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Calcium channel blockers for inhibiting preterm labour and birth (Review)

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[Intervention Review]

Calcium channel blockers for inhibiting preterm labour and birth

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ABSTRACT

Background

Preterm birth is a major contributor to perinatal mortality and morbidity, affecting around 9% of births in high-income countries and an estimated 13% of births in low- and middle-income countries. Tocolytics are drugs used to suppress uterine contractions for women in preterm labour. The most widely used tocolytic are the betamimetics, however, these are associated with a high frequency of unpleasant and sometimes severe maternal side effects. Calcium channel blockers (CCBs) (such as nifedipine) may have similar tocolytic efficacy with less side effects than betamimetics. Oxytocin receptor antagonists (ORAs) (e.g. atosiban) also have a low side-effect profile.

Objectives

To assess the effects on maternal, fetal and neonatal outcomes of CCBs, administered as a tocolytic agent, to women in preterm labour.

Search methods

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register (12 November 2013).

Selection criteria

All published and unpublished randomised trials in which CCBs were used for tocolysis for women in labour between 20 and 36 completed weeks' gestation.

Data collection and analysis

Two review authors independently assessed trial eligibility, undertook quality assessment and data extraction. Results are presented using risk ratio (RR) for categorical data and mean difference (MD) for data measured on a continuous scale with the 95% confidence interval (CI). The number needed to treat to benefit (NNTB) and the number needed to treat to harm (NNTH) were calculated for categorical outcomes that were statistically significantly different.

Main results

This update includes 26 additional trials involving 2511 women, giving a total of 38 included trials (3550 women). Thirty-five trials used nifedipine as the CCB and three trials used nicardipine. Blinding of intervention and outcome assessment was undertaken in only one

of the trials (a placebo controlled trial). However, objective outcomes defined according to timing of birth and perinatal mortality were considered to have low risk of detection bias.

Two small trials comparing CCBs with placebo or no treatment showed a significant reduction in birth less than 48 hours after trial entry (RR 0.30, 95% CI 0.21 to 0.43) and an increase in maternal adverse effects (RR 49.89, 95% CI 3.13 to 795.02, one trial of 89 women). Due to substantial heterogeneity, outcome data for preterm birth (less than 37 weeks) were not combined; one placebo controlled trial showed no difference (RR 0.96, 95% CI 0.89 to 1.03) while the other (non-placebo controlled trial) reported a reduction (RR 0.44, 95% CI 0.31 to 0.62). No other outcomes were reported.

Comparing CCBs (mainly nifedipine) with other tocolytics by type (including betamimetics, glyceryl trinitrate (GTN) patch, non-steriodal anti inflammatories (NSAID), magnesium sulphate and ORAs), no significant reductions were shown in primary outcome measures of birth within 48 hours of treatment or perinatal mortality.

Comparing CCBs with betamimetics, there were fewer maternal adverse effects (average RR 0.36, 95% CI 0.24 to 0.53) and fewer maternal adverse effects requiring discontinuation of therapy (average RR 0.22, 95% CI 0.10 to 0.48). Calcium channel blockers resulted in an increase in the interval between trial entry and birth (average MD 4.38 days, 95% CI 0.25 to 8.52) and gestational age (MD 0.71 weeks, 95% CI 0.34 to 1.09), while decreasing preterm and very preterm birth (RR 0.89, 95% CI 0.80 to 0.98 and RR 0.78, 95% CI 0.66 to 0.93); respiratory distress syndrome (RR 0.64, 95% CI 0.48 to 0.86); necrotising enterocolitis (RR 0.21, 95% CI 0.05 to 0.96); intraventricular haemorrhage (RR 0.53, 95% CI 0.34 to 0.84); neonatal jaundice (RR 0.72, 95% CI 0.57 to 0.92); and admissions to neonatal intensive care unit (NICU) (average RR 0.74, 95% CI 0.63 to 0.87). No difference was shown in one trial of outcomes at nine to twelve years of age.

Comparing CCBs with ORA, data from one study (which did blind the intervention) showed an increase in gestational age at birth (MD 1.20 completed weeks, 95% CI 0.25 to 2.15) and reductions in preterm birth (RR 0.64, 95% CI 0.47 to 0.89); admissions to the NICU (RR 0.59, 95% CI 0.41 to 0.85); and duration of stay in the NICU (MD -5.40 days,95% CI -10.84 to 0.04). Maternal adverse effects were increased in the CCB group (average RR 2.61, 95% CI 1.43 to 4.74).

Comparing CCBs with magnesium sulphate, maternal adverse effects were reduced (average RR 0.52, 95% CI 0.40 to 0.68), as was duration of stay in the NICU (days) (MD -4.55, 95% CI -8.17 to -0.92). No differences were shown in the comparisons with GTN patch or NSAID, although numbers were small.

No differences in outcomes were shown in trials comparing nicardipine with other tocolytics, although with limited data no strong conclusions can be drawn. No differences were evident in a small trial that compared higher- versus lower-dose nifedipine, though findings tended to favour a high dose on some measures of neonatal morbidity.

Authors' conclusions

Calcium channel blockers (mainly nifedipine) for women in preterm labour have benefits over placebo or no treatment in terms of postponement of birth thus, theoretically, allowing time for administration of antenatal corticosteroids and transfer to higher level care. Calcium channel blockers were shown to have benefits over betamimetics with respect to prolongation of pregnancy, serious neonatal morbidity, and maternal adverse effects. Calcium channel blockers may also have some benefits over ORAs and magnesium sulphate, although ORAs results in fewer maternal adverse effects. However, it must be noted that no difference was shown in perinatal mortality, and data on longer-term outcomes were limited. Further, the lack of blinding of the intervention diminishes the strength of this body of evidence. Further well-designed tocolytic trials are required to determine short- and longer-term infant benefit of CCBs over placebo or no treatment and other tocolytics, particularly ORAs. Another important focus for future trials is identifying optimal dosage regimens of different types of CCBs (high versus low, particularly addressing speed of onset of uterine quiescence) and formulation (capsules versus tablets). All future trials on tocolytics for women in preterm labour should employ blinding of the intervention and outcome assessment, include measurement of longer-term effects into early childhood, and also costs.

PLAIN LANGUAGE SUMMARY

Calcium channel blockers for inhibiting preterm labour and birth

Preterm birth is when a baby is born between 20 and 36 completed weeks' gestation. These babies are generally more ill and are less likely to survive than babies born at term. Preterm babies are also more likely to have some disability, and the earlier the baby is born the more likely they are to have problems. Even short-term postponement of preterm birth can improve outcomes for babies, as this gives time for the mother to be given a steroid injection to help develop the baby's lungs develop prior to birth. Short-term postponement of preterm birth may also give the chance to transfer the mother, if required, to somewhere where there is more expert care for the baby available. Drugs used to try and stop labour are called tocolytics. The most common drugs used are betamimetics, but calcium channel blockers (CCBs) are another option. CCBs are commonly used for reducing high blood pressure, but they can also relax uterine contractions. We looked to see if CCBs were effective in postponing labour and improving outcomes for babies, and also whether CCBs were better than betamimetics and other types of tocolytics used to postpone preterm labour and birth.

We found 38 trials involving 3550 women, some comparing CCBs (mainly nifedipine) with no tocolytics and others comparing CCBs with tocolytics. The trials included in this review were considered to be of fair quality. We found that CCBs, specifically nifedipine, is better

than no tocolytics for postponing preterm birth for 48 hours, which may help improve outcomes for babies. Compared with betamimetics, CCBs were more effective at postponing birth, had fewer side effects for women, and appeared to improve some important short-term outcomes for the baby (breathing difficulties, gut infections, and admission to special care units). Calcium channel blockers were better than other types of tocolytics for some outcomes only. Oxytocin receptor antagonists (ORAs) appear to have fewer side effects for women than CCBs, but ORAs are not as good at reducing preterm birth. Another type of CCB, nicardipine, was only used in three trials, but was not more effective than other tocolytics. Longer-term infant and childhood outcomes were not able to be assessed due to lack of available information. In general, CCBs are more effective than betamimetics, but only sometimes more effective than other types of tocolytics.

BACKGROUND

Description of the condition

Preterm birth, defined as birth occurring between 20 and 36 completed weeks of gestation is a major contributor to perinatal mortality and morbidity. The rate of preterm birth is increasing across low- and middle-income countries, affecting 8.6% of births in high-income countries and between 7.4% to 13.3% in low- and middle-income countries (WHO 2012). Preterm birth is a leading cause of perinatal morbidity including respiratory distress syndrome (RDS), chronic lung disease, intraventricular haemorrhage (IVH), sepsis, cerebral palsy and other forms of neuro-developmental impairment (Gladstone 2011), blindness and deafness. The birth of a preterm infant who requires intensive care for survival is a crisis, not only for the infant, but also for the parents (McCain 1993). The costs to the parents, community and society as a whole, both economic and emotional, are substantial (Petrou 2011).

Approximately 65% to 70% are spontaneous preterm births either following spontaneous preterm labour (40% to 45%) or those following preterm rupture of membranes (25% to 30%) (Goldenberg 2008). While the cause of spontaneous preterm birth is often unclear, some risk factors have been identified including: maternal age (adolescence and advanced age); history of preterm birth; race; multiple pregnancy, short inter-pregnancy interval; infections; medical conditions; poor nutrition; psychological factors and genetic predisposition (Goldenberg 2008).

Despite improvements in the standards in obstetric and neonatal care over recent years, no progress has been made over the last two decades in reducing the incidence of preterm birth in high-income countries. In fact, rates of preterm birth are rising, in part due to increasing obstetric intervention (Goldenberg 2008; Norman 2009). Some benefits have been identified from prolongation of pregnancy, which theoretically allows time for corticosteroids to be administered to the mother to hasten fetal lung maturation (Roberts 2006), to effect transfer to a centre with neonatal intensive care facilities (Powell 1995) and magnesium sulphate administration to reduce the risk of cerebral palsy (Doyle 2009). For these reasons, short-term tocolytic therapy is commonly used to inhibit preterm labour and postpone preterm birth.

Description of the intervention

Tocolytic drugs have been used to inhibit preterm labour, in order to allow time for co-intervention and potentially to defer preterm birth, thus improving neonatal outcomes with advancing gestation. A range of tocolytic agents that have been used to inhibit preterm labour are the topics of Cochrane systematic reviews including: nitric oxide donors (glyceryl trinitrate) (Duckitt 2002), oxytocin receptor antagonists (Papatsonis 2005), betamimetics (Neilson 2014), magnesium sulphate (Crowther 2002), cyclo-oxygenase (COX) inhibitors (King 2005) and progesterone (Su 2010), and their relative effects have been explored in a recent network meta-analysis (Haas 2012). The betamimetics, arguably the most commonly used tocolytics, (ritodrine, salbutamol and terbutaline) have been shown to be effective in delaying delivery by seven days and longer, although no impact has yet been shown on perinatal mortality (Neilson 2014). Furthermore, betamimetics have a high frequency of unpleasant, sometimes severe maternal side effects including tachycardia, hypotension, tremor and a range of biochemical disturbances, and they have been associated with life-threatening cardiovascular and respiratory events and deaths. COX inhibitors show promise in earlier gestations but in later gestations there remains a concern regarding premature constriction or closure of the ductus arteriosus (Koren 2006). Calcium channel blockers (CCBs) or calcium antagonists are non-specific smooth muscle relaxants, predominantly used for the treatment of hypertension in adults and are increasingly used as a tocolytic agent for women in preterm labour.

How the intervention might work

Calcium channel blockers exert their tocolytic effect by preventing the influx of extracellular calcium ions into the myometrial cell. They are entirely non-specific for uterine as distinct from other smooth muscle cells, but have been demonstrated in vitro to have a potent relaxant effect on human myometrium (Saade 1994). The most widely used and studied CCB is nifedipine, which along with nicardipine, belongs to the dihydropiridine group. Nifedipine was first reported in an observational study in 1980 to be an effective tocolytic agent with minimal side effects (Ulmsten 1980). Nicardipine can be given orally or by intravenous route, whereas nifedipine can only be administered orally.

Why it is important to do this review

Calcium channel blockers have been proposed as effective agents for inhibiting preterm labour and they have less side effects than betamimetics. Betamimetics have a high frequency of unpleasant, sometimes severe maternal side effects including tachycardia, hypotension, tremor and a range of biochemical disturbances. Furthermore, betamimetic treatment is reported to have been associated with at least 25 maternal deaths, mainly from pulmonary oedema (Papatsonis 2001).There is a need therefore for an effective tocolytic agent with fewer side effects than betamimetics.

However, concerns arose from animal studies (Harake 1987) that the CCB nifedipine may have adverse effects on fetal and placental circulation. Although there have been subsequent studies that failed to confirm this (Guclu 2004; Meyer 1990), it is necessary to review the evidence for the safety and efficacy of this treatment. There have been some incidental case reports that the use of nifedipine in the treatment of preterm labour was associated with more cardiovascular side effects, such as hypotension (van Veen 2005), dyspnoea (van Geijn 2005), pulmonary oedema (Abbas 2006; Vaast 2004), maternal hypoxia (Hodges 2004) and myocardial infarction (Oei 2006; Verhaert 2004). These reported incidents were in women with multiple gestations, premature prolonged rupture of membranes (PPROM), vaginal blood loss, diabetes mellitus, or with a cardiovascular history, or who were treated simultaneously with, or immediately following, betamimetics.

Another tocolytic, oxytocin receptor antagonists (ORA) have been developed specifically as a tocolytic agent, with atosiban being the most researched and used ORA. ORA relax the myometrium by preventing a rise in intracellular calcium. Preliminary studies in pregnant and non-pregnant women have suggested a very low incidence of maternal side effects with ORA (Goodwin 1996; Goodwin 1998), most of which are relatively minor: adverse injection site reaction, nausea, vomiting, headache, chest pain and hypotension (Moutquin 2000; Tsatsaris 2004).

A recent network meta-analysis of tocolytic agents concluded that prostaglandin inhibitors and CCBs had the highest probability of delaying delivery and improving neonatal and maternal outcomes (Haas 2012). There are however, concerns regarding the potentially deleterious effects of prolonged exposure to COX inhibition on the fetal cardiovasculature, gut and kidney (Perron 2013; Walker 2011). In addition, there are concerns regarding the increase in infant mortality with the use of magnesium sulphate for the treatment of preterm birth rightly limit its utility as a first-line tocolytic (Crowther 2002).

It is therefore important to undertake a systematic review of all randomised controlled trials of CCBs used in the management of women in preterm labour to determine the relative risks and benefits of this intervention. A series of Cochrane reviews have assessed the effects of different classes of tocolytics compared with placebo, and with each other (Bain 2013; Crowther 2002; Duckitt 2002; King 2005; Papatsonis 2005; Su 2010; Neilson 2014). A review on combinations of different tocolytics for women in preterm labour is the subject of a review currently in development (Nardin 2006).

OBJECTIVES

1. To assess the effects on maternal, fetal, and neonatal outcomes of CCBs administered as a tocolytic agent to women in preterm labour when compared with either placebo or no intervention.
2. To assess the effects on maternal, fetal, and neonatal outcomes of CCBs administered as a tocolytic agent to women in preterm labour when compared with other tocolytic agents.
3. To assess the effects on maternal, fetal, and neonatal outcomes of different types of CCBs.

METHODS

Criteria for considering studies for this review

Types of studies

All published and unpublished randomised and cluster-randomised trials in which CCBs were used for tocolysis in the management of preterm labour. We excluded trials using quasi-random methods of allocation and cross-over trials.

Types of participants

Women assessed as being in preterm labour (between 20 and 36 completed weeks' gestation) and considered suitable candidates for tocolysis.

Types of interventions

1. CCB administered as a tocolytic by any route compared with placebo, no treatment or any other tocolytic.
2. High-dose nifedipine compared with low-dose nifedipine.

Types of outcome measures

We aimed to examine the effect of CCBs on clinically important outcome measures related to prolonging the duration of pregnancy, as well as infant morbidity and mortality and maternal side effects.

Clinically relevant outcomes for trials of tocolysis for inhibiting preterm labour have been prespecified following consultation with the editors and authors of the individual reviews.

Consensus was reached on a set of six 'core' outcomes, which are highlighted below. These will be included in all tocolysis reviews. In addition to these core outcomes, individual teams may include other outcomes as necessary.

Primary outcomes

Primary outcomes were chosen to be most representative of the clinically important measures of effectiveness and complications. Serious outcomes for the women and their infants are composite endpoints. All these events individually were expected to be rare and a modest change in their incidence more likely to be detected by using composite outcomes. The incidence of individual components was explored in the secondary outcomes. Primary outcomes were:

1. **serious maternal outcome** (defined as death, cardiac arrest, respiratory arrest, admission to intensive care unit);
2. **birth less than 48 hours after trial entry**;
3. **serious infant outcome** (defined as death or chronic lung disease [need for supplemental oxygen at 28 days of life or later], grade three or four intraventricular haemorrhage (IVH) or periventricular leukomalacia (PVL), major neurosensory disability (defined as any of legal blindness, sensorineural deafness requiring hearing aids, moderate or severe cerebral palsy, or developmental delay/intellectual impairment [defined as developmental quotient (DQ) or intelligence quotient (IQ) less than 2 standard deviations below mean]);
4. **perinatal mortality** (stillbirth defined as a birth not showing signs of life defined by any gestational age and birthweight in the trials and neonatal death up to 28 days);
5. **very preterm birth** (before completion of 34 weeks of gestation).

Secondary outcomes

Secondary outcomes include other measures of effectiveness, complications, satisfaction with care and health service use.

For the infant/child these were:

1. gestational age at birth;
2. preterm birth (before completion of 37 weeks of gestation);
3. extremely preterm birth (before completion of 28 weeks of gestation);
4. interval between trial entry and birth;
5. Apgar score less than seven at five minutes;
6. admission to neonatal intensive care (NICU) nursery;
7. respiratory distress syndrome (RDS);
8. chronic lung disease (need for supplemental oxygen at 28 days of life or later);
9. necrotising enterocolitis (NEC);
10. neonatal sepsis;
11. neonatal jaundice;
12. IVH;
13. grade three or four IVH;
14. periventricular leukomalacia (PVL);

15. retinopathy of prematurity (ROP);
16. developmental delay or intellectual impairment;
17. blindness, deafness, cerebral palsy;
18. psychosocial outcome measures; and
19. quality of life.

For the woman these were:

1. admission to intensive care unit;
2. major adverse effects (respiratory depression, hypotension, tachycardia);
3. minor adverse effects of therapy (including nausea, vomiting);
4. discontinuation of therapy for maternal adverse effects;
5. **any maternal adverse effects**;
6. women's satisfaction with the therapy;
7. bleeding episodes (antepartum haemorrhage (APH), postpartum haemorrhage (PPH), need for transfusion);
8. mode of delivery (caesarean section);
9. parental stress/anxiety; and
10. quality of life.

Health services utilisation was assessed via:

1. duration of stay in NICU nursery (days);
2. duration of stay in maternal hospital (days); and
3. cost.

The following methods section of this review is based on a standard template used by the Cochrane Pregnancy and Childbirth Group.

Search methods for identification of studies

Electronic searches

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register by contacting the Trials Search Co-ordinator (12 November 2013).

The Cochrane Pregnancy and Childbirth Group's Trials Register is maintained by the Trials Search Co-ordinator and contains trials identified from:

1. monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL);
2. weekly searches of MEDLINE;
3. weekly searches of Embase;
4. handsearches of 30 journals and the proceedings of major conferences;
5. weekly current awareness alerts for a further 44 journals plus monthly BioMed Central email alerts.

Details of the search strategies for CENTRAL, MEDLINE and Embase, the list of handsearched journals and conference proceedings, and the list of journals reviewed via the current awareness service can be found in the 'Specialized Register' section within the editorial information about the Cochrane Pregnancy and Childbirth Group.

Trials identified through the searching activities described above are each assigned to a review topic (or topics). The Trials Search Co-ordinator searches the register for each review using the topic list rather than keywords.

We did not apply any language restrictions.

Data collection and analysis

For the methods used in the previous version of this review, *see* King 2003.

For this update, we applied the following methods to all previously included and new studies.

Selection of studies

At least two review authors independently assessed for inclusion all the potential studies identified as a result of the search strategy. We resolved any disagreement through discussion or, if required, we consulted a third person.

Data extraction and management

The review authors used the standard methods of The Cochrane Collaboration and considered all potential trials for inclusion. At least two review authors (V Flenady, A Wojcieszek, L Murray, or O Stock) evaluated the methodological quality and extracted trial data independently, as described in the *Cochrane Handbook for Systematic Reviews of Interventions (* Higgins 2011).

We resolved discrepancies through discussion. We entered data into Review Manager software (RevMan 2012) and checked them for accuracy.

When information was unclear, we attempted to contact authors of the original reports to provide further details.

Assessment of risk of bias in included studies

Two review authors independently assessed risk of bias for each study using the criteria outlined in the*Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We resolved any disagreement by discussion or by involving a third assessor.

(1) Random sequence generation (checking for possible selection bias)

We described for each included study the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.

We assessed the method as:

- low risk of bias (any truly random process, e.g. random number table; computer random number generator);
- high risk of bias (any non-random process, e.g. odd or even date of birth; hospital or clinic record number);
- unclear risk of bias.

(2) Allocation concealment (checking for possible selection bias)

We described for each included study the method used to conceal allocation to interventions prior to assignment and assessed whether intervention allocation could have been foreseen in advance of, or during recruitment, or changed after assignment.

We assessed the method as:

- low risk of bias (e.g. telephone or central randomisation; consecutively numbered sealed opaque envelopes);

- high risk of bias (open random allocation; unsealed or non-opaque envelopes, alternation; date of birth);
- unclear risk of bias.

(3.1) Blinding of participants and personnel (checking for possible performance bias)

We described for each included study the methods used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. We considered that studies were at low risk of bias if they were blinded, or if we judged that the lack of blinding would be unlikely to affect results. We assessed blinding separately for different outcomes or classes of outcomes.

We assessed the method as:

- low, high or unclear risk of bias for participants;
- low, high or unclear risk of bias for personnel.

(3.2) Blinding of outcome assessment (checking for possible detection bias)

We described for each included study the methods used, if any, to blind outcome assessors from knowledge of which intervention a participant received. We assessed blinding separately for different outcomes or classes of outcomes.

We assessed methods used to blind outcome assessment as:

- low, high or unclear risk of bias.

With respect to 3.2, we divided the assessment of outcome measures into two groups (subjective and objective) according to the propensity for bias to result in a deviation from the true effect in the absence of blinding. For these groups we considered the likelihood of bias arising as a result of co-intervention and/or lack of clearly stated definitions. Subjective outcomes were those considered to have a potentially higher risk of bias as follows: admission to NICU nursery, length of nursery stay, neonatal morbidity (RDS, NEC, IVH, jaundice, ROP), maternal length of hospital stay, maternal adverse effects, and discontinuation of therapy for maternal adverse effects. Objective measures considered to be less likely influenced by detection or performance bias were: stillbirth, neonatal death, perinatal death, birth within 48 hours of trial entry, preterm birth, and gestation at birth.

(4) Incomplete outcome data (checking for possible attrition bias due to the amount, nature and handling of incomplete outcome data)

We described for each included study, and for each outcome or class of outcomes, the completeness of data including attrition and exclusions from the analysis. We stated whether attrition and exclusions were reported and the numbers included in the analysis at each stage (compared with the total randomised participants), reasons for attrition or exclusion where reported, and whether missing data were balanced across groups or were related to outcomes. Where sufficient information was reported, or was supplied by the trial authors, we re-included missing data in the analyses that we undertook.

We assessed the method as:

- low risk of bias (e.g. no missing outcome data; missing outcome data balanced across groups);
- high risk of bias (e.g. numbers or reasons for missing data imbalanced across groups; 'as treated' analysis done with substantial departure of intervention received from that assigned at randomisation);
- unclear risk of bias.

(5) Selective reporting (checking for reporting bias)

We described for each included study how we investigated the possibility of selective outcome reporting bias and what we found.

We assessed the method as:

- low risk of bias (where it is clear that all of the study's pre-specified outcomes and all expected outcomes of interest to the review have been reported);
- high risk of bias (where not all the study's pre-specified outcomes have been reported; one or more reported primary outcomes were not pre-specified; outcomes of interest are reported incompletely and so cannot be used; study fails to include results of a key outcome that would have been expected to have been reported);
- unclear risk of bias.

(6) Other bias (checking for bias due to problems not covered by (1) to (5) above)

We described for each included study any important concerns we had about other possible sources of bias.

We assessed whether each study was free of other problems that could put it at risk of bias:

- low risk of other bias;
- high risk of other bias;
- unclear whether there is risk of other bias.

(7) Overall risk of bias

We made explicit judgements about whether studies were at high risk of bias, according to the criteria given in the *Handbook* (Higgins 2011). With reference to (1) to (6) above, we assessed the likely magnitude and direction of the bias and whether we consider it is likely to impact on the findings. We planned to explore the impact of the level of bias through undertaking sensitivity analyses - *see* Sensitivity analysis.

Measures of treatment effect

Dichotomous data

For dichotomous data, we present results as summary risk ratios with 95% confidence intervals (CI). Number needed to treat for an additional beneficial outcome (NNTB) and number needed to treat for an additional harmful outcome (NNTH) with 95% confidence interval (CI) presented where appropriate.

Continuous data

For continuous data, we used the mean difference if outcomes are measured in the same way between trials. We planned to use the standardised mean difference to combine trials that measure the same outcome, but used different methods.

Unit of analysis issues

Cross-over trials

We excluded cross-over trials.

Cluster-randomised trials

We did not identify any cluster-randomised trials for inclusion in this review, but we may include trials of this type in future updates.

If cluster-randomised trials are included in future reviews, we plan to include cluster-randomised trials in the analyses along with individually-randomised trials. Their sample sizes will be adjusted using the methods described in the *Handbook* (Higgins 2011) using an estimate of the intracluster correlation co-efficient (ICC) derived from the trial (if possible), or from another source. If ICCs from other sources are used, we will report this and conduct sensitivity analyses to investigate the effect of variation in the ICC. If we identify both cluster-randomised trials and individually-randomised trials, we plan to synthesise the relevant information. We consider it reasonable to combine the results from both if there is little heterogeneity between the study designs and the interaction between the effect of intervention and the choice of randomisation unit is considered to be unlikely. We will also acknowledge heterogeneity in the randomisation unit and perform a sensitivity analysis to investigate the effects of the randomisation units.

Multiple pregnancy

The analysis in this review involves multiple pregnancies, therefore, wherever possible, analyses should be adjusted for clustering to take into account the non-independence of babies from the same pregnancy (Gates 2004). Treating babies from multiple pregnancies as if they are independent, when they are more likely to have similar outcomes than babies from different pregnancies, will overestimate the sample size and give confidence intervals that are too narrow. Each woman can be considered a cluster in multiple pregnancy, with the number of individuals in the cluster being equal to the number of fetuses in her pregnancy. Analysis using cluster trial methods allows calculation of risk ratio and adjustment of confidence intervals. Usually this will mean that the confidence intervals get wider. Although this may make little difference to the conclusion of a trial, it avoids misleading results in those trials where the difference may be substantial.

We planned to adjust for clustering in the analyses, wherever possible, and to use the inverse variance method for adjusted analyses, as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) and in Yelland 2011.

Dealing with missing data

For included studies, we noted levels of attrition. We planned to explore the impact of including studies with high levels of missing data in the overall assessment of treatment effect by using sensitivity analysis.

For all outcomes, we carried out analyses, as far as possible, on an intention-to-treat basis, i.e. we attempted to include all participants randomised to each group in the analyses, and all participants were analysed in the group to which they were allocated, regardless of whether or not they received the allocated intervention. The denominator for each outcome in each trial is the number randomised minus any participants whose outcomes are known to be missing.

Assessment of heterogeneity

We assessed statistical heterogeneity in each meta-analysis using the Tau^2, I^2 and Chi^2 statistics. We regarded heterogeneity as substantial if the I^2 was greater than 30% and either Tau^2 was greater than zero, or there was a low P value (less than 0.10) in the Chi^2 test for heterogeneity.

Assessment of reporting biases

If 10 or more studies had contributed data to meta-analysis for any particular outcome, we investigated reporting biases (such as publication bias) using funnel plots. We assessed possible asymmetry visually. If asymmetry was suggested by a visual assessment, we planned to perform exploratory analyses to investigate it.

Data synthesis

We carried out statistical analysis using the Review Manager software (RevMan 2012). We used fixed-effect meta-analysis for combining data where it is reasonable to assume that studies are estimating the same underlying treatment effect: i.e. where trials are examining the same intervention, and the trials' populations and methods are judged sufficiently similar. If there was clinical heterogeneity sufficient to expect that the underlying treatment effects differ between trials, or if substantial statistical heterogeneity was detected, we used random-effects meta-analysis to produce an overall summary if an average treatment effect across trials was considered clinically meaningful.

The random-effects summary was treated as the average range of possible treatment effects and we discussed the clinical implications of treatment effects differing between trials. If the average treatment effect had not been clinically meaningful, we would not have combined trials.

Where random-effects analyses were used, the results were presented as the average treatment effect with 95% confidence intervals, and the estimates of Tau^2 and I^2.

Subgroup analysis and investigation of heterogeneity

Had we identified substantial heterogeneity, we planned to investigate it using subgroup analyses and consider whether an overall summary was meaningful, and if so, use random-effects analysis to produce it. We planned to assess subgroup differences by interaction tests available within RevMan (RevMan 2012).

We were unable to conduct the planned subgroup analyses to explore the effects at different gestational age thresholds by membrane status and multiple gestation due to the unavailability of data.

A priori subgroup analyses

Subgroup analyses were as follows.

By intervention

- Type of other tocolytic.
- Type of CCB.

By population

- Women with preterm labour prior to 28 weeks' gestation versus women at 28 weeks or more.
- Women with ruptured membranes versus women with intact membranes.
- Women with multiple pregnancy versus women with a singleton pregnancy.

The following outcomes will be used in subgroup analysis in future updates of this review.

- Birth less than 48 hours after trial entry.
- Extremely preterm birth (before completion of 28 weeks of gestation).
- Very preterm birth (before completion of 34 weeks of gestation).
- Preterm birth (before completion of 37 weeks of gestation).
- Perinatal mortality.
- Respiratory distress syndrome.
- Serious infant outcome (defined as death or chronic lung disease [need for supplemental oxygen at 28 days of life or later], grade three or four IVH or PVL, major sensorineural disability (defined as any of legal blindness, sensorineural deafness requiring hearing aids, moderate or severe cerebral palsy, or developmental delay/intellectual impairment [defined as developmental quotient (DQ) or intelligence quotient (IQ) less than 2 standard deviation below mean])).
- Serious maternal outcome (defined as death, cardiac arrest, respiratory arrest, admission to intensive care unit).
- Discontinuation of therapy for maternal adverse effects.

Sensitivity analysis

We planned to carry out sensitivity analyses to explore the effect of trial quality assessed by concealment of allocation, high attrition rates (greater than 20%), or both, with poor-quality studies (including those assessed as low or unknown risk of bias) being excluded from the analyses in order to assess whether this made any difference to the overall result.

RESULTS

Description of studies

Results of the search

In total, 69 studies were identified as potentially eligible for inclusion in this review. Eighteen studies were excluded (Al-Omari 2006; Breart 1979; Carr 1993; Chawanpaiboon 2011; Dasari 2007; Dunstan-Boone 1990; El-Sayed 1998; Husslein 2007; Junejo 2008; Juon 2008; Maitra 2007; Malik 2007; Meyer 1990; Papadopoulos 1997; Piovano 1985; Rodriguez-Escudero 1981; Shim 2006; Smith 1993).

An additional nine studies are awaiting classification awaiting further information from the authors (Chong 1991; de Heus 2009; Dubay 1992; Haghighi 1999; Lotfalizadeh 2010; Mathew 1997; Roy 1993; Sharma 2000; Sofat 1994). For further information, please see Characteristics of studies awaiting classification.

Four ongoing were identified as follows: nifedipine versus atosiban (APOSTEL III 2011; Gonzalez 2011); nifedipine versus magnesium sulphate (Snyder 1989); nifedipine versus placebo (Vis 2009). For further information, please see Characteristics of ongoing studies.

An additional 26 trials involving 2511 women have been included in this update, giving a total of 38 included trials (involving 3550 women) testing the effects of CCB for tocolysis in preterm labour; the previous version included 12 trials and 1039 women.

Included studies

Two included studies (173 women) compared CCB with placebo or no treatment (Ara 2008; Zhang 2002). Thirty-five included trials (3275 women) compared CCB with other tocolytic agents for preterm labour (Al-Qattan 2000; Amorim 2009; Bracero 1991; Cararach 2006; Fan 2003; Ferguson 1990; Floyd 1992; Ganla 1999; Garcia-Velasco 1998; George 1991; Glock 1993; Jaju 2011; Janky 1990; Jannet 1997; Kara 2009; Kashanian 2005; Kashanian 2011; Klauser 2012; Koks 1998; Kose 1995; Kupferminc 1993; Laohapojanart 2007; Larmon 1999; Lyell 2007; Mawaldi 2008; Padovani 2012; Papatsonis 1997; Rayamajhi 2003; Read 1986; Salim 2012; Taherian 2007; Trabelsi 2008; Valdes 2012; Van De Water 2008; Weerakul 2002). Two studies randomised women to one of three groups; Klauser 2012: nifedipine, indomethacin, and magnesium sulphate; and Zhang 2002: two different dosages of nifedipine or no treatment. For the Koks 1998 study, only the subset of trial participants who did not receive prior betamimetic therapy (57 of 102 participants) was included. Another study (Nassar 2009) compared high- with low-dose nifedipine.

Participants

The participants included in these trials were reasonably homogeneous. The minimum gestational age at inclusion ranged from 20 to 30 weeks, and the maximum from 32 to 36 weeks. The mean gestational age at entry, when described, was between 28 and 33 weeks' gestation. Preterm labour was reasonably consistently defined across the trials, most excluding those women with a cervical dilatation of greater than 4 cm. Thirteen trials excluded women with cervical dilatation greater than 3 or 4 cm (Al-Qattan 2000; Ara 2008; Ganla 1999; Jaju 2011; Janky 1990; Kara 2009; Kashanian 2005; Kashanian 2011; Kose 1995; Nassar 2009; Trabelsi 2008; Weerakul 2002; Zhang 2002) and two trials excluded women with cervical dilatation greater than 5 cm (Cararach 2006; Taherian 2007). Twenty trials excluded women with rupture of membranes (Al-Qattan 2000; Bracero 1991; Cararach 2006; Floyd 1992; Garcia-Velasco 1998; George 1991; Glock 1993; Janky 1990; Jannet 1997; Kara 2009; Kashanian 2005; Kashanian 2011; Koks 1998; Kupferminc 1993; Laohapojanart 2007; Larmon 1999; Mawaldi 2008; Read 1986; Salim 2012; Weerakul 2002) and 10 trials included twin pregnancies (Floyd 1992; Janky 1990; Kashanian 2005; Klauser 2012; Koks 1998; Kupferminc 1993; Lyell 2007; Mawaldi 2008; Rayamajhi 2003; Salim 2012). All trials excluded those women who had contra-indications to either CCB or to betamimetics. The standard contra-indications for tocolysis were reported as exclusion criteria in the majority of included trials, i.e. fetal distress, chorioamnionitis, severe pre-eclampsia/eclampsia, and placental abruption.

Tocolysis

Two types of CCBs were captured in this review: nifedipine and nicardipine. Of the 38 studies, only three trials of 261 women used nicardipine (Jannet 1997; Larmon 1999; Trabelsi 2008). Thirty-five trials (3275 women) compared CCBs with other tocolytic agents

(Al-Qattan 2000; Amorim 2009; Ara 2008; Bracero 1991; Cararach 2006; Fan 2003; Ferguson 1990; Floyd 1992; Ganla 1999; Garcia-Velasco 1998; George 1991; Glock 1993; Jaju 2011; Janky 1990; Kara 2009; Kashanian 2005; Kashanian 2011; Klauser 2012; Koks 1998; Kose 1995; Kupferminc 1993; Laohapojanart 2007; Larmon 1999; Lyell 2007; Mawaldi 2008; Padovani 2012; Papatsonis 1997; Rayamajhi 2003; Read 1986; Salim 2012; Taherian 2007; Valdes 2012; Van De Water 2008; Weerakul 2002; Zhang 2002). Twenty-three of these trials (1793 women) used betamimetic agents as the other tocolytic. The largest trial (Klauser 2012, 276 women and 317 neonates) randomised participants to one of three arms: nifedipine, indomethacin, or magnesium sulphate. Initial tocolytic therapy with nifedipine was administered orally or sublingually, as either capsules or tablets (whole, or crushed and dissolved in water). Dosage varied from 30 mg/day to 160 mg/day until uterine contractions stopped. Papatsonis 1997 used a higher dose of nifedipine than most of the included trials (up to 40 mg in the first hour). Twenty-three trials continued oral nifedipine after the initial treatment. Four trials (Ferguson 1990; Bracero 1991; Padovani 2012; Taherian 2007) did not report the total duration of treatment (one of these (Padovani 2012) was reported as an abstract only). Thirteen trials used ritodrine as the other tocolytic. Ritodrine was usually started at 50 µg/minute except for Janky 1990; Papatsonis 1997; Koks 1998; Cararach 2006; Van De Water 2008 Janky 1990; Van De Water 2008; Cararach 2006 and Koks 1998, which started at a loading dose of 100 to 200 µg/minute and the rate was increased up to 300 or 350 µg/minute until uterine contractions stopped. Papatsonis 1997 started ritodrine at a loading dose of 383 µg/minute and gradually decreased to a minimum of 100 µg/minute. Three trials compared nifedipine and isoxsuprine (Ganla 1999; George 1991; Rayamajhi 2003), seven trials compared nifedipine and magnesium sulphate (MgSO4) (Floyd 1992; Glock 1993; Kara 2009; Klauser 2012; Larmon 1999; Lyell 2007; Taherian 2007); two trials compared nifedipine and oxytocin receptor antagonists (ORA), both using atosiban (Kashanian 2005; Salim 2012); four trials compared nifedipine and terbutaline (Laohapojanart 2007; Mawaldi 2008; Padovani 2012; Weerakul 2002); one trial compared nifedipine and glyceryl trinitrate (GTN) patch (Amorim 2009); two trials compared nifedipine and non-steroidal anti-inflammatory drugs (NSAID), both using indomethacin suppository (Kashanian 2011; Klauser 2012); and one trial compared nifedipine and fenoterol (Valdes 2012).

Two trials compared intravenous nicardipine with salbutamol (Jannet 1997; Trabelsi 2008). The doses used were 6 mg/hour and 4 mg/hour respectively. Larmon 1999 used oral nicardipine, at a dose of 40 mg orally then 20 mg 2 hour as necessary up to three doses, with magnesium sulphate (MgSO4). One trial (Nassar 2009) compared a high dose of nifedipine (20 mg sublingual repeated in 30 minutes followed by 120 to 160 mg slow release nifedipine daily for 48 hours) with low-dose nifedipine (10 mg repeated every 15 minutes to a maximum of four doses followed by 60 to 80 mg slow release daily for 48 hours and 60 mg up to 36 weeks).

Outcome measures

There was some inconsistency across the trials with respect to the way in which outcomes were reported. The clinically important outcome of delay in delivery for greater than or equal to 48 hours was reported in 31 of the 38 included trials, discontinuation of treatment because of adverse effects was reported in 21 trials, and perinatal mortality in 24 trials. Extremely preterm birth (before completion of 28 weeks of gestation) was reported in two trials, very preterm birth (before completion of 34 weeks of gestation) in 12 trials, and preterm birth (before completion of 37 weeks of gestation) in 21 trials. With the exception of neonatal mortality, neonatal outcomes were less consistently reported, and definitions were often lacking (e.g. criteria for diagnosing respiratory distress syndrome (RDS), sepsis or for admission to intensive care nursery.

The neonatal outcomes of the trial of Papatsonis 1997 were reported more comprehensively in a subsequent publication, with precise definitions. This second report used a more stringent definition for admission to the NICU than the one used in the initial report. Because the other trials used a more general definition (usually not defined, but presumably any admission to intensive care nursery) in order to maintain consistency, we have chosen to use the data from the primary publication for Papatsonis 1997. Some degree of assessment bias is possible for the neonatal morbidity indices in the trials because neonatal assessment was undertaken by clinicians not blinded to maternal treatment allocation.

Longer-term neonatal assessment was undertaken in only two trials; Houtzager 2005 report nine to 12 year follow-up data by survey for children enrolled in Papatsonis 1997. Questionnaires were completed by the parent, child and teacher. The child's motor functioning was obtained from the parent using the Movement Assessment Battery for Children (Movement ABC) (Hendersen 1998) checklist (Dutch version) (Smits-Engelsman 1998). The total Movement ABC score was used, with a high score referring to less favourable motor functioning. Behavioural–emotional functioning was assessed using the Dutch version of the Child Behavior Check List (CBCL) (Achenbach TM) to be completed by the parent. The child's teacher completed the Teacher Report Form (TRF) (Verhulst 1997). The child's quality of life (QoL) was assessed using the Dutch TNO AZL Children's Quality of Life Questionnare (TACQOL) (Vogels 1998; Vogels 2000). Further, women completed the Dutch Nijmegen Parental Distress Index - Short version (NOSI-K) (Abidin 1992) via a survey to assess parenting distress. Additional information about the child's school level, family demographics and psychosocial care was obtained from the survey of women. In this review, we have included the outcomes of motor quality, behavioural–emotional functioning, parent stress by parent report and the child's quality of life reported by the child. Van De Water 2008 reported two-year outcomes for children. However, we were not able to include these outcomes as data were not presented in a suitable format and further details have been requested from the authors.

Please *see* Characteristics of included studies for further details.

Other unit of analysis issues

One study (Klauser 2012, 276 women and 317 neonates) randomised participants to one of three arms: nifedipine, indomethacin, or magnesium sulphate. For the comparison of CCB with other tocolytic agents (subgrouped by type), for all reported outcomes we divided the number of events and total participants by two in the CCB arms.

Excluded studies

Seven trials were excluded on the basis of quasi-random allocation to treatment (Al-Omari 2006; Dunstan-Boone 1990; Junejo 2008; Maitra 2007; Malik 2007; Papadopoulos 1997; Smith 1993). Ten studies were excluded as they did not fulfil the intervention inclusion criteria as follows: did not use a CCB (Breart 1979;

Shim 2006); a pharmacokinetic study of nifedipine (Juon 2008); compared bed rest or 17-OH progesterone injection to nifedipine (Chawanpaiboon 2011); compared atosiban with clinician choice of one or more other tocolytics (Husslein 2007); psychotherapeutic interventions for women in preterm labour, while using nifedipine as choice of tocolysis (Dasari 2007); the addition of a CCB for women receiving tocolysis with a betamimetic agent (Rodriguez-Escudero 1981; Piovano 1985); maintenance therapy of women following successful tocolysis (Carr 1993; El-Sayed 1998). One study was excluded (Meyer 1990) as women were enrolled only after subcutaneous terbutaline failed to stop regular uterine contractions and this may have introduced a systematic bias favouring nifedipine since only women who did not respond to the beta-adrenergic agonist were admitted to the trial.

Please see Characteristics of excluded studies for further details.

Risk of bias in included studies

Overall the quality of the included trials was fair. Refer to Characteristics of included studies for further details and to Figure 1 and Figure 2 for a summary of 'Risk of bias' assessments.

Figure 1. 'Risk of bias' graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

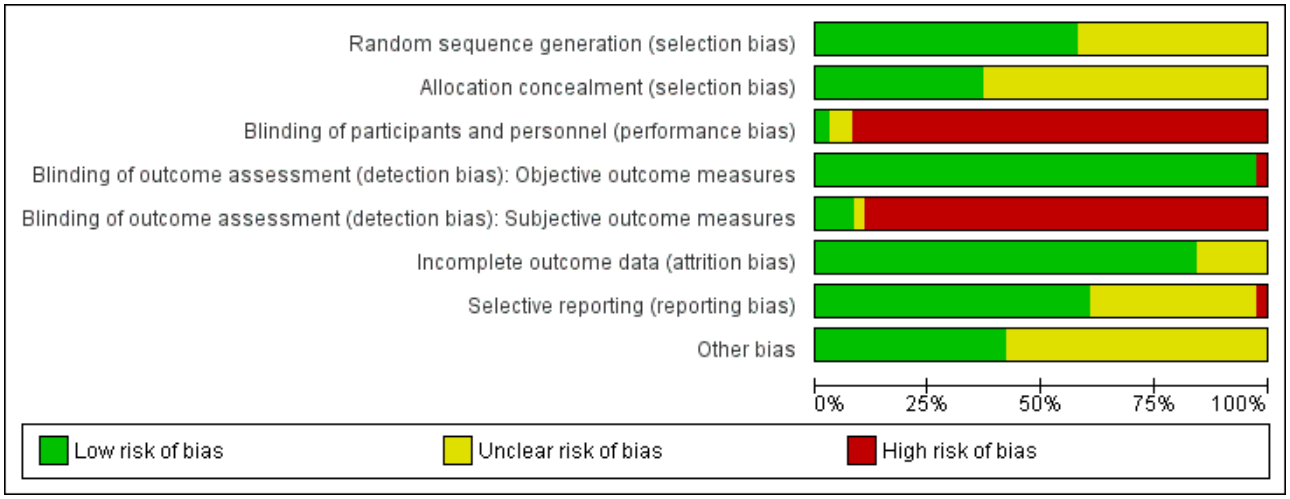


Figure 2. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.

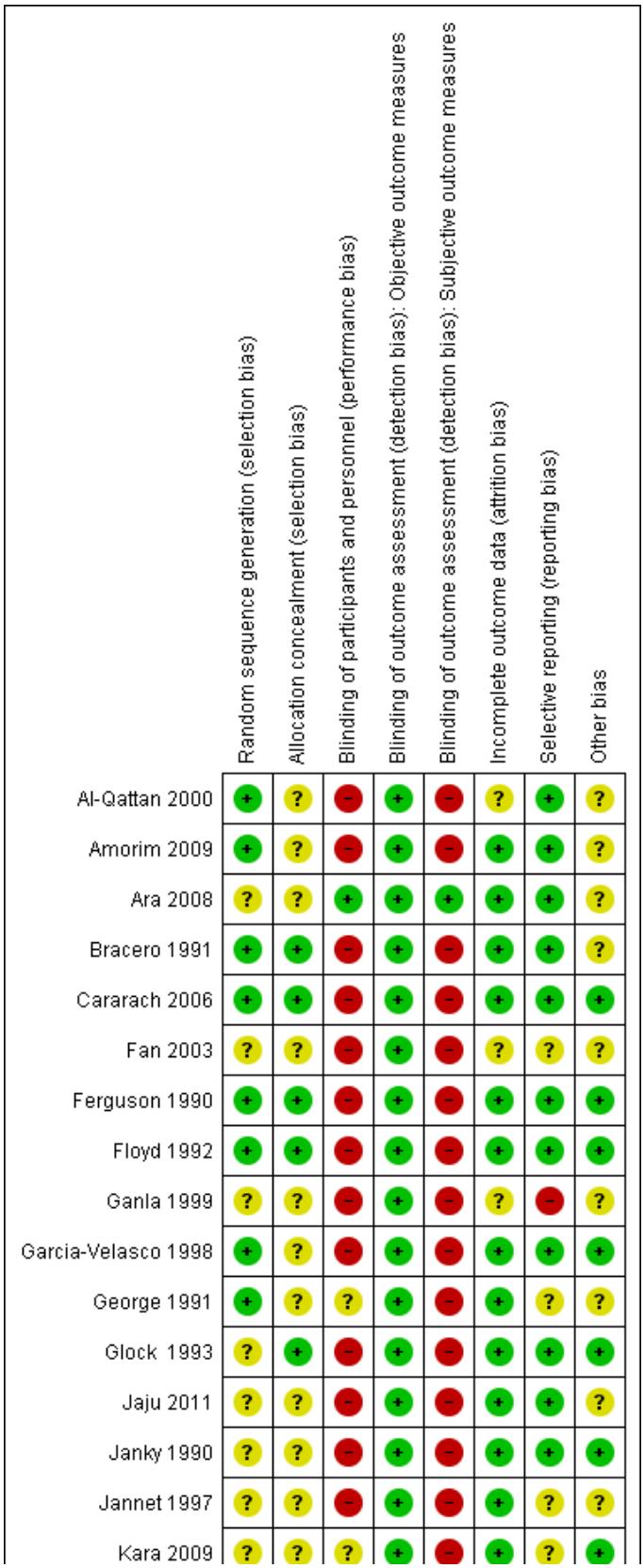
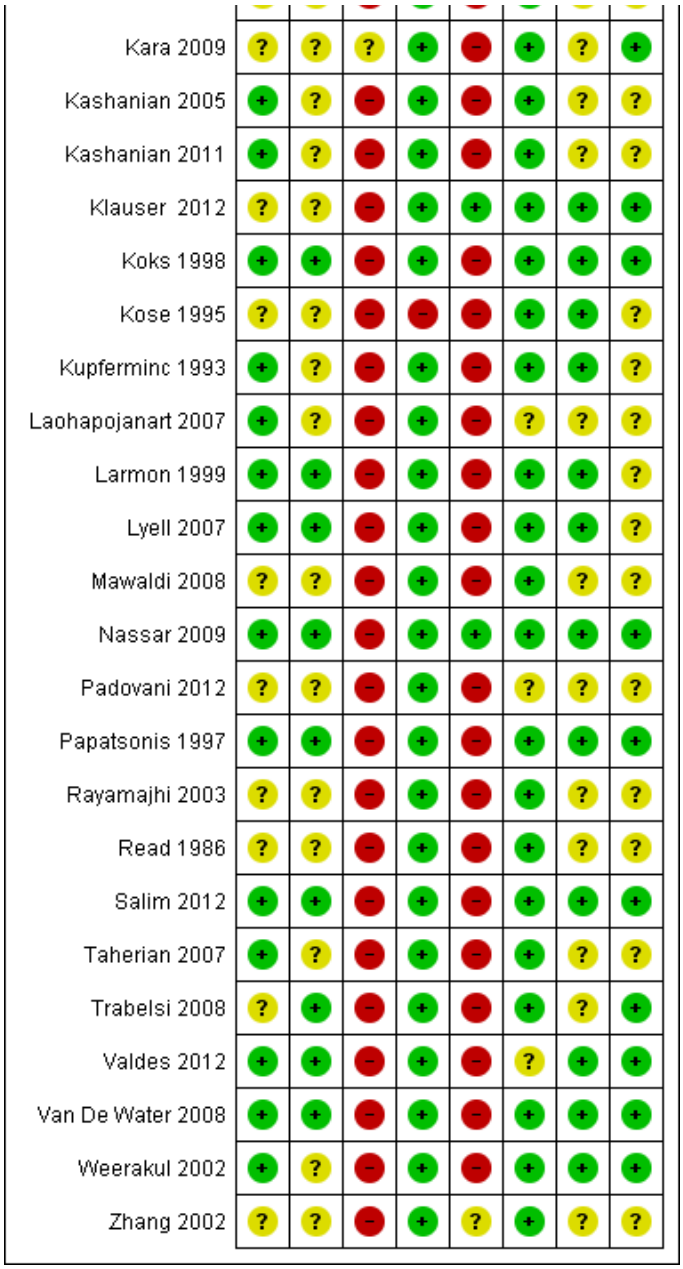


Figure 2. (Continued)



Allocation

The randomisation sequence generation was judged as adequate in 22 of the 38 included studies (Al-Qattan 2000; Amorim 2009; Bracero 1991; Cararach 2006; Ferguson 1990; Floyd 1992; Garcia-Velasco 1998; George 1991; Kashanian 2005; Kashanian 2011; Koks 1998; Kupferminc 1993; Laohapojanart 2007; Larmon 1999; Lyell 2007; Nassar 2009; Papatsonis 1997; Salim 2012; Taherian 2007; Valdes 2012; Van De Water 2008; Weerakul 2002) and therefore assessed as having a low risk of selection bias. In the remaining 16 studies the randomisation sequence generation process was unclear.

Allocation to treatment was adequately concealed in 14 studies and therefore assessed as having a low risk of selection bias (Bracero 1991; Cararach 2006; Ferguson 1990; Floyd 1992; Glock 1993; Koks 1998; Larmon 1999; Lyell 2007; Nassar 2009; Papatsonis 1997; Salim 2012; Trabelsi 2008; Valdes 2012; Van De Water 2008). In the remaining trials the allocation process was unclear.

Blinding

Blinding of the intervention (performance bias) was attempted in only one of the included studies (Ara 2008) - the only placebo controlled trial. For the remaining trials, the lack of blinding of the intervention may be, in part, as a result of the difficulties with adequately blinding such interventions (i.e. presentation of the intervention as either oral versus intravenous and the well-known side effects of certain interventions). For blinding of outcome measures (detection bias), all trials were deemed as having low risk of bias for objective outcomes (interval between trial entry and birth, gestation at birth (preterm birth and mean gestational age), perinatal mortality, stillbirth, and neonatal death).

One trial (Klauser 2012) used blinded assessment of all outcome measures and was considered to have low risk of detection bias for both objective and subjective outcome measures. All other trials were considered to be at high risk of detection bias for subjective outcome measures (i.e. maternal and neonatal morbidity measures).

Incomplete outcome data

The majority of the studies had minimal or no attrition and were therefore assessed as having a low risk of attrition bias. To enable analysis by intention-to-treat, additional information was sought from the investigators of 13 included studies (Bracero 1991; Cararach 2006; Ferguson 1990; Garcia-Velasco 1998; Janky 1990; Kupferminc 1993; Larmon 1999; Nassar 2007; Papatsonis 1997; Read 1986; Taherian 2007; Van De Water 2008; Weerakul 2002) and data were provided and included for 11 of these studies (Cararach 2006; Ferguson 1990; Garcia-Velasco 1998; Janky 1990; Koks 1998; Kupferminc 1993; Larmon 1999; Nassar 2007; Papatsonis 1997; Van De Water 2008; Weerakul 2002).

Selective reporting

Selective reporting was considered possible in one trial (Ganla 1999) where the outcomes of pregnancy prolongation for 48 hours and until 36 weeks were omitted from the results. In this trial, failure to achieve uterine relaxation or development of significant side effects in the mother or fetus was considered treatment "failure", and treatment "success" was only reported as the inverse of this. In 23 trials, we found no obvious evidence of reporting bias (Al-Qattan 2000; Amorim 2009; Ara 2008; Bracero 1991; Cararach 2006; Ferguson 1990; Floyd 1992; Garcia-Velasco 1998; Glock 1993; Jaju 2011; Janky 1990; Klauser 2012; Koks 1998; Kose 1995; Kupferminc 1993; Larmon 1999; Lyell 2007; Nassar 2009; Papatsonis 1997; Salim 2012;Valdes 2012; Van De Water 2008; Weerakul 2002) and judged these trials to be at low risk of bias. In the remaining trials it was unclear whether selective reporting bias was present.

No obvious evidence of selective reporting bias was shown in funnel plots (Figure 3; Figure 4; Figure 5.

Figure 3. Funnel plot of comparison: 2 Calcium channel blockers compared with any other tocolytic agent (subgrouped by other tocolytic), outcome: 2.1 Birth less than 48 hours after trial entry.

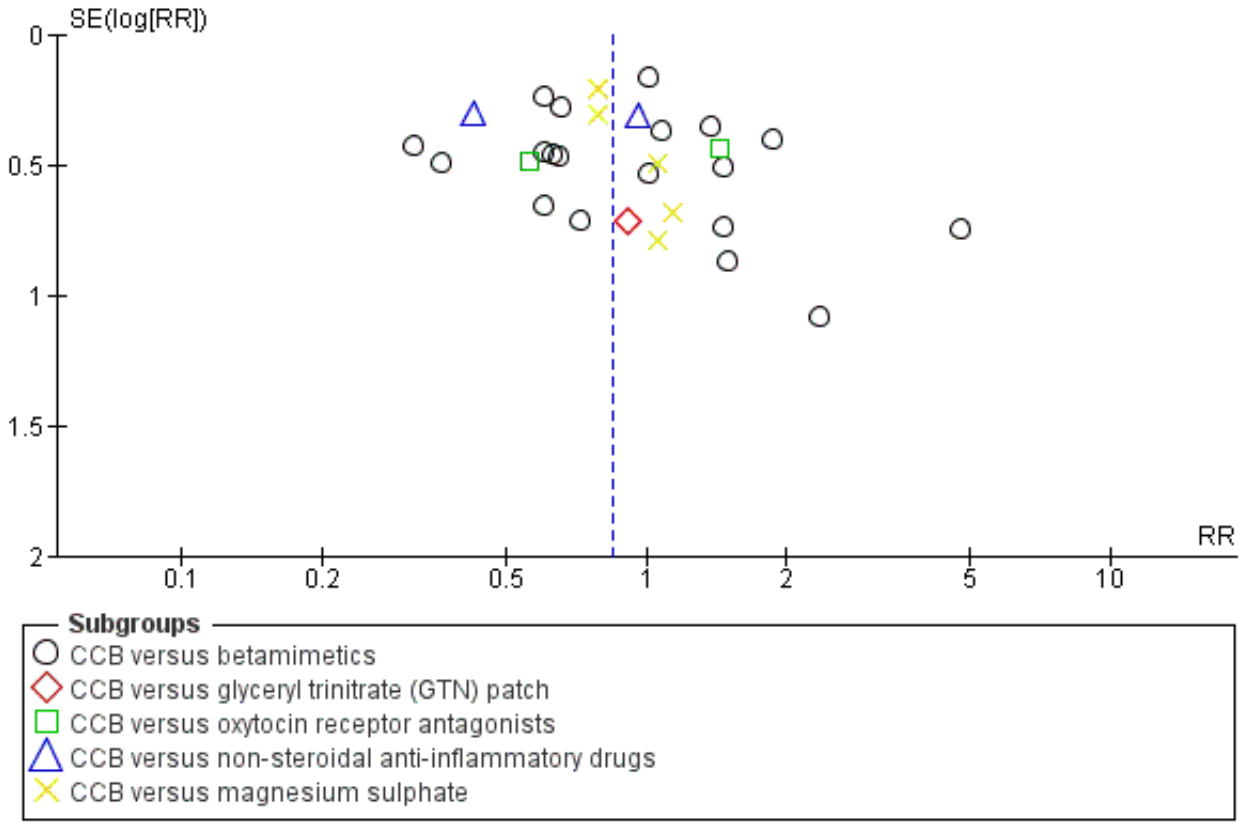


Figure 4. Funnel plot of comparison: 2 Calcium channel blockers compared with any other tocolytic agent (subgrouped by agent), outcome: 2.3 Perinatal mortality.

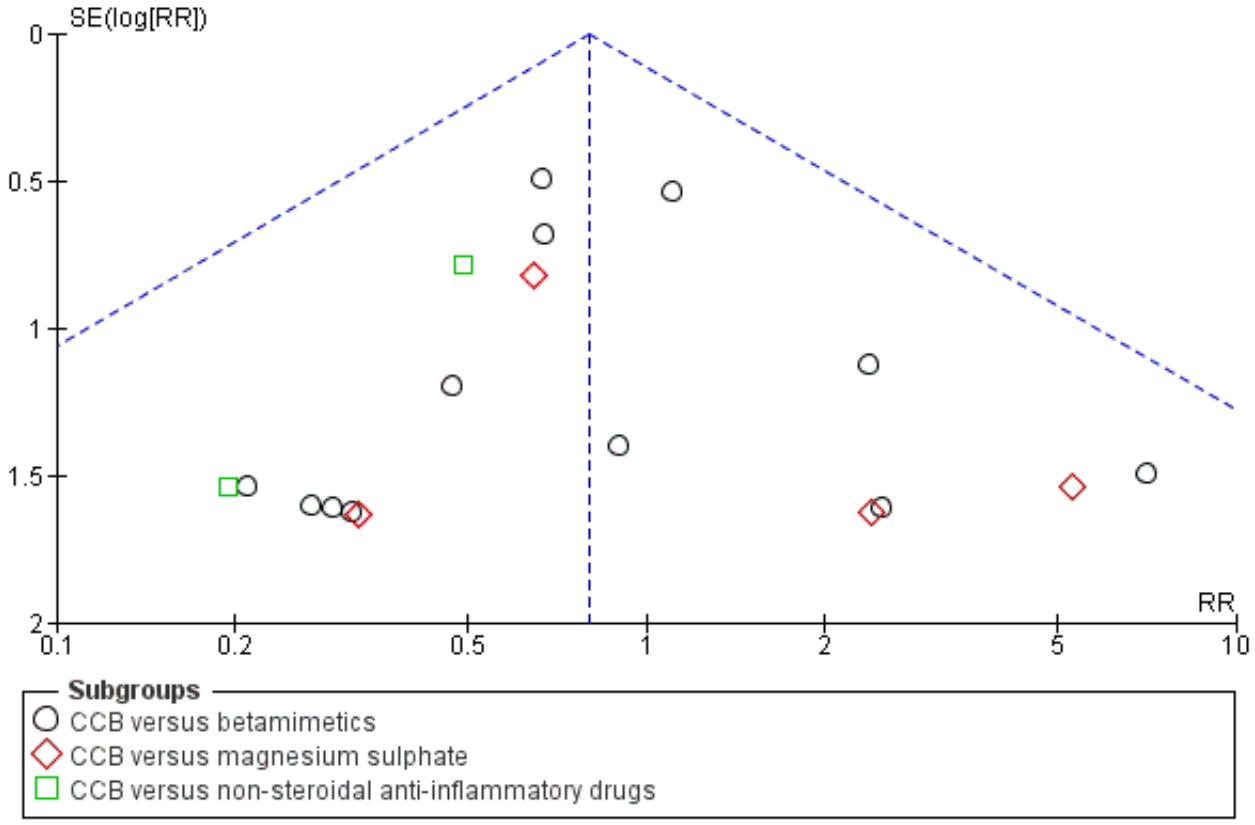
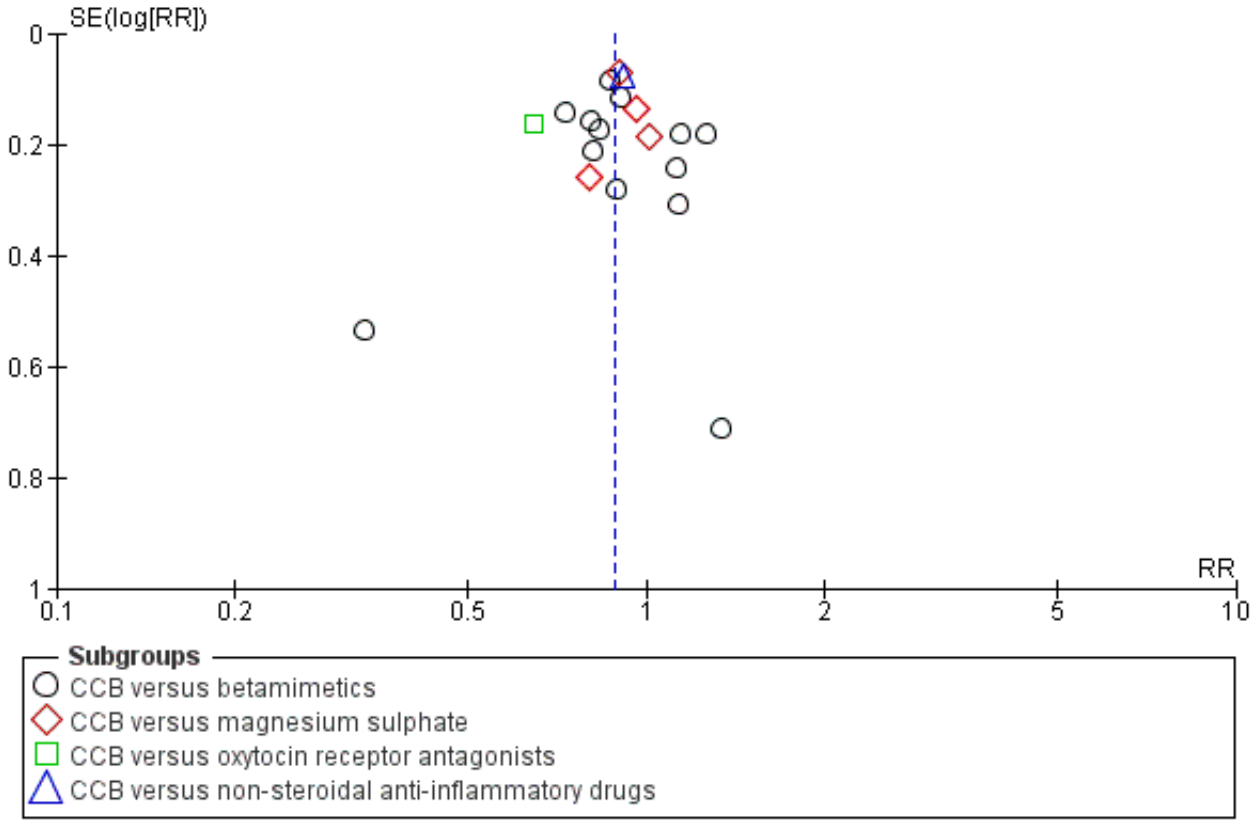


Figure 5. Funnel plot of comparison: 2 Calcium channel blockers compared with any other tocolytic agent (subgrouped by other tocolytic), outcome: 2.9 Preterm birth (before completion of 37 weeks of gestation).



Other potential sources of bias

Sixteen studies were assessed as being at low risk of bias for other potential sources of bias based on baseline characteristics being similar between groups and no other bias apparent (Cararach 2006; Ferguson 1990; Floyd 1992; Garcia-Velasco 1998; Glock 1993; Janky 1990; Kara 2009; Klauser 2012; Koks 1998; Nassar 2009; Papatsonis 1997; Salim 2012; Trabelsi 2008; Valdes 2012; Van De Water 2008; Weerakul 2002). In the remaining 22 studies, the risk of other sources of bias was unclear. Ganla 1999 reported that women in the groups were "well matched" on various characteristics at baseline but no data were provided. Ganla 1999 also concluded that perinatal mortality was reduced by nifedipine, although this outcome was not reported in the results. This research article is housed on a website sponsored by a global pharmaceutical company.

Assessment of studies that included multiple pregnancies

In 10 studies women with a multiple pregnancy were eligible for entry (Floyd 1992; Janky 1990; Kashanian 2005; Klauser 2012; Koks 1998; Kupferminc 1993; Lyell 2007; Mawaldi 2008; Rayamajhi 2003; Salim 2012), although Janky 1990 did not appear to recruit any women with a multiple pregnancy. Of the nine studies that included twins or multiples, seven reported neonatal outcomes Floyd 1992; Klauser 2012; Koks 1998; Kupferminc 1993; Lyell 2007; Rayamajhi 2003; Salim 2012. Where possible, we adjusted neonatal outcomes for clustering to take into account the non-independence of babies from the same pregnancy. Statistics were adjusted according to methods described in the *Handbook* (Higgins 2011) and using an estimate of the ICC of 0.2, as recommended by Yelland 2011. For dichotomous outcomes, the numerator and denominator were adjusted and for continuous outcomes the denominator only was adjusted.

Effects of interventions

Comparisons and subgroup analyses were undertaken as follows:

- Comparison 1: any CCB compared with placebo or no intervention.
- Comparison 2: any CCB compared with any other tocolytic agent subgrouped by type of tocolytic: betamimetics, magnesium sulphate, oxytocin receptor antagonists (ORA), non-steroidal anti-inflammatory drugs (NSAIDs), glyceryl trinitrate (GTN) patch.
- Comparison 3: any CCB compared with betamimetics subgrouped by type of CCB: nifedipine, nicardipine.
- Comparison 4: any CCB compared with magnesium sulphate subgrouped by type of CCB: nifedipine, nicardipine.
- Comparison 5: higher dose CCBs compared with lower dose CCBs.

We were unable to conduct the planned subgroup analyses to explore the effects at different gestational age thresholds by membrane status and multiple gestation due to the unavailability of data. Comparisons for CCB versus ORA, NSAID, and GTN patch

subgrouped by type of CCB were not undertaken due to insufficient data.

Comparison 1: CCB compared with placebo or no treatment

Two studies including 173 women are included in this comparison (Ara 2008; Zhang 2002). One trial (Zhang 2002) randomised women to one of three groups: two different dosages of nifedipine or no treatment. In this comparison we combined the two nifedipine groups.

Primary outcomes

Birth less than 48 hours after trial entry (Analysis 1.1)

Comparing CCB versus placebo or no treatment, a reduction in birth less than 48 hours after trial entry was shown (risk ratio (RR) 0.30, 95% confidence interval (CI) 0.21 to 0.43; number needed to treat for an additional beneficial outcome (NNTB) 2, 95% CI 2 to 3), (two trials with 173 women).

No other primary outcomes were reported.

Secondary outcomes

For the infant/child

Preterm birth (before completion of 37 weeks of gestation)

Two trials (173 women) reported the outcome of preterm birth (before completion of 37 weeks of gestation). Due to substantial heterogeneity ($T^2 = 0.88$, $Chi^2 = 53.79$, df = 1 ($P < 0.001$), $I^2 = 98\%$), these outcome data were not combined (Analysis 1.2).

One placebo controlled trial (89 women) (Ara 2008) showed no difference in preterm birth (RR 0.96, 95% CI 0.89 to 1.03) while the other (non-placebo controlled trial) (84 women) (Zhang 2002) reported a reduction (RR 0.44, 95% CI 0.31 to 0.62; NNTB 2, 95% CI 2 to 3).

For the woman

Maternal adverse effects (Analysis 1.3)

An increase in maternal adverse effects was shown for CCB compared with placebo or no treatment (one trial; 89 women; RR 49.89, 95% CI 3.13 to 795.02; no events were reported in the control group).

No other outcomes were reported.

Comparison 2: CCB compared with any other tocolytic agent by type of tocolytic

A total of 35 studies including 3275 women are included in the comparisons of CCB versus other tocolytics as follows:

- CCB versus betamimetics: 23 studies with 1793 women.
- CCB versus magnesium sulphate: seven studies with 943 women.
- CCB versus NSAID: two studies with 358 women.
- CCB versus ORA: two studies with 225 women.
- CCB versus GTN patch: one study with 54 women.

Primary outcomes

Birth less than 48 hours after trial entry (Analysis 2.1)

A moderate degree of statistically heterogeneity was evident for this outcome measure in the comparisons of CCB versus betamimetics, NSAID and ORA. However, upon exploration of the possible reasons for the heterogeneity by examining clinical features of the studies, we considered an overall summary was meaningful using a random-effects analysis.

While a trend towards fewer women giving birth less than 48 hours after trial entry was evident, this was not statistically significant for any tocolytic comparison groups as follows:

- CCB versus betamimetics (19 studies; 1505 women; average RR 0.86, 95% CI 0.67 to 1.10), ($T^2 = 0.09$, $Chi^2 = 28.52$, df = 18 ($P = 0.05$), $I^2 = 37\%$).
- CCB versus magnesium sulphate (five studies; 651 women; average RR 0.83, 95% CI 0.61 to 1.13).
- CCB versus NSAID (two studies; 218 women; average RR 0.63, 95% CI 0.29 to 1.41), ($T^2 = 0.23$, $Chi^2 = 3.43$, df = 1 ($P = 0.06$), $I^2 = 71\%$).
- CCB versus ORA (two studies; 225 women; average RR 0.92, 95% CI 0.37 to 2.30), ($T^2 = 0.22$, $Chi^2 = 2.04$, df = 1 ($P = 0.15$), $I^2 = 51\%$).
- CCB versus GTN patch (one study; 53 women; average RR 0.91, 95% CI 0.22 to 3.66).

A funnel plot for this analysis (Figure 3) was reasonably symmetrical, suggesting the absence of important bias or small-study effects in the set of studies.

Very preterm birth (before completion of 34 weeks of gestation) (Analysis 2.2)

A statistically significant reduction in very preterm birth was shown for:

- CCB versus betamimetics (six studies; 630 women; RR 0.78, 95% CI 0.66 to 0.93; NNTB 11, 95% CI 7 to 33).

No differences were shown for other tocolytic comparisons as follows:

- CCB versus magnesium sulphate (four studies; 429 women; RR 0.95, 95% CI 0.76 to 1.20).
- CCB versus ORA (one study; 145 women; RR 0.59, 95% CI 0.31 to 1.12).
- CCB versus NSAID (one study; 139 women; RR 1.10, 95% CI 0.86 to 1.42).

No data were available for the CCB versus GTN patch comparison.

Perinatal mortality (Analysis 2.3)

No statistically significant differences in perinatal mortality were shown for any of the tocolytic subgroups as follows:

- CCB versus betamimetics (17 studies; 1233 babies; RR 0.85, 95% CI 0.52 to 1.38).
- CCB versus magnesium sulphate (five studies; 657 babies; RR 1.07, 95% CI 0.36 to 3.13).
- CCB versus NSAID (two studies; 239 babies; RR 0.39, 95% CI 0.10 to 1.51).

No data were available for the other subgroup comparisons.

A funnel plot for this analysis (Figure 4) was reasonably symmetrical, suggesting the absence of important bias or small-study effects in the set of studies.

Stillbirth (Analysis 2.4)

No statistically significant differences in stillbirth were shown for any of the tocolytic subgroups as follows:

- CCB versus betamimetics (13 studies; 934 women; RR 1.03, 95% CI 0.15 to 7.23).
- CCB versus magnesium sulphate (five studies; 657 women; RR 2.39, 95% CI 0.10 to 57.18).
- CCB versus NSAID (one study; 160 women; RR not estimable (no stillbirths reported)).

No data were available for the other subgroup comparisons.

Neonatal death (Analysis 2.5)

No statistically significant differences in neonatal death were shown for any of the tocolytic subgroups as follows:

- CCB versus betamimetics (15 studies; 1068 babies; RR 0.96, 95% CI 0.53 to 1.75).
- CCB versus magnesium sulphate (five studies; 657 babies; RR 0.94, 95% CI 0.30 to 3.00).
- CCB versus ORA (one study; 179 babies; RR not estimable (no neonatal deaths reported)).
- CCB versus NSAID (two studies; 239 babies; RR 0.39, 95% CI 0.10 to 1.51).

No data were available for the CCB versus GTN patch subgroup comparison.

Maternal death (Analysis 2.6)

There were no maternal deaths reported in one study of 276 women (Klauser 2012, (three-armed trial) comparing CCB with magnesium sulphate and NSAID (RR not estimable).

No data were available for the other tocolytic comparisons.

No data were available for other serious maternal outcomes (cardiac arrest, respiratory arrest, admission to intensive care unit).

Secondary outcomes

For the infant/child

Interval between trial entry and birth (days) (Analysis 2.7)

A moderate degree of statistical heterogeneity was evident for this outcome measure in the comparison of CCB versus betamimetics (T^2 = 22.52, Chi^2 = 23.51, df = 9 (P = 0.005), I^2 = 62%). However, upon exploration of the possible reasons for the heterogeneity by examining clinical features of the studies, we considered an overall summary was meaningful using a random-effects analysis.

A statistically significant increase in the interval between trial entry and birth was shown for:

- CCB versus betamimetics (10 studies; 830 women; average mean difference (MD) 4.38 days, 95% CI 0.25 to 8.52).

No differences were shown for the other tocolytic comparisons as follows:

- CCB versus magnesium sulphate (two studies; 212 women; average MD -1.63, 95% CI -8.80 to 5.54).
- CCB versus ORA (one study; 145 women; average MD 5.70, 95% CI -0.96 to 12.36).

No data were available for the other tocolytic comparisons.

Gestational age at birth (completed weeks) (Analysis 2.8)

A statistically significant increase in gestational age at birth was shown for:

- CCB versus betamimetics (14 studies; 1063 women; MD 0.71 weeks, 95% CI 0.34 to 1.09); and
- CCB versus ORA (one study; 145 women; MD 1.20 weeks, 95% CI 0.25 to 2.15).

No differences were shown for other tocolytic comparisons as follows:

- CCB versus magnesium sulphate (five studies; 651 women; MD 0.15, 95% CI -0.22 to 0.52).
- CCB versus NSAID (one study; 139 women; MD 0.00, 95% CI -1.51 to 1.51).

No data were available for the GTN patch comparison.

Preterm birth (before completion of 37 weeks of gestation) (Analysis 2.9)

A statistically significant reduction in preterm birth was shown for:

- CCB versus betamimetics (13 studies; 1111 women; RR 0.89, 95% CI 0.80 to 0.98; NNTB 16, 95% CI 9 to 86); and
- CCB versus ORA (one study; 145 women; RR 0.64, 95% CI 0.47 to 0.89; NNTB 5, 95% CI 3 to 15).

A funnel plot for this analysis (Figure 5) was reasonably symmetrical, suggesting the absence of important bias or small-study effects in the set of studies.

No differences were shown for other tocolytic comparisons as follows:

- CCB versus magnesium sulphate (four studies; 499 women; (RR 0.92, 95% CI 0.81 to 1.06).
- CCB versus NSAID (one study; 139 women; (RR 0.91, 95% CI 0.78 to 1.06).

No data were available for the GTN patch comparison.

Extremely preterm birth (before completion of 28 weeks of gestation) (Analysis 2.10)

No statistically significant difference in extremely preterm birth was shown for:

- CCB versus ORA (one study; 145 women; RR 0.47, 95% CI 0.04 to 5.03).

Apgar score less than seven at five minutes (Analysis 2.11)

No statistically significant differences in Apgar score less than seven at five minutes was shown for:

- CCB versus betamimetics (six studies; 557 babies; RR 0.53, 95% CI 0.26 to 1.06).
- CCB versus magnesium sulphate (two studies; 217 babies; RR 1.10, 95% CI 0.48 to 2.51).
- CCB versus ORA (one study; 179 babies; RR 1.85, 95% CI 0.17 to 20.03).

No data were available for the other tocolytic comparisons.

Admissions to NICU (Analysis 2.12)

A statistically significant reduction in NICU admission shown for:

- CCB versus betamimetics (12 studies; 999 babies; average RR 0.74, 95% CI 0.63 to 0.87; NNTB 12, 95% CI 9 to 23).
- CCB versus ORA (one study; 179 babies; average RR 0.59, 95% CI 0.41 to 0.85; NNTB 5, 95% CI 4 to 14).

No differences were shown for:

- CCB versus magnesium sulphate (two studies; 331 babies; average RR 1.00, 95% CI 0.48 to 2.08),(T^2 = 0.21, Chi^2 = 3.86, df = 1 (P = 0.05), I^2 = 74%).

No data were available for the other tocolytic comparisons.

Respiratory distress syndrome (RDS) (Analysis 2.13)

A statistically significant reduction in RDS was shown for:

- CCB versus betamimetics (16 studies; 1293 babies; RR 0.64, 95% CI 0.48 to 0.86; NNTB 19, 95% CI 13 to 47).

No differences were shown for other tocolytic comparisons as follows:

- CCB versus magnesium sulphate (four studies; 577 babies; RR 0.76, 95% CI 0.56 to 1.05).
- CCB versus ORA (one study; 179 babies; RR 0.72, 95% CI 0.28 to 1.85).
- CCB versus NSAID (one study; 160 babies; RR 0.71, 95% CI 0.45 to 1.13).

No data were available for the GTN patch comparison.

Chronic lung disease (Analysis 2.14)

There were no cases of chronic lung disease in one study of 91 babies (Van De Water 2008) comparing CCB with betamimetics (RR not estimable).

No data were available for the other tocolytic comparisons.

Necrotising enterocolitis (NEC) (Analysis 2.15)

A statistically significant reduction in NEC was shown for:

- CCB versus betamimetics (five studies; 490 babies; RR 0.21, 95% CI 0.05 to 0.96; NNTB 38, 95% CI 32 to 747).

No differences were shown for other tocolytic comparisons as follows:

- CCB versus magnesium sulphate (two studies; 360 babies; RR 0.64, 95% CI 0.13 to 3.20).
- CCB versus ORA (one study; 179 babies; RR 0.10, 95% CI 0.01 to 1.88).
- CCB versus NSAID (one study; 160 babies; RR 0.68, 95% CI 0.14 to 3.42).

No data were available for the CCB versus GTN patch other tocolytic comparison.

Neonatal sepsis (Analysis 2.16)

No statistically significant differences in neonatal sepsis was shown for the following:

- CCB versus betamimetics (seven studies; 618 babies; RR 0.72, 95% CI 0.47 to 1.11).
- CCB versus magnesium sulphate (two studies; 360 babies; RR 0.71, 95% CI 0.31 to 1.63).
- CCB versus ORA (one study; 179 babies; RR 1.39, 95% CI 0.24 to 8.10).
- CCB versus NSAID (one study; 160 babies; RR 0.66, 95% CI 0.25 to 1.75).

No data were available for the comparison of CCB versus GTN patch.

Neonatal jaundice (Analysis 2.17)

A statistically significant reduction in neonatal jaundice was shown for:

- CCB versus betamimetics (three studies; 334 babies; RR 0.72, 95% CI 0.57 to 0.92; NNTB 9, 95% CI 6 to 31).

No data were available for the other tocolytic comparisons.

Intraventricular haemorrhage (IVH) (Analysis 2.18)

A statistically significant reduction in IVH was shown for:

- CCB versus betamimetics (seven studies; 596 babies; RR 0.53, 95% CI 0.34 to 0.84; NNTB 15, 95% CI 11 to 44).

No differences were shown for other subgroups as follows:

- CCB versus magnesium sulphate (two studies; 360 babies; RR 0.71, 95% CI 0.30 to 1.69).
- CCB versus ORA (one study; 179 babies; RR 0.46, 95% CI 0.09 to 2.46).
- CCB versus NSAID (one study; 160 babies; RR 0.61, 95% CI 0.23 to 1.61).

No data were available for the CCB versus GTN patch comparison.

Grades three or four IVH (Analysis 2.19)

No statistically significant difference was shown in grades three or four IVH for:

- CCB versus betamimetics (six studies; 560 babies; RR 0.63, 95% CI 0.23 to 1.74).

No data were available for the other tocolytic comparisons.

Periventricular leukomalacia (PVL) (Analysis 2.20)

No statistically significant difference in PVL was shown in the single study reporting this outcome (Klauser 2012) as follows:

- CCB versus magnesium sulphate (one study; 151 babies; no events reported).
- CCB versus NSAID (one study; 160 babies; RR 0.34, 95% CI 0.02 to 6.96).

No data were available for the other subgroup comparisons.

Retinopathy of prematurity (ROP) (Analysis 2.21)

No statistically significant differences in ROP was shown for:

- CCB versus betamimetics (two studies; 276 babies; RR 0.15, 95% CI 0.02 to 1.28).
- CCB versus ORA (one study; 179 babies; RR 0.46, 95% CI 0.04 to 5.01).

No data were available for the other tocolytic comparisons.

For the woman

Maternal adverse effects (Analysis 2.22)

Statistical heterogeneity was evident within the CCB versus betamimetic comparison. However, upon exploration of the possible reasons for the heterogeneity by examining clinical features of the studies within this comparison, we considered an overall summary was meaningful using a random-effects analysis. Differences were evident across these comparisons: Test for subgroup differences: $Chi^2 = 39.20$, df = 4 (P <0.01) $I^2 = 89.9\%$.

Statistically significant fewer maternal adverse effects were shown for CCB when compared to betamimetics and magnesium sulphate:

- CCB versus betamimetics (15 studies; 1305 women; average RR 0.36, 95% CI 0.24 to 0.53; NNTB 4, 95% CI 3), ($T^2 = 0.36$, $Chi^2 = 62.40$, df = 14 (P < 0.01), $I^2 = 78\%$).
- CCB versus magnesium sulphate (five studies; 604 women; average RR 0.52, 95% CI 0.40 to 0.68; NNTB 7, 95% CI 6 to 10).

CCB resulted in statistically significant more maternal adverse effects when compared with ORA:

- CCB versus ORA (two studies; 225 women; average RR 2.61, 95% CI 1.43 to 4.74; number needed to treat for an additional harmful outcome (NNTH) 6, 95% CI 3 to 22).

No differences were shown for the comparisons of CCB versus NSAID or GTN patches as follows:

- CCB versus NSAID (one study; 79 women; average RR 1.51, 95% CI 0.81 to 2.79).
- CCB versus GTN patch (one study; 50 women; average RR 0.60, 95% CI 0.23 to 1.54).

Discontinuation of therapy for maternal adverse effects (Analysis 2.23)

Statistical heterogeneity was evident for the CCB versus magnesium sulphate comparison. However, upon exploration of the possible reasons for the heterogeneity by examining clinical features of the studies within this comparison, we considered an overall summary was meaningful using a random-effects analysis.

CCB resulted in statistically significant less maternal adverse effects requiring discontinuation of therapy when compared to betamimetic:

- CCB versus betamimetics (16 studies; 1217 women; average RR 0.22, 95% CI 0.10 to 0.48; NNTB 15, 95% CI 13 to 23).

No differences were shown for other tocolytic comparisons as follows:

- CCB versus magnesium sulphate (three studies; 339 women; average RR 1.61, 95% CI 0.10 to 25.91). Test for statistical heterogeneity: $T^2 = 3.68$, $Chi^2 = 5.14$, df = 2 (P = 0.08), $I^2 = 61\%$.
- CCB versus ORA (one study; 145 women; average RR 2.80, 95% CI 0.12 to 67.68).
- CCB versus NSAID (one study; 139 women; average RR 0.84, 95% CI 0.22 to 3.20).

No data were available for the CCB versus GTN patch tocolytic comparison.

Caesarean section (Analysis 2.24).

No statistically significant differences in caesarean section was shown for:

- CCB versus betamimetics (one study; 107 women; RR 0.72, 95% CI 0.38 to 1.38).
- CCB versus ORA (one study; 145 women; RR 0.75, 95% CI 0.21 to 2.67).

No data were available for the other tocolytic comparison.

No other maternal outcomes were reported.

Long-term outcomes

- CCB (nifedipine) versus betamimetics.

Child outcomes at nine to 12 years of age, collected by survey, were included from one study (Papatsonis 1997) (reported by Houtzager 2005). Of survivors, 48 of 88 (55%) originally randomised to the nifedipine group responded to the survey compared with 54 of 83 (65%) originally randomised to the ritodrine group were included.

No difference was shown in: parent report of the child's behavioural problems score (MD -2.00, 95% CI -6.42 to 2.42) (Analysis 2.27); motor quality score (MD -4.30, 95% CI -9.96 to 1.36) (Analysis 2.29); need for special education (RR 0.82, 95% CI 0.19 to 3.45) (Analysis 2.28); or child report of quality of life measures for any of the six domains (Physical, Motor, Autonomy, Cognitive, Social, Poisitve emotion, Negative emotion) Analysis 2.30.

No difference was shown in parent distress scores (for the woman) (MD -1.00, 95% CI -9.25 to 7.25) (Analysis 2.37).

No data were available for other tocolytic comparison.

Health service utilisation

Duration of stay in NICU (days) (Analysis 2.25)

A reduction in the length of NICU stay was shown for:

- CCB versus magnesium sulphate (two studies; 360 babies; MD -4.55, 95% CI -8.17 to -0.92).

- CCB versus ORA. (one study; 179 babies; MD -5.40, 95% CI -10.84 to 0.04).

No difference was shown for:

- CCB versus NSAID (one study; 160 women; MD 3.60, 95% CI -8.27 to 15.47).

No data were available for the other tocolytic comparison.

Duration of stay in maternal hospital (days) (Analysis 2.26)

- CCB versus betamimetics. No difference was shown in the duration of maternal hospital stay (one trial, 52 women) (MD 0.18 days, 95% CI -1.04 to 1.40).

No data were available for the other tocolytic comparison.

Comparison 3: CCB compared with betamimetics (subgrouped by type of CCB)

A total of 23 studies with 1793 women are included in the comparison of CCB versus betamimetics subgrouped by type; three studies used nicardipine (Jannet 1997; Larmon 1999; Trabelsi 2008) and the remainder used nifedipine. No differences were evident by type of tocolytic for any included outcomes measures.

Primary outcomes

Birth less than 48 hours after trial entry (Analysis 3.1)

Statistical heterogeneity was evident for the CCB versus betamimetics comparison. However, upon exploration of the possible reasons for the heterogeneity by examining clinical features of the studies within this comparison, we considered an overall summary was meaningful using a random-effects analysis.

- Nifedipine versus betamimetics. No statistically significant difference in number of women giving birth less than 48 hours after trial entry was shown: (19 studies; 1505 women; average RR 0.86, 95% CI 0.67 to 1.10) (T^2 = 0.09, Chi^2 = 28.52, df = 18 (P = 0.05), I^2 = 37%).
- Nicardipine versus betamimetics. No data were available.

Very preterm birth (before completion of 34 weeks of gestation) (Analysis 3.2)

- Nifedipine versus betamimetics. A significant reduction in very preterm birth was shown (five studies; 544 women; RR 0.78, 95% CI 0.66 to 0.93; NNTB 10, 95% CI 6 to 29).
- Nicardipine versus betamimetics. No difference was shown (one study; 86 women; RR 0.50, 95% CI 0.05 to 5.31).

Perinatal mortality (Analysis 3.3)

No statistically significant differences in perinatal mortality were shown as follows:

- Nifedipine versus betamimetics (16 studies; 1188 babies; RR 0.88, 95%, CI 0.53 to 1.44).
- Nicardipine versus betamimetics (one study; 45 babies; RR 0.29, 95% CI 0.01 to 6.84).

No data were available for other primary outcome measures.

Secondary outcomes

For the infant/child

Interval between trial entry and birth (days) (Analysis 3.4)

Statistical heterogeneity was evident for the CCB versus betamimetics comparison. However, upon exploration of the possible reasons for the heterogeneity by examining clinical features of the studies within this comparison, we considered an overall summary was meaningful using a random-effects analysis.

A statistically significant increase in interval between trial entry and birth was shown for:

- Nifedipine versus betamimetics. An increase in interval between trial entry and birth was shown (10 studies; 830 women; average MD (days) 4.38, 95% CI 0.25 to 8.52), (T^2 = 22.52, Chi^2 = 23.51, df = 9 (P = 0.005), I^2 = 62%).
- Nicardipine versus betamimetics. No data were available.

Respiratory distress syndrome (RDS) (Analysis 3.5)

Nifedipine versus betamimetics. A statistically significant reduction in RDS was shown (16 studies; 1293 babies; RR 0.64, 95% CI 0.48 to 0.86; NNTB 19, 95% CI 13 to 47).

- Nicardipine versus betamimetics. No data were available.

For the woman

Discontinuation of therapy for maternal adverse effects (Analysis 3.6)

- Nifedipine versus betamimetics. Statistically significantly fewer women required discontinuation of therapy for maternal adverse effects with the use of nifedipine ((15 studies; 1172 women, RR 0.21, 95% CI 0.11 to 0.40; NNTB 17, 95% CI 15 to 22).
- Nicardipine versus betamimetics. A marginally non-significant reduction was shown (1 study; 45 women; RR 0.07, 95% CI 0.00 to 1.13).

Comparison 4: CCB compared with magnesium sulphate (subgrouped by type of CCB)

Seven studies with 943 women are included in the comparison of magnesium sulphate subgrouped by type of CCB; one study used nicardipine (Larmon 1999) and the remainder used nifedipine.

Primary outcomes

Birth less than 48 hours after trial entry (Analysis 4.1)

No statistically significant differences in number of women giving birth prior to 48 hours were shown:

- Nifedipine versus magnesium sulphate (four studies; 529 women; RR 0.83, 95% CI 0.60 to 1.14).
- Nicardipine versus magnesium sulphate (one study; 122 women; RR 1.14, 95% CI 0.30 to 4.35).

Very preterm birth (before completion of 34 weeks of gestation) (Analysis 4.2)

No statistically significant differences in very preterm birth were shown:

- Nifedipine versus magnesium sulphate (three studies; 307 women; RR 0.98, 95% CI 0.78 to 1.23).
- Nicardipine versus magnesium sulphate (one study; 122 women; RR 0.71, 95% CI 0.25 to 2.06).

Perinatal mortality (Analysis 4.3)

No statistically significant difference in perinatal mortality were shown:

- Nifedipine versus magnesium sulphate (four studies; 535 babies; RR 1.07, 95% CI 0.36 to 3.13).
- Nicardipine versus magnesium sulphate. (one study; 122 babies); no cases of perinatal mortality were reported.

Maternal death (Analysis 4.4)

There were no cases of maternal deaths reported in one study of 276 women (Klauser 2012, three-armed trial) comparing nifedipine with magnesium sulphate (RR not estimable).

No data were available for the nicardipine subgroup comparison.

Secondary outcomes

For the infant/child

Interval between trial entry and birth (Analysis 4.5)

No statistically significant differences in interval between trial entry and birth were shown for:

- Nifedipine versus magnesium sulphate (one study; 90 women; MD -5.80, 95% CI -18.59 to 6.99).
- Nicardipine versus magnesium sulphate (one study; 122 women; MD 0.28, 95% CI -8.37 to 8.93).

Respiratory distress syndrome (RDS) (Analysis 4.6)

No statistically significant differences in RDS was shown for:

- Nifedipine versus magnesium sulphate (three studies; 455 babies; RR 0.78, 95% CI 0.56 to 1.09).
- Nicardipine versus magnesium sulphate (one study; 122 babies; RR 0.63, 95% CI 0.23 to 1.78).

For the woman

Discontinuation of therapy for maternal adverse effects (Analysis 4.7)

Statistical heterogeneity was evident for the CCB versus magnesium sulphate comparison. However, upon exploration of the possible reasons for the heterogeneity by examining clinical features of the studies within this comparison, we considered an overall summary was meaningful using a random-effects analysis.

No differences were shown in the need for discontinuation of therapy for maternal adverse effects for:

- Nifedipine versus magnesium sulphate (two studies; 217 women; average RR 1.14, 95% CI 0.01 to 101.65, random-effects), (T^2 = 8.28, Chi^2 = 4.74, df = 1 (P = 0.03), I^2 = 79%).
- Nicardipine versus magnesium sulphate (one study; 122 women; average RR 3.41, 95% CI 0.14 to 82.18).

Comparison 5: Higher versus lower dosage of CCB

One study of 102 women (Nassar 2009) compared a higher dose with a lower dose of oral nifedipine and comprehensive unpublished outcome data provided by the authors were included in the review.

Primary outcomes

Birth within 48 hrs after trial entry (Analysis 5.1).

No difference was shown in the outcomes of birth within 48 hours after trial entry (RR 0.77, 95% CI 0.26 to 2.27).

Perinatal mortality (Analysis 5.4)**, Stillbirth** (Analysis 5.5) **and Neonatal death** (Analysis 5.6)

No difference was shown in perinatal mortality (RR 0.15, 95% CI 0.01 to 2.92), stillbirth (RR 0.36, 95% CI 0.02 to 8.64), or neonatal death (RR 0.15, 95% CI 0.01 to 2.92).

Very preterm birth (before completion of 34 weeks of gestation) (Analysis 5.2)

No difference was shown in very preterm birth (before completion of 34 weeks of gestation) (RR 0.60, 95% CI 0.31 to 1.17).

Maternal death (Analysis 5.7)

No maternal deaths were reported during the trial period.

No data were available for any of the other primary outcome measures.

Secondary outcomes

For the infant/child

Interval between trial entry and birth (days) (Analysis 5.8)

No difference was shown in the interval between trial entry and birth (MD 7.30 weeks, 95% CI -2.21 to 16.81).

Gestational age at birth (completed weeks) (Analysis 5.9)

The mean gestational age at birth was marginally statistically significantly higher for babies of women receiving high-dose nifedipine (completed weeks) (MD 1.30 weeks, 95% CI 0.03 to 2.57).

Preterm birth (before 37 weeks' gestation) (Analysis 5.10)

No difference was shown in preterm birth (RR 0.83, 95% CI 0.63 to 1.10).

No statistically significant differences were shown for the secondary measures of neonatal morbidity and effect estimates are imprecise due to small numbers; the findings tended to favour the high-dose group as follows:

Apgar score less than seven at five minutes (RR 0.09, 95% CI 0.01 to 1.53) (Analysis 5.11).

Admission to the NICU (RR 0.57, 95% CI 0.31 to 1.05) (Analysis 5.12).

Respiratory distress syndrome (RDS) (RR 0.65, 95% CI 0.26 to 1.65) (Analysis 5.13).

Necrotising enterocolitis (NEC) (RR 0.22, 95% CI 0.01 to 4.39) (Analysis 5.14).

Neonatal sepsis (RR 1.08, 95% CI 0.23 to 5.11) (Analysis 5.15).

Neonatal jaundice (RR 0.57, 95% CI 0.31 to 1.05) (Analysis 5.16).

Intraventicular haemorrhage (IVH) (RR 0.12, 95% CI 0.01 to 2.18) (Analysis 5.17).

For the woman

No statistically significant differences were shown for maternal adverse effects as follows:

Maternal adverse effects (RR 1.08, 95% CI 0.33 to 3.51) (Analysis 5.18).

Discontinuation for maternal adverse effects (RR 5.40, 95% CI 0.27 to 109.76) (Analysis 5.19).

Health service utilisation

Duration of stay in NICU (days) (Analysis 5.20)

A reduction was shown in the duration of NICU stay with the use of higher dose nifedipine (MD days, -4.80 95% CI -8.73 to -0.87).

Duration of maternal hospital stay (days) (Analysis 5.21)

No difference was shown in maternal length of hospital stay (MD 0.90, 95% CI -1.59 to 3.39).

DISCUSSION

Summary of main results

This review update includes 38 included trials involving 3550 women. Of these 38 trials, all but three used nifedipine as the CCB. The remaining three trials (261 women) used nicardipine as the CCB, and no differences in outcomes were shown in trials comparing nicardipine to other tocolytics, although with limited data no strong conclusions can be drawn. It must be noted that the majority of trials did not use blinding of the intervention or outcome assessment.

Two small studies with 173 women, (one used a placebo control and the other did not) (Ara 2008; Zhang 2002) comparing CCB with placebo or no treatment were included showing a reduction in birth less than 48 hours after trial entry NNTB 2, 95% CI 2 to 3). The Zhang 2002 trial of CCB versus no treatment showed a significant reduction in preterm birth, while the placebo controlled Ara 2008 trial showed no difference. Maternal side effects from nifedipine were reported (percentage of women receiving nifedipine versus percentage receiving placebo); however, none were severe (flushing, headache and vertigo). Unfortunately, small numbers do not allow firm conclusions to be made.

Comparing CCB (mainly nifedipine) with other tocolytics by type (including betamimetics, glyceryl trinitrate (GTN), non-steriodal anti inflammatories (NSAID), magnesium sulphate and oxytocin receptor antagonist (ORA)), no significant reductions were shown in the primary outcome measures of birth within 48 hours of treatment or perinatal mortality.

In 23 studies of 1793 women, CCB was shown to prolong pregnancy by an average of four days and reduce preterm birth, very preterm birth, and important neonatal morbidity. Long-term data were limited, although in one study no difference in the child's behavioural/emotional outcome, motor quality, need for special education, quality of life or parent stress (for the woman). Comparing CCB with ORA one study (145 women) showed a significant increase in gestational age at birth (average of one week) and a significant reduction in preterm birth with NNTB on average 5 (95% CI 3 to 15). Comparing CCB with magnesium sulphate (five studies; 651 women) neonatal duration of stay in the NICU was reduced by an average of around five days. No differences were shown in the comparisons with GTN, NSAID although numbers were small.

CCB resulted in fewer maternal adverse drug side reactions when compared to betamimetics, but more maternal adverse drug side reactions when compared to ORA and to placebo or no treatment. While cost-effectiveness data were not available, reductions in NICU admission provides further support for the use of CCB over betamimetics or ORA, and reduced NICU stay (on average four days less) for CCB over magnesium sulphate and ORA.

No differences were evident in one small study (102 women), which compared higher- versus lower-dose nifedipine, though findings tended to favour a high dose on some measures of neonatal morbidity (Nassar 2009). One of the largest trials in this analysis (Papatsonis 1997), which had the most favourable outcomes, compared betamimetics with a higher-dosage regimen for nifedipine than that used in most of the other trials (up to 40 mg in the first hour). However, based on the results of this review, it is not possible to draw any conclusions about optimal nifedipine dosage.

Overall completeness and applicability of evidence

The benefit in terms of postponement of birth and less short-term neonatal morbidity supports the use of CCB over other tocolytics. However, it must be noted that with the lack of blinding of the intervention and outcome assessment in all trials included in this analysis, the possibility of important bias cannot be ruled out. This is of particularly importance for the less objective outcomes such as measures of neonatal morbidity. Further, these positive effects did not confer benefit in terms of reducing perinatal deaths and the effects on longer-term outcomes of death and neurosensory impairment are unclear. While robust measures of neurodevelopmental outcome were not available, data collected by survey of women enrolled in one trial (Papatsonis 1997) and their children at nine to 12 years of age showed no difference between nifedipine and ritodrine in terms of quality of life and measures of behaviour/emotion, educational and motor quality reported by parents. No data were available on longer-term outcomes for children of women randomised to tocolytics versus placebo.

Of the 38 included trials, all but three used nifedipine as the CCB. The remaining three trials (261 women) used nicardipine as the CCB, and no differences in outcomes were shown in trials comparing nicardipine with other tocolytics, although with limited data no strong conclusions can be drawn. Most of the experience with clinical use of nicardipine is by the intravenous (IV) route. Several cases of pulmonary oedema have been reported in the last 10 years (Akerman 2007; Perbet 2008; Philippe 2009). Although risk factors were present in most of these reports

(multiple pregnancy, concomitant use of corticosteroids and/or of betamimetics, cardiovascular history), all of these cases occurred under IV treatment and one of the main factors associated with pulmonary oedema was the high volume of IV fluids perfused. Clinical use of IV nicardipine should cautiously take into account all possible risk factors for pulmonary oedema and the lack of evidence in favour of IV treatment.

Comparing CCB with magnesium sulphate, some benefit was shown in terms of reducing neonatal duration of stay in the NICU. No differences were shown in the comparisons with glyceryl trinitrate (GTN), non-steriodal anti inflammatories (NSAID) although numbers were small.

Oxytocin receptor antagonists (ORA) have recently been proposed as a safe and effective tocolytic agent. This review includes two small trials (total of 225 women) comparing CCB (nifedipine) with the ORA atosiban (Kashanian 2011; Salim 2012). Due to small numbers, no conclusions could be drawn on the superiority of one agent over the other. The results of two ongoing trials of atosiban and nifedipine (APOSTEL III 2011; Gonzalez 2011) are awaited. The role of ORA for tocolysis is the focus of another Cochrane review (review update in progress: Papatsonis 2005).

There is a substantial amount of evidence from potentially eligible controlled trials (nine studies) that we were unable to include in this review due to insufficient information. Six of these trials compared CCB with betamimetic agents (Chong 1991; Dubay 1992; Mathew 1997; Roy 1993; Sharma 2000; Sofat 1994), two compared CCB with magnesium sulphate (Haghighi 1999; Lotfalizadeh 2010) and in one trial, CCB was compared with atosiban (de Heus 2009). The review authors regard this as an important deficiency. However, in reviewing the information currently available from these trials, it does not appear that as a group, their results differ substantially or systematically from the trials included in this review.

Research into treatments to prevent preterm birth are challenged by the underlying mechanisms that lead to preterm labour. Preterm birth is the common final outcome of a number of interrelated pathophysiological pathways. These include intrauterine infection and inflammation, uterine overdistension (in multiple pregnancy or polyhydramnios), fetal stress responses and utero-placental insufficiency. Tocolytic therapies largely act on the final common means which lead to labour and birth. To have a greater impact on clinical infant/child outcomes, treatments may need to address the higher order causes of preterm birth and act before the cascade of changes is set in motion. This remains a focus of ongoing scientific and clinical research.

Quality of the evidence

As blinding of intervention and outcome assessment was undertaken in only one of the included trials (a placebo controlled trial), the overall quality of the included trials is considered fair only. However, we defined objectively measured outcomes as those according to timing of birth and perinatal mortality and considered these measures to be at low risk of detection bias. One trial (Klauser 2012) used blinded assessment of all outcome measures and was considered to have low risk of detection bias for both objective and subjective outcome measures. All other trials were considered to be at high risk of detection bias for subjective outcome measures (i.e. maternal and neonatal morbidity measures).

Sample attrition was not considered a serious source of bias as the majority had minimal or no attrition. To enable analysis by intention-to-treat, additional information was sought from the investigators of 13 included studies and data were provided and included for 11 of these studies.

Selective reporting was considered possible in one trial (Ganla 1999) where the outcomes of pregnancy prolongation for 48 hours and until 36 weeks were omitted from the results. In 23 trials, we found no obvious evidence of reporting bias and judged these trials to be at low risk of bias. In the remaining trials it was unclear whether selective reporting bias was present.

Sixteen studies were assessed as being at low risk of bias for other potential sources of bias based on baseline characteristics being similar between groups and no other bias apparent. In the remaining 22 studies, the risk of other sources of bias was unclear**.** One study Ganla 1999 also concluded that perinatal mortality was reduced by nifedipine, although this outcome was not reported in the results. This research article is housed on a website sponsored by a global pharmaceutical company.

Potential biases in the review process

We are aware that the review process itself is subject to bias, and we took steps to minimise bias. At least two review authors carried out data extraction and assessed risk of bias independently; however, a different review team may not have made identical decisions.

Agreements and disagreements with other studies or reviews

A series of Cochrane reviews assessed the effects of different classes of tocolytics compared with placebo, and with each other (Bain 2013; Crowther 2002; Duckitt 2002; King 2005; Papatsonis 2005; Su 2010; Neilson 2014). A review on combinations of different tocolytics for women in preterm labour is currently in development (Nadin 2006).

A recent review of tocolytic trials, which included both network and pair-wise meta-analysis, examined a range of tocolytics (betamimetics, magnesium sulphate, CCB, COX inhibitors, ORA, nitric oxide donors and other drugs) (Haas 2012). The results of this review suggest that all types of tocolytics were better than placebo in terms of prolonging pregnancy beyond 48 hours, but that betamimetics performed less well than other types of tocolytics. CCB and COX inhibitors were reported to have the highest probability of delaying delivery and improving neonatal and maternal outcomes.

The evidence regarding side effects from this review (Haas 2012) suggested that COX inhibitors and ORA were associated with fewer maternal side effects compared with other types of tocolytics. Our review showed a higher adverse effects profile for betamimetics and that tocolysis with CCB was associated with clinically important fewer events. A higher adverse event profile for betamimetics was shown in the Cochrane review of betamimetics compared with placebo (Neilson 2014).

Another review, using indirect comparison of randomised trials, of the CCB (nifedipine) with ORA atosiban concluded that nifedipine was more effective than atosiban and lowered the incidence of respiratory distress syndrome (Coomarasamy 2003). While, we did not show clear evidence for benefit for CCB over ORA, one small trial

(145) women (which did not employ blinding of the intervention) showed some benefit in terms of preterm birth and admission to neonatal intensive care unit. Our findings are consistent with the Cochrane review on ORA for inhibiting preterm labour, which also found no clear benefit for ORA over CCB (review update in progress Papatsonis 2005) although ORA has advantages over CCB and other tocolytics of less maternal adverse effects.

The CCB, nifedipine has the advantage of ease of oral administration and is very inexpensive compared with atosiban (Papatsonis 2004). However, more robust evidence from well-designed, randomised trials with direct comparisons of nifedipine and ORA are required before strong recommendations for clinical practice can be made. Consistent with our conclusions, Hass et al (Haas 2012) also supported further well designed, randomised, placebo controlled trials to evaluate CCB versus ORA in prolonging pregnancy for women in preterm labour. Two such studies are ongoing (APOSTEL III 2011; Gonzalez 2011). Adequate comparison of CCBs with COX inhibitors (such as indomethacin) for preterm labour is also lacking.

AUTHORS' CONCLUSIONS

Implications for practice

CCBs (mainly nifedipine) for women in preterm labour have benefits over placebo or no treatment in terms of postponement of birth thus, theoretically, allowing time for administration of antenatal corticosteroids and transfer to higher level care. CCBs were shown to have benefits over betamimetics with respect to prolongation of pregnancy, serious neonatal morbidity, and maternal adverse effects. CCBs may also have some benefits over ORA and magnesium sulphate, although ORA results in fewer maternal adverse effects. The quality of included studies limits the ability for firm conclusions to be drawn.

Implications for research

Further well-designed tocolytic trials are required to determine short- and longer-term infant benefit of CCB over placebo or no treatment and other tocolytics, particularly ORA. Another important focus for future trials is identifying optimal dosage regimens of nifedipine (high versus low, particularly addressing speed of onset of uterine quiescence) and formulation (capsules versus tablets). All future trials on tocolytics for women in preterm labour should employ blinding of the intervention and outcome assessment and include measurement of longer-term effects into early childhood, and also costs.

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As part of the pre-publication editorial process, this review has been commented on by three peers (an editor and two referees who are external to the editorial team), a member of the Pregnancy and Childbirth Group's international panel of consumers and the Group's Statistical Adviser.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Al-Qattan 2000

Methods	Randomised controlled trial, standard parallel group design.
Participants	60 women in preterm labour at 24-34 weeks. Setting: Kuwait University and Maternity Hospital, Kuwait. Exclusion criteria: cardiac disease; abruptio placentae; hyperthyroidism; severe pre-eclampsia/eclampsia; clinical signs of infection: WCC > 15,000/ccm; and positive HVS culture; Polyhydramnios; cervix > 4 cm; any fetal pathology; breech presentation; IUFD; fetal distress; congenital malformations; ROM; multiple pregnancy.
Interventions	CCB group: nifedipine. 30 mg po initially then if uterine contractions persisted after 2 hrs a second dose of 20 mg. Following uterine quiescence 20 mg po every 6 hrs. Control group: ritodrine, 50 µg/min. Following uterine quiescence 10 mg po every 4-6 hrs. Both groups: maintenance therapy until 34 weeks and no rescue therapy.
Outcomes	Maternal: delivery < 24 hrs; delivery < 48 hrs; delivery < 7 days; delivery < 36 weeks; maternal adverse drug reaction; maternal adverse drug reaction requiring cessation of treatment. Neonatal: birthweight; low birthweight; admission to NICU; RDS; IVH; NEC; BPD; perinatal mortality; GA at birth.
Notes	Additional data not requested. Sample size calculation: not reported.

Al-Qattan 2000 *(Continued)*

	Antenatal corticosteroids: yes, Dexamethasone 2 doses of 12 mg every 12 hrs. GBS protocol: not reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random numbers table.
Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding of participants and personnel (performance bias)	High risk	Intervention was not blinded.
Blinding of outcome assessment (detection bias) Objective outcome measures	Low risk	Blinding of intervention or outcomes not apparent. However, the outcomes were judged to be at low risk of performance and ascertainment bias.
Blinding of outcome assessment (detection bias) Subjective outcome measures	High risk	Blinding of intervention or outcomes not apparent and outcomes were not clearly defined.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	7 post randomisation exclusions in the ritodrine group; 2 withdrew and 5 due to side effects.
Selective reporting (reporting bias)	Low risk	Data presented as expected.
Other bias	Unclear risk	Unable to determine.

Amorim 2009

Methods	Randomised controlled trial, standard parallel group design.
Participants	54 women in preterm labour between 24 and 34 weeks with cervical dilatation < 4 cm and intact membranes. Exclusion criteria: pre-eclampsia, diabetes, fetal anomaly, placental abruption, prior use of tocolytic drugs.
Interventions	CCB group: 10 mg nifedipine sublingually, repeated after 30 mins, if contractions persisted 20 mg 6 hourly. Control group: 10 mg GTN patch, second 10 mg GTN patch applied after 6 hrs if contractions persisted.
Outcomes	Time to effective tocolysis, delivery within 48 hrs, maternal adverse drug effects.
Notes	

Risk of bias

Amorim 2009 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer random number generation.
Allocation concealment (selection bias)	Unclear risk	Opaque sealed envelopes. Not reported if sequentially numbered.
Blinding of participants and personnel (performance bias)	High risk	Intervention not blinded.
Blinding of outcome assessment (detection bias) Objective outcome measures	Low risk	Outcome assessment not blinded; however, objective outcomes judged to be low risk.
Blinding of outcome assessment (detection bias) Subjective outcome measures	High risk	Outcome assessment not blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	4 post-randomisation exclusions; 3 in the GTN patch group (1 developed pre-eclampsia and 1 suspected abruption, and another due to an error on GA) and 2 in the nifedipine group (due to developing pre-eclampsia).
Selective reporting (reporting bias)	Low risk	Data presented as expected.
Other bias	Unclear risk	Not able to be determined.

Ara 2008

Methods	Randomised controlled trial, standard parallel group design.
Participants	89 women with preterm labour (minimum 4 contractions in 30 mins and cervical dilatation < 3 cm) between 30-34 weeks' gestation with singleton pregnancy and intact membrane. Setting: Institute of Child & Mother Health Matuail Dhaka and a private hospital. Exclusion criteria: cervical dilatation > 3 cm, evidence of maternal infection, vaginal bleeding, severe pre-eclampsia, fetal growth restriction and oligohydramnios.
Interventions	CCB group: nifedipine. Loading dose of 30 mg (20 mg oral and 10 mg sublingually), followed by 20 mg (mode of administration not given, assumed oral) every 4-6 hrs "depending on the uterine activity". Treatment was deemed to have failed after 12 hrs from treatment commencement with no subsidence of contractions. Control group: placebo. No details provided.
Outcomes	Subsidence of contractions (maternal self-report), pregnancy prolongation for 48 hrs/7 days/until 36 weeks, maternal adverse side effects.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement

Ara 2008 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	"Lottery method" used (no further details provided).
Allocation concealment (selection bias)	Unclear risk	No information provided.
Blinding of participants and personnel (performance bias)	Low risk	Placebo controlled.
Blinding of outcome assessment (detection bias) Objective outcome measures	Low risk	Not clear, but probably low risk as the trial was placebo controlled.
Blinding of outcome assessment (detection bias) Subjective outcome measures	Low risk	Not clear, but probably low risk as the trial was placebo controlled.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No post-randomisation exclusions or losses at follow-up reported.
Selective reporting (reporting bias)	Low risk	Data presented as expected.
Other bias	Unclear risk	Not able to determine.

Bracero 1991

Methods	Randomised controlled trial, standard parallel group design.
Participants	49 women in preterm labour at 20-36 weeks. Setting: Westchester county medical centre, New York Exclusion criteria: ROM; multiple pregnancy.
Interventions	CCB group: nifedipine. 30 mg po initially then 20 mg every 6 hrs for 24 hrs then 20 mg every 8 hrs for 24 hrs followed by maintenance 20 mg every 8-12 hrs prn. Control group: ritodrine, 100 µg/min increasing by 50 µg/min every 10 min prn to a maximum of 350 µg/min. Oral maintenance 10-20 mg every 4-6 hrs.
Outcomes	Maternal: delivery < 48 hrs; pregnancy prolongation; maternal adverse drug reaction; maternal adverse drug reaction requiring cessation of treatment. Fetal: fetal death. Neonatal: admission to NICU; RDS; neonatal jaundice; neonatal sepsis; NEC; neonatal death; GA at birth.
Notes	No additional data received. Sample size calculation: not reported. Antenatal corticosteroids: not reported. GBS protocol: not reported.
Risk of bias	

Bracero 1991 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Not specified entirely "envelopes chosen by individual patients".
Allocation concealment (selection bias)	Low risk	Sealed envelopes.
Blinding of participants and personnel (performance bias)	High risk	Intervention not blinded.
Blinding of outcome assessment (detection bias) Objective outcome measures	Low risk	Outcome assessment not blinded; however, objective outcomes judged to be low risk.
Blinding of outcome assessment (detection bias) Subjective outcome measures	High risk	Outcome assessment not blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	7 post-randomisation exclusions: 4 in the ritodrine group (2 were lost to follow-up, and 2 withdrawn due to severe side effects); and 3 in the nifedipine group (2 woman due to continuing contractions, and 1 due to suspected abruption).
Selective reporting (reporting bias)	Low risk	Addtional outcome data received.
Other bias	Unclear risk	Not able to determine.

Cararach 2006

Methods	Randomised controlled trial, standard parallel group design.
Participants	80 women in preterm labour at 22-35 weeks in Barcelona, Spain. Exclusion criteria: cervical dilatation > 5 cm; polyhydramnios; fetal anomalies; fetal distress; suspected IUGR; contraindication to the use of betamimetics; previous treatment with tocolytic in this pregnancy; ROM; multiple pregnancy.
Interventions	CCB group: nifedipine. 30 mg (10 mg s/l and 20 mg po) followed by 20 mg every 6 hrs for 48 hrs. Control group: ritodrine, IV 100 µg/min increasing by 50 µg every 20 min up to a maximum of 350 µg/min for up to 48 hrs. Then oral maintenance 10 mg q6h until hospital discharge. Rescue therapy: women were considered treatment failure if contractions persisted beyond 48 hrs and were then given indomethacin. Subsequent episodes of preterm labour were treated according to the group allocation.
Outcomes	Maternal: delivery < 2 hrs, delivery < 48 hrs, delivery < 7 days; delivery < 37 weeks; treatment to delivery interval; maternal adverse drug reaction; maternal adverse drug reaction requiring cessation of treatment. Fetal: deaths.

Cararach 2006 *(Continued)*

	Neonatal: RDS; neonatal deaths; GA at birth; birthweight; Apgar score < 7 at 5 min; hyperbilirubinaemia; neonatal infection.
Notes	Additional data received. Sample size calculation: not reported. Antenatal corticosteroids: yes, all women enrolled. GBS protocol: no.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Not stated apart from 1:1 randomisation.
Allocation concealment (selection bias)	Low risk	Opaque sealed envelopes.
Blinding of participants and personnel (performance bias)	High risk	Intervention not blinded.
Blinding of outcome assessment (detection bias) Objective outcome measures	Low risk	Outcome assessment not blinded; however, objective outcomes judged to be low risk.
Blinding of outcome assessment (detection bias) Subjective outcome measures	High risk	Outcome assessment not blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	4 post-randomisation exclusions: 1 in the ritodrine group was lost to follow-up; and 3 in the nifedipine group were excluded (1 lost to follow-up and 2 withdrawn due to protocol violations).
Selective reporting (reporting bias)	Low risk	Additional data received, no evidence of selective reporting.
Other bias	Low risk	No evidence of other bias.

Fan 2003

Methods	Randomised controlled trial, standard parallel group design.
Participants	61 women in preterm labour 28 to 38 weeks' gestation. Inclusion criteria: contractions occurring once/10 mins, lasting 30 seconds for a period of at least 1 hr accompanied by a cervical dilation of 2 cm or by a rupture of the fetal membrane.
Interventions	CCB: nifedipine (n = 31) Initial oral dose 20 mg, another 20 mg if further uterine contraction after 30 mins, maximum dosage within the first hr is 40 mg. If contraction weakened, dosage changed to 20 mg every 8 hrs until gestation week 35. Control: ritodrine (n = 30) 50 mg dissolved in grape sugar for IV injection, initial dosage 50 ug/min, increase 50 ug/min every 15 min according to uterine contraction until uterine contraction suppressed, maximum dosage 350 ug/min, stop vein injection after 12 hrs of effective dosage, change to oral dosage

Fan 2003 *(Continued)*

	30 mins before the stop of vein injection. Initial oral dosage is 10 mg/2 hrs and then 10 mg/6 hrs until gestation week 35.
Outcomes	Delay in births for 48 hrs, 7 days and to 35 weeks; outcome for newborn and side effects of medication.
Notes	Translated from Chinese.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Stated "randomly divided".
Allocation concealment (selection bias)	Unclear risk	Not reported.
Blinding of participants and personnel (performance bias)	High risk	Not stated but unlikely to be blinded.
Blinding of outcome assessment (detection bias) Objective outcome measures	Low risk	Outcome assessment not blinded; however, objective outcomes judged to be low risk.
Blinding of outcome assessment (detection bias) Subjective outcome measures	High risk	Outcome assessment not blinded.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not able to be determined.
Selective reporting (reporting bias)	Unclear risk	Not able to be determined.
Other bias	Unclear risk	Not able to be determined.

Ferguson 1990

Methods	Randomised controlled trial, standard parallel group design.
Participants	66 women in preterm labour at 20-36 weeks' gestation. Exclusion criteria: multiple pregnancy.
Interventions	CCB group: nifedipine. 10 mg capsule s/l repeated in 20 min oral maintenance 20 mg every 4-6 hrs. Control group: ritodrine, 50 µg/min increasing by 50 µg 15-30 min up to a maximum of 350 µg/min. Oral maintenance 10-20 every 4-6 hrs.
Outcomes	Maternal: delivery < 37 weeks; delivery < 48 hrs; maternal adverse drug reaction; maternal adverse drug reaction requiring cessation of treatment. Fetal: fetal deaths.

Ferguson 1990 *(Continued)*

	Neonatal: RDS; IVH all grades; neonatal deaths.
Notes	Additional data received. Sample size calculation: not reported. Antenatal corticosteroids: yes. GBS protocol: vaginal cultures and intrapartum AB for GBS positive.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random number table.
Allocation concealment (selection bias)	Low risk	Sequentially numbered sealed envelopes.
Blinding of participants and personnel (performance bias)	High risk	Intervention not blinded.
Blinding of outcome assessment (detection bias) Objective outcome measures	Low risk	Outcome assessment not blinded; however, objective outcomes were judged to be low risk.
Blinding of outcome assessment (detection bias) Subjective outcome measures	High risk	Outcome assessment not blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	3 post-randomisation exclusions reported.
Selective reporting (reporting bias)	Low risk	Additional data received, no evidence of selective reporting.
Other bias	Low risk	No evidence of other bias.

Floyd 1992

Methods	Randomised controlled trial, standard parallel group design.
Participants	52 women in preterm labour at 20-34 weeks defined as regular contractions at least every 10 mins accompanied by cervical change. Exclusion criteria: women with ruptured membranes, chorioamnionitis, previous exposure to tocolytics in the current pregnancy, allergy to study medication, or any serious medical or obstetric condition which precluded treatment with the study medication.
Interventions	CCB group: nifedipine. 30 mg orally (3 x 10 mg capsules) then 20 mg orally 8 hourly until 37 weeks or birth. Control group: IV 4 g MgSO4 over 20 mins then 4-6 hourly until uterine quiescence then oral Mg gluconate 2 g every 4 hrs until 37 weeks or birth.

Floyd 1992 *(Continued)*

Outcomes	Maternal: delivery < 37 weeks and < 34 weeks; pregnancy prolongation; maternal adverse drug reaction requiring cessation of treatment. Neonatal: birthweight; RDS, Apgar score < 7 at 5 mins, perinatal mortality, stillbirth and neonatal death.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Random number table generated by computer".
Allocation concealment (selection bias)	Low risk	"Consecutively numbered, sealed, opaque envelopes".
Blinding of participants and personnel (performance bias)	High risk	Intervention and outcome assessment not blinded.
Blinding of outcome assessment (detection bias) Objective outcome measures	Low risk	Outcome assessment not blinded; however, objective outcomes judged to be low risk.
Blinding of outcome assessment (detection bias) Subjective outcome measures	High risk	Intervention and outcome assessment not blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No post-randomisation exclusions or losses at follow-up reported.
Selective reporting (reporting bias)	Low risk	No indication of selective reporting.
Other bias	Low risk	No evidence of other bias.

Ganla 1999

Methods	Randomised controlled trial, standard parallel group design.
Participants	100 women with preterm labour (painful regular contractions < 10 mins apart for at least 30 mins) between 26-36 weeks' gestation and no previous tocolytics administered for 7 days. Setting: Wadia Maternity Hospital, Parel, Mumbai. Exclusion criteria: maternal diabetes, hyperthyroidism, cardiac disease, severe PIH, eclampsia, placental abruption, chorioamnionitis, cervical dilation > 3 cm, severe IUGR, foetal anomaly incompatible with life, fetal distress.
Interventions	CCB group: nifedipine. IV ringer lactate @ 100 mL/hr, till 5 mg sublingually nifedipine to maximum of 40 mg over 2 hrs. If contractions continued, Rx ceased (considered failure), ongoing 10 mg oral nifedipine 3 hrs after last dose and ongoing 10 mg 8 hourly for 48 hrs, then nifedipine SR 10 or 20 mg 12 hourly till 36 weeks.

Ganla 1999 *(Continued)*

	Control: Isoxsuprine in 5% dextrose - started at 0.5 mg/min and increased to 10 mg/min and continued after contractions ceased for 12 hrs then 10 mg isoxsuprine IM 8 hourly for 48 hrs followed by 10-20 mg oral 8 hourly till 36 weeks. Both groups received erythromycin, head low position and steroids x 2 then weekly till 36 weeks.
Outcomes	GA at delivery, pregnancy prolongation for 48 hrs/until 36 weeks, maternal and fetal side effects including hyaline membrane disease +/- requiring cessation, "failure of treatment", GA at treatment, Apgar scores, birthweight, neonatal death.
Notes	Study is housed on a website sponsored by Dr Reddy's Laboratories, a global pharmaceutical company based in Hyderabad, India.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"randomly allotted to two groups" (no other details provided).
Allocation concealment (selection bias)	Unclear risk	No information provided.
Blinding of participants and personnel (performance bias)	High risk	Unblinded. Differing treatment regimens (dose and mode of administration).
Blinding of outcome assessment (detection bias) Objective outcome measures	Low risk	Intervention and outcome assessment not blinded; however, objective outcomes judged to be low risk.
Blinding of outcome assessment (detection bias) Subjective outcome measures	High risk	Intervention and outcome assessment not blinded.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not able to be confidently determined.
Selective reporting (reporting bias)	High risk	Pregnancy prolongation for 48 hrs/until 36 weeks, hyaline membrane disease not reported as expected. Treatment "success" and "failure" reported only. Failure to achieve uterine relaxation or development of significant side in mother or fetus was considered treatment "failure" and treatment "success" was only reported as the inverse of this. Paper concludes that perinatal mortality is reduced by nifedipine when this outcome is not reported in the results.
Other bias	Unclear risk	Authors report that patients in the groups were "well matched" on various characteristics at baseline but no information on statistical significance provided.

Garcia-Velasco 1998

Methods	Randomised controlled trial, standard parallel group design.
Participants	52 women in preterm labour at 26-34 weeks.

Garcia-Velasco 1998 *(Continued)*

	Exclusion criteria: women with ruptured membranes, multiple pregnancy.
Interventions	CCB group: nifedipine. 10 mg s/l and 20 mg po then 10-20 every 4-6 hrs prn. If after 12 hrs of tocolysis uterine activity was present or treatment was not well tolerated this was considered tocolysis failure. Control group: IV ritodrine, 50 µg/min increasing by 50 ug every 20 min to max of 350 µg/min maintained for 12 hrs. Oral maintenance 5 mg every 3 hrs. Both groups: indomethacin given for continued uterine activity after 12 hrs or if treatment was not well tolerated.
Outcomes	Maternal: delivery < 48 hrs; delivery < 37 weeks; pregnancy prolongation; maternal adverse drug reaction requiring cessation of treatment; maternal length of hospital stay. Neonatal: birthweight; admission to NICU; RDS.
Notes	Additional data received. Sample size calculation: yes - based on change in maternal BP and pulse. Antenatal corticosteroids: yes. GBS protocol: not reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computerised random number table.
Allocation concealment (selection bias)	Unclear risk	Sealed envelopes.
Blinding of participants and personnel (performance bias)	High risk	Intervention not blinded.
Blinding of outcome assessment (detection bias) Objective outcome measures	Low risk	Outcome assessment not blinded; however, objective outcomes judged to be low risk.
Blinding of outcome assessment (detection bias) Subjective outcome measures	High risk	Outcome assessment not blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	No post-randomisation exclusions or losses at follow-up reported.
Selective reporting (reporting bias)	Low risk	Additional data received, no evidence of selective reporting.
Other bias	Low risk	No evidence of other bias.

George 1991

Methods	Randomised controlled trial, standard parallel group design.

George 1991 *(Continued)*

Participants	25 women in with a singleton pregnancy 28 to 36 weeks' gestation in preterm labour; 14 in nifedipine group and 11 in isoxsuprine group. Inclusions: contractions occurring at least once every 10 mins and lasting for 30 seconds or more on external tocography and cervical dilation less than 2 cm. Exclusions were: ruptured membranes, intrauterine infections, malformed fetus, hydramnios, and medical complications.
Interventions	CCB: nifedipine (initially 30 mg, followed by 20 mg every 8 hrs for 48 hrs orally). Control: isoxuprine (40 mg in 500 mL of D5W was started at a drip rate of 30 drops/min and accelerated with close monitoring for 4 hrs. Then administered intramuscularly at 30 mg/24 hrs for 2 days.
Outcomes	Prolongation of pregnancy for 48 hrs from beginning of therapy, maternal blood pressure and pulse rate, and fetal heart rate.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Table of random numbers.
Allocation concealment (selection bias)	Unclear risk	Not reported.
Blinding of participants and personnel (performance bias)	Unclear risk	Intervention not blinded.
Blinding of outcome assessment (detection bias) Objective outcome measures	Low risk	Outcome assessment not blinded; however, objective outcomes judged to be low risk.
Blinding of outcome assessment (detection bias) Subjective outcome measures	High risk	Outcome assessment not blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No post-randomisation exclusions or losses at follow-up reported.
Selective reporting (reporting bias)	Unclear risk	Unclear. Minimal data reported.
Other bias	Unclear risk	Not able to be determined.

Glock 1993

Methods	Randomised controlled trial, standard parallel group design.

Glock 1993 *(Continued)*

Participants	100 women in preterm labour less than 34 weeks' gestation. Exclusion criteria: multiple pregnancy; ROM; tocolysis this pregnancy; maternal medical complications; congenital malformations; IUGR.
Interventions	CCB: nifedipine 10 mg s/l repeated prn every 20 min to max of 40 mg in first hr. Once contractions ceased 20 mg every 4 hrs for 48 hrs, then maintenance 10 mg every 8 hrs until 34 weeks. Control group: MgSO4 load 6 g IV over 30 min then 2 g/h IV up to 4 g/h as required for 24 hrs, then weaned at 0.5 g every 4-6 hrs, then maintenance therapy of oral terbutaline 5 mg every 6 hrs until 34 weeks.
Outcomes	Maternal: delivery < 48 hrs; delivery < 37 weeks; delivery < 34 weeks; pregnancy prolongation index; maternal adverse drug reaction requiring cessation of treatment. Neonatal: birthweight; perinatal mortality.
Notes	Sample size calculation: no. Antenatal corticosteroids: yes. GBS protocol: vaginal culture and intrapartum AB for GBS positive.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Does not state exactly how randomised.
Allocation concealment (selection bias)	Low risk	Sealed envelopes.
Blinding of participants and personnel (performance bias)	High risk	Intervention not blinded.
Blinding of outcome assessment (detection bias) Objective outcome measures	Low risk	Outcome assessment not blinded; however, objective outcomes judged to be low risk.
Blinding of outcome assessment (detection bias) Subjective outcome measures	High risk	Outcome assessment not blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	20 post enrolment/pre-randomisation exclusions reported. No post-randomisation exclusions or losses at follow-up reported.
Selective reporting (reporting bias)	Low risk	No indication of selective reporting.
Other bias	Low risk	No evidence.

Jaju 2011

Methods	Randomised controlled trial, standard parallel group design.

Jaju 2011 *(Continued)*

Participants	120 women in preterm labour (4 contractions in 20 min with cervical dilatation of 1 cm and effacement of > 80%) with singleton pregnancy and vertex presentation 28-36 weeks. Intact membrane and cervical dilatation no greater than 3 cm. Setting: Shri. B. M. Patil Medical College Hospital and Research Centre, Bijapur, India. Exclusions: APH, PIH, congenital anomaly, IUG retardation, bronchial asthma, diabetes mellitus, cardiovascular diseases, severe anaemia, hydramnios, chorioamnionitis.
Interventions	CCB group: nifedipine. Loading dose of 30 mg orally with 20 mg given orally if contractions did not subside after 90 min. Maintenance dose of 20 mg orally every 8 hrs till 37 weeks or till delivery. Treatment was deemed to have "failed" if contractions had not subsided 60 min after the second dose. Control group: 100 mg IV ritodrine (2 x 50 mg ampoules in 500 mL ringer lactate). 50 µg/min IV ritodrine increased by 50 µg every 15 min till contractions stopped with maximum of 350 µg/min. IV ritodrine for 24 hrs after contractions stopped. 10 mg oral ritodrine (tablet) given 30 min before stopping IV drip and continued every 6 hrs until 37 weeks or delivery.
Outcomes	Pregnancy prolongation to 48 hrs/7 days until 37 weeks, maternal drug side effects, treatment failure, GA at birth, Apgar scores, neonatal outcomes.
Notes	Mean age of women in the control group reported to be "2".

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Allocations conducted "by simple randomisation technique". No further details given.
Allocation concealment (selection bias)	Unclear risk	No information provided.
Blinding of participants and personnel (performance bias)	High risk	Intervention not blinded.
Blinding of outcome assessment (detection bias) Objective outcome measures	Low risk	Intervention and outcome assessment not blinded; however, objective outcomes judged to be low risk.
Blinding of outcome assessment (detection bias) Subjective outcome measures	High risk	Intervention and outcome assessment not blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No post-randomisation exclusions or losses at follow-up reported.
Selective reporting (reporting bias)	Low risk	All outcomes reported as expected.
Other bias	Unclear risk	Groups reported to be similar in terms of age, gestation at entry, and parity but no data given bar > .05 P value. Mean maternal age for ritodrine group reported to be "2". Not able to adequately determine due to erroneous data.

Janky 1990

Methods	Randomised controlled trial, standard parallel group design.
Participants	62 women in preterm labour at 28-36 weeks' gestation. Exclusion criteria: chorioamnionitis and maternal medical conditions, cervix > 4 cm, ROM after 34 weeks.
Interventions	CCB group: nifedipine. 10 mg s/l then 20 mg every 8 hrs. Ceased after 7 days. Control group: IV ritodrine, 200 to 300 µg/min until contractions ceased then 100 µg/min for 24 hrs then oral maintenance 20 mg 4-6 hrs for 6 days.
Outcomes	Maternal: pregnancy prolongation; maternal adverse drug reaction requiring cessation of treatment. Fetal: fetal death. Neonatal: birthweight; neonatal death.
Notes	Additional data received. Sample size calculation: not reported. Antenatal corticosteroids: not reported. GBS protocol: not reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Does not state exactly how.
Allocation concealment (selection bias)	Unclear risk	Sealed envelopes.
Blinding of participants and personnel (performance bias)	High risk	Intervention not blinded.
Blinding of outcome assessment (detection bias) Objective outcome measures	Low risk	Outcome assessment not blinded; however, objective outcomes judged to be low risk.
Blinding of outcome assessment (detection bias) Subjective outcome measures	High risk	Outcome assessment not blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No post-randomisation exclusions or losses at follow-up reported.
Selective reporting (reporting bias)	Low risk	Additional data received, no evidence of selective reporting.
Other bias	Low risk	No evidence of other bias.

Jannet 1997

Methods	Randomised controlled trial, standard parallel group design.
Participants	90 women in preterm labour 25 to 35.5 weeks. Exclusion criteria: multiple pregnancy; ROM; maternal medical conditions; standard contraindications to tocolytic.
Interventions	CCB group: IV nicardipine 3 mg/h for 2 hrs increasing prn up to a maximum of 6 mg/h until contractions cease then oral 20 mg every 8 hrs until 37 weeks. Control group: IV salbutamol 150 µg/h, increasing after 2 hrs to 300 µg/h maintained for 48 hrs then oral maintenance 8 mg every 6 hrs po and 2 rectal suppositories of salbutamol 2 mg daily until 37 weeks.
Outcomes	Maternal: delivery < 37 hrs; delivery < 34 weeks; maternal adverse drug reaction; GA at birth. Neonatal: birthweight; admission to NICU.
Notes	4 post randomisation exclusions (2 in each group). Sample size calculation: no. Antenatal steroids: not reported. GBS protocol: not reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Does not state exactly how, states randomised.
Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding of participants and personnel (performance bias)	High risk	Intervention not blinded.
Blinding of outcome assessment (detection bias) Objective outcome measures	Low risk	Outcome assessment not blinded; however, objective outcomes judged to be low risk.
Blinding of outcome assessment (detection bias) Subjective outcome measures	High risk	Outcome assessment not blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No post-randomisation exclusions or losses at follow-up reported.
Selective reporting (reporting bias)	Unclear risk	Unclear, although data appears to be reported as expected.
Other bias	Unclear risk	Not able to determine.

Kara 2009

Methods	Randomised controlled trial, standard parallel group design.
Participants	77 women with a singleton pregnancies in threatened preterm labour (painful and palpable contractions < 10 mins apart of 30 seconds duration) with or without cervical dilatation and effacement, between 20-36 weeks' gestation. Setting: Agri Women's and Children's Hospital, Agri, Turkey. Exclusion criteria: pre-eclampsia, eclampsia, placental abruption, placenta previa, cervical dilatation > 4 cm, ruptured membranes, chorioamnionitis, fetal death, fetal distress, major fetal anomalies, IUGR, diabetes, hyperthyroidism, cardiovascular diseases, uterine leiomyoma, multiple gestation, and polyhydramnios.
Interventions	CCB group: nifedipine. Initial dose of 10 mg oral (sublingual) capsule. Additional 10 mg dose sublingual given with no subsidence of contractions after 20 mins and repeated every 20 mins until contractions subsided with a maximum dose of 40 mg within the first hr. 20 mg oral nifedipine administered every 4 hrs after uterine activity subsided and continued up to 48 hrs. Maintenance therapy of 10 mg every 8 hrs until the end of 36th week. Control group: MgSO4. Initial dose of 6 mg MgSO4 in 150 mL of 5% dextrose bolus IV administered over 20 mins. Maintenance therapy of 24 mg MgSO4 in 1000 mL of 5% dextrose at 2 g/hr increased to a maximum of 4 g/hr until contractions subsided or side effects occurred. Maintained for 24 hrs after contractions subsided, then 5 mg oral terbutaline tablets every 4-6 hrs until the end of the 36th week.
Outcomes	Pregnancy prolongation for 48 hrs/7 days/until 36 weeks, GA at birth, days of pregnancy prolongation, maternal and fetal side effects, birthweight, Apgar scores, stillbirth, and neonatal death.
Notes	Further information on method of randomisation is awaited from the authors. No antenatal corticosteroids administered in either group.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Stated "randomly" included in the study groups.
Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding of participants and personnel (performance bias)	Unclear risk	Blinding not performed.
Blinding of outcome assessment (detection bias) Objective outcome measures	Low risk	Outcome assessment not blinded; however, objective outcomes judged to be low risk.
Blinding of outcome assessment (detection bias) Subjective outcome measures	High risk	Outcome assessment not blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No post-randomisation exclusions or losses at follow-up reported.

Kara 2009 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	Minimal neonatal data reported.
Other bias	Low risk	None identified.

Kashanian 2005

Methods	Randomised controlled trial, standard parallel group design.
Participants	80 women with GA between 26 and 34 weeks documented by a definite LMP and sonography in the first trimester. Preterm labour defined as 4 contractions in 20 min or 8 in 60 min, cervical dilation of 1 cm or greater and cervical effacement of 50% or more. Multiple pregnancy included. Exclusions: PROM, vaginal bleeding, fetal distress or fetal death, IUGR, a history of trauma, cervical dilation > 3 cm, systemic disorders of the mother, a known uterine anomaly and BP < 90/50.
Interventions	CCB: nifedipine 10 mg s/l every 20 mins for 4 doses, if contractions inhibited nifedipine continued po (20 mg) every 6 hrs for the first 24 hrs and then every 8 hrs for the last 24 hrs. Control group: Atosiban 300 µg/min by IV continued for a maximum of 12 hrs or 6 hrs after the patient's contractions ceased.
Outcomes	Maternal: delivery within 7 days; delivery with in 48 hrs; maternal adverse drug reactions. No neonatal outcomes.
Notes	Drug side effect distributive - some patients experienced 2-3 side effects.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "4-part, ABCD, block-random allocation was used".
Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding of participants and personnel (performance bias)	High risk	Intervention not blinded. Quote: "because the two drugs are completely different in shape and form a blind study was not an option".
Blinding of outcome assessment (detection bias) Objective outcome measures	Low risk	Outcome assessment not blinded; however, objective outcomes judged to be low risk.
Blinding of outcome assessment (detection bias) Subjective outcome measures	High risk	Outcome assessment not blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No post-randomisation exclusions or losses at follow-up reported.

Kashanian 2005 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	Minimal neonatal outcome data reported.
Other bias	Unclear risk	Not able to determine

Kashanian 2011

Methods	Randomised controlled trial, block randomisation
Participants	82 nulliparous women with GA between 26 and 33 weeks documented by a definite LMP and ultrasound in the first trimester. Preterm labour defined as 4 contractions in 20 mins or 8 in 60 mins, cervical dilation of 1 cm or greater and cervical effacement of 50% or more. Exclusion criteria: multiple pregnancy, PROM, vaginal bleeding, fetal distress or fetal death, IUGR, a history of trauma, cervical dilation > 4 cm, systemic disorders of the mother including pre-eclampsia, a known uterine anomaly, smoking, other drug use, fetal anomaly, polyhydramnios, oligohydramnios, suspicion of intrauterine infection, previous use of tocolytic and BP < 90/50.
Interventions	CCB group: nifedipine. 10 mg orally every 20 mins till contractions ceased or dose of 40 mg total, then 20 mg 6 hourly for 24 hrs, then 20 mg 8 hourly for 24 hrs then 10 mg 8 hourly for 24 hrs. Control group: 100 mg indomethacin suppository, repeated after 1 hr if contractions continued, maximum dose of 200 mg
Outcomes	Maternal: cessation of contractions after 2 hrs, delivery within 48 hrs, delivery within 7 days, adverse drug reactions. Neonatal death - reported but not prespecified.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Block randomisation, 4 part, ABCD.
Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding of participants and personnel (performance bias)	High risk	Intervention not blinded.
Blinding of outcome assessment (detection bias) Objective outcome measures	Low risk	Outcome assessment not blinded; however, objective outcomes judged to be low risk.
Blinding of outcome assessment (detection bias) Subjective outcome measures	High risk	Outcome assessment not blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	2 women in nifedipine group excluded post-randomisation due to hypotension, 1 woman in indomethacin group excluded - not explained.

Kashanian 2011 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	Minimal neonatal outcome data reported.
Other bias	Unclear risk	Not able to determine.

Klauser 2012

Methods	Randomised controlled trial, 3-arm design.
Participants	276 women with “idiopathic preterm labor" with intact membranes and singleton or twin pregnancy between 20-32 weeks. Vertex presentation, sufficient effacement, decrease in station. Preterm labour defined as regular contractions < 5 min apart, with cervical dilatation of 1-6 cm or dilatation altered from the previous IE. Setting: The University of Mississippi Medical Center, USA. Exclusion criteria: significant medical/surgical reasons for early delivery including severe pre-eclampsia, placental abruption, fetal malformations inconsistent with life, chorioamnionitis, IUGR (< fifth percentile), non-reassuring FHR, maternal non-consent to randomisation.
Interventions	CCB group: nifedipine. 30 mg orally then 20–30 mg every 4–6 hrs until contractions stopped. Control group: indomethacin. 100 mg rectal suppository repeated up to once after 2 hrs if contractions continued. Then 50 mg oral indomethacin every 6 hrs for 12 hrs until contractions ceased. Total treatment cycle of 48 hrs. 20 mg oral twice per day. 20 mg oral pepcid given twice per day to minimise gastrointestinal symptoms. Control group: 6 g IV MgSO4 over 20 mins, maintained at 4-6 g per hr till 1-2 hrs after contractions ceased. All arms: no maintenance therapy, no antibiotics and no antenatal steroids given.
Outcomes	Maternal: proportion of women undelivered after 48 hrs/7 days; delivery after 37, 34 and 30 weeks’; maternal drug side effects; tachycardia; fetal ductal constriction; oligohydramnios. Neonatal: composite measure of "adverse neonatal morbidity" (including RDS, PDA, sepsis, IVH, PVL, NEC), GA at birth, birthweight, acidosis, days of mechanical ventilation, neonatal length of stay.
Notes	For subgroup comparisons, the authors of this review have split data from the CCB arm into 2 groups with smaller sample size, to achieve reasonably independent comparisons (i.e. (1) CCB versus MgS04, and (2) CCB versus indomethacin).

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Drugs were distributed by the University pharmacy by opening consecutive opaque envelopes containing a card advising group allocation. The cards were "generated by random selection" but no details as to how. May be low risk but remains unclear.
Allocation concealment (selection bias)	Unclear risk	Sequentially opened opaque envelopes. Probably low risk, but no details as to whether envelopes were sealed and tamper-proof.
Blinding of participants and personnel (performance bias)	High risk	Not blinded, diverging treatment regimens.
Blinding of outcome assessment (detection bias) Objective outcome measures	Low risk	"Those assessing outcomes were not privy to group assignment as they were not involved in their clinical care."

Klauser 2012 *(Continued)*

Blinding of outcome assessment (detection bias) Subjective outcome measures	Low risk	"Those assessing outcomes were not privy to group assignment as they were not involved in their clinical care."
Incomplete outcome data (attrition bias) All outcomes	Low risk	25 of 301 women were lost to attrition, reasons for each loss are provided (e.g. delivered elsewhere, no medications available).
Selective reporting (reporting bias)	Low risk	Neonatal and maternal outcomes reported in separate papers, all as expected.
Other bias	Low risk	None evident.

Koks 1998

Methods	Randomised controlled trial, standard parallel group design.
Participants	102 women in preterm labour at 24-34 weeks. Twin pregnancies included. Exclusion criteria: maternal medical conditions, chorioamnionitis.
Interventions	CCB group: nifedipine. s/l 30 mg then po 20 mg every 4-12 hrs reducing to 20 mg every 8 hrs to 34 weeks prn. Control group: IV ritodrine, 200 µg/min up to max of 400 µg/min then oral maintenance 80 mg every 8 h to 34 weeks.
Outcomes	Maternal: delivery < 34 weeks; delivery < 48 hrs; delivery < 7 days; maternal adverse drug reaction requiring cessation of treatment. Neonatal: GA at birth; birthweight; Apgar score < 7 at 5 mins; NICU admission; RDS; neonatal jaundice; neonatal death.
Notes	Outcomes for a subset of trial participants (57) included in review. Additional data received. Sample size calculation: not reported. Antenatal corticosteroids: yes - weekly to 32 weeks. GBS protocol: vaginal culture and intrapartum AB for GBS positive. Twin data accounted for.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Stated "equal random assignment".
Allocation concealment (selection bias)	Low risk	Sealed envelopes.
Blinding of participants and personnel (performance bias)	High risk	Not possible, diverging treatment regimens.
Blinding of outcome assessment (detection bias)	Low risk	Not evident; however, objective outcomes judged to be low risk.

Koks 1998 *(Continued)*

Objective outcome measures		
Blinding of outcome assessment (detection bias) Subjective outcome measures	High risk	Blinded assessment not evident.
Incomplete outcome data (attrition bias) All outcomes	Low risk	2 post-randomisation exclusions.
Selective reporting (reporting bias)	Low risk	Extra data supplied with no conflict of published data.
Other bias	Low risk	Not evident.

Kose 1995

Methods	Randomised controlled trial.
Participants	73 singleton pregnancies, between 22-36 gestational weeks in preterm labour. Inclusion criteria: uterine contractions with progressive cervical dilatation and effacement. Exclusions: cervical dilatation > 4 cm, preterm premature rupture of membranes, severe pre-eclampsia-eclampsia, placental abruption, placenta praevia, chorioamnionitis, severe fetal growth restriction, fetal death, fetal anomalies incompatible with life, multiple pregnancy, diabetes mellitus, hyperthyroidism, pregnant women diagnosed with heart disease, tocolytic agent previously used during the current pregnancy.
Interventions	CCB: oral nifedipine (52 women). Tocolysis with nifedipine was initiated with 30 mg of nifedipine given orally. In addition, when contractions did not cease, an additional dose similar to the initial dose was given. When there was a suppression of contractions after 6 hrs a maintenance dose of nifedipine of 20 mg was given every 6 hrs. After 24 hrs the maintenance dose was reduced to 20 mg nifedipine every 8 hrs for 2 days. Maintenance nifedipine was continued with a minimum dose of 10 mg every 4 hrs until 37 weeks. Control: IV ritodrine (21 women): 2 ampoules of ritodrine with a total of 50 mg were dissolved in 500 mL 2% dextrose resulting in a concentration of ritodrine of 0.2 mg/mL. The initial starting dose of ritodrine was 0.05 mg/min. According response, the participant received 0.05 mg/min for 15 mins or until contractions ceased. If there was no cessation of contractions the dose was increased until it reached the maximum dose of 0.35 mg/min, or until there were severe side effects. After reaching cessation of contractions the ritodrine level was decreased until a level of 0.05 mg/min and continued for 12 hrs. Maintenance treatment was oral treatment with 10 mg ritodrine tablets, 10 mg every 6 hrs was started and continued until 37 weeks.
Outcomes	Deferred labour (therapy was found unsuccessful with deferred labour less than 38 hrs, greater than 38 hrs and to 37 gestational week), maternal side effects.
Notes	Translated from Turkish.

Risk of bias

Bias	Authors' judgement	Support for judgement

Kose 1995 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	"randomly assigned"; no further details.
Allocation concealment (selection bias)	Unclear risk	Not reported.
Blinding of participants and personnel (performance bias)	High risk	Intervention not blinded.
Blinding of outcome assessment (detection bias) Objective outcome measures	High risk	Outcome assessment not blinded; however, objective outcomes judged to be low risk.
Blinding of outcome assessment (detection bias) Subjective outcome measures	High risk	Outcome assessment not blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No post-randomisation exclusions or losses at follow-up reported.
Selective reporting (reporting bias)	Low risk	Outcomes reported as expected.
Other bias	Unclear risk	Not able to determine.

Kupferminc 1993

Methods	Randomised controlled trial, standard parallel group design.
Participants	71 women in preterm labour at 26-34 weeks. Exclusion criteria: women with ruptured membranes.
Interventions	CCB group: nifedipine. 30 mg po then 20 mg after 90 mins if required then maintenance 20 mg every 8 hrs until 34-35 weeks. Switch to ritodrine if contractions continue after 150 mins. Control group: IV ritodrine 50 µg/min increasing by 15 µg every 15 mins to a maximum of 300 ug/min for 12 hrs, oral maintenance 10 mg every 3 hrs until 34-35 weeks.
Outcomes	Maternal: delivery < 37 weeks; delivery < 48 hrs; delivery < 7 days; maternal adverse drug reaction requiring cessation of treatment. Neonatal: NICU admission; RDS; neonatal death. Fetal: fetal death.
Notes	Additional data received. Sample size calculation: yes - based on maternal cardiovascular changes. Antenatal corticosteroids: yes. GBS protocol: not reported.

Risk of bias

Bias	Authors' judgement	Support for judgement

Kupferminc 1993 *(Continued)*

Random sequence generation (selection bias)	Low risk	Computerised list.
Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding of participants and personnel (performance bias)	High risk	Intervention not blinded.
Blinding of outcome assessment (detection bias) Objective outcome measures	Low risk	Outcome assessment not blinded; however, objective outcomes judged to be low risk.
Blinding of outcome assessment (detection bias) Subjective outcome measures	High risk	Outcome assessment not blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No post-randomisation exclusions or losses at follow-up reported.
Selective reporting (reporting bias)	Low risk	Additional outcome data received.
Other bias	Unclear risk	Not able to determine.

Laohapojanart 2007

Methods	Randomised controlled trial, standard parallel group design.
Participants	40 women with a single gestation between 24-26 weeks with preterm labour. Preterm labour defined as > or 4 uterine contractions per 20 mins, cervical dilation 1-4 cm and changing cervical effacement documented by obstetricians. Exclusion criteria: heart disease; real disease; hypertension; chorioamnionitis; placental abruption; placental previa; pre-eclampsia; multiple pregnancy; diabetes and thyrotoxicosis.
Interventions	CCB group: nifedipine 10 mg tablet, further 10 mg given every 10 mins if contractions continued to a maximum of 40 mg within the first hr of treatment. 20 mg given after the first hr every 4-6 hrs consecutively for 72 hrs. Control group: 10 µg terbutaline per min infusion increased by 5 µg every 10 mins until 25 µg was reached. Once uterine contractions stopped infusion was maintained for 2-6 hrs before switching to subcutaneous injections of terbutaline 0.25 mg every 4 hrs for 24 hrs.
Outcomes	Maternal: delivery < 37 weeks; delivery < 7 days; delivery < 48 hrs; maternal adverse drug reactions requiring treatment cessation. Neonatal: admission to NICU; RDS; IVH all grades; perinatal mortality; neonatal death; GA at birth; birthweight.
Notes	Dexamethasone < 34 weeks, 6 g IM every 12 hrs x 4 Indocid given if failed.

Laohapojanart 2007 *(Continued)*

	11 patients in the nifedipine group stopped treatment after the maximum dose of 40 mg in the first hr was reached. 1 of these patients delivered 2 hrs later and 10 were switched to terbutaline IV.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomised in blocks of 4, 6 and 8".
Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding of participants and personnel (performance bias)	High risk	Intervention not blinded.
Blinding of outcome assessment (detection bias) Objective outcome measures	Low risk	Outcome assessment not blinded; however, objective outcomes were judged to be low risk.
Blinding of outcome assessment (detection bias) Subjective outcome measures	High risk	Outcome assessment not blinded.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	4 lost to follow-up in the terbutaline group.
Selective reporting (reporting bias)	Unclear risk	Not all expected neonatal outcomes reported.
Other bias	Unclear risk	Not able to determine.

Larmon 1999

Methods	Randomised controlled trial, standard parallel group design.
Participants	122 women in preterm labour between 22-34 weeks. Exclusion criteria: multiple pregnancy; ROM; chorioamnionitis; medical conditions; standard contraindications to tocolytics.
Interventions	CCB group: Nicardipine. 40 mg po then 20 mg 2 hrs prn up to 3 doses then oral maintenance 45 mg every 12 hrs until 37 weeks. Control group: IV MgSO4 loading dose of 6 g then 2 g/h increasing up to a maximum of 4 g/hr prn. Oral maintenance magnesium lactate 4 tablets every 12 hrs until 37 weeks.
Outcomes	Maternal: maternal adverse reaction; pregnancy prolongation. Fetal: fetal death. Neonatal: NICU admission; GA at birth; birthweight; neonatal death. Additional data received for: Maternal: delivery < 37 weeks; delivery < 34 week; delivery < 48 hrs; delivery < 7 days; maternal adverse drug reaction requiring cessation of treatment.

Larmon 1999 *(Continued)*

	Neonatal: Apgar score < 7 at 5 mins; RDS.
Notes	Sample size calculation: yes - based on successful tocolysis at 6 hrs. Antenatal steroids: yes, for women 24-34 weeks' gestation. GBS protocol: all women received ampicillin awaiting results of vaginal culture for GBS, 7 day course for those GBS positive. Addtional data and information were received from authors and included in the review.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random number table.
Allocation concealment (selection bias)	Low risk	Sequentially numbered sealed opaque envelopes.
Blinding of participants and personnel (performance bias)	High risk	Intervention not blinded.
Blinding of outcome assessment (detection bias) Objective outcome measures	Low risk	Outcome assessment not blinded; however, objective outcomes judged to be low risk.
Blinding of outcome assessment (detection bias) Subjective outcome measures	High risk	Outcome assessment not blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No post-randomisation exclusions or losses at follow-up reported.
Selective reporting (reporting bias)	Low risk	All outcomes reported as expected; additional data received.
Other bias	Unclear risk	Not able to determine.

Lyell 2007

Methods	Randomised controlled trial, standard parallel group design.
Participants	196 women in preterm labour between 24-33 weeks and 6 days gestation. Preterm labour defined by 2 or more contractions every 10 mins with cervical change, ruptured membranes, or 2 cm or more dilation and 80% effacement. Exclusion criteria: placental abruption, placenta previa, non-reassuring fetal status, IUGR, chorioamnionitis, maternal medical disease.
Interventions	CCB group: nifedipine. 10 mg s/l every 20 mins for 3 doses total, followed by 20 mg po every 4 or 6 hrs based on physician judgement. Treatment continued until at least 12 hrs of uterine quiescence within the first 48 hrs.

Lyell 2007 *(Continued)*

	Control group: MgSO4. 4 g bolus followed by a 2 g/hr infusion, an additional 2 g boluses allowed as needed for persistent preterm labour, as was increasing the infusion rate to 4 g/hr.
Outcomes	Maternal: delivery prior to 37 weeks; delivery within 48 hrs; maternal adverse drug reactions. Neonatal: admission to NICU; RDS; neonatal sepsis; NEC; IVH; neonatal deaths; birthweight; GA at birth; duration of stay in neonatal nursery.
Notes	Betamethasone 12 mg IM x 2 IM X 2 24 hrs apart GBS prophylaxis. PROM - Erythromycin and 500 mL hydration with lactated Ringer's solution before tocolysis. Composite outcome of time to delivery and uterine activity. Multiple pregnancy accounted for in denominators.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random numbers table.
Allocation concealment (selection bias)	Low risk	Opaque sequentially numbered envelopes.
Blinding of participants and personnel (performance bias)	High risk	Intervention not blinded.
Blinding of outcome assessment (detection bias) Objective outcome measures	Low risk	Outcome assessment not blinded; however, objective outcomes were judged to be low risk.
Blinding of outcome assessment (detection bias) Subjective outcome measures	High risk	Outcome assessment not blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	4 excluded before analysis, unclear from which study group.
Selective reporting (reporting bias)	Low risk	None evident.
Other bias	Unclear risk	Not able to determine.

Mawaldi 2008

Methods	Randomised controlled trial, standard parallel group design.
Participants	174 pregnant with preterm labour 24-34 weeks' gestation, preterm labour defined as 1-3 contractions per 10 mins for at least 60 mins. Cervical dilation between 0 and 3 cm for primigravidas and between 1 and 3 cm for multigravidas with cervical effacement less than 50%.

Mawaldi 2008 *(Continued)*

	Exclusion criteria: high order pregnancy, major APH, ROM, major medical disorders, a temperature greater than 37.5 degrees celsius, BP less than 90/50 mmHg, a compromised fetus or fetus with lethal congenital anomalities, multiple pregnancy not mentioned.
Interventions	CCB group: nifedipine. 30 mg loading dose po followed by 20 mg after 90 mins, if contractions did not cease, 20 mg of nifedipine was given every 8 hrs for 48 hrs. Control group: 0.25 mg loading dose of terbutaline s/c and repeated every 45 mins if contractions persisted and pulse < 120 BPM.
Outcomes	Maternal: delivery < 48 hrs maternal adverse drug reactions; maternal length of hospital stay. No neonatal outcomes.
Notes	Sample size calculation: reported. Antenatal corticosteroids: no. GBS protocol: no.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Reported as "Simple randomisation process".
Allocation concealment (selection bias)	Unclear risk	Sealed envelopes used; whether opaque or sequentially numbered is unknown. Stated "Allocation concealment was ensured by having the treating physician draw a sealed envelope form a supply previously prepared and sealed by another staff member".
Blinding of participants and personnel (performance bias)	High risk	Intervention not blinded.
Blinding of outcome assessment (detection bias) Objective outcome measures	Low risk	Outcome assessment not blinded; however, objective outcomes were judged to be low risk.
Blinding of outcome assessment (detection bias) Subjective outcome measures	High risk	Outcome assessment not blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No post-randomisation exclusions or losses at follow-up reported.
Selective reporting (reporting bias)	Unclear risk	No neonatal outcome data reported.
Other bias	Unclear risk	Not able to determine.

Nassar 2009

Methods	Randomised controlled trial comparing high-dose and low-dose nifedipine.

Nassar 2009 *(Continued)*

Participants	102 women with singleton pregnancies, intact membranes, and active preterm labour at 24-34 weeks' gestation Exclusion criteria: cervical dilation > 4 cm; IUGR; congenital malformations; non-reassuring fetal heart monitoring; chorioamnionitis; prior tocolysis in the current pregnancy; BP < 05/50 mmHg; maternal medical diseases (renal insufficiency, hepatic dysfunction, or cardiac disease); obstetric complications (placenta previa, abruption or hypertensive disorders of pregnancy).
Interventions	Group 1: high-dose nifedipine, 20 mg s/l repeated in 30 mins followed by 120-160 mg slow release nifedipine daily for 48 hrs and 80-120 mg up to 36 weeks. Group 2: low-dose nifedipine, 10 mg repeated every 15 mins to a maximum of 4 doses followed by 60-80 mg slow release daily for 48 hrs and 60 mg up to 36 weeks.
Outcomes	Maternal: delivery < 37 weeks; delivery < 34 weeks; delivery < 7 days; delivery < 48 hrs; maternal adverse drug reactions; maternal adverse drug reactions requiring treatment cessation; APH; PPH; maternal length of hospital stay (days); pregnancy prolongation (days). Neonatal: Apgar score < 7 at 5 mins; admission to NICU; RDS; neonatal jaundice; neonatal sepsis; NEC; IVH all grades; neonatal deaths; neonatal deaths excluding congenital abnormalities; GA at birth; birthweight; neonatal length of hospital stay (days). Fetal: fetal deaths; fetal deaths excluding congenital abnormality.
Notes	Additional information received, no information on sample calculation, steroids or GBS available at this time.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated number table.
Allocation concealment (selection bias)	Low risk	Sequentially numbered opaque envelopes.(did not state whether sealed but assumed so as trial methods were of a high quality).
Blinding of participants and personnel (performance bias)	High risk	Not blinded.
Blinding of outcome assessment (detection bias) Objective outcome measures	Low risk	Assessment of outcomes performed by person blinded to treatment allocation, participants and trial staff not blinded to allocation after randomisation; however, objective outcomes judged to be low risk.
Blinding of outcome assessment (detection bias) Subjective outcome measures	Low risk	Assessment of outcomes performed by person blinded to treatment allocation, participants and trial staff not blinded to allocation after randomisation.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No post-randomisation exclusions or losses at follow-up reported.
Selective reporting (reporting bias)	Low risk	All outcomes reported as expected; additional data received.
Other bias	Low risk	No evidence of other bias.

Padovani 2012

Methods	Described as "Randomised controlled trial".
Participants	49 women with single gestation with preterm labour. Setting: described as "Two hospitals in Sorocaba, Brazil" in study abstract. Exclusion criteria: data limited - only reported as an abstract.
Interventions	CCB group: nifedipine. 20 mg orally (maintenance regimen not stated). Control group: terbutaline. 5 mg/min IV, increased by 5 mg/min every 15 mins.
Outcomes	Tocolysis within 12 hrs, time needed for tocolysis, recurrence frequency, progression to preterm delivery. Maternal, fetal and neonatal adverse effects (tachycardia, bradycardia, hypotension, headache). NICU admission and duration, Apgar, complications of prematurity and neonatal death.
Notes	Reported as an abstract. Data not included in subgroup analyses as we cannot determine whether nifedipine was high or low dose.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported.
Allocation concealment (selection bias)	Unclear risk	Not reported.
Blinding of participants and personnel (performance bias)	High risk	Intervention not blinded.
Blinding of outcome assessment (detection bias) Objective outcome measures	Low risk	Outcome assessment not blinded; however, objective outcomes were judged to be low risk.
Blinding of outcome assessment (detection bias) Subjective outcome measures	High risk	Outcome assessment not blinded.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unable to determine; study reported as an abstract only.
Selective reporting (reporting bias)	Unclear risk	Unable to determine; study reported as an abstract only.
Other bias	Unclear risk	Unable to determine; study reported as an abstract only.

Papatsonis 1997

Methods	Randomised controlled trial, standard parallel group design.
Participants	185 women in preterm labour at 20-34 weeks.

Papatsonis 1997 *(Continued)*

	Exclusion criteria: multiple pregnancy, chorioamnionitis, maternal medical conditions.
Interventions	CCB group: nifedipine. 10 mg s/l, repeated if necessary po 10 mg every 15 mins up to 40 mg in the first hr. Maintenance 60-160 mg/day up to 34 weeks. Control group: ritodrine commencing at 383 µg/min increasing prn until cessation of contractions then decreasing depending on the time lag after which tocolysis is established (minimum 100 µg/min) and continued for 3 days. Maintenance 40 mg po every 8 hrs up to 34 weeks in 2 of the 3 participating hospitals.
Outcomes	Maternal: delivery < 37 weeks; delivery < 34 weeks; delivery < 7 days; delivery < 48 hrs; GA; maternal adverse drug reaction requiring cessation of treatment. Fetal: fetal death. Neonatal: NICU admission; RDS; neonatal death; Apgar score < 7 at 5 mins; neonatal jaundice; NEC; IVH; birthweight.
Notes	12 exclusions in published report - additional data received and included. Sample size calculation: yes - based on delay in delivery < 7 days. Antenatal corticosteroids: yes. GBS protocol: vaginal culture on admission and AB for positive GBS.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random numbers.
Allocation concealment (selection bias)	Low risk	Sequentially numbered opaque sealed envelopes.
Blinding of participants and personnel (performance bias)	High risk	Intervention not blinded.
Blinding of outcome assessment (detection bias) Objective outcome measures	Low risk	Outcome assessment not blinded; however, objective outcomes were judged to be low risk.
Blinding of outcome assessment (detection bias) Subjective outcome measures	High risk	Outcome assessment not blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No post-randomisation exclusions or losses at follow-up reported for short-term neonatal and maternal outcomes.
Selective reporting (reporting bias)	Low risk	All outcomes reported as expected; additional data received.
Other bias	Low risk	No evidence of other bias.

Rayamajhi 2003

Methods	Randomised controlled trial, standard parallel group design.
Participants	67 pregnant women with threatened preterm labour 28-36 weeks, intact membranes. Multiple pregnancy included in nifedipine group. Exclusion criteria: pre-eclampsia; eclampsia; APH; hydramnios; chorioamnionitis; cardiac history; thyroid history; advanced labour; IUGR; oligoamnios; abnormalities incompatible with life.
Interventions	CCB group: nifedipine. 500 mL crystalloid solution IV over 30-45 mins, maintenance at 100 mL/h. Maintenance dose 4-6 hrs after the last s/l dose, nifedipine 10-20 mg po, 6-8 hourly for no more than 7 days. Loading dose: nifedipine 10 mg s/l. Control group: Isoxsuprine. 40 mg in 500 mL Ringer lactate at 0.08 mg/min, increasing the infusion rate up to 0.24 mg/min depending on the status of uterine contractions and occurrence of side effects. Maintained on oral isoxsuprine 10 mg 8 hourly for up to 7 days.
Outcomes	Maternal: delivery < 37 weeks; delivery < 7 days; delivery < 48 hrs; maternal adverse drug reactions requiring treatment cessation; pregnancy prolongation (days). Fetal: fetal deaths; fetal deaths excluding deaths from congenital abnormality (CA). Neonatal: neonatal deaths; GA at birth; birthweight; perinatal mortality.
Notes	Sample size calculation: not reported. Antenatal corticosteroids: yes, all women enrolled, 2 doses of 12 mg IM dexamethasone given 12 hrs apart. GBS protocol: not reported although all women received oral AB. Only 1 twin pregnancy included. No denominator reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Stated as "parallel randomisation".
Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding of participants and personnel (performance bias)	High risk	Intervention not blinded.
Blinding of outcome assessment (detection bias) Objective outcome measures	Low risk	Outcome assessment not blinded. However, objective outcomes were judged to be low risk.
Blinding of outcome assessment (detection bias) Subjective outcome measures	High risk	Outcome assessment not blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	5 patients lost to follow-up (unsure from which group).

Rayamajhi 2003 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	Very few neonatal outcomes were reported.
Other bias	Unclear risk	Not able to determine.

Read 1986

Methods	Randomised controlled trial, standard parallel group design.
Participants	40 women in preterm labour at 20-35 weeks. Exclusion criteria: multiple pregnancy; chorioamnionitis; maternal medical conditions; ROM.
Interventions	CCB group: nifedipine. 30 mg po then 20 mg every 8 hrs for 3 days. ritodrine started after 2 hrs if contractions were undiminished. Control group: ritodrine 50 µg/min increasing by 50 µg every 10 mins to a maximum of 300 µg. Maintained for 12 hrs then oral maintenance for 48 hrs.
Outcomes	Maternal: delivery < 48 hrs; maternal adverse drug reaction, pregnancy prolongation. Neonatal: birthweight.
Notes	No additional outcomes data available. Sample size calculation: no. Antenatal corticosteroids: not reported. GBS protocol: not reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated.
Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding of participants and personnel (performance bias)	High risk	Intervention not blinded.
Blinding of outcome assessment (detection bias) Objective outcome measures	Low risk	Outcome assessment not blinded. However, objective outcomes were judged to be low risk.
Blinding of outcome assessment (detection bias) Subjective outcome measures	High risk	Outcome assessment not blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No post-randomisation exclusions or losses at follow-up reported.
Selective reporting (reporting bias)	Unclear risk	Extra data requested and not supplied.

Read 1986 *(Continued)*

Other bias	Unclear risk	Not able to determine.

Salim 2012

Methods	Randomised controlled trial between January 2008 and December 2011.
Participants	149 women in preterm labour (> 4 contractions lasting > 30 seconds within 30 mins, confirmed by external topography, 50% cervical effacement and < 4 cm dilatation for nulliparous women and 1-4 cm dilatation for multiparous) with intact membrane between 24-33+6 weeks. Singletons and twins included. Setting: Emek Medical Center, Afula, Israel. Exclusion criteria: rupture of membranes, vaginal bleeding from placenta previa or placental abruption, fever > 38°C, severe pre-eclampsia, cardiovascular or liver disease, systolic BP < 90 mm Hg, known uterine malformation, IUGR below 5th percentile, non-reassuring fetal status, antepartum diagnosis of major fetal malformations, multiple gestations of triplets or greater, fetal death.
Interventions	CCB group: nifedipine. Loading dose of 20 mg orally followed by 2 x 20 mg doses 20-30 mins apart "as needed". After 6 hrs, maintenance of 20-40 mg 4 times daily for 48 hrs. Control group: atosiban. Loading dose of 6.75 mg IV in 0.9% sodium chloride solution, then 300 micrograms/min IV infusion in 0.9% sodium chloride solution for the first 3 hrs followed by 100 mcg/min for another 45 hrs. Both groups: group B strep prophylactic antibiotics and corticosteroids. No maintenance therapy after 48 hrs. Cross-over of study drugs was carried out if labour progressed between 1-48 hrs or if adverse effects occurred. indomethacin given if both study drugs failed to stop progression.
Outcomes	Tocolytic efficacy and tolerability profile by pregnancy prolongation for 48 hrs without need for an alternate tocolytic (primary), pregnancy prolongation for 7 days without need for an alternate tocolytic, pregnancy prolongation for 48 hrs/7 days, preterm birth, interval between enrolment and delivery, maternal adverse drug effects, GA at delivery, neonatal morbidity and mortality related to prematurity.
Notes	Cross-over assignment used.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Blocked randomisation in blocks of 10 using a "computer randomisation sequence generation program".
Allocation concealment (selection bias)	Low risk	Not clear. However, stated that allocations were kept "in the labor and delivery ward in a closed study box". Probably low risk as the study reports that allocations were revealed only immediately before drug administration.
Blinding of participants and personnel (performance bias)	High risk	Not blinded. Quote: "Because the study drugs were administered by different roots, blinding of participants or care providers was not performed".
Blinding of outcome assessment (detection bias) Objective outcome measures	Low risk	Outcome assessment not blinded. However, objective outcomes were judged to be low risk.
Blinding of outcome assessment (detection bias) Subjective outcome measures	High risk	Outcome assessment not blinded.

Salim 2012 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	2 post randomisation exclusions in each study group: Nifedipine: 2 women did not receive nifedipine; both had progressed beyond 4 cm Atosiban: 2 women did not receive atosiban;1 progressed beyond 4 cm, and 1 withdrew.
Selective reporting (reporting bias)	Low risk	No evidence of selective reporting bias. The trial was registered in a publicly available trials registry and all expected outcomes were reported in the publication.
Other bias	Low risk	None evident.

Taherian 2007

Methods	Randomised, clinical trial, table of random numbers.
Participants	120 women with preterm labour between 26-36 weeks' gestation with intact membranes. Contractions ≥ 4 per 10 mins with duration of 30 seconds. Exclusion criteria: taking other tocolytics, cervical dilatation ≥ 5 cm, pre-eclampsia, lethal fetal anomalies, chorioamnionitis, significant antepartum haemorrhage, maternal cardiac or liver diseases.
Interventions	CCB group: nifedipine. 10 mg tablet orally, repeated every 20 mins (maximum dose of 40 mg in first hr). If contractions subsided, then maintenance dose of 10-20 mg every 6 hrs. Patients were observed in the labour room for 24-48 hrs. Control group: MgSO4. Loading dose of 4 g intravenously over 15 mins, then a maintenance dose of 2-3 g/hr infusion.
Outcomes	Maternal: arresting preterm labour duration, safety, side effects, treatment failure, GA at delivery. Neonatal: birthweight, Apgar score at 1 min and 5 mins.
Notes	Some discrepancy with outcome reporting. Outcomes not specified and delivery data unclear. Results appear to be transposed in text. Side effects described, but no results. No neonatal data available. Additional information requested. Antenatal corticosteroids: yes. GBS prophylaxis: yes. No mention of multiple pregnancy.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Random numbers table used.
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not stated.

Taherian 2007 *(Continued)*

Blinding of participants and personnel (performance bias)	High risk	Intervention not blinded.
Blinding of outcome assessment (detection bias) Objective outcome measures	Low risk	Outcome assessment not blinded. However, objective outcomes were judged to be low risk.
Blinding of outcome assessment (detection bias) Subjective outcome measures	High risk	Outcome assessment not blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No post-randomisation exclusions or losses at follow-up reported.
Selective reporting (reporting bias)	Unclear risk	Additional data requested.
Other bias	Unclear risk	Not able to determine.

Trabelsi 2008

Methods	Prospective randomised study. Approved by hospital Ethics Committee. Signed consent before randomisation.
Participants	45 (24 women in CCB group and 21 in salbutamol group) pregnant women with singleton pregnancies admitted for preterm labour, with intact membranes between 28 and 35 weeks' gestation. Preterm labour defined as persistence of at least 2 symptomatic uterine contractions, within a 10-min period, each lasting 30 seconds, cervix length reduced to 50%. Exclusion criteria: cervix dilatation greater than 3 cm, pre-eclampsia or chronic arterial hypertension, oligohydramnios, fetal anomalies, signs of fetal distress, suspected intrauterine infection or growth restriction, placenta praevia, maternal diseases, contraindication or allergy to constituents to beta-adrenergic drugs or nicardipine.
Interventions	CCB group: Nicardipine. Initial IV infusion at a rate of 2 mg/min, increased every 30 mins until uterine contractions suppressed or intolerable side effects appeared or limit dose of 4 mg/h reached. Control group: Salbutamol. Initial dose of 0.125 mg/h. Monitored for 6 hrs. If uterine contractions reduced after 24 hrs, then oral therapy. If contractions start, then to re-commence original IV treatment.
Outcomes	Maternal: disappearance of uterine contractions, failure of tocolysis, side effects. Neonatal weight, Apgar score at 1 and 5 mins, NICU, duration of hospitalisation, GA at birth and neonatal complications.
Notes	3 women excluded post randomisation, as did not deliver at facility. GBS protocol reported: no. Antenatal corticosteroids reported: no. Sample size calculation reported: no. No additional outcomes data reported.

Trabelsi 2008 *(Continued)*

	No data for < 28 weeks.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Reported "1:1 randomisation".
Allocation concealment (selection bias)	Low risk	Sealed opaque, consecutively numbered envelopes.
Blinding of participants and personnel (performance bias)	High risk	Not performed.
Blinding of outcome assessment (detection bias) Objective outcome measures	Low risk	Outcome assessment not blinded. However, objective outcomes were judged to be low risk.
Blinding of outcome assessment (detection bias) Subjective outcome measures	High risk	Outcome assessment not blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	3 patients lost to follow-up (did not birth in study hospital).
Selective reporting (reporting bias)	Unclear risk	Unable to determine.
Other bias	Low risk	No evidence of other bias.

Valdes 2012

Methods	Prospective randomised controlled trial between May 2007 and November 2008.
Participants	132 consenting women with TPL (> 1 painful contractions every 10 min irrespective of cervical length and dilation and not eased by hydration at rest for 1 hr) between 23-34 weeks with singleton pregnancy, intact membrane and known GA. Setting: The University of Chile Clinical Hospital, Barros Luco-Trudeau and El Pino Hospitals. Exclusion criteria: IU infection, congenital fetal abnormality, placental abruption, severe IUGR, diabetes mellitus, cardiovascular disease, hyperthyroidism, other contraindications of therapy.
Interventions	CCB group: 20 mg oral nifedipine with 2nd and 3rd 20 mg dose given after 20 mins if contractions persisted. Maximum dose of 60 mg in the first hr. Maintenance therapy of 20 mg oral every 6 hrs after contractions subsided. Dose could be progressively lowered to min 10 mg after the second day, then slow-release nifedipine every 6 hrs till 48 hrs after subsidence of contractions. Control group: continuous fenoterol IV infusion, initial dose of 1 g/min and increased every 30 mins till contractions subsided with max dose of 4 g/min. Max permitted maternal HR of 120 beats/min. Once contractions subsided, IV infusion at same dose for 12 hrs then maintenance therapy of 0.5–1 g/min till 48 hrs after subsidence of contractions. Both groups: All mothers between 24 and 34 weeks received antenatal corticosteroids.

Valdes 2012 *(Continued)*

Outcomes	Pregnancy prolongation (primary), maternal adverse drug side effects, "clinical, metabolic and hemodynamic characteristics", perinatal outcomes (secondary).
Notes	Denominators for some outcomes were unclear in manuscript. Further detail on outcomes was provided by the lead author for the purpose of this review. As part of correspondence, the author noted that the hospitals involved in the study did not know the randomisation schedule, that an aleatory computed system was used for randomisation, and that corticosteroids were given to mothers between 24 and 34 weeks' gestation.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Central randomisation, permuted block design.
Allocation concealment (selection bias)	Low risk	Performed centrally. Reported that collaborators were unaware of enrolment order (no further details given).
Blinding of participants and personnel (performance bias)	High risk	Intervention was not blinded.
Blinding of outcome assessment (detection bias) Objective outcome measures	Low risk	Outcome assessment not blinded; however, objective outcomes judged to be low risk.
Blinding of outcome assessment (detection bias) Subjective outcome measures	High risk	Outcome assessment not blinded.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	10 were lost to follow-up after discharge (8 in the nifedipine group and 2 in fenoterol).
Selective reporting (reporting bias)	Low risk	All expected outcomes were reported.
Other bias	Low risk	No evidence of other bias.

Van De Water 2008

Methods	Randomised controlled trial, standard parallel group design.
Participants	93 pregnant women with imminent preterm labour between 24-34 weeks (imminent preterm labour: more than 1 uterine contraction every 10 mins for at least 1 hr). Exclusion criteria: multiple pregnancy; intrauterine infection; congenital defects of the fetus; (partial) placental abruption; diabetes mellitus; cardiovascular diseases; hyperthyroidism and pre-eclampsia.
Interventions	CCB group: nifedipine: beginning of tocolysis, Tocolysis < 30 mins: 2 x 10 mg capsules maintenance dosage: sustained release preparation of 90 mg nifedipine per day.

Van De Water 2008 *(Continued)*

	If > 30 mins no tocolysis: 120 mg nifedipine capsule. Maintenance dosage: sustained release preparation of 120 mg nifedipine per day. After 48 hrs, 90 mg sustained release preparation of nifedipine once daily for 7 days. Control group: ritodrine IV starting with 200 µg/min and increasing by 50 µg every 30 mins until tocolysis achieved, then maintained for 48 hrs. After 48 hrs ritodrine decreased to 50 µg/min, then IV ritodrine stopped and a maintenance dosage of oral Prepar retard (80 mg) 3 times daily was administered for a total duration of tocolysis of 7 days.
Outcomes	Maternal: delivery < 34 weeks; delivery < 28 weeks; delivery < 7 days; delivery < 48 hrs; maternal adverse drug reactions; maternal adverse drug reactions requiring treatment cessation. Neonatal: admission to NICU; RDS; neonatal sepsis; NEC; IVH all grades; long-term disability; neonatal length of hospital stay; duration of stay in neonatal nursery. Additional data received on the following: maternal: maternal sepsis; maternal death; neonatal: neonatal positive blood cultures; ROP all grades; chronic neonatal lung disease - oxygen at 28 postnatal weeks; neonatal deaths; birthweight; IVH grade 3 and 4.
Notes	28% loss to follow-up after 2 years. Small subset examined for developmental delay, authors respond no different at 2 years.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	1:1 randomisation, stratified by hospital and presence of ruptured membranes.
Allocation concealment (selection bias)	Low risk	Sequentially numbered opaque sealed envelopes.
Blinding of participants and personnel (performance bias)	High risk	Intervention not blinded.
Blinding of outcome assessment (detection bias) Objective outcome measures	Low risk	Outcome assessment not blinded; however. objective outcomes judged to be low risk.
Blinding of outcome assessment (detection bias) Subjective outcome measures	High risk	Outcome assessment not blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	2 lost to follow-up.
Selective reporting (reporting bias)	Low risk	Extra data supplied to support published data.
Other bias	Low risk	Not evident.

Weerakul 2002

Methods	Randomised controlled trial, standard parallel group design.
Participants	90 women in preterm labour with a singleton pregnancy between 28-34 weeks' gestation. Exclusion criteria: multiple pregnancy; ruptured membranes; previous tocolytic; cervix > 3 cm dilated; chorioamnionitis; infection; fetal distress; fetal anomalies; medical or obstetric complications.
Interventions	CCB group: nifedipine 10 mg s/l capsule crushed repeated after 15 mins then 20 mg after 30 mins to a maximum in the first hr of 40 mg. Maintenance of 60-120 mg daily for 3 days. Control group: terbutaline IV loading of 0.25 mg, then infusion commencing at 5 µg/min increasing by 5 µg/min every 15 mins depending on contractions to a maximum of 15 µg/min. Following uterine quiescence infusion maintained for 2 hrs then subcutaneous injection 0.25 mg every 4 hrs for 24 hrs.
Outcomes	Maternal: delivery after 48 hrs; delivery after 7 days; delivery after 37 weeks; pregnancy prolongation; GA at birth; maternal adverse drug reaction. Neonatal: birthweight. Additional data received on the following: Maternal: delivery < 48 hrs; delivery < 7 days; delivery within 37 weeks; delivery < 34 weeks; use of antenatal steroids; Maternal sepsis, maternal death, APH, PPH. Neonatal: Apgar score < 7 at 5 mins; admission to NICU; neonatal mechanical ventilation, jaundice, sepsis, NEC, IVH, ROP; perinatal death.
Notes	Additional information on methods and outcomes data were received. Sample size calculation: yes - no details given. Antenatal corticosteroids: yes - all women enrolled. GBS protocol: no. 1 post-randomisation exclusion in the other tocolytic group (terbutaline) due to patient transfer to private hospital.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computerised random table.
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias)	High risk	Intervention not blinded.
Blinding of outcome assessment (detection bias) Objective outcome measures	Low risk	Outcome assessment not blinded; however, objective outcomes were judged to be low risk.
Blinding of outcome assessment (detection bias) Subjective outcome measures	High risk	Outcome assessment not blinded.

Weerakul 2002 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	1 post-randomisation exclusion.
Selective reporting (reporting bias)	Low risk	Extra data supplied that supported published data.
Other bias	Low risk	No evidence of other bias.

Zhang 2002

Methods	Randomised controlled trial.
Participants	84 women in preterm labour between 28 and 35 weeks' gestation. Inclusion: premature labour defined as contractions 1 in 10 mins for 1 hr, or lasting for 30 seconds or longer or cervical dilation of 1 to 2 cm. Exclusions; severe fetal growth restriction, congenital abnormality, signs of uterine infections, cervical dilation greater than 3 cm, allergy, diabetes, cardiac condition or other contraindication to nifedipine, placental abruption, pre-eclampsia, intrauterine asphyxia.
Interventions	Group A (n = 28): nifedipine 10 mg orally. In 30 mins if still contracting a further 20 mg was given to a maximum of 40 mg. Maintenance of 10 mg every 8 hrs was continued until 35 weeks' gestation. Group B (n = 28): nifedipine 20 mg orally. In 30 mins if still contracting a further 20 mg was given to a maximum of 40 mg. Maintenance of 20 mg every 8 hrs was continued until 35 weeks' gestation. Group C (n = 28): no tocolysis. Luminal given for anxiety if required.
Outcomes	Prolongation of pregnancy, birth outcomes and maternal side effects.
Notes	All women received antenatal corticosteroids; IM dexamethasone 10 mg daily for 2 days. Article was translated from Chinese.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Stated "randomly divided"; no further details.
Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding of participants and personnel (performance bias)	High risk	Intervention not blinded.
Blinding of outcome assessment (detection bias) Objective outcome measures	Low risk	Outcome assessment not blinded; however, objective outcomes were judged to be low risk.
Blinding of outcome assessment (detection bias)	Unclear risk	Outcome assessment not blinded.

Zhang 2002 *(Continued)*

Subjective outcome measures		
Incomplete outcome data (attrition bias) All outcomes	Low risk	No post-randomisation exclusions or losses at follow-up reported.
Selective reporting (reporting bias)	Unclear risk	Unable to assess.
Other bias	Unclear risk	Unbale to assess.

AB: antibiotics
APH: antepartum haemorrhage
BP: blood pressure
BPM: beats per minute
BPD: bronchopulmonary dysplasia
CCB: calcium channel blocker
D5W: 5% dextrose in water
GA: gestational age
GBS: group B Streptococcus
GTN: glyceryl trinitrate
h/hrs: hour/hours
HVS: high vaginal swab
IM: intramuscular
IUFD: intrauterine fetal death
IUGR: intrauterine growth restriction
IV: intravenous
IVH: intraventricular haemorrhage
LMP: last menstrual period
MgSO4: magnesium sulphate
mg: milligrams
min/mins: minute/minutes
NEC: neonatal necrotising enterocolitis
NICU: neonatal intensive care unit
PDA: patent ductus arteriosus
PIH: pregnancy induced hypertension
po: orally
PPH: postpartum haemorrhage
PROM: premature rupture of membranes
PVL: periventricular leukomalacia
prn: as necessary
q6h: every six hours
RDS: neonatal respiratory distress syndrome
ROM: rupture of membranes
ROP: retinopathy of prematurity
s/l: sublingual
TPL: threatened premature labour
µg: micrograms
WCC: white cell count

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

Study	Reason for exclusion
Al-Omari 2006	Quasi-random allocation to treatment.

Study	Reason for exclusion
Breart 1979	Did not assess a calcium channel blocker (the intervention was ritodrine versus ifenprodit).
Carr 1993	Trial of maintenance tocolytic therapy.
Chawanpaiboon 2011	The comparison group was not another tocolytic.
Dasari 2007	Psychotherapeutic interventions for women in preterm labour.
Dunstan-Boone 1990	Quasi-random allocation to treatment.
El-Sayed 1998	Trial of maintenance tocolytic therapy.
Husslein 2007	Trial comparing atosiban with clinician choice of 1 or more other tocolytics.
Junejo 2008	Quasi-experimental design.
Juon 2008	Pharmacokinetic study of nifedipine.
Maitra 2007	Quasi-random allocation to treatment.
Malik 2007	Quasi-random allocation to treatment.
Meyer 1990	Women were eligible for trial entry only after subcutaneous terbutaline failed to stop regular uterine contractions and the numbers in each group (34 versus 24) raise concerns about the randomisation process.
Papadopoulos 1997	Quasi-random allocation to treatment.
Piovano 1985	Trial tested the addition of a calcium channel blocker for women receiving tocolysis with a betamimetic agent.
Rodriguez-Escudero 1981	Trial tested the addition of a calcium channel blocker for women receiving tocolysis with a betamimetic agent.
Shim 2006	Did not use calcium channel blockers.
Smith 1993	Quasi-random allocation to treatment.

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

Chong 1991

Methods	Controlled study.
Participants	Pregnant women in preterm labour (details not specified).
Interventions	Group 1: nifedipine (doses not specified). Group 2: ritodrine (doses not specified).
Outcomes	Lag time, success rate, Apgar score of neonates before 34 weeks of gestation, maternal cardiovascular side effects.

Chong 1991 *(Continued)*

Notes	Authors have been contacted for additional data and information on method of allocation to the study interventions.

de Heus 2009

Methods	Randomised controlled study.
Participants	40 women between 25-33 weeks' gestation with preterm labour requiring tocolytic treatment not previously treated with tocolytics. Exclusion criteria: multiple pregnancy, severe vaginal bleeding, fetal congenital anomaly and signs of uterine infection.
Interventions	CCB group: nifedipine. Capsules of 10 mg given 4 times 15 min apart followed by 30 mg slow-release at 8 hrs apart up to 48 hrs. ORA group: atosiban. 6.75 mg in 0.9 mL 0.9% sodium chloride (single bolus dose, IV) followed by infusion 300 µg/min in 5% dextrose for 3 hrs, then 100 µg/min in 5% dextrose up to 48 hrs.
Outcomes	Primary outcomes: effects of the tocolytics on fetal heart rate and its variation. Secondary outcomes: effects of the tocolytics on fetal movement and blood flow parameters.
Notes	While the trial was not designed to measure any of the prespecified clinical outcomes of this review, additional outcome data which may be available has been requested from the authors.

Dubay 1992

Methods	Controlled study.
Participants	300 newborns, born to mothers who received nifedipine or isoxsuprine.
Interventions	Group 1: nifedipine (mothers given 30 mg stat orally and then 20 mg 8 hourly for 3 days). Group 2: Isoxsuprine (mothers given 120-150 mg per minute (60 mg/540 mL in 5% dextrose at rate of 15-20 drops per minute and was increased by 50-75 mg per minute every 15 minutes till uterine activity ceased).
Outcomes	Apgar score and birthweight of infants, side effects.
Notes	Authors have been contacted for additional data and methods of allocation to the study interventions.

Haghighi 1999

Methods	Controlled study (random selection).
Participants	74 pregnant women with singleton pregnancies at 23-26 weeks in preterm labour.
Interventions	Group 1: nifedipine (10 mg orally every 20 minutes if contractions persisted, up to a maximal dose of 40 mg during first hour of treatment). If contractions stopped then oral therapy with 20 mg of nifedipine was initiated 6 hrs after the last sublingual capsule and this dose was repeated at 6-hourly intervals during first 24 hrs and 20 mg every 8 hrs on second day.

Haghighi 1999 *(Continued)*

	Group 2: magnesium sulphate (IV loading dose of 6 g over 15 min followed by an infusion of 2 g/hr increasing to a max rate of 4 g/hr as needed to stop contractions for up to 48 hrs. Infusion continued 12 hrs after contractions ceased and then women placed on oral terbutaline 5 mg every 6 hrs. Magnesium sulphate discontinued if contracted persisted > 48 hrs or cervical dilatation > 4 cm.
Outcomes	Arresting uterine contractions, side effects.
Notes	Authors have been contacted for additional data and information on method of allocation to the study interventions.

Lotfalizadeh 2010

Methods	Described as "clinical-trial study" in study abstract.
Participants	80 women in preterm labour (regular contractions < 10 mins apart, with effacement and dilatation unresponsive to pethidine, best rest and fluid therapy) between 26-34 weeks. Setting: "obstetric clinic of Imam Reza and Ghaem hospitals". Exclusion criteria: data limited - abstract available only.
Interventions	CCB group: oral nifedipine. Control group: IV magnesium sulphate.
Outcomes	Efficacy in pregnancy prolongation and adverse drug side effects, cost.
Notes	

Mathew 1997

Methods	Controlled study "random selection".
Participants	60 pregnant women admitted with preterm labour.
Interventions	Group 1: CCB- nifedipine. Group 2: isoxsuprine hydrochloride.
Outcomes	Tocolysis, prolongation of pregnancy (days), maternal side effects, birthweight.
Notes	Authors have been contacted for additional data and information on method of allocation to the study interventions.

Roy 1993

Methods	Controlled trial. Unclear if randomised.
Participants	40 women in preterm labour between 28 and 36 weeks' gestation. Exclusions were: multiple pregnancy, cervical dilation more than 4 cm, and major pregnancy complications.
Interventions	Nifedipine: 5 mg every 8 hrs, followed by 5 mg 12-hourly maintenance until 38 weeks. Isoxsuprine: 10 mg 8 hourly, followed by 10 mg 12 hourly until 38 weeks.

Roy 1993 *(Continued)*

Outcomes	Time from randomisation to birth, birth before 38 weeks, adverse drug reaction, births with malformations, post partum haemorrhage, caesarean section.
Notes	Authors reported that women were randomly allocated but also reported that 20 women received nifedipine and another 20 gravida and gestation period matched women received Isoxsuprine. Authors have been contacted for additional data and information on method of allocation to the study interventions.

Sharma 2000

Methods	"Retrospective randomised controlled trial".
Participants	560 pregnant women having gestational age below 34 weeks, who had established uterine contractions associated with cervical changes & with or without premature rupture of membranes.
Interventions	Group 1: nifedipine orally. Group 2: ritodrine IV.
Outcomes	Prolongation of pregnancy.
Notes	Authors have been contacted for additional data and information on method of allocation to the study interventions.

Sofat 1994

Methods	Randomised prospective study.
Participants	70 pregnant women of preterm labour between 20-35 weeks' gestation.
Interventions	Group 1: IV Isoxsuprine (later IM and then orally 10 mg 8 hourly for 2-3 weeks). Group 2: nifedipine (30 mg stat orally, then 20mg 8 hourly for 3 days).
Outcomes	Suppressant of labour, prolongation of pregnancy, newborn birthweight, side effects.
Notes	Authors have been contacted for additional data and information on method of allocation to the study interventions.

CCB: calcium channel blockers
hrs: hours
IM: intramuscular
IV: intravenous
ORA: oxytocin receptor antagonists

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

APOSTEL III 2011

Trial name or title	APOSTEL III study.
Methods	Multicentre randomised controlled trial. Netherlands.

APOSTEL III 2011 *(Continued)*

Participants	500 pregnant women with threatened preterm labour between 25 and 34 weeks' gestational age.
Interventions	Nifedipine: (dosage 0.10 mg fast acting then in 30 mins 10 mg fast acting, in 60 mins 20 mg nifedipine, then, 20 mg every 6 hrs up to 48 hrs) versus atosiban (dosage: bolus injection of 6.75 mg IV in 1 minute, followed by 18 mg/hour for 3 hrs followed by a maintenance dosage of 6 mg/hour for 45 hrs) for 48 hrs. replace nifedpine dose with: Nifedipine: (dosage 0.10 mg fast acting then in 30mins 10 mg fast acting, in 60 mins 20 mg nifedipine. Then, 20 mg every 6 hrs up to 48 hrs)
Outcomes	The primary outcome of the study will be a composite for poor neonatal outcome. This outcome will include bronchopulmonary dysplasia (BPD), periventricular leukomalacia > grade 1, intracerebral haemorrhage > grade 2, NEC > stage 1, proven sepsis and in-hospital death. Secondary outcomes will be time to delivery, gestational age at delivery, number of days on ventilation support, in NICU and total days of the baby alive outside the hospital counted from a gestational age of 37 weeks and maternal side effects.
Starting date	July 2011. Estimated 36 month recruitment phase and ongoing as at November 2013.
Contact information	Dr. M.A. Oudijk, consultant obstetrician, Dept. of Obstetrics UMC Utrecht. E-mail:m.a.oudijk-3@umcutrecht.nl
Notes	Registered in *Dutch consortium for studies in women's health and reproductivity*. http://www.studies-obsgyn.nl/home/page.asp?page_id=326

Gonzalez 2011

Trial name or title	Administration of Nifidepine versus Atosiban in pregnant women with a threat of premature labour.
Methods	Randomised trial, standard parallel design.
Participants	Pregnant women in the 24th and 33+6th weeks of pregnancy with threatened preterm labour according to the American College of Obstetricians and Gynaecologists (ACOG's) criteria. Setting: Hospital Clinico Universitario de Santiago, Spain. Exclusion criteria: prior treatment with magnesium sulphate or a different tocolytic, major fetal malformations, various maternal complications (e.g. chorioamnionitis, premature rupture of membranes, severe hypertensive disorder).
Interventions	Experimental group: nifedipine. Initial dose - 10 mg oral capsules and maintenance dose of 20 mg every 6 hrs (2 x 10 mg capsules). Control group: IV atosiban. Initial dose - bolus injection during 1 minute plus IV infusion of 7.5 mg/mL during 3 hrs, followed by maintenance with IV infusion 7.5 mg/mL at least 18 hrs to a maximum of 45 hrs. Treatment administered for a maximum of 48 hrs for both groups.
Outcomes	Maternal: Prolongation of pregnancy, duration and type of labour, adverse drug side effects Neonatal: Intracranial haemorrhage, RDS, NEC, ROP.
Starting date	July 2011.
Contact information	Manuel Macía Cortiñas: manuel.macia.cortinas@sergas.es / María Teresa Oreiro García: maria.teresa.oreiro.garcia@sergas.es

Gonzalez 2011 *(Continued)*

Notes	Study not yet open for participant recruitment.

Snyder 1989

Trial name or title	Controlled trial.
Methods	Not specified.
Participants	Women in preterm labour.
Interventions	Nifedipine vs magnesium sulphate.
Outcomes	
Starting date	
Contact information	
Notes	Notification of an ongoing trial. No details of outcome have been found.

Vis 2009

Trial name or title	Cost-effectiveness of fibronectin testing in a triage in women with threatened preterm labour: alleviation of pregnancy outcome by suspending tocolysis in early labour (APOSTEL-I trial).
Methods	Randomised controlled trial.
Participants	Women in preterm labour, with intact membranes, between 24-34 weeks' gestation. Those with a short cervix (10-30 mm) and negative fibronectin will be enrolled in a randomised controlled trial of nifedipine compared with placebo.
Interventions	CCB group: nifedipine 80-120 mg over 24 hrs for total of 48 hrs. Control group: placebo given at same time as nifedipine dosing for 48 hrs. Both groups: corticosteroids given at attending physician's discretion.
Outcomes	Number of days to delivery truncated at 7 days after trial entry (primary), neonatal mortality and morbidity, maternal drug side effects, health-related quality of life, cost (secondary).
Starting date	Not stated. Protocol submitted to journal July 2009.
Contact information	Jolande Y Vis: j.y.vis@amc.nl
Notes	

CCB: calcium channel blockers
dd:
hrs: hours
IV: intravenous
NEC: necrotising enterocolitis
RDS: respiratory distress syndrome
ROP: retinopathy of prematurity

NICU: neonatal intersive care unit
VS: versus

DATA AND ANALYSES

Comparison 1. Calcium channel blockers compared with placebo or no treatment

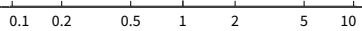
Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Birth within 48 hours after trial entry	2	173	Risk Ratio (M-H, Fixed, 95% CI)	0.30 [0.21, 0.43]
2 Preterm birth (before completion of 37 weeks of gestation)	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3 Maternal adverse effects	1	89	Risk Ratio (M-H, Fixed, 95% CI)	49.89 [3.13, 795.02]

Analysis 1.1. Comparison 1 Calcium channel blockers compared with placebo or no treatment, Outcome 1 Birth within 48 hours after trial entry.

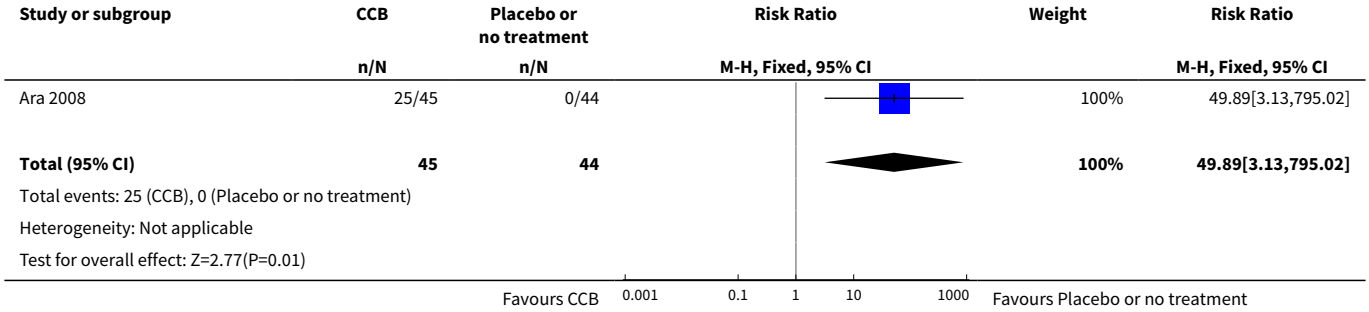
Study or subgroup	CCB	Placebo or no treatment	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Fixed, 95% CI		M-H, Fixed, 95% CI
Ara 2008	10/45	39/44		56.26%	0.25[0.14,0.44]
Zhang 2002	17/56	23/28		43.74%	0.37[0.24,0.57]
Total (95% CI)	**101**	**72**		**100%**	**0.3[0.21,0.43]**
Total events: 27 (CCB), 62 (Placebo or no treatment)					
Heterogeneity: Tau^2=0; Chi^2=1.26, df=1(P=0.26); I^2=20.47%					
Test for overall effect: Z=6.63(P<0.0001)					

Analysis 1.2. Comparison 1 Calcium channel blockers compared with placebo or no treatment, Outcome 2 Preterm birth (before completion of 37 weeks of gestation).

Study or subgroup	CCB	Placebo or no treatment	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Fixed, 95% CI		M-H, Fixed, 95% CI
Ara 2008	43/45	44/44		0%	0.96[0.89,1.03]
Zhang 2002	22/56	25/28		0%	0.44[0.31,0.62]



Analysis 1.3. Comparison 1 Calcium channel blockers compared with placebo or no treatment, Outcome 3 Maternal adverse effects.



Comparison 2. Calcium channel blockers compared with any other tocolytic agent (subgrouped by other tocolytic)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Birth less than 48 hours after trial entry	28		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 CCB versus betamimetics	19	1505	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.67, 1.10]
1.2 CCB versus glyceryl trinitrate (GTN) patch	1	53	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.22, 3.66]
1.3 CCB versus oxytocin receptor antagonists	2	225	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.37, 2.30]
1.4 CCB versus non-steroidal anti-inflammatory drugs	2	218	Risk Ratio (M-H, Random, 95% CI)	0.63 [0.29, 1.41]
1.5 CCB versus magnesium sulphate	5	651	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.61, 1.13]
2 Very preterm birth (before completion of 34 weeks of gestation)	11		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 CCB versus betamimetics	6	630	Risk Ratio (M-H, Fixed, 95% CI)	0.78 [0.66, 0.93]
2.2 CCB versus magnesium sulphate	4	429	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.76, 1.20]
2.3 CCB versus oxytocin receptor antagonists	1	145	Risk Ratio (M-H, Fixed, 95% CI)	0.59 [0.31, 1.12]
2.4 CCB versus non-steroidal anti-inflammatory drugs	1	139	Risk Ratio (M-H, Fixed, 95% CI)	1.10 [0.86, 1.42]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3 Perinatal mortality (stillbirth and neonatal death up to 28 days)	23	2129	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.53, 1.22]
3.1 CCB versus betamimetics	17	1233	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.52, 1.38]
3.2 CCB versus magnesium sulphate	5	657	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.36, 3.13]
3.3 CCB versus non-steroidal anti-inflammatory drugs	2	239	Risk Ratio (M-H, Fixed, 95% CI)	0.39 [0.10, 1.51]
4 Stillbirth	18		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 CCB versus betamimetics	13	934	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.15, 7.23]
4.2 CCB versus magnesium sulphate	5	657	Risk Ratio (M-H, Fixed, 95% CI)	2.39 [0.10, 57.18]
4.3 CCB versus non-steroidal anti-inflammatory drugs	1	160	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
5 Neonatal death	22		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 CCB versus betamimetics	15	1068	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.53, 1.75]
5.2 CCB versus magnesium sulphate	5	657	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.30, 3.00]
5.3 CCB versus oxytocin receptor antagonists	1	179	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
5.4 CCB versus non-steroidal anti-inflammatory drugs	2	239	Risk Ratio (M-H, Fixed, 95% CI)	0.39 [0.10, 1.51]
6 Maternal death	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.1 CCB versus magnesium sulphate	1	137	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.2 CCB versus non-steroidal anti-inflammatory drugs	1	139	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
7 Interval between trial entry and birth (days)	13		Mean Difference (IV, Random, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7.1 CCB versus betamimetics	10	830	Mean Difference (IV, Random, 95% CI)	4.38 [0.25, 8.52]
7.2 CCB versus magnesium sulphate	2	212	Mean Difference (IV, Random, 95% CI)	-1.63 [-8.80, 5.54]
7.3 CCB versus oxytocin receptor antagonists	1	145	Mean Difference (IV, Random, 95% CI)	5.70 [-0.96, 12.36]
8 Gestational age at birth (completed weeks)	20		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
8.1 CCB versus betamimetics	14	1063	Mean Difference (IV, Fixed, 95% CI)	0.71 [0.34, 1.09]
8.2 CCB versus magnesium sulphate	5	651	Mean Difference (IV, Fixed, 95% CI)	0.15 [-0.22, 0.52]
8.3 CCB versus oxytocin receptor antagonists	1	145	Mean Difference (IV, Fixed, 95% CI)	1.20 [0.25, 2.15]
8.4 CCB versus non-steroidal anti-inflammatory drugs	1	139	Mean Difference (IV, Fixed, 95% CI)	0.0 [-1.51, 1.51]
9 Preterm birth (before completion of 37 weeks of gestation)	18		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
9.1 CCB versus betamimetics	13	1111	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.80, 0.98]
9.2 CCB versus magnesium sulphate	4	499	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.81, 1.06]
9.3 CCB versus oxytocin receptor antagonists	1	145	Risk Ratio (M-H, Fixed, 95% CI)	0.64 [0.47, 0.89]
9.4 CCB versus non-steroidal anti-inflammatory drugs	1	139	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.78, 1.06]
10 Extremely preterm birth (before completion of 28 weeks of gestation)	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
10.1 CCB versus oxytocin receptor antagonists	1	145	Risk Ratio (M-H, Fixed, 95% CI)	0.47 [0.04, 5.03]
11 Apgar score < 7 at 5 minutes	9		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
11.1 CCB versus betamimetics	6	557	Risk Ratio (M-H, Fixed, 95% CI)	0.53 [0.26, 1.06]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
11.2 CCB versus magnesium sulphate	2	217	Risk Ratio (M-H, Fixed, 95% CI)	1.10 [0.48, 2.51]
11.3 CCB versus oxytocin receptor antagonists	1	179	Risk Ratio (M-H, Fixed, 95% CI)	1.85 [0.17, 20.03]
12 Admission to NICU	15		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
12.1 CCB versus betamimetics	12	999	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.63, 0.87]
12.2 CCB versus magnesium sulphate	2	331	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.48, 2.08]
12.3 CCB versus oxytocin receptor antagonists	1	179	Risk Ratio (M-H, Random, 95% CI)	0.59 [0.41, 0.85]
13 Respiratory distress syndrome	21		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
13.1 CCB versus betamimetics	16	1293	Risk Ratio (M-H, Fixed, 95% CI)	0.64 [0.48, 0.86]
13.2 CCB versus magnesium sulphate	4	577	Risk Ratio (M-H, Fixed, 95% CI)	0.76 [0.56, 1.05]
13.3 CCB versus oxytocin receptor antagonists	1	179	Risk Ratio (M-H, Fixed, 95% CI)	0.72 [0.28, 1.85]
13.4 CCB versus non-steroidal anti-inflammatory drugs	1	160	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.45, 1.13]
14 Chronic lung disease	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
14.1 CCB versus betamimetics	1	91	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
15 Necrotising enterocolitis	8		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
15.1 CCB versus betamimetics	5	490	Risk Ratio (M-H, Fixed, 95% CI)	0.21 [0.05, 0.96]
15.2 CCB versus magnesium sulphate	2	360	Risk Ratio (M-H, Fixed, 95% CI)	0.64 [0.13, 3.20]
15.3 CCB versus oxytocin receptor antagonists	1	179	Risk Ratio (M-H, Fixed, 95% CI)	0.10 [0.01, 1.88]
15.4 CCB versus non-steroidal anti-inflammatory drugs	1	160	Risk Ratio (M-H, Fixed, 95% CI)	0.68 [0.14, 3.42]
16 Neonatal sepsis	10		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
16.1 CCB versus betamimetics	7	618	Risk Ratio (M-H, Fixed, 95% CI)	0.72 [0.47, 1.11]
16.2 CCB versus magnesium sulphate	2	360	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.31, 1.63]
16.3 CCB versus oxytocin receptor antagonists	1	179	Risk Ratio (M-H, Fixed, 95% CI)	1.39 [0.24, 8.10]
16.4 CCB versus non-steroidal anti-inflammatory drugs	1	160	Risk Ratio (M-H, Fixed, 95% CI)	0.66 [0.25, 1.75]
17 Neonatal jaundice	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
17.1 CCB versus betamimetics	3	334	Risk Ratio (M-H, Fixed, 95% CI)	0.72 [0.57, 0.92]
18 Intraventricular haemorrhage	10		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
18.1 CCB versus betamimetics	7	596	Risk Ratio (M-H, Fixed, 95% CI)	0.53 [0.34, 0.84]
18.2 CCB versus magnesium sulphate	2	360	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.30, 1.69]
18.3 CCB versus oxytocin receptor antagonists	1	179	Risk Ratio (M-H, Fixed, 95% CI)	0.46 [0.09, 2.46]
18.4 CCB versus non-steroidal anti-inflammatory drugs	1	160	Risk Ratio (M-H, Fixed, 95% CI)	0.61 [0.23, 1.61]
19 Intraventricular haemorrhage grades 3 or 4	6		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
19.1 CCB versus betamimetics	6	560	Risk Ratio (M-H, Fixed, 95% CI)	0.63 [0.23, 1.74]
20 Periventricular leukomalacia (PVL)	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
20.1 CCB versus magnesium sulphate	1	151	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
20.2 CCB versus non-steroidal anti-inflammatory drugs	1	160	Risk Ratio (M-H, Fixed, 95% CI)	0.34 [0.02, 6.96]
21 Retinopathy of prematurity	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
21.1 CCB versus betamimetics	2	276	Risk Ratio (M-H, Fixed, 95% CI)	0.15 [0.02, 1.28]
21.2 CCB versus oxytocin receptor antagonists	1	179	Risk Ratio (M-H, Fixed, 95% CI)	0.46 [0.04, 5.01]
22 Maternal adverse effects	24		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
22.1 CCB versus betamimetics	15	1305	Risk Ratio (M-H, Random, 95% CI)	0.36 [0.24, 0.53]
22.2 CCB versus magnesium sulphate	5	604	Risk Ratio (M-H, Random, 95% CI)	0.52 [0.40, 0.68]
22.3 CCB versus oxytocin receptor antagonists	2	225	Risk Ratio (M-H, Random, 95% CI)	2.61 [1.43, 4.74]
22.4 CCB versus non-steroidal anti-inflammatory drugs	1	79	Risk Ratio (M-H, Random, 95% CI)	1.51 [0.81, 2.79]
22.5 CCB versus glyceryl trinitrate (GTN) patch	1	50	Risk Ratio (M-H, Random, 95% CI)	0.60 [0.23, 1.54]
23 Discontinuation of therapy for maternal adverse effects	20		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
23.1 CCB versus betamimetics	16	1217	Risk Ratio (M-H, Random, 95% CI)	0.22 [0.10, 0.48]
23.2 CCB versus magnesium sulphate	3	339	Risk Ratio (M-H, Random, 95% CI)	1.61 [0.10, 25.91]
23.3 CCB versus oxytocin receptor antagonists	1	145	Risk Ratio (M-H, Random, 95% CI)	2.80 [0.12, 67.68]
23.4 CCB versus non-steroidal anti-inflammatory drugs	1	139	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.22, 3.20]
24 Caesarean section	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
24.1 CCB versus betamimetics	1	107	Risk Ratio (M-H, Fixed, 95% CI)	0.72 [0.38, 1.38]
24.2 CCB versus oxytocin receptor antagonists	1	145	Risk Ratio (M-H, Fixed, 95% CI)	0.75 [0.21, 2.67]
25 Duration of stay in NICU (days)	3		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
25.1 CCB versus magnesium sulphate	2	360	Mean Difference (IV, Fixed, 95% CI)	-4.55 [-8.17, -0.92]

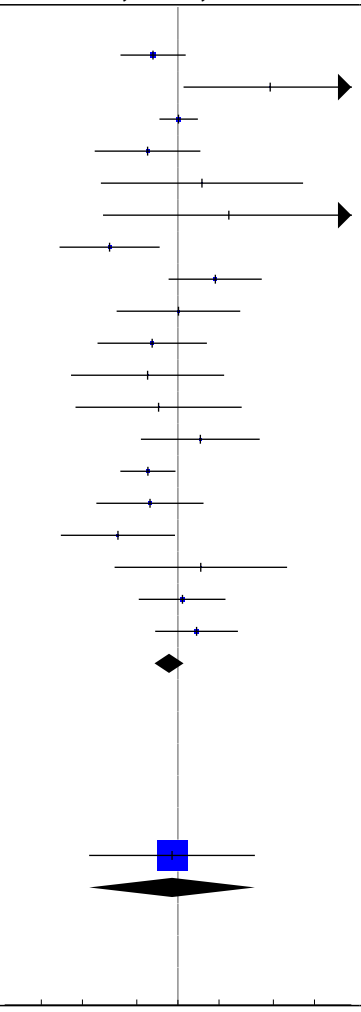
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
25.2 CCB versus oxytocin receptor antagonists	1	179	Mean Difference (IV, Fixed, 95% CI)	-5.4 [-10.84, 0.04]
25.3 CCB versus non-steroidal anti-inflammatory drugs	1	160	Mean Difference (IV, Fixed, 95% CI)	3.60 [-8.27, 15.47]
26 Duration of maternal hospital stay (days)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
26.1 CCB versus betamimetics	1	52	Mean Difference (IV, Fixed, 95% CI)	0.18 [-1.04, 1.40]
27 Behavioural-emotional problems at 9-12 years	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
27.1 CCB versus betamimetics	1	95	Mean Difference (IV, Fixed, 95% CI)	-2.0 [-6.42, 2.42]
28 Special education at 9-12 years	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
28.1 CCB versus betamimetics	1	96	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.19, 3.45]
29 Motor quality at 9-12 years	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
29.1 CCB versus betamimetics	1	79	Mean Difference (IV, Fixed, 95% CI)	-4.30 [-9.96, 1.36]
30 Quality of life at 9-12 years: physical	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
30.1 CCB versus betamimetics	1	94	Mean Difference (IV, Fixed, 95% CI)	-1.0 [-3.00, 1.00]
30.2 Motor	1	94	Mean Difference (IV, Fixed, 95% CI)	0.0 [-1.15, 1.15]
30.3 Autonomy	1	94	Mean Difference (IV, Fixed, 95% CI)	0.0 [-0.57, 0.57]
30.4 Cognitive	1	94	Mean Difference (IV, Fixed, 95% CI)	0.0 [-1.58, 1.58]
30.5 Social	1	94	Mean Difference (IV, Fixed, 95% CI)	0.0 [-0.99, 0.99]
30.6 Positive emotion	1	94	Mean Difference (IV, Fixed, 95% CI)	-1.0 [-2.04, 0.04]
30.7 Negative emotion	1	94	Mean Difference (IV, Fixed, 95% CI)	-1.0 [-2.02, 0.02]
31 Quality of life at 9-12 years: motor	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
31.1 CCB versus betamimetics	1	94	Mean Difference (IV, Fixed, 95% CI)	0.0 [-1.15, 1.15]

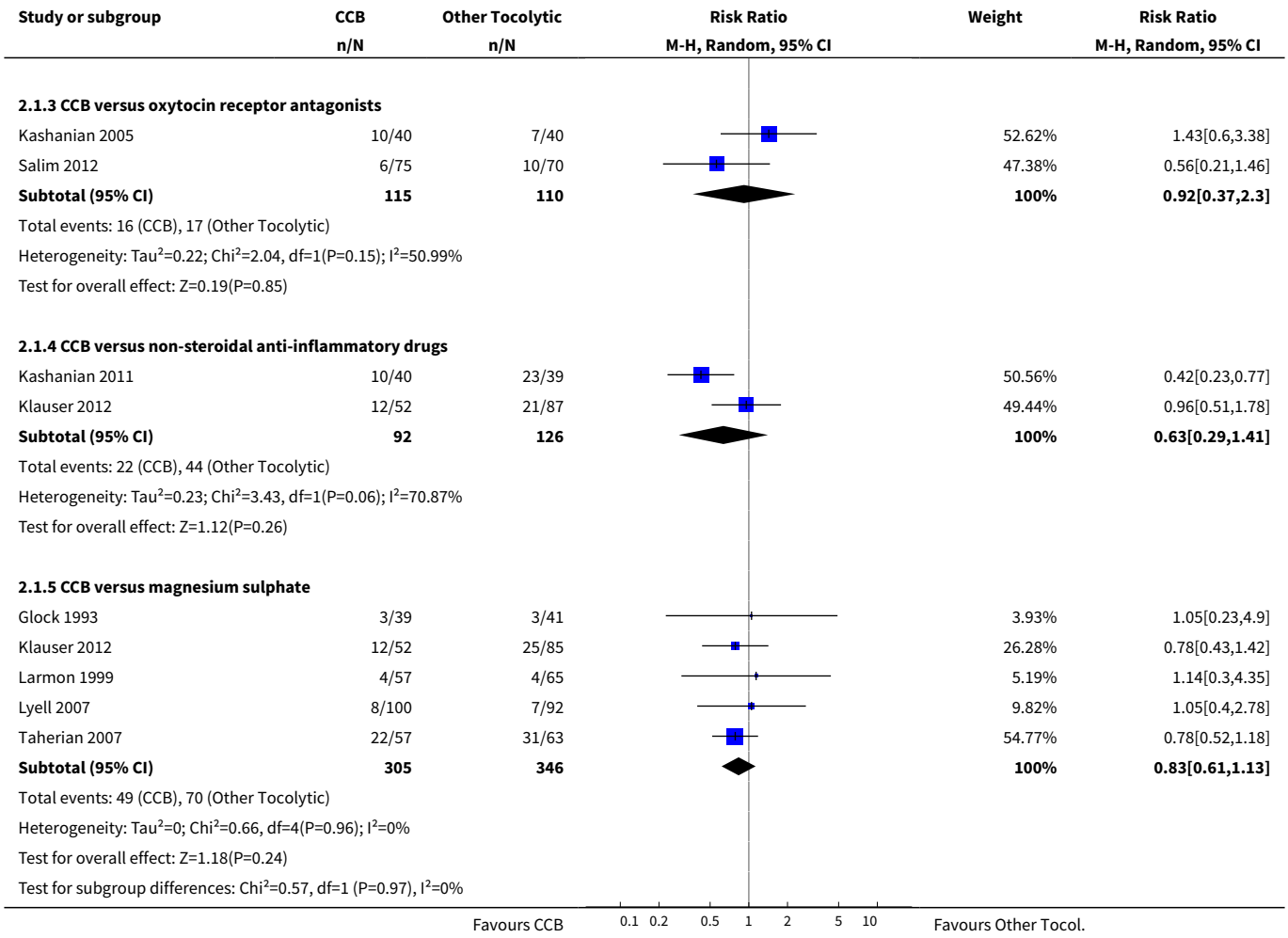
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
31.2 Autonomy	1	94	Mean Difference (IV, Fixed, 95% CI)	0.0 [-0.57, 0.57]
31.3 Cognitive	1	94	Mean Difference (IV, Fixed, 95% CI)	0.0 [-1.58, 1.58]
31.4 Social	1	94	Mean Difference (IV, Fixed, 95% CI)	0.0 [-0.99, 0.99]
31.5 Positive emotion	1	94	Mean Difference (IV, Fixed, 95% CI)	-1.0 [-2.04, 0.04]
31.6 Negative emotion	1	94	Mean Difference (IV, Fixed, 95% CI)	-1.0 [-2.02, 0.02]
32 Quality of life at 9-12 years: autonomy	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
32.1 CCB versus betamimetics	1	94	Mean Difference (IV, Fixed, 95% CI)	0.0 [-0.57, 0.57]
32.2 Cognitive	1	94	Mean Difference (IV, Fixed, 95% CI)	0.0 [-1.58, 1.58]
32.3 Social	1	94	Mean Difference (IV, Fixed, 95% CI)	0.0 [-0.99, 0.99]
32.4 Positive emotion	1	94	Mean Difference (IV, Fixed, 95% CI)	-1.0 [-2.04, 0.04]
32.5 Negative emotion	1	94	Mean Difference (IV, Fixed, 95% CI)	-1.0 [-2.02, 0.02]
33 Quality of life at 9-12 years: cognitive	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
33.1 CCB versus betamimetics	1	94	Mean Difference (IV, Fixed, 95% CI)	0.0 [-1.58, 1.58]
33.2 Social	1	94	Mean Difference (IV, Fixed, 95% CI)	0.0 [-0.99, 0.99]
33.3 Positive emotion	1	94	Mean Difference (IV, Fixed, 95% CI)	-1.0 [-2.04, 0.04]
33.4 Negative emotion	1	94	Mean Difference (IV, Fixed, 95% CI)	-1.0 [-2.02, 0.02]
34 Quality of life at 9-12 years: social	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
34.1 CCB versus betamimetics	1	94	Mean Difference (IV, Fixed, 95% CI)	0.0 [-0.99, 0.99]
34.2 Positive emotion	1	94	Mean Difference (IV, Fixed, 95% CI)	-1.0 [-2.04, 0.04]
34.3 Negative emotion	1	94	Mean Difference (IV, Fixed, 95% CI)	-1.0 [-2.02, 0.02]
35 Quality of life at 9-12 years: positive emotion	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
35.1 CCB versus betamimetics	1	94	Mean Difference (IV, Fixed, 95% CI)	-1.0 [-2.04, 0.04]
35.2 Negative emotion	1	94	Mean Difference (IV, Fixed, 95% CI)	-1.0 [-2.02, 0.02]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
36 Quality of life at 9-12 years: negative emotion	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
36.1 CCB versus betamimetics	1	94	Mean Difference (IV, Fixed, 95% CI)	-1.0 [-2.02, 0.02]
37 Parent distress scores at 9-12 years	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
37.1 CCB versus betamimetics	1	96	Mean Difference (IV, Fixed, 95% CI)	-1.0 [-9.25, 7.25]

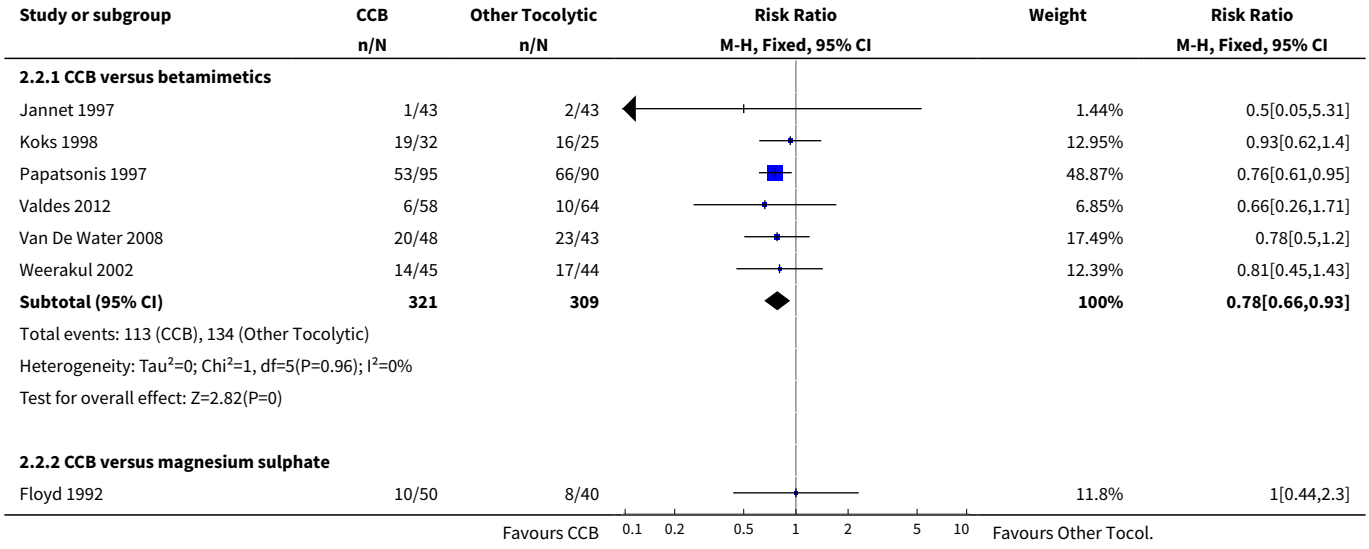
Analysis 2.1. Comparison 2 Calcium channel blockers compared with any other tocolytic agent (subgrouped by other tocolytic), Outcome 1 Birth less than 48 hours after trial entry.

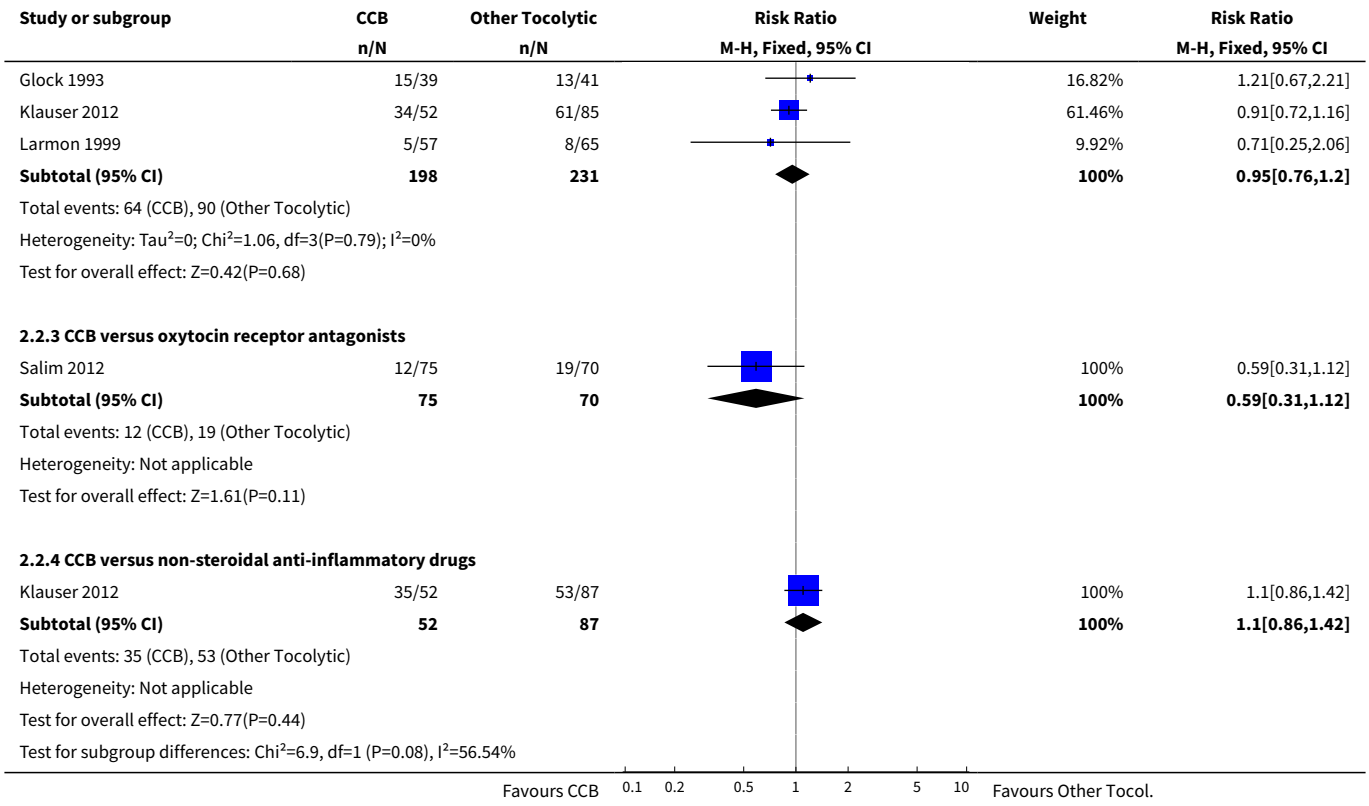
Study or subgroup	CCB n/N	Other Tocolytic n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
2.1.1 CCB versus betamimetics					
Al-Qattan 2000	12/30	14/23		9.12%	0.66[0.38,1.14]
Cararach 2006	9/37	2/39		2.4%	4.74[1.1,20.52]
Fan 2003	22/31	21/30		12.93%	1.01[0.73,1.4]
Ferguson 1990	6/33	10/33		5.22%	0.6[0.25,1.46]
Garcia-Velasco 1998	3/26	2/26		1.84%	1.5[0.27,8.25]
George 1991	3/14	1/11		1.23%	2.36[0.28,19.66]
Jaju 2011	6/60	19/60		5.59%	0.32[0.14,0.74]
Koks 1998	15/32	6/24		6.15%	1.88[0.86,4.11]
Kose 1995	10/52	4/21		4.15%	1.01[0.36,2.86]
Kupferminc 1993	6/36	9/35		4.96%	0.65[0.26,1.63]
Laohapojanart 2007	3/20	5/20		2.96%	0.6[0.17,2.18]
Mawaldi 2008	3/79	5/95		2.59%	0.72[0.18,2.93]
Padovani 2012	7/24	5/25		4.4%	1.46[0.54,3.97]
Papatsonis 1997	21/95	33/90		10.44%	0.6[0.38,0.96]
Rayamajhi 2003	6/32	9/30		5.09%	0.63[0.25,1.54]
Read 1986	4/20	11/20		4.67%	0.36[0.14,0.95]
Valdes 2012	4/58	3/64		2.42%	1.47[0.34,6.3]
Van De Water 2008	12/48	10/43		6.72%	1.08[0.52,2.23]
Weerakul 2002	14/45	10/44		7.11%	1.37[0.68,2.75]
Subtotal (95% CI)	**772**	**733**		**100%**	**0.86[0.67,1.1]**
Total events: 166 (CCB), 179 (Other Tocolytic)					
Heterogeneity: Tau^2=0.09; Chi^2=28.52, df=18(P=0.05); I^2=36.9%					
Test for overall effect: Z=1.19(P=0.23)					
2.1.2 CCB versus glyceryl trinitrate (GTN) patch					
Amorim 2009	3/24	4/29		100%	0.91[0.22,3.66]
Subtotal (95% CI)	**24**	**29**		**100%**	**0.91[0.22,3.66]**
Total events: 3 (CCB), 4 (Other Tocolytic)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.14(P=0.89)					



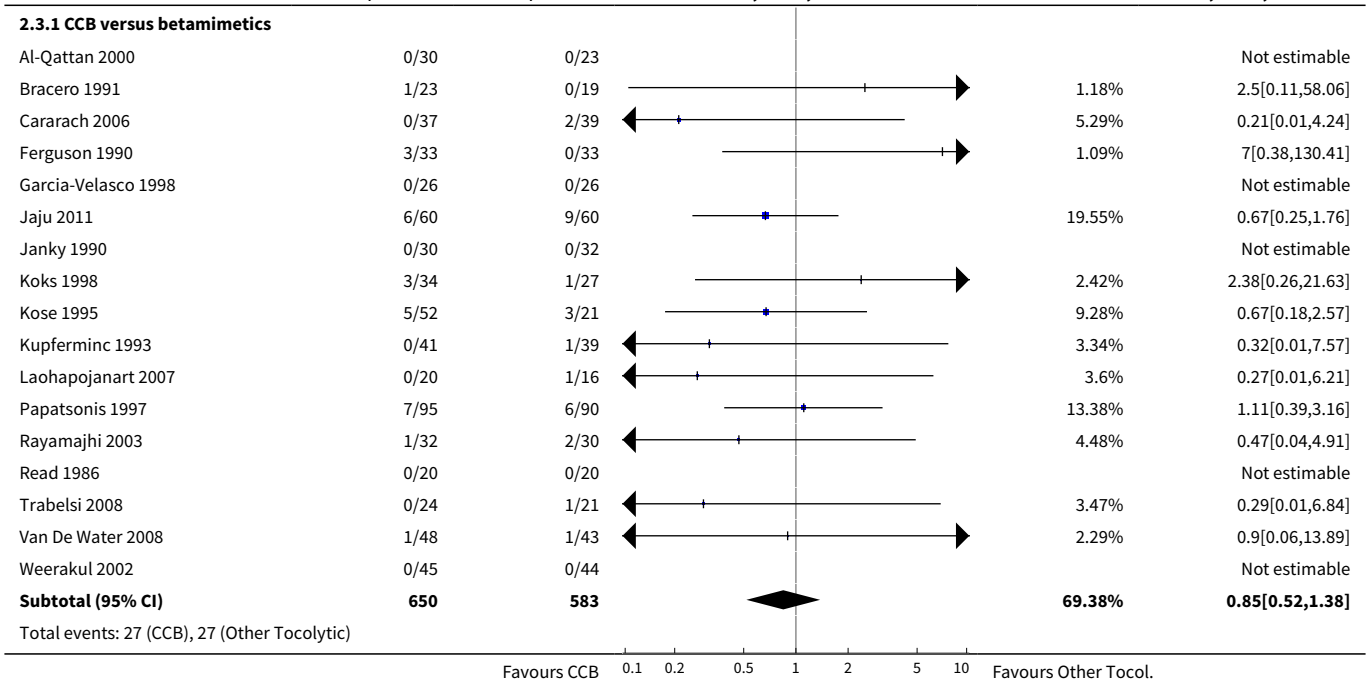


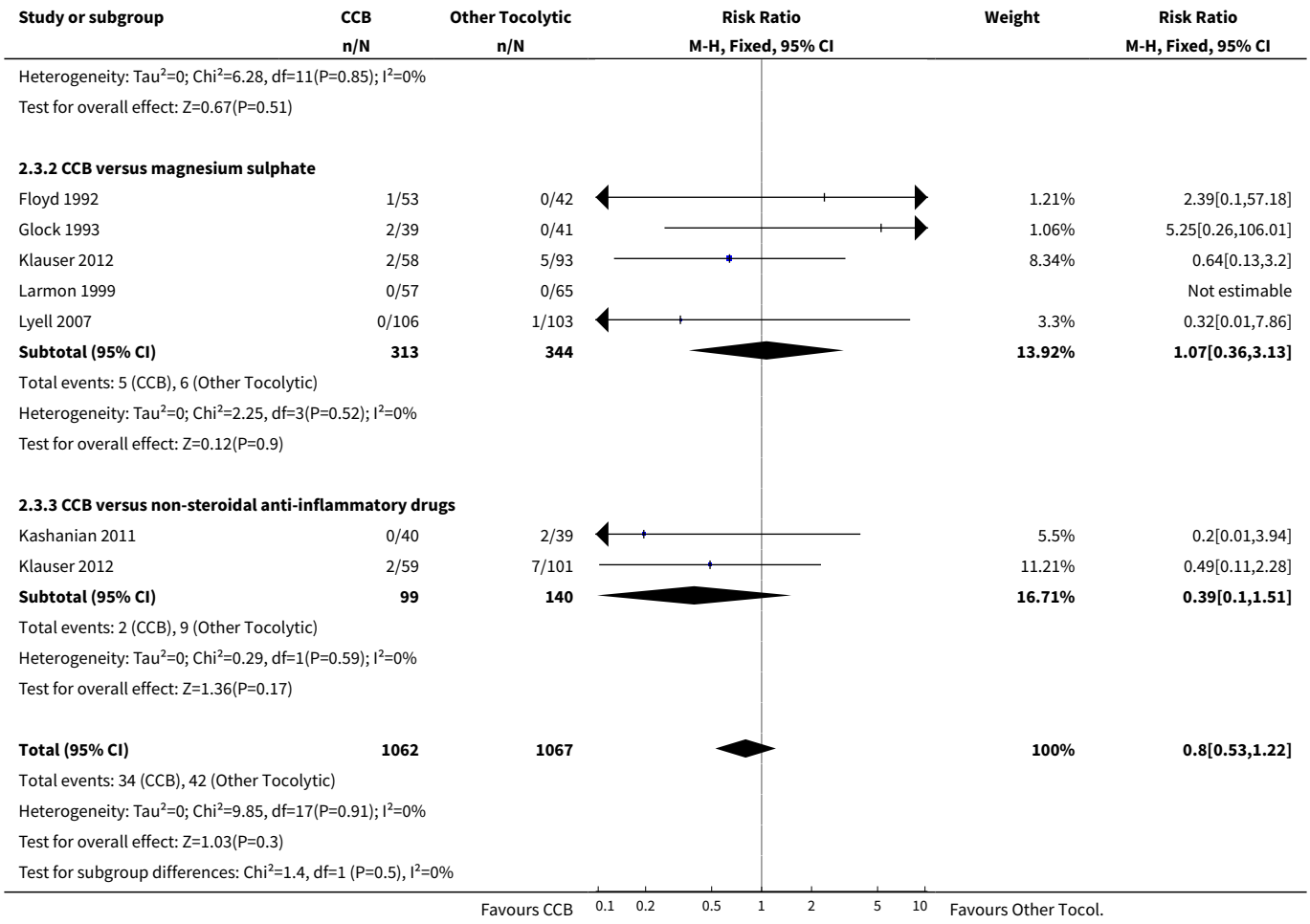
Analysis 2.2. Comparison 2 Calcium channel blockers compared with any other tocolytic agent (subgrouped by other tocolytic), Outcome 2 Very preterm birth (before completion of 34 weeks of gestation).



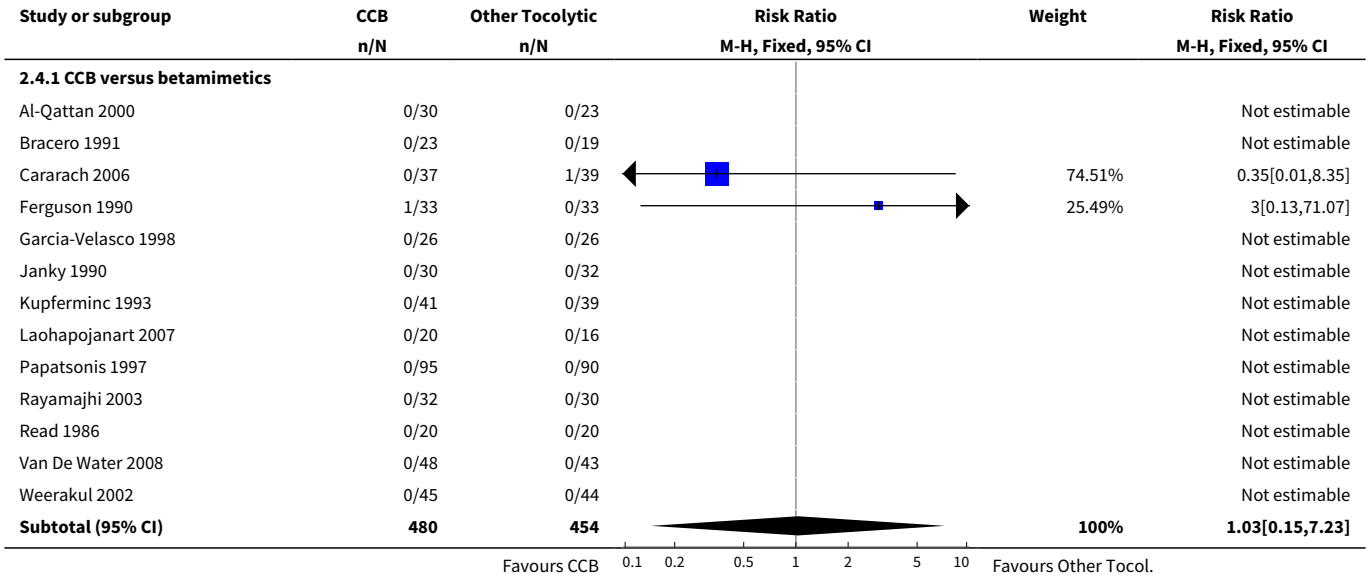


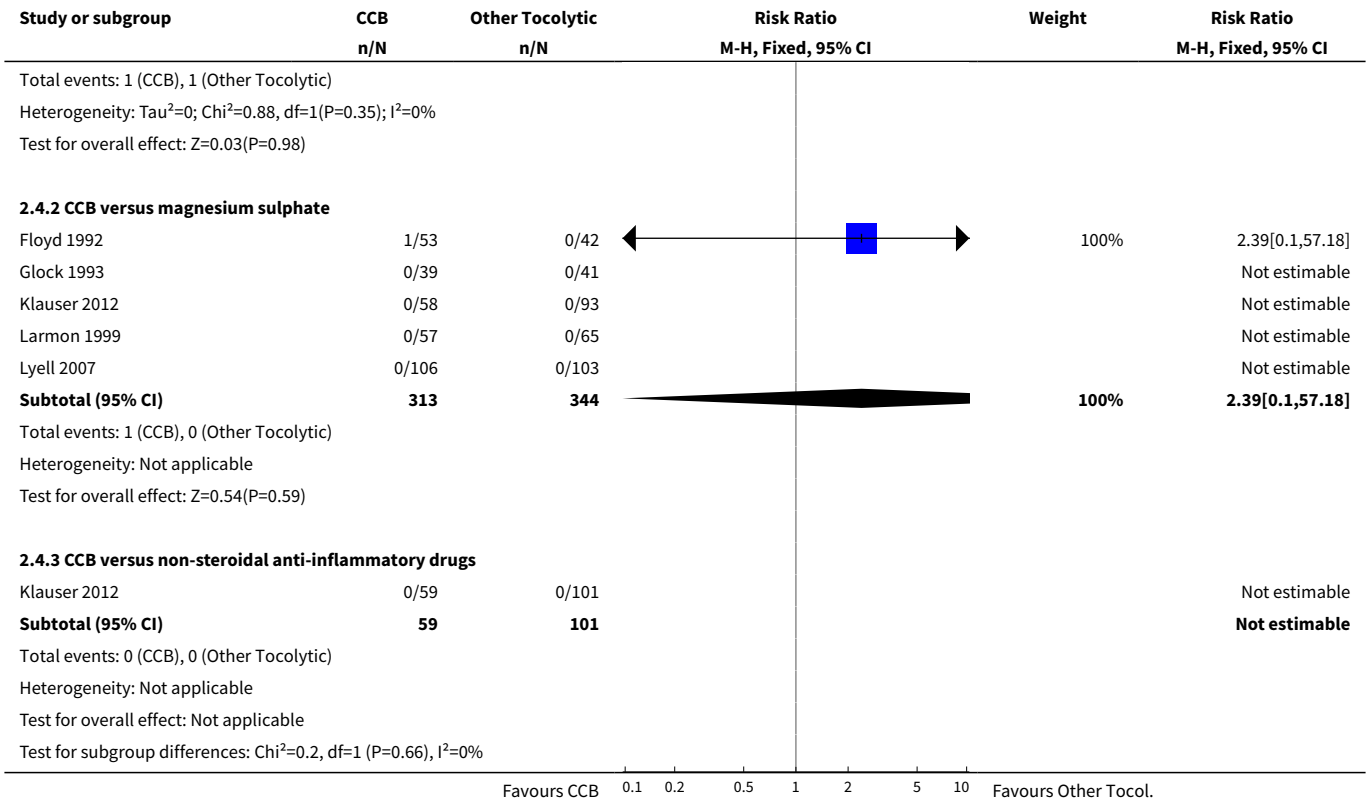
Analysis 2.3. Comparison 2 Calcium channel blockers compared with any other tocolytic agent (subgrouped by other tocolytic), Outcome 3 Perinatal mortality (stillbirth and neonatal death up to 28 days).



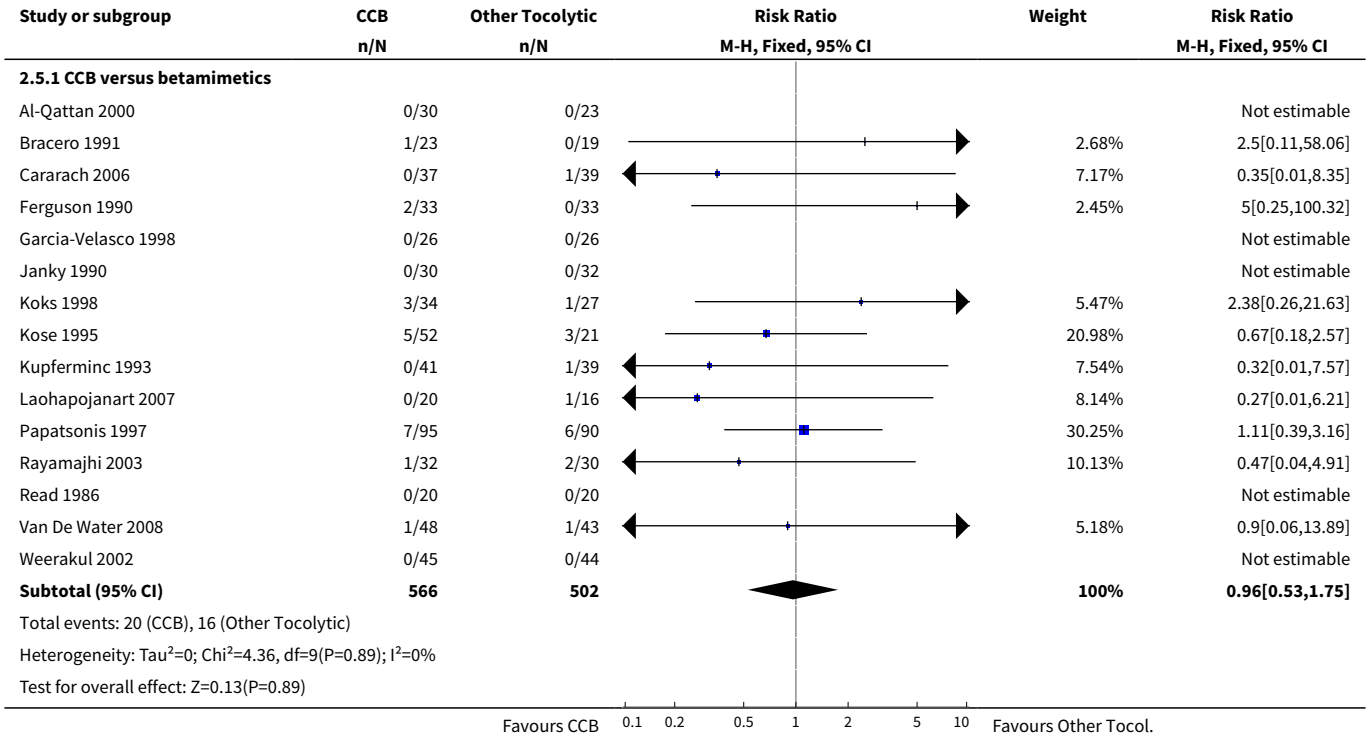


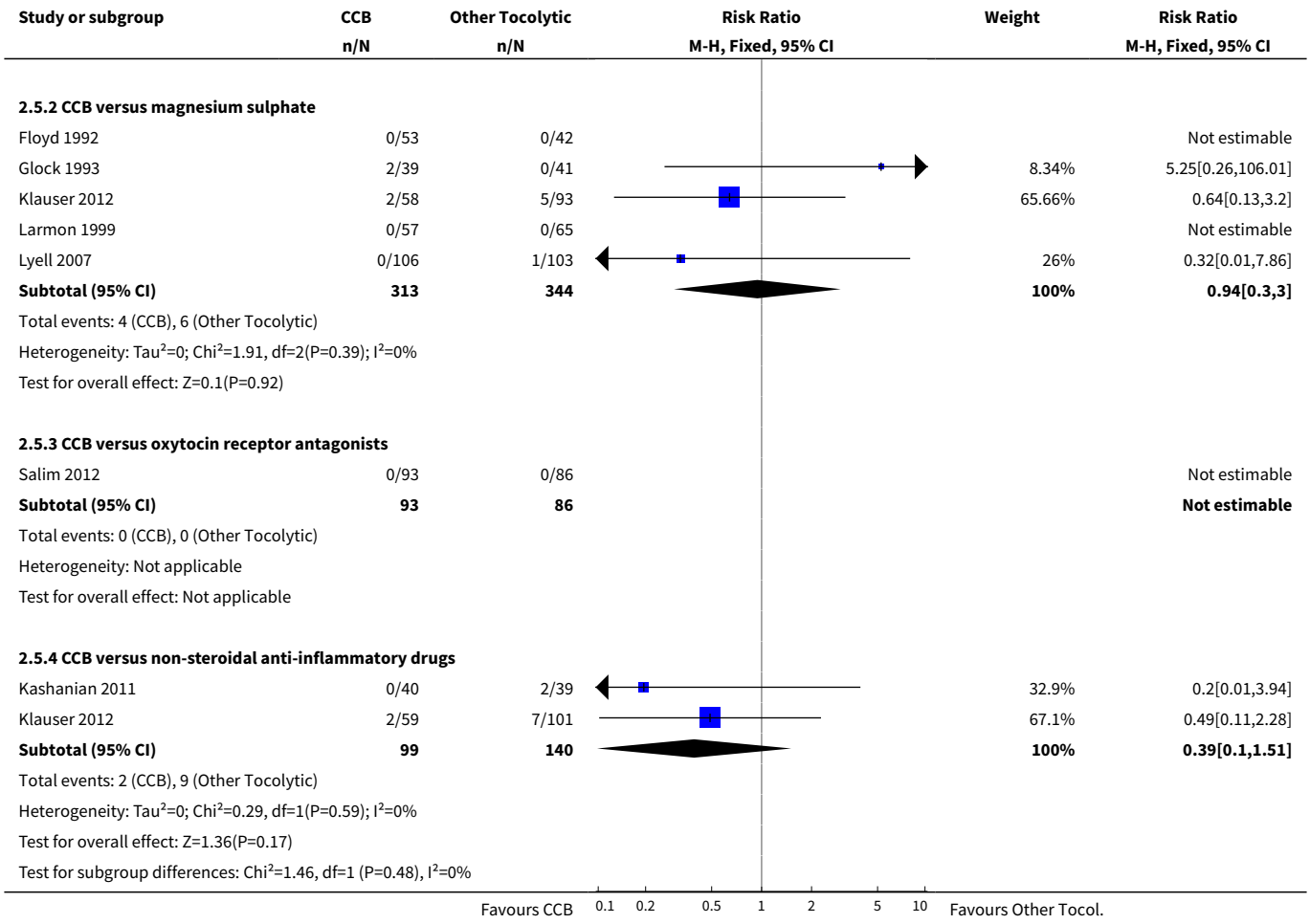
Analysis 2.4. Comparison 2 Calcium channel blockers compared with any other tocolytic agent (subgrouped by other tocolytic), Outcome 4 Stillbirth.



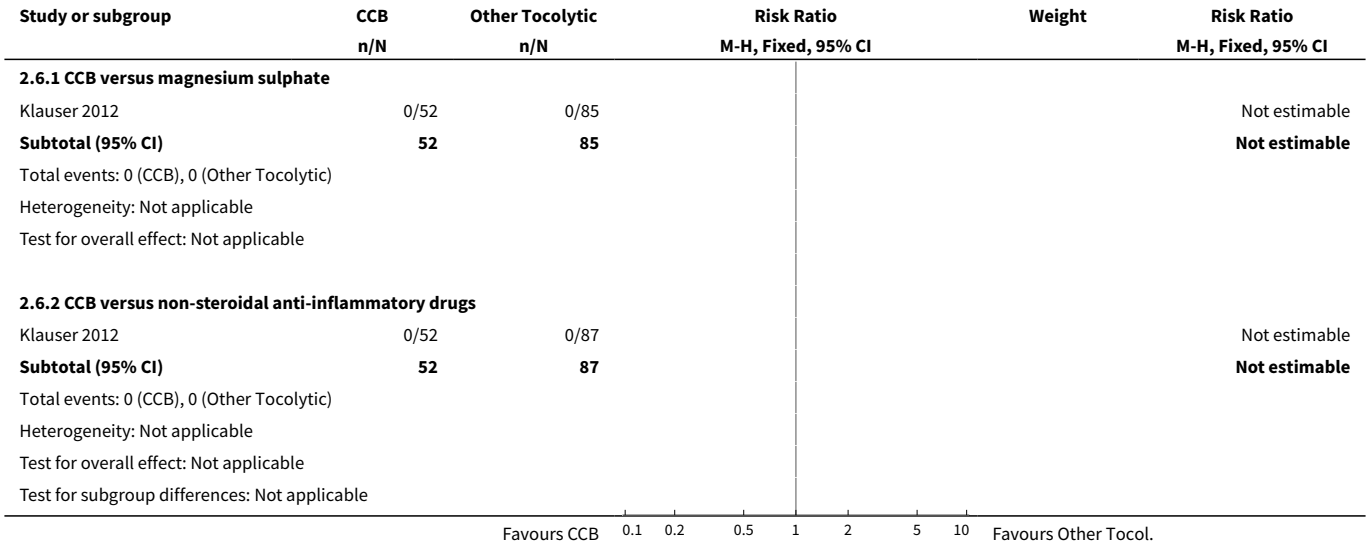


Analysis 2.5. Comparison 2 Calcium channel blockers compared with any other tocolytic agent (subgrouped by other tocolytic), Outcome 5 Neonatal death.



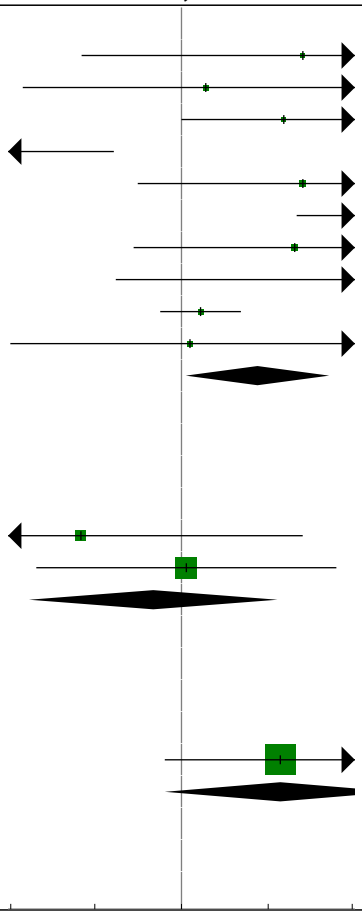


Analysis 2.6. Comparison 2 Calcium channel blockers compared with any other tocolytic agent (subgrouped by other tocolytic), Outcome 6 Maternal death.



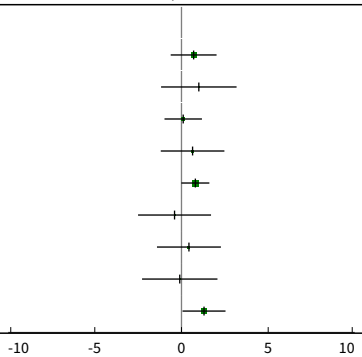
Analysis 2.7. Comparison 2 Calcium channel blockers compared with any other tocolytic agent (subgrouped by other tocolytic), Outcome 7 Interval between trial entry and birth (days).

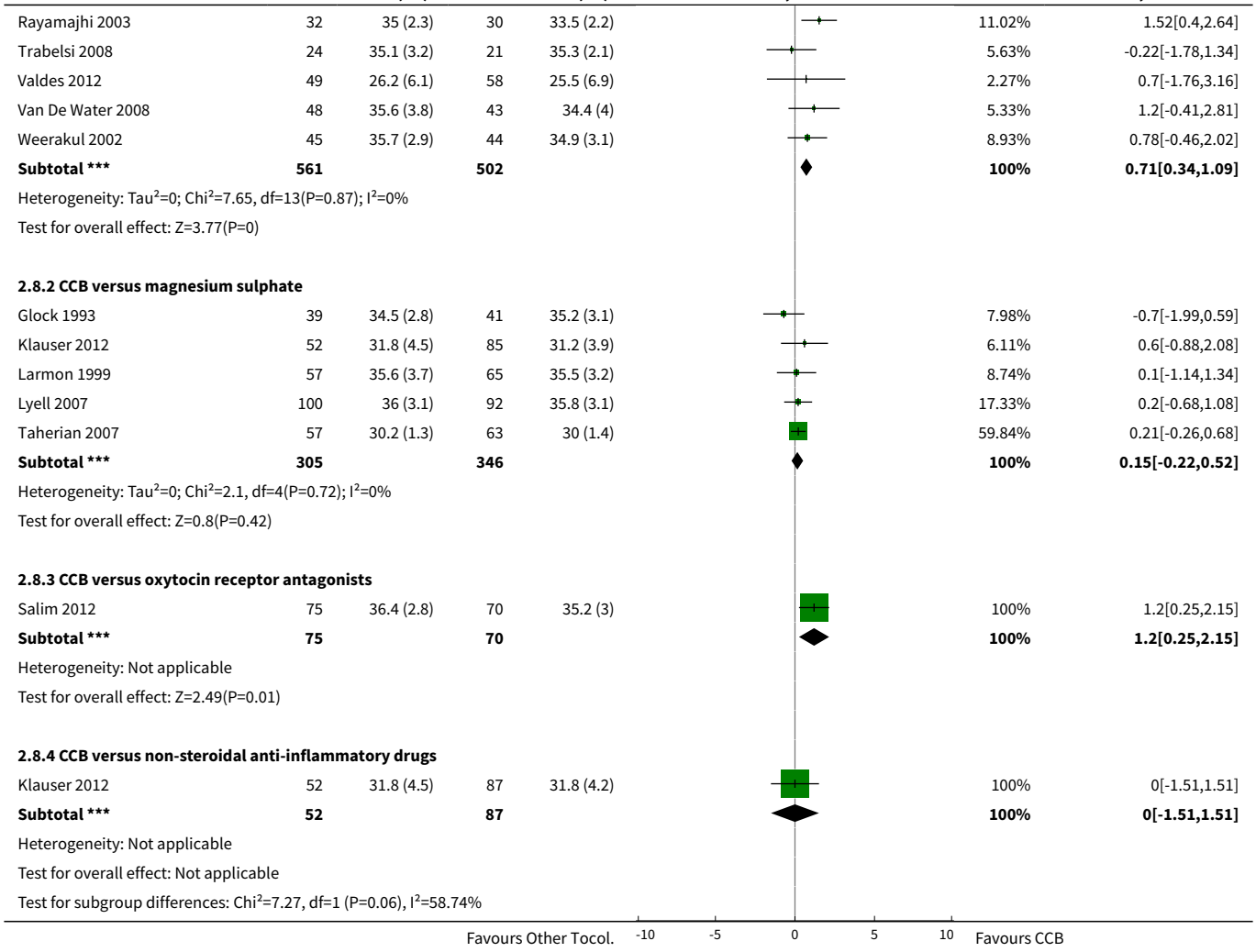
Study or subgroup	CCB N	CCB Mean(SD)	Other Tocolytic N	Other Tocolytic Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
2.7.1 CCB versus betamimetics							
Bracero 1991	23	28 (21)	19	21 (21)		6.86%	7[-5.76,19.76]
Cararach 2006	37	29.4 (25.1)	39	28 (21.6)		8.65%	1.4[-9.15,11.95]
Ganla 1999	50	22.4 (15.6)	50	16.5 (14.5)		14.1%	5.9[-0,11.8]
Garcia-Velasco 1998	26	43.7 (21.6)	26	64 (36.8)		4.81%	-20.3[-36.7,-3.9]
Janky 1990	30	42 (21.9)	32	35 (15.6)		9.66%	7[-2.52,16.52]
Papatsonis 1997	95	32.2 (23.8)	90	18.9 (22.4)		13.08%	13.3[6.64,19.96]
Rayamajhi 2003	32	25.7 (19.5)	30	19.2 (17.8)		9.9%	6.53[-2.76,15.82]
Read 1986	20	36.3 (22.8)	20	25.1 (25.5)		5.5%	11.2[-3.79,26.19]
Valdes 2012	58	26.7 (6.4)	64	25.6 (6.7)		18.62%	1.1[-1.23,3.43]
Weerakul 2002	45	27.5 (24.1)	44	27 (25.7)		8.83%	0.49[-9.87,10.85]
Subtotal ***	**416**		**414**			**100%**	**4.38[0.25,8.52]**
Heterogeneity: Tau^2=22.52; Chi^2=23.51, df=9(P=0.01); I^2=61.72%							
Test for overall effect: Z=2.08(P=0.04)							
2.7.2 CCB versus magnesium sulphate							
Floyd 1992	50	37.5 (26)	40	43.3 (34.1)		31.39%	-5.8[-18.59,6.99]
Larmon 1999	57	34.9 (25.9)	65	34.7 (22.4)		68.61%	0.28[-8.37,8.93]
Subtotal ***	**107**		**105**			**100%**	**-1.63[-8.8,5.54]**
Heterogeneity: Tau^2=0; Chi^2=0.6, df=1(P=0.44); I^2=0%							
Test for overall effect: Z=0.45(P=0.66)							
2.7.3 CCB versus oxytocin receptor antagonists							
Salim 2012	75	37.4 (20.3)	70	31.7 (20.6)		100%	5.7[-0.96,12.36]
Subtotal ***	**75**		**70**			**100%**	**5.7[-0.96,12.36]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.68(P=0.09)							
Test for subgroup differences: Chi^2=2.56, df=1 (P=0.28), I^2=21.89%							



Analysis 2.8. Comparison 2 Calcium channel blockers compared with any other tocolytic agent (subgrouped by other tocolytic), Outcome 8 Gestational age at birth (completed weeks).

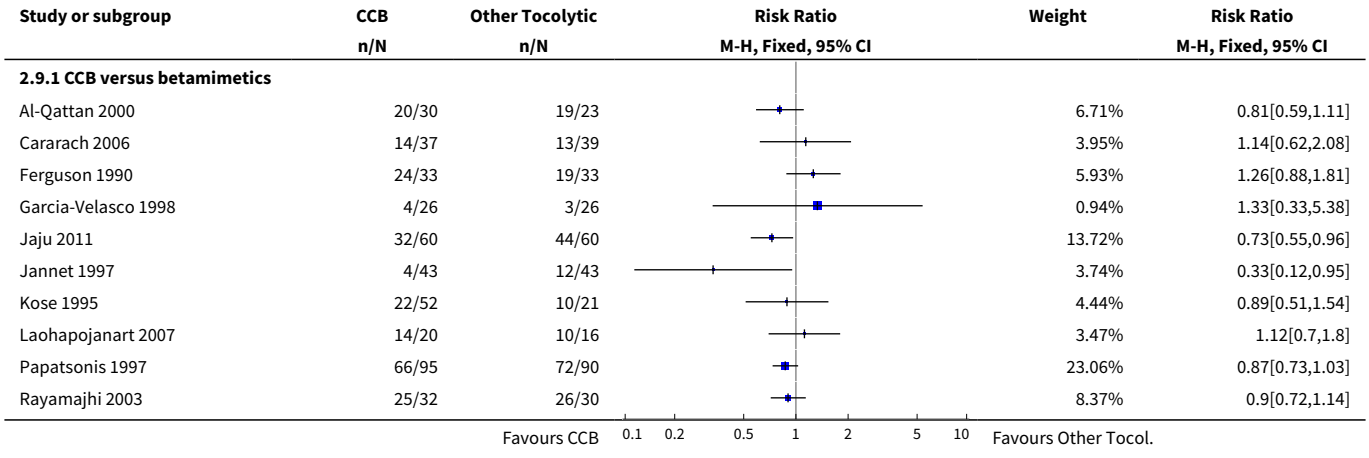
Study or subgroup	CCB N	CCB Mean(SD)	Other Tocolytic N	Other Tocolytic Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
2.8.1 CCB versus betamimetics							
Al-Qattan 2000	30	30.2 (2.6)	23	29.5 (2.3)		7.87%	0.7[-0.62,2.02]
Bracero 1991	23	36 (3)	19	35 (4)		2.91%	1[-1.18,3.18]
Cararach 2006	37	36.2 (2.4)	39	36.1 (2.4)		11.81%	0.1[-0.98,1.18]
Fan 2003	31	34.7 (2.8)	30	34.1 (4.4)		4.09%	0.64[-1.19,2.47]
Jannet 1997	43	38.4 (1.7)	43	37.6 (2.1)		21.11%	0.8[-0.01,1.61]
Koks 1998	32	32.5 (4.4)	25	32.9 (3.7)		3.11%	-0.4[-2.5,1.7]
Kose 1995	52	36.1 (3.2)	21	35.7 (3.8)		4.05%	0.43[-1.41,2.27]
Laohapojanart 2007	20	34.5 (2.9)	16	34.6 (3.6)		2.91%	-0.1[-2.27,2.07]
Papatsonis 1997	95	33.4 (4.5)	90	32.1 (4.1)		8.96%	1.3[0.06,2.54]



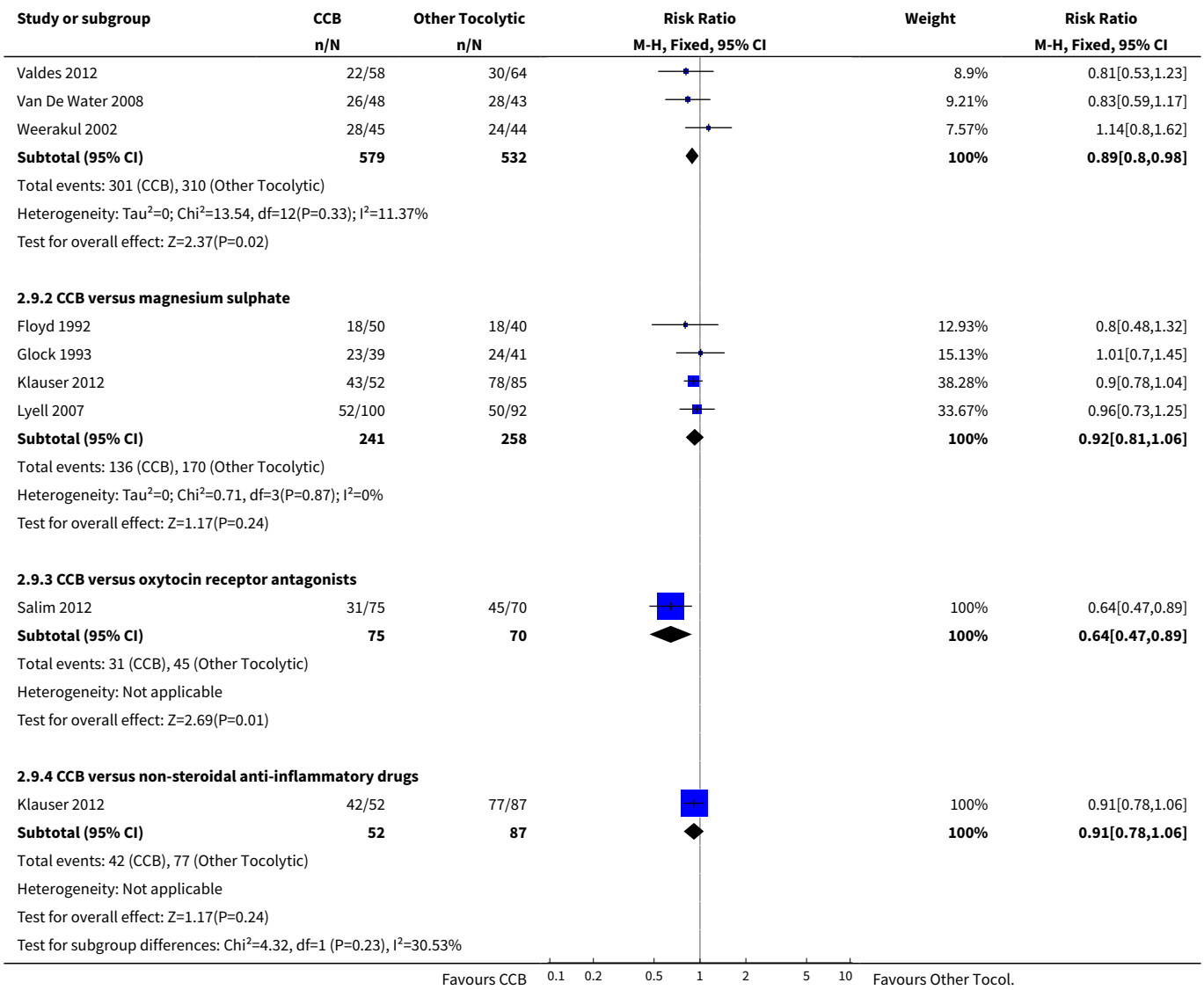


Study or subgroup	CCB N	CCB Mean(SD)	Other Tocolytic N	Other Tocolytic Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Rayamajhi 2003	32	35 (2.3)	30	33.5 (2.2)		11.02%	1.52[0.4,2.64]
Trabelsi 2008	24	35.1 (3.2)	21	35.3 (2.1)		5.63%	-0.22[-1.78,1.34]
Valdes 2012	49	26.2 (6.1)	58	25.5 (6.9)		2.27%	0.7[-1.76,3.16]
Van De Water 2008	48	35.6 (3.8)	43	34.4 (4)		5.33%	1.2[-0.41,2.81]
Weerakul 2002	45	35.7 (2.9)	44	34.9 (3.1)		8.93%	0.78[-0.46,2.02]
Subtotal * **	**561**		**502**			**100%**	**0.71[0.34,1.09]**
Heterogeneity: Tau²=0; Chi²=7.65, df=13(P=0.87); I²=0%							
Test for overall effect: Z=3.77(P=0)							
2.8.2 CCB versus magnesium sulphate							
Glock 1993	39	34.5 (2.8)	41	35.2 (3.1)		7.98%	-0.7[-1.99,0.59]
Klauser 2012	52	31.8 (4.5)	85	31.2 (3.9)		6.11%	0.6[-0.88,2.08]
Larmon 1999	57	35.6 (3.7)	65	35.5 (3.2)		8.74%	0.1[-1.14,1.34]
Lyell 2007	100	36 (3.1)	92	35.8 (3.1)		17.33%	0.2[-0.68,1.08]
Taherian 2007	57	30.2 (1.3)	63	30 (1.4)		59.84%	0.21[-0.26,0.68]
Subtotal * **	**305**		**346**			**100%**	**0.15[-0.22,0.52]**
Heterogeneity: Tau²=0; Chi²=2.1, df=4(P=0.72); I²=0%							
Test for overall effect: Z=0.8(P=0.42)							
2.8.3 CCB versus oxytocin receptor antagonists							
Salim 2012	75	36.4 (2.8)	70	35.2 (3)		100%	1.2[0.25,2.15]
Subtotal * **	**75**		**70**			**100%**	**1.2[0.25,2.15]**
Heterogeneity: Not applicable							
Test for overall effect: Z=2.49(P=0.01)							
2.8.4 CCB versus non-steroidal anti-inflammatory drugs							
Klauser 2012	52	31.8 (4.5)	87	31.8 (4.2)		100%	0[-1.51,1.51]
Subtotal * **	**52**		**87**			**100%**	**0[-1.51,1.51]**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
Test for subgroup differences: Chi²=7.27, df=1 (P=0.06), I²=58.74%							

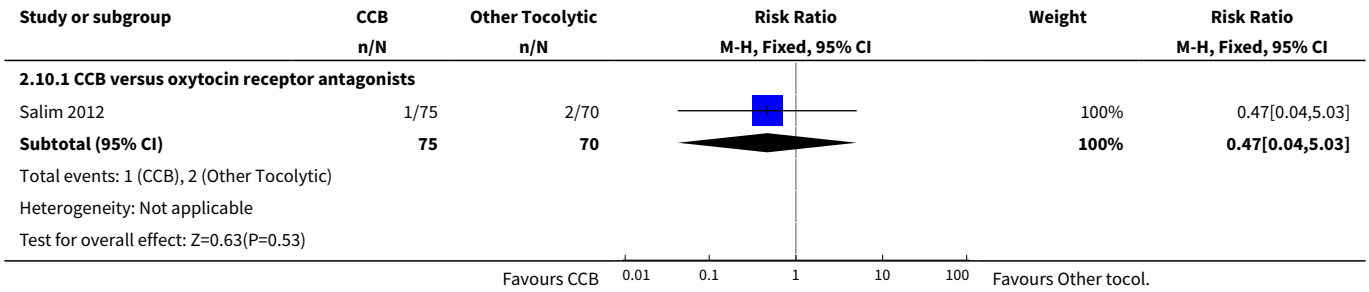
Analysis 2.9. Comparison 2 Calcium channel blockers compared with any other tocolytic agent (subgrouped by other tocolytic), Outcome 9 Preterm birth (before completion of 37 weeks of gestation).



Study or subgroup	CCB n/N	Other Tocolytic n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
2.9.1 CCB versus betamimetics					
Al-Qattan 2000	20/30	19/23		6.71%	0.81[0.59,1.11]
Cararach 2006	14/37	13/39		3.95%	1.14[0.62,2.08]
Ferguson 1990	24/33	19/33		5.93%	1.26[0.88,1.81]
Garcia-Velasco 1998	4/26	3/26		0.94%	1.33[0.33,5.38]
Jaju 2011	32/60	44/60		13.72%	0.73[0.55,0.96]
Jannet 1997	4/43	12/43		3.74%	0.33[0.12,0.95]
Kose 1995	22/52	10/21		4.44%	0.89[0.51,1.54]
Laohapojanart 2007	14/20	10/16		3.47%	1.12[0.7,1.8]
Papatsonis 1997	66/95	72/90		23.06%	0.87[0.73,1.03]
Rayamajhi 2003	25/32	26/30		8.37%	0.9[0.72,1.14]



Analysis 2.10. Comparison 2 Calcium channel blockers compared with any other tocolytic agent (subgrouped by other tocolytic), Outcome 10 Extremely preterm birth (before completion of 28 weeks of gestation).



Analysis 2.11. Comparison 2 Calcium channel blockers compared with any other tocolytic agent (subgrouped by other tocolytic), Outcome 11 Apgar score < 7 at 5 minutes.

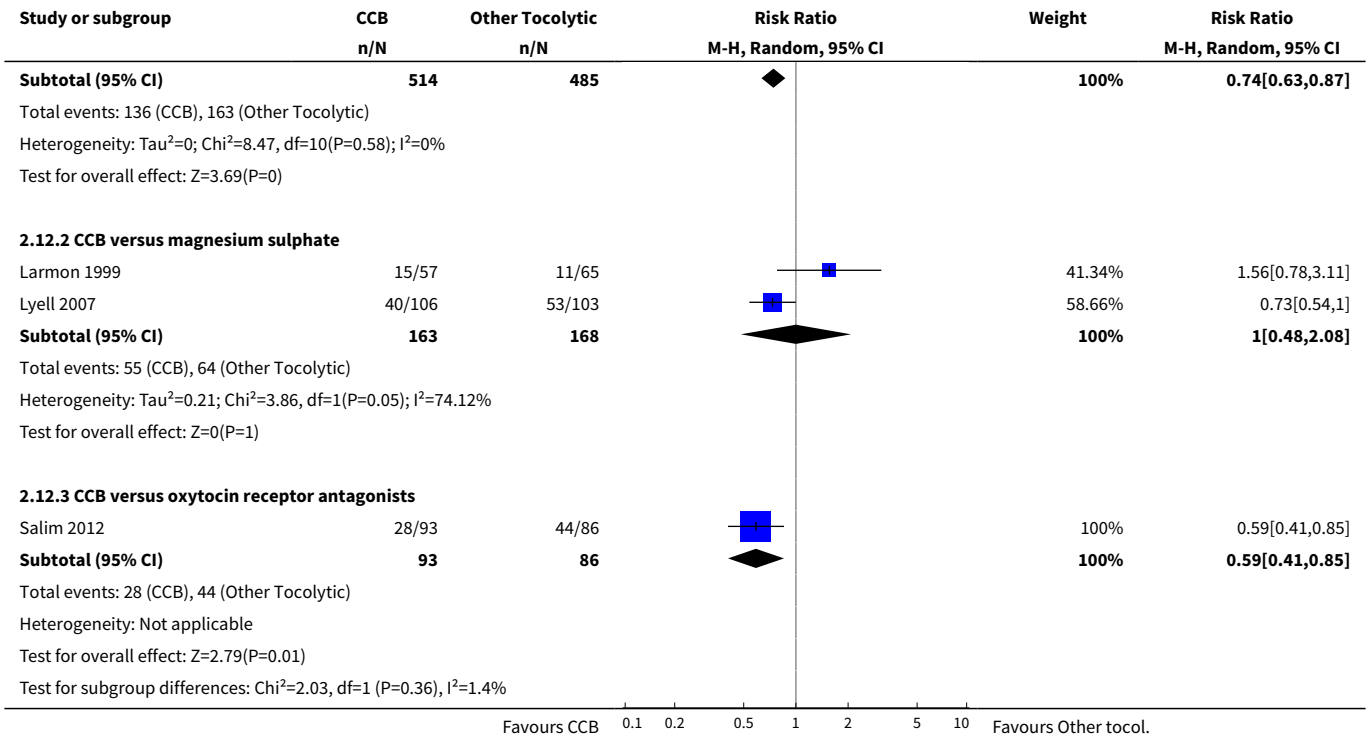
Study or subgroup	CCB n/N	Other Tocolytic n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
2.11.1 CCB versus betamimetics					
Cararach 2006	2/37	3/39		13.83%	0.7[0.12,3.97]
Kupferminc 1993	2/41	2/39		9.7%	0.95[0.14,6.43]
Laohapojanart 2007	1/20	0/16		2.62%	2.43[0.11,55.89]
Papatsonis 1997	4/95	8/90		38.89%	0.47[0.15,1.52]
Van De Water 2008	2/48	7/43		34.96%	0.26[0.06,1.17]
Weerakul 2002	0/45	0/44			Not estimable
Subtotal (95% CI)	**286**	**271**		**100%**	**0.53[0.26,1.06]**
Total events: 11 (CCB), 20 (Other Tocolytic)					
Heterogeneity: Tau^2=0; Chi^2=2.29, df=4(P=0.68); I^2=0%					
Test for overall effect: Z=1.79(P=0.07)					
2.11.2 CCB versus magnesium sulphate					
Floyd 1992	7/53	6/42		70.49%	0.92[0.34,2.54]
Larmon 1999	4/57	3/65		29.51%	1.52[0.36,6.51]
Subtotal (95% CI)	**110**	**107**		**100%**	**1.1[0.48,2.51]**
Total events: 11 (CCB), 9 (Other Tocolytic)					
Heterogeneity: Tau^2=0; Chi^2=0.3, df=1(P=0.58); I^2=0%					
Test for overall effect: Z=0.23(P=0.82)					
2.11.3 CCB versus oxytocin receptor antagonists					
Salim 2012	2/93	1/86		100%	1.85[0.17,20.03]
Subtotal (95% CI)	**93**	**86**		**100%**	**1.85[0.17,20.03]**
Total events: 2 (CCB), 1 (Other Tocolytic)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.51(P=0.61)					
Test for subgroup differences: Chi^2=2.36, df=1 (P=0.31), I^2=15.12%					

Favours CCB — Favours Other Tocol.

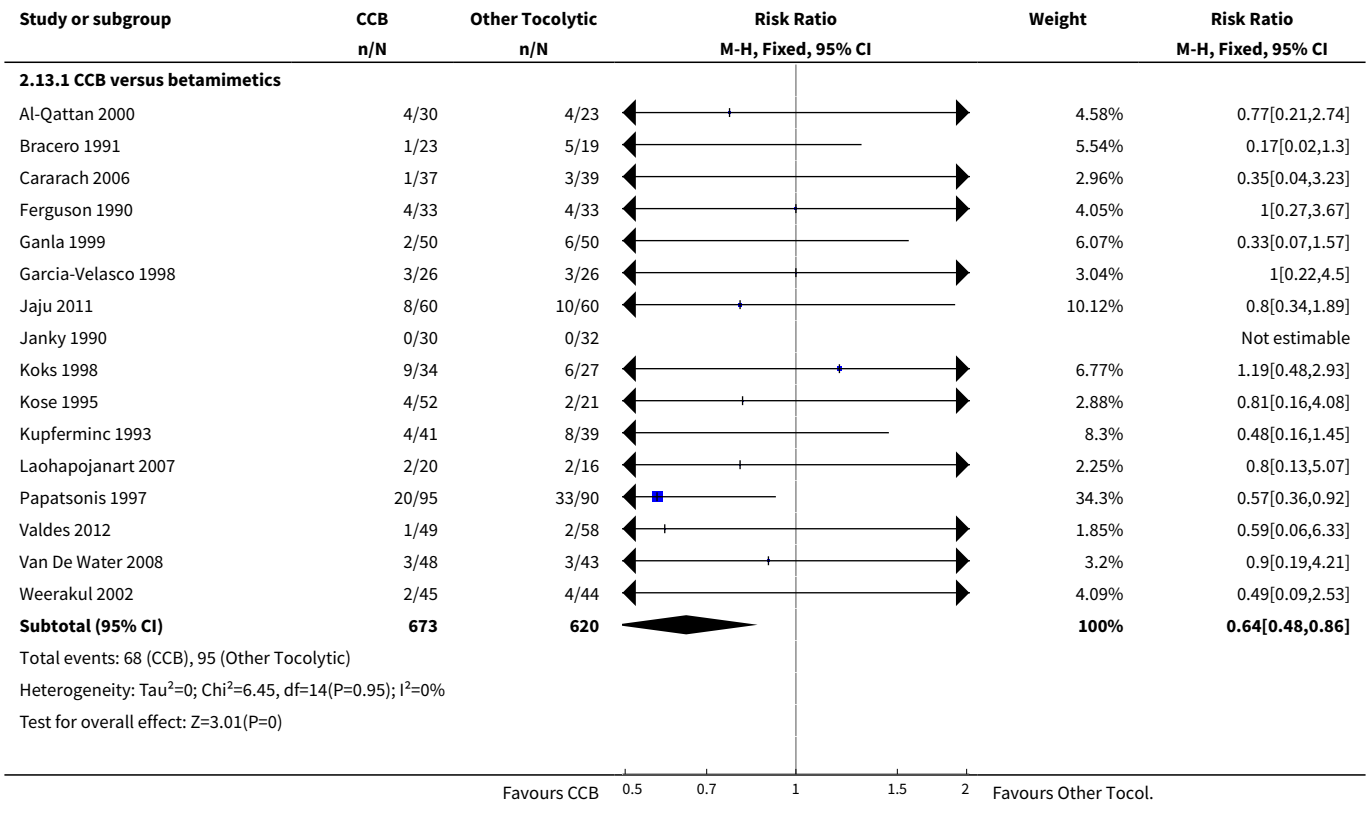
Analysis 2.12. Comparison 2 Calcium channel blockers compared with any other tocolytic agent (subgrouped by other tocolytic), Outcome 12 Admission to NICU.

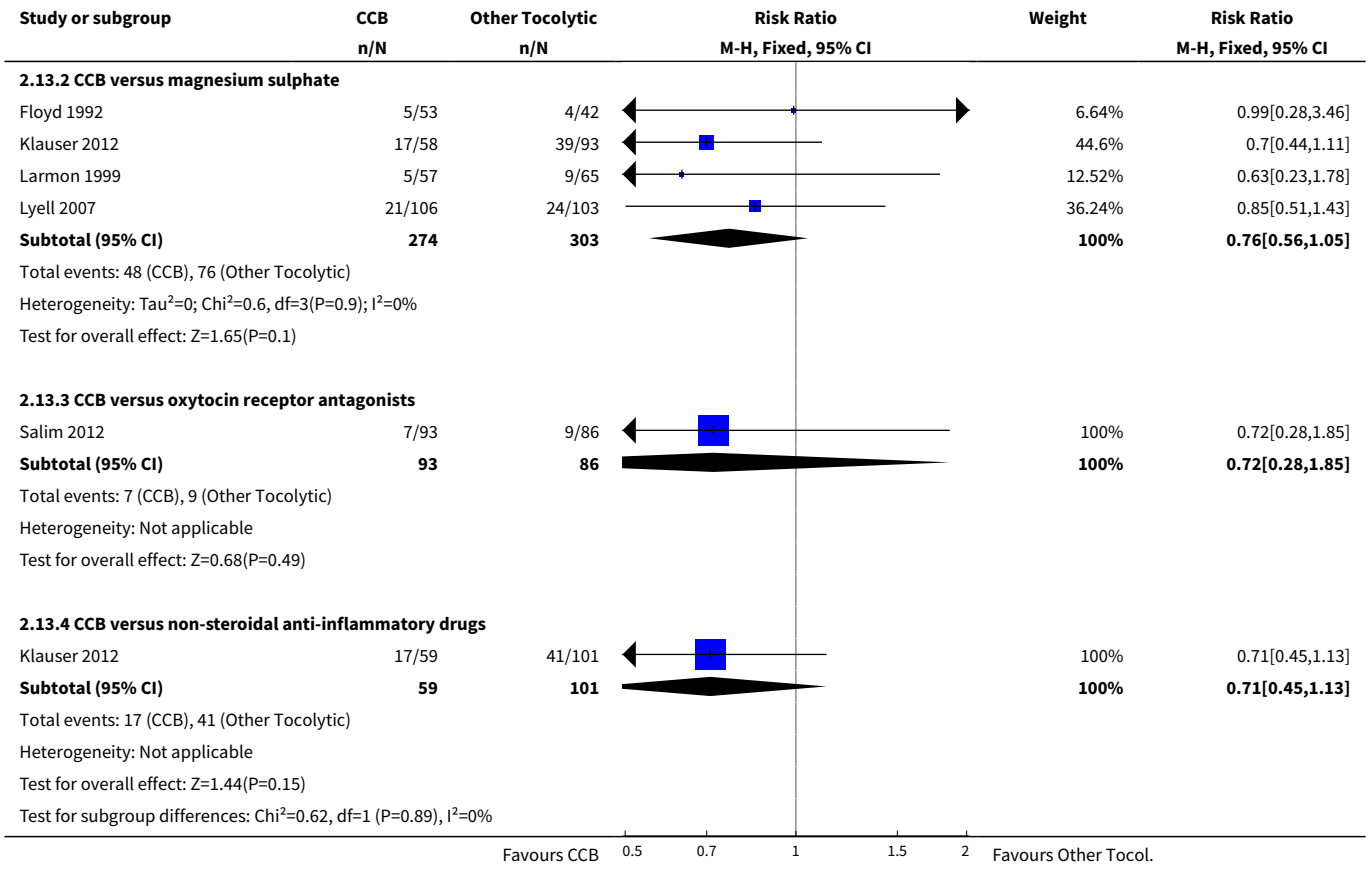
Study or subgroup	CCB n/N	Other Tocolytic n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
2.12.1 CCB versus betamimetics					
Bracero 1991	6/23	11/19		4.05%	0.45[0.2,0.99]
Garcia-Velasco 1998	3/26	2/26		0.86%	1.5[0.27,8.25]
Jaju 2011	33/60	39/60		28.93%	0.85[0.63,1.14]
Janky 1990	0/30	0/32			Not estimable
Jannet 1997	5/43	7/43		2.21%	0.71[0.25,2.08]
Koks 1998	16/34	10/27		6.81%	1.27[0.69,2.33]
Kupferminc 1993	12/41	15/39		6.54%	0.76[0.41,1.41]
Laohapojanart 2007	1/20	2/16		0.47%	0.4[0.04,4.02]
Papatsonis 1997	47/95	59/78		43.96%	0.65[0.51,0.83]
Valdes 2012	1/49	1/58		0.33%	1.18[0.08,18.43]
Van De Water 2008	11/48	13/43		5.29%	0.76[0.38,1.51]
Weerakul 2002	1/45	4/44		0.54%	0.24[0.03,2.1]

Favours CCB — Favours Other tocol.

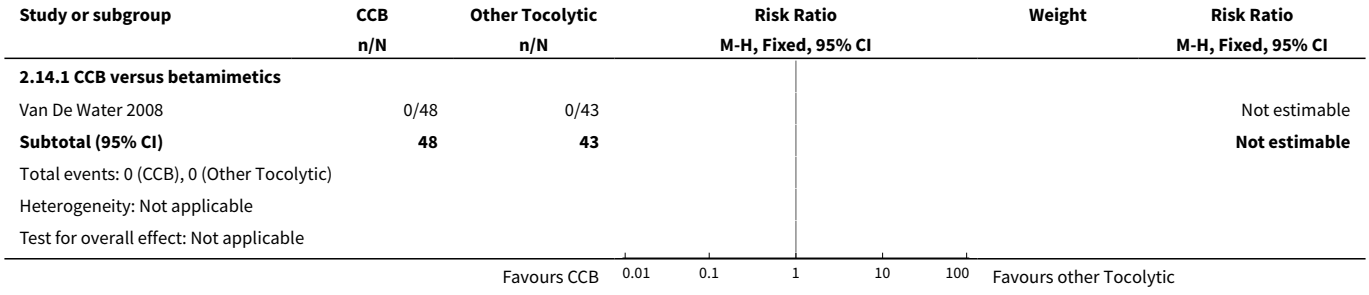


Analysis 2.13. Comparison 2 Calcium channel blockers compared with any other tocolytic agent (subgrouped by other tocolytic), Outcome 13 Respiratory distress syndrome.

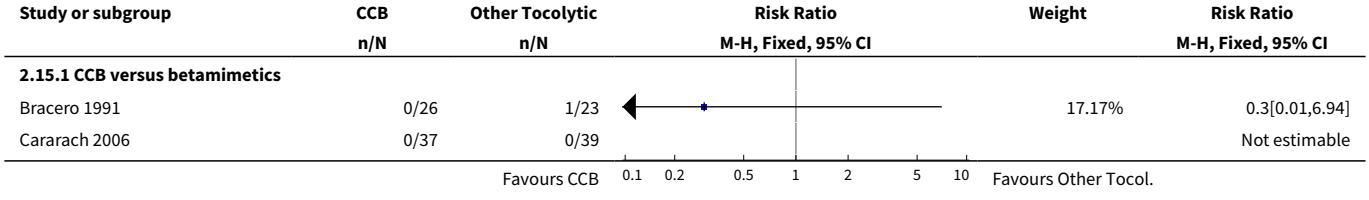


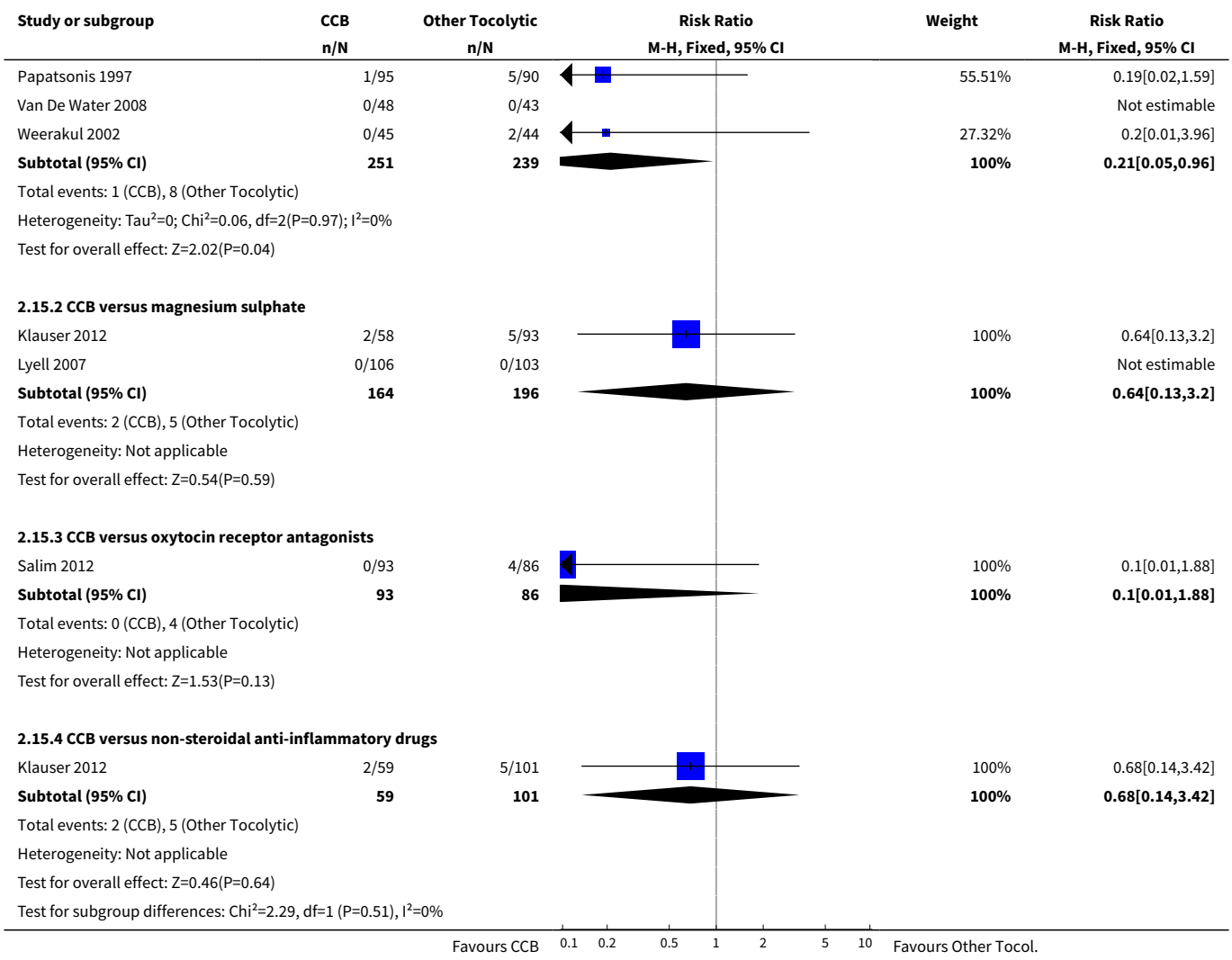


Analysis 2.14. Comparison 2 Calcium channel blockers compared with any other tocolytic agent (subgrouped by other tocolytic), Outcome 14 Chronic lung disease.

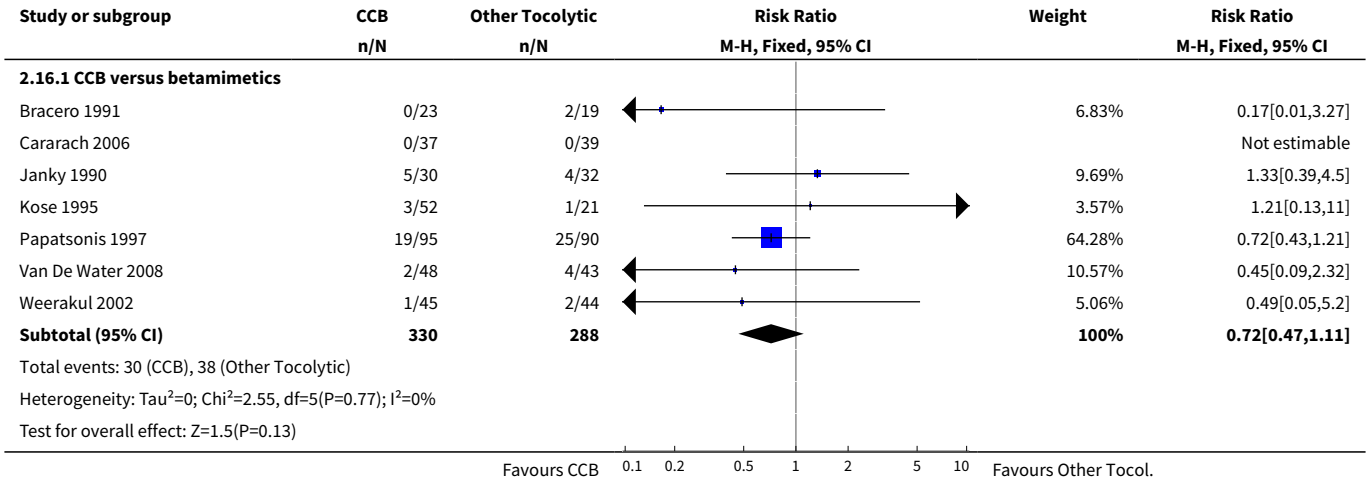


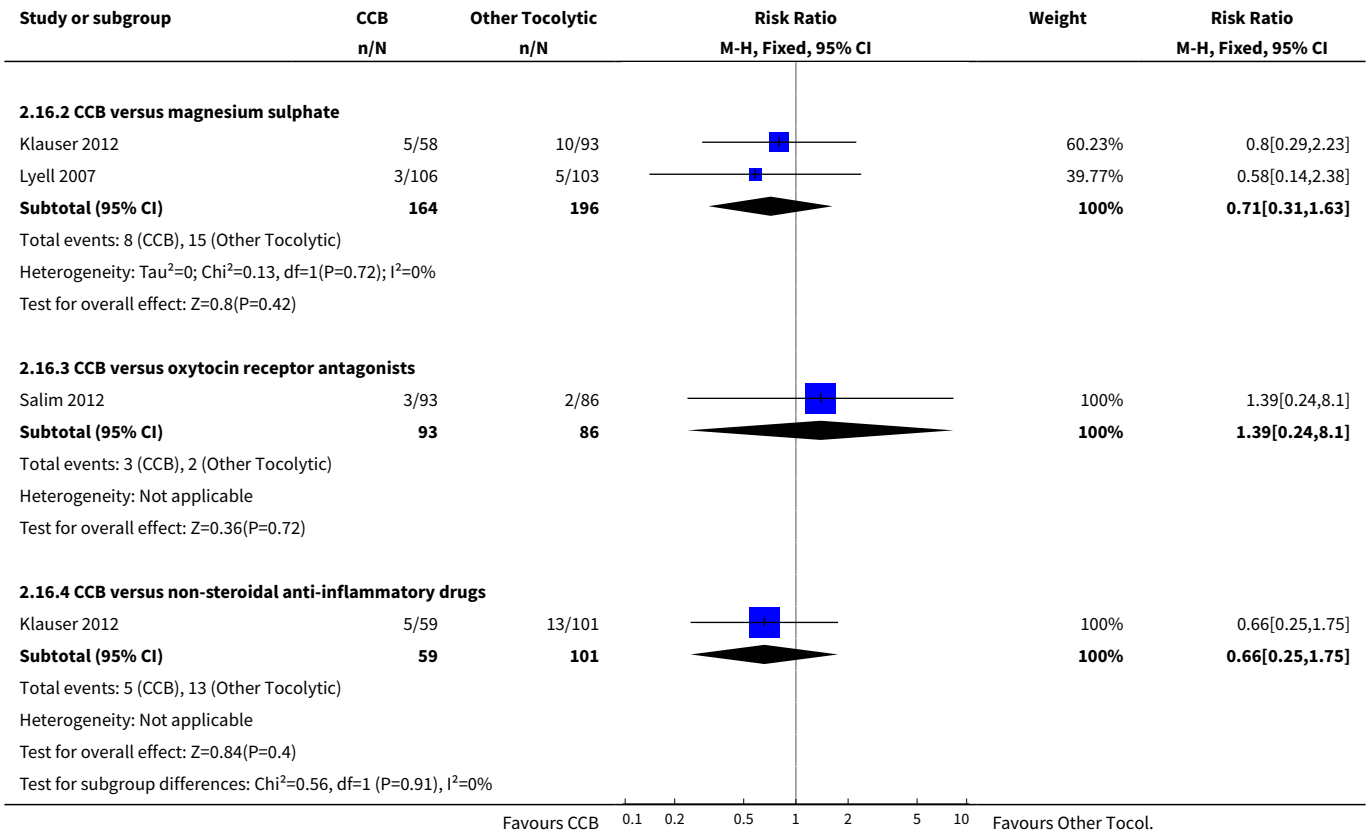
Analysis 2.15. Comparison 2 Calcium channel blockers compared with any other tocolytic agent (subgrouped by other tocolytic), Outcome 15 Necrotising enterocolitis.



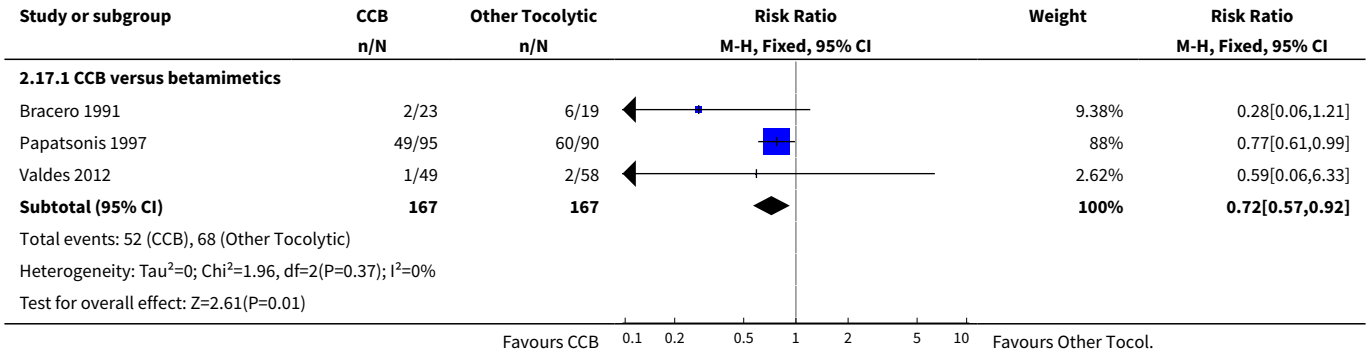


Analysis 2.16. Comparison 2 Calcium channel blockers compared with any other tocolytic agent (subgrouped by other tocolytic), Outcome 16 Neonatal sepsis.

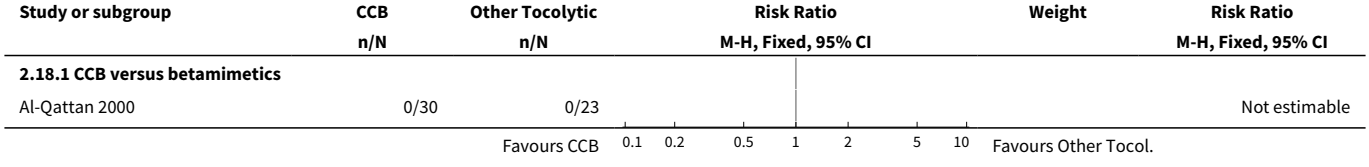


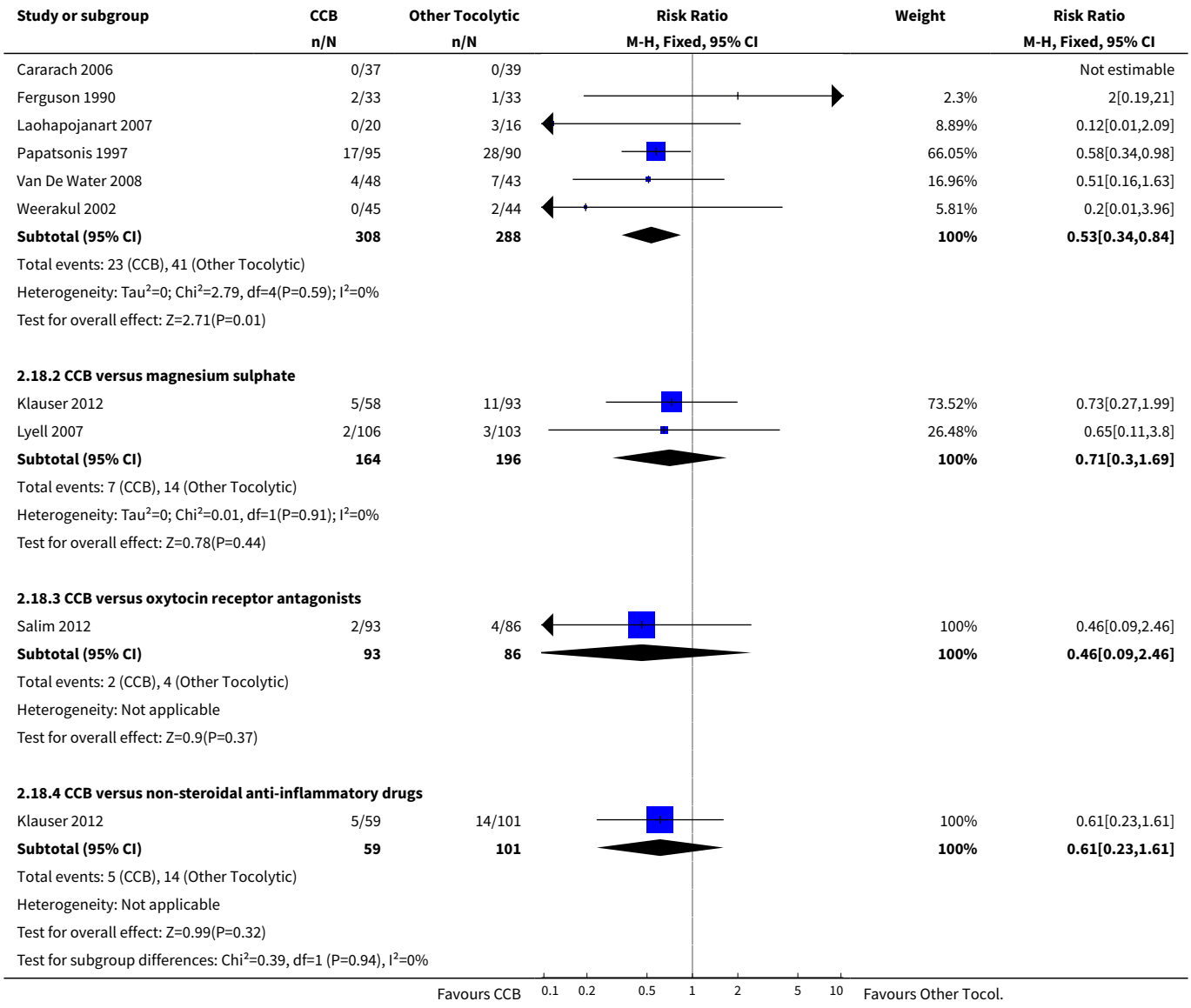


Analysis 2.17. Comparison 2 Calcium channel blockers compared with any other tocolytic agent (subgrouped by other tocolytic), Outcome 17 Neonatal jaundice.

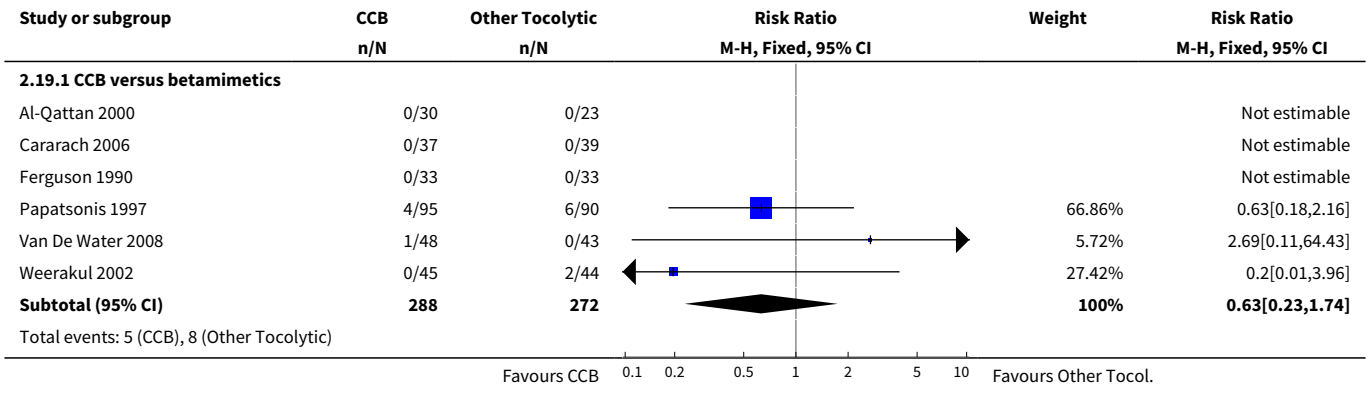


Analysis 2.18. Comparison 2 Calcium channel blockers compared with any other tocolytic agent (subgrouped by other tocolytic), Outcome 18 Intraventricular haemorrhage.

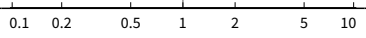




Analysis 2.19. Comparison 2 Calcium channel blockers compared with any other tocolytic agent (subgrouped by other tocolytic), Outcome 19 Intraventricular haemorrhage grades 3 or 4.



Study or subgroup	CCB n/N	Other Tocolytic n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Heterogeneity: Tau²=0; Chi²=1.39, df=2(P=0.5); I²=0%					
Test for overall effect: Z=0.89(P=0.37)					



Analysis 2.20. Comparison 2 Calcium channel blockers compared with any other tocolytic agent (subgrouped by other tocolytic), Outcome 20 Periventricular leukomalacia (PVL).

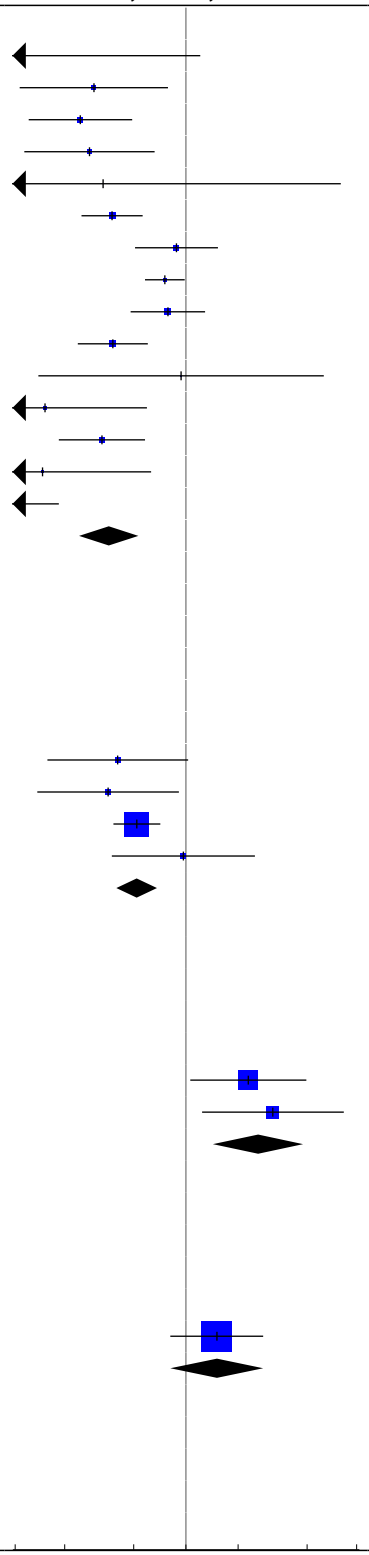
Study or subgroup	CCB n/N	Other Tocolytic n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
2.20.1 CCB versus magnesium sulphate					
Klauser 2012	0/58	0/93			Not estimable
Subtotal (95% CI)	**58**	**93**			**Not estimable**
Total events: 0 (CCB), 0 (Other Tocolytic)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
2.20.2 CCB versus non-steroidal anti-inflammatory drugs					
Klauser 2012	0/59	2/101		100%	0.34[0.02,6.96]
Subtotal (95% CI)	**59**	**101**		**100%**	**0.34[0.02,6.96]**
Total events: 0 (CCB), 2 (Other Tocolytic)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.7(P=0.48)					
Test for subgroup differences: Not applicable					

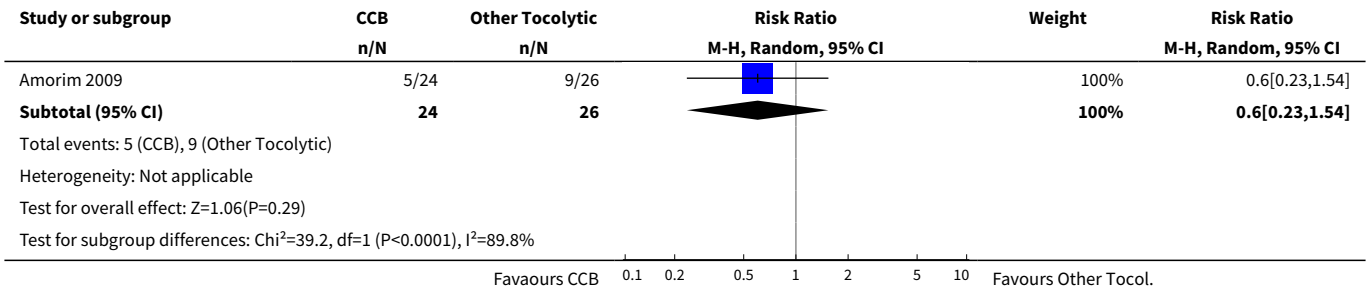
Analysis 2.21. Comparison 2 Calcium channel blockers compared with any other tocolytic agent (subgrouped by other tocolytic), Outcome 21 Retinopathy of prematurity.

Study or subgroup	CCB n/N	Other Tocolytic n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
2.21.1 CCB versus betamimetics					
Papatsonis 1997	0/95	4/90		74.51%	0.11[0.01,1.93]
Van De Water 2008	0/48	1/43		25.49%	0.3[0.01,7.16]
Subtotal (95% CI)	**143**	**133**		**100%**	**0.15[0.02,1.28]**
Total events: 0 (CCB), 5 (Other Tocolytic)					
Heterogeneity: Tau²=0; Chi²=0.23, df=1(P=0.63); I²=0%					
Test for overall effect: Z=1.73(P=0.08)					
2.21.2 CCB versus oxytocin receptor antagonists					
Salim 2012	1/93	2/86		100%	0.46[0.04,5.01]
Subtotal (95% CI)	**93**	**86**		**100%**	**0.46[0.04,5.01]**
Total events: 1 (CCB), 2 (Other Tocolytic)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.63(P=0.53)					
Test for subgroup differences: Chi²=0.45, df=1 (P=0.5), I²=0%					

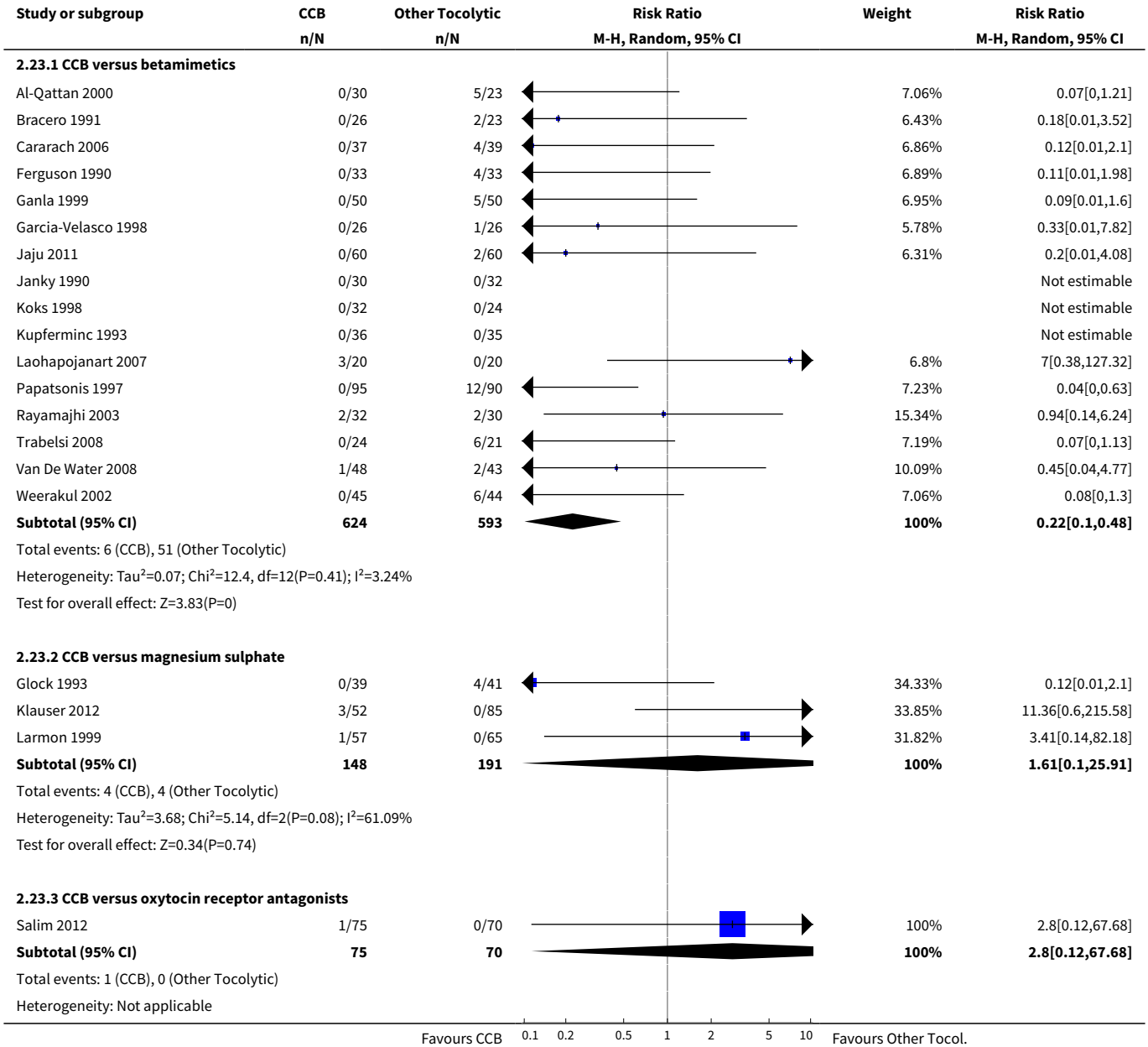
Analysis 2.22. Comparison 2 Calcium channel blockers compared with any other tocolytic agent (subgrouped by other tocolytic), Outcome 22 Maternal adverse effects.

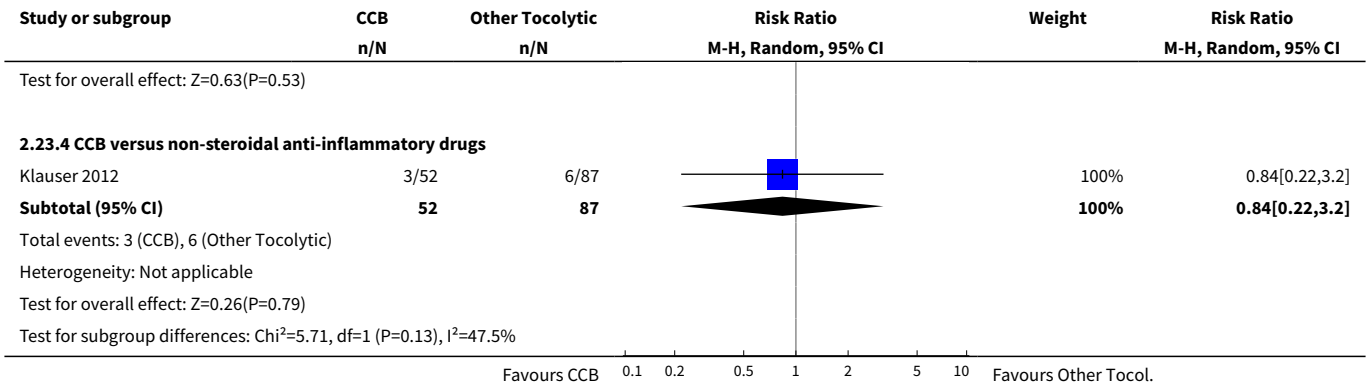
Study or subgroup	CCB n/N	Other Tocolytic n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
2.22.1 CCB versus betamimetics					
Al-Qattan 2000	0/30	5/23		1.63%	0.07[0,1.21]
Bracero 1991	4/26	12/23		6.57%	0.29[0.11,0.79]
Cararach 2006	7/37	30/39		8.29%	0.25[0.12,0.49]
Ferguson 1990	5/33	18/33		7.23%	0.28[0.12,0.66]
Garcia-Velasco 1998	0/26	1/26		1.37%	0.33[0.01,7.82]
Jaju 2011	18/60	48/60		9.94%	0.38[0.25,0.56]
Jannet 1997	15/43	17/43		9.13%	0.88[0.51,1.53]
Laohapojanart 2007	15/20	20/20		10.59%	0.76[0.58,0.98]
Mawaldi 2008	19/79	29/95		9.45%	0.79[0.48,1.29]
Papatsonis 1997	18/95	45/90		9.63%	0.38[0.24,0.6]
Rayamajhi 2003	2/32	2/30		3.11%	0.94[0.14,6.24]
Read 1986	2/20	13/20		4.8%	0.15[0.04,0.6]
Valdes 2012	11/58	37/64		9%	0.33[0.19,0.58]
Van De Water 2008	2/48	12/43		4.47%	0.15[0.04,0.63]
Weerakul 2002	2/45	41/44		4.79%	0.05[0.01,0.19]
Subtotal (95% CI)	**652**	**653**		**100%**	**0.36[0.24,0.53]**
Total events: 120 (CCB), 330 (Other Tocolytic)					
Heterogeneity: Tau^2=0.36; Chi^2=62.4, df=14(P<0.0001); I^2=77.57%					
Test for overall effect: Z=5.1(P<0.0001)					
2.22.2 CCB versus magnesium sulphate					
Floyd 1992	0/50	0/40			Not estimable
Glock 1993	5/39	13/41		8.36%	0.4[0.16,1.03]
Larmon 1999	5/57	16/65		8.27%	0.36[0.14,0.91]
Lyell 2007	34/100	60/92		75.28%	0.52[0.38,0.71]
Taherian 2007	7/57	8/63		8.09%	0.97[0.37,2.5]
Subtotal (95% CI)	**303**	**301**		**100%**	**0.52[0.4,0.68]**
Total events: 51 (CCB), 97 (Other Tocolytic)					
Heterogeneity: Tau^2=0; Chi^2=2.55, df=3(P=0.47); I^2=0%					
Test for overall effect: Z=4.75(P<0.0001)					
2.22.3 CCB versus oxytocin receptor antagonists					
Kashanian 2005	16/40	7/40		59.81%	2.29[1.06,4.95]
Salim 2012	17/75	5/70		40.19%	3.17[1.24,8.14]
Subtotal (95% CI)	**115**	**110**		**100%**	**2.61[1.43,4.74]**
Total events: 33 (CCB), 12 (Other Tocolytic)					
Heterogeneity: Tau^2=0; Chi^2=0.28, df=1(P=0.59); I^2=0%					
Test for overall effect: Z=3.14(P=0)					
2.22.4 CCB versus non-steroidal anti-inflammatory drugs					
Kashanian 2011	17/40	11/39		100%	1.51[0.81,2.79]
Subtotal (95% CI)	**40**	**39**		**100%**	**1.51[0.81,2.79]**
Total events: 17 (CCB), 11 (Other Tocolytic)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.3(P=0.19)					
2.22.5 CCB versus glyceryl trinitrate (GTN) patch					



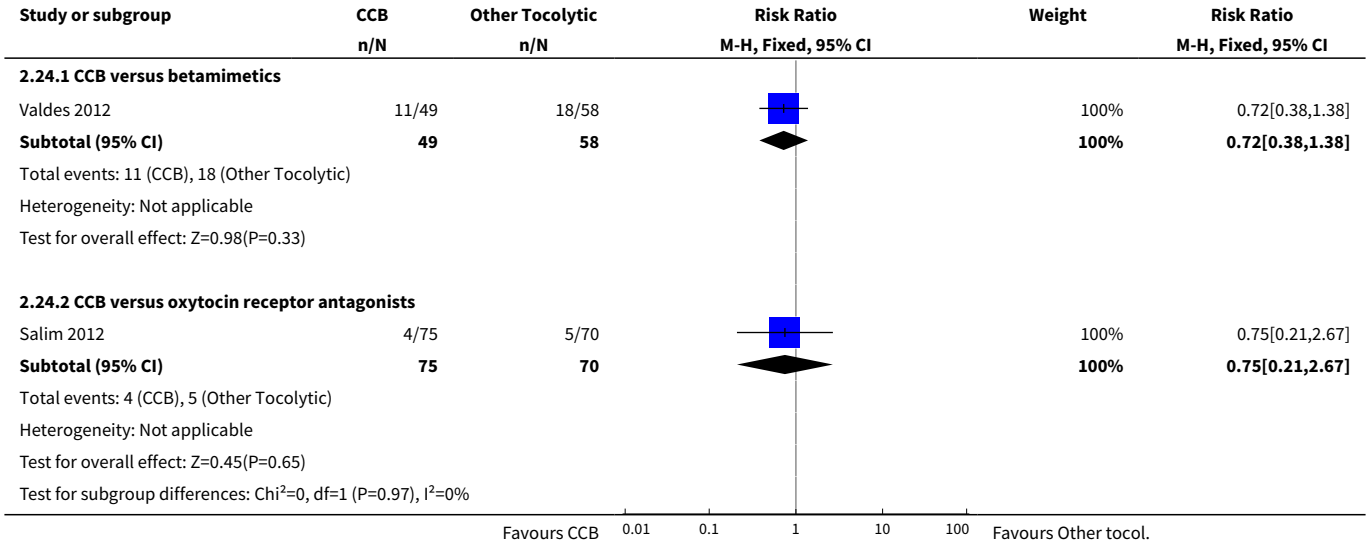


Analysis 2.23. Comparison 2 Calcium channel blockers compared with any other tocolytic agent (subgrouped by other tocolytic), Outcome 23 Discontinuation of therapy for maternal adverse effects.

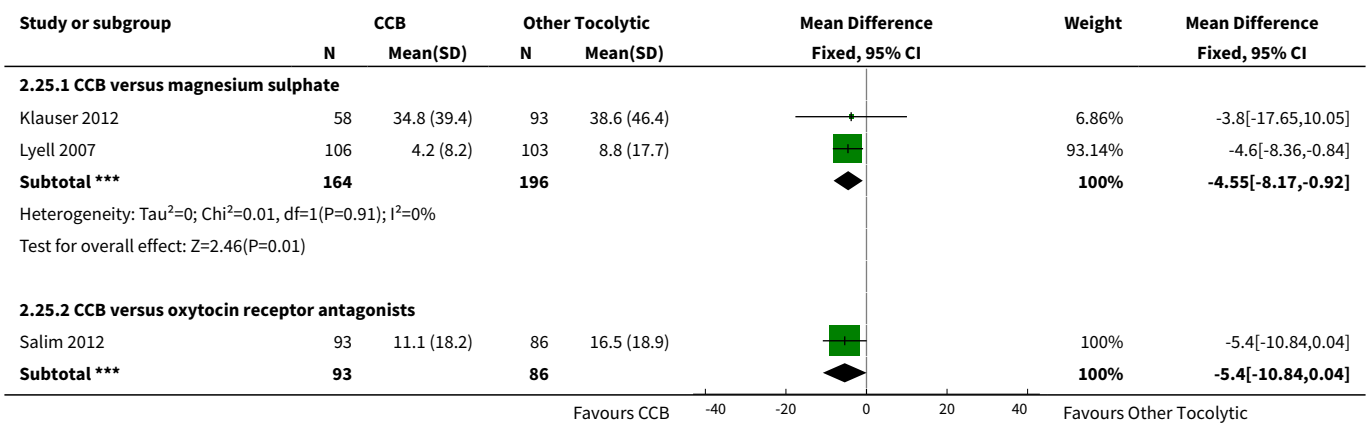


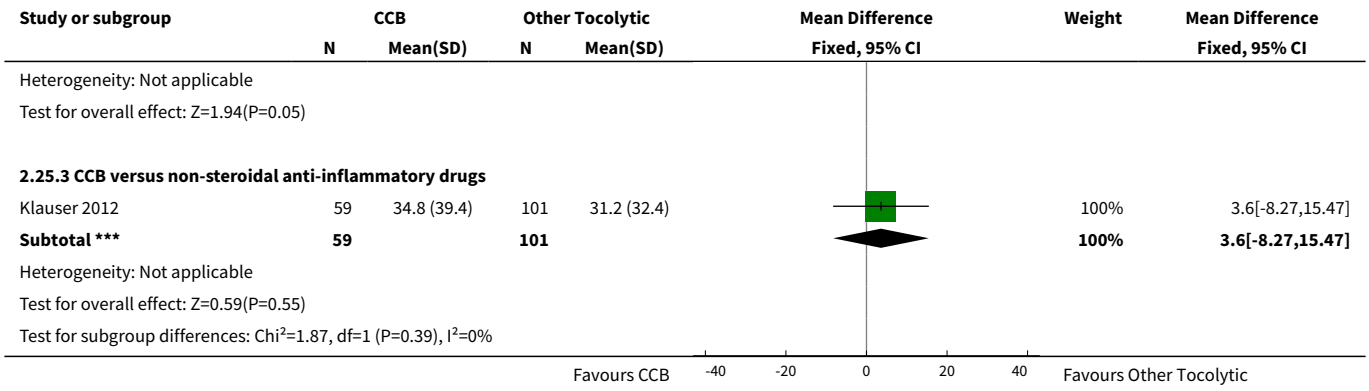


Analysis 2.24. Comparison 2 Calcium channel blockers compared with any other tocolytic agent (subgrouped by other tocolytic), Outcome 24 Caesarean section.

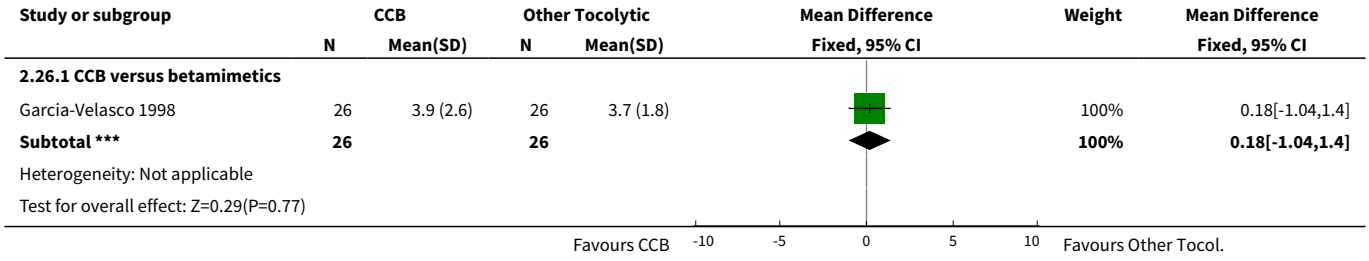


Analysis 2.25. Comparison 2 Calcium channel blockers compared with any other tocolytic agent (subgrouped by other tocolytic), Outcome 25 Duration of stay in NICU (days).

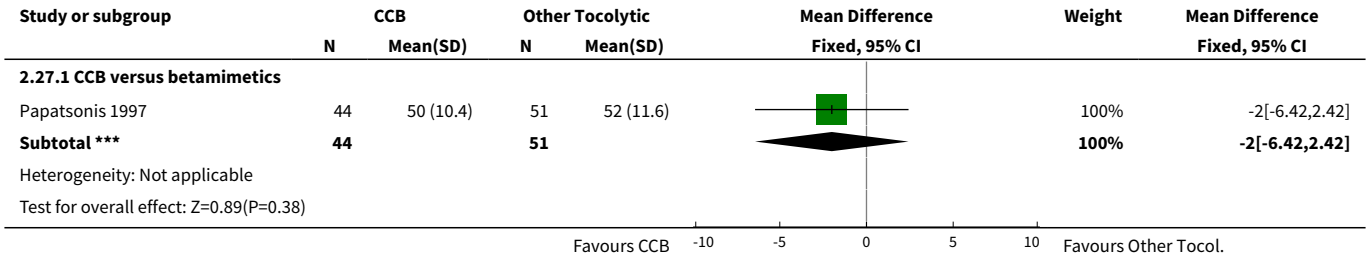




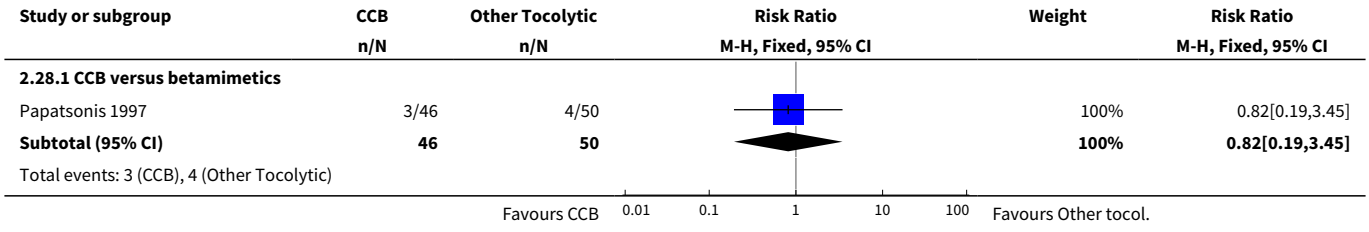
Analysis 2.26. Comparison 2 Calcium channel blockers compared with any other tocolytic agent (subgrouped by other tocolytic), Outcome 26 Duration of maternal hospital stay (days).

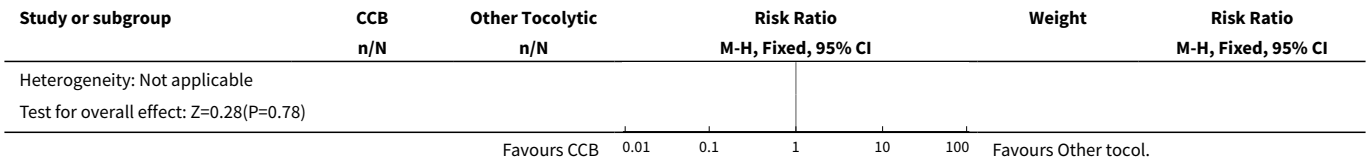


Analysis 2.27. Comparison 2 Calcium channel blockers compared with any other tocolytic agent (subgrouped by other tocolytic), Outcome 27 Behavioural-emotional problems at 9-12 years.

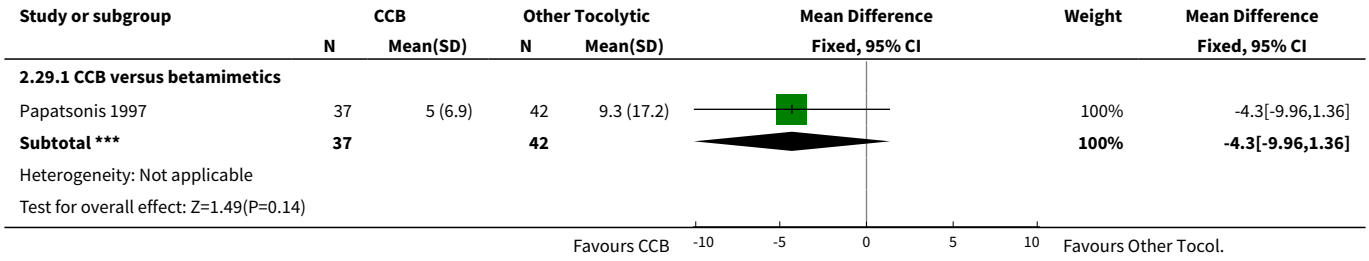


Analysis 2.28. Comparison 2 Calcium channel blockers compared with any other tocolytic agent (subgrouped by other tocolytic), Outcome 28 Special education at 9-12 years.

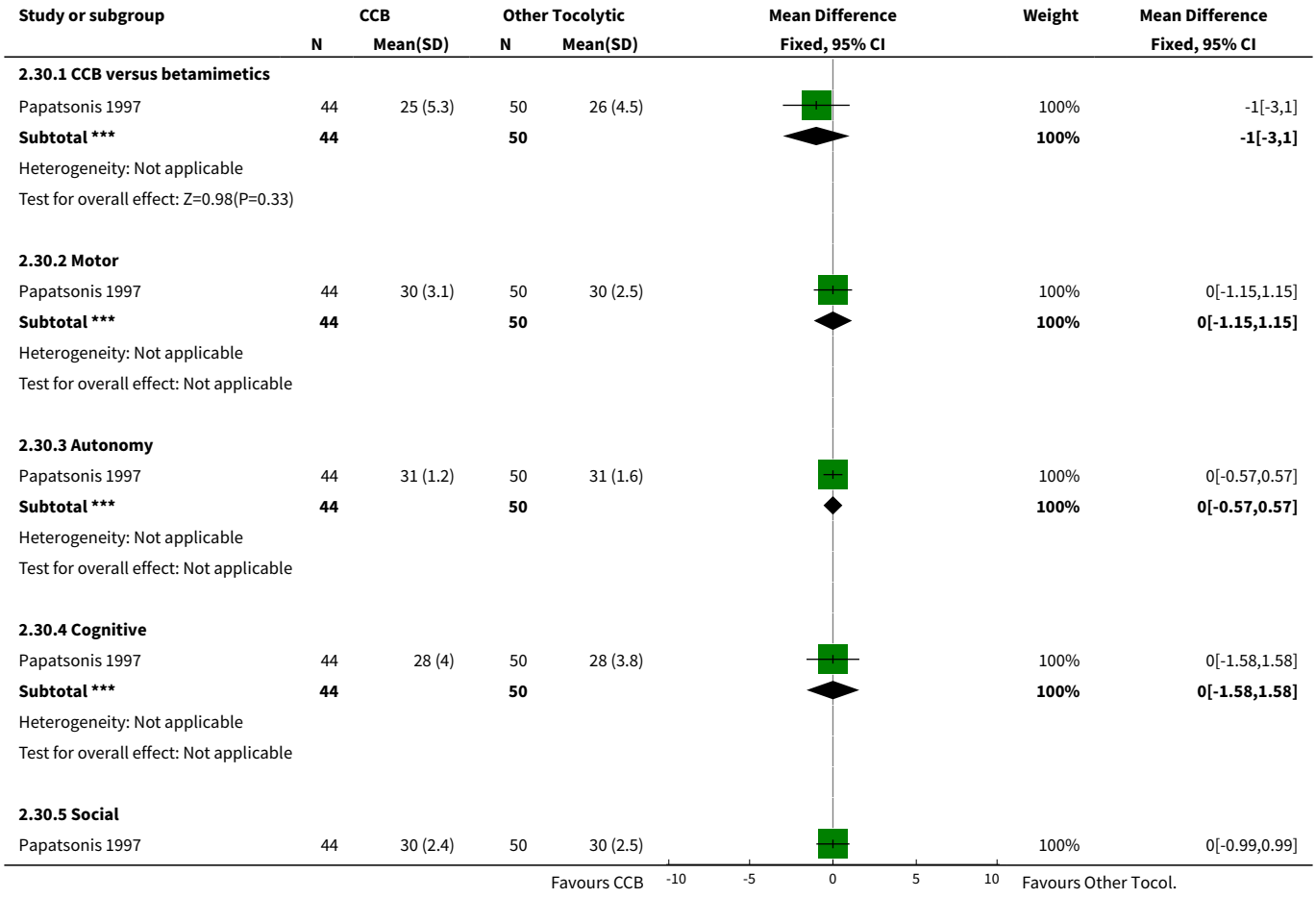


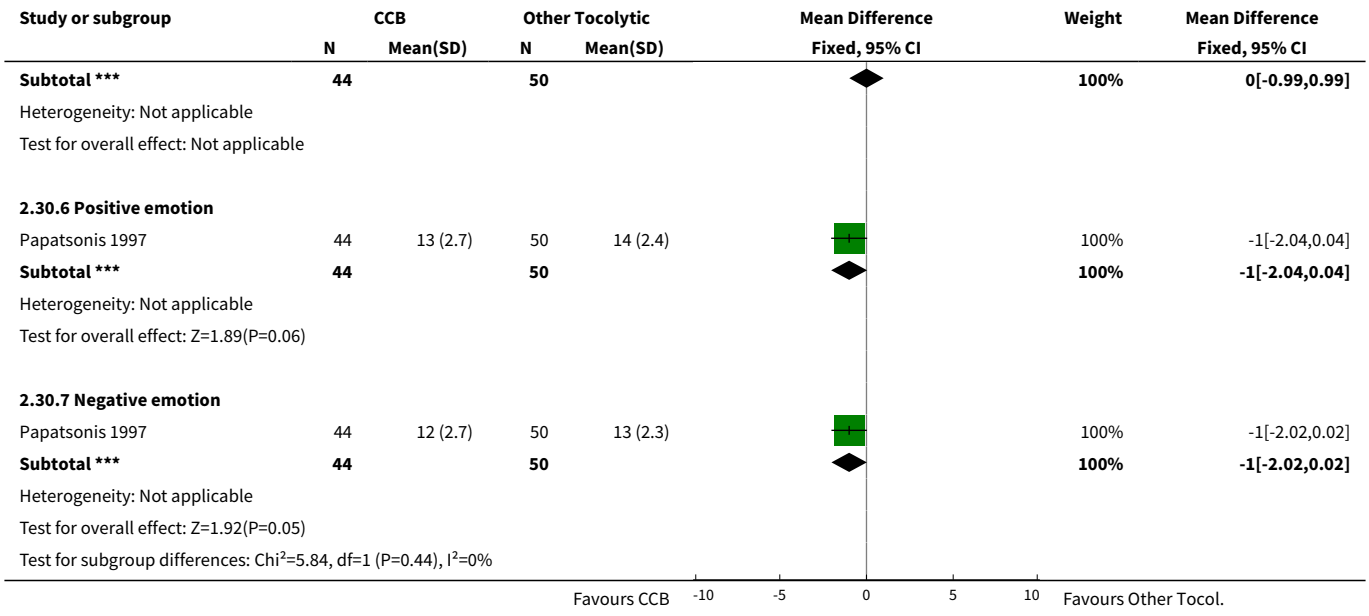


Analysis 2.29. Comparison 2 Calcium channel blockers compared with any other tocolytic agent (subgrouped by other tocolytic), Outcome 29 Motor quality at 9-12 years.

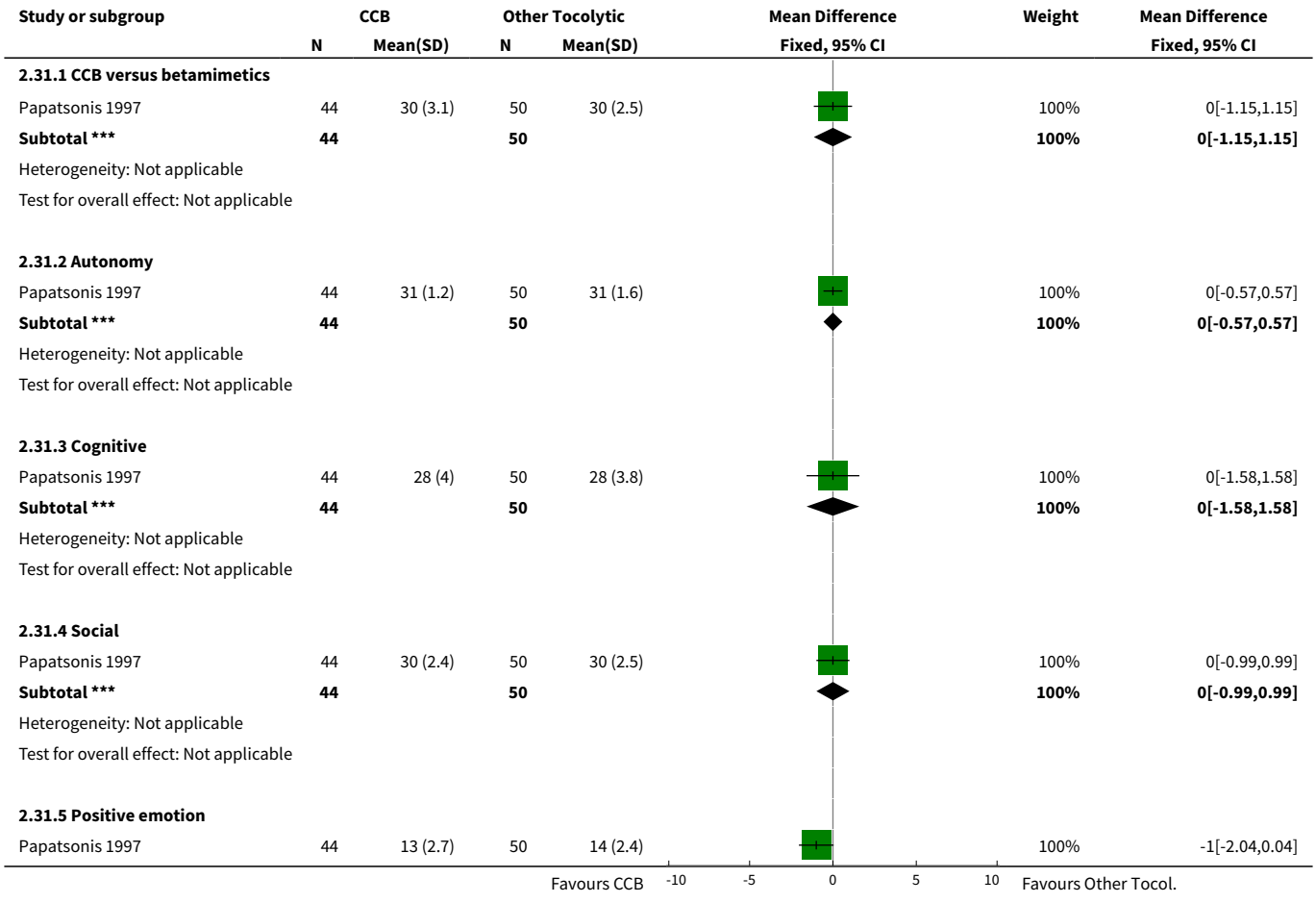


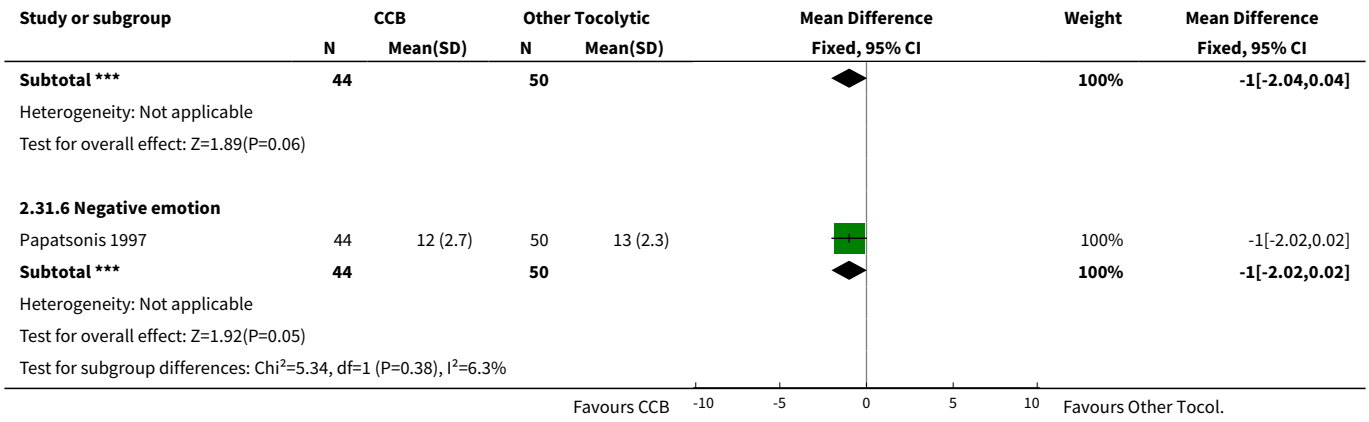
Analysis 2.30. Comparison 2 Calcium channel blockers compared with any other tocolytic agent (subgrouped by other tocolytic), Outcome 30 Quality of life at 9-12 years: physical.



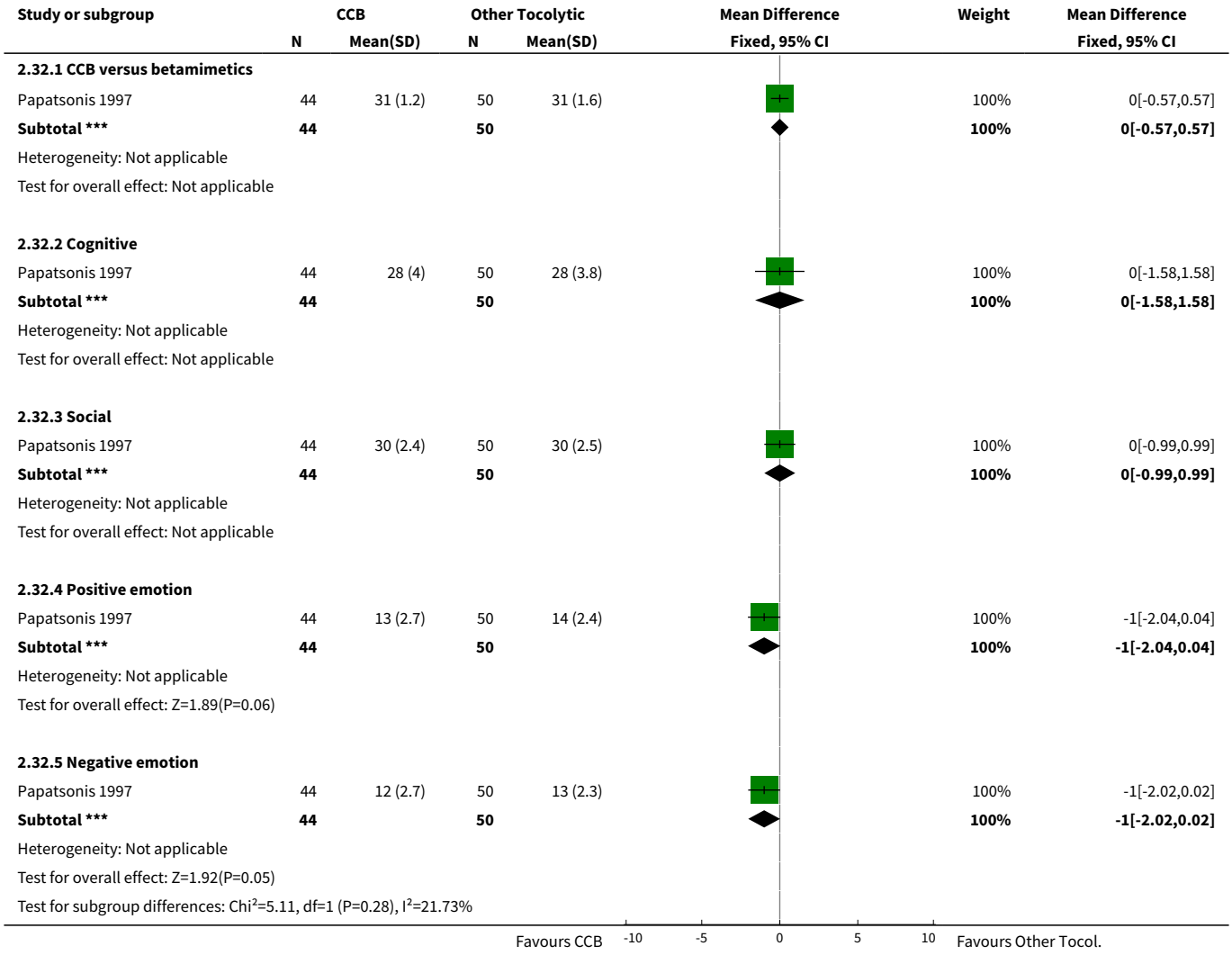


Analysis 2.31. Comparison 2 Calcium channel blockers compared with any other tocolytic agent (subgrouped by other tocolytic), Outcome 31 Quality of life at 9-12 years: motor.



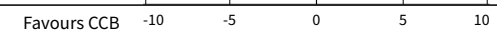


Analysis 2.32. Comparison 2 Calcium channel blockers compared with any other tocolytic agent (subgrouped by other tocolytic), Outcome 32 Quality of life at 9-12 years: autonomy.



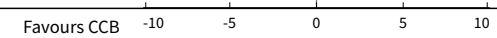
Analysis 2.33. Comparison 2 Calcium channel blockers compared with any other tocolytic agent (subgrouped by other tocolytic), Outcome 33 Quality of life at 9-12 years: cognitive.

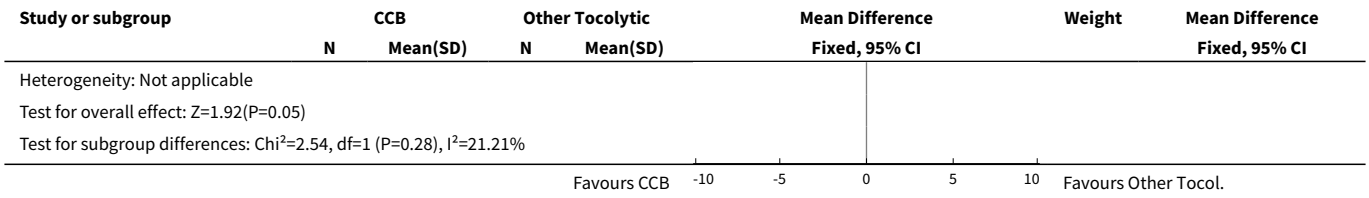
Study or subgroup	CCB N	CCB Mean(SD)	Other Tocolytic N	Other Tocolytic Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
2.33.1 CCB versus betamimetics							
Papatsonis 1997	44	28 (4)	50	28 (3.8)		100%	0[-1.58,1.58]
Subtotal ***	**44**		**50**			**100%**	**0[-1.58,1.58]**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
2.33.2 Social							
Papatsonis 1997	44	30 (2.4)	50	30 (2.5)		100%	0[-0.99,0.99]
Subtotal ***	**44**		**50**			**100%**	**0[-0.99,0.99]**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
2.33.3 Positive emotion							
Papatsonis 1997	44	13 (2.7)	50	14 (2.4)		100%	-1[-2.04,0.04]
Subtotal ***	**44**		**50**			**100%**	**-1[-2.04,0.04]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.89(P=0.06)							
2.33.4 Negative emotion							
Papatsonis 1997	44	12 (2.7)	50	13 (2.3)		100%	-1[-2.02,0.02]
Subtotal ***	**44**		**50**			**100%**	**-1[-2.02,0.02]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.92(P=0.05)							
Test for subgroup differences: Chi^2=3.11, df=1 (P=0.38), I^2=3.44%							



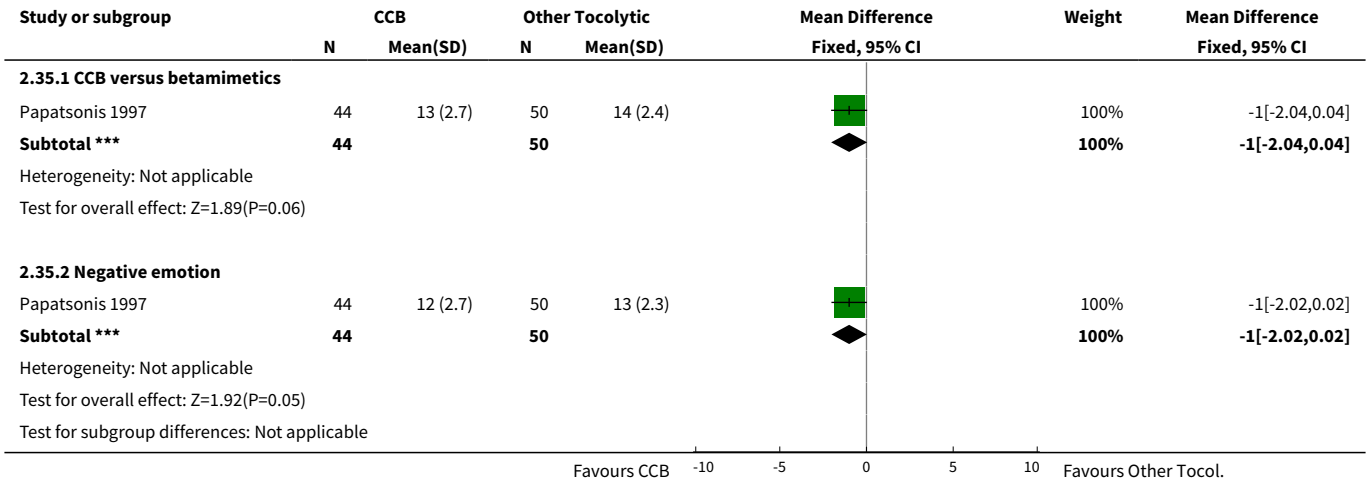
Analysis 2.34. Comparison 2 Calcium channel blockers compared with any other tocolytic agent (subgrouped by other tocolytic), Outcome 34 Quality of life at 9-12 years: social.

Study or subgroup	CCB N	CCB Mean(SD)	Other Tocolytic N	Other Tocolytic Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
2.34.1 CCB versus betamimetics							
Papatsonis 1997	44	30 (2.4)	50	30 (2.5)		100%	0[-0.99,0.99]
Subtotal ***	**44**		**50**			**100%**	**0[-0.99,0.99]**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
2.34.2 Positive emotion							
Papatsonis 1997	44	13 (2.7)	50	14 (2.4)		100%	-1[-2.04,0.04]
Subtotal ***	**44**		**50**			**100%**	**-1[-2.04,0.04]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.89(P=0.06)							
2.34.3 Negative emotion							
Papatsonis 1997	44	12 (2.7)	50	13 (2.3)		100%	-1[-2.02,0.02]
Subtotal ***	**44**		**50**			**100%**	**-1[-2.02,0.02]**

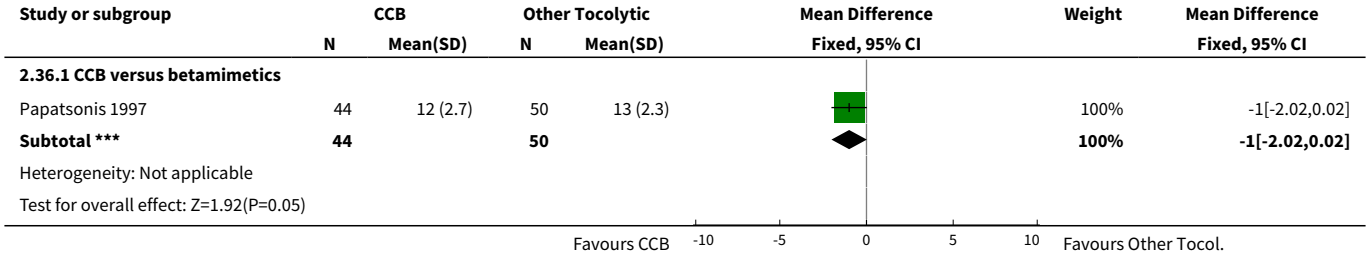




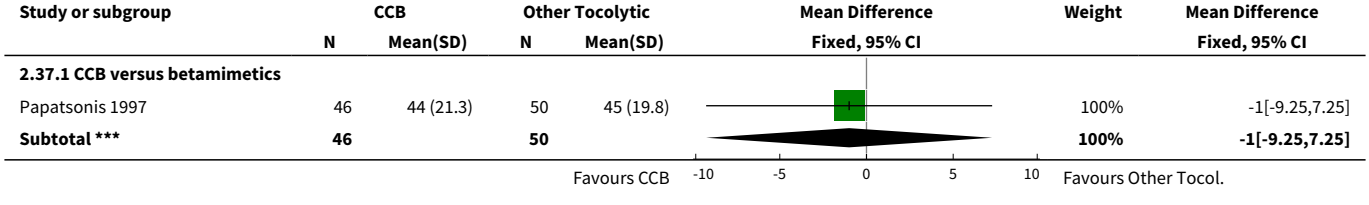
Analysis 2.35. Comparison 2 Calcium channel blockers compared with any other tocolytic agent (subgrouped by other tocolytic), Outcome 35 Quality of life at 9-12 years: positive emotion.

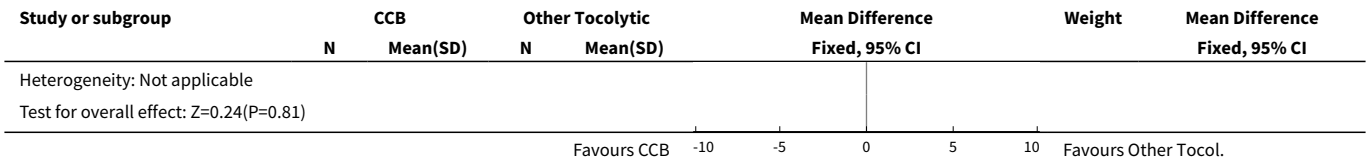


Analysis 2.36. Comparison 2 Calcium channel blockers compared with any other tocolytic agent (subgrouped by other tocolytic), Outcome 36 Quality of life at 9-12 years: negative emotion.



Analysis 2.37. Comparison 2 Calcium channel blockers compared with any other tocolytic agent (subgrouped by other tocolytic), Outcome 37 Parent distress scores at 9-12 years.





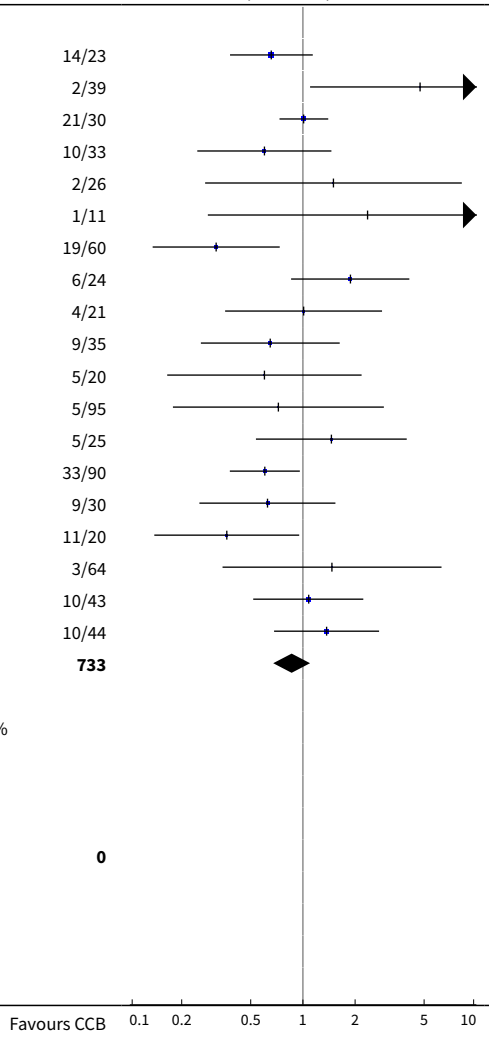
Comparison 3. Calcium channel blockers compared with betamimetics (subgrouped by type of CCB)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Birth within 48 hours after trial entry	19		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Nifedipine compared with betamimetics	19	1505	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.67, 1.10]
1.2 Nicardipine compared with betamimetics	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2 Very preterm birth (before completion of 34 weeks of gestation)	6		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Nifedipine compared with betamimetics	5	544	Risk Ratio (M-H, Fixed, 95% CI)	0.78 [0.66, 0.93]
2.2 Nicardipine compared with betamimetics	1	86	Risk Ratio (M-H, Fixed, 95% CI)	0.5 [0.05, 5.31]
3 Perinatal mortality (fetal death and neonatal death up to 28 days)	17		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 Nifedipine compared with betamimetics	16	1188	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.53, 1.44]
3.2 Nicardipine compared with betamimetics	1	45	Risk Ratio (M-H, Fixed, 95% CI)	0.29 [0.01, 6.84]
4 Interval between trial entry and birth (days)	10		Mean Difference (IV, Random, 95% CI)	Subtotals only
4.1 Nifedipine compared with betamimetics	10	830	Mean Difference (IV, Random, 95% CI)	4.38 [0.25, 8.52]
4.2 Nicardipine compared with betamimetics	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
5 Respiratory distress syndrome	16		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 Nifedipine compared with betamimetics	16	1293	Risk Ratio (M-H, Fixed, 95% CI)	0.64 [0.48, 0.86]
5.2 Nicardipine compared with betamimetics	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6 Discontinuation of therapy for maternal adverse effects	16		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.1 Nifedipine compared with betamimetics	15	1172	Risk Ratio (M-H, Fixed, 95% CI)	0.21 [0.11, 0.40]
6.2 Nicardipine compared with betamimetics	1	45	Risk Ratio (M-H, Fixed, 95% CI)	0.07 [0.00, 1.13]

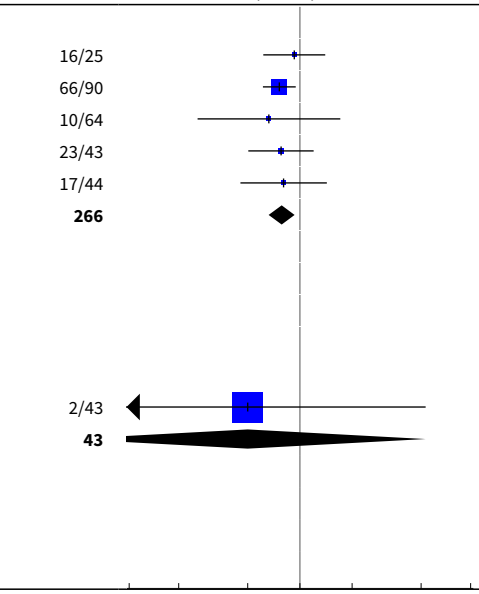
Analysis 3.1. Comparison 3 Calcium channel blockers compared with betamimetics (subgrouped by type of CCB), Outcome 1 Birth within 48 hours after trial entry.

Study or subgroup	CCB n/N	Betamimetics n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
3.1.1 Nifedipine compared with betamimetics					
Al-Qattan 2000	12/30	14/23		9.12%	0.66[0.38,1.14]
Cararach 2006	9/37	2/39		2.4%	4.74[1.1,20.52]
Fan 2003	22/31	21/30		12.93%	1.01[0.73,1.4]
Ferguson 1990	6/33	10/33		5.22%	0.6[0.25,1.46]
Garcia-Velasco 1998	3/26	2/26		1.84%	1.5[0.27,8.25]
George 1991	3/14	1/11		1.23%	2.36[0.28,19.66]
Jaju 2011	6/60	19/60		5.59%	0.32[0.14,0.74]
Koks 1998	15/32	6/24		6.15%	1.88[0.86,4.11]
Kose 1995	10/52	4/21		4.15%	1.01[0.36,2.86]
Kupferminc 1993	6/36	9/35		4.96%	0.65[0.26,1.63]
Laohapojanart 2007	3/20	5/20		2.96%	0.6[0.17,2.18]
Mawaldi 2008	3/79	5/95		2.59%	0.72[0.18,2.93]
Padovani 2012	7/24	5/25		4.4%	1.46[0.54,3.97]
Papatsonis 1997	21/95	33/90		10.44%	0.6[0.38,0.96]
Rayamajhi 2003	6/32	9/30		5.09%	0.63[0.25,1.54]
Read 1986	4/20	11/20		4.67%	0.36[0.14,0.95]
Valdes 2012	4/58	3/64		2.42%	1.47[0.34,6.3]
Van De Water 2008	12/48	10/43		6.72%	1.08[0.52,2.23]
Weerakul 2002	14/45	10/44		7.11%	1.37[0.68,2.75]
Subtotal (95% CI)	**772**	**733**		**100%**	**0.86[0.67,1.1]**
Total events: 166 (CCB), 179 (Betamimetics)					
Heterogeneity: Tau^2=0.09; Chi^2=28.52, df=18(P=0.05); I^2=36.9%					
Test for overall effect: Z=1.19(P=0.23)					
3.1.2 Nicardipine compared with betamimetics					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (CCB), 0 (Betamimetics)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
Test for subgroup differences: Not applicable					



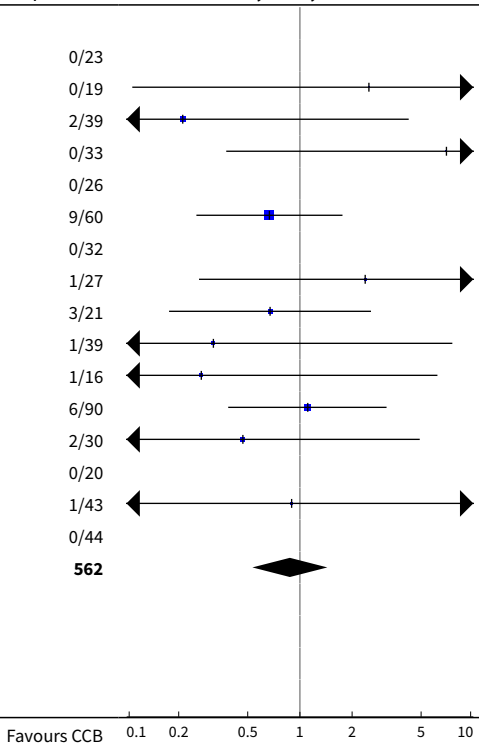
Analysis 3.2. Comparison 3 Calcium channel blockers compared with betamimetics (subgrouped by type of CCB), Outcome 2 Very preterm birth (before completion of 34 weeks of gestation).

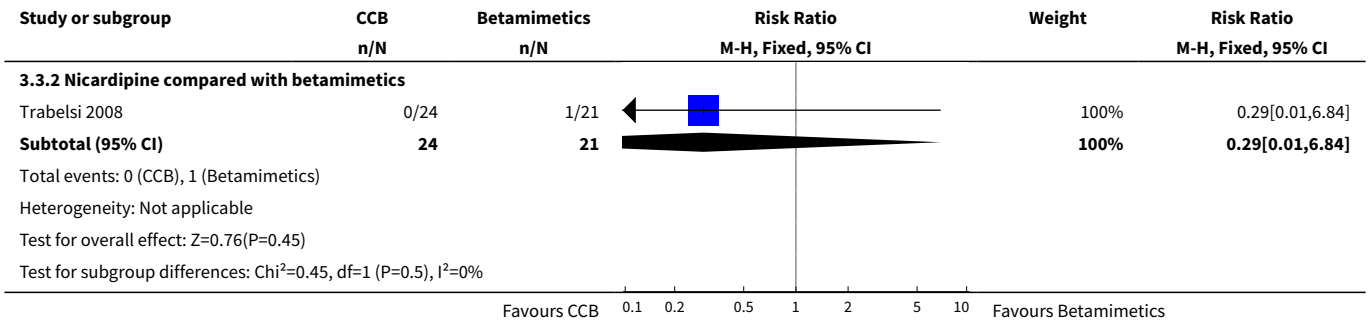
Study or subgroup	CCB n/N	Betamimetic n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
3.2.1 Nifedipine compared with betamimetics					
Koks 1998	19/32	16/25		13.14%	0.93[0.62,1.4]
Papatsonis 1997	53/95	66/90		49.58%	0.76[0.61,0.95]
Valdes 2012	6/58	10/64		6.95%	0.66[0.26,1.71]
Van De Water 2008	20/48	23/43		17.75%	0.78[0.5,1.2]
Weerakul 2002	14/45	17/44		12.57%	0.81[0.45,1.43]
Subtotal (95% CI)	**278**	**266**		**100%**	**0.78[0.66,0.93]**
Total events: 112 (CCB), 132 (Betamimetic)					
Heterogeneity: Tau²=0; Chi²=0.85, df=4(P=0.93); I²=0%					
Test for overall effect: Z=2.76(P=0.01)					
3.2.2 Nicardipine compared with betamimetics					
Jannet 1997	1/43	2/43		100%	0.5[0.05,5.31]
Subtotal (95% CI)	**43**	**43**		**100%**	**0.5[0.05,5.31]**
Total events: 1 (CCB), 2 (Betamimetic)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.57(P=0.57)					
Test for subgroup differences: Chi²=0.14, df=1 (P=0.71), I²=0%					



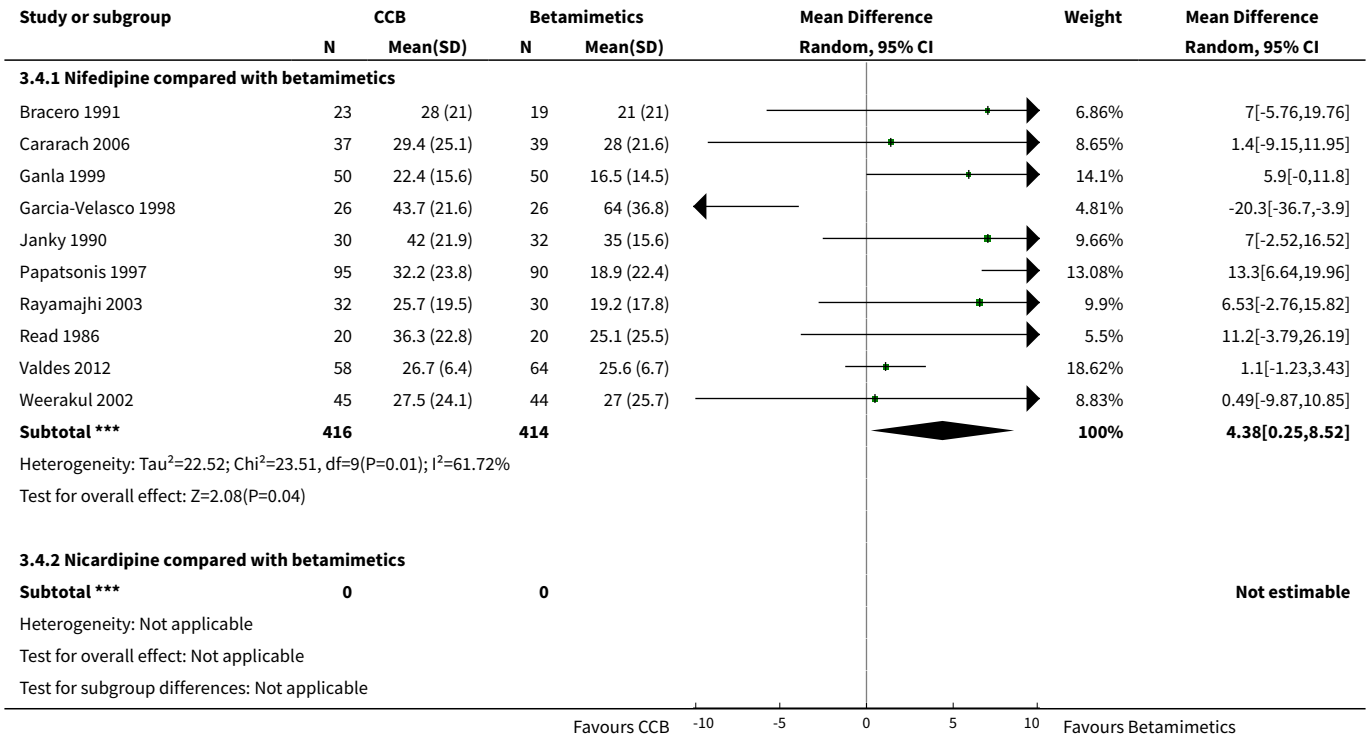
Analysis 3.3. Comparison 3 Calcium channel blockers compared with betamimetics (subgrouped by type of CCB), Outcome 3 Perinatal mortality (fetal death and neonatal death up to 28 days).

Study or subgroup	CCB n/N	Betamimetics n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
3.3.1 Nifedipine compared with betamimetics					
Al-Qattan 2000	0/30	0/23			Not estimable
Bracero 1991	1/23	0/19		1.8%	2.5[0.11,58.06]
Cararach 2006	0/37	2/39		8.03%	0.21[0.01,4.24]
Ferguson 1990	3/33	0/33		1.65%	7[0.38,130.41]
Garcia-Velasco 1998	0/26	0/26			Not estimable
Jaju 2011	6/60	9/60		29.66%	0.67[0.25,1.76]
Janky 1990	0/30	0/32			Not estimable
Koks 1998	3/34	1/27		3.67%	2.38[0.26,21.63]
Kose 1995	5/52	3/21		14.08%	0.67[0.18,2.57]
Kupferminc 1993	0/41	1/39		5.06%	0.32[0.01,7.57]
Laohapojanart 2007	0/20	1/16		5.46%	0.27[0.01,6.21]
Papatsonis 1997	7/95	6/90		20.31%	1.11[0.39,3.16]
Rayamajhi 2003	1/32	2/30		6.8%	0.47[0.04,4.91]
Read 1986	0/20	0/20			Not estimable
Van De Water 2008	1/48	1/43		3.48%	0.9[0.06,13.89]
Weerakul 2002	0/45	0/44			Not estimable
Subtotal (95% CI)	**626**	**562**		**100%**	**0.88[0.53,1.44]**
Total events: 27 (CCB), 26 (Betamimetics)					
Heterogeneity: Tau²=0; Chi²=5.87, df=10(P=0.83); I²=0%					
Test for overall effect: Z=0.52(P=0.6)					

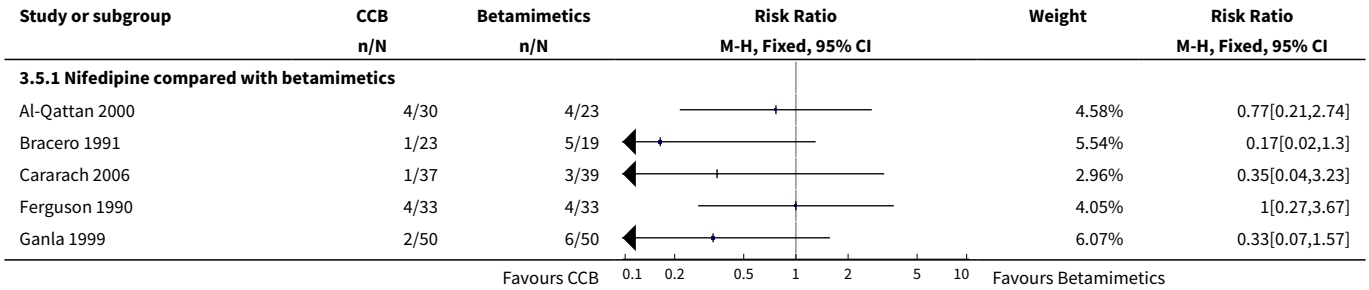


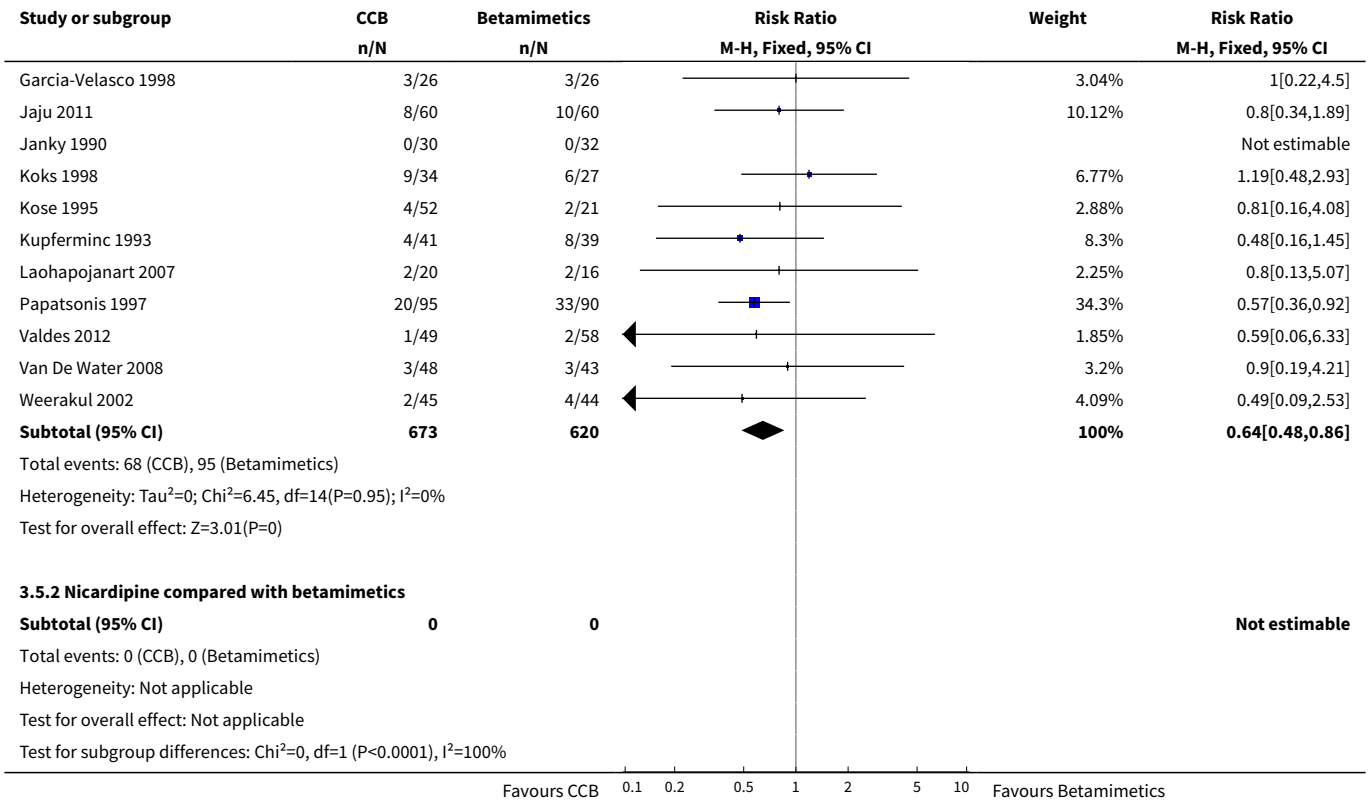


Analysis 3.4. Comparison 3 Calcium channel blockers compared with betamimetics (subgrouped by type of CCB), Outcome 4 Interval between trial entry and birth (days).

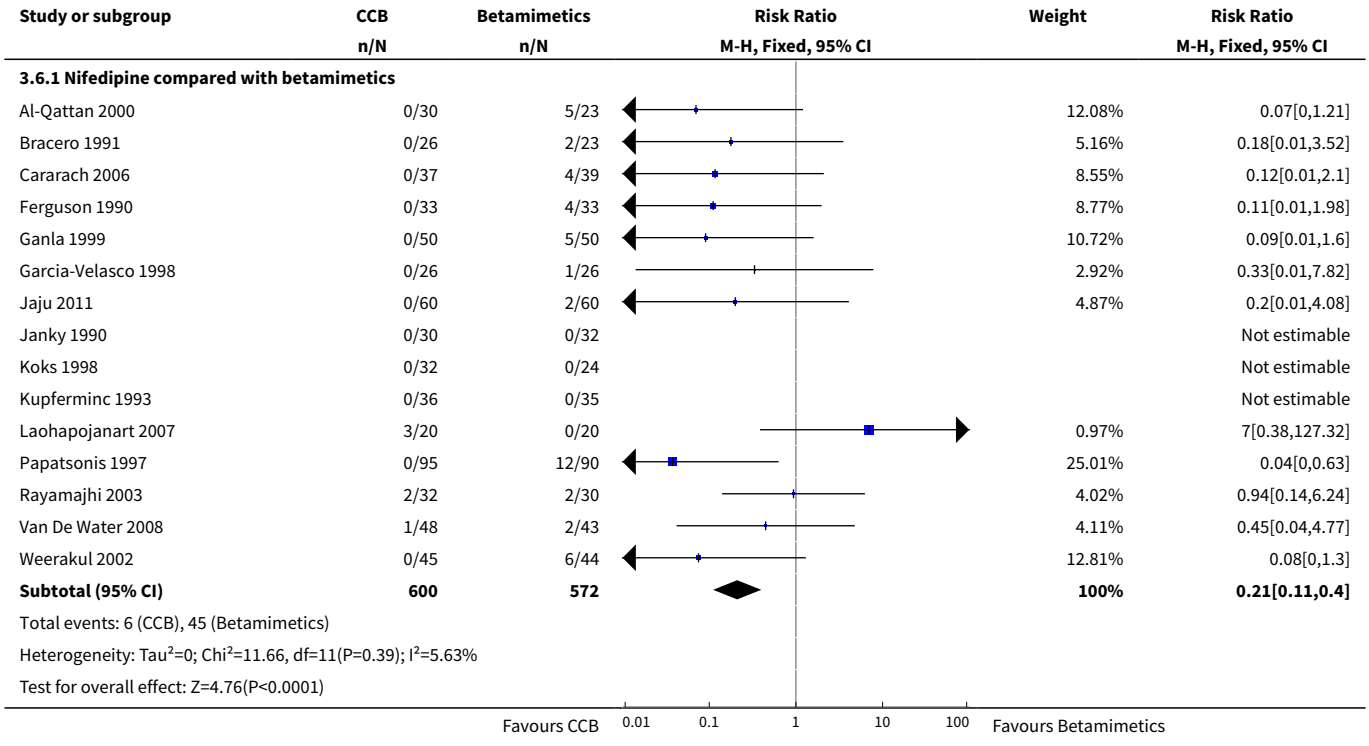


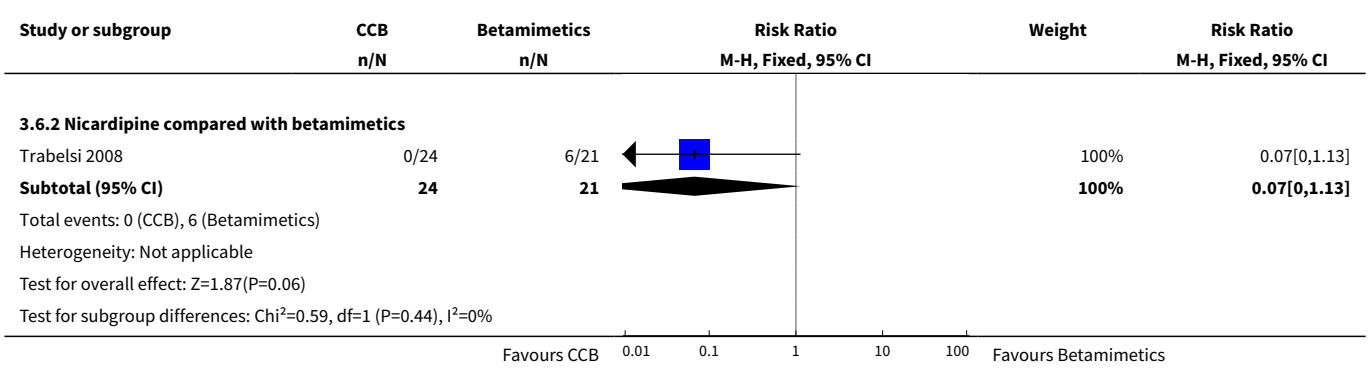
Analysis 3.5. Comparison 3 Calcium channel blockers compared with betamimetics (subgrouped by type of CCB), Outcome 5 Respiratory distress syndrome.





Analysis 3.6. Comparison 3 Calcium channel blockers compared with betamimetics (subgrouped by type of CCB), Outcome 6 Discontinuation of therapy for maternal adverse effects.





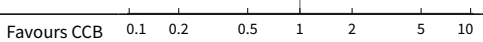
Comparison 4. Calcium channel blockers compared with magnesium sulphate (subgrouped by type of CCB)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Birth within 48 hours after trial entry	5		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Nifedipine compared with magnesium sulphate	4	529	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.60, 1.14]
1.2 Nicardipine compared with magnesium sulphate	1	122	Risk Ratio (M-H, Fixed, 95% CI)	1.14 [0.30, 4.35]
2 Very preterm birth (before completion of 34 weeks of gestation)	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Nifedipine compared with magnesium sulphate	3	307	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.78, 1.23]
2.2 Nicardipine compared with magnesium sulphate	1	122	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.25, 2.06]
3 Perinatal mortality (fetal death and neonatal death up to 28 days)	5		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 Nifedipine compared with with magnesium sulphate	4	535	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.36, 3.13]
3.2 Nicardipine compared with with magnesium sulphate	1	122	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4 Maternal death	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 Nifedipine compared with with magnesium sulphate	1	137	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.2 Nicardipine compared with with magnesium sulphate	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
5 Interval between trial entry and birth (days)	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.1 Nifedipine compared with with magnesium sulphate	1	90	Mean Difference (IV, Fixed, 95% CI)	-5.80 [-18.59, 6.99]
5.2 Nicardipine compared with with magnesium sulphate	1	122	Mean Difference (IV, Fixed, 95% CI)	0.28 [-8.37, 8.93]
6 Respiratory distress syndrome	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
6.1 Nifedipine compared with magnesium sulphate	3	455	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.56, 1.09]
6.2 Nicardipine compared with with magnesium sulphate	1	122	Risk Ratio (M-H, Random, 95% CI)	0.63 [0.23, 1.78]
7 Discontinuation of therapy for maternal adverse effects	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
7.1 Nifedipine compared with with magnesium sulphate	2	217	Risk Ratio (M-H, Random, 95% CI)	1.14 [0.01, 101.65]
7.2 Nicardipine compared with with magnesium sulphate	1	122	Risk Ratio (M-H, Random, 95% CI)	3.41 [0.14, 82.18]

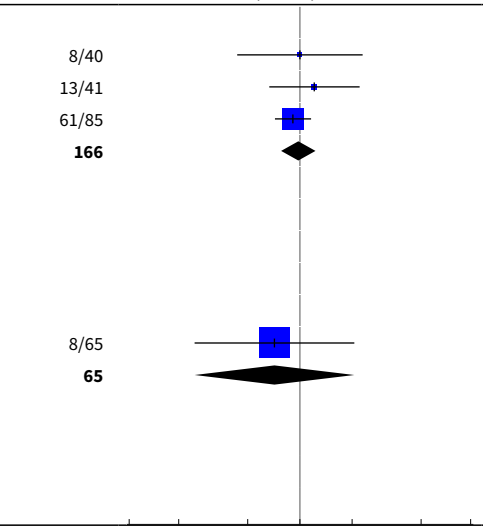
Analysis 4.1. Comparison 4 Calcium channel blockers compared with magnesium sulphate (subgrouped by type of CCB), Outcome 1 Birth within 48 hours after trial entry.

Study or subgroup	CCB n/N	MgSO4 n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
4.1.1 Nifedipine compared with magnesium sulphate					
Glock 1993	3/39	3/41		4.99%	1.05[0.23,4.9]
Klauser 2012	12/52	25/85		32.36%	0.78[0.43,1.42]
Lyell 2007	8/100	7/92		12.43%	1.05[0.4,2.78]
Taherian 2007	22/57	31/63		50.22%	0.78[0.52,1.18]
Subtotal (95% CI)	**248**	**281**		**100%**	**0.83[0.6,1.14]**
Total events: 45 (CCB), 66 (MgSO4)					
Heterogeneity: Tau^2=0; Chi^2=0.42, df=3(P=0.94); I^2=0%					
Test for overall effect: Z=1.14(P=0.25)					
4.1.2 Nicardipine compared with magnesium sulphate					
Larmon 1999	4/57	4/65		100%	1.14[0.3,4.35]
Subtotal (95% CI)	**57**	**65**		**100%**	**1.14[0.3,4.35]**
Total events: 4 (CCB), 4 (MgSO4)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.19(P=0.85)					
Test for subgroup differences: Chi^2=0.2, df=1 (P=0.65), I^2=0%					



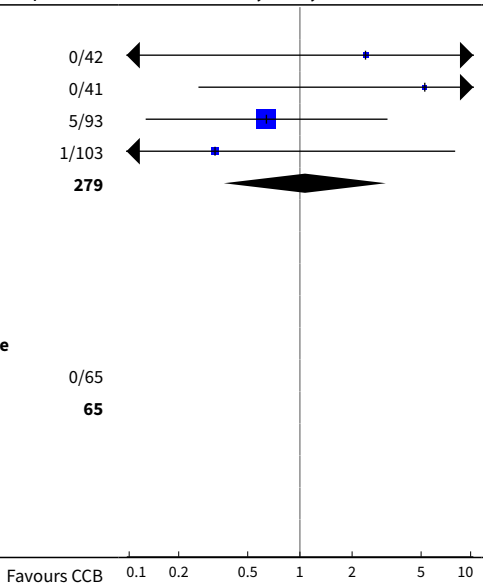
Analysis 4.2. Comparison 4 Calcium channel blockers compared with magnesium sulphate (subgrouped by type of CCB), Outcome 2 Very preterm birth (before completion of 34 weeks of gestation).

Study or subgroup	CCB n/N	MgSO4 n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
4.2.1 Nifedipine compared with magnesium sulphate					
Floyd 1992	10/50	8/40		13.1%	1[0.44,2.3]
Glock 1993	15/39	13/41		18.68%	1.21[0.67,2.21]
Klauser 2012	34/52	61/85		68.23%	0.91[0.72,1.16]
Subtotal (95% CI)	**141**	**166**		**100%**	**0.98[0.78,1.23]**
Total events: 59 (CCB), 82 (MgSO4)					
Heterogeneity: Tau^2=0; Chi^2=0.84, df=2(P=0.66); I^2=0%					
Test for overall effect: Z=0.18(P=0.86)					
4.2.2 Nicardipine compared with magnesium sulphate					
Larmon 1999	5/57	8/65		100%	0.71[0.25,2.06]
Subtotal (95% CI)	**57**	**65**		**100%**	**0.71[0.25,2.06]**
Total events: 5 (CCB), 8 (MgSO4)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.63(P=0.53)					
Test for subgroup differences: Chi^2=0.33, df=1 (P=0.57), I^2=0%					



Analysis 4.3. Comparison 4 Calcium channel blockers compared with magnesium sulphate (subgrouped by type of CCB), Outcome 3 Perinatal mortality (fetal death and neonatal death up to 28 days).

Study or subgroup	Oral CCB n/N	MgSO4 n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
4.3.1 Nifedipine compared with with magnesium sulphate					
Floyd 1992	1/53	0/42		8.69%	2.39[0.1,57.18]
Glock 1993	2/39	0/41		7.61%	5.25[0.26,106.01]
Klauser 2012	2/58	5/93		59.95%	0.64[0.13,3.2]
Lyell 2007	0/106	1/103		23.75%	0.32[0.01,7.86]
Subtotal (95% CI)	**256**	**279**		**100%**	**1.07[0.36,3.13]**
Total events: 5 (Oral CCB), 6 (MgSO4)					
Heterogeneity: Tau^2=0; Chi^2=2.25, df=3(P=0.52); I^2=0%					
Test for overall effect: Z=0.12(P=0.9)					
4.3.2 Nicardipine compared with with magnesium sulphate					
Larmon 1999	0/57	0/65			Not estimable
Subtotal (95% CI)	**57**	**65**			**Not estimable**
Total events: 0 (Oral CCB), 0 (MgSO4)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
Test for subgroup differences: Not applicable					



Analysis 4.4. Comparison 4 Calcium channel blockers compared with magnesium sulphate (subgrouped by type of CCB), Outcome 4 Maternal death.

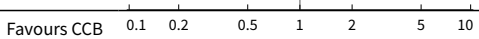
Study or subgroup	CCB n/N	Other tocolytic n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
4.4.1 Nifedipine compared with with magnesium sulphate					
Klauser 2012	0/52	0/85			Not estimable
Subtotal (95% CI)	**52**	**85**			**Not estimable**
Total events: 0 (CCB), 0 (Other tocolytic)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
4.4.2 Nicardipine compared with with magnesium sulphate					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (CCB), 0 (Other tocolytic)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
Test for subgroup differences: Not applicable					

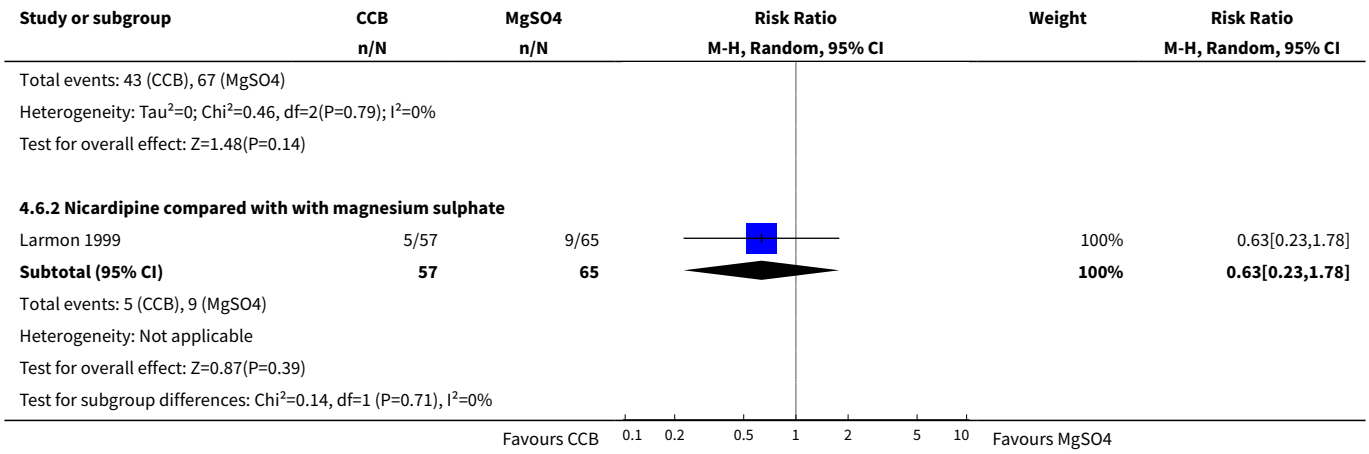
Analysis 4.5. Comparison 4 Calcium channel blockers compared with magnesium sulphate (subgrouped by type of CCB), Outcome 5 Interval between trial entry and birth (days).

Study or subgroup	Oral Nifedipine N	Mean(SD)	ORA N	Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
4.5.1 Nifedipine compared with with magnesium sulphate							
Floyd 1992	50	37.5 (26)	40	43.3 (34.1)		100%	-5.8[-18.59,6.99]
Subtotal ***	**50**		**40**			**100%**	**-5.8[-18.59,6.99]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.89(P=0.37)							
4.5.2 Nicardipine compared with with magnesium sulphate							
Larmon 1999	57	34.9 (25.9)	65	34.7 (22.4)		100%	0.28[-8.37,8.93]
Subtotal ***	**57**		**65**			**100%**	**0.28[-8.37,8.93]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.06(P=0.95)							
Test for subgroup differences: Chi^2=0.6, df=1 (P=0.44), I^2=0%							

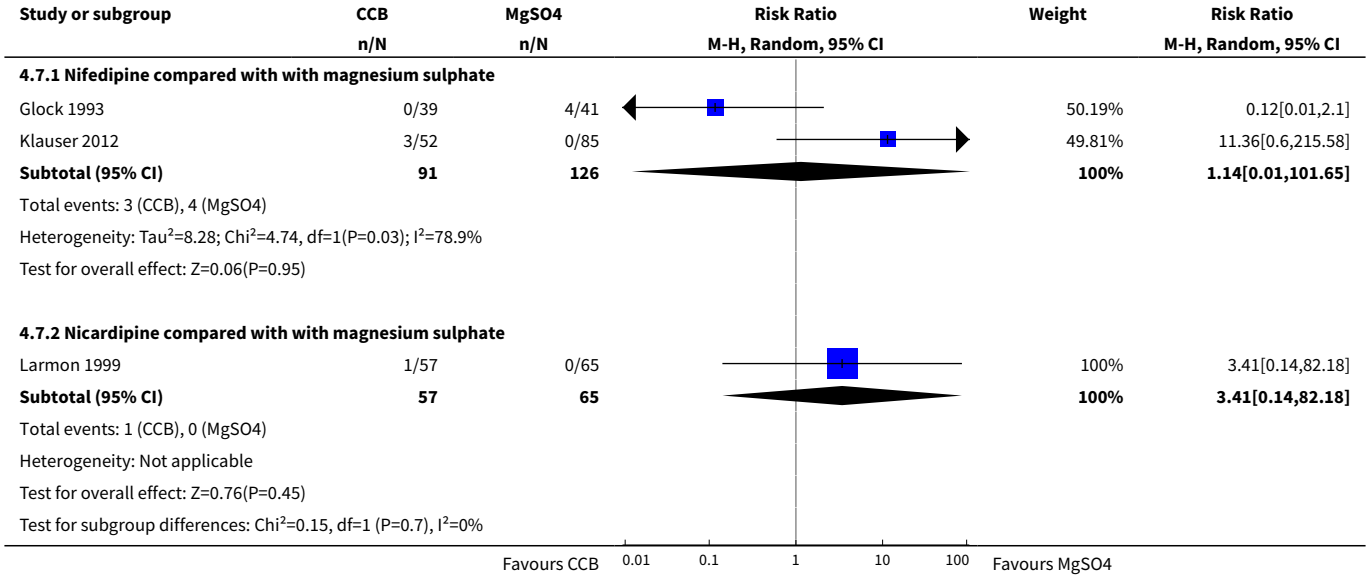
Analysis 4.6. Comparison 4 Calcium channel blockers compared with magnesium sulphate (subgrouped by type of CCB), Outcome 6 Respiratory distress syndrome.

Study or subgroup	CCB n/N	MgSO4 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
4.6.1 Nifedipine compared with magnesium sulphate					
Floyd 1992	5/53	4/42		7.13%	0.99[0.28,3.46]
Klauser 2012	17/58	39/93		51.45%	0.7[0.44,1.11]
Lyell 2007	21/106	24/103		41.42%	0.85[0.51,1.43]
Subtotal (95% CI)	**217**	**238**		**100%**	**0.78[0.56,1.09]**





Analysis 4.7. Comparison 4 Calcium channel blockers compared with magnesium sulphate (subgrouped by type of CCB), Outcome 7 Discontinuation of therapy for maternal adverse effects.

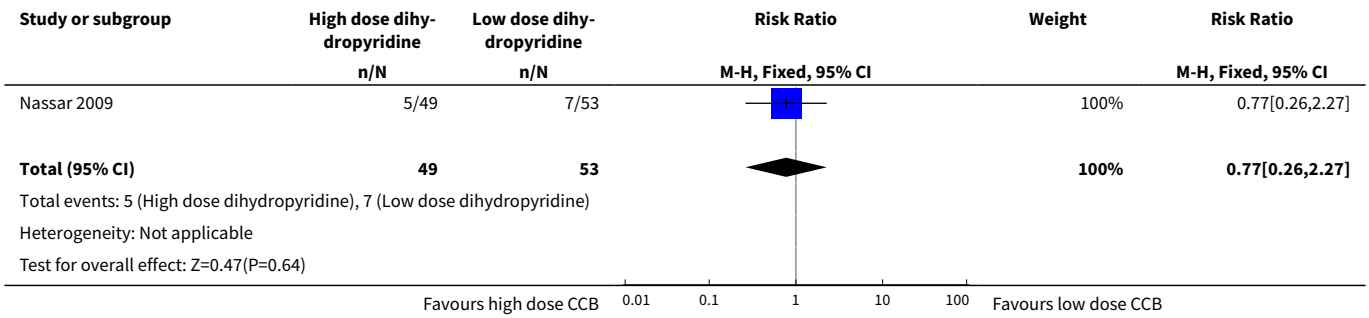


Comparison 5. Higher dose calcium channel blockers compared with lower dose calcium channel blockers

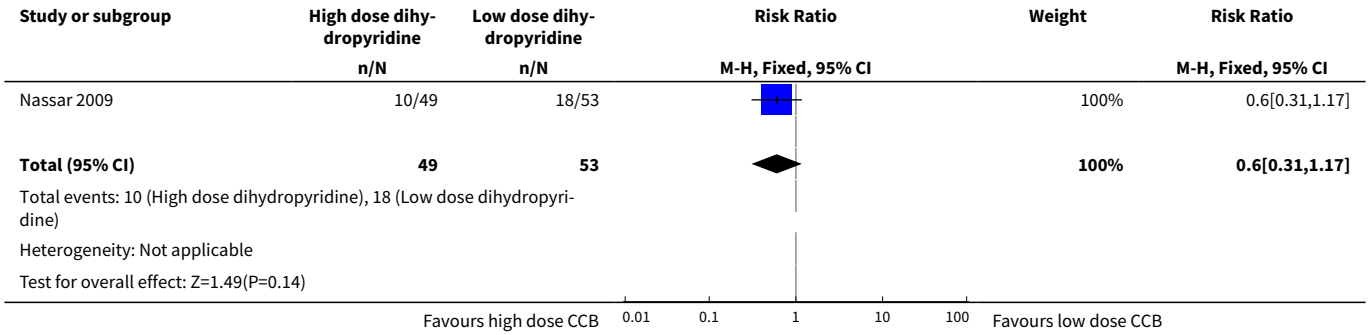
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Birth within 48 hours after trial entry	1	102	Risk Ratio (M-H, Fixed, 95% CI)	0.77 [0.26, 2.27]
2 Very preterm birth (before completion of 34 weeks of gestation)	1	102	Risk Ratio (M-H, Fixed, 95% CI)	0.60 [0.31, 1.17]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3 Extremely preterm birth (before completion of 28 weeks of gestation)	1	102	Risk Ratio (M-H, Fixed, 95% CI)	0.54 [0.05, 5.78]
4 Perinatal mortality (stillbirth and neonatal death up to 28 days)	1	100	Risk Ratio (M-H, Fixed, 95% CI)	0.15 [0.01, 2.92]
5 Stillbirth	1	100	Risk Ratio (M-H, Fixed, 95% CI)	0.36 [0.02, 8.64]
6 Neonatal death	1	100	Risk Ratio (M-H, Fixed, 95% CI)	0.15 [0.01, 2.92]
7 Maternal death	1	102	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
8 Interval between trial entry and birth (days)	1	102	Mean Difference (IV, Fixed, 95% CI)	7.30 [-2.21, 16.81]
9 Gestational age at birth (completed weeks)	1	102	Mean Difference (IV, Fixed, 95% CI)	1.30 [0.03, 2.57]
10 Preterm birth (before completion of 37 weeks of gestation)	1	102	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.63, 1.10]
11 Apgar score < 7 at 5 minutes	1	97	Risk Ratio (M-H, Fixed, 95% CI)	0.09 [0.01, 1.53]
12 Admission to NICU	1	100	Risk Ratio (M-H, Fixed, 95% CI)	0.57 [0.31, 1.05]
13 Respiratory distress syndrome	1	100	Risk Ratio (M-H, Fixed, 95% CI)	0.65 [0.26, 1.65]
14 Necrotising enterocolitis	1	100	Risk Ratio (M-H, Fixed, 95% CI)	0.22 [0.01, 4.39]
15 Neonatal sepsis	1	100	Risk Ratio (M-H, Fixed, 95% CI)	1.08 [0.23, 5.11]
16 Neonatal jaundice	1	100	Risk Ratio (M-H, Random, 95% CI)	0.57 [0.31, 1.05]
17 Intraventricular haemorrhage	1	100	Risk Ratio (M-H, Fixed, 95% CI)	0.12 [0.01, 2.18]
18 Maternal adverse effects	1	102	Risk Ratio (M-H, Fixed, 95% CI)	1.08 [0.33, 3.51]
19 Discontinuation of therapy for maternal adverse effects	1	102	Risk Ratio (M-H, Fixed, 95% CI)	5.4 [0.27, 109.76]
20 Duration of stay in NICU (days)	1	100	Mean Difference (IV, Fixed, 95% CI)	-4.80 [-8.73, -0.87]
21 Duration of maternal hospital stay (days)	1	102	Mean Difference (IV, Fixed, 95% CI)	0.90 [-1.59, 3.39]

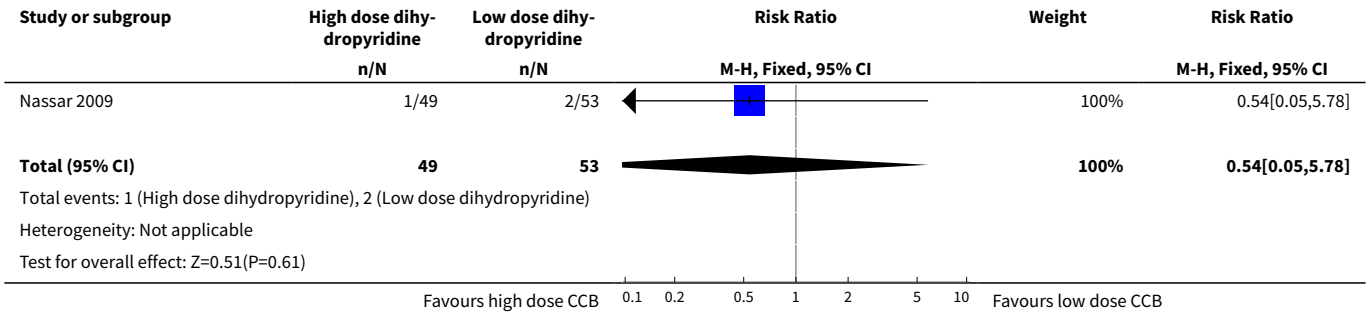
Analysis 5.1. Comparison 5 Higher dose calcium channel blockers compared with lower dose calcium channel blockers, Outcome 1 Birth within 48 hours after trial entry.



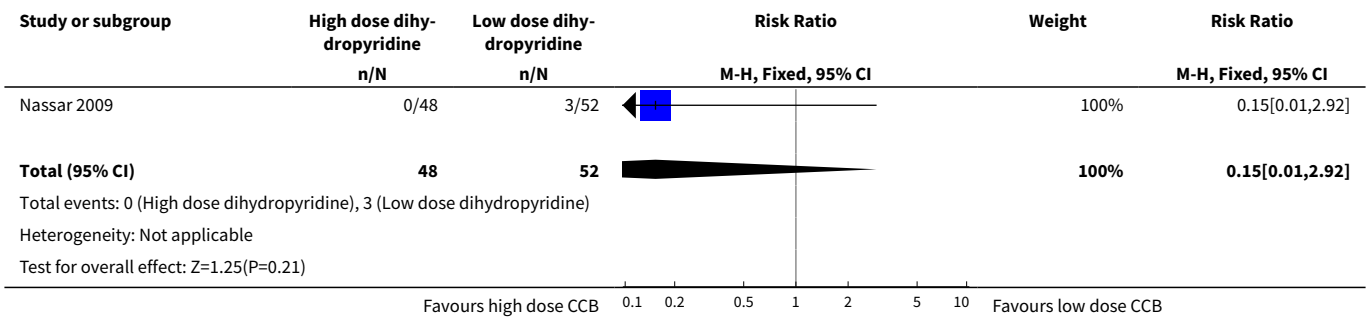
Analysis 5.2. Comparison 5 Higher dose calcium channel blockers compared with lower dose calcium channel blockers, Outcome 2 Very preterm birth (before completion of 34 weeks of gestation).



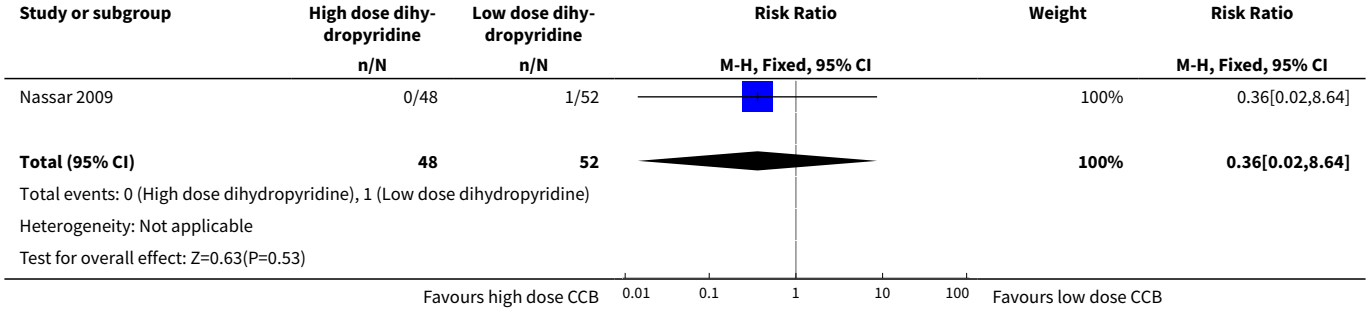
Analysis 5.3. Comparison 5 Higher dose calcium channel blockers compared with lower dose calcium channel blockers, Outcome 3 Extremely preterm birth (before completion of 28 weeks of gestation).



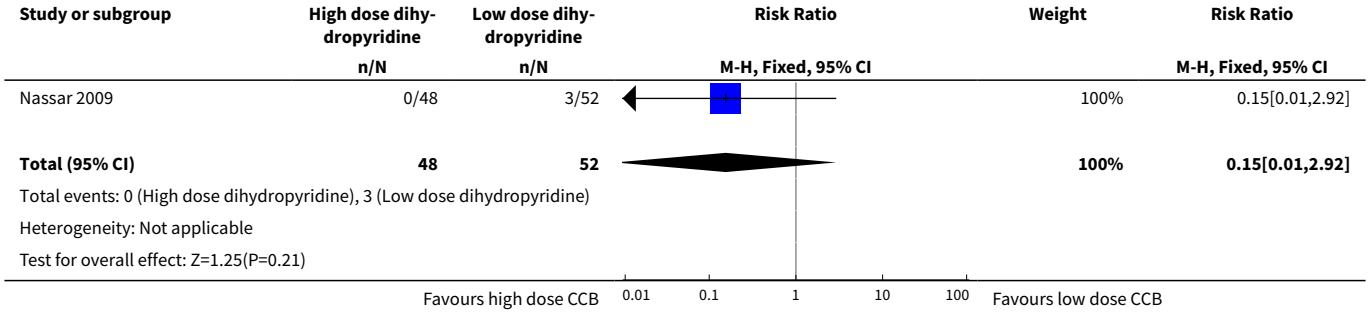
Analysis 5.4. Comparison 5 Higher dose calcium channel blockers compared with lower dose calcium channel blockers, Outcome 4 Perinatal mortality (stillbirth and neonatal death up to 28 days).



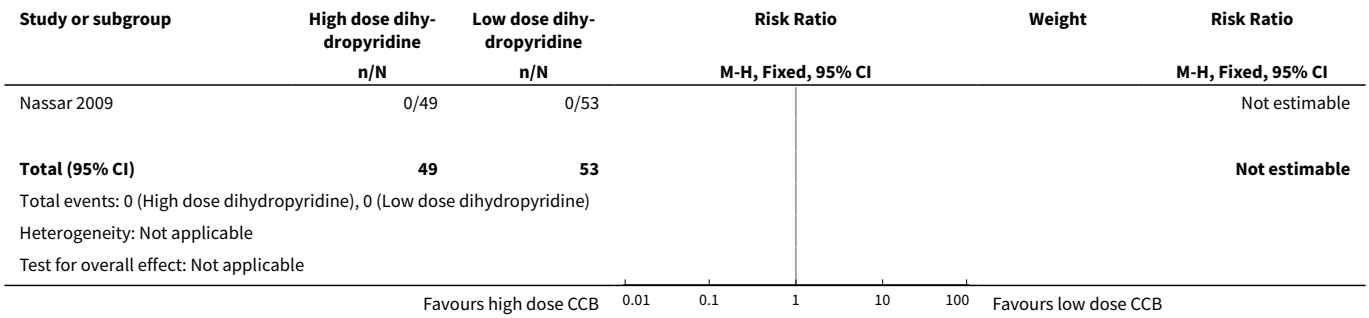
Analysis 5.5. Comparison 5 Higher dose calcium channel blockers compared with lower dose calcium channel blockers, Outcome 5 Stillbirth.



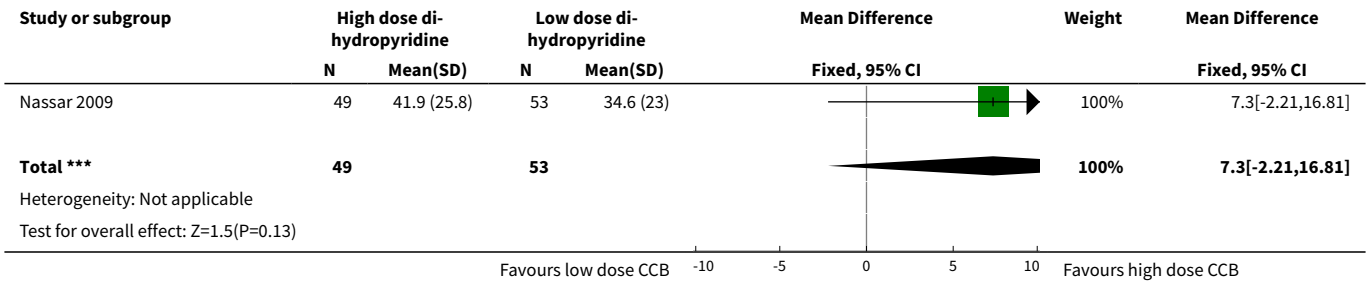
Analysis 5.6. Comparison 5 Higher dose calcium channel blockers compared with lower dose calcium channel blockers, Outcome 6 Neonatal death.



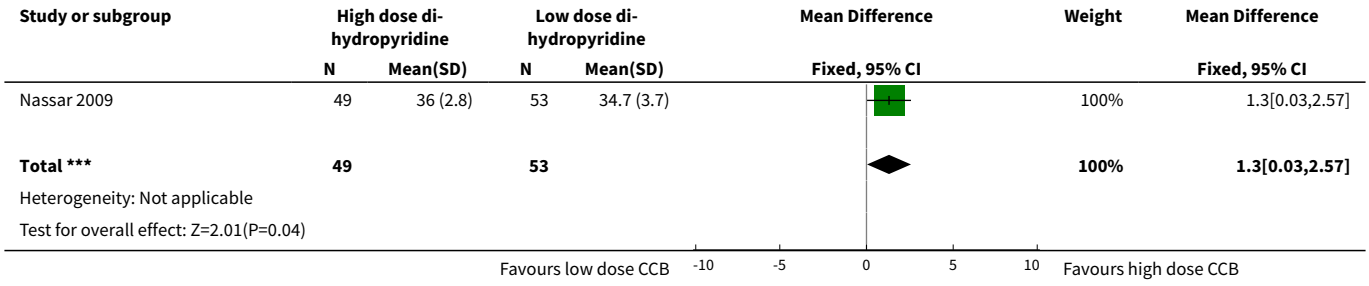
Analysis 5.7. Comparison 5 Higher dose calcium channel blockers compared with lower dose calcium channel blockers, Outcome 7 Maternal death.



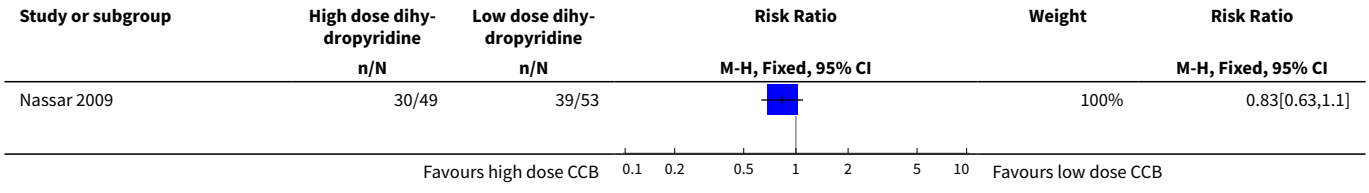
Analysis 5.8. Comparison 5 Higher dose calcium channel blockers compared with lower dose calcium channel blockers, Outcome 8 Interval between trial entry and birth (days).

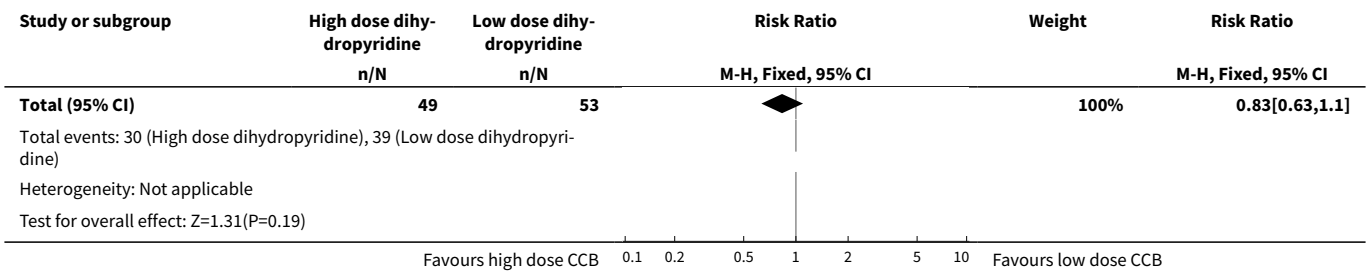


Analysis 5.9. Comparison 5 Higher dose calcium channel blockers compared with lower dose calcium channel blockers, Outcome 9 Gestational age at birth (completed weeks).

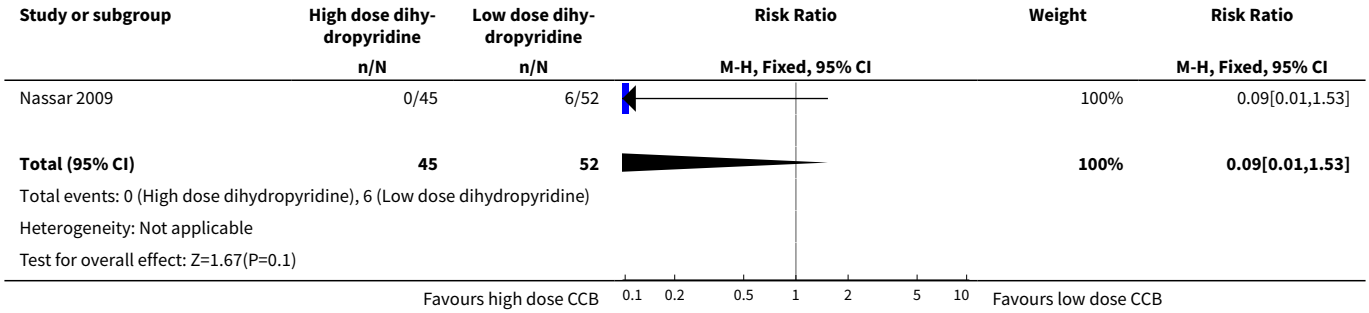


Analysis 5.10. Comparison 5 Higher dose calcium channel blockers compared with lower dose calcium channel blockers, Outcome 10 Preterm birth (before completion of 37 weeks of gestation).

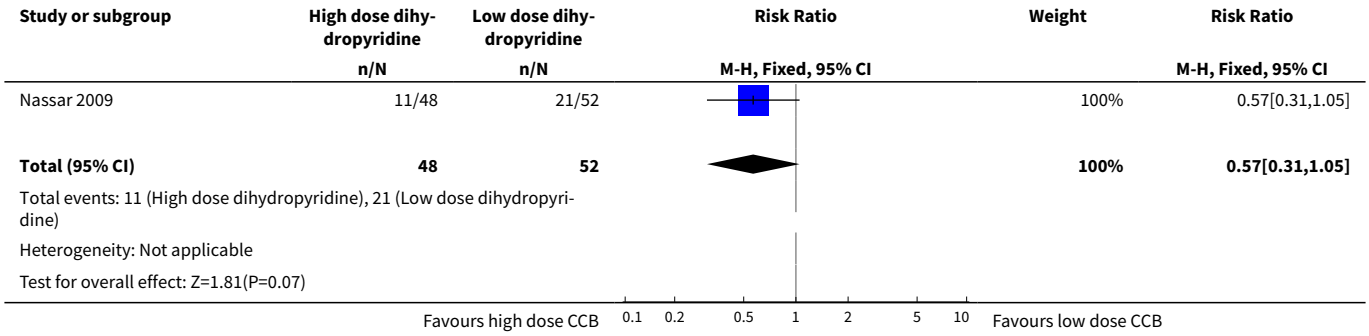




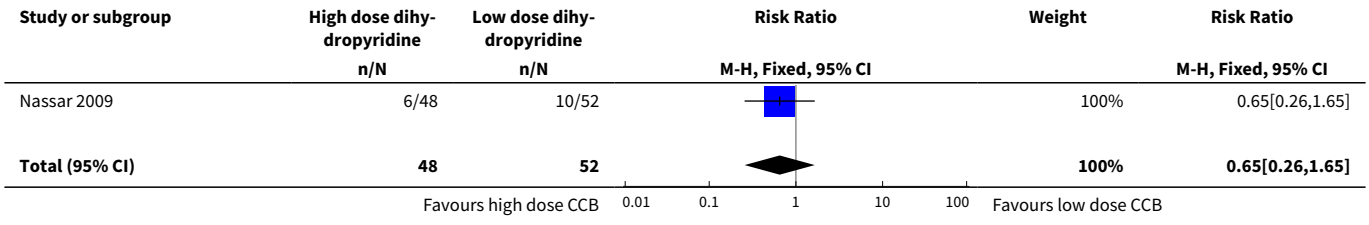
Analysis 5.11. Comparison 5 Higher dose calcium channel blockers compared with lower dose calcium channel blockers, Outcome 11 Apgar score < 7 at 5 minutes.

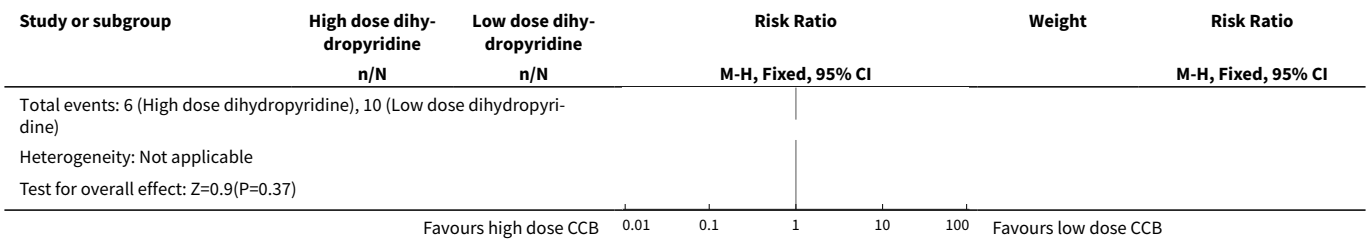


Analysis 5.12. Comparison 5 Higher dose calcium channel blockers compared with lower dose calcium channel blockers, Outcome 12 Admission to NICU.

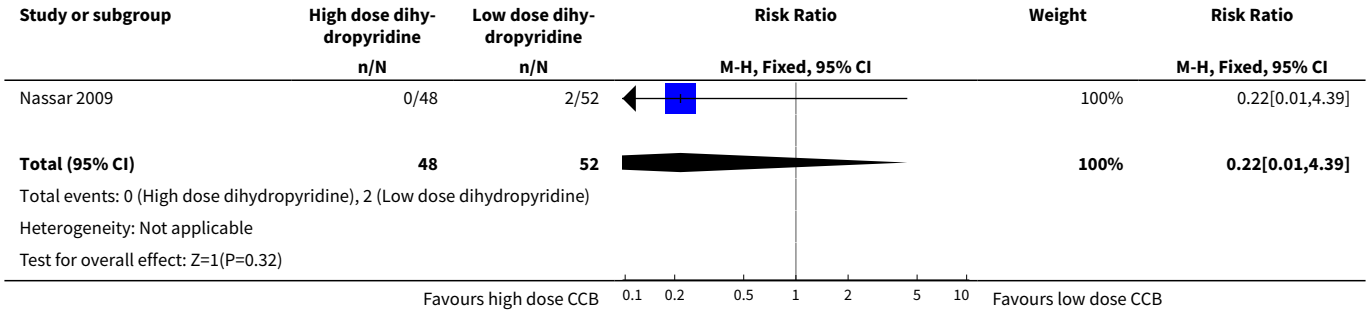


Analysis 5.13. Comparison 5 Higher dose calcium channel blockers compared with lower dose calcium channel blockers, Outcome 13 Respiratory distress syndrome.

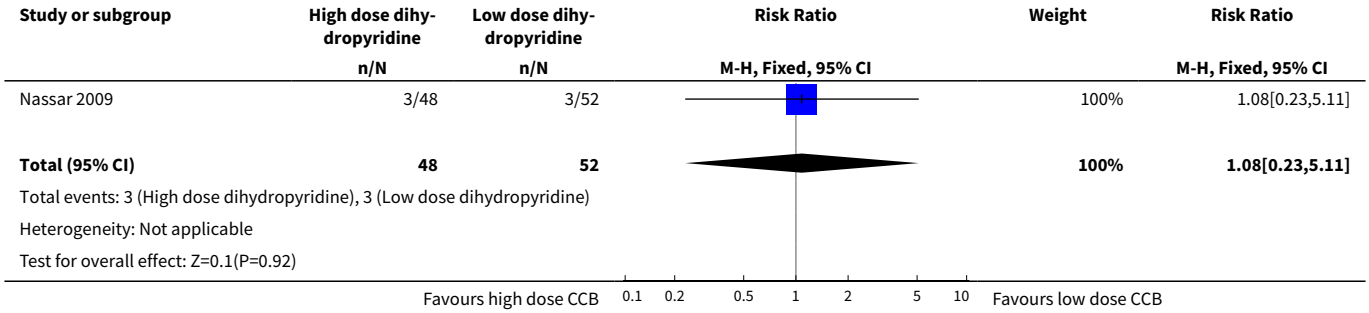




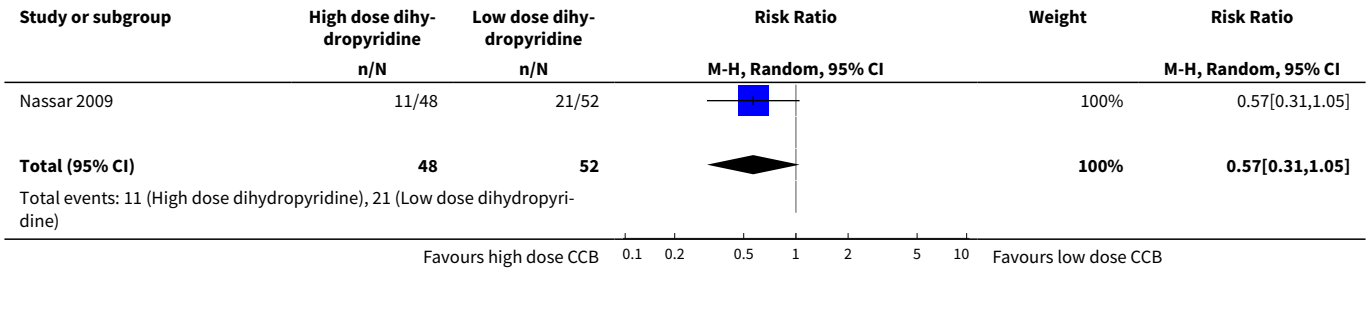
Analysis 5.14. Comparison 5 Higher dose calcium channel blockers compared with lower dose calcium channel blockers, Outcome 14 Necrotising enterocolitis.

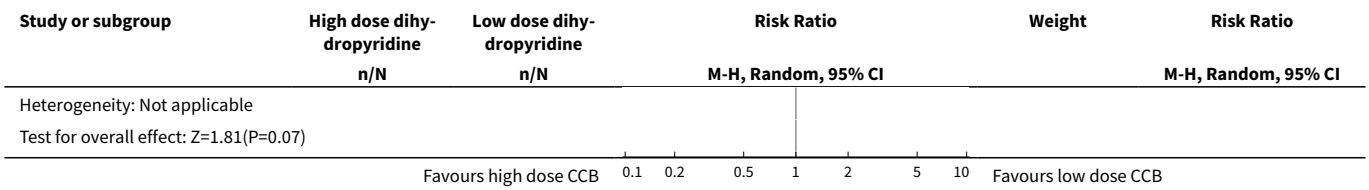


Analysis 5.15. Comparison 5 Higher dose calcium channel blockers compared with lower dose calcium channel blockers, Outcome 15 Neonatal sepsis.

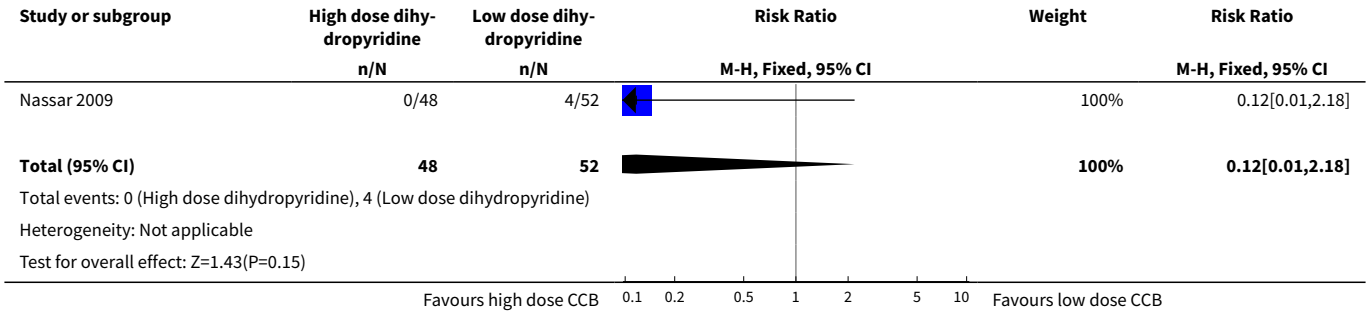


Analysis 5.16. Comparison 5 Higher dose calcium channel blockers compared with lower dose calcium channel blockers, Outcome 16 Neonatal jaundice.

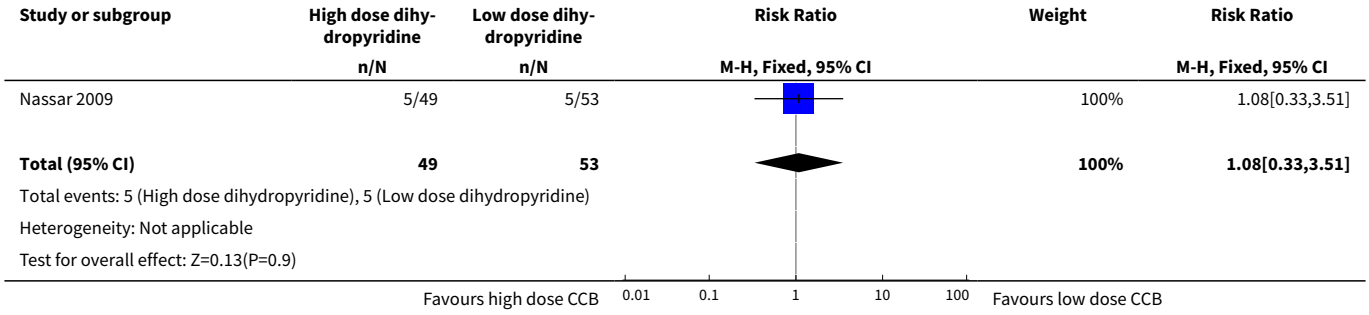




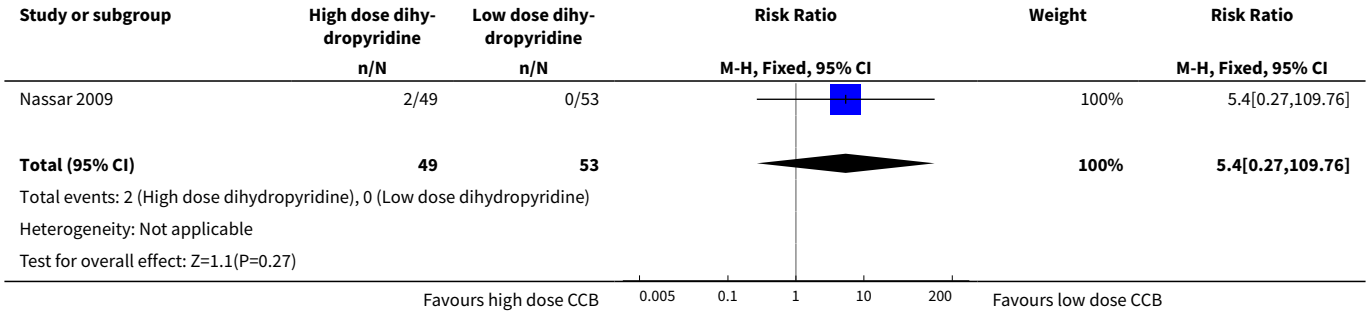
Analysis 5.17. Comparison 5 Higher dose calcium channel blockers compared with lower dose calcium channel blockers, Outcome 17 Intraventricular haemorrhage.



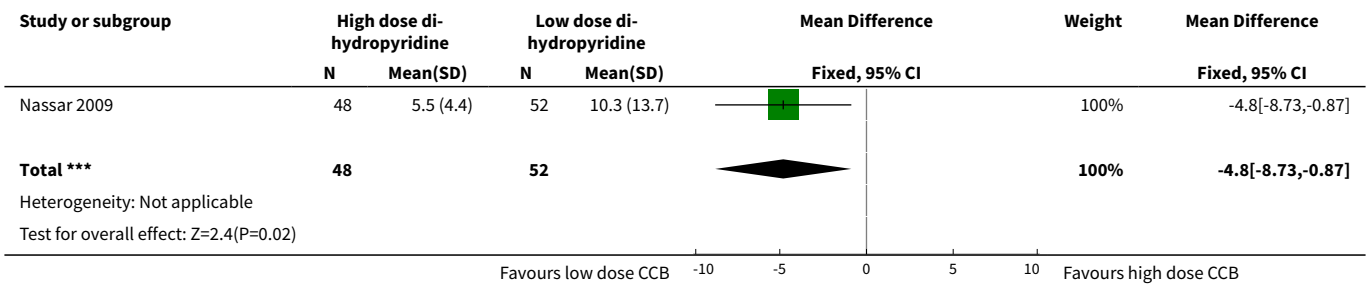
Analysis 5.18. Comparison 5 Higher dose calcium channel blockers compared with lower dose calcium channel blockers, Outcome 18 Maternal adverse effects.



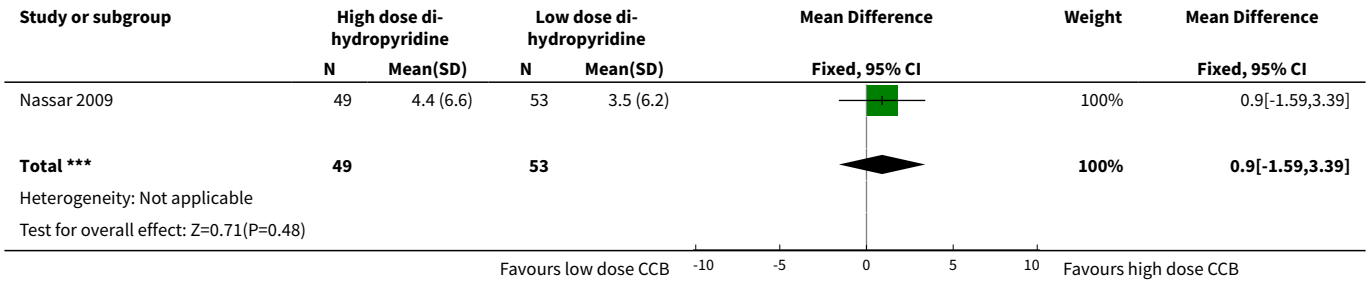
Analysis 5.19. Comparison 5 Higher dose calcium channel blockers compared with lower dose calcium channel blockers, Outcome 19 Discontinuation of therapy for maternal adverse effects.



Analysis 5.20. Comparison 5 Higher dose calcium channel blockers compared with lower dose calcium channel blockers, Outcome 20 Duration of stay in NICU (days).



Analysis 5.21. Comparison 5 Higher dose calcium channel blockers compared with lower dose calcium channel blockers, Outcome 21 Duration of maternal hospital stay (days).



F E E D B A C K

Thornton, 1 July 2006

Summary

I am concerned that there is unintentional bias in favour of the use of calcium channel blockers and against oxytocin antagonists in two recent Cochrane reviews, this one and the review of oxytocin antagonists (1).

Objective judgement of trial quality
Four studies of oxytocin antagonists (European 2001, French/Austr. 2001, Moutquin 2000, and Romero 2000) in the review of oxytocin antagonists (1) are recorded as 'Blinding outcome assessment: unknown' despite their using a double dummy technique with no mention that the blinding was broken. Another, Goodwin 1994, is classified as 'Blinding outcome assessment: no' despite the review authors correctly noting that a double dummy technique was used. The relevant section of the published paper reads as follows: "the pharmacist would open the envelope to reveal the patient's treatment assignment for the purpose of preparing the study drug infusion solution. The treatment assignment was not revealed to other persons, and the individual preparing the drug was not involved in patient care." Surely all five trials should be classified as 'Blinding outcome assessment: yes'.

Subjective judgement of trial quality
In the text of the calcium channel review, the trials are classified as of reasonable quality and no statement is made about quality in the abstract.

In fact none were blinded; they were all relatively small (mean group size 43) and only four had performed a sample size calculation. The lack of blinding is particularly important since all the reported outcomes favouring calcium channel blockers are susceptible to biased ascertainment, and the only hard outcome, perinatal death, showed a trend against calcium channel blockers (see below).

In contrast the oxytocin antagonist reviewers classify Goodwin 1996a as 'not high quality' because it was unblinded.

Choice of outcomes to report in the abstract

The calcium channel review abstract finds space to report seven beneficial effects of calcium channel blockers on surrogate outcomes, either prolongation of labour or surrogate fetal outcomes, but fails to mention perinatal deaths which had a relative risk 1.65 (95% CI 0.74-3.64) favouring other tocolytics. Nor are total pregnancy losses mentioned. These would include the four neonatal deaths reported by Koks 1993 in a ratio of 3:1 against calcium channel blockers.

In the oxytocin antagonist review (1) abstract, five unfavourable conclusions against placebo are reported. Although all of them might be explained by the gestational age imbalance at trial entry in the relevant trial (Romero 2000), this qualification is only mentioned in relation to one, infant death, and is removed from the synopsis where the association is repeated. In the comparison with beta-mimetics, the first outcome reported is birth weight under 1,500g, an outcome which was not pre-specified in the review methods and which is the only statistically significant outcome out of 21 reported for this comparison. Only later is the reduction in adverse drug reactions compared to beta-mimetics reported.

Choice of language
In the review of calcium channel blockers, all of the seven sentences in the abstract conclusions and the plain language summary contain a favourable opinion of calcium channel blockers. The single exception is a call for research into the effect of different dosing regimes, with the implication that the primary effectiveness question has been answered.

The authors' conclude: "it is considered unlikely that [placebo controlled trials of calcium channel blockers] will be conducted given the unequivocal impact that this method of tocolysis has on short term postponement of delivery". This statement is much too strong. It is based entirely on unblended trials against other tocolytics. Two of the five relevant outcomes (birth prior to 37 weeks, and birth within 48 hours) showed only a non-significant effect, two (birth prior to 34 weeks and within seven days) just reached the 0.05 level, and the final outcome (pregnancy prolongation in days), while statistically significant, shows significant heterogeneity between trials.

In neither the abstract nor the conclusion section of the calcium channel blocker review is it mentioned that there have been no placebo-controlled trials of calcium channel blockers in preterm labour.

In contrast, instead of saying that oxytocin antagonists had shown equivalent efficacy to other tocolytics in four high quality trials, the authors phrase their summaries as either 'has failed to demonstrate superiority' or 'is no better than other drugs'. This seems gratuitous negativity.

Choice of outcomes to report
The outcomes selected for the oxytocin review differ significantly from those chosen for the calcium channel blocker review. The reason is not clear.

Finally, the oxytocin antagonist review claims to be going to look at predefined outcomes measured related to the prolongation of pregnancy. However the predefined outcomes for the two placebo-controlled trials, namely 'time to delivery' or 'therapeutic failure' were not reported.

Authorship of the reviews
I note that both these reviews share an author, Dimitri Papatsonis, who is the first author of the largest trial of calcium channel blockers, upon which many of the favourable calcium channel blocker meta analyses depend.

I recognise that it is probably impossible to always avoid using trial authors to write systematic reviews, and that Dr Papatsonis acknowledges his possible conflict of interest. Nor do I accuse him, or any of the review authors, of any intentional bias. Nevertheless, I am concerned about possible unintentional bias against commercially developed pharmacological agents. This risks harming the future development of drugs for use in pregnancy, something which I am sure everyone would support.

Conflict of Interest
I have acted as advisor to Ferring and when I was editor of BJOG the journal received sponsorship from Ferring to publish supplements.

Jim Thornton, July 2006

References
Papatsonis D, Flenady V, Cole S, Liley H. Oxytocin receptor antagonists for inhibiting preterm labour. Cochrane Database of Systematic Reviews 2005, Issue 3. Art. No.: CD004452. DOI: 10.1002/14651858.CD004452.pub2.

Reply

On behalf of the review authors, we respond to Professor Thornton's comments about the review of calcium channel blockers (CCB) [1] and the review of oxytocin receptor antagonists (ORA) [2] for preventing preterm birth.

Judgement of trial quality
For the ORA review, blinding of the intervention is not synonymous with blinding of outcome assessment. Unless authors stated so in their original reports, or in response to further queries, we cannot presume that those assessing the outcome of interest were blinded to the allocated intervention. For example, in trials comparing betamimetics with atosiban, blinding of the intervention is difficult due to the

maternal and fetal side effects of betamimetics, particularly tachycardia and maternal palpitations. Therefore, until further information is received from the trial authors, blinding of assessment of outcome is classified as "unknown" for these four trials (European 2001, French/Austr. 2001, Moutquin 2000, and Romero 2000). We agree Goodwin 1994 should also be classified as "unknown", and this is now corrected.

We disagree that assessment of trial quality was subjective. The statements "reasonable quality" used in the calcium channel blocker (CCB) review and "not high quality" in the ORA review are intended to imply that the trials were neither poor quality nor high quality. Studies were judged to be of poor quality if no adequate method of allocation concealment was described, as this is one of the most important quality indicators regardless of whether the intervention was blinded. In accordance with Cochrane methodology, small numbers and lack of sample size calculations were not considered indicators of trial quality.

Choice of outcomes to report in the abstract
For the CCB review, we believe we have adequately acknowledged the potential for bias in the ascertainment of neonatal outcomes. We also note that the results were consistent across the included trials, but acknowledge that this does not rule out bias. A statement regarding trial quality will be included in the abstract for the next update of the CCB review

The outcome measures in the abstract of the CCB review were considered to be clinically important outcomes for this review. We will include the outcome of perinatal mortality in the abstract for the next update of the review.

In the ORA review abstract, the potential for bias due to the gestational age imbalance at trial entry in the Romero trial is acknowledged. We have made it clearer how this relates to the other data presented by stating at the start of this paragraph the number of trials and women in this comparison. We prespecified birthweight as a clinically important outcome measure for the review, and considered it reasonable to include the finding of birthweight <1500gms in the abstract. In the abstract results, the ordering of text on maternal drug reaction for the comparison of ORA with betamimetics provides consistency with the reporting of the outcomes for the comparison of atosiban versus placebo.

Choice of language
We appreciate that the upper confidence interval for a number of the statistically significant outcomes reported approached 1, no difference. However, based on the point estimates of the effects and the consistency in the findings across these outcomes, we believe that the conclusions of the CCB review and wording of the abstract accurately reflects the findings. The statistical heterogeneity found for the outcome of pregnancy prolongation we believe was appropriately managed in this review with the use of a random-effects model for the meta-analysis of this outcome.

While we feel the language used in the ORA review abstract accurately reflects the results, we will rephrase to take account of the perception we may have been too negative about atosiban.

Choice of outcomes to report
We accept the outcomes for the ORA and CCB reviews differ, as they do in other tocolysis reviews, and that this is not helpful for readers of the review. As there is overlap between the review teams for these two reviews, we will rectify this during the next update of these reviews.

Regarding the use of 'predefined' outcomes, this term relates to outcomes chosen by the reviewers as clinically meaningful and defined in the review protocol before the review begins. These outcomes may or may not match those reported for individual trials. If reported outcomes did not match those pre-specified for the review, wherever possible, additional information was sought from authors. For the placebo controlled trials in the ORA review, data on pregnancy prolongation was not provided in a format to enable inclusion in the review; while additional data were sought from the authors, these were not forthcoming. The outcome of "therapeutic failure" was reported in the individual trials, but was not chosen as an outcome for either the ORA or CCB reviews as it was considered susceptible to bias.

Authorship of the reviews
Whilst it is appropriate and common practice for experts to undertake systematic reviews within their area of expertise, we agree that this carries with it the potential for bias. For Cochrane reviews, however (including the ORA and CCB reviews), a number of steps are in place to ensure that this risk is minimised. These steps include: transparency of the review process through publication of the protocol for the review prior to commencement, rigorous peer review (including an external referee) of the protocol and the review, multiple review authors aiming for a mix of expertise and experience, and a feedback system which allows anyone to comment on reviews and protocols. In addition, the regular updating of reviews means that any errors or misperceptions can be corrected. We think it unlikely therefore that any harm will come to future development of drugs for use in pregnancy due to bias, whether intentional or not, in our review.

(Summary of response, October 2007: Vicki Flenady, Dimitri Papatsonis, James King and Helen Liley on behalf of the authors for the ORA and CCB reviews.)

References

[1] King JF, Flenady VJ, Papatsonis DNM, Dekker GA, Carbonne B. Calcium channel blockers for inhibiting preterm labour. Cochrane Database of Systematic Reviews 2003, Issue 1. Art. No.: CD002255. DOI: 10.1002/14651858.CD002255.

[2] Papatsonis D, Flenady V, Cole S, Liley H. Oxytocin receptor antagonists for inhibiting preterm labour. Cochrane Database of Systematic Reviews 2005, Issue 3. Art. No.: CD004452. DOI: 10.1002/14651858.CD004452.pub2.

Contributors

Feedback: Jim Thornton
Response: Vicki Flenady, Dimitri Papatsonis, James King and Helen Liley on behalf of the authors for the ORA and CCB reviews

WHAT'S NEW

Date	Event	Description
30 June 2014	Amended	Risk of bias tables amended to include correct domain headings.

HISTORY

Protocol first published: Issue 3, 2000
Review first published: Issue 2, 2002

Date	Event	Description
1 April 2014	New citation required but conclusions have not changed	Review updated. This review update includes 26 additional trials involving 2511 women, giving a total of 38 included trials involving 3550 women. The review now includes two trials (173 women) comparing calcium channel blockers (nifedipine) with placebo or no treatment. Primary and secondary outcomes were revised to more clearly and comprehensively address important outcome measures and to enhance consistency with other Cochrane reviews of tocolytics for preterm birth. Subgroup analyses according to intervention were also revised for greater clinical relevance, and new subgroup analyses have been introduced to allow comparisons of calcium channel blockers with specific classes of tocolytics and also by type of calcium channel blockers.
12 November 2013	New search has been performed	Search updated.
10 January 2011	Amended	Contact details updated.
4 January 2010	Amended	Search updated. Twenty-six reports added to Studies awaiting classification.
29 January 2009	Amended	Author contact details edited.
31 October 2008	Amended	Converted to new review format.
14 November 2007	Feedback has been incorporated	Response to feedback added.
1 October 2002	New search has been performed	This review updates the review 'Calcium channel blockers for inhibiting preterm labour ' which was first published in *The Cochrane Library* Issue 2, 2002. This update includes published and unpublished data from one additional trial (Weerakul 2002) and unpublished information from the author of one previously included trial (Larmon

Date	Event	Description
		1999). The review now contains twelve trials which enrolled 1029 women. The extra data included in this review result in a marginal decrease in the previously demonstrated effect on the outcome of birth within 48 hours of commencement of treatment (no longer statistically significant) but show a reduction (which reached statistical significance) in the outcome of birth prior to 34 weeks associated with the use of calcium channel blockers. These additional data strengthen the beneficial effect of calcium channel blockers on several neonatal outcomes. The conclusions of the earlier version of the review remain basically unchanged. Calcium channel blockers are a safer and more effective tocolytic agent than betamimetics for mothers and babies

CONTRIBUTIONS OF AUTHORS

Vicki Flenady, Linda Murray, Aleena M Wojcieszek and Owen Stock undertook data extraction, quality assessments and revisions of the review for the current update. All authors assisted with the interpretation and final editing of the review.

James King, Vicki Flenady and Dimitri Papatsonis undertook independent quality assessments, data extraction, resolved differences by discussion and assembled the initial version of the review.

DECLARATIONS OF INTEREST

Vicki Flenady: nothing to declare.

Aleena M Wojcieszek: nothing to declare.

Dimitri NM Papatsonis: D Papatsonis is a co-author on a non-Cochrane systematic review of nifedipine and beta-agonists (Tsatsaris 2001) and was a co-author of a randomised trial of nifedipine and ritodrine for preterm labour (Papatsonis 1997).

Owen M Stock: I am supported by an NHMRC Medical/Dental Postgraduate Scholarship as I am currently undertaking a PhD.

Linda Murray: nothing to declare.

Luke A Jardine: nothing to declare.

Bruno Carbonne: B Carbonne is a co-author on a non-Cochrane systematic review of nifedipine and beta-agonists (Tsatsaris 2001). B Carbonne assisted in the organisation of a symposium with Ferring laboratories and has also participated as a speaker in meetings/symposia organised by Ferring. Funds in relation to these activities were provided by Ferring to B Carbonne's institution.

SOURCES OF SUPPORT

Internal sources

- Department of Perinatal Medicine, Royal Women's Hospital, Melbourne, Victoria, Australia.
- Centre for Clinical Studies-Women's and Children's Health, Mater Hospital, South Brisbane, Queensland, Australia.
- J P Kelly Research Foundation, Mater Hospital, South Brisbane, Queensland, Australia.

External sources

- Department of Health and Ageing, Commonwealth Government, Canberra, Supporting Centre for Clinical Studies, Mater Hospital, Brisbane, Australia.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We revised the objectives and outcome measures to conform with recent consensus following consultation with the editors and authors of the individual tocolysis reviews of the Cochrane Pregnancy and Childbirth Group i.e. comparisons by class of drug rather than specific drug. We also included a subgroup analysis by type of CCB.

INDEX TERMS

Medical Subject Headings (MeSH)

Adrenergic beta-Agonists [therapeutic use]; Calcium Channel Blockers [*therapeutic use]; Nifedipine [therapeutic use]; Obstetric Labor, Premature [*prevention & control]; Premature Birth [prevention & control]; Randomized Controlled Trials as Topic; Tocolytic Agents [*therapeutic use]

MeSH check words

Female; Humans; Pregnancy