43 ± 6 years Donor age: 34 ± 6 years Cold ischaemia time (hours): 25 ± 3 Warm ischaemia time (min): 37 ± 6 HLA mismatch: 1.7 ± 0.9 Diuresis - donor (mL/h): 324 ± 76 Donor creatinine: 102 ±13 umol/L CONTROL GROUP Number: 11 Age: 48 ± 3 years Donor age: 35 ± 3 years Cold ischaemia time (hours): 25 ± 0 Warm ischaemia time (min): 40 ± 7 HLA mismatch: 1.7 ± 1.3 Diuresis - donor (mL/h): 385 ± 90 Donor creatinine: 104 ± 10 umol/L EXCLUSION CRITERIA No consent, systolic BP < 91 mm Hg, CCF, heart block without pacemaker, history of bleeding
Interventions	Grafts perfused with Euro-Collins solution. Kidney not pre treated with calcium antagonist. Treatment group: Recipient - bolus diltiazem 0.28 mg/kg then infusion 0.002 mg/kg/m for 2 days, then 60 mg bd for 396 +/- 79 days. Immunosuppression: For both groups - cyclosporin, prednisolone.
Outcomes	1. Primary graft function. 2. Delayed graft function 3. HD post transplant 4. Rejection episodes
Notes	Three randomised studies in one paper. Study two suitable for inclusion. Results have been converted from mean ± SEM to mean ± SD. Primary graft function defined as no HD required within the first 7 days post transplant.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Oppenheimer 1992

Methods	Randomised: yes Blinded: unknown Intention-to-treat: unknown
Participants	No inclusion or exclusion criteria specified. TREATMENT GROUP (diltiazem) Number: 25 Age: 46.91 years Donor age: 34.86 years Cold ischaemia time (hours): 14.8 Warm ischaemia time (min): not reported HLA mismatch: not reported Diuresis - donor (mL/h): not reported Donor creatinine: not reported

Oppenheimer 1992 *(Continued)*

	CONTROL GROUP Number: 30 Age: 43.9 years Donor age: 29.66 years Cold ischaemia time (hours): 15.9 Warm ischaemia time (min): not reported HLA mismatch: not reported Diuresis - donor (mL/h): not reported Donor creatinine: not reported
Interventions	Graft perfused with Euro-Collins ± diltiazem 20 mg/L. TREATMENT GROUP Did not receive dopamine Recipients: Given Diltiazem bolus 0.28 mg/kg followed by an infusion 0.12 mg/kg/h for 72 hours, then 60 mg bd from day 4-6 weeks. CONTROL GROUP Had dopamine infusion. IMMUNOSUPPRESSION CSA only (both groups).
Outcomes	1. Incidence and duration of ATN 2. Rejection episodes 3. Renal function 4. CSA level
Notes	25 patients randomised to diltiazem group in text but table only has 23 patients in diltiazem group, with no mention in the text as to what happened to the other 2 patients ?typographical error Definition of ATN: Dialysis needed within first week post transplant.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Tenschert 1991

Methods	Randomised: yes Blinded: no Intention-to-treat: yes
Participants	TREATMENT GROUP (diltiazem) Number: 23 Age: 42.65 ± 14.22 years Donor age: not reported Cold ischaemia time (hours): 27.75 ± 8.33 Warm ischaemia time (min): not reported HLA mismatch: not reported Diuresis - donor (mL/h): not reported Donor creatinine: not reported CONTROL GROUP Number: 23 Age: 43.37 ± 15.12 years Donor age: not reported

Tenschert 1991 *(Continued)*

	Cold ischaemia time (hours): 27.89 ± 5.51 Warm ischaemia time (min): not reported HLA mismatch: not reported Diuresis - donor (mL/h): not reported Donor creatinine: not reported
Interventions	Grafts not perfused. TREATMENT GROUP Recipients: diltiazem 1.7 mg/kg/24 h immediately post-op for 72 hours, then 30 mg tid or qid. IMMUNOSUPPRESSION For both groups - prednisolone, azathioprine, CSA.
Outcomes	1. Rejection episodes 2. Dialysis therapy 3. Length of hospital stay
Notes	HD stopped when creatinine < 442 umol/L during the dialysis free interval

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Wilkie 1994

Methods	Randomised: yes Double blind: yes Intention-to-treat: no
Participants	TREATMENT GROUP (nifedipine) Number: 16 Age: 40 ± 14 years Donor age: not reported Cold ischaemia time (hours): not reported Warm ischaemia time (min): not reported HLA mismatch: not reported Diuresis - donor (mL/h): not reported Donor creatinine: not reported CONTROL GROUP Number: 17 Age: 44 ± 13 years Donor Age: not reported Cold ischaemia time (hours): not reported Warm ischaemia time (min): not reported HLA mismatch: not reported Diuresis - donor (mL/h): not reported Donor creatinine: not reported
Interventions	TREATMENT GROUP Nifedipine LA 20 mg bd for 48 hours followed by placebo for a total of three months CONTROL GROUP Placebo for 3 months

Wilkie 1994 *(Continued)*

	IMMUNOSUPPRESSION Azathioprine, prednisolone and CSA
Outcomes	1. Early graft function 2. Renal function at 3 and 6 months post transplantation
Notes	Paper includes three study groups P (placebo) and NS (Nifedipine) are suitable for inclusion. Definition of DGF - requirement for dialysis in the immediate post transplant period.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

BP - blood pressure; CCB - calcium channel blocker; CCF - chronic cardiac failure; CSA - cyclosporin; DGF - delayed graft function; MMF - mycophenolate mofetil

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

Study	Reason for exclusion
Aros 2005	Study investigated the correlation between concentration of CSA 2 hours after dosing with absorption area under the curve over the first 4 hours.
Barenbrock 1995	Looking at effect of nitrendipine on graft function - randomisation into study 6-12 weeks post-transplant.
Berg 1991	Not given in peri-operative period. Not RCT, no data re type of donors.
Calo 2002	Study looking at the anti-oxidant effect of carvedilol in post-transplant patients. Uses nifedipine as control.
Chanard 2003	Study is comparing the effect of amlodipine versus tertatolol on CSA-induced hyperuricaemia in post-renal transplant recipients with hypertension.
Cuharadoglu 1993	Study presented in abstract form and looks at effect of verapamil on graft survival and CSA levels.
Dawidson 1989	Calcium antagonist not started until day three post-operatively - study is really looking at the effect of calcium antagonist on rejection.
Dawidson 1992	Summary of two prospective and one retrospective studies. Study 1 published and possible for inclusion but excluded because verapamil not started until day 3 post operatively. Study 2 has already been included in review. Study 3 retrospective.
Donmez 1999	Includes living-related transplants.
Duggan 1985	Only gave verapamil to the donor.
el-Agroudy 2003	This study evaluates the effect of losartan on TGF-Beta 1 plasma levels and proteinuria in hypertensive transplant recipients. Two comparison groups - one receiving captopril, the other amlodipine.
Ferguson 1990	Retrospective study.

Study	Reason for exclusion
Gossmann 2002	Study looks at the effect of gallopamil on renal plasma flow and GFR in patients transplanted at least 6 months before.
Harper 1992	Paper is assessing the effect of nifedipine on high dose CSA.
Harper 1996	Includes living-related donors.
Kelly 1990	Didn't look at the data we are interested in.
Kumana 2003	Study assesses whether diltiazem co-treatment achieves worthwhile dose reduction of Neoral.
Lehtonen 2000	Unable to confirm donor population.
Madsen 1998	Didn't look at the outcome data we are interested in. Includes living donors.
McLaughlin 2005	Assesses effect of theophylline and loop diuretic in acute tacrolimus nephrotoxicity.
McNally 1990	Looks at the effect of nifedipine on renal haemodynamics 6 months post-transplant.
Midtvedt 1999	Study is looking at the effect of nifedipine on acute rejection in hypertensive post-transplant patients.
Midtvedt 2001	Study compared the effect of lisinopril with controlled release nifedipine in treatment of post-transplant hypertension focusing on changes in LVH.
Parrott 1990	Didn't use calcium antagonist.
Pedersen 1995	Abstract. Study examines the effect of felodipine on CSA nephrotoxicity.
Pedersen 1996	Didn't look at the outcome data we are interested in.
Pirsch 1993	Didn't look at the outcome data we are interested in. Not all patients started verapamil immediately post-op (7.9 ± 0.9 days post-transplant).
Po 1994	Study examines the effect of calcium channel blockers on proteinuria in renal transplant patients.
Propper 1989	Didn't look at the outcome data we are interested in.
Puig 1991	Retrospective controls.
Santos 2002	Study looks at the effect of diltiazem on dose of CSA.
Scheuermann 1995	Looks at the effect of gallopamil on renal function in post-transplant patients on gallopamil. Patients at least 6 months post-transplant.
Schott 1994	Didn't look at the data we are interested in.
Sennesael 1996	Study looks at effects of amlodipine and perindopril on blood pressure, glomerular haemodynamics and tubule function in hypertensive cyclosporin treated renal transplant patients.
Sobh 1989	Includes living-related donors.
Sonzogni 1995	Study looking at effect of lacidipine on renal haemodynamics and cyclosporin pharmacokinetics - stable post transplant patients.

Study	Reason for exclusion
van Riemsdijk 2000	Includes living-related transplants - details not split.
Venkat 1995	Study is looking at the effect amlodipine has on pharmacokinetics of CSA in stable post-transplant patients.
Wahlberg 1992	Didn't look at the outcome data we are interested in.

DATA AND ANALYSES

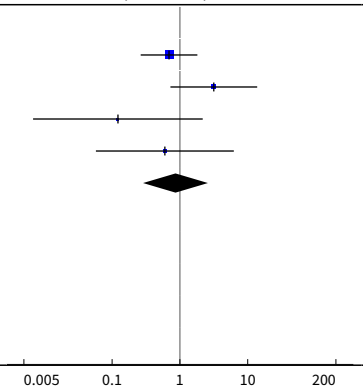
Comparison 1. Calcium channel blockers versus placebo/no treatment

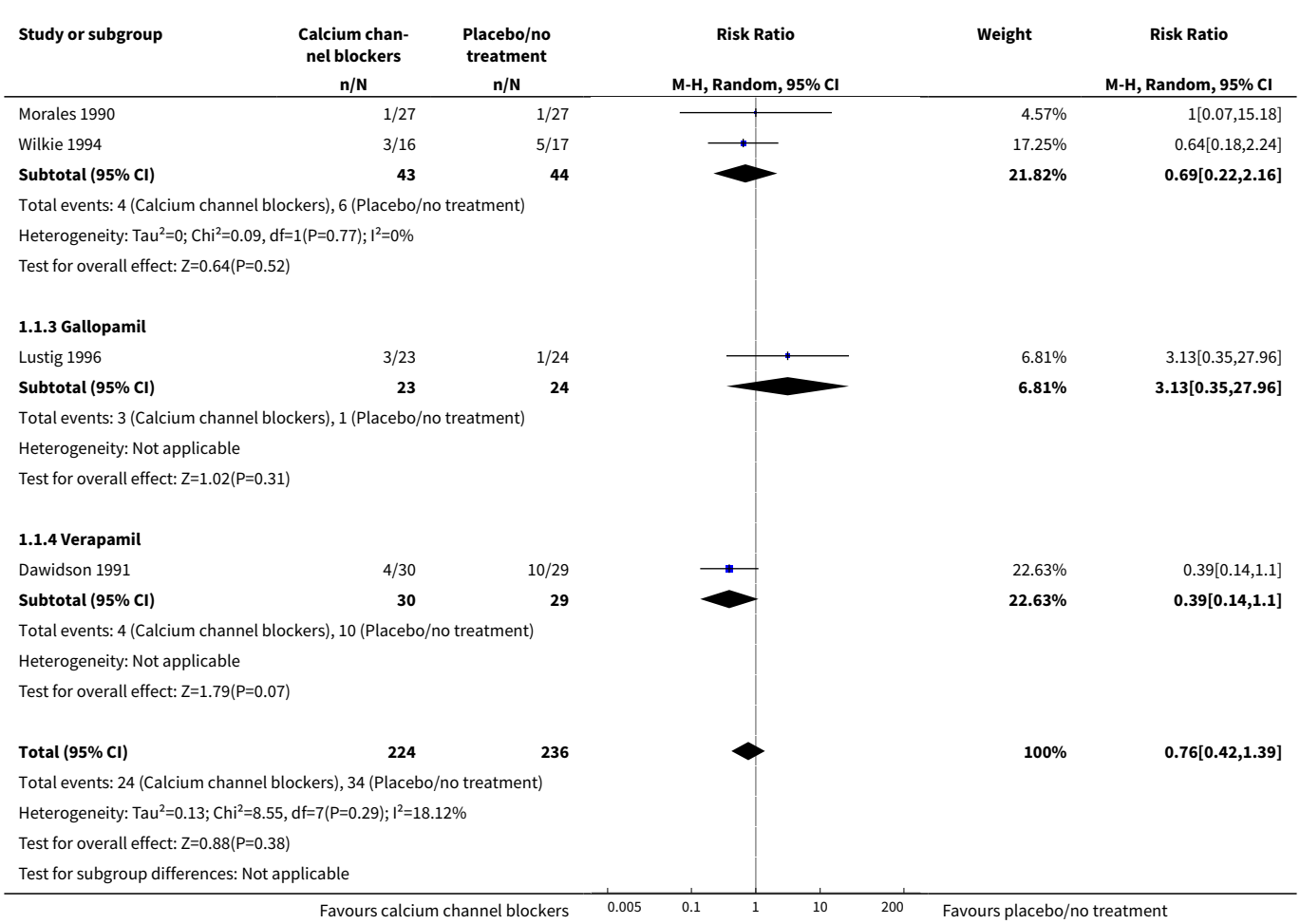
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Graft loss	8	460	Risk Ratio (M-H, Random, 95% CI)	0.76 [0.42, 1.39]
1.1 Diltiazem	4	267	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.29, 2.59]
1.2 Nifedipine	2	87	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.22, 2.16]
1.3 Gallopamil	1	47	Risk Ratio (M-H, Random, 95% CI)	3.13 [0.35, 27.96]
1.4 Verapamil	1	59	Risk Ratio (M-H, Random, 95% CI)	0.39 [0.14, 1.10]
2 Mortality	7	397	Risk Ratio (M-H, Random, 95% CI)	0.55 [0.13, 2.35]
2.1 Diltiazem	3	204	Risk Ratio (M-H, Random, 95% CI)	3.15 [0.14, 72.88]
2.2 Gallopamil	1	47	Risk Ratio (M-H, Random, 95% CI)	0.21 [0.01, 4.12]
2.3 Nifedipine	2	87	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.07, 15.60]
2.4 Verapamil	1	59	Risk Ratio (M-H, Random, 95% CI)	0.14 [0.01, 2.56]
3 Acute tubular necrosis post-transplant	8	403	Risk Ratio (M-H, Random, 95% CI)	0.62 [0.46, 0.85]
3.1 Diltiazem	6	302	Risk Ratio (M-H, Random, 95% CI)	0.53 [0.33, 0.83]
3.2 Gallopamil	1	47	Risk Ratio (M-H, Random, 95% CI)	0.66 [0.31, 1.41]
3.3 Nifedipine	1	54	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.49, 1.34]
4 GFR/creatinine clearance	4		Mean Difference (IV, Random, 95% CI)	Subtotals only
4.1 Day 1-4	1	21	Mean Difference (IV, Random, 95% CI)	-2.70 [-10.54, 5.14]
4.2 Day 7	1	21	Mean Difference (IV, Random, 95% CI)	-6.50 [-33.42, 20.42]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.3 1 month	1	118	Mean Difference (IV, Random, 95% CI)	10.0 [-0.24, 20.24]
4.4 3 months	3	190	Mean Difference (IV, Random, 95% CI)	-3.44 [-22.79, 15.91]
4.5 6 months	2	151	Mean Difference (IV, Random, 95% CI)	-2.20 [-25.56, 21.16]
5 Serum creatinine umol/L	9		Mean Difference (IV, Random, 95% CI)	Subtotals only
5.1 Day 2	1	48	Mean Difference (IV, Random, 95% CI)	-248.0 [-441.17, -54.83]
5.2 Day 7	2	95	Mean Difference (IV, Random, 95% CI)	-87.61 [-147.95, -27.27]
5.3 Day 14	1	52	Mean Difference (IV, Random, 95% CI)	-129.0 [-149.74, -108.26]
5.4 At discharge	1	46	Mean Difference (IV, Random, 95% CI)	-32.70 [-76.04, 10.64]
5.5 1 month	4	337	Mean Difference (IV, Random, 95% CI)	-14.21 [-47.79, 19.37]
5.6 3 months	4	314	Mean Difference (IV, Random, 95% CI)	0.45 [-27.15, 28.06]
5.7 6 months	2	228	Mean Difference (IV, Random, 95% CI)	-6.82 [-20.20, 6.56]
6 Delayed graft function	9	524	Risk Ratio (M-H, Random, 95% CI)	0.55 [0.42, 0.73]
6.1 Diltiazem	4	208	Risk Ratio (M-H, Random, 95% CI)	0.39 [0.23, 0.65]
6.2 Nifedipine	3	139	Risk Ratio (M-H, Random, 95% CI)	0.61 [0.33, 1.12]
6.3 Lacidipine	1	118	Risk Ratio (M-H, Random, 95% CI)	0.64 [0.36, 1.12]
6.4 Verapamil	1	59	Risk Ratio (M-H, Random, 95% CI)	0.41 [0.12, 1.45]

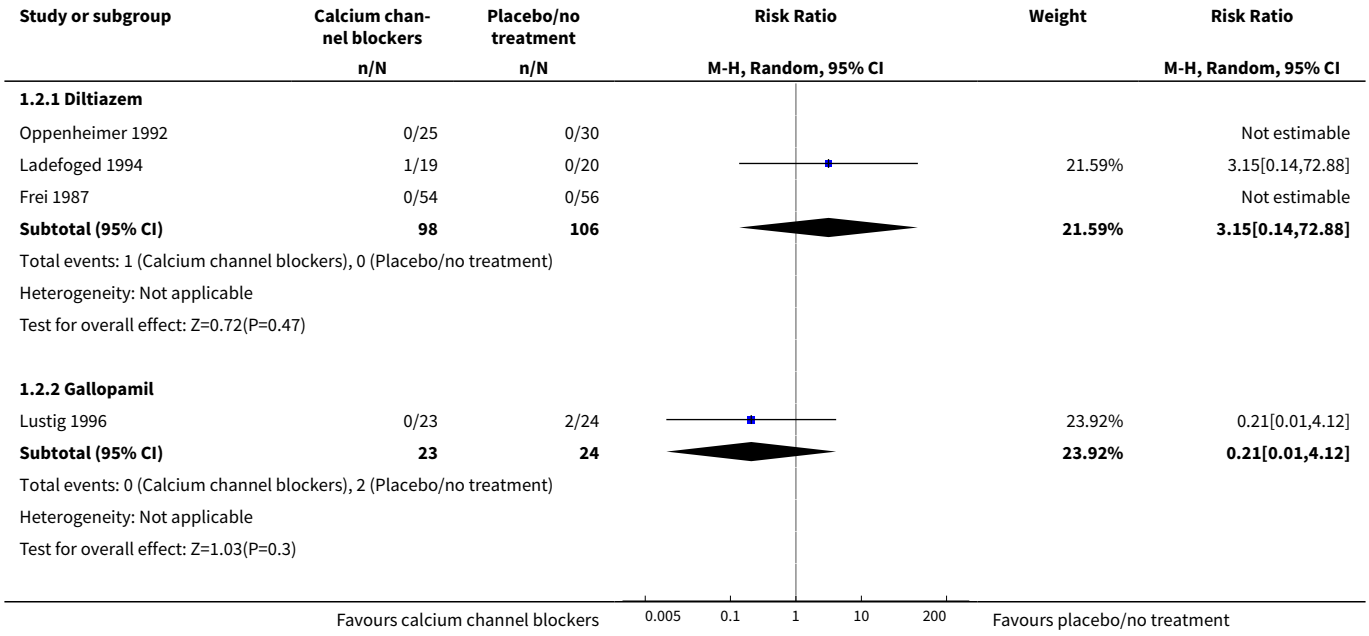
Analysis 1.1. Comparison 1 Calcium channel blockers versus placebo/no treatment, Outcome 1 Graft loss.

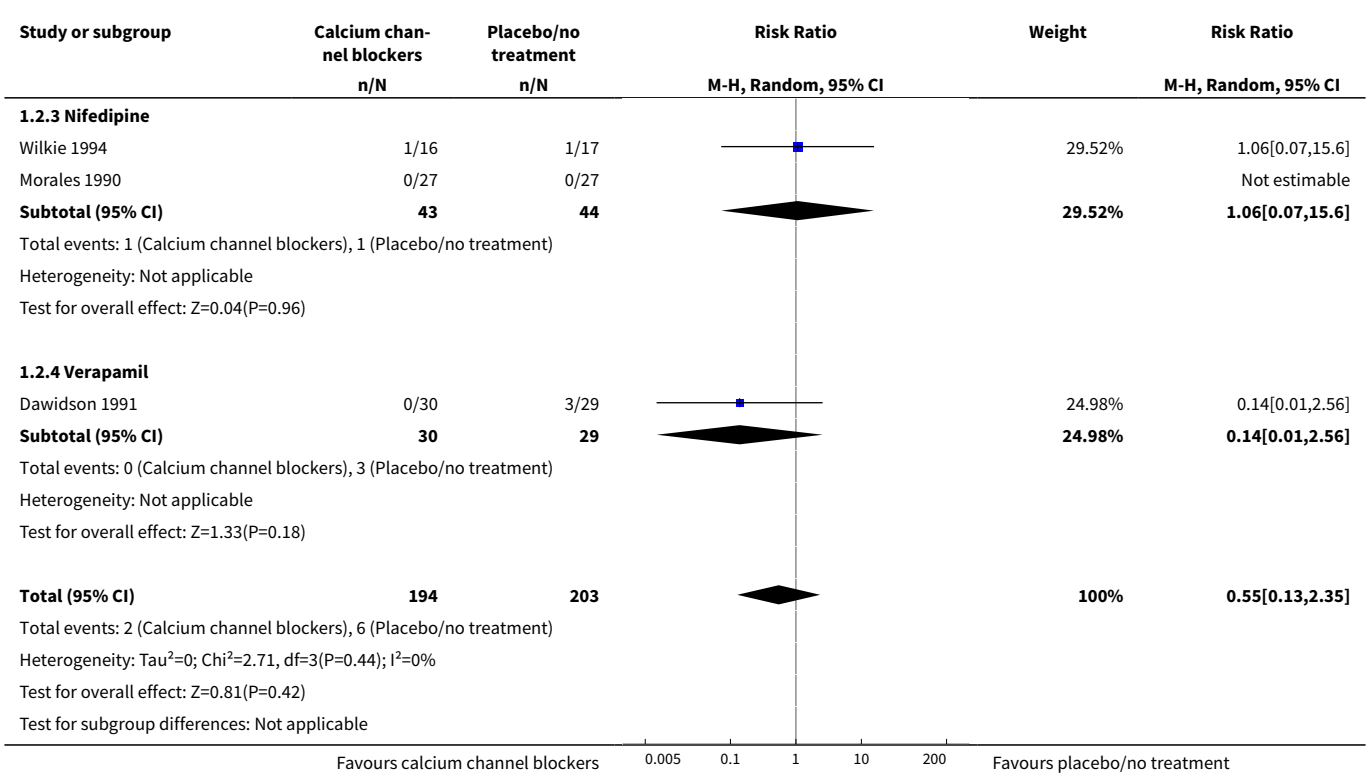
Study or subgroup	Calcium channel blockers n/N	Placebo/no treatment n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.1.1 Diltiazem					
Frei 1987	6/54	9/56		25.09%	0.69[0.26,1.81]
Ladefoged 1994	6/19	2/20		13.49%	3.16[0.72,13.76]
Neumayer 1992a	0/30	4/33		4.11%	0.12[0.01,2.17]
Oppenheimer 1992	1/25	2/30		6.04%	0.6[0.06,6.24]
Subtotal (95% CI)	**128**	**139**		**48.73%**	**0.86[0.29,2.59]**
Total events: 13 (Calcium channel blockers), 17 (Placebo/no treatment)					
Heterogeneity: Tau^2=0.51; Chi^2=5.09, df=3(P=0.17); I^2=41.09%					
Test for overall effect: Z=0.27(P=0.79)					
1.1.2 Nifedipine					



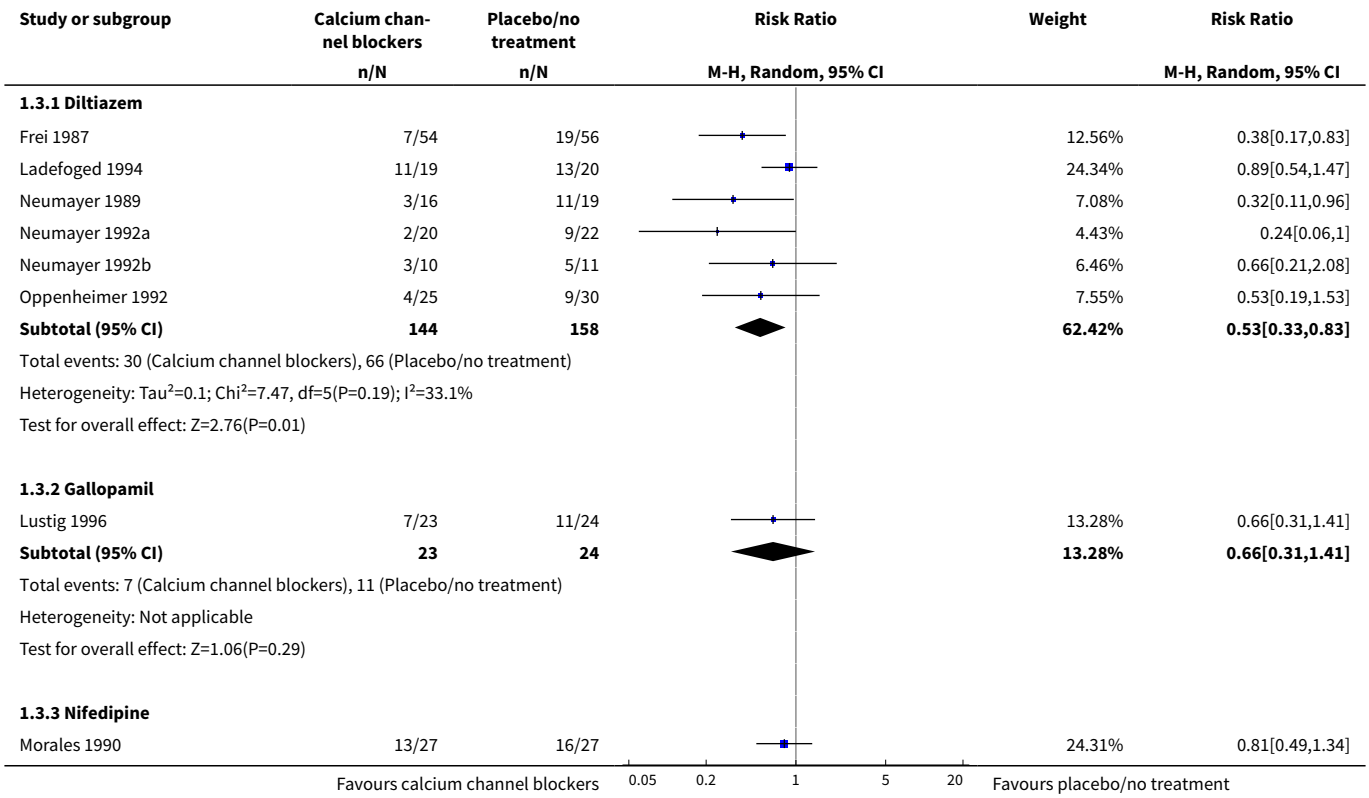


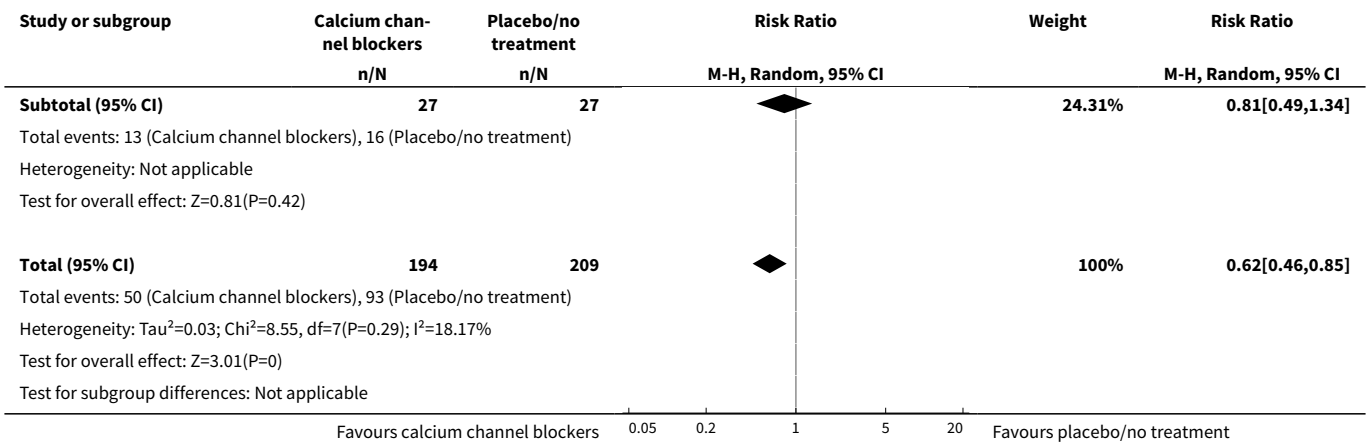
Analysis 1.2. Comparison 1 Calcium channel blockers versus placebo/no treatment, Outcome 2 Mortality.



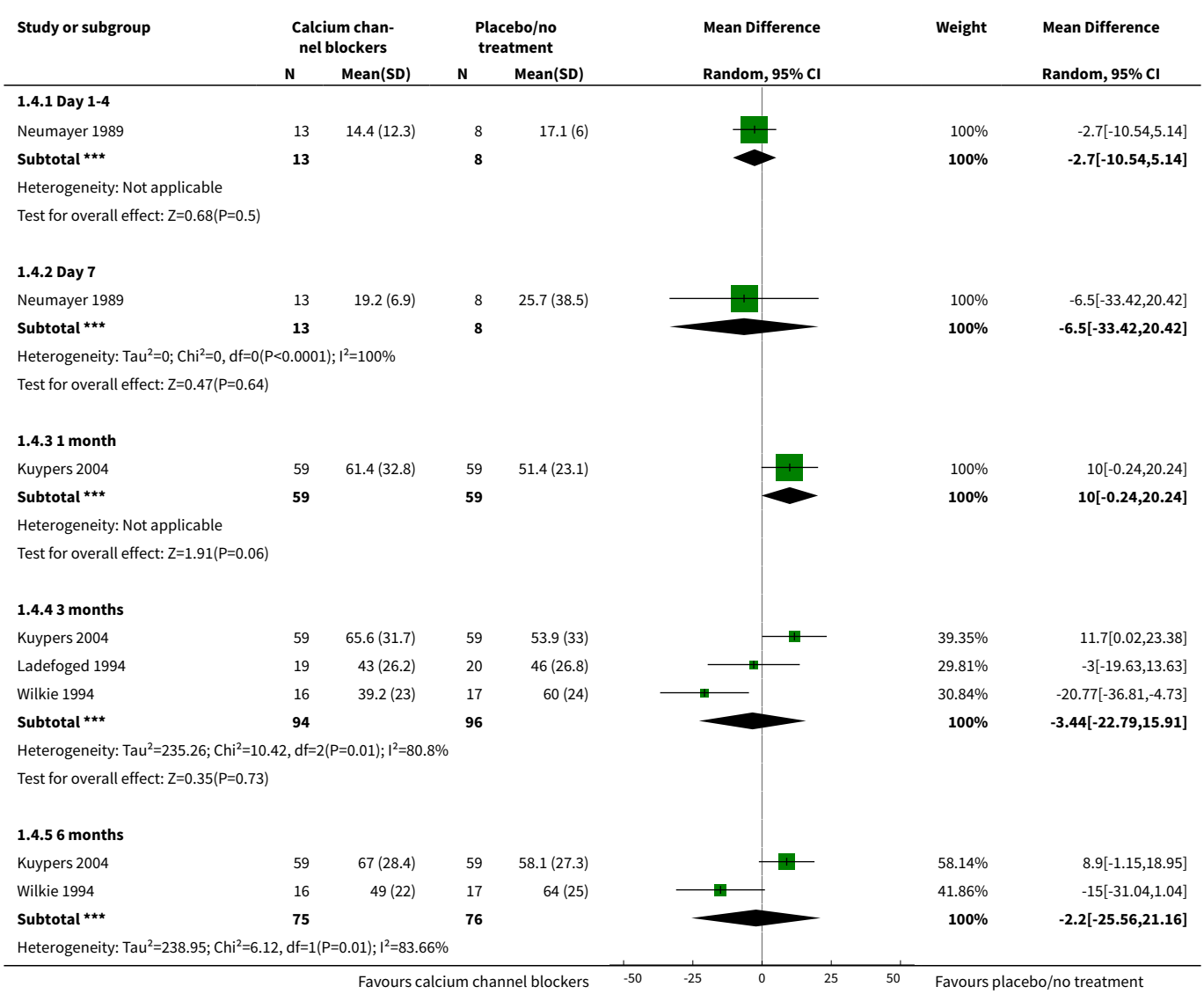


Analysis 1.3. Comparison 1 Calcium channel blockers versus placebo/no treatment, Outcome 3 Acute tubular necrosis post-transplant.





Analysis 1.4. Comparison 1 Calcium channel blockers versus placebo/no treatment, Outcome 4 GFR/creatinine clearance.

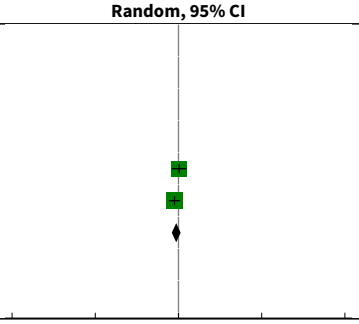


Study or subgroup	Calcium channel blockers N	Mean(SD)	Placebo/no treatment N	Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Test for overall effect: Z=0.18(P=0.85)							

Analysis 1.5. Comparison 1 Calcium channel blockers versus placebo/no treatment, Outcome 5 Serum creatinine umol/L.

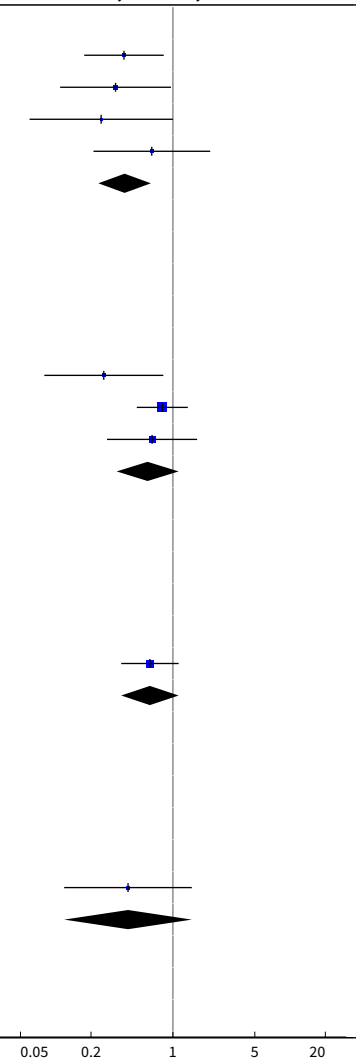
Study or subgroup	Calcium channel blockers N	Mean(SD)	Placebo/no treatment N	Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
1.5.1 Day 2							
Lustig 1996	24	442 (309)	24	690 (371)		100%	-248[-441.17,-54.83]
Subtotal ***	**24**		**24**			**100%**	**-248[-441.17,-54.83]**
Heterogeneity: Not applicable							
Test for overall effect: Z=2.52(P=0.01)							
1.5.2 Day 7							
Dawidson 1991	26	132.6 (22.1)	22	221 (150.3)		79.27%	-88.4[-151.78,-25.02]
Lustig 1996	23	371 (336)	24	451 (354)		20.73%	-80[-277.27,117.27]
Subtotal ***	**49**		**46**			**100%**	**-87.61[-147.95,-27.27]**
Heterogeneity: Tau^2=0; Chi^2=0.01, df=1(P=0.94); I^2=0%							
Test for overall effect: Z=2.85(P=0)							
1.5.3 Day 14							
Harper 1997	28	154 (10)	24	283 (51)		100%	-129[-149.74,-108.26]
Subtotal ***	**28**		**24**			**100%**	**-129[-149.74,-108.26]**
Heterogeneity: Not applicable							
Test for overall effect: Z=12.19(P<0.0001)							
1.5.4 At discharge							
Tenschert 1991	23	156.5 (42.4)	23	189.2 (97.2)		100%	-32.7[-76.04,10.64]
Subtotal ***	**23**		**23**			**100%**	**-32.7[-76.04,10.64]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.48(P=0.14)							
1.5.5 1 month							
Frei 1987	54	167 (58)	56	176 (98)		30.21%	-9[-38.97,20.97]
Kuypers 2004	59	155 (106)	59	173 (77)		29.51%	-18[-51.43,15.43]
Morales 1990	27	150 (88)	27	268 (248)		15.34%	-118[-217.26,-18.74]
Oppenheimer 1992	25	221 (115)	30	194 (80)		24.94%	27[-26.4,80.4]
Subtotal ***	**165**		**172**			**100%**	**-14.21[-47.79,19.37]**
Heterogeneity: Tau^2=592.78; Chi^2=6.59, df=3(P=0.09); I^2=54.48%							
Test for overall effect: Z=0.83(P=0.41)							
1.5.6 3 months							
Frei 1987	54	158 (51)	56	151 (61)		25.44%	7[-13.98,27.98]
Kuypers 2004	59	141 (46)	59	165 (53)		25.79%	-24[-41.91,-6.09]
Ladefoged 1994	19	225 (47)	20	189 (25)		25.08%	36[12.2,59.8]
Lustig 1996	23	150 (53)	24	168 (62)		23.7%	-18[-50.93,14.93]
Subtotal ***	**155**		**159**			**100%**	**0.45[-27.15,28.06]**

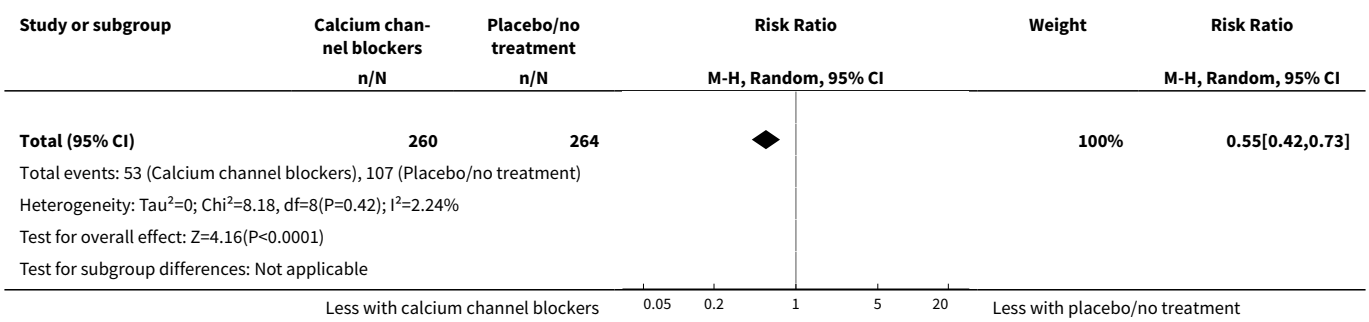
Study or subgroup	Calcium channel blockers N	Mean(SD)	Placebo/no treatment N	Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Heterogeneity: Tau²=643.32; Chi²=17.19, df=3(P=0); I²=82.55%							
Test for overall effect: Z=0.03(P=0.97)							
1.5.7 6 months							
Frei 1987	54	152 (51)	56	150 (66)		49.43%	2[-20,24]
Kuypers 2004	59	138 (51)	59	150 (42)		50.57%	-12[-28.86,4.86]
Subtotal ***	**113**		**115**			**100%**	**-6.82[-20.2,6.56]**
Heterogeneity: Tau²=0; Chi²=0.98, df=1(P=0.32); I²=0%							
Test for overall effect: Z=1(P=0.32)							



Analysis 1.6. Comparison 1 Calcium channel blockers versus placebo/no treatment, Outcome 6 Delayed graft function.

Study or subgroup	Calcium channel blockers n/N	Placebo/no treatment n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.6.1 Diltiazem					
Frei 1987	7/54	19/56		12.25%	0.38[0.17,0.83]
Neumayer 1989	3/16	11/19		6.39%	0.32[0.11,0.96]
Neumayer 1992a	2/20	9/22		3.85%	0.24[0.06,1]
Neumayer 1992b	3/10	5/11		5.78%	0.66[0.21,2.08]
Subtotal (95% CI)	**100**	**108**		**28.27%**	**0.39[0.23,0.65]**
Total events: 15 (Calcium channel blockers), 44 (Placebo/no treatment)					
Heterogeneity: Tau²=0; Chi²=1.37, df=3(P=0.71); I²=0%					
Test for overall effect: Z=3.6(P=0)					
1.6.2 Nifedipine					
Harper 1997	3/28	10/24		5.56%	0.26[0.08,0.83]
Morales 1990	13/27	16/27		28.75%	0.81[0.49,1.34]
Wilkie 1994	5/16	8/17		9.63%	0.66[0.27,1.61]
Subtotal (95% CI)	**71**	**68**		**43.94%**	**0.61[0.33,1.12]**
Total events: 21 (Calcium channel blockers), 34 (Placebo/no treatment)					
Heterogeneity: Tau²=0.12; Chi²=3.42, df=2(P=0.18); I²=41.56%					
Test for overall effect: Z=1.6(P=0.11)					
1.6.3 Lacidipine					
Kuypers 2004	14/59	22/59		22.94%	0.64[0.36,1.12]
Subtotal (95% CI)	**59**	**59**		**22.94%**	**0.64[0.36,1.12]**
Total events: 14 (Calcium channel blockers), 22 (Placebo/no treatment)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.57(P=0.12)					
1.6.4 Verapamil					
Dawidson 1991	3/30	7/29		4.85%	0.41[0.12,1.45]
Subtotal (95% CI)	**30**	**29**		**4.85%**	**0.41[0.12,1.45]**
Total events: 3 (Calcium channel blockers), 7 (Placebo/no treatment)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.38(P=0.17)					





ADDITIONAL TABLES

Table 1. Electronic search strategies

Database searched	Search terms
CENTRAL	1. CALCIUM CHANNEL BLOCKERS 2. (calcium next antagonist*) 3. (calcium next blocker*) 4. amlodipine 5. diltiazem 6. felodipine 7. nicardipine 8. nifedipine 9. nimodipine 10.nisoldipine 11.nitrendipine 12.verapamil 13.(#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12) 14.KIDNEY TUBULAR NECROSIS ACUTE 15.(acute next tubular next necrosis) 16.atn 17.(#14 or #15 or #16) 18.(#13 and #17) 19.KIDNEY TRANSPLANTATION 20.(graft next function*) 21.((kidney next transplant*) or (renal next transplant*) or (kidney next graft*) or (renal next graft*)) 22.((graft near reject*) or (graft near surviv*)) 23.GRAFT SURVIVAL 24.GRAFT REJECTION 25.post-transplant* 26.posttransplant* 27.(acute next rejection) 28.(marginal next donor*) 29.(aged next donor*) 30.(cadaver* next donor*) 31.(#19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30) 32.(#13 and #31) 33.(#18 or #32)

Table 1. Electronic search strategies *(Continued)*

MEDLINE (from 1966)	1. exp Calcium Channel Blockers/ 2. calcium antagonist$.tw. 3. calcium block$.tw. 4. calcium inhibit$.tw. 5. amlodipine.tw. 6. amrinone.tw. 7. bencyclane.tw. 8. bepridil.tw. 9. cinnarizine.tw. 10.conotoxin$.tw. 11.diltiazem.tw. 12.felodipine.tw. 13.fendiline.tw. 14.flunarizine.tw. 15.gallopamil.tw. 16.isradipine.tw. 17.lidoflazine.tw. 18.magnesium sulphate.tw. 19.mibefradil.tw. 20.nicardipine.tw. 21.nifedipine.tw. 22.nimodipine.tw. 23.nisoldipine.tw. 24.nitrendipine.tw. 25.perhexiline.tw. 26.prenylamine.tw. 27.verapamil.tw. 28.(omega- agatoxin$ or omega-conotoxin$).tw. 29.or/1-27 30.Kidney Tubular Necrosis, Acute/ 31.acute tubular necrosis.tw. 32.ATN.tw. 33.exp Kidney Transplantation/ 34.graft rejection/ or graft survival/ 35.((kidney or renal) and (transplant$ or graft$ or donor$ or recipient$)).tw. 36.(kidney function$ or renal function$ or graft function$ or dgf).tw. 37.or/30-36 38.29 and 37
EMBASE (from 1980)	1. exp Calcium Channel Blocking agent/ 2. calcium antagonist$.tw. 3. calcium block$.tw. 4. calcium inhibit$.tw. 5. amlodipine.tw. 6. anipamil.tw. 7. amrinone.tw. 8. bencyclane.tw. 9. bepridil.tw. 10.cinnarizine.tw. 11.conotoxin$.tw. 12.diltiazem.tw.

Table 1. Electronic search strategies *(Continued)*

13.felodipine.tw.
14.fendiline.tw.
15.flunarizine.tw.
16.gallopamil.tw.
17.isradipine.tw.
18.lidoflazine.tw.
19.magnesium sulphate.tw.
20.mibefradil.tw.
21.nicardipine.tw.
22.nifedipine.tw.
23.nimodipine.tw.
24.nisoldipine.tw.
25.nitrendipine.tw.
26.perhexiline.tw.
27.prenylamine.tw.
28.verapamil.tw.
29.(omega-agatoxin$ or omega-conotoxin$).tw.
30.or/1-29
31.Acute Kidney Tubule Necrosis/
32.acute tubular necrosis.tw.
33.ATN.tw.
34.exp Kidney Transplantation/
35.graft rejection/ or graft survival/
36.((kidney or renal) and (transplant$ or graft$ or donor$)).tw.
37.(kidney function$ or renal function$ or graft function$ or dgf).tw.
38.or/31-37
39.30 and 38

WHAT'S NEW

Date	Event	Description
22 September 2008	Amended	Converted to new review format.

HISTORY

Protocol first published: Issue 1, 2002
Review first published: Issue 1, 2004

Date	Event	Description
15 February 2007	New search has been performed	Three new studies included

CONTRIBUTIONS OF AUTHORS

Ilona Shilliday: Design, trial selection, quality assessment, data extraction, data analysis, interpretation of results, reporting (first reviewer)
Mohammed Sherif: trial selection, quality assessment, data extraction, data analysis, interpretation of results, reporting (second reviewer)

DECLARATIONS OF INTEREST

None known

INDEX TERMS

Medical Subject Headings (MeSH)

Calcium Channel Blockers [*therapeutic use]; Kidney Transplantation [*adverse effects]; Kidney Tubular Necrosis, Acute [*prevention & control]; Randomized Controlled Trials as Topic

MeSH check words

Humans