Antihypertensive drug therapy for mild to moderate hypertension during pregnancy (Review)

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ABSTRACT

Background
Mild to moderate hypertension during pregnancy is common. Antihypertensive drugs are often used in the belief that lowering blood pressure will prevent progression to more severe disease, and thereby improve outcome.

Objectives
To assess the effects of antihypertensive drug treatments for women with mild to moderate hypertension during pregnancy.

Search strategy
We searched the Cochrane Pregnancy and Childbirth Group's Trials Register (March 2006), the Cochrane Central Register of Controlled Trials (*The Cochrane Library* 2005, Issue 3), MEDLINE (1966 to November 2005), LILACS (1984 to November 2005) and EMBASE (1974 to November 2005).

Selection criteria
All randomised trials evaluating any antihypertensive drug treatment for mild to moderate hypertension during pregnancy defined, whenever possible, as systolic blood pressure 140 to 169 mmHg and diastolic blood pressure 90 to 109 mmHg. Comparisons were of one or more antihypertensive drug(s) with placebo, with no antihypertensive drug, or with another antihypertensive drug, and where treatment was planned to continue for at least seven days.

Data collection and analysis
Two review authors independently extracted data.

Main results
Forty-six trials (4282 women) were included. Twenty-eight trials compared an antihypertensive drug with placebo/no antihypertensive drug (3200 women). There is a halving in the risk of developing severe hypertension associated with the use of antihypertensive drug(s) (19 trials, 2409 women; relative risk (RR) 0.50; 95% confidence interval (CI) 0.41 to 0.61; risk difference (RD) -0.10 (-0.12 to -0.07); number needed to treat (NNT) 10 (8 to 13)) but little evidence of a difference in the risk of pre-eclampsia (22 trials, 2702 women; RR 0.97; 95% CI 0.83 to 1.13). Similarly, there is no clear effect on the risk of the baby dying (26 trials, 3081 women; RR 0.73; 95% CI 0.50 to 1.08), preterm birth (14 trials, 1992 women; RR 1.02; 95 % CI 0.89 to 1.16), or small-for-gestational-age babies (19 trials, 2437 women; RR 1.04; 95 % CI 0.84 to 1.27). There were no clear differences in any other outcomes.

Nineteen trials (1282 women) compared one antihypertensive drug with another. Beta blockers seem better than methyldopa for reducing the risk of severe hypertension (10 trials, 539 women, RR 0.75 (95 % CI 0.59 to 0.94); RD -0.08 (-0.14 to 0.02); NNT 12 (6 to 275)). There is no clear difference between any of the alternative drugs in the risk of developing proteinuria/pre-eclampsia. Other outcomes were only reported by a small proportion of studies, and there were no clear differences.

Authors' conclusions
It remains unclear whether antihypertensive drug therapy for mild to moderate hypertension during pregnancy is worthwhile.

PLAIN LANGUAGE SUMMARY

Not enough evidence to show whether antihypertensive drug treatment for mild to moderate hypertension during pregnancy is worthwhile

During the early weeks of normal pregnancy, blood pressure falls and climbs slowly in later pregnancy to reach pre-pregnancy levels at term. Mild to moderate hypertension (high blood pressure) is common during pregnancy. In some women, it can become more serious, resulting in hospital admission, pre-eclampsia (a complication of pregnancy that includes high blood pressure) and possible premature delivery. Antihypertensive drugs are often used to lower blood pressure in the belief that they will prevent this progression. The review of 46 trials, involving 4282 women, found there was not enough evidence to show the benefit of antihypertensive drugs for mild to moderate hypertension during pregnancy. More research is needed.

BACKGROUND

During the early weeks of normal pregnancy blood pressure falls, climbing slowly in later pregnancy to reach pre-pregnancy levels at term (Hytten 1980; Villar 1989). These changes are related to multiple physiological and environmental factors, they complicate the diagnosis of hypertension during pregnancy. There is no consensus about the definition of hypertensive disorders during pregnancy (Chappell 1999), and several classifications have been suggested (ASSHP 1993; Davey 1988; Gifford 1990; North 1999; Roberts 1993). Nevertheless, there is now general agreement about the broad categories. These are: (a) gestational hypertension or pregnancy-induced hypertension, which is hypertension without proteinuria; (b) pre-eclampsia, which is hypertension with proteinuria; (c) chronic hypertension, or essential hypertension, which is pre-existing hypertension; and (d) chronic hypertension with superimposed pre-eclampsia.

Variations in the systems for classification are largely to do with how high blood pressure is defined. The system suggested by the International Society for the Study of Hypertension in Pregnancy defines hypertension as a diastolic blood pressure of 90 mmHg or above on two consecutive occasions at least four hours apart, or a single diastolic blood pressure of 110 mmHg or more (Davey 1988). In the past there was disagreement about which auscultatory sound to use for measuring diastolic blood pressure. However, Korotkoff phase V (disappearance of sounds) is now widely recommended as more reliable than phase IV (muffling)(Brown 2001; Rubin 1996).

The suggestion that a change in blood pressure is more important than any absolute level (Redman 1988) is no longer included in the definition of gestational hypertension due to lack of evidence that it is related to outcome (Brown 2000; Brown 2001; NHBPEP 2000). Pre-eclampsia is defined as high blood pressure (using the criteria above) plus significant proteinuria, usually taken as at least 300 mg/24 hour or 1+ on dipsticks (Davey 1988).

For this review we have accepted broad and pragmatic criteria for identifying women with mild to moderate hypertension during pregnancy. This reflects clinical practice, and is justifiable in the context of randomised trials as within each study the same criteria will have been used for women in both groups.

Hypertension during pregnancy is common. One in 10 women will have high blood pressure at some time before delivery, and pre-eclampsia complicates between 2% to 8% of pregnancies (WHO 1988). Pre-eclampsia is discussed in more detail in the generic protocol of interventions for prevention of pre-eclampsia (Meher 2005).

The role of antihypertensive therapy for pregnant women with mild to moderate hypertension is unclear. As there is no immediate need to lower blood pressure, the rationale for treatment is that it will prevent or delay progression to more severe disease, thereby benefiting the woman or her baby, or both, and reducing consumption of health service resources. As well as reducing blood pressure, the belief has been that these drugs reduce the risk of preterm delivery and placental abruption and improve fetal growth. A wide variety of drugs have been advocated, and each group has different potential side-effects and adverse events.

In this review we evaluate individual agents within the class or family to which they belong, as each class has a similar mechanism of action. Alpha agonists inhibit vasoconstriction via a centrally mediated effect (Ingenito 1970). Methyldopa is the most widely used alpha agonist, and became available in 1963. Clonidine is also an alpha agonist, although it has the disadvantage that sudden withdrawal may cause a hypertensive crisis (Isaac 1980). Beta-adrenoceptor blocking drugs block adrenoceptors in the heart, peripheral blood vessels, airways, pancreas and liver (Frishman 1979). Labetalol has an additional arteriolar vasodilating action that lowers peripheral resistance, but is usually classified as with the beta blockers. Calcium channel blockers include nifedipine, nicardipine, nimodipine and verapamil. These drugs inhibit influx of calcium ions to vascular smooth muscle resulting in arterial vasodilatation (Robinson 1980). Hydralazine is a vasodilator with a direct relaxing effect on smooth muscle in the blood vessels, predominantly in the arterioles (Stunkard 1954). Ketanserin, is a selective serotonin receptor antagonist with weak adrenergic receptor blocking properties (Frishman 1995). The drug is effective in lowering blood pressure in essential hypertension. It also

inhibits platelet aggregation. Glyceryl trinitrate is a nitric oxide donor with vasodilator effect in perivascular smooth-muscle cells (Seligman 1994).

There are other types of interventions for women with mild to moderate hypertension during pregnancy that are not considered in this review. Interventions covered by other reviews include salt restriction (Duley 1999), antiplatelet agents (Knight 2000), abdominal decompression (Hofmeyr 1996) and bed rest with or without hospitalisation (Meher 2005a). Diuretics are no longer widely used in pregnancy, and are usually reserved for women with renal or cardiac problems (ASSHP 1993; CHSCC 1997). The role of diuretics for women with hypertension during pregnancy is covered by a separate Cochrane review (Churchill 2003), as is prevention and treatment of postpartum hypertension (Magee 2005).

For women with severe hypertension, usually defined as 160 to 170 mmHg or more systolic blood pressure or 110 mmHg or more diastolic blood pressure, there is a risk of direct arterial damage and so antihypertensive drugs are used to lower blood pressure (Gifford 1990; Redman 1993). The question of which drug is best in this situation is considered in another Cochrane review and not discussed further here (Duley 2006).

A separate review assessing the effect of oral beta blockers in mild to moderate hypertension during pregnancy is available (Magee 2003). However, beta blockers are included in this review as part of all the spectrum of antihypertensive drugs.

The aim of this review is to assess the potential benefits and hazards, to the woman and baby, of antihypertensive drugs for the treatment of mild to moderate hypertension during pregnancy. If antihypertensive agents are overall beneficial, a secondary aim will be to assess the comparative effects of alternative agents.

OBJECTIVES

To determine the possible benefits, risks and side-effects of antihypertensive drug treatments for women with mild to moderate hypertension during pregnancy (defined whenever possible as a systolic blood pressure of 140 to 169 mmHg or diastolic blood pressure of 90 to 109 mmHg, or both). Also, to compare the differential effects of alternative drug regimens.

The comparisons are of:
(1) any antihypertensive drug with either no drug or placebo;
(2) one antihypertensive drug compared with another. For this review, the commonly used drugs are regarded as control and compared with all other agents (for example, any antihypertensive versus methyldopa, any antihypertensive versus calcium channel blockers).

CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

Types of studies

All randomised trials evaluating any antihypertensive drug treatment for mild to moderate hypertension during pregnancy. Quasi-randomised designs were excluded.

Types of participants

The review includes women with mild to moderate hypertension during pregnancy, defined whenever possible as those with systolic blood pressure 140 to 169 mmHg and diastolic blood pressure 90 to 109 mmHg. Studies in which participants were described as having 'mild to moderate' hypertension but the range of blood pressures was not clearly specified were also included. Women were included regardless of whether they had proteinuria or not, and irrespective of previous antihypertensive treatment or whether the pregnancy was singleton or multiple.

Women who had given birth before trial entry were excluded, as were women with severe hypertension (defined whenever possible as either systolic blood pressure of 170 mmHg or more, or diastolic blood pressure 110 mmHg or more). Studies that included a substantial proportion of women who did not have mild to moderate hypertension were excluded, unless data were available on outcome for those with mild to moderate hypertension only.

Types of intervention

Any comparison of one or more antihypertensive drug with either placebo, no antihypertensive drug was included, as were comparisons of one antihypertensive drug with another. Studies were excluded if the intention was to treat for less than seven days, as a longer period of treatment would be necessary for any substantive clinical effect. Comparisons of two drugs of the same class are also excluded, although these may be included in future updates if clinically relevant.

Drugs that aimed to reduce the risk of pregnancy-induced hypertension progressing to pre-eclampsia but are not antihypertensive agents were also excluded.

Types of outcome measures

(i) For the woman

- Severe hypertension: defined whenever possible as either systolic blood pressure 170 mmHg or more, or diastolic blood pressure 110 mmHg or more. Trials where the definition of severe hypertension was not clear, or where the cut-off was up to 10 mmHg lower were also included and were clearly documented.
- Proteinuria: defined whenever possible as new proteinuria (1+ or more or 300 mg/24 hour).
- Severe pre-eclampsia: defined whenever possible as severe hypertension with proteinuria 2+ or more, or 2 g or more/24 hour,

with or without other signs of symptoms, or as moderate hypertension with proteinuria 3+ or more. Haemolysis, elevated liver enzymes and low platelets (HELLP) syndrome is a form of severe pre-eclampsia, so it was included here as well as a separate measure. Trials reporting imminent eclampsia, or where the definition of severe pre-eclampsia was not clear were also included.

- Eclampsia.
- HELLP syndrome.
- Severe maternal morbidity: such as liver or renal failure, disseminated intravascular coagulation and cerebrovascular accident (stroke).
- Need for another drug to control blood pressure.
- Miscarriage (fetal losses before viability, usually taken as before 20 or 24 weeks).
- Elective delivery: combines elective caesarean sections and elective induction of labour at term or before term.
- Caesarean section.
- Antenatal hospital admission and length of stay more than seven days: hospital and day care unit were to be reported separately.
- Placental abruption.
- Side-effects: any reported side-effects or severe adverse events.
- Drug stopped because of side-effects.

(ii) For the baby

- Death: fetal deaths included miscarriage (fetal losses before viability, usually taken as 20 or 24 weeks) and stillbirths (after 24 weeks, or however defined). Perinatal deaths are stillbirths plus deaths in the first week of life. Neonatal deaths are deaths in the first 28 days.
- Small-for-gestational age: low birthweight for gestational age, below the third, fifth or 10th percentile, using the most severe reported.
- Preterm birth: all births before 37 completed weeks and more severe prematurity, such as less than 32 or less than 34 weeks.
- Very low, less than four, five minute Apgar score.
- Admission to neonatal or intensive care nursery.
- Respiratory distress syndrome.
- Other morbidity possibly related to maternal drug therapy, such as hypo or hypertension, hypoglycaemia and bradycardia (with beta blockers).
- Impaired long-term growth and development in infancy and childhood.

Main outcomes were prespecified as severe hypertension, pre-eclampsia, any reported baby death, preterm birth and small-for-gestational age.

SEARCH METHODS FOR IDENTIFICATION OF STUDIES

See: methods used in reviews.

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register by contacting the Trials Search Co-ordinator (March 2006).

The Cochrane Pregnancy and Childbirth Group's Trials Register is maintained by the Trials Search Co-ordinator and contains trials identified from:
(1) quarterly searches of the Cochrane Central Register of Controlled Trials (CENTRAL);
(2) monthly searches of MEDLINE;
(3) handsearches of 30 journals and the proceedings of major conferences;
(4) weekly current awareness search of a further 37 journals.

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

Trials identified through the searching activities described above are given a code (or codes) depending on the topic. The codes are linked to review topics. The Trials Search Co-ordinator searches the register for each review using these codes rather than keywords.

In addition, we searched the Cochrane Central Register of Controlled Trials (*The Cochrane Library* 2005, Issue 3), MEDLINE (1966 to November 2005), LILACS (1984 to November 2005) and EMBASE (1974 to November 2005) using the terms hypertens*, pre-eclamp*, preeclamp*, pre eclamp* and pregnan*.

We did not apply any language restrictions.

METHODS OF THE REVIEW

Selection of studies
Two authors (E Abalos (EA), L Duley (LD)) assessed for inclusion all potential studies identified as a result of the search strategy. Disagreements were resolved through discussion. If agreement could not be reached, a third review author (DW Steyn) was consulted.

Data extraction and management

Data were extracted and entered into Review Manager (RevMan 2003) by EA, and checked by LD. Neonatal data extraction was checked by DJ Henderson-Smart. Review authors were not blinded to the authors, sources of the articles, or results. Discrepancies were resolved by discussion between the two review authors and, when necessary, the two remaining review authors were consulted.

Assessment of methodological quality of included studies

(1) Concealment of allocation

A quality score for concealment of allocation was assigned to each trial, using the following criteria:
(a) adequate concealment of allocation, such as telephone randomisation, consecutively-numbered, sealed opaque envelopes;
(b) unclear whether adequate concealment of allocation;
(c) inadequate concealment of allocation such as open random-number tables, sealed envelopes that are not numbered and opaque.
Only properly randomised trials were included, so quasi-random designs were excluded.

(2) Attrition bias (loss of participants, for example, withdrawals, dropouts, protocol deviations)

Completeness of follow up was assessed using the following criteria:
(a) less than 5% of participants excluded from analysis;
(b) from 5% to 9.9% of participants excluded from analysis;
(c) from 10% to 19.9% of participants excluded from analysis.
Trials were excluded if it was not possible to enter data on an intention-to-treat basis or 20% or more participants were excluded, or both.

(3) Performance bias (blinding of participants, researchers and outcome assessment)

Blinding was assessed in the following way:
(a) blinding of participant (yes/no/unclear or not specified);
(b) blinding of caregiver (yes/no/unclear or not specified);
(c) blinding of outcome assessment (yes/no/unclear or not specified).

Data extraction and entry

Two authors extracted data, and discrepancies were resolved through discussion. Data were entered onto the Review Manager software (RevMan 2003), and checked for accuracy.

Statistical analyses

Statistical analyses were carried out using the Review Manager software (RevMan 2003). All outcomes were dichotomous data, with results presented as summary relative risk with 95% confidence intervals. Results were pooled using a fixed-effect model. The I^2 statistic was used to assess heterogeneity between trials, where relevant. If heterogeneity was apparent between trials, as evidenced by a value for I^2 above 50%, we will explore possible causes by prespecified subgroup analyses, and by sensitivity analysis excluding studies of poor quality.

Subgroup analyses

For the comparison of antihypertensive drug/s with placebo or no treatment the following subgroup analyses were prespecified:
(i) by class of drug (such as alpha agonists, beta blockers and calcium channel blockers);
(ii) by type of hypertensive disorder at trial entry: mild to moderate hypertension alone; mild to moderate hypertension with proteinuria; chronic hypertension; unspecified;
(iii) by gestational age at trial entry: less than about 32 weeks' gestation; about 32 weeks or more gestation; or unclassified/mixed;
(iv) by whether a placebo was used: placebo, no placebo.

The subgroup analysis by type of drug is presented for all outcomes. The remaining subgroups are presented for the prespecified main outcomes only.

DESCRIPTION OF STUDIES

Details for each trial can be found in the 'Characteristics of included studies' table and the 'Characteristics of excluded studies' table.

Forty-six trials (4282 women) were included in this review. Of these, 34 (3480 women) were conducted in industrialised countries (Australia, France, Hong Kong, Ireland, Israel, Italy, Sweden, UK and USA), and 12 (802 women) were performed in middle-low income countries (Argentina, Brazil, Caribbean Islands, India, South Africa, Sudan and Venezuela). Three trials were published in the 1960s and 1970s, 22 in the 1980s, 17 in the 1990s, and four after the year 2000. All included trials are small. The largest study recruited 300 women; this three-arm trial is included in the comparison of any antihypertensive with placebo/no antihypertensive, and in the comparison of one drug with another. Only five studies had comparison arms containing more than 100 women.

Interventions

The antihypertensive drugs used in these trials include: alpha agonists (methyldopa), beta blockers (acebutolol, atenolol, labetalol, mepindolol, metoprolol, pindolol and propranolol), calcium channel blockers (isradipine, nicardipine, nifedipine and verapamil), vasodilators (hydralazine and prazozin), ketanserin and glyceryl trinitrate (GTN). All drugs were given orally, except glyceryl trinitrate that was given transdermally. The dose for several agents varied considerably between studies, in both amount and duration of therapy.

The antihypertensive drug was compared with placebo, or no antihypertensive drug, in 28 trials (3200 women). Of these trials, 16 evaluated beta blockers (1552 women), seven of these used a placebo for the control group and nine did not. Methyldopa was evaluated in six trials (800 women), one comparison with

placebo, and five with no antihypertensive treatment. One trial (118 women) compared isradipine with placebo, another trial (199 women) compared verapamil with placebo, and three studies (583 women) compared nifedipine with no drug treatment. Prazozin was compared with placebo in one trial (32 women), and GTN was compared with placebo patches in another (16 women).

Alternative drug regimens were compared in 19 trials (1282 women). Seventeen of these studies compared methyldopa with another agents. In 14 trials (1077 women) the comparison was with beta blockers, in two it was nifedipine (49 women), and in another ketanserin (20 women). One small trial (36 women) compared nifedipine with glyceryl trinitrate. In one study (100 women), metoprolol was compared with nicardipine.

Gestation at trial entry

Eighteen of the 46 included studies recruited women during the second trimester of pregnancy, and 19 recruited during the third trimester. Only two studies recruited women during the first trimester (Argentina 1988; USA 1990). Gestational age at trial entry was not reported in seven studies.

Severity and type of hypertension disease at trial entry

Mild to moderate hypertension was defined as a diastolic blood pressure of 90 mmHg or more in 32 studies. In seven trials, the definition was 95 mmHg or more. In two trials, the cut-off was 85 mmHg, In five studies, authors merely stated 'mild to moderate hypertension', or 'pregnancy-induced hypertension', or 'diagnosed hypertension'. Women with proteinuria were excluded from trial entry in 17 studies whilst in five trials all women had proteinuria at recruitment. Eleven trials included women regardless of whether or not they had proteinuria, and the proportion of women with proteinuria ranged from 4% to 47%. In the remaining 13 trials the presence of proteinuria at trial entry was not reported.

Eight studies only recruited women with chronic hypertension. Women with chronic hypertension were excluded from 13 trials (13/46). Nine trials included women regardless of whether or not they had chronic hypertension, although outcome was often not reported separately. In the remaining 16 trials, chronic hypertension at trial entry was not mentioned.

Methods for measuring blood pressure

Only four trials masked the assessment of blood pressure by using a random zero sphygmomanometer (Australia 1983; UK 1976; UK 1983; UK 1983a). For assessment of diastolic blood pressure, Korotkoff phase IV sound was used in 14 trials and Korotkoff phase V was used for seven studies. Criteria for blood pressure measurement were not mentioned in 25 trials.

Definition of small-for-gestational age

Small-for-gestational age was defined in a variety of ways in the 27 trials reporting this outcome. Four studies used birthweight below the fifth centile and 10 used below the 10th centile. Five trials used other definitions, and in the remaining eight trials, small-for-gestational age was not defined.

One outcome specified in our protocol, very low (less than four) five minute Apgar score, is not included in this review as it was not reported by any trial.

Excluded studies

Sixty-two studies were excluded from the review. Of these, 30 were conducted in high income-countries (Australia, Belgium, Denmark, Finland, France, Hong Kong, Israel, Italy, Japan, Spain, Sweden, UK and USA), and 32 in low- and middle-income countries (Argentina, Brazil, China, Cuba, Czech Republic, Dominican Republic, Egypt, Hungary, India, Iran, Kuwait, Pakistan, Philippines, Russia, Singapore, South Africa, Sri Lanka and Venezuela). The oldest excluded study was published 1957, one was published in 1978, 50 were published in the 1980s and 1990s, and 10 have been published since the millennium.

The language of publication was English (for 47 papers), Chinese (five), Spanish (five), Portuguese (two), French (one), Czech (one) and Russian (one). Language was not a reason for exclusion. Seventeen papers (17/62) were published only as congress abstracts. Authors of nine papers provided additional information about methods and/or clinical outcomes.

The reasons for exclusions were as follows:

- Methodological problems (21 studies): either they were not randomised trials (10 studies) or they used quasi-random methods for treatment allocation (seven), or more than 20% of women were excluded after randomisation (four).
- Participants were not eligible for the review (five studies): either some or all of the women had severe hypertension (two), or some women had normal blood pressure (three), and data were not presented separately for the women with mild to moderate hypertension.
- Intervention was not eligible for the review (28 studies): either the comparison was of drugs within the same class (eight), or the allocated intervention was for less than seven days (11), or it was not an antihypertensive drug (nine).
- No clinical outcomes reported (eight studies): there are no data on relevant clinical outcomes (seven congress abstracts, of which four authors were contacted but with no responses to date).

METHODOLOGICAL QUALITY

Overall, the quality of the studies included in this review is moderate to poor. Concealment of allocation was adequate for only ten of the 46 trials (22%). In 35 trials, it was unclear whether concealment was adequate, and for two it was inadequate. Methods for concealing the allocation included telephone randomisation (Italy 1998), blinded treatment packs (Brazil 1988; Brazil 2000a; Caribbean Is.1990; Israel 1992; Italy 1999; Italy 2000; UK 1989), and consecutive, sealed identical envelopes (UK 1992). Most tri-

als with unclear concealment of allocation were described as 'randomised' with no details on how this was achieved. Some of these studies were stated to be double blind, but with no information about how this was achieved. Two trials with inadequate concealment used random-number tables without mentioning any attempt to conceal the allocation (UK 1980; Venezuela 1988). Methods for generating the random sequence were described in 10 trials (25%). These included: computer generation (Hong Kong 1990; Italy 1998; USA 1987; USA 1990; USA 1992), random-number tables (UK 1980; UK 1989; Venezuela 1988), series of random numbers (Israel 1992), and 'cards shuffled into a random order and numbered in sequence' (Ireland 1991).

Only 12 of the studies evaluating a single agent used a placebo for the control group. None of the trials comparing a single drug against no treatment, or those comparing one agent with another, mentioned blinding in the assessment of outcome.

Consent and other methodological issues

Informed consent was mentioned in the majority of trials. In one study, informed consent was obtained only from women allocated to the treatment arm (Ireland 1991). Sample size and power calculations were reported for five trials (Caribbean Is.1990; France 1987; Ireland 1991; Italy 1998; UK 1989). Four trials described the women who met the study eligibility criteria, but were not randomised (Sweden 1984; Sweden 1985; UK 1976; UK 1983).

RESULTS

This review includes 46 trials, involving 4282 women.

(1) Any antihypertensive drug versus none

Overall, 28 trials with a total of 3200 women compared an antihypertensive drug with placebo or no antihypertensive drug.

Severe hypertension

There is a halving in the risk of developing severe hypertension associated with the use of antihypertensive drug/s (19 trials, 2409 women; relative risk (RR) 0.50; (95% confidence interval (CI) 0.41 to 0.61); risk difference (RD) -0.10 (-0.12 to -0.07); number needed to treat (NNT) 10 (8 to 13)). This effect is strikingly consistent regardless of the class of drug, hypertensive disorder at trial entry, gestation at trial entry, or whether a placebo was used for the control group.

Pre-eclampsia

There is no evidence of an overall difference in the risk of pre-eclampsia/proteinuria in the 22 trials (2702 women) reporting this outcome (RR 0.97; 95% CI 0.83 to 1.13). Similarly, there are no differences in the subgroups based on type of hypertensive disorder, gestation at trial entry, or use of placebo. The only subgroups with statistically significant differences were those for calcium channel blockers versus none (four trials, 725 women; RR 1.40; 95% CI 1.06 to 1.86), and beta blockers versus none (eight trials, 883 women; RR 0.73; 95% CI 0.57 to 0.94).

Fetal or neonatal deaths

Although there is no statistically significant difference in the risk of the baby dying, the point estimate is for a 27% reduction (26 trials, 3081 women; RR 0.73; 95% CI 0.50 to 1.08). The only subgroup in which this reduction reaches statistical significance is for miscarriage (seven trials, 1058 women; RR 0.39; 95% CI 0.17 to 0.93).

Preterm birth (less than 37 weeks)

There is no overall difference in the 14 trials (1992 women) reporting this outcome (RR 1.02; 95% CI 0.89 to 1.16). No differences are found in any of the subgroups considered.

Small-for-gestational age

There is no overall difference in the 19 trials (2437 women) reporting small-for-gestational age (RR 1.04; 95% CI 0.84 to 1.27). This result remains consistent across all the subgroups. However, for the comparison of beta blockers with none there is a strong trend towards an increase (nine trials, 904 women; RR 1.38; 95% CI 0.99 to 1.92). Three of these beta blocker trials (287 women) are the only studies in the subgroup for birthweight less than fifth centile RR 3.04; 95 % CI 1.25 to 7.40).

Other outcomes

Of the remaining outcomes, use of additional antihypertensives was reported in 10 trials (1285 women) (RR 0.42; 95% CI 0.30 to 0.58); changed drugs due to side-effects in 15 trials (1403 women) (RR 2.59; 95% CI 1.33 to 5.04); caesarean section in 19 trials (2475 women) (RR 0.94; 95% CI 0.85 to 1.05); placental abruption in ten trials (1284 women) (RR 1.83; 95% CI 0.77 to 4.37); and admission to special care nursery was reported in eight trials (1321 women) (RR 1.11; 95% CI 0.93 to 1.32). Remaining outcomes were only reported for less than half the women in the comparison.

(2) One hypertensive drug versus another

Overall, 19 trials with a total of 1282 women compared one antihypertensive drug with another.

Severe hypertension

Beta blockers appear to be more effective than methyldopa in avoiding an episode of severe hypertension (eight trials, 493 women, RR 0.79; 95% CI 0.63 to 0.99; RD -0.08 (-0.14 to 0.02); NNT 12 (6 to 275)). There is no clear difference between any of the other drugs. For the comparison of calcium channel blockers with methyldopa (two trials, 46 women) RR is 0.23; 95% CI 0.04 to 1.22, for the comparison of beta blockers with calcium channel blockers (one trial, 100 women) it is 2.14; 95% CI 0.96 to 4.80, and for the comparison of glyceryl trinitrate with nifedipine (one trial, 36 women) it is 1.56; 95% CI 1.07 to 35.67.

Pre-eclampsia

There is no difference in the risk of developing proteinuria/pre-eclampsia (nine trials, 804 women; RR 0.81; 95% CI 0.57 to 1.16) when beta blockers are compared with methyldopa. One trial (92 women) compared beta blockers with calcium channel

blockers (RR 2.67; 95%CI 0.75 to 9.42). The trial comparing glyceryl trinitrate with calcium channel blockers was too small for any reliable conclusion (one trial, 36 women; RR 1.00; 95% CI 0.10 to 9.96).

Total reported fetal deaths or deaths before discharge from hospital

There is no difference in the risk of the baby dying (17 trials, 1130 women; RR 0.67; 95% CI 0.37 to 1.21) when any antihypertensive drug is compared with methyldopa. No differences are found when metoprolol is compared with nicardipine (one trial, 100 women; RR 1.00; 95% CI 0.06 to 15.55).

Preterm birth (less than 37 weeks)

Only eight trials comparing any antihypertensive with methyldopa (524 women) reported this outcome (RR 0.80; 95% CI 0.57 to 1.12).

Small-for-gestational age

Only six small trials reported this outcome. Five trials (478 women) compared beta blockers with methyldopa (RR 0.99; 95% CI 0.57 to 1.70) and one (20 women) compared nifedipine versus methyldopa (RR 0.40; 95% CI 0.10 to 1.60).

Other outcomes

Of the remaining outcomes, use of additional antihypertensives was reported in 11 trials (879 women) comparing any antihypertensive with methyldopa (RR 0.87; 95% CI 0.68 to 1.11), and in one trial (100 women) comparing a metoprolol with nicardipine (RR 2.14; 95% CI 0.96 to 4.80). In the comparison of any antihypertensive with methyldopa changed drugs due to side-effects was reported by four trials (272 women) (RR 2.80; 95% CI 0.12 to 67.91); caesarean section by nine trials (779 women) (RR 0.96; 95% CI 0.79 to 1.15); placental abruption by one trial (173 women) (RR 2.02; 95% CI 0.19 to 21.90); and admission to special care nursery was reported by three trials (379 babies) (RR 0.94; 95% CI 0.68 to 1.29) . Similarly, there were no clear differences in the other comparisons where these outcomes were reported.

DISCUSSION

Antihypertensive drugs half the risk that a pregnant woman with mild or moderate hypertension will have one or more episodes of severe hypertension. This is unsurprising, as the antihypertensive effects of these agents have been well demonstrated in non-pregnant people. Also unsurprising is that women allocated an antihypertensive were less likely to need another agent, and more likely to experience side-effects than those allocated placebo or no antihypertensive treatment. Between 8 to 13 women need to be treated with an antihypertensive drug to prevent an episode of severe hypertension. Whether this reduction in risk would, alone, be worthwhile is likely to depend on whether there are associated reductions in the consequences of severe hypertension, such as admission to hospital and stroke. There are insufficient data for any firm conclusions about these more substantive outcomes. However, if the reduction in severe hypertension was clinically important, you might expect to see an impact in terms of fewer preterm births and fewer caesarean sections. There is no evidence of such an effect in this review.

Beta blockers seem to be more effective than methyldopa for preventing severe hypertension, although the comparative effects on other outcomes are unclear.

One of the main objectives in treating women with mild to moderate hypertension with antihypertensive drugs is to prevent or delay progression to pre-eclampsia. Although this review excludes a large reduction in the risk of pre-eclampsia associated with antihypertensive therapy, a moderate but clinically important effect remains possible. The confidence intervals suggest the true effect is somewhere between a 17% reduction in risk of pre-eclampsia and a 13% increase. Similarly, a moderate but clinically important reduction in the risk of fetal or neonatal death (point estimate 27%, confidence intervals consistent with everything from a 50% reduction in risk to an 8% increase) is possible. Although many studies did not define stillbirths and miscarriages, these data suggest that antihypertensive treatment for mild to moderate hypertension may have a greater potential for reducing early pregnancy loss than later stillbirths or neonatal deaths.

For small-for-gestational-age babies, the confidence intervals include everything from a 16% reduction in the risk of a small-for-gestational-age baby to a 27% increase, and the point estimate is for a 4% increase in risk. It has been argued that lowering maternal blood pressure may cause fetal growth restriction (von Dadelszen 2000). This hypothesis is based on meta-regression, however. So, although the included studies were randomised trials, the analysis is prone to all the biases of observational studies. Also, combining data from all trials there is no overall effect on the relative risk of having a small-for-gestational-age baby (RR 1.04; 95% CI 0.84 to 1.27) for women allocated antihypertensive drugs rather than placebo. Yet amongst the trials of beta blockers an increase appears likely (nine trials, 904 women; RR 1.38; 95% CI 0.99 to 1.92). It therefore remains plausible that the observed association with fetal growth restriction is related to beta-blockers, rather than any general effect of reducing blood pressure.

Being small-for-gestational age is an important marker for neurodevelopmental delay. The ideal timing of delivery for such babies is unclear, regardless of whether the woman has raised blood pressure or not (Thornton 2004).

Few children exposed to antihypertensive drugs in utero have been followed up beyond the perinatal period. Two trials (Italy 1998; UK 1983) have reported follow up of a total of 110 children at age one year, and of 190 children at age 18 months, respectively. Another (UK 1976) reported follow up at 7½ years of age for

children randomised before 28 weeks' gestation. All studies were too small to provide reliable estimates of the benefits and adverse effects for surviving children.

The question of which antihypertensive drug to use is less relevant until it becomes clearer whether attempting to control mild to moderate hypertension during pregnancy is worthwhile. However, beta blockers seem to be better tolerated by women than methyldopa (RR 0.07; 95% CI 0.02 to 0.37), although there is potential for bias as this outcome was only reported by half the trials. Beta blockers also seem to be more effective than methyldopa in avoiding an episode of severe hypertension. However, concerns remain about their possible role in the risk of having small-for-gestational-age babies (*see* above).

A large number of outcomes are reported in these trials, and for many, data are only available from a small number of studies. There is therefore considerable potential to be misled by reporting bias. For example, in the comparison of any antihypertensive with none, only 5 of the 28 trials reported respiratory distress syndrome, and all had results favouring antihypertensive treatment. Without further information, it is impossible to know whether the other 23 trials did not collect this data, or whether they did not report it because it did not favour antihypertensive therapy.

We also report data from a large number of subgroups. Although these subgroups were all prespecified, the numbers in many cells are small, and for 1 in 20 the difference will be statistically significant purely by chance. Results from these subgroups should therefore be interpreted with caution, as there is considerable potential to be misled by random errors.

AUTHORS' CONCLUSIONS

Implications for practice

It remains unclear whether antihypertensive drug therapy for mild to moderate hypertension during pregnancy is worthwhile. Whether the reduction in the risk of severe hypertension is considered sufficient to warrant treatment is a decision that should be made by women in consultation with their obstetrician. If an antihypertensive is used, there is insufficient evidence to conclude that one antihypertensive is better than another. The choice should therefore depend on the previous experience of the clinician and the woman's preference.

Implications for research

Large simple trials are required in order to provide reliable estimates of the benefits and adverse effects of antihypertensive treatment for mild to moderate hypertension. We need to know the effects for both mother and baby, as well as the costs to the health services, to women and to their families. Outcomes relevant to women should be included in such studies, such as admission to hospital, clinic visits, and disruption to their family and working life. Trials should also assess the level of blood pressure at which antihypertensive treatment becomes worthwhile. Long-term follow up of children entered into such trials as fetuses is needed in order to assess whether there are any effects on infant and child development.

POTENTIAL CONFLICT OF INTEREST

None known.

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* *Indicates the major publication for the study*

TABLES

Characteristics of included studies

Study	**Argentina 1985**
Methods	Allocation concealment: not stated. Authors said '...randomly divided into two groups...'.
Participants	60 women with SBP >/= 160 mmHg and/or DBP >/= 100 mmHg x 2, 24 hr apart, with or without proteinuria at trial entry. Excluded: > 1 drug to control BP, or contraindication for beta blockers.
Interventions	Exp: atenolol 50-250 mg/day. Control: methyldopa 750-2000 mg/day.
Outcomes	Women: BP (mean). Babies: gestational age, birthweight, Apgar score, stillbirth, neonatal deaths.
Notes	Main paper in Spanish. Methods for measuring BP not mentioned.
Allocation concealment	B – Unclear

Study	**Argentina 1987**
Methods	Allocation concealment: not stated. Authors said 'open randomised study'.
Participants	20 women with SBP > 159 mmHg and/or DBP > 99 mmHg x 2, 24 hr apart, +/- proteinuria. Excluded: > 1 drug to control BP, or hypertensive emergency.
Interventions	Exp: ketanserin 20-80 mg/day. Control: methyldopa 500-2000 mg/day.

Characteristics of included studies (*Continued*)

Outcomes	Women: none reported. Babies: stillbirth, neonatal death, birthweight (mean), gestation at delivery (mean).
Notes	Interim report of study ongoing in 1987. Methods for measuring BP not mentioned.
Allocation concealment	B – Unclear

Study	**Argentina 1988**
Methods	Allocation concealment: not stated. Authors said 'randomised' 'divided into 2 equal groups'.
Participants	36 women > 14 weeks' gestation with BP >/= 140/90 mmHg and </= 170/110 mmHg.
Interventions	Exp: mepindolol, increasing weekly doses, from 5-10 mg/day. Control: methyldopa, increasing weekly doses from 500-2000 mg/day.
Outcomes	Women: additional antihypertensive, caesarean section, side-effects, maternal complications. Babies: stillbirth, SGA (undefined).
Notes	Methods for measuring BP not mentioned. Available only as an abstract.
Allocation concealment	B – Unclear

Study	**Australia 1983**
Methods	Allocation concealment: not stated. Authors said 'randomly allocated'.
Participants	28 women in antenatal clinics with mild-moderate PIH (BP >/= 140/90 mmHg x 2 at least 24 hr apart). Excluded: impaired renal function.
Interventions	Exp: propranolol 30-160 mg/day. Control: methyldopa 500-1000 mg/day.
Outcomes	Women: severe hypertension, proteinuria (undefined), additional antihypertensive, changed drugs due to side-effects, caesarean section. Babies: perinatal death, preterm delivery, jaundice, bradycardia, hypoglycaemia, birthweight (mean).
Notes	London School of Hygiene sphygmomanometer (random zero) used. No mention of which Korotkoff sound used for DBP.
Allocation concealment	B – Unclear

Study	**Australia 1985**
Methods	Allocation concealment: not stated. Authors said 'allocated by series of random numbers'.
Participants	183 women with singleton pregnancy and mild hypertension (DBP >/= 90 mmHg x 2 24 hr apart, or DBP >/= 95 mmHg x 2, 12 hr apart, or DBP >/= 100 mmHg x 2, 8 hr apart).
Interventions	Exp: oxprenolol 40-320 mg x 2/day. Control: methyldopa 250 mg x 2/day-1000 mg x 3/day. If blood pressure not controlled, hydralazine in both groups.
Outcomes	Women: severe hypertension, proteinuria ('heavy and increasing requiring delivery'), additional antihypertensive, induction of labour, caesarean section, Babies: stillbirth, neonatal death, admission to SCBU, days in SCBU, RDS, birthweight. (mean), Apgar (mean).
Notes	Korotkoff phase IV used for DBP.
Allocation concealment	B – Unclear

Study	**Australia 2001**
Methods	Allocation concealment: central telephone randomisation Although authors stated it was a placebo-controlled trial, data provided by authors suggest that they may have used a patch for the control, but not a matching placebo.

Characteristics of included studies (*Continued*)

Participants	16 women with gestational hypertension, defined as "de novo" hypertension after 20 weeks' gestation of > 140 and/or 90 mmHg on two readings, 6 hr apart; or a rise in systolic pressure of > 25 mmHg or a diastolic of 15 mmHg from a BP pre-pregnancy or in the first trimester.
Interventions	Exp: transdermal glyceryltrinitrate patches 10 mg. Control: patch for the control, but not a matching placebo.
Outcomes	Women: pre-eclampsia, side-effects. Babies: not reported.
Notes	Trial planned to recruit 220 women and stopped early due to side-effects (headache) in the treatment group. Additional data provided by authors.
Allocation concealment	A – Adequate

Study	**Brazil 1985**
Methods	Allocation concealment: not stated. Authors said '...patients were randomly divided into two groups...'.
Participants	100 women with chronic hypertension diagnosed before 20th week, BP >/= 140/90 mmHg x 2, five min apart. With no proteinuria and no contraindication to beta blockers.
Interventions	Exp: pindolol 10-30 mg/day. Control: no treatment.
Outcomes	Women: MAP, severe pre-eclampsia, side-effects. Babies: abortions, fetal deaths, neonatal deaths, gestational age, birthweight, IUGR, Apgar score, congenital malformations, hypoglycaemia.
Notes	Methods for measuring blood pressure not mentioned. Main paper in Portuguese.
Allocation concealment	B – Unclear

Study	**Brazil 1988**
Methods	Allocation concealment: consecutive numbered treatment boxes.
Participants	40 pregnant women with chronic hypertension with DBP =/> 95 mmHg, without proteinuria.
Interventions	Exp: pindolol 10-30 mg/day. Control: methyldopa 500-2000 mg/day.
Outcomes	Women: BP, need for additional antihypertensives, severe HT, superimposed pre-eclampsia. Babies: birthweight, Apgar score, fetal and neonatal death, preterm birth, SGA (undefined).
Notes	Main paper in Portuguese. Methods for measuring BP not mentioned. Additional data provided by authors.
Allocation concealment	A – Adequate

Study	**Brazil 2000a**
Methods	Allocation concealment: trial drug supplied by pharmacy in packs with serial numbers. Withdrawals: 15 women (7.5%) excluded from the analysis (5 delivered in other hospitals, 9 dropped the study or failed to comply with treatment, 1 due to side-effects).
Participants	199 singleton pregnant women with mild/moderate chronic hypertension (DBP > 90 mmHg and =/< 110 mmHg before 20 weeks' gestation, or with history of chronic hypertension), before 25 weeks' gestation and giving informed consent. Excluded: renal, cardiac or hepatic disease, IUGR diagnosed before trial entry, alcohol/drug abuse.
Interventions	Exp: verapamil 240 mg x 3/day. Control: placebo.
Outcomes	Women: BP, heart rate, severe hypertension, superimposed pre-eclampsia, side-effects, mode of delivery. Babies: birthweight, gestational age, SGA, Apgar score, jaundice, hypoglycaemia, mortality.

Characteristics of included studies (*Continued*)

Notes	Korotkoff phase IV used for DBP. Main report in Portuguese, presented as a Doctoral Thesis. Additional data provided by authors.
Allocation concealment	A – Adequate

Study	**Caribbean Is.1990**
Methods	Allocation concealment: women given number corresponding to sealed envelope and treatment batch. Envelope contained unblinding, kept by investigator and only opened when necessary. Envelopes collected at end of study. 2 centres. Withdrawals: 1 woman, from placebo group.
Participants	155 women with singleton pregnancy at 20-36 weeks' gestation, DBP < 85 mmHg x 2 before 20 weeks and > 84 mmHg after 20 weeks. Excluded: type I diabetes, congestive heart failure, cardiac block, asthma, pre-pregnancy hypertension, antihypertensive treatment during current pregnancy.
Interventions	Exp: oxprenolol 160-320 mg x 2/day. Hydralazine 50-100 mg added if necessary to keep DBP < 86 mmHg. Control: placebo, identical appearance.
Outcomes	Women: death, mean BP, severe hypertension, proteinuria (> 1+ or 0.25 g/L), additional antihypertensive, eclampsia, changed drugs due to side-effects, elective delivery, caesarean section, hospital admission, days in hospital, placental abruption. Babies: perinatal death, preterm delivery (< 37 weeks), birthweight (mean), SGA (undefined, excludes stillbirth), 5 min Apgar < 7, admission to SCBU, RDS.
Notes	Korotkoff phase IV used for DBP. For 23 women (15%), treatment unblinded and other treatment started. 16 for uncontrolled BP (5 exp, 11 control) and 7 for poor compliance/side-effects (4 exp, 3 control). Additional data provided by authors.
Allocation concealment	A – Adequate

Study	**France 1987**
Methods	Allocation concealment: 'blinded envelopes'. Stratified in blocks of 10 at each clinic. Multicentre, 12 hospitals. Withdrawals: 12 women (6%). 5 labetalol (3 lost to follow up and 2 given methyldopa) and 7 methyldopa (all lost to follow up).
Participants	188 women with singleton pregnancy at 12-34 weeks' gestation, booked < 20 weeks and DBP >/= 90 mmHg. Excluded: previous antihypertensive treatment this pregnancy, diabetes, depression, contraindication to beta blockers.
Interventions	Exp: labetalol 200-600 mg x 2/day. Control: methyldopa 250-750 mg x 2/day.
Outcomes	Women: proteinuria (> 2+ or 0.5 g/L), admission to hospital, caesarean section, elective delivery, additional antihypertensive, side-effects, changed drugs due to side-effects. Babies: stillbirth, neonatal death, admission to SCBU, SGA (< 5th centile, excludes stillbirths), preterm delivery (< 37 weeks), 5 min Apgar < 8.
Notes	Korotkoff phase IV used for DBP.
Allocation concealment	B – Unclear

Study	**France 1988**
Methods	Allocation concealment: not stated. Authors said 'random order'. Three-arm study.
Participants	63 women at 7-36 weeks' gestation with DBP > 90 mmHg x 2, 8 days apart).
Interventions	Exp: (1) acebutolol 400-1200 mg; (2) labetalol 400-1200 mg.

Characteristics of included studies (*Continued*)

	Control: methyldopa 500-1500 mg.
Outcomes	Women: PE, caesarean section. Babies: perinatal death, preterm delivery, birthweight (mean), Apgar, admission to SCBU, hypoglycaemia.
Notes	No mention about Korotkoff sound considered for DBP. Main paper in French.
Allocation concealment	B – Unclear

Study	**France 1994**
Methods	Allocation concealment: sealed envelopes drawn by physician. Ordered using list of computer-generated random numbers.
Participants	100 women with singleton pregnancy at > 20 weeks' gestation and mild-moderate hypertension (BP >/= 140/90 mmHg x 2). No other antihypertensive medication at trial entry.
Interventions	Exp: nicardipine 20 mg x 3/day. Control: metroprolol (slow release) 200 mg/day.
Outcomes	Women: severe hypertension, proteinuria (undefined), HELLP syndrome, additional antihypertensive, changed drug due to side-effects, induction of labour, caesarean section. Babies: perinatal death, umbilical Doppler, admission to SCBU.
Notes	Korotkoff phase IV used for DBP.
Allocation concealment	B – Unclear

Study	**Hong Kong 1990**
Methods	Allocation concealment: not stated. Authors said: 'randomised double-blind' .
Participants	41 healthy nulliparous women admitted for PE (BP >/= 140/90 mmHg x 2 within 24 hours).
Interventions	Exp: labetalol 200 mg x 3/day. Control: placebo (character not stated).
Outcomes	Women: mean BP, severe hypertension, additional antihypertensive. Babies: birthweight (mean), SGA (< 10th centile), gestation at delivery (mean).
Notes	Trial reported as in progress in 1990. Missing data for some babies. No description of how BP measured. Available only as an abstract.
Allocation concealment	B – Unclear

Study	**India 1992**
Methods	Allocation concealment: not stated. Authors said 'randomly allocated'.
Participants	30 primigravid women at 24-37 weeks' gestation with mild-moderate PIH (BP>/ = 140/90 mmHg x 2, 6 hr apart). Excluded: UTI, heart disease or other cause of hypertension.
Interventions	Exp: metoprolol 50-150 mg x 2/day. Control: methyldopa 250 mg x 3/day, increased to 2000 mg/day.
Outcomes	Women: severe hypertension. Babies: perinatal death, preterm delivery, gestation at delivery, birthweight, Apgar at 1 and 5 min (mean).
Notes	Method for measuring BP not mentioned.
Allocation concealment	B – Unclear

Study	**Ireland 1991**
Methods	Allocation concealment: cards with 'test' or 'control' sealed in envelopes, shuffled and then numbered in sequence. Consecutive envelopes opened.

Characteristics of included studies (*Continued*)

Participants	36 women < 38 weeks' gestation with BP >/= 140/90 mmHg on two separate days, without proteinuria. Excluded: if lived too far from the hospital to attend for frequent examinations.
Interventions	Exp: choice between atenolol 50-100 mg/day and methyldopa 750-2250 mg/day. If monotherapy inadequate, two drugs combined. Bendrofluazide 2.5-5.0 mg added as a third agent when necessary. Control: no antihypertensive.
Outcomes	Women: MAP, proteinuria. Babies: perinatal death, Apgar, gestation age at delivery, birthweight, birthweight < 50th centile.
Notes	Korotkoff phase V used for DBP. Additional data provided by authors.
Allocation concealment	B – Unclear

Study	**Israel 1986**
Methods	Allocation concealment: not stated. Authors said 'randomly allocated'.
Participants	32 women with singleton pregnancy at 27-33 weeks' gestation with PIH (DBP >/= 95 mmHg x 2 at least 6 hr apart). Excluded: history of chronic renal disease or essential hypertension.
Interventions	Exp: pindolol 15 mg/day. Control: methyldopa up to 2000 mg/day (no other details).
Outcomes	Women: severe hypertension, new proteinuria (> 2+ or 0.5 g/L), eclampsia, side-effects, additional antihypertensive, changed drugs due to side-effects. Babies: neonatal death, birthweight (mean), abnormal antenatal fetal heart rate, gestation at delivery (mean).
Notes	Methods for BP measurement not mentioned.
Allocation concealment	B – Unclear

Study	**Israel 1986a**
Methods	Allocation concealment: not stated. Authors said 'randomly allocated'. 2 women with side-effects on hydralazine crossed over to pindolol + hydralazine, and reported in this group. Data only included if available as intention to treat.
Participants	44 women at < 37 weeks with BP >/= 150/90 mmHg x 2 at least 24 hr apart. Excluded: insulin-dependent diabetes, obstructive lung disease, contraindication to pindolol or hydralazine.
Interventions	Exp: hydralazine 50-100 mg/day + pindolol 10-25 mg/day (in 2 daily doses). Control: hydralazine 50-100 mg/day (in 2 daily doses).
Outcomes	Women: severe hypertension, proteinuria (> 1 g in 24 hr), side-effects, changed drug due to side-effects, caesarean section. Babies: preterm delivery, SGA (< 250 on Usher's curve), hypoglycaemia, hypothermia, low Apgar score.
Notes	No mention of which Korotkoff sound used.
Allocation concealment	B – Unclear

Study	**Israel 1992**
Methods	Allocation concealment: trial drug supplied by pharmacy in packs with serial numbers, in blocks of 6.
Participants	60 women < 35 weeks' gestation with DBP 85-99 mmHg x 2, 12 hours apart, and no treatment for hypertension during this pregnancy. Excluded: multiple pregnancy, contraindication to beta blockers or insulin-dependent diabetes.
Interventions	Exp: pindolol 5 mg x 2/day. If DBP still >/= 85 mmHg on day 3, increased to 5 mg x 3/day, if no response next day, increased to 10 mg x 2/day. Control: identical placebo.

Characteristics of included studies (*Continued*)

	If DBP 100-109 mmHg x2 or > 110 mmHg x1, hydralazine added for pindolol group. In placebo group, pindolol given first, followed by hydralazine if DBP > 100 mmHg.
Outcomes	Women: additional antihypertensive, days in hospital, proteinuria > 2+ or > 0.5 g/L, treatment stopped due to side-effects, caesarean section. Babies: perinatal death, gestation at delivery (mean), birthweight, 5 min Apgar > 7, SGA (< 10th centile), hypoglycaemia, jaundice.
Notes	Korotkoff IV used for DBP.
Allocation concealment	A – Adequate

Study	**Israel 1995**
Methods	Allocation concealment: not stated. Authors said 'randomly allocated'. Three- arm trial.
Participants	51 women with BP 140-160/95-110 mmHg. Excluded: proteinuria > 2+, contraindication to beta blockers, or any other disease.
Interventions	Exp: (1) hydralazine 60-200 mg/day + propranolol 40-120 mg/day; (2) hydralazine 60-200 mg/day + pindolol 5-15 mg/day. Control: hydralazine 60-200 mg/day.
Outcomes	Women: eclampsia, severe maternal morbidity, side-effects, caesarean section. Babies: perinatal death, preterm delivery, SGA (< 10th centile), birthweight (mean).
Notes	Korotkoff phase V used for DBP.
Allocation concealment	B – Unclear

Study	**Italy 1997**
Methods	Allocation concealment: not stated. Authors said: 'randomly allocated'.
Participants	100 primigravid women at 26-36 weeks' gestation with SBP 140-160 mmHg, and DBP 90-110 mmHg in first 24 hr after admission and proteinuria < 300 mg/24 hr. Excluded: if other medical maternal or fetal pathology (IUGR or altered biophysical profile).
Interventions	Exp: nifedipine 40-120 mg/day orally and bed rest. Control: bed rest alone.
Outcomes	Women: severe hypertension, proteinuria, days in hospital before delivery. Babies: stillbirth, neonatal death, gestation at delivery (mean), birthweight, placental weight, SGA (undefined).
Notes	Methods for measuring blood pressure not stated. Article in Italian.
Allocation concealment	B – Unclear

Study	**Italy 1998**
Methods	Allocation concealment: central telephone randomisation, stratified by centre and type of hypertension (chronic, gestational or unclassified). Multicentre, 33 hospitals. Withdrawals: 22 women (8%), 13 exp and 9 control lost to follow up. Follow up of children at 18 months: 190/252 (77%) responded to postal survey.
Participants	283 women at 12-34 weeks' gestation, with mild-moderate hypertension (DBP 90-110 mmHg x 2, 4 hours apart). Excluded: chronic diseases (such as diabetes or renal disease), fetal malformations, previous antihypertensive treatment or contraindications to nifedipine.
Interventions	Exp: slow-release nifedipine 20-80 mg x 2/day orally. Control: no antihypertensive.

Characteristics of included studies (*Continued*)

Outcomes	Women: severe hypertension, proteinuria, caesarean section, admission to intensive care. Babies: perinatal death, birthweight, SGA (< 10th centile), preterm delivery (< 34 and < 37 weeks), admission to SCBU, hyperglycaemia, jaundice, RDS, other serious neonatal problems.
Notes	Classification of hypertensive disorders using Davey and MacGillivray system. Methods for measuring blood pressure not mentioned. Data from follow up excluded as > 20% lost.
Allocation concealment	A – Adequate

Study	**Italy 1999**
Methods	Allocation concealment: consecutive-numbered, opaque, sealed envelopes. Three-arm study. 6 women (17%) left the study due to side-effects (2 women) or mother's or baby's worsening conditions (4).
Participants	36 women with singleton pregnancy, gestation > 24 weeks and PIH or PE (BP 140/90 mmHg or more, PE if proteinuria > 300 mg/24 hr). Excluded: fetal abnormalities or chromosomic disorders, renal or hepatic disease, chronic hypertension.
Interventions	Exp (1): transdermal glyceryl trinitrate 10 mg continuously 24 hr/day. Exp (2): transdermal glyceryl trinitrate 10 mg intermittently for 16 hr/day. Control: Nifedipine 40 mg/day orally.
Outcomes	Women: caesarean section, BP (mean), stopped drug due to side-effects, severe hypertension, proteinuria/ pre-eclampsia. Babies: birthweight, fetal/neonatal deaths, preterm birth, IUGR, gestation at birth (mean).
Notes	Korotkoff phase IV used for DBP. In the analysis the two GTN arms have been combined. Additional data provided by authors.
Allocation concealment	A – Adequate

Study	**Italy 2000**
Methods	Allocation concealment: consecutive-numbered treatment boxes.
Participants	20 women with pre-eclampsia (no further details).
Interventions	Exp: nifedipine GITS 30-60 mg/day. Control: methyldopa 500-1000 mg/day.
Outcomes	Women: BP, PE, Doppler abnormalities, need for drug adjustment, severe hypertension. Babies: fetal and neonatal death, preterm birth, SGA (undefined), Apgar score.
Notes	Published as an abstract only. Method for measuring BP not stated. Additional data provided by authors.
Allocation concealment	A – Adequate

Study	**South Africa 1991**
Methods	Allocation concealment: cards labelled R and Q picked blindly from a box, these identified drug container.
Participants	32 women at 12-30 weeks' gestation with a singleton pregnancy and BP >/= 140/90 mmHg x 2 at least 6 hr apart, no proteinuria, no antihypertensive therapy and no other drug treatment.
Interventions	Exp: prazosin 1-5 mg x 3/day. Control: identical placebo.
Outcomes	Women: severe hypertension, proteinuria, duration of treatment, placental abruption, caesarean section. Babies: perinatal death, gestation at delivery (mean), birthweight, SGA (< 10th centile) preterm delivery (< 37 weeks).
Notes	Method for measuring blood pressure not mentioned. The trial stopped early.
Allocation concealment	B – Unclear

Characteristics of included studies (*Continued*)

Study	**South Africa 1993**
Methods	Allocation concealment: not stated. Authors said: 'randomised open study'. Withdrawals: 3 women (10%) lost to follow up, but outcome for babies reported.
Participants	29 women at 29-36 weeks' gestation with mild-moderate hypertension (DBP 90-110 mmHg).
Interventions	Exp: nifedipine started at 30 mg/day. Control: methyldopa started at 750 mg/day. Stated that 'dose adjustments were made, when necessary, every second day until control of BP was obtained'.
Outcomes	Women: additional antihypertensive, caesarean section, induction of labour, side-effects. Babies: stillbirth, preterm delivery, gestation at delivery (mean), admission to SCBU.
Notes	Method for measuring BP not mentioned.
Allocation concealment	B – Unclear

Study	**Sudan 2002**
Methods	Allocation concealment: not stated. Authors said: '...patients were randomly allocated...'.
Participants	70 primigravid women with pre-eclampsia (BP =/> 90/109 mmHg x 2, 6 hr apart plus 2+ proteinuria in dipsticks) at 28-36 weeks' gestation. Singleton pregnancy.
Interventions	Exp: methyldopa 750-4000 mg/day Control: no drug treatment. All women in both groups were admitted to hospital for bed rest.
Outcomes	Women: BP, abruptio, imminent eclampsia, eclampsia, preterm delivery, caesarean section, maternal death. Babies: birthweight, IUGR, admission to SCBU (reported as 'referral of baby'), perinatal deaths, Apgar score.
Notes	Korotkoff IV sound used for DBP.
Allocation concealment	B – Unclear

Study	**Sweden 1984**
Methods	Allocation concealment: telephone randomisation, no further details.
Participants	52 women in antenatal clinic at < 37 weeks' gestation with singleton pregnancy, BP >/= 140/90 mmHg or an increase of at least 30 mmHg SBP or 15 mmHg DBP x 2 within 24 hr. Excluded: imminent eclampsia, serious fetal distress, severe hypertension (> 170/110 mm Hg), Rh disease, diabetes, contraindication to beta blockers, 'social or psychological handicaps'.
Interventions	Exp: metoprolol 100-200 mg x 2/day. Control: identical placebo x 2/day.
Outcomes	Women: proteinuria (>/= 2+), severe hypertension, changed drugs due to side-effects, hospital admission, placental abruption, caesarean section. Babies: perinatal death, gestation at delivery (mean) Apgar (mean).
Notes	Korotkoff phase V used for DBP. Additional data provided by authors.
Allocation concealment	B – Unclear

Study	**Sweden 1985**
Methods	Allocation concealment: 'envelope randomisation'. No further information. Withdrawals: 7 women (4%) dropped out (4 exp, 3 control). Multicentre, not stated how many hospitals.
Participants	168 women in antenatal ward with singleton pregnancy at < 37 weeks, DBP >/= 90 mmHg x 2, no proteinuria. Excluded: diabetes, asthma, heart disease, psychiatric or psychological disorders.
Interventions	Exp: metoprolol 50-200 mg/day + hydralazine 50-300 mg/day.

Characteristics of included studies (*Continued*)

	Control: no antihypertensive.
Outcomes	Women: severe hypertension, proteinuria (> 1+ or 0.25 g/L), changed drugs due to side-effects, placental abruption, caesarean section. Babies: stillbirth, neonatal death, preterm delivery (< 37 and < 34 weeks), SGA (undefined), bradycardia, hypoglycaemia, Apgar < 7 at 1 and 5 min, RDS.
Notes	Korotkoff phase V used for DBP. Additional data provided by authors.
Allocation concealment	B – Unclear

Study	**Sweden 1995**
Methods	Allocation concealment: authors said: 'randomised by numbers to treatment with capsules'. Randomisation in blocks of 6. Information about allocation kept in sealed envelopes, opened if severe complications or side-effects. 5 centres in Sweden, 1 in Denmark. Withdrawals: 7 women (6%), 1 dropout, 6 not re-evaluated after 3 days (4 exp, 2 control).
Participants	118 women at 26-37 weeks, with singleton pregnancy and DBP 95-110 mmHg. Excluded: if delivery expected within a week, history of alcohol or drug abuse, or other medication known to be toxic.
Interventions	Exp: isradipine (slow release) 5 mg x 2/day. Control: placebo x 2/day.
Outcomes	Women: eclampsia, severe hypertension (DBP >/= 110 mmHg), proteinuria >/=2+, need for additional antihypertensive, MAP, caesarean section, induction of labour, side-effects. Babies: perinatal death, gestation at delivery (mean), admission to SCBU, birthweight (mean), placental weight.
Notes	Korotkoff phase IV used for DBP. Description of BP measurements technique, and of criteria used to define hypertension and proteinuria.
Allocation concealment	B – Unclear

Study	**UK 1968**
Methods	Allocation concealment: not stated. Authors said 'allocated at random'.
Participants	100 pregnant women with DBP >/= 90 mmHg or more x 2, 48 hr apart.
Interventions	Exp: methyldopa 250-1,000 mg x 2/day + bendrofluazide 5-10 mg/day. Control: no treatment.
Outcomes	Women: mean BP, proteinuria, residual hypertension, length of gestation. Babies: birthweight (mean), perinatal death.
Notes	Methods for measuring BP not mentioned. According with BP at entry, women were divided in two groups: 'moderate' for those with DBP = or > 90 mmHg at entry (n = 42), and 'severe' for those with DBP = or > 100 mmHg (n = 58). For the main outcomes results are presented together.
Allocation concealment	B – Unclear

Study	**UK 1976**
Methods	Allocation concealment: not stated. Authors said 'randomly allocated'. Withdrawals: 5 women (2%) withdrawn from exp group. Follow up of 202 live born children. At 4 years, 34 (17%) lost to follow up. At 7, years 7 (3%) lost to follow up.
Participants	247 women with BP >/= 140/90 mmHg if < 28 weeks' gestation, or >/= 150/95 mmHg if > 28 weeks' gestation x 2 24 hr apart. Excluded: diabetes, multiple pregnancy, Rh immunisation. Women > 36 weeks' gestation excluded during first year of the trial, thereafter excluded if > 32 weeks' gestation.

Characteristics of included studies (*Continued*)

Interventions	Exp: methyldopa 750-4000 mg/day. Control: no antihypertensive. Hydralazine if severe hypertension.
Outcomes	Women: severe hypertension, proteinuria, caesarean section, elective delivery, side-effects, changed drug due to side-effects. Babies: perinatal death, birthweight (mean), gestation at delivery (mean), SGA (< 2 SD below mean), babies nursed in an incubator, neurodevelopment at 4 and 7 years.
Notes	Korotkoff phase IV used for DBP. Random zero sphygmomanometer.
Allocation concealment	B – Unclear

Study	**UK 1980**
Methods	Allocation concealment: randomly allocated using random-number table.
Participants	26 women < 38 weeks' gestation with PIH and no contraindication to beta blockers.
Interventions	Exp: labetalol 400-800 mg/day. Control: methyldopa 750-1500 mg/day.
Outcomes	Women: proteinuria, severe hypertension, caesarean section, induction of labour, side-effects. Babies: stillbirth, birthweight (mean), gestation at delivery (mean), 1 min Apgar, admission to SCBU, jaundice.
Notes	Korotkoff phase IV used for DBP.
Allocation concealment	C – Inadequate

Study	**UK 1982**
Methods	Allocation concealment: envelope randomisation, no further information.
Participants	126 women with either chronic hypertension or PIH, and DBP > 95 mmHg if < 20 weeks or 95-109 mmHg if > 20 weeks.
Interventions	Exp: labetalol 100 mg x 2/day, increased to maximum of 1200 mg/day. Control: no antihypertensive. If BP not controlled, hydralazine 25 mg x 3/day, increased to maximum of 200 mg/day.
Outcomes	Women: severe hypertension, proteinuria (undefined), caesarean section, placental abruption. Babies: perinatal death, SGA (< 10th centile).
Notes	Methods for measuring BP not mentioned. Additional data provided by authors.
Allocation concealment	B – Unclear

Study	**UK 1983**
Methods	Allocation concealment: authors said 'allocated in double-blind and randomised manner'. Withdrawals: some data missing for 35 women (29%). Data for each outcome only included if < 20% excluded. Follow up: 110 children (92%) seen at 1 year.
Participants	120 women with PIH in third trimester admitted for bed rest, SBP 140-170 mmHg and DBP 90-110 mmHg x 2, 24 hr apart. Excluded: women with contraindication to beta blockers.
Interventions	Exp: atenolol 100-200 mg/day. Control: placebo.
Outcomes	Women: proteinuria (> 0.5 g/24 hr), severe hypertension, additional antihypertensive, changed treatment due to side-effects, side-effects, admission to hospital prior to delivery, caesarean section.

	Babies: perinatal death, SGA (< 10th centile), bradycardia, hypoglycaemia, jaundice, RDS. At 1 year: cerebral palsy, IQ < 1 SD below mean, weight.
Notes	Korotkoff phase IV used for DBP. Random zero sphygmomanometer used for measuring blood pressure.
Allocation concealment	B – Unclear

Study	**UK 1983a**
Methods	Allocation concealment: not stated. Authors said 'allocated at random'. Stratified by gestational age.
Participants	100 women with singleton pregnancy and DBP >/= 95 mmHg x 2 at least 24 hr apart, or > 105 mmHg x 1. Excluded: asthma, heart failure, or heart block, diabetes, renal disease, or taking other hypertensive medication.
Interventions	Exp: oxprenolol 80-320 mg x 2/day. Control: methyldopa 250-1000 mg x 3/day. If BP not controlled, hydralazine added to both groups.
Outcomes	Women: severe hypertension, proteinuria (> trace on dipstick), induction of labour, caesarean section, additional antihypertensive, hospital admission. Babies: perinatal death, birthweight (mean), 5 min Apgar < 7, antenatal fetal heart rate.
Notes	Korotkoff phase IV used for DBP. Random zero sphygmomanometer.
Allocation concealment	B – Unclear

Study	**UK 1984**
Methods	Allocation concealment: not stated. Authors said 'randomised trial'.
Participants	60 women at 18-36 weeks' gestation with undefined hypertension.
Interventions	Exp: atenolol 100 mg/day. Control: methyldopa 250 mg x 3/day.
Outcomes	Women: proteinuria (undefined). Babies: stillbirth, birthweight, SGA (< 10th centile) bradycardia, hypoglycaemia.
Notes	Korotkoff phase V used for DBP.
Allocation concealment	B – Unclear

Study	**UK 1989**
Methods	Allocation concealment: drug and placebo sent by manufacturer to hospital pharmacy with list of random numbers. Then dispensed by pharmacists. 5 centres. Withdrawals: 8 (5%), 6 exp, 2 control. 2 women withdrew, 1 treated with ward stock labetalol, one developed rash, and 4 did not fulfil entry criteria.
Participants	152 women from antenatal wards at 20-38 weeks' gestation with SBP 140-160 mmHg and DBP 90-105 mmHg x 2, 24 hr apart, and no proteinuria. Excluded: history of hypertension, renal, metabolic, cardiovascular, respiratory or collagen disease.
Interventions	Exp: labetalol 100-200 mg x 3/day. Control: identical placebo.
Outcomes	Women: mean BP, severe hypertension, proteinuria (undefined), induction of labour, caesarean section, days in hospital (mean), side-effects. Babies: perinatal death, preterm delivery (< 37 weeks), SGA (< 5th centile), admission to SCBU, RDS.
Notes	Korotkoff phase IV used for DBP. Conventional sphygmomanometers used to measure blood pressure.
Allocation concealment	A – Adequate

Characteristics of included studies (*Continued*)

Study	**UK 1990**
Methods	Allocation concealment: not stated. Authors said 'randomised' but no other information. Withdrawals: 4 (12%), 1 exp (changed her mind), 3 control (2 severe hypertension, 1 breathlessness).
Participants	33 women 12-24 weeks' gestation with SBP 140-170 mmHg and DBP 90-110 mmHg x 2, 24 hr apart. Excluded: if 'usual' contraindications to beta blockers.
Interventions	Exp: atenolol 50-200 mg/day. Control: placebo (character not stated).
Outcomes	Women: mean BP, severe hypertension, stopped drug due to side-effects. Babies: stillbirth, birthweight, SGA (< 5th centile), placental weight, gestation at delivery (mean).
Notes	Korotkoff phase V used for DBP. The trial was stopped early when the principal investigator left Glasgow. Additional data provided by authors.
Allocation concealment	B – Unclear

Study	**UK 1992**
Methods	Allocation concealment: numbered, sealed opaque envelopes. Stratified by parity.
Participants	114 women with singleton pregnancy at 24-39 weeks' gestation with DBP > 90 mmHg for > 24 hr and no proteinuria. Excluded: psychoneurosis, cardiac abnormality, diabetes, asthma, contraindication to beta blockers, antenatal antihypertensive treatment.
Interventions	Exp: labetalol 100 mg x 2/day, increased up to 400 mg x 3/day. Control: no antihypertensive.
Outcomes	Women: proteinuria (> 1+ or 0.25 g/L), duration of stay in hospital (mean), side-effects, changed drug due to side-effects, elective delivery, caesarean section. Babies: perinatal death, gestation at delivery (mean), preterm delivery (< 37 weeks), SGA (<5th centile), admission to SCBU, length of stay in hospital (mean).
Notes	Korotkoff phase IV used for DBP. Additional data provided by authors.
Allocation concealment	A – Adequate

Study	**USA 1979**
Methods	Allocation concealment: not stated. Authors said 'allocated randomly to treatment or no treatment'.
Participants	58 women with hypertension before pregnancy or BP >/= 140/90 mmHg x 2 more than 24 hr apart before 20 weeks' gestation. Excluded: DBP > 100 mmHg, nulliparous, other major medical or obstetric problem.
Interventions	Exp: methyldopa 750-2000 mg/day, hydrochlorothiazide 50 mg/day, hydralazine 75-250 mg/day. Control: no antihypertensive.
Outcomes	Women: severe hypertension, proteinuria (> 1+ or > 300 mg/L in 24 hr), caesarean section. Babies: perinatal death, gestation at delivery, birthweight < 2500 g, fetal distress, SGA (undefined).
Notes	No information about how BP measured. In exp group, 11 women had methyldopa + hydrochlorothiazide, 10 hydralazine + hydrochlorothiazide, 8 had all 3 drugs.
Allocation concealment	B – Unclear

Study	**USA 1987**
Methods	Allocation concealment: physician drew a sealed envelope containing assignment. Withdrawals: 14 women (7%), 8 exp and 6 control refused hospitalisation, but data reported for perinatal death.
Participants	200 primigravid women in hospital at 26-35 weeks' gestation with SBP 140-160 mmHg and DBP 90-110 mmHg, proteinuria > 0.3 g/L and uric acid > 4.6 mg/dL.

Characteristics of included studies (*Continued*)

	Excluded: associated medical and obstetrical complications, other antihypertensive medication.
Interventions	Exp: hospitalisation + labetalol 300 mg/day, increased every few days to max 2400 mg/day. Control: hospitalisation alone.
Outcomes	Women: severe hypertension, increased proteinuria, eclampsia, placental abruption, caesarean section, renal function, days gained during management. Babies: perinatal death, gestation at delivery (mean), birthweight (mean), placental weight, admission to SCBU, SGA (< 10th centile).
Notes	No mention of how BP measured.
Allocation concealment	B – Unclear

Study	**USA 1987a**
Methods	Allocation concealment: not stated. Authors said 'randomly allocated', no further information.
Participants	25 women at < 34 weeks' gestation, singleton pregnancy with BP 140/90 mmHg x 2 at least 6 hr apart and no proteinuria. Presumed chronic hypertension.
Interventions	Exp: methyldopa 750 mg x 3/day to 2000 mg x 4/day. Control: placebo, in the same way. If severe pre-eclampsia, hydralazine or MgSO4 added.
Outcomes	Women: MAP, new proteinuria (2+ or greater on urine dipsticks), PE (defined as a sudden rise of 30 mmHg SBP or 15 mmHg DBP and weight gain > 2 lbs/week, or proteinuria > 2+), elective delivery, side-effects. Babies: perinatal death, gestation at delivery (mean), birthweight (mean and < 50th centile).
Notes	No information about how BP measured.
Allocation concealment	B – Unclear

Study	**USA 1990**
Methods	Allocation concealment: envelope randomisation, using computer-generated random numbers. Three-arm study. Withdrawals: 37 women (12%). 27 exp (21 excluded due to poor compliance, 3 twin, 1 abortion and 2 lost to follow up) and 10 control (8 due to poor compliance, 1 twin and 1 spontaneous abortion).
Participants	300 women in antenatal ward with chronic mild-moderate hypertension at 6-13 weeks' gestation. All had chronic hypertension before pregnancy and no associated medical complications.
Interventions	Exp: (1) methyldopa 750-4000 mg/day (no other details). (2) labetalol 300-2400 mg/day (no other details). Control: no antihypertensive.
Outcomes	Women: PE (defined as hypertension, proteinuria, and hyperuricemia), additional antihypertensive, days in hospital, placental abruption, congestive heart failure, serum creatinine, uric acid. Babies: perinatal death, gestation at delivery, birthweight < 2.5 kg, preterm delivery (< 37 weeks), SGA (undefined), admission to SCBU, hypoglycaemia, 5 min Apgar < 7.
Notes	Korotkoff phase IV used for DBP. 36% of women were taking an antihypertensive at the time of trial entry. Additional data provided by authors.
Allocation concealment	B – Unclear

Study	**USA 1992**
Methods	Allocation concealment: physician drew sealed envelope containing assignment. Computer-generated random numbers. Withdrawals: 3 women (1.5%) lost to follow up (2 exp, 1 control).
Participants	200 primigravid women at 26-36 weeks' gestation with SBP 140-160 mmHg and/or DBP 90-110 mmHg 24 hr after hospitalisation, proteinuria > 300 mg/24 hr, and/or uric acid > 6 mg/dL.

	Excluded: associated medical or obstetric complications, or fetal compromise (suspected abnormal fetal growth by US, abnormal fetal testing).
Interventions	Exp: nifedipine 40-120 mg/day. Control: bed rest alone.
Outcomes	Women: MAP, severe proteinuria (> 5 g/24 hr), antenatal hospital stay (mean), days gained during management, caesarean section, placental abruption, HELLP syndrome. Babies: stillbirth, neonatal death, birthweight, preterm delivery (< 37 weeks), SGA (< 10th centile), admission to SCBU, days in SCBU (mean).
Notes	Method of measuring blood pressure not mentioned.
Allocation concealment	B – Unclear

Study	**Venezuela 1988**
Methods	Allocation concealment: not stated. Treatment assigned using random-number tables.
Participants	31 women > 14 weeks' gestation with either chronic hypertension or mild-moderate PIH (BP 140-169/90-109 mmHg x 2 after 5 min rest). Excluded: contraindication to beta blockers, Rh or haemorrhagic disorders.
Interventions	Exp: mepindolol 5 mg/day, increased weekly to 10 mg/day. Control: methyldopa 250 mg x 2/day increased weekly to 250 mg x 4/day.
Outcomes	Women: severe hypertension, caesarean section, induction of labour. Babies: perinatal death, gestation at delivery, birthweight, Apgar score.
Notes	Main paper in Spanish. Method of measuring blood pressure not mentioned.
Allocation concealment	C – Inadequate

BP: blood pressure
DBP: diastolic blood pressure
exp: experimental
GITS: gastrointestinal therapeutic system
GTN: glyceryl trinitrate
HELLP: syndrome of haemolysis, elevated liver enzymes and low platelets
hr: hour(s)
IUGR: intrauterine growth restriction
IV: intravenous
MAP: mean arterial pressure
MgSO4: magnesium sulphate
min: minutes
PE: pre-eclampsia
PIH: pregnancy-induced hypertension
RDS: respiratory distress syndrome
SBP: systolic blood pressure
SCBU: special care baby unit
SD: standard deviation
SGA: small-for-gestational age
US: ultrasound
UTI: urinary tract infection

Characteristics of excluded studies

Study	**Reason for exclusion**
Argentina 1994	Not clearly randomised. Available as abstract only.

	Methods: 'divided into two groups'. No further information. Participants: 187 women with chronic hypertension (n = 66) or gestational hypertension (n = 121). Interventions: atenolol 40-100 mg/day versus methyldopa 250-2000 mg/day. Outcomes: superimposed pre-eclampsia, maternal BP, birthweight.
Australia 1985a	Comparison of two alpha agonists. Methods: 'prospective, double blinded'. Women entered in a numerical sequence. No numbers missed or used a second time. Participants: 100 women with BP > 130/85 mmHg or a rise of 30/15 mmHg from previous values. Intervention: clonidine 150-1200 mcg/day versus methyldopa 250-2000 mg/day. If additional treatment needed, hydralazine. Outcomes: severe hypertension, need for additional drug, stopped treatment due to side-effects, stillbirth, neonatal death, preterm delivery, birthweight (mean), SGA, 5 min Apgar.
Australia 1991	Entry criteria was DBP greater than one SD above the reported mean for gestational age. Mean BP of recruited women was 129/84 mmHg at entry to the trial (122-136/79-89 mmHg) for the placebo group, and 126/82 mmHg (118-134/79-85) for the treatment group. Participants: 52 nulliparous with singleton pregnancies between 28 and 34 weeks of gestation, without proteinuria. Intervention: clonidine from 200 to 800 mcg a day plus hydralazine from 50 to 200 mg a day, and placebo. Outcomes: severe hypertension, imminent eclampsia, eclampsia, severe proteinuria, antepartum haemorrhage, HELLP syndrome, fetal distress, fetal death, IUGR.
Belgium 1988	Comparison of two beta blockers. Available as abstract only. Methods: 'randomised' , no further information. Participants: 23 women with BP at least 140/90 mmHg x 2 and no proteinuria. Intervention: atenolol 100 mg a day vs pindolol 15 mg a day. Outcomes: umbilical PI, maternal BP, birthweight, Apgar score.
Brazil 2000	Quasi-random design. Main paper in Portuguese. Methods: alternated allocation (data extracted from original thesis). 11 women (10.5%) excluded after trial entry. Participants: 105 women with singleton pregnancies diagnosed with pre-eclampsia, chronic hypertension, and pre-eclampsia superimposed to chronic hypertension. Intervention: isradipine (slow release), 5 mg every 12 hr vs atenolol 50 mg every 12 hr. Outcomes: BP, maternal heart rate, proteinuria, maternal side-effects, mode of delivery, gestational age, birthweight, SGA babies, Apgar score.
Brazil 2000b	40 women (24%) excluded after randomisation. Reasons for exclusion were: missed appointment for Doppler (70%), non-compliance (20%), side-effects (7.5%), preterm delivery (2.5%). Data were not presented by treatment arm. Main paper in Portuguese. Methods: randomised, double-blind, placebo-controlled trial. Participants: 123 pregnant women with chronic hypertension. Intervention: verapamil 240 mg/day vs placebo during 30 days. Outcomes: Doppler PI, RI and S/D ratio, incidence of pre-eclampsia, birthweight, gestational age at delivery, SGA.
China 1991	Herbal medicine vs magnesium sulphate. No clinical data available. Article in Chinese. Only abstract translated into English. Methods: not reported. Authors said: '...randomly designed to...'. Participants: 75 women with 'hypertension syndrome of pregnancy'. Intervention: Magnesium sulphate 20-25 g/day vs ligustrazine 120-160 mg/day. Outcomes: MAP, proteinuria, haematocrit, side-effects, positive rate of NST, Apgar score.
China 1993	Only dose intervention. Sublingual nifedipine previous to caesarean section. Article in Chinese. Only abstract translated into English. Methods: not reported. Indexed as publication type: RCT. Participants: 33 women with pre-eclampsia undergoing emergent caesarean section.

	Intervention: sublingual nifedipine, 16 mg (only dose). Control group not reported in abstract. Outcomes: MAP, systolic and diastolic BP, maternal heart rate, postoperative haematocrit, side-effects.
China 1998	Single -dose intervention. No clinical outcomes studies (effect of nimodipine in retinal blood flow). Article in Chinese. Only abstract translated into English. Methods: not stated. Indexed as publication type: RCT. Participants: 28 women with PIH. Intervention: nimodipine 30 mg orally (only dose) vs IV magnesium sulphate. Outcomes: retinal PI.
China 1999	Herbal medicine + nifedipine vs nifedipine. No clinical outcomes studied. Article in Chinese. Only abstract translated into English. Methods: not stated. Indexed as publication type: RCT. Participants: 95 women with PIH. Intervention: prepared rhubarb + nifedipine vs nifedipine. Outcomes: serum lipids, and other blood tests.
China 2000	Less than 7 days treatment. Treatment was given only during labour. Article in Chinese. Only abstract translated into English. Methods: "64 cases of PIH were randomly divided into...". Participants: 64 women with PIH. Interventions: Nifedipine orally given every 6 hr during labour vs no treatment. Outcomes: postpartum haemorrhage.
Cuba 1994	Quasi-random design. Article in Spanish. Methods: alternate allocation (data provided by author). Participants: 90 pregnant women with chronic hypertension. Intervention: methyldopa (1-2 g/day) or hydralazine (100-200 mg/day) vs no treatment. Outcomes: BP, superimposed pre-eclampsia, abruption, preterm delivery, LBW, Apgar score, RDS, hypoxia, fetal death.
Czech Republic 1993	Comparison of two beta blockers. Article in Czech. Only abstract translated into English. Methods: 'divided at random'. No further information. Participants: 40 women with DBP 95-105 mmHg. Intervention: atenolol 50-100 mg/day versus bisoprolol 5-10 mg/day. Outcomes: BP, maternal heart rate, side-effects.
Denmark 1991	Intervention is not an antihypertensive: magnesium vs placebo. Methods: "...patients were allocated in a double-blind and randomised manner, based in a computer-generated list of numbers...". Participants: 61 women with PIH. Chronic HT excluded. Withdrawals: 3 women (2 from intervention group, 1 from control group) excluded after randomisation. Intervention: 48-hr of either IV magnesium or placebo infusion followed by daily oral magnesium or placebo tablets. Outcomes: MAP, caesarean section, induction of labour, side-effects, gestational age, birthweight, Apgar score, admission to SCBU and days of stay.
Denmark 2000	Intervention is not an antihypertensive: magnesium vs methyldopa. Methods: RCT. Allocation concealment by numbered sealed opaque envelopes. Participants: 33 women with PIH. Chronic HT excluded. Intervention: magnesium, 48-hr IV infusion followed by daily oral magnesium vs methyldopa 250 mg x 4/day. Outcomes: BP, gestational age, birthweight, admission to SCBU and length of stay, serum magnesium.
Dominican Rep 1992	Not a RCT. Article in Spanish. Only abstract translated into English. Methods: not stated. Authors only says "...divided into 2 groups...". Women known as given the drugs under study were also included. Participants: 50 pregnant women with chronic HT + superimposed pre-eclampsia. Intervention: slow-release nifedipine 20 mg every 8 hr vs methyldopa 500 mg every 12 hr.

	Outcomes: BP, Apgar score.
Dominican Rep 1992a	Not a RCT. Article in Spanish. Only abstract translated into English. Methods: not stated. Authors only says "...divided into 2 groups...". Participants: 30 pregnant women with severe pre-eclampsia. Intervention: methyldopa 250-500 mg every 5 hr vs hydralazine 20-50 mg every 8 hr. Outcomes: BP, maternal side-effects.
Egypt 1988	No relevant clinical outcomes reported. Available as abstract only. Methods: 'patients were randomly allocated to three treatment groups'. No further information. Participants: 50 primigravidae with pre-eclamptic toxaemia and 20 multigravidae with essential hypertension in their late pregnancy. Interventions: three-arm trial: bromocriptine 5 mg, methyldopa 1 gr, and placebo, in different combinations. No further information. Outcomes: serum prolactin and serum placental lactogen, BP. One year follow up reported.
Egypt 1993	One-week intervention. Outcomes measured at 30 min, 3 and 7 days. Methods: 'randomly allocated' . Participants: 30 women with PE in the third trimester. 25 women had mild PE with DBP 100-109 mmHg and 5 had severe PE with DBP >/= 110 mmHg. Intervention: nifedipine 20 mg every 8 hr for 7 days or placebo in the same time and duration. Outcomes: BP and fetal heart rate measured at 30 min, 3 and 7 days. Renal function tests and Doppler scans of umbilical cord.
Egypt 1997	The intervention is not an antihypertensive. Naltrexone vs placebo. Available as an abstract only. Methods: "...were randomly allocated to either naltrexone (...) or placebo". Participants: 20 women with PIH at 30-36 weeks' gestation. Intervention: naltrexone (opioid receptor antagonist), 50 mg every 12 hr vs placebo. Outcomes: BP, proteinuria, oedemas, prolactin levels, gestational age, status of the baby at birth.
Finland 1988	Comparison of two beta blockers. Methods: 'according to randomisation table'. No further information. Participants: 51 women with BP > 149/94 mmHg x 2 in sitting position after two days bed rest in hospital. Intervention: atenolol 50-100 mg/day versus pindolol 10-20 mg/day. If needed, hydralazine 150 mg/day added. Outcomes: stillbirths, side-effects, need for additional drug, caesarean section, gestation at delivery (mean), birthweight (mean), 5 min Apgar.
Finland 1988a	No relevant clinical outcomes reported, report of ongoing study. Available as abstract only. Methods: 'randomised pilot trial'. No further information. Participants: 25 women with PIH. Interventions: nifedipine 30-60 mg a day versus no treatment. Outcomes: mean DBP, birthweight (mean).
Finland 1995	Comparison of two beta blockers. Less than 7 days treatment, single-dose study. Women with mild hypertension not reported separately from severe hypertension. Methods: 'randomly chosen'. No further information. Participants: 24 women with a singleton pregnancy at 28-40 weeks, and either mild or severe pre-eclampsia (BP > 160/110 mmHg plus proteinuria > 5 g/24 hr, or BP 140/90-160/110 mmHg plus proteinuria < 5 g/24 hr). Intervention: atenolol 0.15 mg/kg IV vs pindolol 0.006 mg/kg IV in 100 ml of Ringer's solution. Infusion time 15-20 min. Outcomes: utero and umbilicoplacental vascular impedance, fetal haemodynamics and cardiac function.
Finland 1999	Main outcomes were assessed only at 5-7 days of inclusion. 29% of women were excluded from the analysis. Methods: randomised, double-blind, double-dummy study. Participants: 24 women with singleton pregnancies between 29 and 39 weeks with BP > 140/90 mmHg x2, 6 hr apart, and proteinuria > 0.3 g in 24 hr urine collection.

	Intervention: isradipine 2.5 mg twice daily or placebo vs metoprolol 50 mg twice daily or placebo (double-dummy study). Outcomes: insulin sensitivity, uric acid, degree of proteinuria, lipids and lipoproteins, BP, umbilical artery RI, birthweight, placental weight, caesarean section, Apgar scores.
France 1988a	No clinical outcomes reported. Outcomes assessed at 4 weeks after trial entry. Available as abstract only. Methods: 'randomised' no further information. Three-arm study. Participants: 29 women with isolated hypertension after 'a mean period of 18 weeks of pregnancy'. Intervention: pindolol vs atenolol versus methyldopa. Outcomes: BP, maternal heart rate, serum sodium, potasium, uric acid, creatinine, plasma renin activity and aldosterone.
France 1990	No clinical data reported. Available as congress abstracts only (1 in English, 3 in French). Methods: 'randomised protocol'. Participants: 21 women with moderate hypertension (SBP 140-180 mmHg and DBP 90-120 mmHg). Intervention: oral atenolol (n = 12) vs nifedipine (n = 9) (no doses reported). Outcomes: BP, Doppler measures, birthweight and length, Apgar score, admission to SCBU.
Hong Kong 1993	No clinical data available. Abstract report. Methods: allocated in 'randomised double manner'. No further information. 4 women (6.2%) excluded after randomisation. Participants: 65 primigravid women with a singleton pregnancy at > 20 weeks' gestation and BP 140-165/90-105 mmHg x 2, 6 hr apart but no proteinuria. Interventions: labetalol (dose not reported) vs placebo (vitamin C). Outcomes: BP, need for additional antihypertensives, induction of labour, proteinuria, gestational age, mode of delivery, birthweight, Apgar score.
Hungary 1999	28% of women excluded after randomisation (7 because of treatment duration not exceeding 10 days and 2 dropped out). Methods: allocation 'according to randomisation list'. No further information. Participants: 32 healthy primigravidae with BP at least 140/90 mmHg x 2 at least 6 hr apart. Interventions: calcium dobesilate 2 g a day vs placebo. Outcomes: new proteinuria, caesarean section, placental abruption, preterm delivery.
India 1999	Intervention is an antiplatelet agent. Available as abstract only. Methods: randomised, placebo-controlled trial. Participants: 163 women with PIH of 20-32 weeks' gestation. Intervention: aspirin 60 mg a day vs placebo from 22 until 38 weeks of gestation. Outcomes: prevention of PIH grade B (BP 160/110 mmHg x 2, 4 hr apart), proteinuria 2+ or more, perinatal mortality, maternal mortality, eclampsia, SGA (< 10th centile).
Iran 2000	Quasi-random design (data from personal communication). Available as abstract only. Methods: 'patients were sequentially assigned to one of two randomised groups'. Alternate allocation (data obtained from personal communication). Participants: 37 pregnant women over 26 weeks' gestation with blood pressure over 140/90 mmHg (after 24-48 hr resting) + proteinuria or generalised oedema. Intervention: nifedipine 10 mg t.i.d. vs hydralazine 10 mg t.i.d. Outcomes: BP, termination of pregnancy, side-effects.
Israel 1988	Comparison of two beta blockers. Published as abstract only. Methods: 'allocated in blind and randomised manner'. No further information. Participants: 30 women with SBP 140-170 mmHg and DBP 90-110 mmHg x 2, 6 hr apart. Intervention: Atenolol 100 mg plus two placebo tablets vs pindolol 5 mg x 3/day. Outcomes: gestation at delivery (mean).
Israel 1992a	Comparison of two beta blockers. Methods: 'randomly allocated to double blind treatment'. No further information. Participants: 20 women with mild PE, BP >/= 140/90 mmHg.

	Interventions: propranolol 40 mg x 3/day vs pindolol 5 mg x 3/day, for 7 days. Outcomes: BP, umbilical artery Doppler.
Israel 1999	Single-dose intervention. Methods: double-blind, placebo-controlled RCT. Participants: 23 women with PIH. Intervention: sublingual tablet of Isosorbide dinitrate (5 mg) or placebo (single dose). Outcomes: maternal BP and heart rate, umbilical artery Doppler.
Italy 1986	Not an RCT (matched controls). Available as abstract only. Methods: 'randomised protocol', no further information, for group A (nifedipine or atenolol), control group (B) was matched by age and parity with group A. Results in group A were not presented separately. Participants: 10 women with mild-moderate hypertension in the third trimester (group A). Interventions: atenolol 100 mg a day or slow-release nifedipine 20 mg x 2/day (group A) vs diuretics or bed rest (group B). Outcomes: BP, gestational age, birthweight, Apgar score, serum bilirubin, preterm delivery, RDS, side-effects.
Italy 1990	Quasi-randomised design. Two trials with same methods reported in one paper (1) 44 women (2) 50 women. Methods: allocation by 'order of attendance at clinic or department'. Participants: women with BP =/> 140/90 mmHg x 2 over 8 hr, normal BP before pregnancy. Intervention: (1) slow-release verapamil 360-480 mcg/day vs pindolol 15-20 mg/day. (2) slow-release verapamil 360-480 mcg/day vs atenolol 100-150 mg/day. Outcomes: caesarean section, baby death, Apgar (mean), gestation at delivery (mean).
Italy 1990a	Intervention is an antiplatelet agent. No clinical outcomes reported. Available as abstract only. Methods: '...using a random selection...'. No further information. Participants: 20 women with PIH before 36 weeks' gestation. Intervention: picotamide (no dose reported) vs no treatment. Outcomes: platelet aggregation, ADP-threshold values, collagen concentration thresholds.
Italy 2000a	Women had chronic hypertension or history of hypertension or IUGR (results were not presented separately). Methods: "...patients were randomly allocated to two treatments...". Participants: 68 women with either chronic hypertension or with previous history of PE or IUGR. Intervention: glyceryl trinitrate transdermal patch (5 mg/24 hr) for 14-16 hr/day from 16 to 38 weeks' gestation vs observation. Outcomes: hypertensive syndrome, preterm delivery, abruptio, birthweight, IUGR, Apgar score, admission to SCBU, RDS, neonatal death, umbilical and cerebral artery PI.
Italy 2001	Not clearly randomised. No clinical data reported. Available as congress abstract only. Methods: not stated. Participants: 24 women with PIH. Intervention: isosorbide dinitrate sublingual every 6 hr (n = 12) vs nifedipine 20 mg daily (n = 12). Outcomes: apoptosis in placental tissues.
Italy 2002	Intervention is not an antihypertensive. Single-dose treatment. Methods: double-blind, randomised, cross-over design. Participants: 15 pregnant women at 30-34 weeks' gestation with mild/moderate PIH. Intervention: L-Arginine 20 g /500 ml vs placebo infusion. Outcomes: systolic and diastolic BP, fetal heart rate and fetal movements.
Japan 1997	Single-dose intervention. No clinical outcomes studied. Methods: "...randomly allocated into two groups using sealed envelopes...". Participants: 18 pregnant women with SBP = or > 140 mmHg and DBP = or > 90 mmHg, with or without proteinuria and oedema. Intervention: isosorbide dinitrate patches (40 mg, only dose) and bed rest vs bed rest alone. Outcomes: systolic and diastolic BP, uterine and umbilical Doppler velocimetry.
Kuwait 1995	Not clearly randomised. Methods: 'randomly allocated in sequence'. No further information.

	Participants: 120 primigravid women > 26 weeks' gestation, with SBP 120-140 mmHg and DBP 95-105 mmHg persisting for 3 days. Intervention: labetalol 100-300 mg x 3/day vs methyldopa 250-750 mg x 3/day. Outcomes: maternal MAP, proteinuria (undefined), placental abruption, caesarean section, elective delivery, side-effects, 1 min Apgar score < 5, days on SCBU, birthweight (mean).
Pakistan 1994	Intervention is an antiplatelet agent. Methods: 'randomly divided into two groups'. No further information. Participants: 200 women, one group with previous history of PIH (100 women) and other with mild essential hypertension or those developing BP 140/90 mmHg x 2 at least 15 days apart (100 women). Intervention: aspirin 75 mg b.i.d. vs routine antihypertensive treatment with beta blockers or calcium channel blockers when DBP exceeded 100 mmHg. Outcomes: development of PE. No other relevant outcomes reported.
Philippines 2000	Three days treatment. No relevant clinical outcomes studied. Available as abstract only. Methods: randomised, double-blind, placebo-controlled trial. Participants: 16 pre-eclamptics (no further details). Intervention: nitrol patch 5 mg for 16 hr for three consecutive days vs the same regimen using a gauze only. Outcomes: uterine and umbilical Doppler velocimetry.
Russia 1993	Possibly not an RCT. Full text awaiting translation from Russian. Abstract only in English. Participants: 92 women with slight and medium-severe hypertension at 24-39 weeks' gestation. Interventions: venodilators, prazosin and cordafen are all mentioned. Not clear how the groups were constructed.
Singapore 1996	More than 20% of women excluded, 6 women (22%) excluded because delivered in the week after trial entry. Methods: 'by opening a sealed envelope'. Participants: 27 women with singleton pregnancies, DBP 90 mmHg or above and proteinuria. Interventions: isradipine (slow release) 5 mg a day vs methyldopa 750 mg a day. Outcomes: MAP, side-effects, caesarean section, perinatal mortality, birthweight, admission to SCBU, Apgar score, maternal and fetal haemodynamics (by Doppler).
Singapore 1998	No relevant clinical outcomes studied. Methods: 'randomised', no further information. Participants: 30 women with PE, DBP >/= 90 mmHg and proteinuria >/= 300 mg/24 hr. Interventions: methyldopa 250-500 mg x 3/day vs isradipine 5-10 mg once/day. Outcomes: haemostatic parameters only (thrombelastography, fibrinogen, antithrombin III, thrombin-antithrombin-complex, beta-thromboglobulin, plasminogen activators, plasminogen activators inhibitors, and plasminogen).
South Africa 1988	Quasi-random design. Less than 7 days treatment, single-dose study. No clinical outcomes reported. Methods: quasi-random design, using last digit of the hospital number. Participants: 18 women in the last trimester of pregnancy with hypertension +/- proteinuria. Interventions: nifedipine 5 mg vs placebo (single dose). Outcomes: measures of uteroplacental blood flow.
South Africa 1990	Included women with severe hypertension (DBP 100-120 mmHg). Methods: 'randomly allocated', no further information. Participants: 60 women at 28-36 weeks' gestation with mean 24 hr DBP 100-120 mmHg +/- proteinuria. Intervention: indoramin 50 mg twice daily vs methyldopa 1 g twice daily vs placebo 1 tablet daily. Outcomes: MAP, need for additional antihypertensive.
South Africa 1991a	Quasi-random design. Single-dose intervention. Methods: allocation 'by virtue of the last digit of their folder number'. Participants: 19 women at > 28 weeks' gestation, singleton pregnancy and hypertension (defined as mean DBP >/= 90 mmHg). Intervention: sublingual nifedipine 5 mg vs placebo (single dose). Outcomes: DBP (mean), maternal and fetal heart rate, gestational age, side-effects.

South Africa 1997	Most women did not have hypertension. Eligibility criteria DBP >/= 80 mmHg, before 20 weeks' gestation. Of 138 recruited women, less than half had DBP >/= 90 mmHg. Results for this group were not presented separately. Methods: sequentially-numbered sealed boxes containing drug or placebo. Participants: 138 women between 12-20 weeks' gestation with DBP 80-109 mmHg, without antihypertensive therapy. Intervention: ketanserin 40-80 mg a day vs placebo. Outcomes: severe HT, proteinuria, placental abruption, other drugs needed, perinatal deaths, SGA (< 10th centile), birthweight.
Spain 1988	No clinical outcomes reported. Number of women in each group not reported. Available as abstract only. Methods: 'double-blind, placebo-controlled trial', no further information. Participants: 31 women with mild hypertension (BP 140-160/90 110 mmHg) despite bed rest in hospital. Intervention: labetalol 200-600 mg a day vs placebo. Outcomes: severe HT, need for additional antihypertensives, MAP, caesarean section, perinatal deaths, fetal distress.
Sri Lanka 1994	Quasi-random design. Methods: 'patients were alternately allocated'. Participants: 126 women with PIH. Interventions: nifedipine 30-90 mg/day vs methyldopa 750-2000 mg/day. Outcomes: severe hypertension, gestation at delivery (mean), birthweight (mean).
Sweden 1992	Comparison of two beta blockers. Methods: 'randomly allocated' using 'double-blind dummy technique'. No further information. Participants: 32 women admitted to hospital with PIH in the third trimester (BP >/= 140/90 mmHg x 2 at least 4 hr apart) and normotensive in the first trimester. Intervention: atenolol 50 mg x 2/day vs pindolol 5 mg x 2/day, for at least one week. Outcomes: side-effects, caesarean section, maternal haemodynamics, fetal haemodynamics, admission to SCBU, birthweight (mean), 5 min Apgar score.
Sweden 1993	It is not clear from papers whether reported data represent only a subgroup of women. Methods: not stated. Authors said 'allocated at random'. Participants: 20 women at 26-37 weeks' gestation with 'persistent' DBP >/= 100 mmHg and proteinuria. Intervention: labetalol 300-1,00 mg/day orally (if necessary, IV 25 mg bolus followed by 25-65 mg/hr infusion), vs hydralazine 75-400 mg/day orally (if necessary, 1.5-6.0 mg/hr infusion). Outcomes: severe hypertension, additional antihypertensive, caesarean section, neonatal death, birthweight (mean), gestation at delivery (mean), SGA (2 SD below mean), bradycardia, hypotension, hypoglycaemia, 5 min Apgar < 7, RDS, cord pH (< 7.20).
UK 1978	Included women with severe hypertension. Methods: 'randomly allocated'. No further information. Participants: 74 women with singleton pregnancy with DBP >or = to 170/100 mm Hg x 2 at up to 36 weeks' gestation. Intervention: labetalol 100 mg (max 1200 mg daily) vs methyldopa 250 mg (up to 4000 mg daily). Outcomes: severe hypertension, proteinuria ('greater than trace'), additional antihypertensive therapy, changed drugs due to maternal side-effects, caesarean section, perinatal mortality, SGA infants (< 10th centile), intubated, umbilical cord pH.
UK 1991	Less than 7 days treatment, single-dose study. Methods: sequentially-numbered, sealed envelopes. Participants: 30 women with singleton pregnancy and hypertension, defined as BP >/= 140/90 mmHg. Intervention: 10 mg hydralazine IV vs or 100 mg labetalol IV, as single dose. Outcomes: MAP, maternal and fetal heart rate, side-effects, umbilical artery PI.
USA 1957	Not randomised. Although a group of women received placebo, results are presented together with a group of matched controls. Included women with severe hypertension. Methods: not stated.

	Participants: 106 pregnant women with chronic hypertension and 28 women with severe pre-eclampsia. In addition 671 women with chronic hypertension were included as controls. Intervention: oral reserpine 0.25 to 3 mg/day (n = 80) vs placebo (n = 26). 28 women received IV reserpine. Outcomes: status at birth, birthweight.
USA 1981	Study included 63 women, but only 21 randomised. Outcomes not reported separately for randomised women. Methods: 'randomly and blindly assigned'. No further information. Participants: 21 women with BP 140/90 mmHg or above in a seated position or at rest, x 2, 6 or more hr apart. Intervention: hydralazine 25 mg x 3/day vs methyldopa 250 mg x 3/day vs placebo x 3/day. Outcomes: MAP, caesarean section, induction of labour, birthweight.
USA 1991	Not a randomised trial. No clinical outcomes reported. Methods: placebo group were matched as controls. Participants: 16 women at 17-22 weeks' gestation. Intervention: 10 mg sublingual nifedipine vs placebo. Outcomes: S/D ratio of the uterine artery, maternal BP, maternal heart rate.
Venezuela 1985	Not randomised. Included women with severe hypertension. Article in Spanish. Methods: alternated allocation (personal communication). Participants: 32 pregnant women at > 25 weeks' gestation with severe pre-eclampsia (defined as BP 160/110 or 140/90) and symptoms as headache, epigastric pain, blurred vision or hyperreflexia. Intervention: labetalol 200-800 mg/day vs methyldopa 750-2000 mg/day. Outcomes: maternal MAP, maternal pulse rate, gestational age at delivery, birthweight, 1 min Apgar, fetal and neonatal death.
Venezuela 1997	Not a RCT. Matched controls. Article in Spanish. Methods: controls were women treated with methyldopa in the same study period, with the same characteristics than the study group. Participants: 20 women with PIH. Intervention: labetalol 200 to 300 mg orally given every 12 hr vs methyldopa from 500 to 1500 mg/day Outcomes: BP, severe hypertension, gestational age, induction of labour, caesarean section, birthweight.
Venezuela 2001	No relevant clinical outcomes reported. Less than 7 days of treatment. Available as abstract only. Methods: Authors said '...were randomly assigned to...'. No further information. Participants: 30 pre-eclamptic. No further information. Intervention: transdermal nitroglycerin (7 mg for 12 hr for 2 consecutive days) vs placebo. Outcomes: umbilical S/D ratio, PI and RI by Doppler ultrasound.

ADP: adenosine diphosphate
b.i.d.: twice a day
BP: blood pressure
DBP: diastolic blood pressure
IUGR: intrauterine growth retardation
IV: intravenous
LBW: low birthweight
min: minutes
MAP: mean arterial pressure
NST: non-stress test
PIH: pregnancy-induced hypertension
PI: pulsatility index
PE: pre-eclampsia
RCT: randomised controlled trial
RDS: respiratory distress syndrome
RI: resistance index
SBP: systolic blood pressure
SCBU: special care baby unit
SD: standard deviation

Characteristics of excluded studies (*Continued*)

S/D ratio: ratio between peak systolic to end-diastolic flow velocity
SGA: small-for-gestational age
t.i.d.: dosing three times daily
vs: versus

ANALYSES

Comparison 01. Any antihypertensive drug versus none (subgrouped by class of drug)

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Maternal death	4	376	Relative Risk (Fixed) 95% CI	2.85 [0.30, 27.00]
02 Eclampsia	5	578	Relative Risk (Fixed) 95% CI	0.34 [0.01, 8.15]
03 Severe hypertension	19	2409	Relative Risk (Fixed) 95% CI	0.50 [0.41, 0.61]
04 Proteinuria/pre-eclampsia	22	2702	Relative Risk (Fixed) 95% CI	0.97 [0.83, 1.13]
05 Severe pre-eclampsia	2	267	Relative Risk (Fixed) 95% CI	0.61 [0.25, 1.48]
06 HELLP syndrome	1	197	Relative Risk (Fixed) 95% CI	2.02 [0.38, 10.78]
07 Pulmonary oedema	1	176	Relative Risk (Fixed) 95% CI	5.23 [0.25, 107.39]
08 Additional antihypertensive	10	1285	Relative Risk (Fixed) 95% CI	0.42 [0.30, 0.58]
09 Changed/stopped drugs due to maternal side-effects	15	1403	Relative Risk (Fixed) 95% CI	2.59 [1.33, 5.04]
10 Maternal side-effects	11	934	Relative Risk (Fixed) 95% CI	1.53 [1.10, 2.12]
11 Antenatal hospital admission	3	306	Relative Risk (Fixed) 95% CI	0.94 [0.78, 1.12]
12 Induction of labour	5	563	Relative Risk (Fixed) 95% CI	0.91 [0.77, 1.07]
13 Elective delivery (induction of labour + elective caesarean section)	5	710	Relative Risk (Fixed) 95% CI	0.91 [0.83, 1.00]
14 Caesarean section	19	2475	Relative Risk (Fixed) 95% CI	0.94 [0.85, 1.05]
15 Placental abruption	10	1284	Relative Risk (Fixed) 95% CI	1.83 [0.77, 4.37]
16 Total reported fetal or neonatal death (including miscarriage)	26	3081	Relative Risk (Fixed) 95% CI	0.73 [0.50, 1.08]
17 Fetal or neonatal death (subgrouped by time of death)			Relative Risk (Fixed) 95% CI	Subtotals only
18 Preterm birth (< 37 weeks)	14	1992	Relative Risk (Fixed) 95% CI	1.02 [0.89, 1.16]
19 Preterm birth (subgrouped by gestational age)			Relative Risk (Fixed) 95% CI	Subtotals only
20 Small-for-gestational age	19	2437	Relative Risk (Fixed) 95% CI	1.04 [0.84, 1.27]
21 Small-for-gestational age (subgrouped by severity)			Relative Risk (Fixed) 95% CI	Subtotals only
22 Admission to special care baby unit	8	1321	Relative Risk (Fixed) 95% CI	1.11 [0.93, 1.32]
23 Respiratory distress syndrome	5	825	Relative Risk (Fixed) 95% CI	0.28 [0.12, 0.63]
24 Neonatal hypoglycaemia	5	862	Relative Risk (Fixed) 95% CI	0.77 [0.51, 1.17]
25 Neonatal bradycardia	3	418	Relative Risk (Fixed) 95% CI	1.93 [1.05, 3.53]
26 Neonatal jaundice	3	529	Relative Risk (Fixed) 95% CI	0.78 [0.56, 1.09]
27 Follow up of the children at 1 year: cerebral palsy	1	110	Relative Risk (Fixed) 95% CI	0.33 [0.01, 8.01]
28 Follow up of the children at 7 1/2 years			Relative Risk (Fixed) 95% CI	Subtotals only

Comparison 02. Any antihypertensive drug versus none (subgrouped by type of hypertensive disorder at trial entry)

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Severe hypertension	19	2409	Relative Risk (Fixed) 95% CI	0.50 [0.41, 0.61]
02 Proteinuria/pre-eclampsia	22	2702	Relative Risk (Fixed) 95% CI	0.97 [0.83, 1.13]
03 Total reported fetal or neonatal death (including miscarriage)	26	3081	Relative Risk (Fixed) 95% CI	0.73 [0.50, 1.08]
04 Preterm birth (< 37 weeks)	14	1992	Relative Risk (Fixed) 95% CI	1.02 [0.89, 1.16]
05 Small-for-gestational age	19	2437	Relative Risk (Fixed) 95% CI	1.04 [0.84, 1.27]

Comparison 03. Any antihypertensive drug versus none (subgrouped by gestation at trial entry)

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Severe hypertension	19	2409	Relative Risk (Fixed) 95% CI	0.50 [0.41, 0.61]
02 Proteinuria/pre-eclampsia	22	2702	Relative Risk (Fixed) 95% CI	0.97 [0.83, 1.13]
03 Total reported fetal or neonatal death (including miscarriage)	26	3081	Relative Risk (Fixed) 95% CI	0.73 [0.50, 1.08]
04 Preterm birth (< 37 weeks)	14	1992	Relative Risk (Fixed) 95% CI	1.02 [0.89, 1.16]
05 Small-for-gestational age	19	2437	Relative Risk (Fixed) 95% CI	1.04 [0.84, 1.27]

Comparison 04. Any antihypertensive drug versus none (subgrouped by use of placebo)

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Severe hypertension	19	2409	Relative Risk (Fixed) 95% CI	0.50 [0.41, 0.61]
02 Proteinuria/pre-eclampsia	22	2702	Relative Risk (Fixed) 95% CI	0.97 [0.83, 1.13]
03 Total reported fetal or neonatal death (including miscarriage)	26	3081	Relative Risk (Fixed) 95% CI	0.73 [0.50, 1.08]
04 Preterm birth (< 37 weeks)	14	1992	Relative Risk (Fixed) 95% CI	1.02 [0.89, 1.16]
05 Small-for-gestational age	19	2437	Relative Risk (Fixed) 95% CI	1.04 [0.84, 1.27]

Comparison 05. Any antihypertensive versus methyldopa (subgrouped by class of drug)

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Severe hypertension	10	539	Relative Risk (Fixed) 95% CI	0.75 [0.59, 0.94]
02 Proteinuria/pre-eclampsia	9	804	Relative Risk (Fixed) 95% CI	0.81 [0.57, 1.16]
03 Additional antihypertensive	11	879	Relative Risk (Fixed) 95% CI	0.87 [0.68, 1.11]
04 Antenatal hospital admission	1	176	Relative Risk (Fixed) 95% CI	0.89 [0.67, 1.19]
05 Elective delivery (induction of labour + elective caesarean section)	4	333	Relative Risk (Fixed) 95% CI	0.98 [0.84, 1.15]
06 Caesarean section	9	779	Relative Risk (Fixed) 95% CI	0.96 [0.79, 1.15]
07 Maternal side-effects	4	122	Relative Risk (Fixed) 95% CI	0.07 [0.02, 0.37]
08 Changed/stopped drugs due to maternal side-effects	4	272	Relative Risk (Fixed) 95% CI	2.80 [0.12, 67.91]
09 Placental abruption	1	173	Relative Risk (Fixed) 95% CI	2.02 [0.19, 21.90]
10 Total reported fetal or neonatal death (including miscarriage)	17	1130	Relative Risk (Fixed) 95% CI	0.67 [0.37, 1.21]
11 Preterm birth (< 37 weeks)	8	524	Relative Risk (Fixed) 95% CI	0.80 [0.57, 1.12]
12 Small-for-gestational age	6	498	Relative Risk (Fixed) 95% CI	0.88 [0.54, 1.46]

13 Admission to special care baby unit	3	379	Relative Risk (Fixed) 95% CI	0.94 [0.68, 1.29]
14 Neonatal hypoglycaemia	4	321	Relative Risk (Fixed) 95% CI	1.05 [0.50, 2.18]
15 Neonatal bradycardia	1	28	Relative Risk (Fixed) 95% CI	Not estimable
16 Neonatal jaundice	1	28	Relative Risk (Fixed) 95% CI	1.20 [0.47, 3.03]

Comparison 06. Any antihypertensive versus calcium channel blocker (subgrouped by class of drug)

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Severe hypertension	2	136	Relative Risk (Fixed) 95% CI	2.09 [0.96, 4.57]
02 Proteinuria/pre-eclampsia	2	128	Relative Risk (Fixed) 95% CI	2.15 [0.73, 6.38]
03 HELLP syndrome	1	100	Relative Risk (Fixed) 95% CI	1.50 [0.26, 8.60]
04 Additional antihypertensive	1	100	Relative Risk (Fixed) 95% CI	2.14 [0.96, 4.80]
05 Changed/stopped drug due to side-effects	2	136	Relative Risk (Fixed) 95% CI	2.60 [0.13, 50.25]
06 Maternal side-effects	1	100	Relative Risk (Fixed) 95% CI	1.20 [0.39, 3.68]
07 Elective delivery (induction of labour + elective caesarean section)	1	100	Relative Risk (Fixed) 95% CI	0.89 [0.69, 1.15]
08 Caesarean section	1	100	Relative Risk (Fixed) 95% CI	1.57 [0.91, 2.71]
09 Placental abruption	1	100	Relative Risk (Fixed) 95% CI	Not estimable
10 Total reported fetal or neonatal death (including miscarriage)	2	136	Relative Risk (Fixed) 95% CI	1.00 [0.06, 15.55]
11 Preterm birth (< 37 weeks)	1	36	Relative Risk (Fixed) 95% CI	0.63 [0.20, 1.91]
12 Small-for-gestational age	1	36	Relative Risk (Fixed) 95% CI	1.00 [0.10, 9.96]
13 Admission to special care baby unit	1	99	Relative Risk (Fixed) 95% CI	1.47 [0.44, 4.89]

INDEX TERMS

Medical Subject Headings (MeSH)

Antihypertensive Agents [adverse effects; *therapeutic use]; Hypertension [*drug therapy]; Placebo Effect; Pregnancy Complications, Cardiovascular [*drug therapy]; Randomized Controlled Trials

MeSH check words

Female; Humans; Pregnancy

COVER SHEET

Title

Antihypertensive drug therapy for mild to moderate hypertension during pregnancy

Authors

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Contribution of author(s)

E Abalos and L Duley wrote the initial version of the review, performed the methodological assessment of studies, and performed the data extraction. DW Steyn contributed by extracting data from studies and by revising the text of the review. He was consulted for discrepancies. DJ Henderson-Smart checked all neonatal data extraction, revised the text of the review, and was consulted for discrepancies. The text of the updated review was drafted by E Abalos with input by L Duley. All review authors have commented on and agreed the final version.
E Abalos is the guarantor of the review.

Issue protocol first published	2000/3
Review first published	2001/2
Date of most recent amendment	15 November 2006
Date of most recent SUBSTANTIVE amendment	14 November 2006
What's New	March 2006: Search updated. Six new trials were added to included studies. Twenty-seven new trials added to excluded studies (not all are new studies as, for some, new information has become available leading them to be reclassified as excluded). Changes in the outcome tree (calcium channel blockers versus beta blockers are no longer referred to the beta blockers review (Magee 2000) as this comparison is now part of the group 'any antihypertensive versus calcium channel blockers'). Changes in the text to reflect new data. An entire section describing the general characteristics of the excluded trials has been added in the text. Acknowledgements to authors for unpublished data.
Date new studies sought but none found	Information not supplied by author
Date new studies found but not yet included/excluded	Information not supplied by author
Date new studies found and included/excluded	20 March 2006
Date authors' conclusions section amended	Information not supplied by author
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GRAPHS AND OTHER TABLES

Analysis 01.01. Comparison 01 Any antihypertensive drug versus none (subgrouped by class of drug), Outcome 01 Maternal death

Review: Antihypertensive drug therapy for mild to moderate hypertension during pregnancy

Comparison: 01 Any antihypertensive drug versus none (subgrouped by class of drug)

Outcome: 01 Maternal death

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Caribbean Is.1990	1/78	0/76		49.4	2.92 [0.12, 70.68]
× Sudan 2002	0/34	0/36		0.0	Not estimable
× Sweden 1984	0/26	0/26		0.0	Not estimable
UK 1968	1/52	0/48		50.6	2.77 [0.12, 66.49]
Total (95% CI)	190	186		100.0	2.85 [0.30, 27.00]
Total events: 2 (Treatment), 0 (Control)					
Test for heterogeneity chi-square=0.00 df=1 p=0.98 I^2 =0.0%					
Test for overall effect z=0.91 p=0.4					

Analysis 01.02. Comparison 01 Any antihypertensive drug versus none (subgrouped by class of drug), Outcome 02 Eclampsia

Review: Antihypertensive drug therapy for mild to moderate hypertension during pregnancy

Comparison: 01 Any antihypertensive drug versus none (subgrouped by class of drug)

Outcome: 02 Eclampsia

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
× Caribbean Is.1990	0/78	0/76		0.0	Not estimable
× Israel 1995	0/36	0/15		0.0	Not estimable
× Sudan 2002	0/34	0/36		0.0	Not estimable
Sweden 1995	0/58	1/59		100.0	0.34 [0.01, 8.15]
× USA 1987	0/92	0/94		0.0	Not estimable
Total (95% CI)	298	280		100.0	0.34 [0.01, 8.15]
Total events: 0 (Treatment), 1 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.67 p=0.5					

Analysis 01.03. Comparison 01 Any antihypertensive drug versus none (subgrouped by class of drug), Outcome 03 Severe hypertension

Review: Antihypertensive drug therapy for mild to moderate hypertension during pregnancy

Comparison: 01 Any antihypertensive drug versus none (subgrouped by class of drug)

Outcome: 03 Severe hypertension

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 Beta blocker versus none					
Hong Kong 1990	6/20	10/21		4.3	0.63 [0.28, 1.41]
Israel 1992	6/30	15/30		6.5	0.40 [0.18, 0.89]
Sweden 1984	1/26	0/26		0.2	3.00 [0.13, 70.42]
UK 1982	3/64	13/62		5.8	0.22 [0.07, 0.75]
UK 1983	2/60	7/60		3.1	0.29 [0.06, 1.32]
UK 1989	5/70	15/74		6.4	0.35 [0.14, 0.92]
UK 1990	0/16	2/17		1.1	0.21 [0.01, 4.10]
USA 1987	5/92	14/94		6.0	0.36 [0.14, 0.97]
Subtotal (95% CI)	378	384		33.3	0.38 [0.26, 0.57]
Total events: 28 (Treatment), 76 (Control)					
Test for heterogeneity chi-square=4.20 df=7 p=0.76 I^2 =0.0%					
Test for overall effect z=4.81 p<0.00001					
02 Beta blocker + other drug versus none					
Caribbean Is.1990	5/78	11/76		4.9	0.44 [0.16, 1.21]
Sweden 1985	0/86	6/82		2.9	0.07 [0.00, 1.28]
Subtotal (95% CI)	164	158		7.8	0.30 [0.12, 0.77]
Total events: 5 (Treatment), 17 (Control)					
Test for heterogeneity chi-square=1.48 df=1 p=0.22 I^2 =32.4%					
Test for overall effect z=2.52 p=0.01					
03 Methyldopa versus none					
Sudan 2002	3/34	18/36		7.6	0.18 [0.06, 0.55]
UK 1976	9/117	22/123		9.4	0.43 [0.21, 0.90]
Subtotal (95% CI)	151	159		17.0	0.32 [0.17, 0.58]
Total events: 12 (Treatment), 40 (Control)					
Test for heterogeneity chi-square=1.70 df=1 p=0.19 I^2 =41.2%					
Test for overall effect z=3.73 p=0.0002					
04 Methyldopa + other drug versus none					
USA 1979	2/29	3/29		1.3	0.67 [0.12, 3.70]
Subtotal (95% CI)	29	29		1.3	0.67 [0.12, 3.70]

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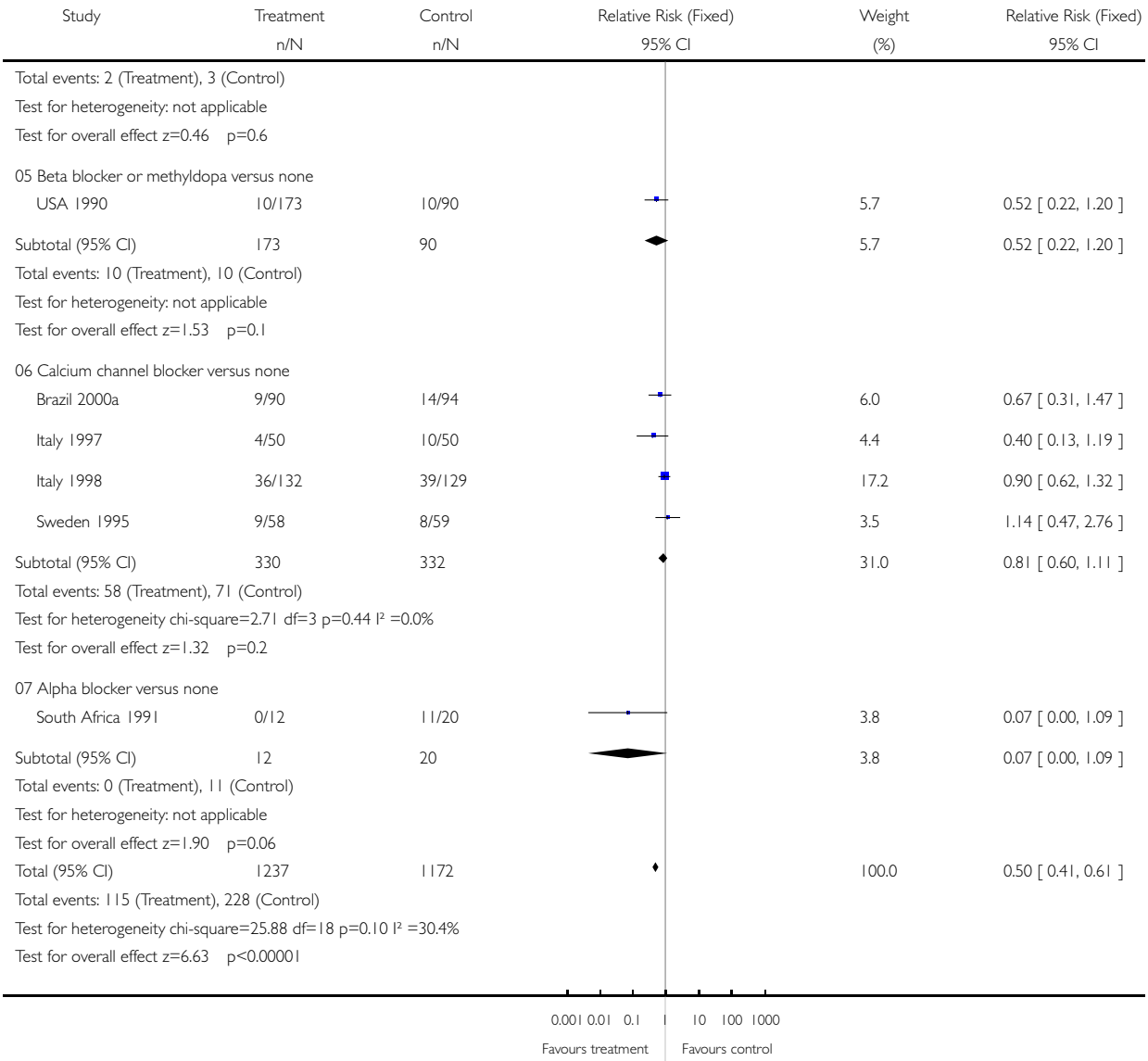

Analysis 01.04. Comparison 01 Any antihypertensive drug versus none (subgrouped by class of drug), Outcome 04 Proteinuria/pre-eclampsia

Review: Antihypertensive drug therapy for mild to moderate hypertension during pregnancy

Comparison: 01 Any antihypertensive drug versus none (subgrouped by class of drug)

Outcome: 04 Proteinuria/pre-eclampsia

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 Beta blocker versus none					
Brazil 1985	5/50	10/50		4.2	0.50 [0.18, 1.36]
Israel 1992	1/29	3/28		1.3	0.32 [0.04, 2.91]
Sweden 1984	6/26	6/26		2.5	1.00 [0.37, 2.70]
UK 1982	4/64	9/62		3.8	0.43 [0.14, 1.33]
UK 1983	3/51	10/53		4.1	0.31 [0.09, 1.07]
UK 1989	31/70	45/74		18.2	0.73 [0.53, 1.00]
UK 1992	13/51	17/63		6.3	0.94 [0.51, 1.76]
USA 1987	10/92	6/94		2.5	1.70 [0.65, 4.49]
Subtotal (95% CI)	433	450		42.8	0.73 [0.57, 0.94]
Total events: 73 (Treatment), 106 (Control)					
Test for heterogeneity chi-square=7.73 df=7 p=0.36 I^2 =9.5%					
Test for overall effect z=2.47 p=0.01					
02 Beta blocker + other drug versus none					
Caribbean Is.1990	7/78	7/76		2.9	0.97 [0.36, 2.65]
Sweden 1985	10/86	6/82		2.6	1.59 [0.60, 4.17]
Subtotal (95% CI)	164	158		5.5	1.26 [0.63, 2.51]
Total events: 17 (Treatment), 13 (Control)					
Test for heterogeneity chi-square=0.48 df=1 p=0.49 I^2 =0.0%					
Test for overall effect z=0.66 p=0.5					
03 Methyldopa versus none					
UK 1976	6/117	5/125		2.0	1.28 [0.40, 4.09]
USA 1987a	5/13	4/12		1.7	1.15 [0.40, 3.31]
Subtotal (95% CI)	130	137		3.7	1.22 [0.55, 2.71]
Total events: 11 (Treatment), 9 (Control)					
Test for heterogeneity chi-square=0.02 df=1 p=0.89 I^2 =0.0%					
Test for overall effect z=0.50 p=0.6					
04 Methyldopa + other drug versus none					
UK 1968	15/52	17/48		7.4	0.81 [0.46, 1.44]
USA 1979	1/29	3/29		1.2	0.33 [0.04, 3.02]

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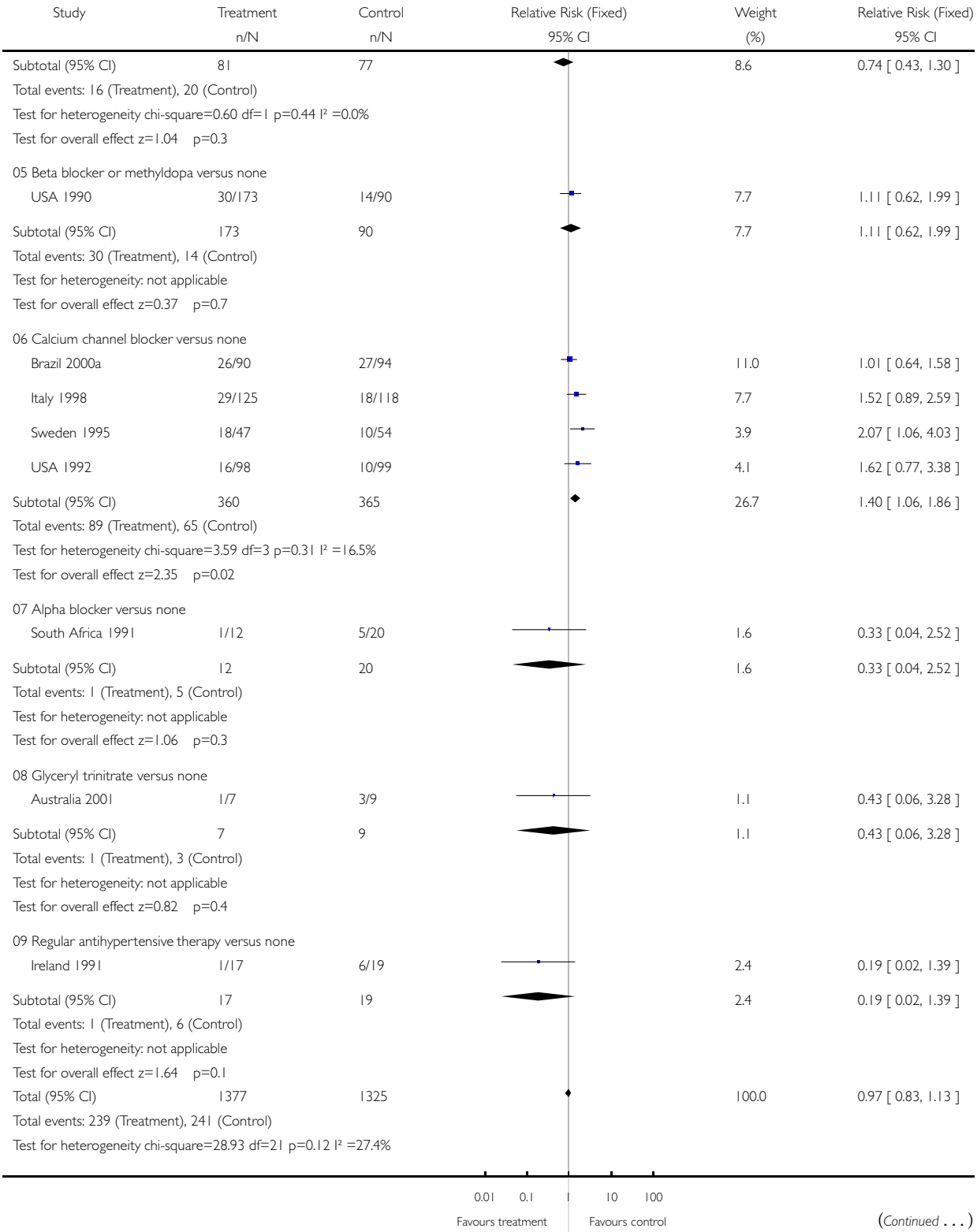

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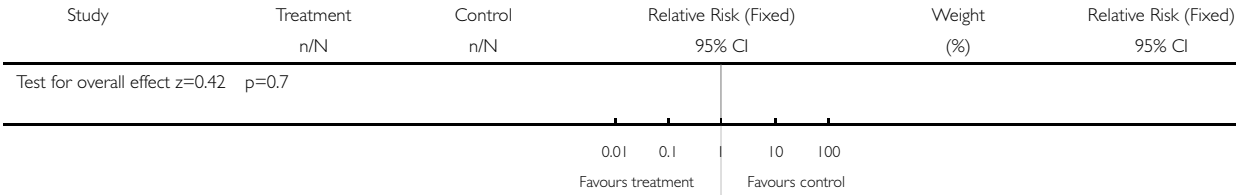
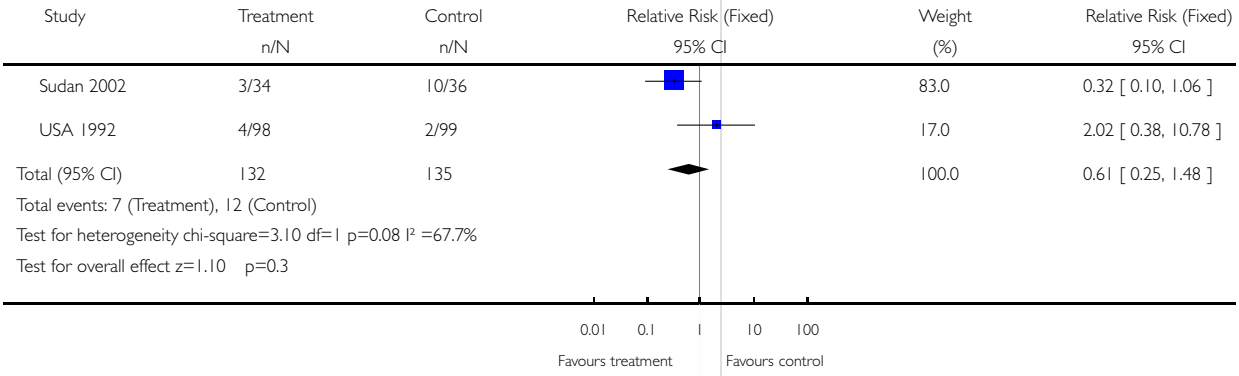


Analysis 01.05. Comparison 01 Any antihypertensive drug versus none (subgrouped by class of drug), Outcome 05 Severe pre-eclampsia

Review: Antihypertensive drug therapy for mild to moderate hypertension during pregnancy

Comparison: 01 Any antihypertensive drug versus none (subgrouped by class of drug)

Outcome: 05 Severe pre-eclampsia

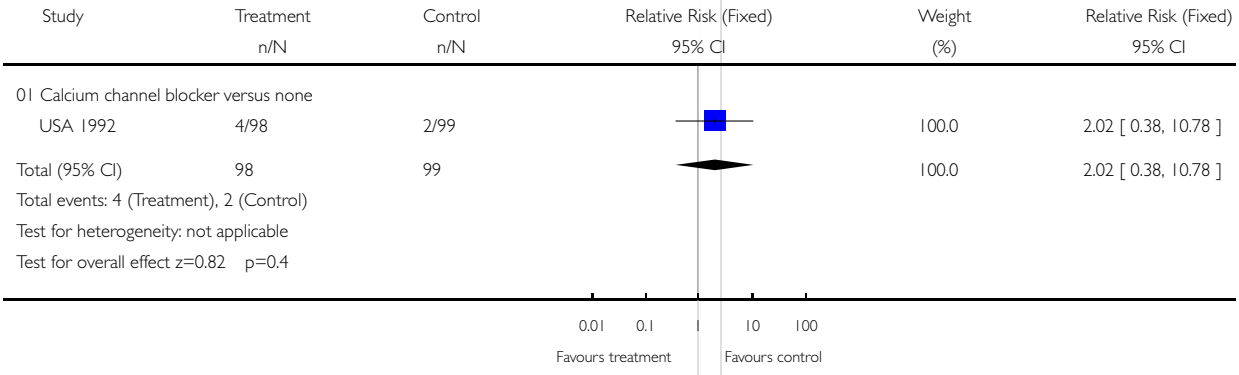


Analysis 01.06. Comparison 01 Any antihypertensive drug versus none (subgrouped by class of drug), Outcome 06 HELLP syndrome

Review: Antihypertensive drug therapy for mild to moderate hypertension during pregnancy

Comparison: 01 Any antihypertensive drug versus none (subgrouped by class of drug)

Outcome: 06 HELLP syndrome



Analysis 01.07. Comparison 01 Any antihypertensive drug versus none (subgrouped by class of drug), Outcome 07 Pulmonary oedema

Review: Antihypertensive drug therapy for mild to moderate hypertension during pregnancy

Comparison: 01 Any antihypertensive drug versus none (subgrouped by class of drug)

Outcome: 07 Pulmonary oedema

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 Beta blocker versus none					
USA 1990	2/86	0/90		100.0	5.23 [0.25, 107.39]
Total (95% CI)	86	90		100.0	5.23 [0.25, 107.39]
Total events: 2 (Treatment), 0 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.07 p=0.3					

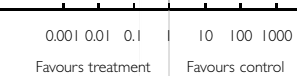
Analysis 01.08. Comparison 01 Any antihypertensive drug versus none (subgrouped by class of drug), Outcome 08 Additional antihypertensive

Review: Antihypertensive drug therapy for mild to moderate hypertension during pregnancy

Comparison: 01 Any antihypertensive drug versus none (subgrouped by class of drug)

Outcome: 08 Additional antihypertensive

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 Beta blocker versus none					
Hong Kong 1990	6/20	10/21		9.4	0.63 [0.28, 1.41]
Israel 1992	6/30	15/30		14.4	0.40 [0.18, 0.89]
UK 1989	1/70	8/74		7.5	0.13 [0.02, 1.03]
Subtotal (95% CI)	120	125		31.3	0.40 [0.23, 0.70]
Total events: 13 (Treatment), 33 (Control)					
Test for heterogeneity chi-square=2.30 df=2 p=0.32 I^2 =13.0%					
Test for overall effect z=3.21 p=0.001					
02 Beta blocker + other drug versus none					
Caribbean Is.1990	5/78	11/76		10.7	0.44 [0.16, 1.21]
Sweden 1985	0/82	5/79		5.4	0.09 [0.00, 1.56]
Subtotal (95% CI)	160	155		16.1	0.32 [0.13, 0.82]
Total events: 5 (Treatment), 16 (Control)					
Test for heterogeneity chi-square=1.16 df=1 p=0.28 I^2 =13.9%					
Test for overall effect z=2.37 p=0.02					



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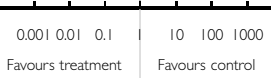
Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
03 Methyldopa + other drug versus none					
USA 1979	4/29	13/29		12.5	0.31 [0.11, 0.83]
Subtotal (95% CI)	29	29		12.5	0.31 [0.11, 0.83]
Total events: 4 (Treatment), 13 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=2.32 p=0.02					
04 Beta blocker or methyldopa versus none					
USA 1990	10/173	10/90		12.7	0.52 [0.22, 1.20]
Subtotal (95% CI)	173	90		12.7	0.52 [0.22, 1.20]
Total events: 10 (Treatment), 10 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.53 p=0.1					
05 Calcium channel blocker versus none					
Italy 1998	4/132	6/129		5.8	0.65 [0.19, 2.26]
Sweden 1995	9/54	14/57		13.1	0.68 [0.32, 1.44]
Subtotal (95% CI)	186	186		18.9	0.67 [0.35, 1.28]
Total events: 13 (Treatment), 20 (Control)					
Test for heterogeneity chi-square=0.00 df=1 p=0.96 I^2 =0.0%					
Test for overall effect z=1.22 p=0.2					
06 Alpha blocker versus none					
South Africa 1991	0/12	11/20		8.5	0.07 [0.00, 1.09]
Subtotal (95% CI)	12	20		8.5	0.07 [0.00, 1.09]
Total events: 0 (Treatment), 11 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.90 p=0.06					
Total (95% CI)	680	605		100.0	0.42 [0.30, 0.58]
Total events: 45 (Treatment), 103 (Control)					
Test for heterogeneity chi-square=7.73 df=9 p=0.56 I^2 =0.0%					
Test for overall effect z=5.30 p<0.00001					



Analysis 01.09. Comparison 01 Any antihypertensive drug versus none (subgrouped by class of drug), Outcome 09 Changed/stopped drugs due to maternal side-effects

Review: Antihypertensive drug therapy for mild to moderate hypertension during pregnancy

Comparison: 01 Any antihypertensive drug versus none (subgrouped by class of drug)

Outcome: 09 Changed/stopped drugs due to maternal side-effects

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 Beta blocker versus none					
Israel 1986a	0/21	2/23		21.1	0.22 [0.01, 4.30]
Israel 1992	2/30	0/30		4.4	5.00 [0.25, 99.95]
× Israel 1995	0/36	0/15		0.0	Not estimable
Sweden 1984	1/26	0/26		4.4	3.00 [0.13, 70.42]
UK 1982	4/64	0/62		4.5	8.72 [0.48, 158.71]
UK 1983	2/60	1/60		8.8	2.00 [0.19, 21.47]
UK 1989	1/71	0/74		4.3	3.13 [0.13, 75.46]
UK 1990	0/16	1/17		12.9	0.35 [0.02, 8.08]
× UK 1992	0/51	0/63		0.0	Not estimable
Subtotal (95% CI)	375	370		60.5	1.90 [0.76, 4.75]
Total events: 10 (Treatment), 4 (Control)					
Test for heterogeneity chi-square=4.77 df=6 p=0.57 I^2 =0.0%					
Test for overall effect z=1.37 p=0.2					
02 Beta blocker + other drug versus none					
Caribbean Is.1990	4/78	3/76		26.9	1.30 [0.30, 5.61]
× Sweden 1985	0/82	0/79		0.0	Not estimable
Subtotal (95% CI)	160	155		26.9	1.30 [0.30, 5.61]
Total events: 4 (Treatment), 3 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.35 p=0.7					
03 Methyldopa versus none					
× USA 1987a	0/13	0/12		0.0	Not estimable
Subtotal (95% CI)	13	12		0.0	Not estimable
Total events: 0 (Treatment), 0 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
04 Calcium channel blocker versus none					
Brazil 2000a	1/91	0/94		4.3	3.10 [0.13, 75.07]
Sweden 1995	2/58	0/59		4.4	5.08 [0.25, 103.68]

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Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Subtotal (95% CI)	149	153		8.7	4.10 [0.46, 36.21]
Total events: 3 (Treatment), 0 (Control)					
Test for heterogeneity chi-square=0.05 df=1 p=0.82 I^2 =0.0%					
Test for overall effect z=1.27 p=0.2					
05 Glyceryl trinitrate versus none					
Australia 2001	7/7	0/9		3.9	18.75 [1.25, 281.11]
Subtotal (95% CI)	7	9		3.9	18.75 [1.25, 281.11]
Total events: 7 (Treatment), 0 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=2.12 p=0.03					
Total (95% CI)	704	699		100.0	2.59 [1.33, 5.04]
Total events: 24 (Treatment), 7 (Control)					
Test for heterogeneity chi-square=8.24 df=10 p=0.61 I^2 =0.0%					
Test for overall effect z=2.81 p=0.005					

Analysis 01.10. Comparison 01 Any antihypertensive drug versus none (subgrouped by class of drug), Outcome 10 Maternal side-effects

Review: Antihypertensive drug therapy for mild to moderate hypertension during pregnancy

Comparison: 01 Any antihypertensive drug versus none (subgrouped by class of drug)

Outcome: 10 Maternal side-effects

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 Beta blocker versus none					
Brazil 1985	4/50	0/50		1.1	9.00 [0.50, 162.89]
Israel 1992	2/30	0/30		1.1	5.00 [0.25, 99.95]
Israel 1995	13/36	8/15		25.0	0.68 [0.36, 1.29]
Sweden 1984	1/26	0/26		1.1	3.00 [0.13, 70.42]
UK 1989	8/70	0/74		1.1	17.96 [1.06, 305.41]
UK 1990	0/16	1/17		3.2	0.35 [0.02, 8.08]
UK 1992	5/51	0/63		1.0	13.54 [0.77, 239.22]
Subtotal (95% CI)	279	275		33.6	2.07 [1.21, 3.54]
Total events: 33 (Treatment), 9 (Control)					
Test for heterogeneity chi-square=18.11 df=6 p=0.006 I^2 =66.9%					

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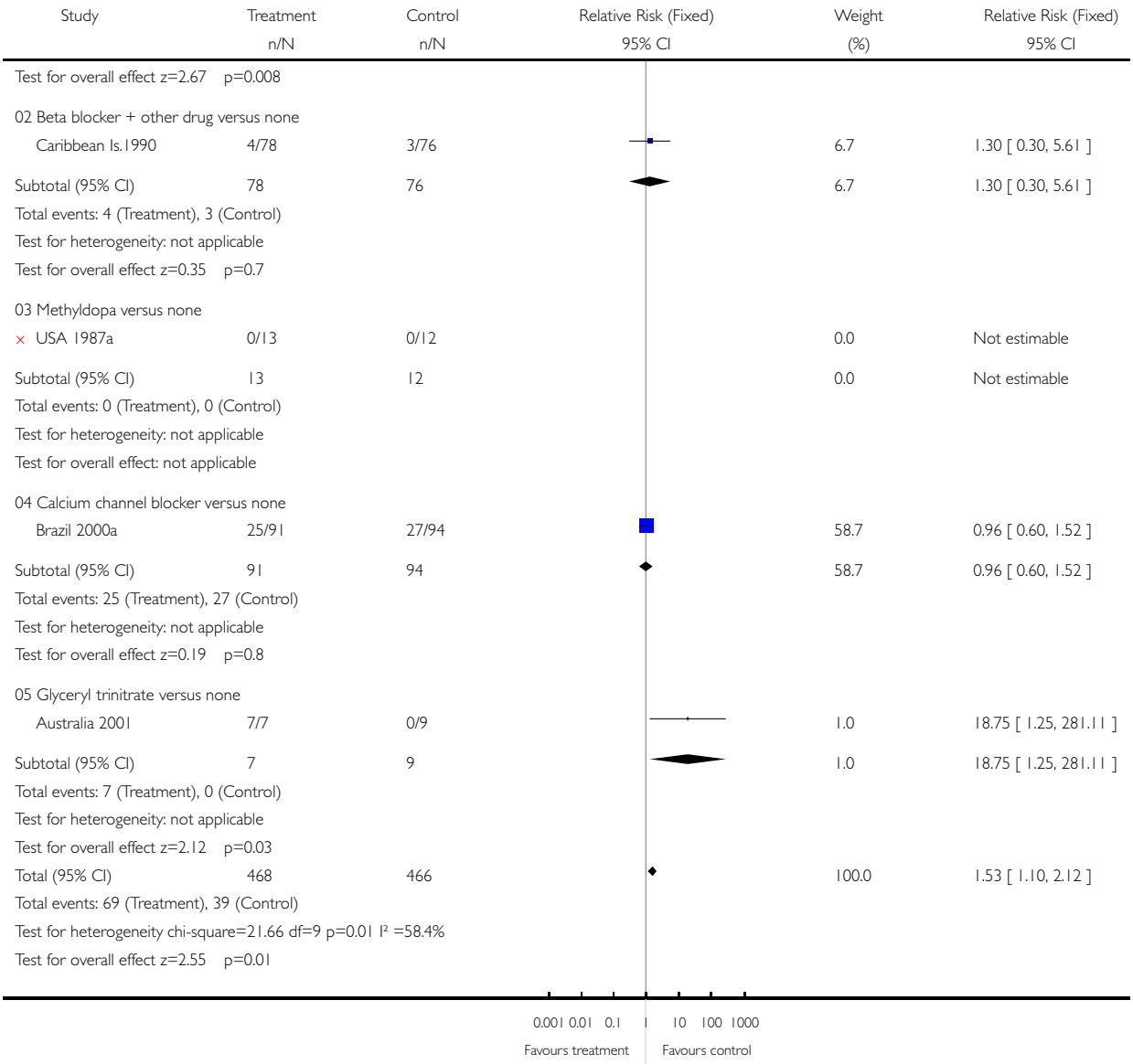


Analysis 01.11. Comparison 01 Any antihypertensive drug versus none (subgrouped by class of drug), Outcome 11 Antenatal hospital admission

Review: Antihypertensive drug therapy for mild to moderate hypertension during pregnancy

Comparison: 01 Any antihypertensive drug versus none (subgrouped by class of drug)

Outcome: 11 Antenatal hospital admission

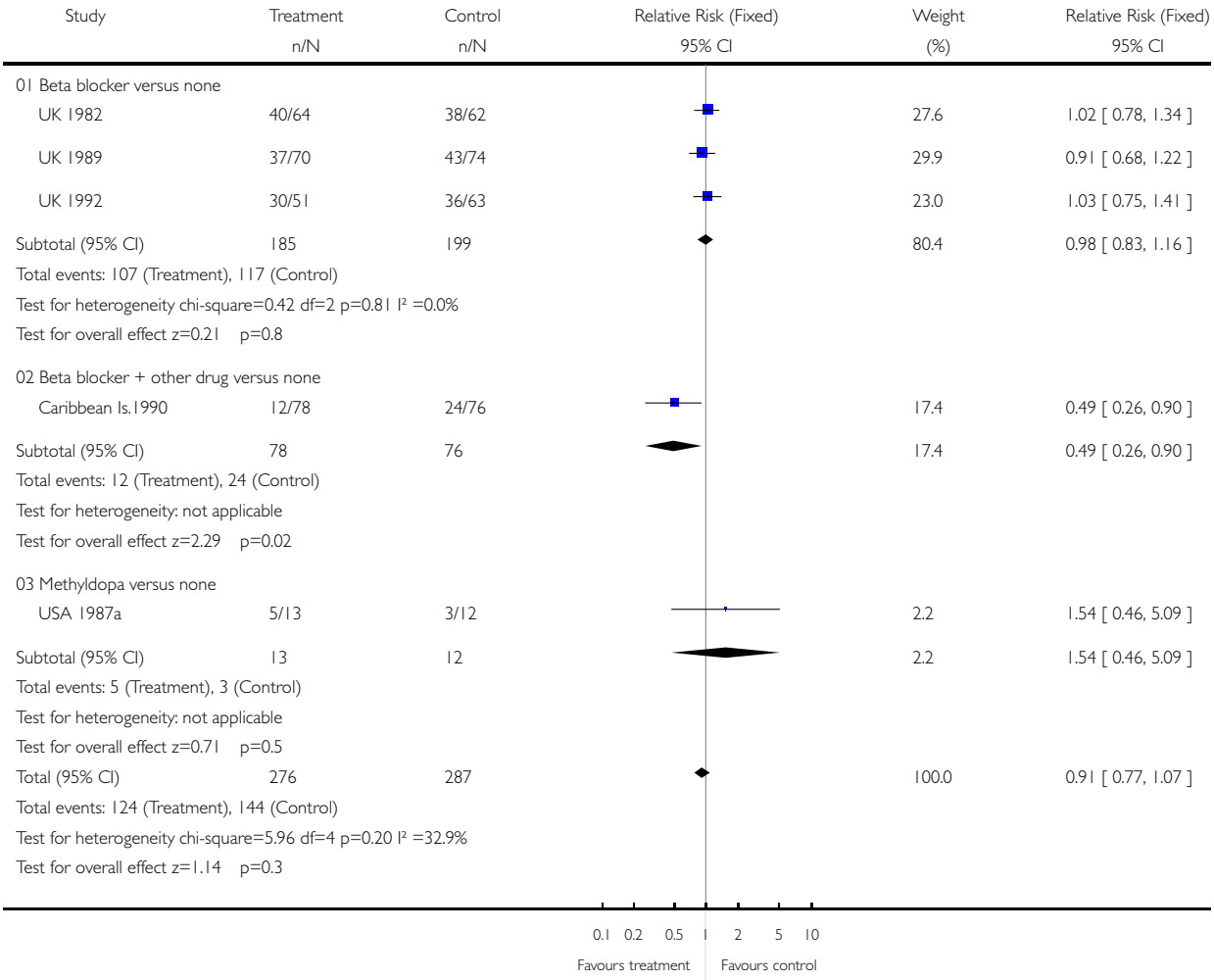
Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 Beta blocker versus none					
Sweden 1984	16/26	19/26		19.7	0.84 [0.57, 1.24]
Subtotal (95% CI)	26	26		19.7	0.84 [0.57, 1.24]
Total events: 16 (Treatment), 19 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.88 p=0.4					
02 Beta blocker + other drug versus none					
Caribbean Is.1990	48/78	46/76		48.2	1.02 [0.79, 1.31]
Italy 1997	27/50	31/50		32.1	0.87 [0.62, 1.22]
Subtotal (95% CI)	128	126		80.3	0.96 [0.78, 1.17]
Total events: 75 (Treatment), 77 (Control)					
Test for heterogeneity chi-square=0.52 df=1 p=0.47 I^2 =0.0%					
Test for overall effect z=0.41 p=0.7					
Total (95% CI)	154	152		100.0	0.94 [0.78, 1.12]
Total events: 91 (Treatment), 96 (Control)					
Test for heterogeneity chi-square=0.88 df=2 p=0.64 I^2 =0.0%					
Test for overall effect z=0.73 p=0.5					

Analysis 01.12. Comparison 01 Any antihypertensive drug versus none (subgrouped by class of drug), Outcome 12 Induction of labour

Review: Antihypertensive drug therapy for mild to moderate hypertension during pregnancy

Comparison: 01 Any antihypertensive drug versus none (subgrouped by class of drug)

Outcome: 12 Induction of labour



Analysis 01.13. Comparison 01 Any antihypertensive drug versus none (subgrouped by class of drug), Outcome 13 Elective delivery (induction of labour + elective caesarean section)

Review: Antihypertensive drug therapy for mild to moderate hypertension during pregnancy

Comparison: 01 Any antihypertensive drug versus none (subgrouped by class of drug)

Outcome: 13 Elective delivery (induction of labour + elective caesarean section)

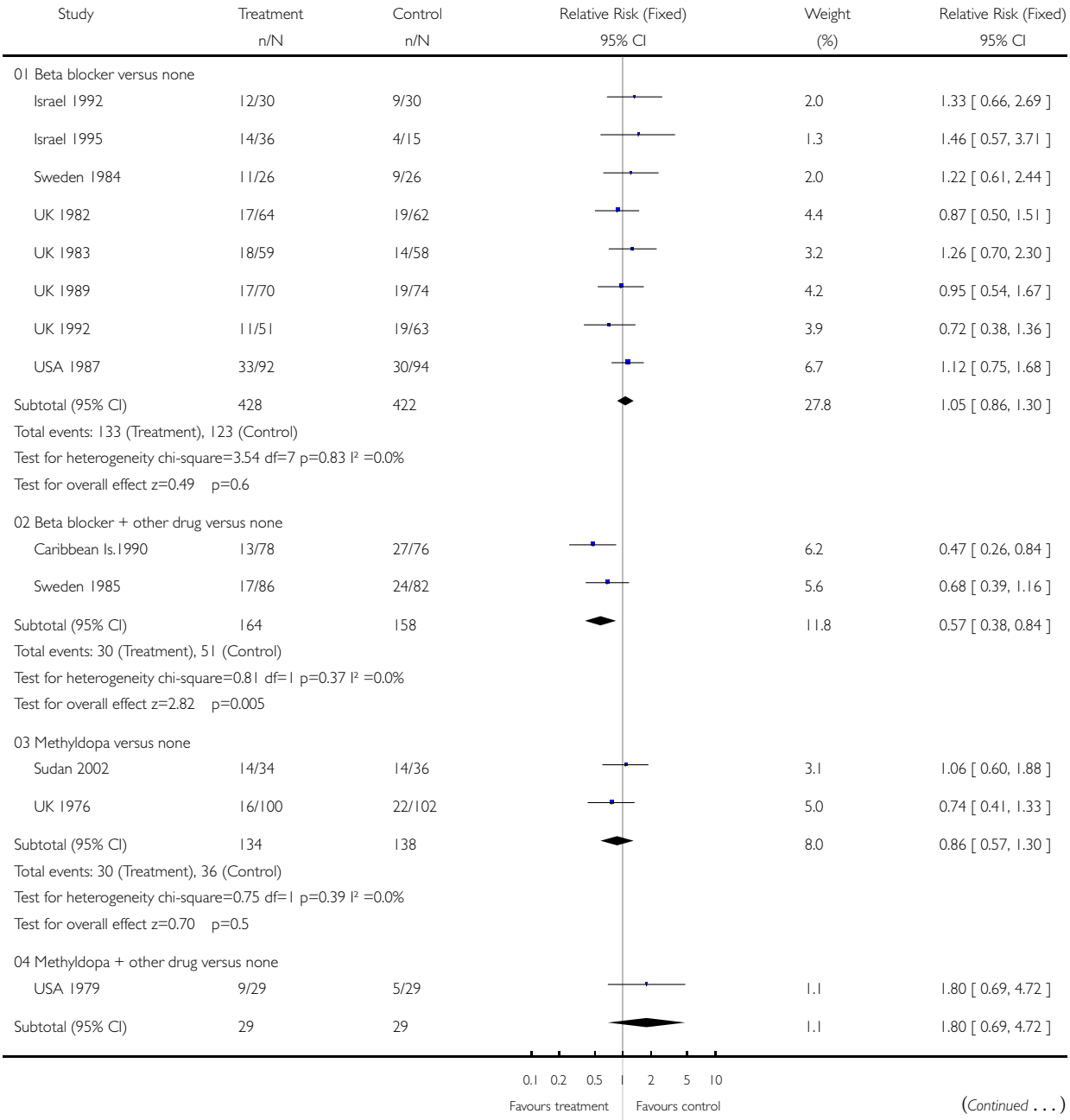
Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 Beta blocker versus none					
UK 1982	49/64	50/62		20.0	0.95 [0.79, 1.14]
UK 1992	35/51	43/63		15.2	1.01 [0.78, 1.29]
Subtotal (95% CI)	115	125		35.2	0.97 [0.84, 1.13]
Total events: 84 (Treatment), 93 (Control)					
Test for heterogeneity chi-square=0.14 df=1 p=0.71 I^2 =0.0%					
Test for overall effect z=0.35 p=0.7					
02 Beta blocker + other drug versus none					
Caribbean Is.1990	24/78	38/76		15.2	0.62 [0.41, 0.92]
UK 1976	80/100	88/102		34.4	0.93 [0.82, 1.05]
UK 1992	35/51	43/63		15.2	1.01 [0.78, 1.29]
Subtotal (95% CI)	229	241		64.8	0.87 [0.77, 0.99]
Total events: 139 (Treatment), 169 (Control)					
Test for heterogeneity chi-square=5.05 df=2 p=0.08 I^2 =60.4%					
Test for overall effect z=2.19 p=0.03					
Total (95% CI)	344	366		100.0	0.91 [0.83, 1.00]
Total events: 223 (Treatment), 262 (Control)					
Test for heterogeneity chi-square=5.21 df=4 p=0.27 I^2 =23.2%					
Test for overall effect z=1.99 p=0.05					

Analysis 01.14. Comparison 01 Any antihypertensive drug versus none (subgrouped by class of drug), Outcome 14 Caesarean section

Review: Antihypertensive drug therapy for mild to moderate hypertension during pregnancy

Comparison: 01 Any antihypertensive drug versus none (subgrouped by class of drug)

Outcome: 14 Caesarean section



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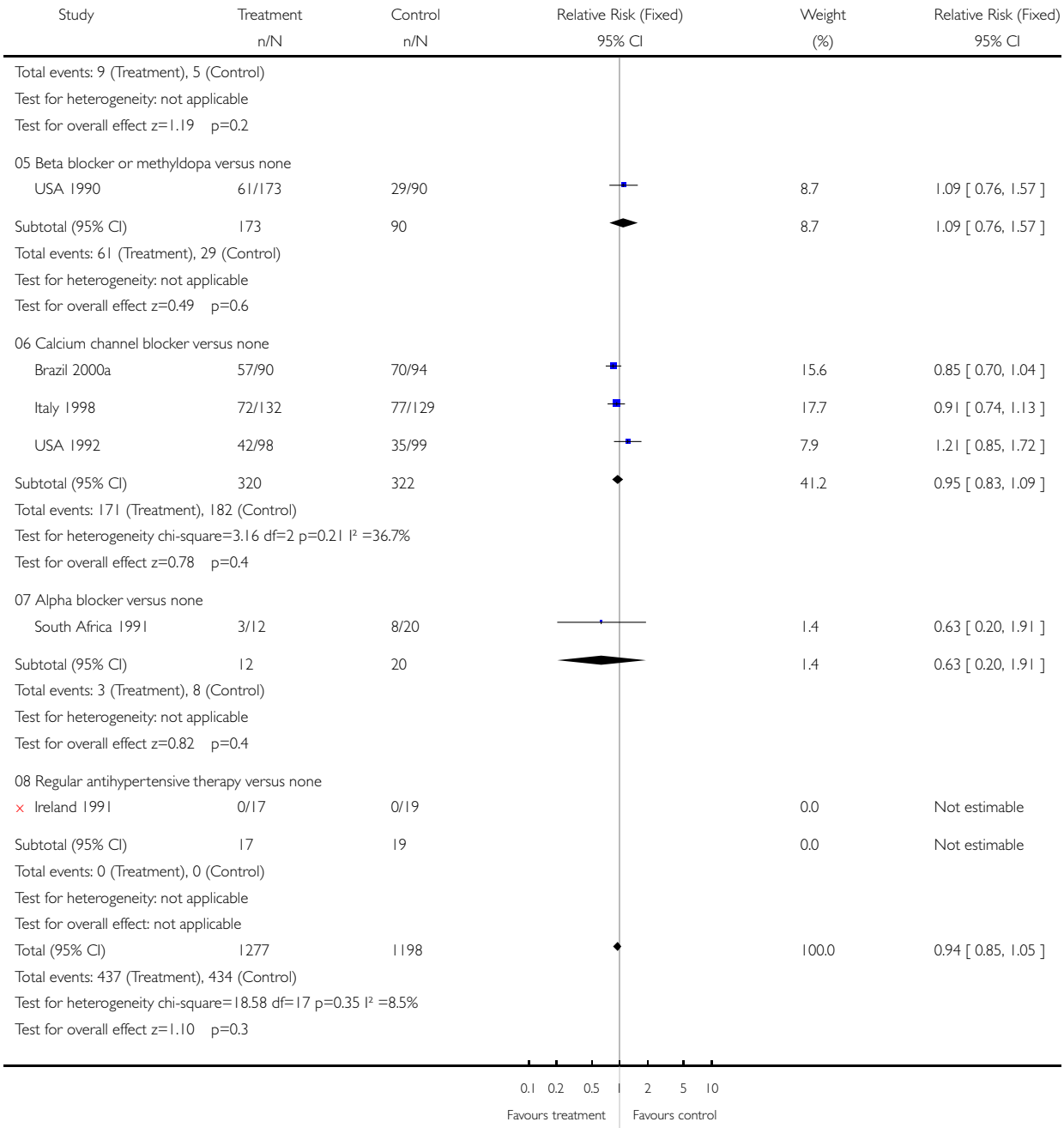


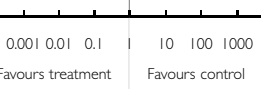
Analysis 01.15. Comparison 01 Any antihypertensive drug versus none (subgrouped by class of drug), Outcome 15 Placental abruption

Review: Antihypertensive drug therapy for mild to moderate hypertension during pregnancy

Comparison: 01 Any antihypertensive drug versus none (subgrouped by class of drug)

Outcome: 15 Placental abruption

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 Beta blocker versus none					
× Sweden 1984	0/26	0/26		0.0	Not estimable
× UK 1982	0/64	0/62		0.0	Not estimable
USA 1987	2/92	0/94		6.7	5.11 [0.25, 104.96]
Subtotal (95% CI)	182	182		6.7	5.11 [0.25, 104.96]
Total events: 2 (Treatment), 0 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.06 p=0.3					
02 Beta blocker + other drug versus none					
Caribbean Is.1990	1/78	0/76		6.8	2.92 [0.12, 70.68]
Sweden 1985	2/86	1/82		13.8	1.91 [0.18, 20.63]
Subtotal (95% CI)	164	158		20.7	2.24 [0.34, 14.98]
Total events: 3 (Treatment), 1 (Control)					
Test for heterogeneity chi-square=0.04 df=1 p=0.83 I^2 =0.0%					
Test for overall effect z=0.83 p=0.4					
03 Methyldopa versus none					
× Sudan 2002	0/34	0/36		0.0	Not estimable
Subtotal (95% CI)	34	36		0.0	Not estimable
Total events: 0 (Treatment), 0 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
04 Beta blocker or methyldopa versus none					
USA 1990	3/173	2/90		35.6	0.78 [0.13, 4.59]
Subtotal (95% CI)	173	90		35.6	0.78 [0.13, 4.59]
Total events: 3 (Treatment), 2 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.27 p=0.8					
05 Calcium blocker versus none					
USA 1992	3/98	2/99		26.9	1.52 [0.26, 8.87]
Subtotal (95% CI)	98	99		26.9	1.52 [0.26, 8.87]
Total events: 3 (Treatment), 2 (Control)					
Test for heterogeneity: not applicable					



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Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Test for overall effect z=0.46 p=0.6					
06 Alpha blocker versus none					
South Africa 1991	2/12	1/20		10.1	3.33 [0.34, 32.96]
Subtotal (95% CI)	12	20		10.1	3.33 [0.34, 32.96]
Total events: 2 (Treatment), 1 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.03 p=0.3					
07 Regular antihypertensive therapy versus none					
× Ireland 1991	0/17	0/19		0.0	Not estimable
Subtotal (95% CI)	17	19		0.0	Not estimable
Total events: 0 (Treatment), 0 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
Total (95% CI)	680	604		100.0	1.83 [0.77, 4.37]
Total events: 13 (Treatment), 6 (Control)					
Test for heterogeneity chi-square=1.72 df=5 p=0.89 I^2 =0.0%					
Test for overall effect z=1.36 p=0.2					

Analysis 01.16. Comparison 01 Any antihypertensive drug versus none (subgrouped by class of drug), Outcome 16 Total reported fetal or neonatal death (including miscarriage)

Review: Antihypertensive drug therapy for mild to moderate hypertension during pregnancy

Comparison: 01 Any antihypertensive drug versus none (subgrouped by class of drug)

Outcome: 16 Total reported fetal or neonatal death (including miscarriage)

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 Beta blocker versus none					
Brazil 1985	5/50	4/50		7.0	1.25 [0.36, 4.38]
× Israel 1986a	0/21	0/23		0.0	Not estimable
Israel 1992	1/30	0/30		0.9	3.00 [0.13, 70.83]
× Israel 1995	0/36	0/15		0.0	Not estimable
Sweden 1984	0/26	1/26		2.6	0.33 [0.01, 7.82]
× UK 1982	0/64	0/62		0.0	Not estimable
UK 1983	1/60	2/60		3.5	0.50 [0.05, 5.37]
× UK 1989	0/70	0/74		0.0	Not estimable
UK 1990	1/15	0/14		0.9	2.81 [0.12, 63.83]
UK 1992	0/51	2/63		3.9	0.25 [0.01, 5.02]
USA 1987	1/102	0/103		0.9	3.03 [0.12, 73.50]
Subtotal (95% CI)	525	520		19.6	1.02 [0.46, 2.29]
Total events: 9 (Treatment), 9 (Control)					
Test for heterogeneity chi-square=3.08 df=6 p=0.80 I^2 =0.0%					
Test for overall effect z=0.05 p=1					
02 Beta blocker + other drug versus none					
Caribbean Is.1990	2/78	3/76		5.3	0.65 [0.11, 3.78]
Sweden 1985	3/86	1/82		1.8	2.86 [0.30, 26.95]
Subtotal (95% CI)	164	158		7.1	1.21 [0.33, 4.43]
Total events: 5 (Treatment), 4 (Control)					
Test for heterogeneity chi-square=1.04 df=1 p=0.31 I^2 =4.2%					
Test for overall effect z=0.28 p=0.8					
03 Methyldopa versus none					
Sudan 2002	4/34	6/36		10.2	0.71 [0.22, 2.29]
UK 1976	1/117	9/125		15.2	0.12 [0.02, 0.92]
× USA 1987a	0/13	0/12		0.0	Not estimable
Subtotal (95% CI)	164	173		25.3	0.35 [0.13, 0.94]
Total events: 5 (Treatment), 15 (Control)					

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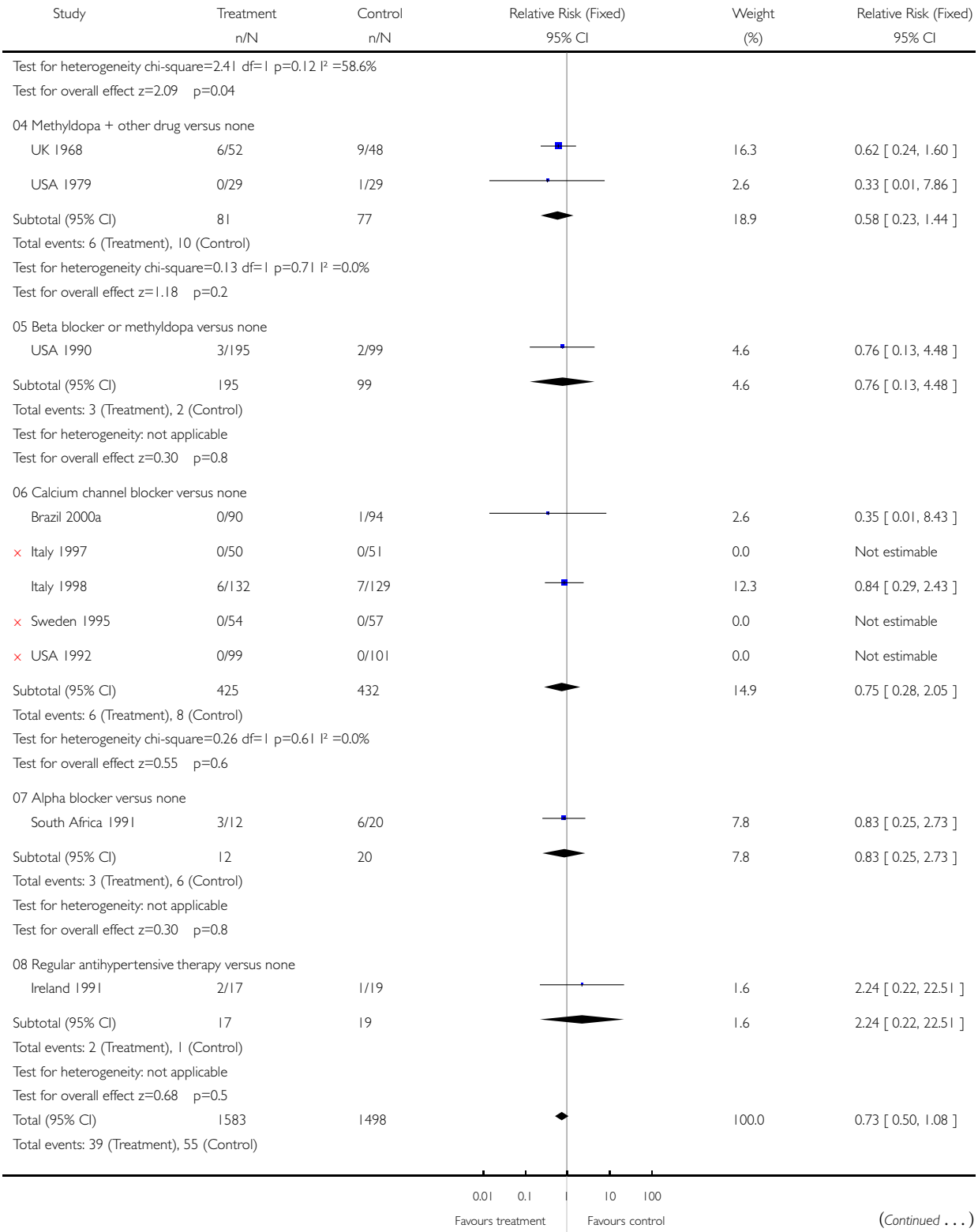

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Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Test for heterogeneity chi-square=9.81 df=17 p=0.91 I² =0.0%					
Test for overall effect z=1.58 p=0.1					

Analysis 01.17. Comparison 01 Any antihypertensive drug versus none (subgrouped by class of drug), Outcome 17 Fetal or neonatal death (subgrouped by time of death)

Review: Antihypertensive drug therapy for mild to moderate hypertension during pregnancy

Comparison: 01 Any antihypertensive drug versus none (subgrouped by class of drug)

Outcome: 17 Fetal or neonatal death (subgrouped by time of death)

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 Miscarriage					
Brazil 1985	3/50	3/50		17.0	1.00 [0.21, 4.72]
Italy 1998	1/132	3/129		17.2	0.33 [0.03, 3.09]
South Africa 1991	1/12	3/20		12.8	0.56 [0.06, 4.76]
UK 1968	0/52	3/48		20.7	0.13 [0.01, 2.49]
UK 1976	0/117	4/125		24.7	0.12 [0.01, 2.18]
× UK 1990	0/15	0/14		0.0	Not estimable
USA 1990	1/195	1/99		7.5	0.51 [0.03, 8.03]
Subtotal (95% CI)	573	485		100.0	0.39 [0.17, 0.93]
Total events: 6 (Treatment), 17 (Control)					
Test for heterogeneity chi-square=2.73 df=5 p=0.74 I² =0.0%					
Test for overall effect z=2.12 p=0.03					
02 Stillbirth					
Brazil 1985	2/47	1/47		5.9	2.00 [0.19, 21.31]
Brazil 2000a	0/90	1/94		8.7	0.35 [0.01, 8.43]
Caribbean Is.1990	2/78	1/76		6.0	1.95 [0.18, 21.05]
Ireland 1991	2/17	1/19		5.6	2.24 [0.22, 22.51]
Israel 1992	1/30	0/30		2.9	3.00 [0.13, 70.83]
Italy 1998	3/132	2/129		11.9	1.47 [0.25, 8.63]
South Africa 1991	1/12	3/20		13.3	0.56 [0.06, 4.76]

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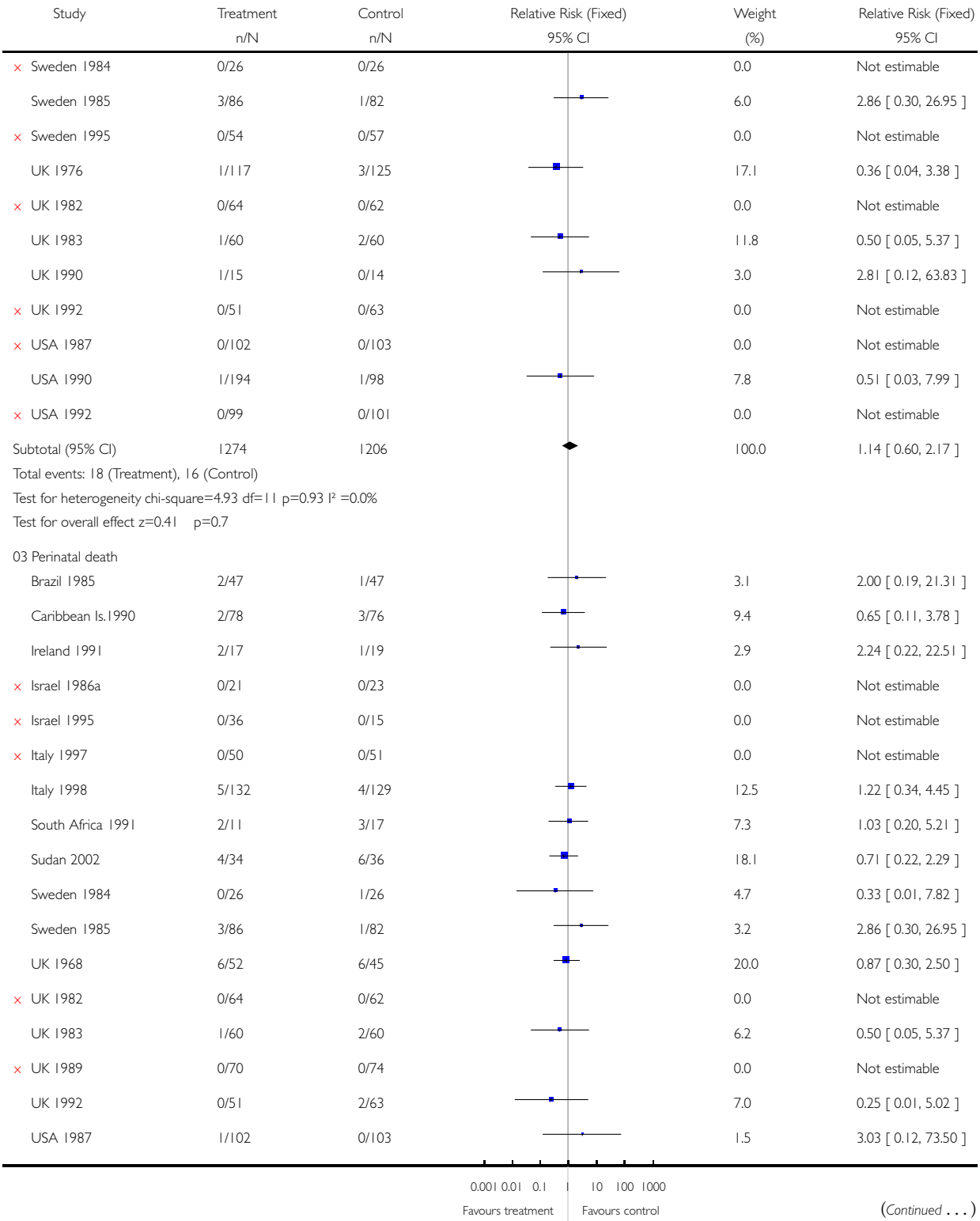

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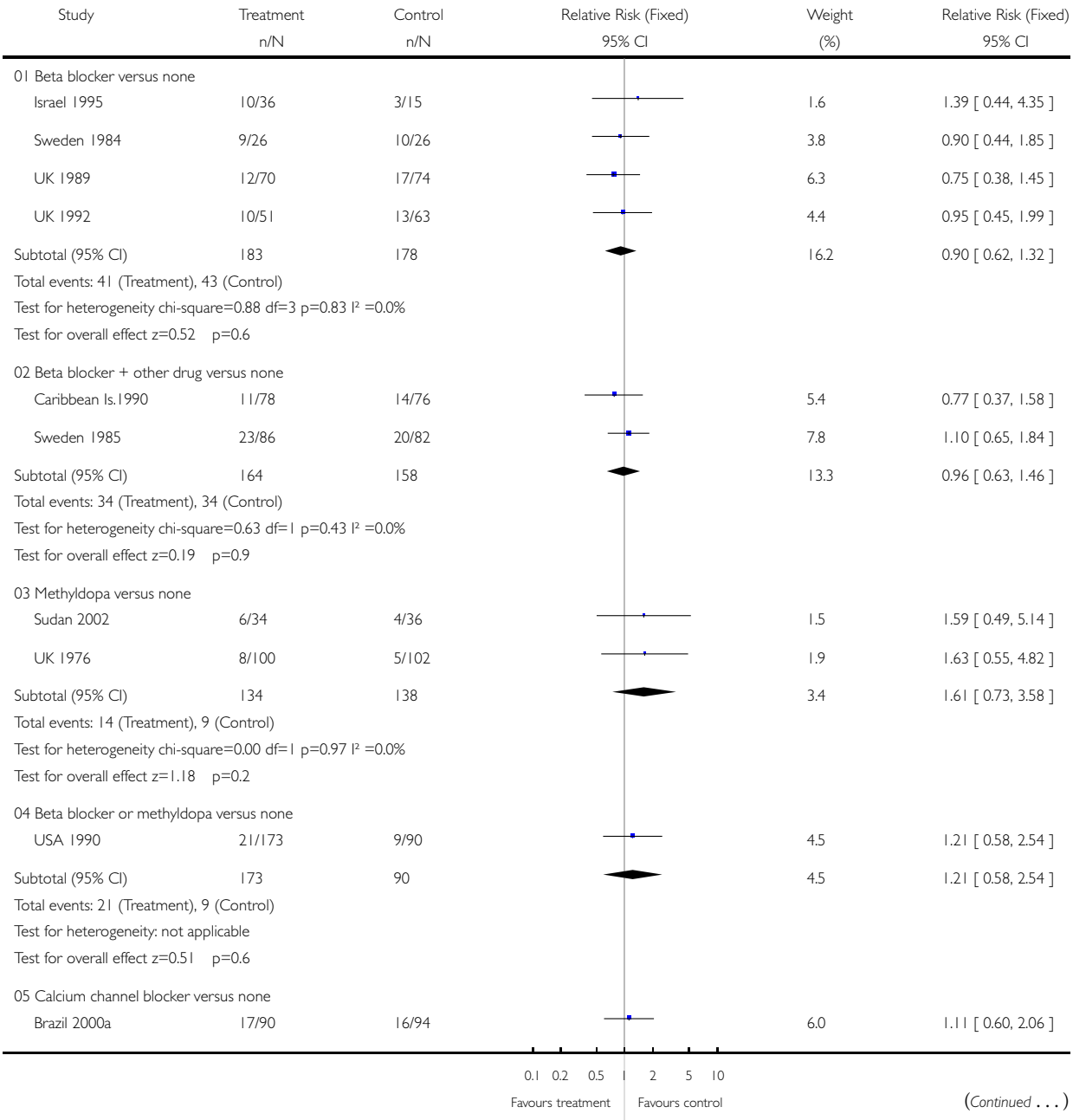
Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
× USA 1987a	0/13	0/12		0.0	Not estimable
USA 1990	2/194	1/98		4.1	1.01 [0.09, 11.01]
× USA 1992	0/99	0/101		0.0	Not estimable
Subtotal (95% CI)	1243	1139		100.0	0.96 [0.60, 1.54]
Total events: 30 (Treatment), 31 (Control)					
Test for heterogeneity chi-square=4.43 df=12 p=0.97 I^2 =0.0%					
Test for overall effect z=0.17 p=0.9					
04 Neonatal death					
× Brazil 1985	0/45	0/46		0.0	Not estimable
South Africa 1991	1/10	0/14		14.9	4.09 [0.18, 91.23]
UK 1976	0/117	2/125		85.1	0.21 [0.01, 4.40]
× USA 1992	0/99	0/101		0.0	Not estimable
Subtotal (95% CI)	271	286		100.0	0.79 [0.14, 4.34]
Total events: 1 (Treatment), 2 (Control)					
Test for heterogeneity chi-square=1.80 df=1 p=0.18 I^2 =44.3%					
Test for overall effect z=0.27 p=0.8					

Analysis 01.18. Comparison 01 Any antihypertensive drug versus none (subgrouped by class of drug), Outcome 18 Preterm birth (< 37 weeks)

Review: Antihypertensive drug therapy for mild to moderate hypertension during pregnancy

Comparison: 01 Any antihypertensive drug versus none (subgrouped by class of drug)

Outcome: 18 Preterm birth (< 37 weeks)



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Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Italy 1997	24/50	22/50		8.4	1.09 [0.71, 1.67]
Italy 1998	71/132	77/129		29.8	0.90 [0.73, 1.11]
USA 1992	49/98	41/99		15.6	1.21 [0.89, 1.64]
Subtotal (95% CI)	370	372		59.8	1.03 [0.88, 1.21]
Total events: 161 (Treatment), 156 (Control)					
Test for heterogeneity chi-square=2.67 df=3 p=0.45 I^2 =0.0%					
Test for overall effect z=0.35 p=0.7					
06 Alpha blocker versus none					
South Africa 1991	4/12	10/20		2.9	0.67 [0.27, 1.66]
Subtotal (95% CI)	12	20		2.9	0.67 [0.27, 1.66]
Total events: 4 (Treatment), 10 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.87 p=0.4					
Total (95% CI)	1036	956		100.0	1.02 [0.89, 1.16]
Total events: 275 (Treatment), 261 (Control)					
Test for heterogeneity chi-square=6.90 df=13 p=0.91 I^2 =0.0%					
Test for overall effect z=0.24 p=0.8					

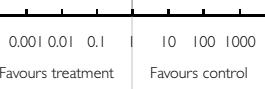
Analysis 01.19. Comparison 01 Any antihypertensive drug versus none (subgrouped by class of drug), Outcome 19 Preterm birth (subgrouped by gestational age)

Review: Antihypertensive drug therapy for mild to moderate hypertension during pregnancy

Comparison: 01 Any antihypertensive drug versus none (subgrouped by class of drug)

Outcome: 19 Preterm birth (subgrouped by gestational age)

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 < 37 weeks					
Brazil 2000a	17/90	16/94		6.9	1.11 [0.60, 2.06]
Caribbean Is.1990	11/78	14/76		6.3	0.77 [0.37, 1.58]
Italy 1998	71/132	77/129		34.4	0.90 [0.73, 1.11]
South Africa 1991	4/12	10/20		3.3	0.67 [0.27, 1.66]
Sweden 1984	9/26	10/26		4.4	0.90 [0.44, 1.85]
Sweden 1985	23/86	20/82		9.0	1.10 [0.65, 1.84]
UK 1989	12/70	17/74		7.3	0.75 [0.38, 1.45]
UK 1992	10/51	13/63		5.1	0.95 [0.45, 1.99]
USA 1990	21/173	9/90		5.2	1.21 [0.58, 2.54]
USA 1992	49/98	41/99		18.0	1.21 [0.89, 1.64]
Subtotal (95% CI)	816	753		100.0	0.98 [0.85, 1.13]
Total events: 227 (Treatment), 227 (Control)					
Test for heterogeneity chi-square=4.88 df=9 p=0.84 I^2 =0.0%					
Test for overall effect z=0.28 p=0.8					
02 < 36 weeks					
Brazil 2000a	11/90	10/94		64.0	1.15 [0.51, 2.57]
UK 1983	0/60	5/60		36.0	0.09 [0.01, 1.61]
Subtotal (95% CI)	150	154		100.0	0.77 [0.37, 1.59]
Total events: 11 (Treatment), 15 (Control)					
Test for heterogeneity chi-square=3.08 df=1 p=0.08 I^2 =67.5%					
Test for overall effect z=0.71 p=0.5					
03 < 34 weeks					
Brazil 2000a	7/90	2/94		5.9	3.66 [0.78, 17.13]
Caribbean Is.1990	3/78	6/76		18.3	0.49 [0.13, 1.88]
Italy 1998	20/132	13/129		39.5	1.50 [0.78, 2.89]
South Africa 1991	3/12	8/20		18.0	0.63 [0.20, 1.91]
Sweden 1985	6/82	6/79		18.4	0.96 [0.32, 2.86]
Subtotal (95% CI)	394	398		100.0	1.19 [0.77, 1.83]



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Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Total events: 39 (Treatment), 35 (Control)					
Test for heterogeneity chi-square=5.62 df=4 p=0.23 I^2 =28.8%					
Test for overall effect z=0.77 p=0.4					
04 Unspecified					
Israel 1995	10/36	3/15		12.1	1.39 [0.44, 4.35]
Italy 1997	24/50	22/50		62.7	1.09 [0.71, 1.67]
Sudan 2002	6/34	4/36		11.1	1.59 [0.49, 5.14]
UK 1976	8/100	5/102		14.1	1.63 [0.55, 4.82]
Subtotal (95% CI)	220	203		100.0	1.26 [0.87, 1.82]
Total events: 48 (Treatment), 34 (Control)					
Test for heterogeneity chi-square=0.83 df=3 p=0.84 I^2 =0.0%					
Test for overall effect z=1.23 p=0.2					

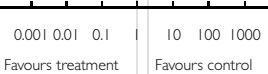
Analysis 01.20. Comparison 01 Any antihypertensive drug versus none (subgrouped by class of drug), Outcome 20 Small-for-gestational age

Review: Antihypertensive drug therapy for mild to moderate hypertension during pregnancy

Comparison: 01 Any antihypertensive drug versus none (subgrouped by class of drug)

Outcome: 20 Small-for-gestational age

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 Beta blocker versus none					
Brazil 1985	3/47	8/47		5.3	0.38 [0.11, 1.33]
Hong Kong 1990	3/18	4/20		2.5	0.83 [0.22, 3.23]
Israel 1995	13/36	4/15		3.8	1.35 [0.53, 3.48]
UK 1982	12/64	11/62		7.5	1.06 [0.50, 2.21]
UK 1983	9/59	8/58		5.4	1.11 [0.46, 2.67]
UK 1989	6/70	1/74		0.6	6.34 [0.78, 51.37]
UK 1990	5/15	0/14		0.3	10.31 [0.62, 170.96]
UK 1992	6/51	5/63		3.0	1.48 [0.48, 4.58]
USA 1987	18/94	9/97		5.9	2.06 [0.98, 4.36]
Subtotal (95% CI)	454	450		34.4	1.38 [0.99, 1.92]



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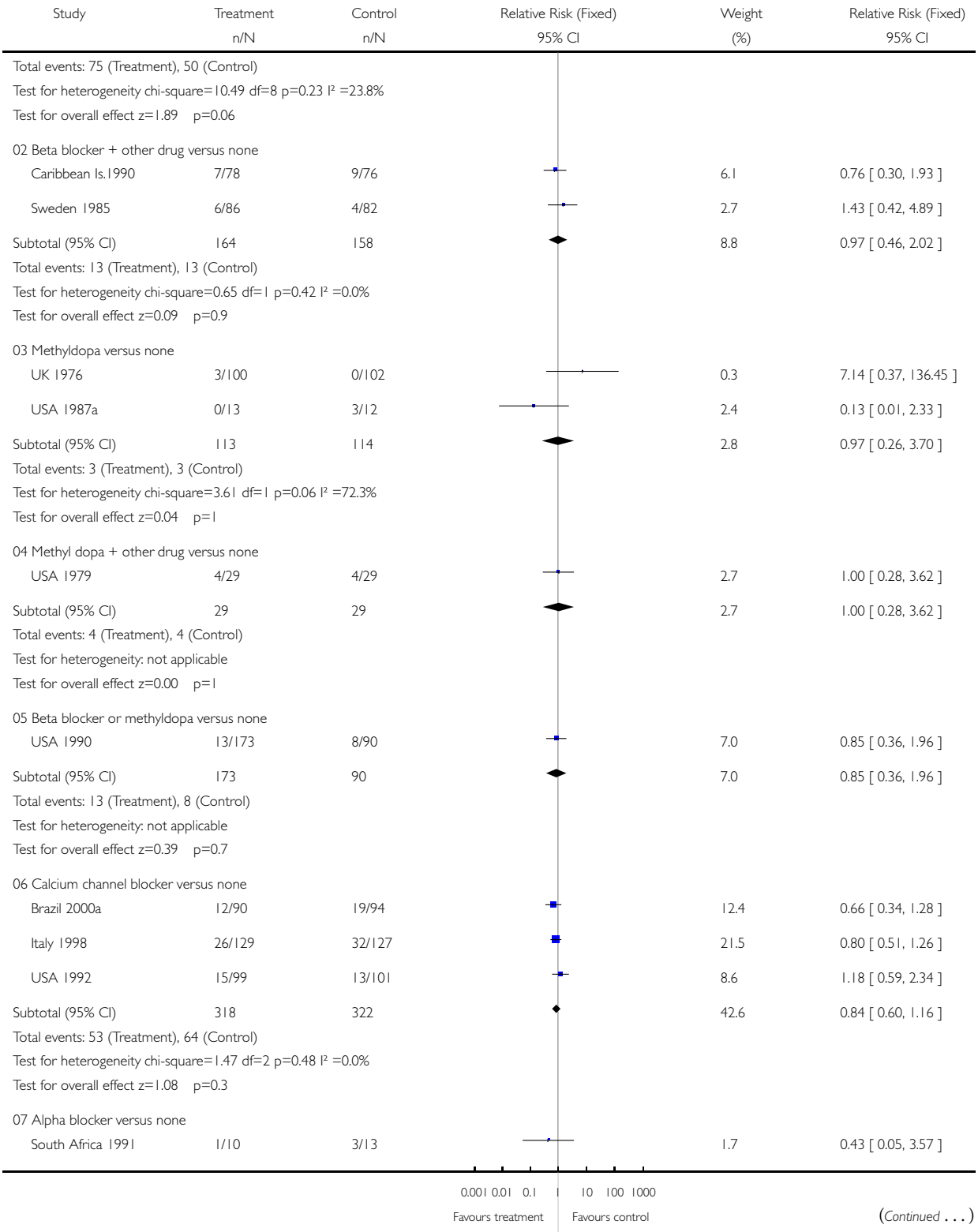

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Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Subtotal (95% CI)	10	13		1.7	0.43 [0.05, 3.57]
Total events: 1 (Treatment), 3 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.78 p=0.4					
Total (95% CI)	1261	1176		100.0	1.04 [0.84, 1.27]
Total events: 162 (Treatment), 145 (Control)					
Test for heterogeneity chi-square=20.36 df=18 p=0.31 I^2 =11.6%					
Test for overall effect z=0.33 p=0.7					

Analysis 01.21. Comparison 01 Any antihypertensive drug versus none (subgrouped by class of drug), Outcome 21 Small-for-gestational age (subgrouped by severity)

Review: Antihypertensive drug therapy for mild to moderate hypertension during pregnancy

Comparison: 01 Any antihypertensive drug versus none (subgrouped by class of drug)

Outcome: 21 Small-for-gestational age (subgrouped by severity)

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 Birthweight < 10th centile					
Hong Kong 1990	3/18	4/20		4.1	0.83 [0.22, 3.23]
Israel 1995	13/36	4/15		6.1	1.35 [0.53, 3.48]
Italy 1998	26/129	32/127		34.6	0.80 [0.51, 1.26]
South Africa 1991	1/10	3/13		2.8	0.43 [0.05, 3.57]
UK 1982	12/64	11/62		12.0	1.06 [0.50, 2.21]
UK 1983	9/59	8/58		8.6	1.11 [0.46, 2.67]
UK 1992	10/51	9/63		8.6	1.37 [0.60, 3.12]
USA 1987	18/94	9/97		9.5	2.06 [0.98, 4.36]
USA 1992	15/99	13/101		13.8	1.18 [0.59, 2.34]
Subtotal (95% CI)	560	556		100.0	1.10 [0.86, 1.42]
Total events: 107 (Treatment), 93 (Control)					
Test for heterogeneity chi-square=6.02 df=8 p=0.64 I^2 =0.0%					
Test for overall effect z=0.76 p=0.4					
02 Birthweight < 5th centile					
UK 1989	6/70	1/74		16.3	6.34 [0.78, 51.37]

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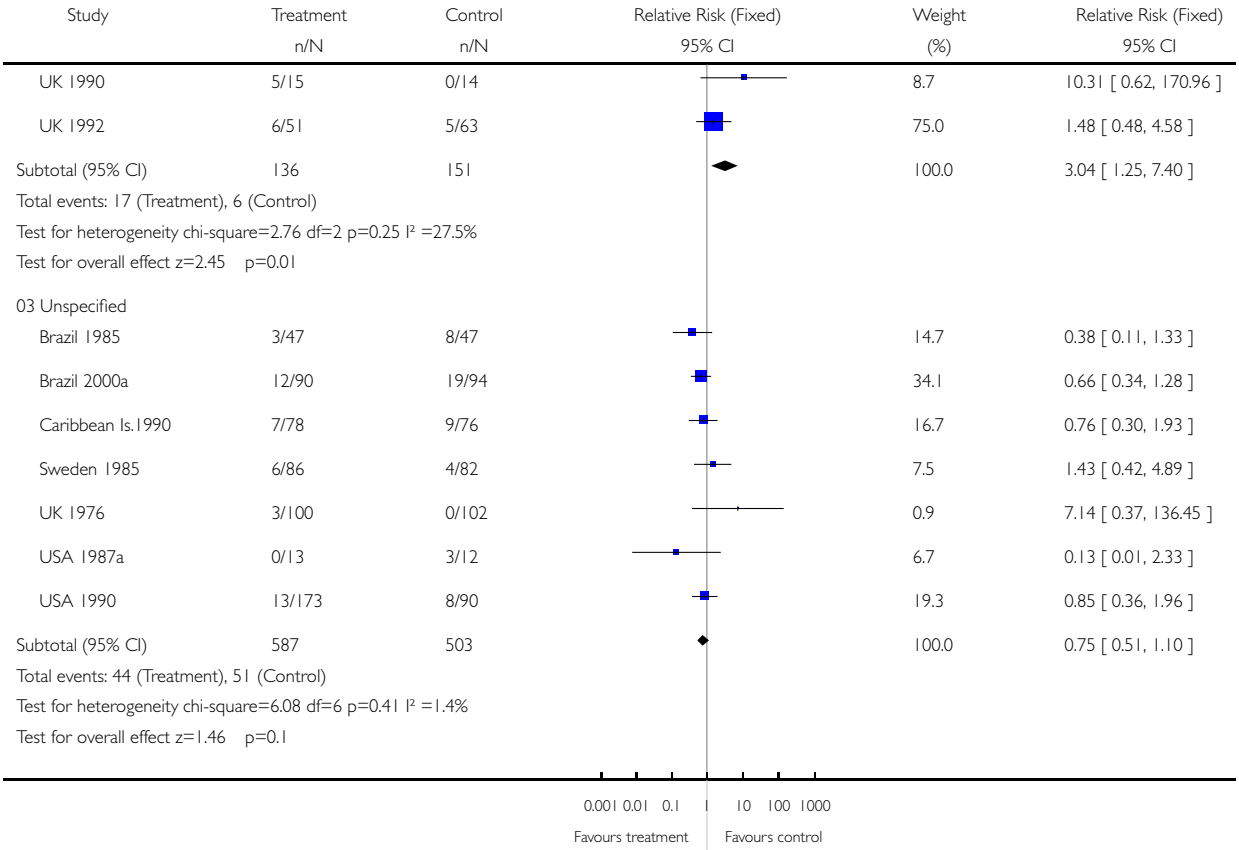


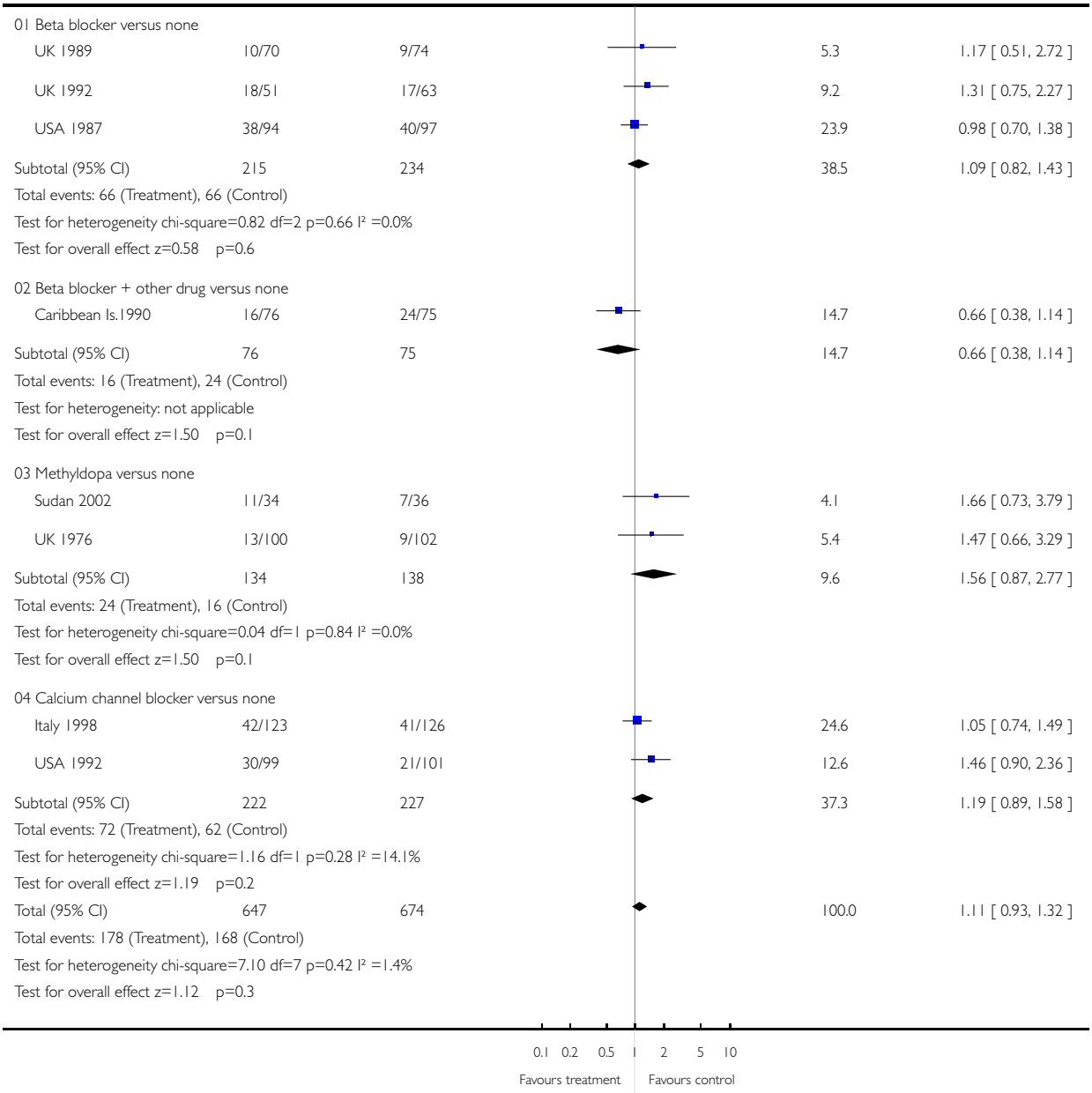
Analysis 01.22. Comparison 01 Any antihypertensive drug versus none (subgrouped by class of drug), Outcome 22 Admission to special care baby unit

Review: Antihypertensive drug therapy for mild to moderate hypertension during pregnancy

Comparison: 01 Any antihypertensive drug versus none (subgrouped by class of drug)

Outcome: 22 Admission to special care baby unit

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 Beta blocker versus none					
UK 1989	10/70	9/74		5.3	1.17 [0.51, 2.72]
UK 1992	18/51	17/63		9.2	1.31 [0.75, 2.27]
USA 1987	38/94	40/97		23.9	0.98 [0.70, 1.38]
Subtotal (95% CI)	215	234		38.5	1.09 [0.82, 1.43]
Total events: 66 (Treatment), 66 (Control)					
Test for heterogeneity chi-square=0.82 df=2 p=0.66 I² =0.0%					
Test for overall effect z=0.58 p=0.6					
02 Beta blocker + other drug versus none					
Caribbean Is.1990	16/76	24/75		14.7	0.66 [0.38, 1.14]
Subtotal (95% CI)	76	75		14.7	0.66 [0.38, 1.14]
Total events: 16 (Treatment), 24 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.50 p=0.1					
03 Methyldopa versus none					
Sudan 2002	11/34	7/36		4.1	1.66 [0.73, 3.79]
UK 1976	13/100	9/102		5.4	1.47 [0.66, 3.29]
Subtotal (95% CI)	134	138		9.6	1.56 [0.87, 2.77]
Total events: 24 (Treatment), 16 (Control)					
Test for heterogeneity chi-square=0.04 df=1 p=0.84 I² =0.0%					
Test for overall effect z=1.50 p=0.1					
04 Calcium channel blocker versus none					
Italy 1998	42/123	41/126		24.6	1.05 [0.74, 1.49]
USA 1992	30/99	21/101		12.6	1.46 [0.90, 2.36]
Subtotal (95% CI)	222	227		37.3	1.19 [0.89, 1.58]
Total events: 72 (Treatment), 62 (Control)					
Test for heterogeneity chi-square=1.16 df=1 p=0.28 I² =14.1%					
Test for overall effect z=1.19 p=0.2					
Total (95% CI)	647	674		100.0	1.11 [0.93, 1.32]
Total events: 178 (Treatment), 168 (Control)					
Test for heterogeneity chi-square=7.10 df=7 p=0.42 I² =1.4%					
Test for overall effect z=1.12 p=0.3					



Analysis 01.23. Comparison 01 Any antihypertensive drug versus none (subgrouped by class of drug), Outcome 23 Respiratory distress syndrome

Review: Antihypertensive drug therapy for mild to moderate hypertension during pregnancy

Comparison: 01 Any antihypertensive drug versus none (subgrouped by class of drug)

Outcome: 23 Respiratory distress syndrome

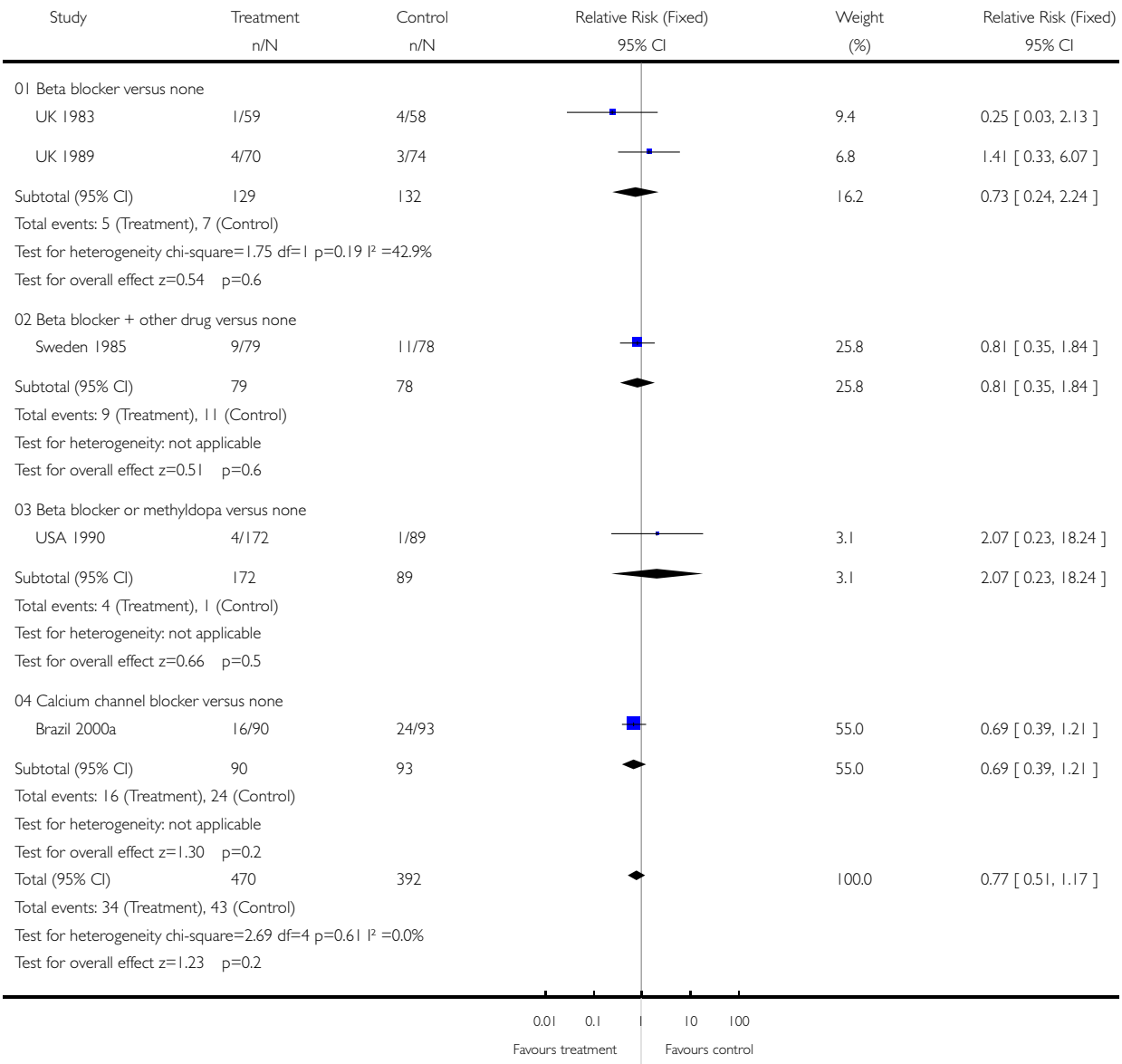
Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 Beta blocker versus none					
Caribbean Is.1990	4/76	10/75		40.1	0.39 [0.13, 1.20]
UK 1983	0/59	6/58		26.1	0.08 [0.00, 1.31]
UK 1989	1/70	3/74		11.6	0.35 [0.04, 3.31]
Subtotal (95% CI)	205	207		77.9	0.28 [0.11, 0.71]
Total events: 5 (Treatment), 19 (Control)					
Test for heterogeneity chi-square=1.21 df=2 p=0.55 I^2 =0.0%					
Test for overall effect z=2.70 p=0.007					
02 Beta blocker + other drug versus none					
Sweden 1985	1/79	3/78		12.0	0.33 [0.03, 3.10]
Subtotal (95% CI)	79	78		12.0	0.33 [0.03, 3.10]
Total events: 1 (Treatment), 3 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.97 p=0.3					
03 Calcium channel blocker versus none					
Italy 1998	0/129	2/127		10.0	0.20 [0.01, 4.06]
Subtotal (95% CI)	129	127		10.0	0.20 [0.01, 4.06]
Total events: 0 (Treatment), 2 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.05 p=0.3					
Total (95% CI)	413	412		100.0	0.28 [0.12, 0.63]
Total events: 6 (Treatment), 24 (Control)					
Test for heterogeneity chi-square=1.29 df=4 p=0.86 I^2 =0.0%					
Test for overall effect z=3.06 p=0.002					

Analysis 01.24. Comparison 01 Any antihypertensive drug versus none (subgrouped by class of drug), Outcome 24 Neonatal hypoglycaemia

Review: Antihypertensive drug therapy for mild to moderate hypertension during pregnancy

Comparison: 01 Any antihypertensive drug versus none (subgrouped by class of drug)

Outcome: 24 Neonatal hypoglycaemia



Analysis 01.25. Comparison 01 Any antihypertensive drug versus none (subgrouped by class of drug), Outcome 25 Neonatal bradycardia

Review: Antihypertensive drug therapy for mild to moderate hypertension during pregnancy

Comparison: 01 Any antihypertensive drug versus none (subgrouped by class of drug)

Outcome: 25 Neonatal bradycardia

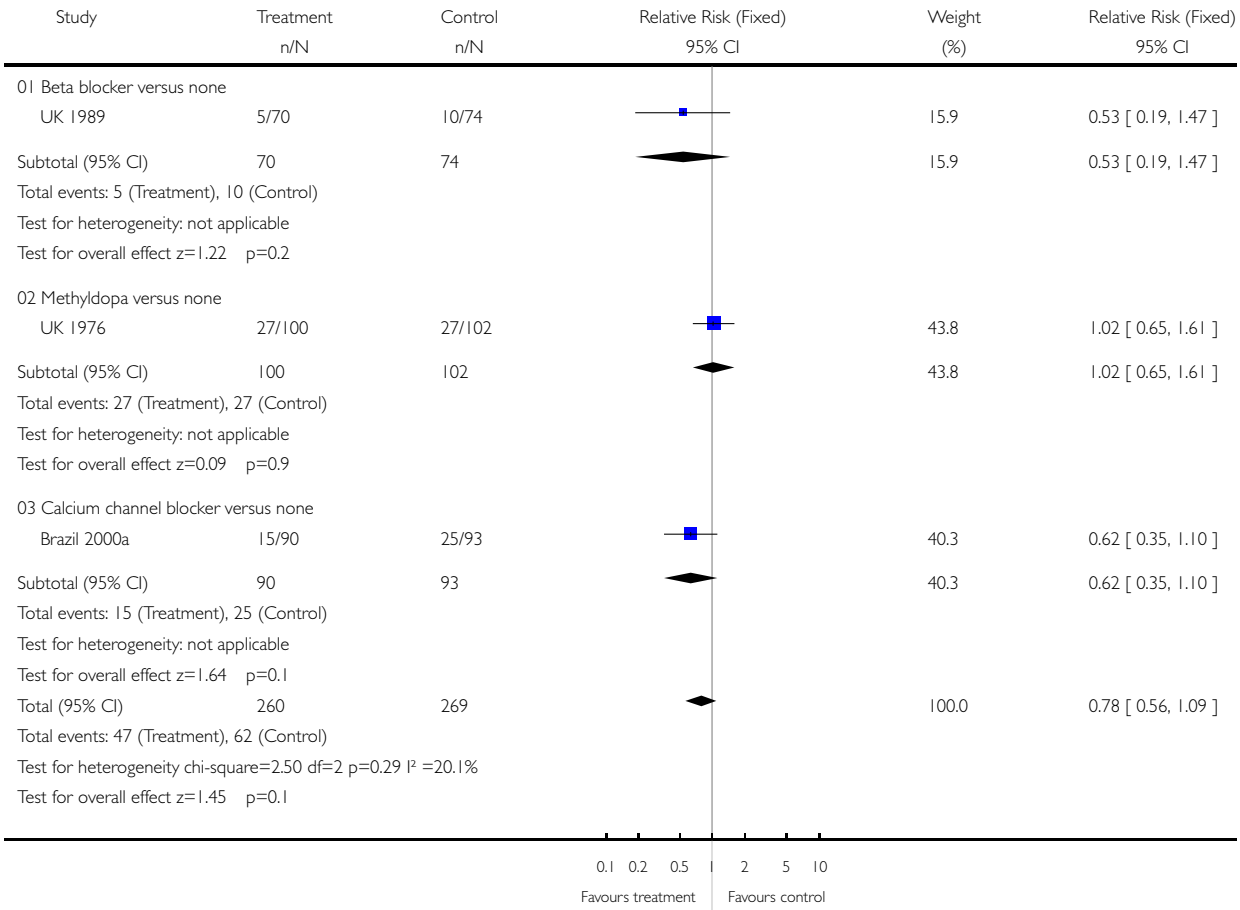
Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 Beta blocker versus none					
UK 1983	22/59	6/58		43.3	3.60 [1.58, 8.24]
UK 1989	4/70	4/74		27.8	1.06 [0.27, 4.06]
Subtotal (95% CI)	129	132		71.2	2.61 [1.32, 5.15]
Total events: 26 (Treatment), 10 (Control)					
Test for heterogeneity chi-square=2.32 df=1 p=0.13 I^2 =56.8%					
Test for overall effect z=2.76 p=0.006					
02 Beta blocker + other drug versus none					
Sweden 1985	1/79	4/78		28.8	0.25 [0.03, 2.16]
Subtotal (95% CI)	79	78		28.8	0.25 [0.03, 2.16]
Total events: 1 (Treatment), 4 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.26 p=0.2					
Total (95% CI)	208	210		100.0	1.93 [1.05, 3.53]
Total events: 27 (Treatment), 14 (Control)					
Test for heterogeneity chi-square=6.42 df=2 p=0.04 I^2 =68.8%					
Test for overall effect z=2.12 p=0.03					

Analysis 01.26. Comparison 01 Any antihypertensive drug versus none (subgrouped by class of drug), Outcome 26 Neonatal jaundice

Review: Antihypertensive drug therapy for mild to moderate hypertension during pregnancy

Comparison: 01 Any antihypertensive drug versus none (subgrouped by class of drug)

Outcome: 26 Neonatal jaundice



Analysis 01.27. Comparison 01 Any antihypertensive drug versus none (subgrouped by class of drug), Outcome 27 Follow up of the children at 1 year: cerebral palsy

Review: Antihypertensive drug therapy for mild to moderate hypertension during pregnancy

Comparison: 01 Any antihypertensive drug versus none (subgrouped by class of drug)

Outcome: 27 Follow up of the children at 1 year: cerebral palsy

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
UK 1983	0/55	1/55		100.0	0.33 [0.01, 8.01]
Total (95% CI)	55	55		100.0	0.33 [0.01, 8.01]
Total events: 0 (Treatment), 1 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.68 p=0.5					

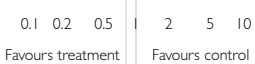
Analysis 01.28. Comparison 01 Any antihypertensive drug versus none (subgrouped by class of drug), Outcome 28 Follow up of the children at 7 1/2 years

Review: Antihypertensive drug therapy for mild to moderate hypertension during pregnancy

Comparison: 01 Any antihypertensive drug versus none (subgrouped by class of drug)

Outcome: 28 Follow up of the children at 7 1/2 years

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 Chronic ill health					
UK 1976	3/98	4/92		100.0	0.70 [0.16, 3.06]
Subtotal (95% CI)	98	92		100.0	0.70 [0.16, 3.06]
Total events: 3 (Treatment), 4 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.47 p=0.6					
02 Impaired hearing					
UK 1976	7/98	6/92		100.0	1.10 [0.38, 3.14]
Subtotal (95% CI)	98	92		100.0	1.10 [0.38, 3.14]
Total events: 7 (Treatment), 6 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.17 p=0.9					
03 Impaired vision					
UK 1976	7/98	14/92		100.0	0.47 [0.20, 1.11]
Subtotal (95% CI)	98	92		100.0	0.47 [0.20, 1.11]
Total events: 7 (Treatment), 14 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.72 p=0.09					



Analysis 02.01. Comparison 02 Any antihypertensive drug versus none (subgrouped by type of hypertensive disorder at trial entry), Outcome 01 Severe hypertension

Review: Antihypertensive drug therapy for mild to moderate hypertension during pregnancy

Comparison: 02 Any antihypertensive drug versus none (subgrouped by type of hypertensive disorder at trial entry)

Outcome: 01 Severe hypertension

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 Hypertension alone					
South Africa 1991	0/12	11/20		3.8	0.07 [0.00, 1.09]
Sweden 1985	0/86	6/82		2.9	0.07 [0.00, 1.28]
UK 1989	5/70	15/74		6.4	0.35 [0.14, 0.92]
Subtotal (95% CI)	168	176		13.1	0.21 [0.09, 0.49]
Total events: 5 (Treatment), 32 (Control)					
Test for heterogeneity chi-square=2.27 df=2 p=0.32 I^2 =12.1%					
Test for overall effect z=3.61 p=0.0003					
02 Hypertension + proteinuria					
Sudan 2002	3/34	18/36		7.6	0.18 [0.06, 0.55]
USA 1987	5/92	14/94		6.0	0.36 [0.14, 0.97]
Subtotal (95% CI)	126	130		13.7	0.26 [0.13, 0.54]
Total events: 8 (Treatment), 32 (Control)					
Test for heterogeneity chi-square=0.91 df=1 p=0.34 I^2 =0.0%					
Test for overall effect z=3.62 p=0.0003					
03 Chronic hypertension					
Brazil 2000a	9/90	14/94		6.0	0.67 [0.31, 1.47]
UK 1990	0/16	2/17		1.1	0.21 [0.01, 4.10]
USA 1979	2/29	3/29		1.3	0.67 [0.12, 3.70]
USA 1990	10/173	10/90		5.7	0.52 [0.22, 1.20]
Subtotal (95% CI)	308	230		14.1	0.57 [0.34, 0.98]
Total events: 21 (Treatment), 29 (Control)					
Test for heterogeneity chi-square=0.67 df=3 p=0.88 I^2 =0.0%					
Test for overall effect z=2.04 p=0.04					
04 Unclassified/mixed					
Caribbean Is.1990	5/78	11/76		4.9	0.44 [0.16, 1.21]
Hong Kong 1990	6/20	10/21		4.3	0.63 [0.28, 1.41]
Israel 1992	6/30	15/30		6.5	0.40 [0.18, 0.89]
Italy 1997	4/50	10/50		4.4	0.40 [0.13, 1.19]
Italy 1998	36/132	39/129		17.2	0.90 [0.62, 1.32]

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Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Sweden 1984	1/26	0/26		0.2	3.00 [0.13, 70.42]
Sweden 1995	9/58	8/59		3.5	1.14 [0.47, 2.76]
UK 1976	9/117	22/123		9.4	0.43 [0.21, 0.90]
UK 1982	3/64	13/62		5.8	0.22 [0.07, 0.75]
UK 1983	2/60	7/60		3.1	0.29 [0.06, 1.32]
Subtotal (95% CI)	635	636		59.1	0.60 [0.47, 0.77]
Total events: 81 (Treatment), 135 (Control)					
Test for heterogeneity chi-square=13.56 df=9 p=0.14 I^2 =33.7%					
Test for overall effect z=4.06 p=0.00005					
Total (95% CI)	1237	1172		100.0	0.50 [0.41, 0.61]
Total events: 115 (Treatment), 228 (Control)					
Test for heterogeneity chi-square=25.88 df=18 p=0.10 I^2 =30.4%					
Test for overall effect z=6.63 p<0.00001					

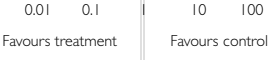
Analysis 02.02. Comparison 02 Any antihypertensive drug versus none (subgrouped by type of hypertensive disorder at trial entry), Outcome 02 Proteinuria/pre-eclampsia

Review: Antihypertensive drug therapy for mild to moderate hypertension during pregnancy

Comparison: 02 Any antihypertensive drug versus none (subgrouped by type of hypertensive disorder at trial entry)

Outcome: 02 Proteinuria/pre-eclampsia

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 Hypertension alone					
Australia 2001	1/7	3/9		1.1	0.43 [0.06, 3.28]
Ireland 1991	1/17	6/19		2.4	0.19 [0.02, 1.39]
South Africa 1991	1/12	5/20		1.6	0.33 [0.04, 2.52]
Sweden 1985	10/86	6/82		2.6	1.59 [0.60, 4.17]
UK 1989	31/70	45/74		18.2	0.73 [0.53, 1.00]
UK 1992	13/51	17/63		6.3	0.94 [0.51, 1.76]
USA 1987a	5/13	4/12		1.7	1.15 [0.40, 3.31]
Subtotal (95% CI)	256	279		33.8	0.79 [0.61, 1.03]
Total events: 62 (Treatment), 86 (Control)					
Test for heterogeneity chi-square=6.10 df=6 p=0.41 I^2 =1.6%					



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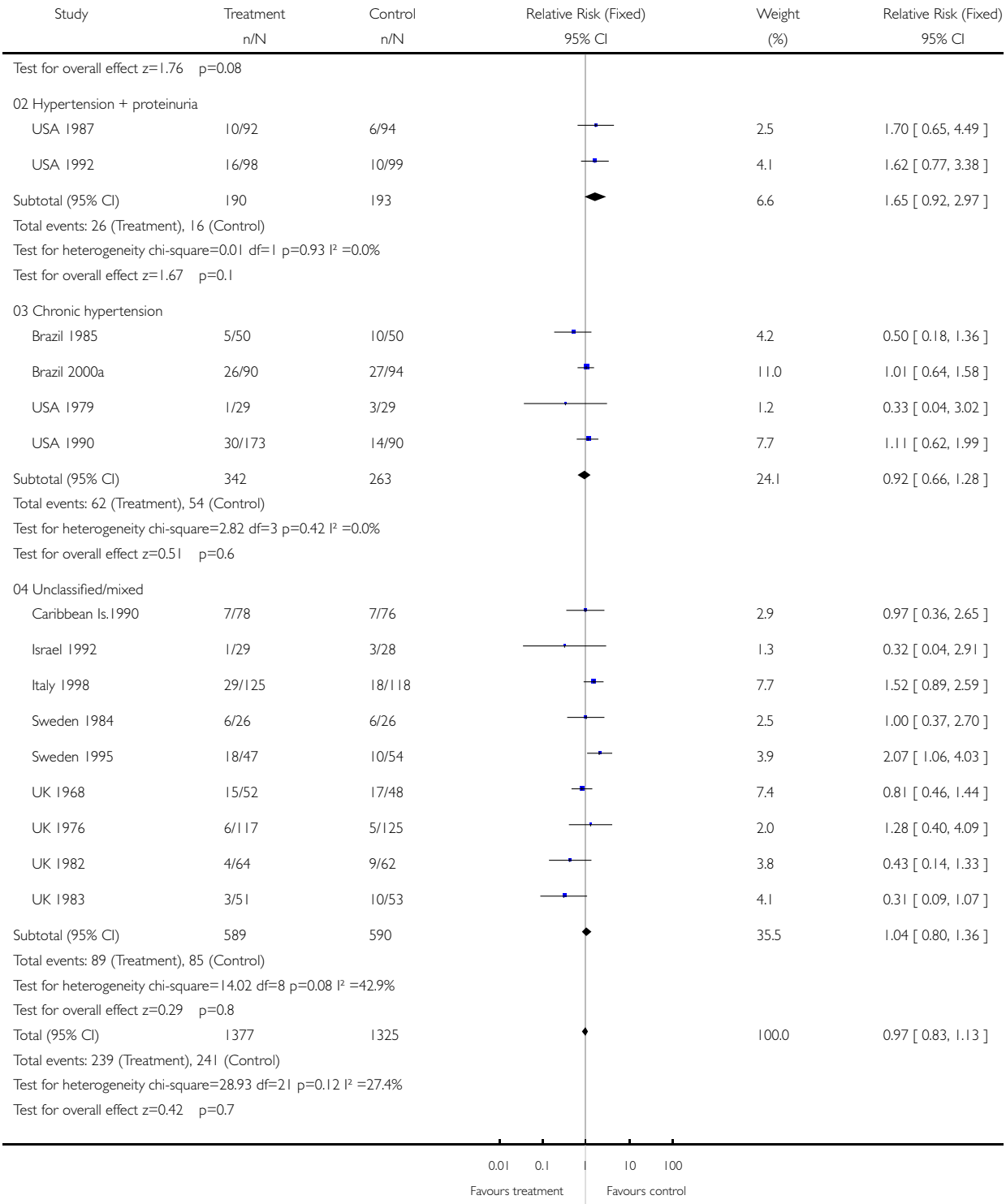
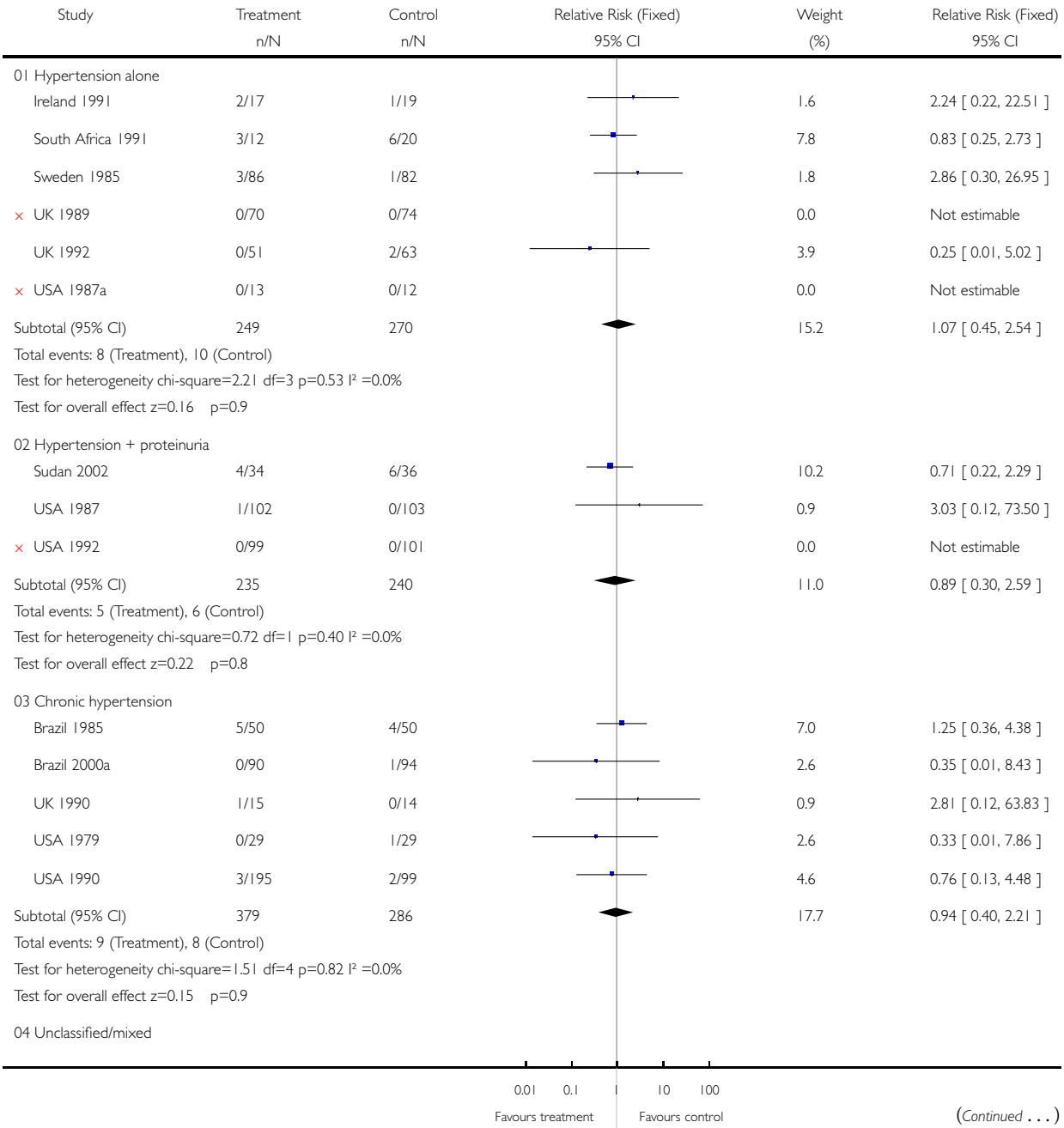


Analysis 02.03. Comparison 02 Any antihypertensive drug versus none (subgrouped by type of hypertensive disorder at trial entry), Outcome 03 Total reported fetal or neonatal death (including miscarriage)

Review: Antihypertensive drug therapy for mild to moderate hypertension during pregnancy

Comparison: 02 Any antihypertensive drug versus none (subgrouped by type of hypertensive disorder at trial entry)

Outcome: 03 Total reported fetal or neonatal death (including miscarriage)



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Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Caribbean Is.1990	2/78	3/76		5.3	0.65 [0.11, 3.78]
× Israel 1986a	0/21	0/23		0.0	Not estimable
Israel 1992	1/30	0/30		0.9	3.00 [0.13, 70.83]
× Israel 1995	0/36	0/15		0.0	Not estimable
× Italy 1997	0/50	0/51		0.0	Not estimable
Italy 1998	6/132	7/129		12.3	0.84 [0.29, 2.43]
Sweden 1984	0/26	1/26		2.6	0.33 [0.01, 7.82]
× Sweden 1995	0/54	0/57		0.0	Not estimable
UK 1968	6/52	9/48		16.3	0.62 [0.24, 1.60]
UK 1976	1/117	9/125		15.2	0.12 [0.02, 0.92]
× UK 1982	0/64	0/62		0.0	Not estimable
UK 1983	1/60	2/60		3.5	0.50 [0.05, 5.37]
Subtotal (95% CI)	720	702		56.1	0.55 [0.31, 0.96]
Total events: 17 (Treatment), 31 (Control)					
Test for heterogeneity chi-square=4.05 df=6 p=0.67 I^2 =0.0%					
Test for overall effect z=2.09 p=0.04					
Total (95% CI)	1583	1498		100.0	0.73 [0.50, 1.08]
Total events: 39 (Treatment), 55 (Control)					
Test for heterogeneity chi-square=9.81 df=17 p=0.91 I^2 =0.0%					
Test for overall effect z=1.58 p=0.1					

Analysis 02.04. Comparison 02 Any antihypertensive drug versus none (subgrouped by type of hypertensive disorder at trial entry), Outcome 04 Preterm birth (< 37 weeks)

Review: Antihypertensive drug therapy for mild to moderate hypertension during pregnancy

Comparison: 02 Any antihypertensive drug versus none (subgrouped by type of hypertensive disorder at trial entry)

Outcome: 04 Preterm birth (< 37 weeks)

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 Hypertension alone					
South Africa 1991	4/12	10/20		2.9	0.67 [0.27, 1.66]
Sweden 1985	23/86	20/82		7.8	1.10 [0.65, 1.84]
UK 1989	12/70	17/74		6.3	0.75 [0.38, 1.45]
UK 1992	10/51	13/63		4.4	0.95 [0.45, 1.99]
Subtotal (95% CI)	219	239		21.5	0.91 [0.65, 1.26]
Total events: 49 (Treatment), 60 (Control)					
Test for heterogeneity chi-square=1.30 df=3 p=0.73 I^2 =0.0%					
Test for overall effect z=0.59 p=0.6					
02 Hypertension + proteinuria					
Sudan 2002	6/34	4/36		1.5	1.59 [0.49, 5.14]
USA 1992	49/98	41/99		15.6	1.21 [0.89, 1.64]
Subtotal (95% CI)	132	135		17.1	1.24 [0.92, 1.67]
Total events: 55 (Treatment), 45 (Control)					
Test for heterogeneity chi-square=0.20 df=1 p=0.65 I^2 =0.0%					
Test for overall effect z=1.41 p=0.2					
03 Chronic hypertension					
Brazil 2000a	17/90	16/94		6.0	1.11 [0.60, 2.06]
USA 1990	21/173	9/90		4.5	1.21 [0.58, 2.54]
Subtotal (95% CI)	263	184		10.5	1.15 [0.72, 1.86]
Total events: 38 (Treatment), 25 (Control)					
Test for heterogeneity chi-square=0.03 df=1 p=0.85 I^2 =0.0%					
Test for overall effect z=0.59 p=0.6					
04 Unclassified/mixed					
Caribbean Is.1990	11/78	14/76		5.4	0.77 [0.37, 1.58]
Israel 1995	10/36	3/15		1.6	1.39 [0.44, 4.35]
Italy 1997	24/50	22/50		8.4	1.09 [0.71, 1.67]
Italy 1998	71/132	77/129		29.8	0.90 [0.73, 1.11]
Sweden 1984	9/26	10/26		3.8	0.90 [0.44, 1.85]
UK 1976	8/100	5/102		1.9	1.63 [0.55, 4.82]

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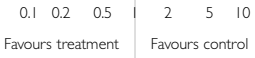
Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Subtotal (95% CI)	422	398		50.9	0.96 [0.80, 1.15]
Total events: 133 (Treatment), 131 (Control)					
Test for heterogeneity chi-square=2.42 df=5 p=0.79 I^2 =0.0%					
Test for overall effect z=0.44 p=0.7					
Total (95% CI)	1036	956		100.0	1.02 [0.89, 1.16]
Total events: 275 (Treatment), 261 (Control)					
Test for heterogeneity chi-square=6.90 df=13 p=0.91 I^2 =0.0%					
Test for overall effect z=0.24 p=0.8					



Analysis 02.05. Comparison 02 Any antihypertensive drug versus none (subgrouped by type of hypertensive disorder at trial entry), Outcome 05 Small-for-gestational age

Review: Antihypertensive drug therapy for mild to moderate hypertension during pregnancy

Comparison: 02 Any antihypertensive drug versus none (subgrouped by type of hypertensive disorder at trial entry)

Outcome: 05 Small-for-gestational age

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 Hypertension alone					
South Africa 1991	1/10	3/13		1.7	0.43 [0.05, 3.57]
Sweden 1985	6/86	4/82		2.7	1.43 [0.42, 4.89]
UK 1989	6/70	1/74		0.6	6.34 [0.78, 51.37]
UK 1992	6/51	5/63		3.0	1.48 [0.48, 4.58]
USA 1987a	0/13	3/12		2.4	0.13 [0.01, 2.33]
Subtotal (95% CI)	230	244		10.5	1.28 [0.68, 2.42]
Total events: 19 (Treatment), 16 (Control)					
Test for heterogeneity chi-square=5.76 df=4 p=0.22 I^2 =30.6%					
Test for overall effect z=0.78 p=0.4					
02 Hypertension + proteinuria					
USA 1987	18/94	9/97		5.9	2.06 [0.98, 4.36]
USA 1992	15/99	13/101		8.6	1.18 [0.59, 2.34]
Subtotal (95% CI)	193	198		14.5	1.54 [0.93, 2.54]
Total events: 33 (Treatment), 22 (Control)					
Test for heterogeneity chi-square=1.17 df=1 p=0.28 I^2 =14.7%					
Test for overall effect z=1.68 p=0.09					

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Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
03 Chronic hypertension					
Brazil 1985	3/47	8/47		5.3	0.38 [0.11, 1.33]
Brazil 2000a	12/90	19/94		12.4	0.66 [0.34, 1.28]
UK 1990	5/15	0/14		0.3	10.31 [0.62, 170.96]
USA 1979	4/29	4/29		2.7	1.00 [0.28, 3.62]
USA 1990	13/173	8/90		7.0	0.85 [0.36, 1.96]
Subtotal (95% CI)	354	274		27.8	0.80 [0.53, 1.23]
Total events: 37 (Treatment), 39 (Control)					
Test for heterogeneity chi-square=5.04 df=4 p=0.28 I^2 =20.6%					
Test for overall effect z=1.00 p=0.3					
04 Unclassified/mixed					
Caribbean Is.1990	7/78	9/76		6.1	0.76 [0.30, 1.93]
Hong Kong 1990	3/18	4/20		2.5	0.83 [0.22, 3.23]
Israel 1995	13/36	4/15		3.8	1.35 [0.53, 3.48]
Italy 1998	26/129	32/127		21.5	0.80 [0.51, 1.26]
UK 1976	3/100	0/102		0.3	7.14 [0.37, 136.45]
UK 1982	12/64	11/62		7.5	1.06 [0.50, 2.21]
UK 1983	9/59	8/58		5.4	1.11 [0.46, 2.67]
Subtotal (95% CI)	484	460		47.1	0.96 [0.71, 1.30]
Total events: 73 (Treatment), 68 (Control)					
Test for heterogeneity chi-square=3.35 df=6 p=0.76 I^2 =0.0%					
Test for overall effect z=0.26 p=0.8					
Total (95% CI)	1261	1176		100.0	1.04 [0.84, 1.27]
Total events: 162 (Treatment), 145 (Control)					
Test for heterogeneity chi-square=20.36 df=18 p=0.31 I^2 =11.6%					
Test for overall effect z=0.33 p=0.7					

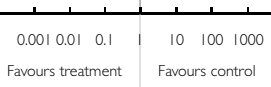
Analysis 03.01. Comparison 03 Any antihypertensive drug versus none (subgrouped by gestation at trial entry), Outcome 01 Severe hypertension

Review: Antihypertensive drug therapy for mild to moderate hypertension during pregnancy

Comparison: 03 Any antihypertensive drug versus none (subgrouped by gestation at trial entry)

Outcome: 01 Severe hypertension

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 Entry < 32 weeks					
Brazil 2000a	9/90	14/94		6.0	0.67 [0.31, 1.47]
Italy 1998	36/132	39/129		17.2	0.90 [0.62, 1.32]
South Africa 1991	0/12	11/20		3.8	0.07 [0.00, 1.09]
UK 1976	9/117	22/123		9.4	0.43 [0.21, 0.90]
UK 1990	0/16	2/17		1.1	0.21 [0.01, 4.10]
USA 1979	2/29	3/29		1.3	0.67 [0.12, 3.70]
USA 1990	10/173	10/90		5.7	0.52 [0.22, 1.20]
Subtotal (95% CI)	569	502		44.5	0.63 [0.47, 0.83]
Total events: 66 (Treatment), 101 (Control)					
Test for heterogeneity chi-square=7.67 df=6 p=0.26 I^2 =21.7%					
Test for overall effect z=3.23 p=0.001					
02 Entry > 32 weeks					
UK 1983	2/60	7/60		3.1	0.29 [0.06, 1.32]
Subtotal (95% CI)	60	60		3.1	0.29 [0.06, 1.32]
Total events: 2 (Treatment), 7 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.60 p=0.1					
03 Unclassified/mixed					
Caribbean Is.1990	5/78	11/76		4.9	0.44 [0.16, 1.21]
Hong Kong 1990	6/20	10/21		4.3	0.63 [0.28, 1.41]
Israel 1992	6/30	15/30		6.5	0.40 [0.18, 0.89]
Italy 1997	4/50	10/50		4.4	0.40 [0.13, 1.19]
Sudan 2002	3/34	18/36		7.6	0.18 [0.06, 0.55]
Sweden 1984	1/26	0/26		0.2	3.00 [0.13, 70.42]
Sweden 1985	0/86	6/82		2.9	0.07 [0.00, 1.28]
Sweden 1995	9/58	8/59		3.5	1.14 [0.47, 2.76]
UK 1982	3/64	13/62		5.8	0.22 [0.07, 0.75]
UK 1989	5/70	15/74		6.4	0.35 [0.14, 0.92]



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Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
USA 1987	5/92	14/94		6.0	0.36 [0.14, 0.97]
Subtotal (95% CI)	608	610		52.4	0.40 [0.30, 0.55]
Total events: 47 (Treatment), 120 (Control)					
Test for heterogeneity chi-square=12.62 df=10 p=0.25 I^2 =20.7%					
Test for overall effect z=5.79 p<0.00001					
Total (95% CI)	1237	1172		100.0	0.50 [0.41, 0.61]
Total events: 115 (Treatment), 228 (Control)					
Test for heterogeneity chi-square=25.88 df=18 p=0.10 I^2 =30.4%					
Test for overall effect z=6.63 p<0.00001					

Analysis 03.02. Comparison 03 Any antihypertensive drug versus none (subgrouped by gestation at trial entry), Outcome 02 Proteinuria/pre-eclampsia

Review: Antihypertensive drug therapy for mild to moderate hypertension during pregnancy

Comparison: 03 Any antihypertensive drug versus none (subgrouped by gestation at trial entry)

Outcome: 02 Proteinuria/pre-eclampsia

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 Entry < 32 weeks					
Brazil 1985	5/50	10/50		4.2	0.50 [0.18, 1.36]
Brazil 2000a	26/90	27/94		11.0	1.01 [0.64, 1.58]
Italy 1998	29/125	18/118		7.7	1.52 [0.89, 2.59]
South Africa 1991	1/12	5/20		1.6	0.33 [0.04, 2.52]
UK 1976	6/117	5/125		2.0	1.28 [0.40, 4.09]
USA 1979	1/29	3/29		1.2	0.33 [0.04, 3.02]
USA 1987a	5/13	4/12		1.7	1.15 [0.40, 3.31]
USA 1990	30/173	14/90		7.7	1.11 [0.62, 1.99]
Subtotal (95% CI)	609	538		37.1	1.05 [0.81, 1.36]
Total events: 103 (Treatment), 86 (Control)					
Test for heterogeneity chi-square=6.48 df=7 p=0.49 I^2 =0.0%					
Test for overall effect z=0.36 p=0.7					
02 Entry > 32 weeks					
Australia 2001	1/7	3/9		1.1	0.43 [0.06, 3.28]

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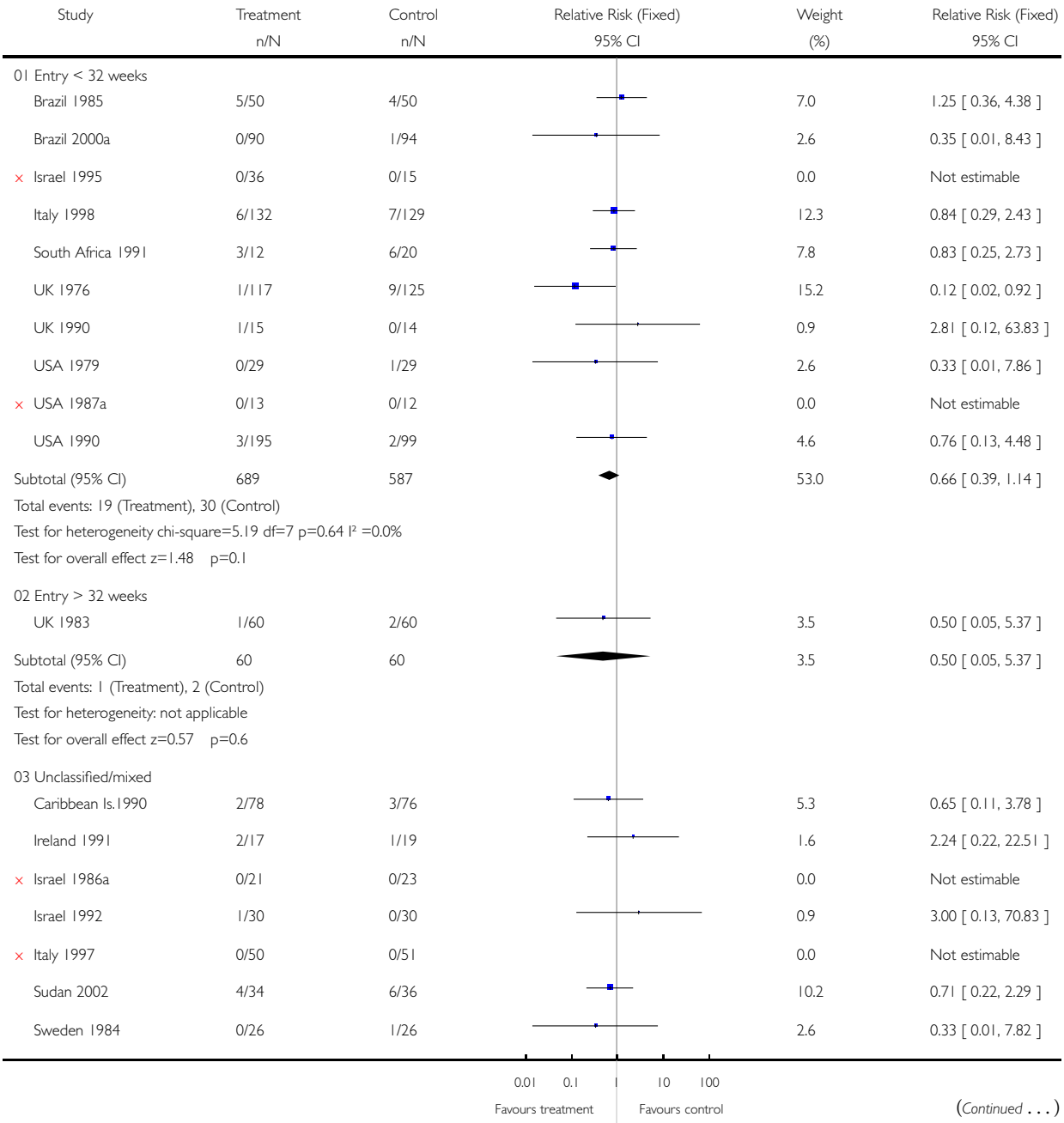
Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
UK 1983	3/51	10/53		4.1	0.31 [0.09, 1.07]
Subtotal (95% CI)	58	62		5.2	0.34 [0.12, 0.96]
Total events: 4 (Treatment), 13 (Control)					
Test for heterogeneity chi-square=0.07 df=1 p=0.79 I^2 =0.0%					
Test for overall effect z=2.03 p=0.04					
03 Unclassified/mixed					
Caribbean Is.1990	7/78	7/76		2.9	0.97 [0.36, 2.65]
Ireland 1991	1/17	6/19		2.4	0.19 [0.02, 1.39]
Israel 1992	1/29	3/28		1.3	0.32 [0.04, 2.91]
Sweden 1984	6/26	6/26		2.5	1.00 [0.37, 2.70]
Sweden 1985	10/86	6/82		2.6	1.59 [0.60, 4.17]
Sweden 1995	18/47	10/54		3.9	2.07 [1.06, 4.03]
UK 1968	15/52	17/48		7.4	0.81 [0.46, 1.44]
UK 1982	4/64	9/62		3.8	0.43 [0.14, 1.33]
UK 1989	31/70	45/74		18.2	0.73 [0.53, 1.00]
UK 1992	13/51	17/63		6.3	0.94 [0.51, 1.76]
USA 1987	10/92	6/94		2.5	1.70 [0.65, 4.49]
USA 1992	16/98	10/99		4.1	1.62 [0.77, 3.38]
Subtotal (95% CI)	710	725		57.8	0.97 [0.79, 1.19]
Total events: 132 (Treatment), 142 (Control)					
Test for heterogeneity chi-square=18.07 df=11 p=0.08 I^2 =39.1%					
Test for overall effect z=0.30 p=0.8					
Total (95% CI)	1377	1325		100.0	0.97 [0.83, 1.13]
Total events: 239 (Treatment), 241 (Control)					
Test for heterogeneity chi-square=28.93 df=21 p=0.12 I^2 =27.4%					
Test for overall effect z=0.42 p=0.7					

Analysis 03.03. Comparison 03 Any antihypertensive drug versus none (subgrouped by gestation at trial entry), Outcome 03 Total reported fetal or neonatal death (including miscarriage)

Review: Antihypertensive drug therapy for mild to moderate hypertension during pregnancy

Comparison: 03 Any antihypertensive drug versus none (subgrouped by gestation at trial entry)

Outcome: 03 Total reported fetal or neonatal death (including miscarriage)



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Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Sweden 1985	3/86	1/82		1.8	2.86 [0.30, 26.95]
× Sweden 1995	0/54	0/57		0.0	Not estimable
UK 1968	6/52	9/48		16.3	0.62 [0.24, 1.60]
× UK 1982	0/64	0/62		0.0	Not estimable
× UK 1989	0/70	0/74		0.0	Not estimable
UK 1992	0/51	2/63		3.9	0.25 [0.01, 5.02]
USA 1987	1/102	0/103		0.9	3.03 [0.12, 73.50]
× USA 1992	0/99	0/101		0.0	Not estimable
Subtotal (95% CI)	834	851		43.5	0.84 [0.48, 1.46]
Total events: 19 (Treatment), 23 (Control)					
Test for heterogeneity chi-square=4.62 df=8 p=0.80 I^2 =0.0%					
Test for overall effect z=0.62 p=0.5					
Total (95% CI)	1583	1498		100.0	0.73 [0.50, 1.08]
Total events: 39 (Treatment), 55 (Control)					
Test for heterogeneity chi-square=9.81 df=17 p=0.91 I^2 =0.0%					
Test for overall effect z=1.58 p=0.1					

Analysis 03.04. Comparison 03 Any antihypertensive drug versus none (subgrouped by gestation at trial entry), Outcome 04 Preterm birth (< 37 weeks)

Review: Antihypertensive drug therapy for mild to moderate hypertension during pregnancy

Comparison: 03 Any antihypertensive drug versus none (subgrouped by gestation at trial entry)

Outcome: 04 Preterm birth (< 37 weeks)

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 Entry < 32 weeks					
Brazil 2000a	17/90	16/94		6.0	1.11 [0.60, 2.06]
Israel 1995	10/36	3/15		1.6	1.39 [0.44, 4.35]
Italy 1998	71/132	77/129		29.8	0.90 [0.73, 1.11]
South Africa 1991	4/12	10/20		2.9	0.67 [0.27, 1.66]
UK 1976	8/100	5/102		1.9	1.63 [0.55, 4.82]
USA 1990	21/173	9/90		4.5	1.21 [0.58, 2.54]
Subtotal (95% CI)	543	450		46.7	0.99 [0.82, 1.20]
Total events: 131 (Treatment), 120 (Control)					
Test for heterogeneity chi-square=3.06 df=5 p=0.69 I^2 =0.0%					
Test for overall effect z=0.10 p=0.9					
02 Entry > 32 weeks					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Treatment), 0 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
03 Unclassified/mixed					
Caribbean Is.1990	11/78	14/76		5.4	0.77 [0.37, 1.58]
Italy 1997	24/50	22/50		8.4	1.09 [0.71, 1.67]
Sudan 2002	6/34	4/36		1.5	1.59 [0.49, 5.14]
Sweden 1984	9/26	10/26		3.8	0.90 [0.44, 1.85]
Sweden 1985	23/86	20/82		7.8	1.10 [0.65, 1.84]
UK 1989	12/70	17/74		6.3	0.75 [0.38, 1.45]
UK 1992	10/51	13/63		4.4	0.95 [0.45, 1.99]
USA 1992	49/98	41/99		15.6	1.21 [0.89, 1.64]
Subtotal (95% CI)	493	506		53.3	1.04 [0.86, 1.26]
Total events: 144 (Treatment), 141 (Control)					
Test for heterogeneity chi-square=3.36 df=7 p=0.85 I^2 =0.0%					
Test for overall effect z=0.41 p=0.7					
Total (95% CI)	1036	956		100.0	1.02 [0.89, 1.16]
Total events: 275 (Treatment), 261 (Control)					
Test for heterogeneity chi-square=6.90 df=13 p=0.91 I^2 =0.0%					
Test for overall effect z=0.24 p=0.8					

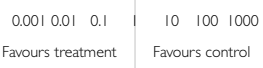
Analysis 03.05. Comparison 03 Any antihypertensive drug versus none (subgrouped by gestation at trial entry), Outcome 05 Small-for-gestational age

Review: Antihypertensive drug therapy for mild to moderate hypertension during pregnancy

Comparison: 03 Any antihypertensive drug versus none (subgrouped by gestation at trial entry)

Outcome: 05 Small-for-gestational age

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 Entry < 32 weeks					
Brazil 1985	3/47	8/47		5.3	0.38 [0.11, 1.33]
Brazil 2000a	12/90	19/94		12.4	0.66 [0.34, 1.28]
Israel 1995	13/36	4/15		3.8	1.35 [0.53, 3.48]
Italy 1998	26/129	32/127		21.5	0.80 [0.51, 1.26]
South Africa 1991	1/10	3/13		1.7	0.43 [0.05, 3.57]
UK 1976	3/100	0/102		0.3	7.14 [0.37, 136.45]
UK 1990	5/15	0/14		0.3	10.31 [0.62, 170.96]
USA 1979	4/29	4/29		2.7	1.00 [0.28, 3.62]
USA 1987a	0/13	3/12		2.4	0.13 [0.01, 2.33]
USA 1990	13/173	8/90		7.0	0.85 [0.36, 1.96]
Subtotal (95% CI)	642	543		57.6	0.84 [0.63, 1.11]
Total events: 80 (Treatment), 81 (Control)					
Test for heterogeneity chi-square=10.21 df=9 p=0.33 I^2 =11.9%					
Test for overall effect z=1.23 p=0.2					
02 Entry > 32 weeks					
UK 1983	9/59	8/58		5.4	1.11 [0.46, 2.67]
Subtotal (95% CI)	59	58		5.4	1.11 [0.46, 2.67]
Total events: 9 (Treatment), 8 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.22 p=0.8					
03 Unclassified/mixed					
Caribbean Is.1990	7/78	9/76		6.1	0.76 [0.30, 1.93]
Hong Kong 1990	3/18	4/20		2.5	0.83 [0.22, 3.23]
Sweden 1985	6/86	4/82		2.7	1.43 [0.42, 4.89]
UK 1982	12/64	11/62		7.5	1.06 [0.50, 2.21]
UK 1989	6/70	1/74		0.6	6.34 [0.78, 51.37]
UK 1992	6/51	5/63		3.0	1.48 [0.48, 4.58]
USA 1987	18/94	9/97		5.9	2.06 [0.98, 4.36]



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Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
USA 1992	15/99	13/101		8.6	1.18 [0.59, 2.34]
Subtotal (95% CI)	560	575		37.0	1.34 [0.97, 1.85]
Total events: 73 (Treatment), 56 (Control)					
Test for heterogeneity chi-square=5.86 df=7 p=0.56 I^2 =0.0%					
Test for overall effect z=1.75 p=0.08					
Total (95% CI)	1261	1176		100.0	1.04 [0.84, 1.27]
Total events: 162 (Treatment), 145 (Control)					
Test for heterogeneity chi-square=20.36 df=18 p=0.31 I^2 =11.6%					
Test for overall effect z=0.33 p=0.7					

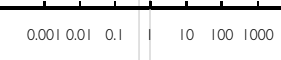
Analysis 04.01. Comparison 04 Any antihypertensive drug versus none (subgrouped by use of placebo), Outcome 01 Severe hypertension

Review: Antihypertensive drug therapy for mild to moderate hypertension during pregnancy

Comparison: 04 Any antihypertensive drug versus none (subgrouped by use of placebo)

Outcome: 01 Severe hypertension

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 Placebo					
Brazil 2000a	9/90	14/94		6.0	0.67 [0.31, 1.47]
Caribbean Is.1990	5/78	11/76		4.9	0.44 [0.16, 1.21]
Hong Kong 1990	6/20	10/21		4.3	0.63 [0.28, 1.41]
Israel 1992	6/30	15/30		6.5	0.40 [0.18, 0.89]
South Africa 1991	0/12	11/20		3.8	0.07 [0.00, 1.09]
Sweden 1984	1/26	0/26		0.2	3.00 [0.13, 70.42]
Sweden 1995	9/58	8/59		3.5	1.14 [0.47, 2.76]
UK 1983	2/60	7/60		3.1	0.29 [0.06, 1.32]
UK 1989	5/70	15/74		6.4	0.35 [0.14, 0.92]
UK 1990	0/16	2/17		1.1	0.21 [0.01, 4.10]
Subtotal (95% CI)	460	477		39.7	0.50 [0.36, 0.69]
Total events: 43 (Treatment), 93 (Control)					
Test for heterogeneity chi-square=9.19 df=9 p=0.42 I^2 =2.1%					
Test for overall effect z=4.15 p=0.00003					



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Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
02 No placebo					
Italy 1997	4/50	10/50		4.4	0.40 [0.13, 1.19]
Italy 1998	36/132	39/129		17.2	0.90 [0.62, 1.32]
Sudan 2002	3/34	18/36		7.6	0.18 [0.06, 0.55]
Sweden 1985	0/86	6/82		2.9	0.07 [0.00, 1.28]
UK 1976	9/117	22/123		9.4	0.43 [0.21, 0.90]
UK 1982	3/64	13/62		5.8	0.22 [0.07, 0.75]
USA 1979	2/29	3/29		1.3	0.67 [0.12, 3.70]
USA 1987	5/92	14/94		6.0	0.36 [0.14, 0.97]
USA 1990	10/173	10/90		5.7	0.52 [0.22, 1.20]
Subtotal (95% CI)	777	695		60.3	0.50 [0.39, 0.65]
Total events: 72 (Treatment), 135 (Control)					
Test for heterogeneity chi-square=16.67 df=8 p=0.03 I^2 =52.0%					
Test for overall effect z=5.16 p<0.00001					
Total (95% CI)	1237	1172		100.0	0.50 [0.41, 0.61]
Total events: 115 (Treatment), 228 (Control)					
Test for heterogeneity chi-square=25.88 df=18 p=0.10 I^2 =30.4%					
Test for overall effect z=6.63 p<0.00001					

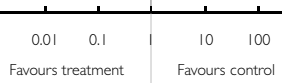
Analysis 04.02. Comparison 04 Any antihypertensive drug versus none (subgrouped by use of placebo), Outcome 02 Proteinuria/pre-eclampsia

Review: Antihypertensive drug therapy for mild to moderate hypertension during pregnancy

Comparison: 04 Any antihypertensive drug versus none (subgrouped by use of placebo)

Outcome: 02 Proteinuria/pre-eclampsia

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 Placebo					
Australia 2001	1/7	3/9		1.1	0.43 [0.06, 3.28]
Brazil 2000a	26/90	27/94		11.0	1.01 [0.64, 1.58]
Caribbean Is.1990	7/78	7/76		2.9	0.97 [0.36, 2.65]
Israel 1992	1/29	3/28		1.3	0.32 [0.04, 2.91]
South Africa 1991	1/12	5/20		1.6	0.33 [0.04, 2.52]
Sweden 1984	6/26	6/26		2.5	1.00 [0.37, 2.70]
Sweden 1995	18/47	10/54		3.9	2.07 [1.06, 4.03]
UK 1983	3/51	10/53		4.1	0.31 [0.09, 1.07]
UK 1989	31/70	45/74		18.2	0.73 [0.53, 1.00]
USA 1987a	5/13	4/12		1.7	1.15 [0.40, 3.31]
Subtotal (95% CI)	423	446		48.2	0.88 [0.71, 1.09]
Total events: 99 (Treatment), 120 (Control)					
Test for heterogeneity chi-square=13.23 df=9 p=0.15 I^2 =32.0%					
Test for overall effect z=1.17 p=0.2					
02 No placebo					
Brazil 1985	5/50	10/50		4.2	0.50 [0.18, 1.36]
Ireland 1991	1/17	6/19		2.4	0.19 [0.02, 1.39]
Italy 1998	29/125	18/118		7.7	1.52 [0.89, 2.59]
Sweden 1985	10/86	6/82		2.6	1.59 [0.60, 4.17]
UK 1968	15/52	17/48		7.4	0.81 [0.46, 1.44]
UK 1976	6/117	5/125		2.0	1.28 [0.40, 4.09]
UK 1982	4/64	9/62		3.8	0.43 [0.14, 1.33]
UK 1992	13/51	17/63		6.3	0.94 [0.51, 1.76]
USA 1979	1/29	3/29		1.2	0.33 [0.04, 3.02]
USA 1987	10/92	6/94		2.5	1.70 [0.65, 4.49]
USA 1990	30/173	14/90		7.7	1.11 [0.62, 1.99]
USA 1992	16/98	10/99		4.1	1.62 [0.77, 3.38]



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Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Subtotal (95% CI)	954	879		51.8	1.05 [0.84, 1.31]
Total events: 140 (Treatment), 121 (Control)					
Test for heterogeneity chi-square=14.26 df=11 p=0.22 I^2 =22.9%					
Test for overall effect z=0.42 p=0.7					
Total (95% CI)	1377	1325		100.0	0.97 [0.83, 1.13]
Total events: 239 (Treatment), 241 (Control)					
Test for heterogeneity chi-square=28.93 df=21 p=0.12 I^2 =27.4%					
Test for overall effect z=0.42 p=0.7					

Analysis 04.03. Comparison 04 Any antihypertensive drug versus none (subgrouped by use of placebo), Outcome 03 Total reported fetal or neonatal death (including miscarriage)

Review: Antihypertensive drug therapy for mild to moderate hypertension during pregnancy

Comparison: 04 Any antihypertensive drug versus none (subgrouped by use of placebo)

Outcome: 03 Total reported fetal or neonatal death (including miscarriage)

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 Placebo					
Brazil 2000a	0/90	1/94		2.6	0.35 [0.01, 8.43]
Caribbean Is.1990	2/78	3/76		5.3	0.65 [0.11, 3.78]
Israel 1992	1/30	0/30		0.9	3.00 [0.13, 70.83]
South Africa 1991	3/12	6/20		7.8	0.83 [0.25, 2.73]
Sweden 1984	0/26	1/26		2.6	0.33 [0.01, 7.82]
× Sweden 1995	0/54	0/57		0.0	Not estimable
UK 1983	1/60	2/60		3.5	0.50 [0.05, 5.37]
× UK 1989	0/70	0/74		0.0	Not estimable
UK 1990	1/15	0/14		0.9	2.81 [0.12, 63.83]
× USA 1987a	0/13	0/12		0.0	Not estimable
Subtotal (95% CI)	448	463		23.6	0.79 [0.37, 1.69]
Total events: 8 (Treatment), 13 (Control)					
Test for heterogeneity chi-square=2.06 df=6 p=0.91 I^2 =0.0%					
Test for overall effect z=0.61 p=0.5					
02 No placebo					

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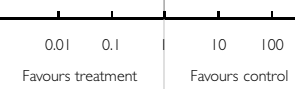
Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Brazil 1985	5/50	4/50		7.0	1.25 [0.36, 4.38]
Ireland 1991	2/17	1/19		1.6	2.24 [0.22, 22.51]
× Israel 1986a	0/21	0/23		0.0	Not estimable
× Israel 1995	0/36	0/15		0.0	Not estimable
× Italy 1997	0/50	0/51		0.0	Not estimable
Italy 1998	6/132	7/129		12.3	0.84 [0.29, 2.43]
Sudan 2002	4/34	6/36		10.2	0.71 [0.22, 2.29]
Sweden 1985	3/86	1/82		1.8	2.86 [0.30, 26.95]
UK 1968	6/52	9/48		16.3	0.62 [0.24, 1.60]
UK 1976	1/117	9/125		15.2	0.12 [0.02, 0.92]
× UK 1982	0/64	0/62		0.0	Not estimable
UK 1992	0/51	2/63		3.9	0.25 [0.01, 5.02]
USA 1979	0/29	1/29		2.6	0.33 [0.01, 7.86]
USA 1987	1/102	0/103		0.9	3.03 [0.12, 73.50]
USA 1990	3/195	2/99		4.6	0.76 [0.13, 4.48]
× USA 1992	0/99	0/101		0.0	Not estimable
Subtotal (95% CI)	1135	1035		76.4	0.72 [0.46, 1.12]
Total events: 31 (Treatment), 42 (Control)					
Test for heterogeneity chi-square=7.78 df=10 p=0.65 I^2 =0.0%					
Test for overall effect z=1.47 p=0.1					
Total (95% CI)	1583	1498		100.0	0.73 [0.50, 1.08]
Total events: 39 (Treatment), 55 (Control)					
Test for heterogeneity chi-square=9.81 df=17 p=0.91 I^2 =0.0%					
Test for overall effect z=1.58 p=0.1					



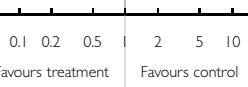
Analysis 04.04. Comparison 04 Any antihypertensive drug versus none (subgrouped by use of placebo), Outcome 04 Preterm birth (< 37 weeks)

Review: Antihypertensive drug therapy for mild to moderate hypertension during pregnancy

Comparison: 04 Any antihypertensive drug versus none (subgrouped by use of placebo)

Outcome: 04 Preterm birth (< 37 weeks)

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 Placebo					
Brazil 2000a	17/90	16/94		6.0	1.11 [0.60, 2.06]
Caribbean Is.1990	11/78	14/76		5.4	0.77 [0.37, 1.58]
South Africa 1991	4/12	10/20		2.9	0.67 [0.27, 1.66]
Sweden 1984	9/26	10/26		3.8	0.90 [0.44, 1.85]
UK 1989	12/70	17/74		6.3	0.75 [0.38, 1.45]
Subtotal (95% CI)	276	290		24.4	0.85 [0.62, 1.17]
Total events: 53 (Treatment), 67 (Control)					
Test for heterogeneity chi-square=1.24 df=4 p=0.87 I^2 =0.0%					
Test for overall effect z=0.97 p=0.3					
02 No placebo					
Israel 1995	10/36	3/15		1.6	1.39 [0.44, 4.35]
Italy 1997	24/50	22/50		8.4	1.09 [0.71, 1.67]
Italy 1998	71/132	77/129		29.8	0.90 [0.73, 1.11]
Sudan 2002	6/34	4/36		1.5	1.59 [0.49, 5.14]
Sweden 1985	23/86	20/82		7.8	1.10 [0.65, 1.84]
UK 1976	8/100	5/102		1.9	1.63 [0.55, 4.82]
UK 1992	10/51	13/63		4.4	0.95 [0.45, 1.99]
USA 1990	21/173	9/90		4.5	1.21 [0.58, 2.54]
USA 1992	49/98	41/99		15.6	1.21 [0.89, 1.64]
Subtotal (95% CI)	760	666		75.6	1.07 [0.92, 1.24]
Total events: 222 (Treatment), 194 (Control)					
Test for heterogeneity chi-square=4.55 df=8 p=0.80 I^2 =0.0%					
Test for overall effect z=0.88 p=0.4					
Total (95% CI)	1036	956		100.0	1.02 [0.89, 1.16]
Total events: 275 (Treatment), 261 (Control)					
Test for heterogeneity chi-square=6.90 df=13 p=0.91 I^2 =0.0%					
Test for overall effect z=0.24 p=0.8					



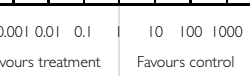
Analysis 04.05. Comparison 04 Any antihypertensive drug versus none (subgrouped by use of placebo), Outcome 05 Small-for-gestational age

Review: Antihypertensive drug therapy for mild to moderate hypertension during pregnancy

Comparison: 04 Any antihypertensive drug versus none (subgrouped by use of placebo)

Outcome: 05 Small-for-gestational age

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 Placebo					
Brazil 2000a	12/90	19/94		12.4	0.66 [0.34, 1.28]
Caribbean Is.1990	7/78	9/76		6.1	0.76 [0.30, 1.93]
Hong Kong 1990	3/18	4/20		2.5	0.83 [0.22, 3.23]
South Africa 1991	1/10	3/13		1.7	0.43 [0.05, 3.57]
UK 1983	9/59	8/58		5.4	1.11 [0.46, 2.67]
UK 1989	6/70	1/74		0.6	6.34 [0.78, 51.37]
UK 1990	5/15	0/14		0.3	10.31 [0.62, 170.96]
USA 1987a	0/13	3/12		2.4	0.13 [0.01, 2.33]
Subtotal (95% CI)	353	361		31.6	0.94 [0.64, 1.38]
Total events: 43 (Treatment), 47 (Control)					
Test for heterogeneity chi-square=9.76 df=7 p=0.20 I^2 =28.3%					
Test for overall effect z=0.33 p=0.7					
02 No placebo					
Brazil 1985	3/47	8/47		5.3	0.38 [0.11, 1.33]
Israel 1995	13/36	4/15		3.8	1.35 [0.53, 3.48]
Italy 1998	26/129	32/127		21.5	0.80 [0.51, 1.26]
Sweden 1985	6/86	4/82		2.7	1.43 [0.42, 4.89]
UK 1976	3/100	0/102		0.3	7.14 [0.37, 136.45]
UK 1982	12/64	11/62		7.5	1.06 [0.50, 2.21]
UK 1992	6/51	5/63		3.0	1.48 [0.48, 4.58]
USA 1979	4/29	4/29		2.7	1.00 [0.28, 3.62]
USA 1987	18/94	9/97		5.9	2.06 [0.98, 4.36]
USA 1990	13/173	8/90		7.0	0.85 [0.36, 1.96]
USA 1992	15/99	13/101		8.6	1.18 [0.59, 2.34]
Subtotal (95% CI)	908	815		68.4	1.08 [0.84, 1.38]
Total events: 119 (Treatment), 98 (Control)					
Test for heterogeneity chi-square=9.94 df=10 p=0.45 I^2 =0.0%					



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Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Test for overall effect z=0.61 p=0.5					
Total (95% CI)	1261	1176		100.0	1.04 [0.84, 1.27]
Total events: 162 (Treatment), 145 (Control)					
Test for heterogeneity chi-square=20.36 df=18 p=0.31 I^2 =11.6%					
Test for overall effect z=0.33 p=0.7					

Analysis 05.01. Comparison 05 Any antihypertensive versus methyldopa (subgrouped by class of drug), Outcome 01 Severe hypertension

Review: Antihypertensive drug therapy for mild to moderate hypertension during pregnancy

Comparison: 05 Any antihypertensive versus methyldopa (subgrouped by class of drug)

Outcome: 01 Severe hypertension

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 Beta blocker versus methyldopa					
Brazil 1988	4/20	9/20		10.9	0.44 [0.16, 1.21]
France 1988	4/42	1/21		1.6	2.00 [0.24, 16.79]
India 1992	2/15	3/15		3.6	0.67 [0.13, 3.44]
Israel 1986	6/16	14/16		16.9	0.43 [0.22, 0.83]
UK 1980	0/14	2/12		3.2	0.17 [0.01, 3.29]
UK 1983a	39/49	36/49		43.6	1.08 [0.87, 1.35]
USA 1990	5/86	5/87		6.0	1.01 [0.30, 3.37]
Venezuela 1988	1/16	5/15		6.2	0.19 [0.02, 1.43]
Subtotal (95% CI)	258	235		92.1	0.79 [0.63, 0.99]
Total events: 61 (Treatment), 75 (Control)					
Test for heterogeneity chi-square=16.39 df=7 p=0.02 I^2 =57.3%					
Test for overall effect z=2.02 p=0.04					
02 Calcium channel blockers versus methyldopa					
Italy 2000	1/10	4/10		4.8	0.25 [0.03, 1.86]
South Africa 1993	0/13	2/13		3.0	0.20 [0.01, 3.80]
Subtotal (95% CI)	23	23		7.9	0.23 [0.04, 1.22]
Total events: 1 (Treatment), 6 (Control)					
Test for heterogeneity chi-square=0.02 df=1 p=0.90 I^2 =0.0%					

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Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Test for overall effect z=1.73 p=0.08					
Total (95% CI)	281	258		100.0	0.75 [0.59, 0.94]
Total events: 62 (Treatment), 81 (Control)					
Test for heterogeneity chi-square=20.52 df=9 p=0.01 I² =56.2%					
Test for overall effect z=2.51 p=0.01					

Analysis 05.02. Comparison 05 Any antihypertensive versus methyldopa (subgrouped by class of drug), Outcome 02 Proteinuria/pre-eclampsia

Review: Antihypertensive drug therapy for mild to moderate hypertension during pregnancy

Comparison: 05 Any antihypertensive versus methyldopa (subgrouped by class of drug)

Outcome: 02 Proteinuria/pre-eclampsia

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 Beta blocker versus methyldopa					
Australia 1983	6/14	4/14		6.9	1.50 [0.54, 4.18]
Australia 1985	4/96	5/87		9.0	0.73 [0.20, 2.61]
Brazil 1988	3/20	4/20		6.9	0.75 [0.19, 2.93]
France 1987	8/91	8/85		14.3	0.93 [0.37, 2.38]
France 1988	7/42	4/21		9.2	0.88 [0.29, 2.66]
Israel 1986	0/8	2/9		4.1	0.22 [0.01, 4.04]
UK 1980	0/14	5/12		10.2	0.08 [0.00, 1.29]
UK 1983a	7/49	7/49		12.1	1.00 [0.38, 2.64]
USA 1990	14/86	16/87		27.4	0.89 [0.46, 1.70]
Total (95% CI)	420	384		100.0	0.81 [0.57, 1.16]
Total events: 49 (Treatment), 55 (Control)					
Test for heterogeneity chi-square=5.19 df=8 p=0.74 I² =0.0%					
Test for overall effect z=1.14 p=0.3					

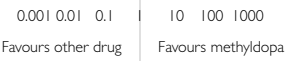
Analysis 05.03. Comparison 05 Any antihypertensive versus methyldopa (subgrouped by class of drug), Outcome 03 Additional antihypertensive

Review: Antihypertensive drug therapy for mild to moderate hypertension during pregnancy

Comparison: 05 Any antihypertensive versus methyldopa (subgrouped by class of drug)

Outcome: 03 Additional antihypertensive

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 Beta blocker versus methyldopa					
Argentina 1988	2/18	4/18		4.2	0.50 [0.10, 2.40]
× Australia 1983	0/14	0/14		0.0	Not estimable
Australia 1985	46/96	30/87		33.2	1.39 [0.97, 1.99]
Brazil 1988	4/20	9/20		9.5	0.44 [0.16, 1.21]
France 1987	12/91	22/85		24.0	0.51 [0.27, 0.96]
France 1988	4/42	1/21		1.4	2.00 [0.24, 16.79]
Israel 1986	6/16	14/16		14.8	0.43 [0.22, 0.83]
UK 1980	0/14	2/12		2.8	0.17 [0.01, 3.29]
UK 1983a	6/48	2/48		2.1	3.00 [0.64, 14.13]
USA 1990	5/86	5/87		5.2	1.01 [0.30, 3.37]
Subtotal (95% CI)	445	408		97.4	0.88 [0.69, 1.13]
Total events: 85 (Treatment), 89 (Control)					
Test for heterogeneity chi-square=20.17 df=8 p=0.010 I^2 =60.3%					
Test for overall effect z=0.97 p=0.3					
02 Calcium channel blocker versus methyldopa					
South Africa 1993	0/13	2/13		2.6	0.20 [0.01, 3.80]
Subtotal (95% CI)	13	13		2.6	0.20 [0.01, 3.80]
Total events: 0 (Treatment), 2 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.07 p=0.3					
Total (95% CI)	458	421		100.0	0.87 [0.68, 1.11]
Total events: 85 (Treatment), 91 (Control)					
Test for heterogeneity chi-square=21.18 df=9 p=0.01 I^2 =57.5%					
Test for overall effect z=1.14 p=0.3					

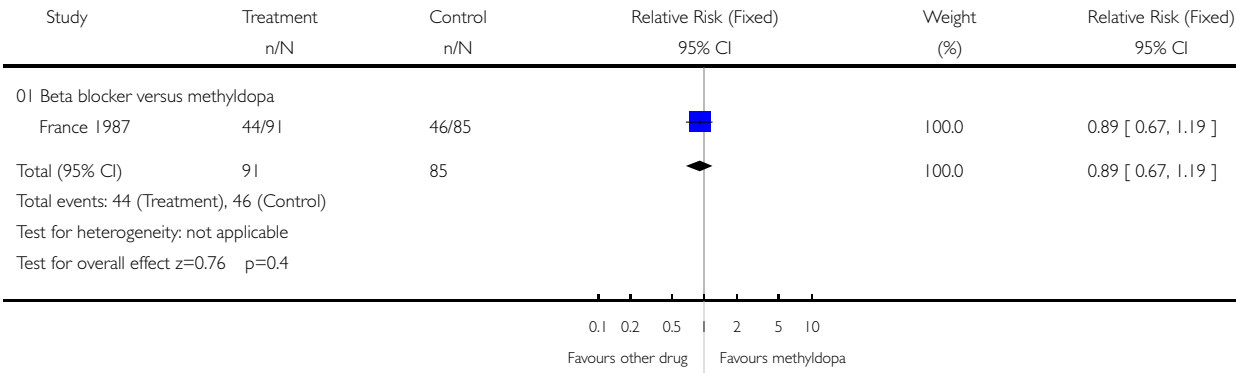


Analysis 05.04. Comparison 05 Any antihypertensive versus methyldopa (subgrouped by class of drug), Outcome 04 Antenatal hospital admission

Review: Antihypertensive drug therapy for mild to moderate hypertension during pregnancy

Comparison: 05 Any antihypertensive versus methyldopa (subgrouped by class of drug)

Outcome: 04 Antenatal hospital admission

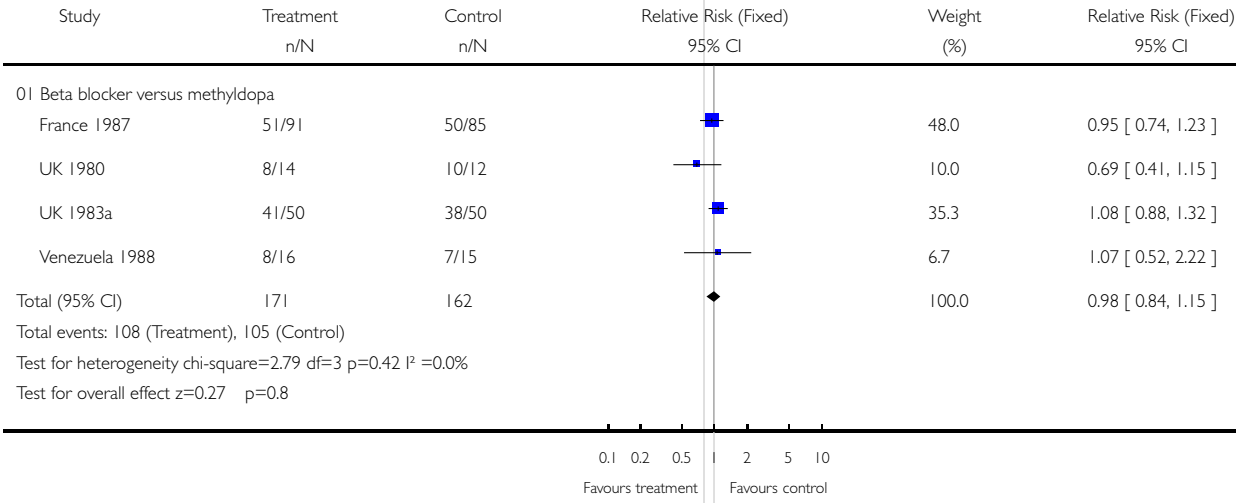


Analysis 05.05. Comparison 05 Any antihypertensive versus methyldopa (subgrouped by class of drug), Outcome 05 Elective delivery (induction of labour + elective caesarean section)

Review: Antihypertensive drug therapy for mild to moderate hypertension during pregnancy

Comparison: 05 Any antihypertensive versus methyldopa (subgrouped by class of drug)

Outcome: 05 Elective delivery (induction of labour + elective caesarean section)

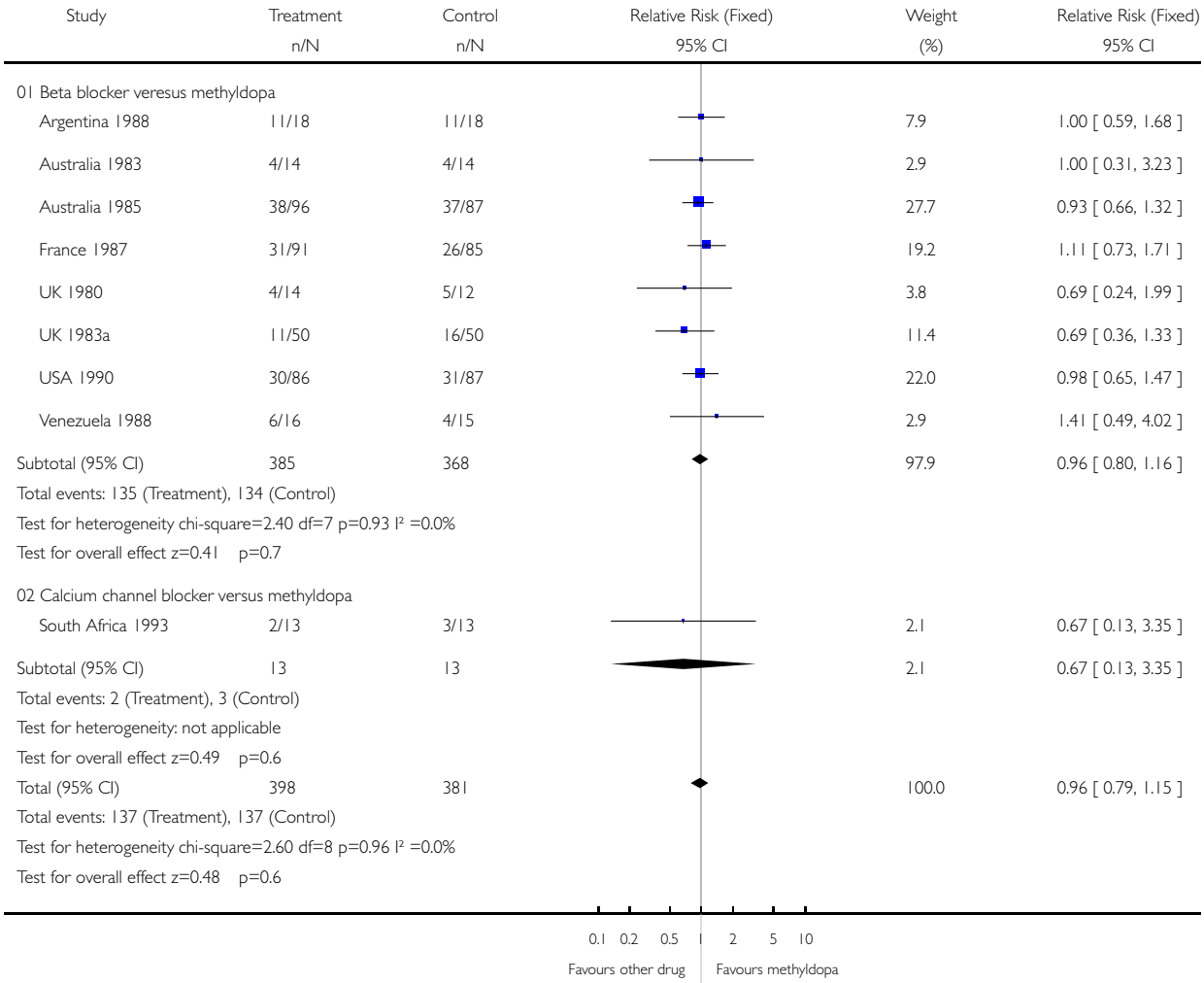


Analysis 05.06. Comparison 05 Any antihypertensive versus methyldopa (subgrouped by class of drug), Outcome 06 Caesarean section

Review: Antihypertensive drug therapy for mild to moderate hypertension during pregnancy

Comparison: 05 Any antihypertensive versus methyldopa (subgrouped by class of drug)

Outcome: 06 Caesarean section



Analysis 05.07. Comparison 05 Any antihypertensive versus methyldopa (subgrouped by class of drug), Outcome 07 Maternal side-effects

Review: Antihypertensive drug therapy for mild to moderate hypertension during pregnancy

Comparison: 05 Any antihypertensive versus methyldopa (subgrouped by class of drug)

Outcome: 07 Maternal side-effects

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 Beta blocker versus methyldopa					
× Argentina 1988	0/18	0/18		0.0	Not estimable
Australia 1983	0/14	11/14		60.4	0.04 [0.00, 0.67]
× Israel 1986	0/16	0/16		0.0	Not estimable
UK 1980	1/14	7/12		39.6	0.12 [0.02, 0.86]
Total (95% CI)	62	60		100.0	0.07 [0.02, 0.37]
Total events: 1 (Treatment), 18 (Control)					
Test for heterogeneity chi-square=0.40 df=1 p=0.53 I^2 =0.0%					
Test for overall effect z=3.17 p=0.002					

Analysis 05.08. Comparison 05 Any antihypertensive versus methyldopa (subgrouped by class of drug), Outcome 08 Changed/stopped drugs due to maternal side-effects

Review: Antihypertensive drug therapy for mild to moderate hypertension during pregnancy

Comparison: 05 Any antihypertensive versus methyldopa (subgrouped by class of drug)

Outcome: 08 Changed/stopped drugs due to maternal side-effects

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 Beta blocker versus methyldopa					
× Argentina 1988	0/18	0/18		0.0	Not estimable
× Australia 1983	0/14	0/14		0.0	Not estimable
France 1987	1/91	0/85		100.0	2.80 [0.12, 67.91]
× Israel 1986	0/16	0/16		0.0	Not estimable
Total (95% CI)	139	133		100.0	2.80 [0.12, 67.91]
Total events: 1 (Treatment), 0 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.63 p=0.5					

Analysis 05.09. Comparison 05 Any antihypertensive versus methyldopa (subgrouped by class of drug), Outcome 09 Placental abruption

Review: Antihypertensive drug therapy for mild to moderate hypertension during pregnancy

Comparison: 05 Any antihypertensive versus methyldopa (subgrouped by class of drug)

Outcome: 09 Placental abruption

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 Beta blocker versus methyldopa					
USA 1990	2/86	1/87		100.0	2.02 [0.19, 21.90]
Total (95% CI)	86	87		100.0	2.02 [0.19, 21.90]
Total events: 2 (Treatment), 1 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.58 p=0.6					

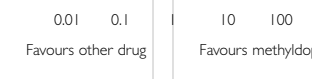
Analysis 05.10. Comparison 05 Any antihypertensive versus methyldopa (subgrouped by class of drug), Outcome 10 Total reported fetal or neonatal death (including miscarriage)

Review: Antihypertensive drug therapy for mild to moderate hypertension during pregnancy

Comparison: 05 Any antihypertensive versus methyldopa (subgrouped by class of drug)

Outcome: 10 Total reported fetal or neonatal death (including miscarriage)

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 Beta blocker versus methyldopa					
Argentina 1985	2/30	1/30		3.9	2.00 [0.19, 20.90]
Argentina 1988	1/18	1/18		3.9	1.00 [0.07, 14.79]
× Australia 1983	0/14	0/14		0.0	Not estimable
Australia 1985	1/96	4/87		16.5	0.23 [0.03, 1.99]
Brazil 1988	4/20	2/20		7.9	2.00 [0.41, 9.71]
France 1987	1/91	4/85		16.3	0.23 [0.03, 2.05]
France 1988	1/42	1/21		5.3	0.50 [0.03, 7.60]
India 1992	1/16	3/15		12.2	0.31 [0.04, 2.68]
Israel 1986	1/16	1/16		3.9	1.00 [0.07, 14.64]
× UK 1980	0/14	0/12		0.0	Not estimable
UK 1983a	1/50	1/50		3.9	1.00 [0.06, 15.55]
× UK 1984	0/30	0/30		0.0	Not estimable



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Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
USA 1990	1/97	2/98		7.8	0.51 [0.05, 5.48]
Venezuela 1988	1/16	1/15		4.1	0.94 [0.06, 13.68]
Subtotal (95% CI)	550	511		85.8	0.67 [0.35, 1.26]
Total events: 15 (Treatment), 21 (Control)					
Test for heterogeneity chi-square=5.44 df=10 p=0.86 I^2 =0.0%					
Test for overall effect z=1.24 p=0.2					
02 Calcium channel blocker versus methyldopa					
× Italy 2000	0/10	0/10		0.0	Not estimable
South Africa 1993	1/15	3/14		12.2	0.31 [0.04, 2.65]
Subtotal (95% CI)	25	24		12.2	0.31 [0.04, 2.65]
Total events: 1 (Treatment), 3 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.07 p=0.3					
03 Ketanserin versus methyldopa					
Argentina 1987	1/10	0/10		2.0	3.00 [0.14, 65.90]
Subtotal (95% CI)	10	10		2.0	3.00 [0.14, 65.90]
Total events: 1 (Treatment), 0 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.70 p=0.5					
Total (95% CI)	585	545		100.0	0.67 [0.37, 1.21]
Total events: 17 (Treatment), 24 (Control)					
Test for heterogeneity chi-square=6.83 df=12 p=0.87 I^2 =0.0%					
Test for overall effect z=1.33 p=0.2					

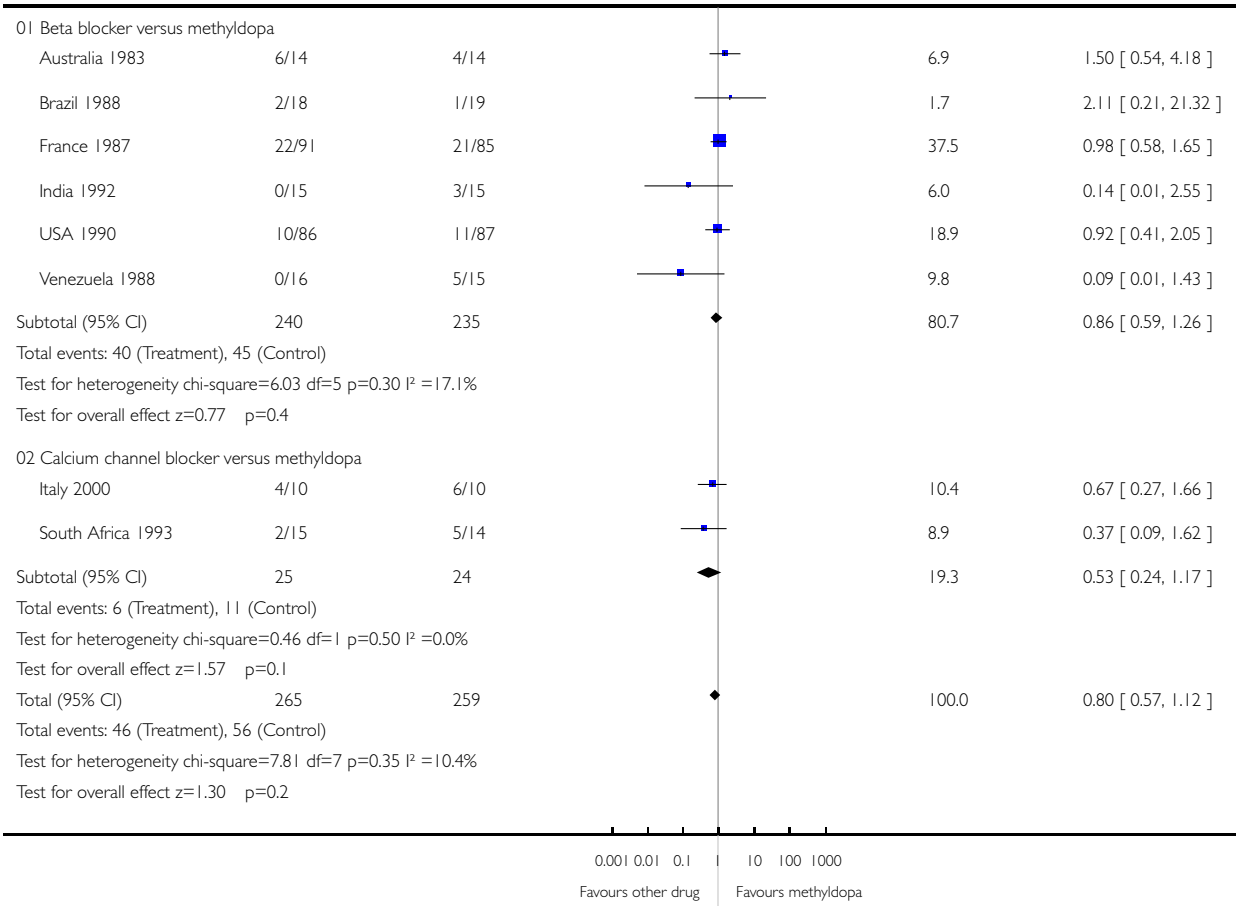
Analysis 05.11. Comparison 05 Any antihypertensive versus methyldopa (subgrouped by class of drug), Outcome 11 Preterm birth (< 37 weeks)

Review: Antihypertensive drug therapy for mild to moderate hypertension during pregnancy

Comparison: 05 Any antihypertensive versus methyldopa (subgrouped by class of drug)

Outcome: 11 Preterm birth (< 37 weeks)

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 Beta blocker versus methyldopa					
Australia 1983	6/14	4/14		6.9	1.50 [0.54, 4.18]
Brazil 1988	2/18	1/19		1.7	2.11 [0.21, 21.32]
France 1987	22/91	21/85		37.5	0.98 [0.58, 1.65]
India 1992	0/15	3/15		6.0	0.14 [0.01, 2.55]
USA 1990	10/86	11/87		18.9	0.92 [0.41, 2.05]
Venezuela 1988	0/16	5/15		9.8	0.09 [0.01, 1.43]
Subtotal (95% CI)	240	235		80.7	0.86 [0.59, 1.26]
Total events: 40 (Treatment), 45 (Control)					
Test for heterogeneity chi-square=6.03 df=5 p=0.30 I^2 =17.1%					
Test for overall effect z=0.77 p=0.4					
02 Calcium channel blocker versus methyldopa					
Italy 2000	4/10	6/10		10.4	0.67 [0.27, 1.66]
South Africa 1993	2/15	5/14		8.9	0.37 [0.09, 1.62]
Subtotal (95% CI)	25	24		19.3	0.53 [0.24, 1.17]
Total events: 6 (Treatment), 11 (Control)					
Test for heterogeneity chi-square=0.46 df=1 p=0.50 I^2 =0.0%					
Test for overall effect z=1.57 p=0.1					
Total (95% CI)	265	259		100.0	0.80 [0.57, 1.12]
Total events: 46 (Treatment), 56 (Control)					
Test for heterogeneity chi-square=7.81 df=7 p=0.35 I^2 =10.4%					
Test for overall effect z=1.30 p=0.2					



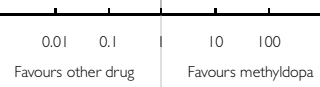
Analysis 05.12. Comparison 05 Any antihypertensive versus methyldopa (subgrouped by class of drug), Outcome 12 Small-for-gestational age

Review: Antihypertensive drug therapy for mild to moderate hypertension during pregnancy

Comparison: 05 Any antihypertensive versus methyldopa (subgrouped by class of drug)

Outcome: 12 Small-for-gestational age

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 Beta blocker versus methyldopa					
Argentina 1988	0/18	1/18		5.3	0.33 [0.01, 7.68]
× Brazil 1988	0/18	0/19		0.0	Not estimable
France 1987	11/91	12/81		45.1	0.82 [0.38, 1.75]
UK 1984	5/30	3/30		10.7	1.67 [0.44, 6.36]
USA 1990	7/86	6/87		21.2	1.18 [0.41, 3.37]
Subtotal (95% CI)	243	235		82.2	0.99 [0.57, 1.70]
Total events: 23 (Treatment), 22 (Control)					
Test for heterogeneity chi-square=1.40 df=3 p=0.71 I² =0.0%					
Test for overall effect z=0.04 p=1					
02 Calcium channel blocker versus methyldopa					
Italy 2000	2/10	5/10		17.8	0.40 [0.10, 1.60]
Subtotal (95% CI)	10	10		17.8	0.40 [0.10, 1.60]
Total events: 2 (Treatment), 5 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.30 p=0.2					
Total (95% CI)	253	245		100.0	0.88 [0.54, 1.46]
Total events: 25 (Treatment), 27 (Control)					
Test for heterogeneity chi-square=2.82 df=4 p=0.59 I² =0.0%					
Test for overall effect z=0.48 p=0.6					

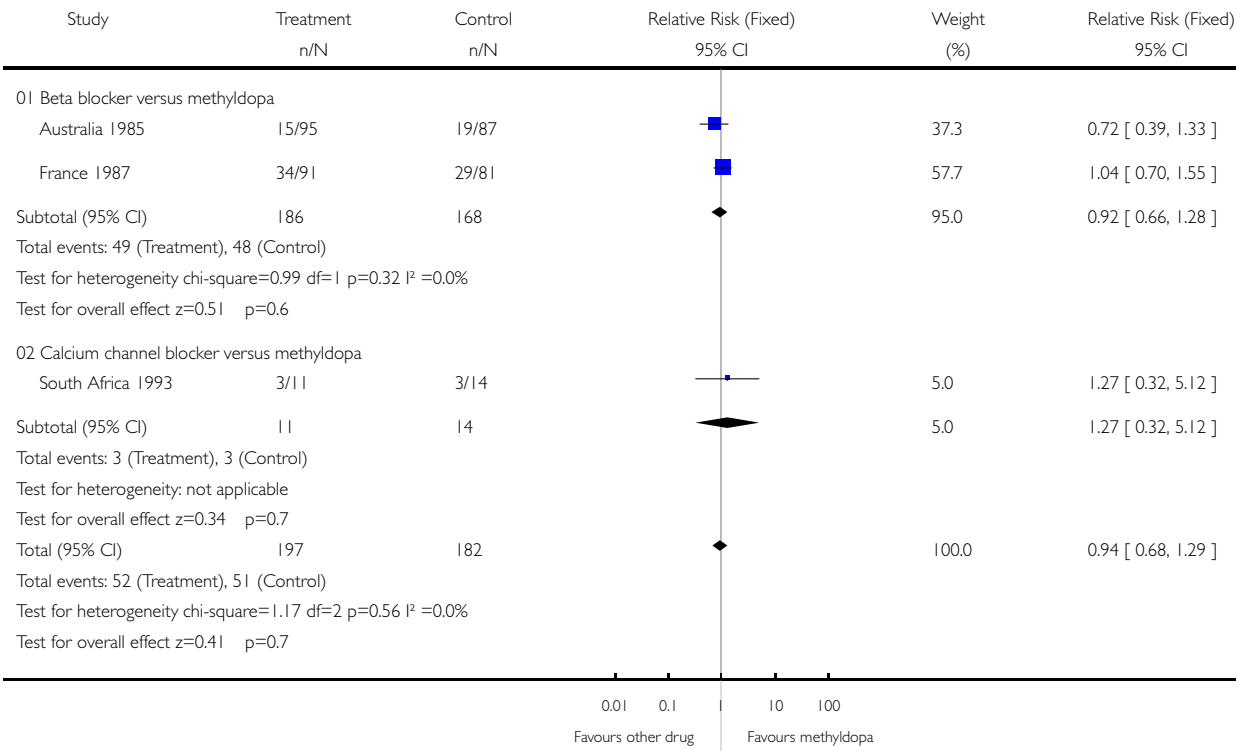


Analysis 05.13. Comparison 05 Any antihypertensive versus methyldopa (subgrouped by class of drug), Outcome 13 Admission to special care baby unit

Review: Antihypertensive drug therapy for mild to moderate hypertension during pregnancy

Comparison: 05 Any antihypertensive versus methyldopa (subgrouped by class of drug)

Outcome: 13 Admission to special care baby unit



Analysis 05.14. Comparison 05 Any antihypertensive versus methyldopa (subgrouped by class of drug), Outcome 14 Neonatal hypoglycaemia

Review: Antihypertensive drug therapy for mild to moderate hypertension during pregnancy

Comparison: 05 Any antihypertensive versus methyldopa (subgrouped by class of drug)

Outcome: 14 Neonatal hypoglycaemia

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 Beta blocker versus methyldopa					
Australia 1983	2/14	0/14		4.3	5.00 [0.26, 95.61]
France 1988	11/41	5/20		57.5	1.07 [0.43, 2.67]
UK 1984	0/30	2/30		21.4	0.20 [0.01, 4.00]
USA 1990	2/85	2/87		16.9	1.02 [0.15, 7.10]
Total (95% CI)	170	151		100.0	1.05 [0.50, 2.18]
Total events: 15 (Treatment), 9 (Control)					
Test for heterogeneity chi-square=2.26 df=3 p=0.52 I^2 =0.0%					
Test for overall effect z=0.12 p=0.9					

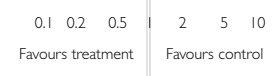
Analysis 05.15. Comparison 05 Any antihypertensive versus methyldopa (subgrouped by class of drug), Outcome 15 Neonatal bradycardia

Review: Antihypertensive drug therapy for mild to moderate hypertension during pregnancy

Comparison: 05 Any antihypertensive versus methyldopa (subgrouped by class of drug)

Outcome: 15 Neonatal bradycardia

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 Beta blocker versus methyldopa					
× Australia 1983	0/14	0/14		0.0	Not estimable
Total (95% CI)	14	14		0.0	Not estimable
Total events: 0 (Treatment), 0 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					

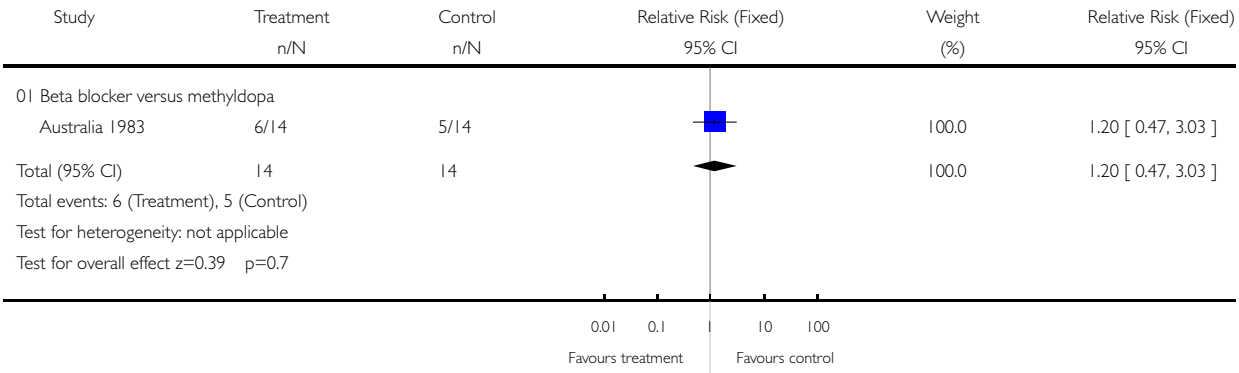


Analysis 05.16. Comparison 05 Any antihypertensive versus methyldopa (subgrouped by class of drug), Outcome 16 Neonatal jaundice

Review: Antihypertensive drug therapy for mild to moderate hypertension during pregnancy

Comparison: 05 Any antihypertensive versus methyldopa (subgrouped by class of drug)

Outcome: 16 Neonatal jaundice

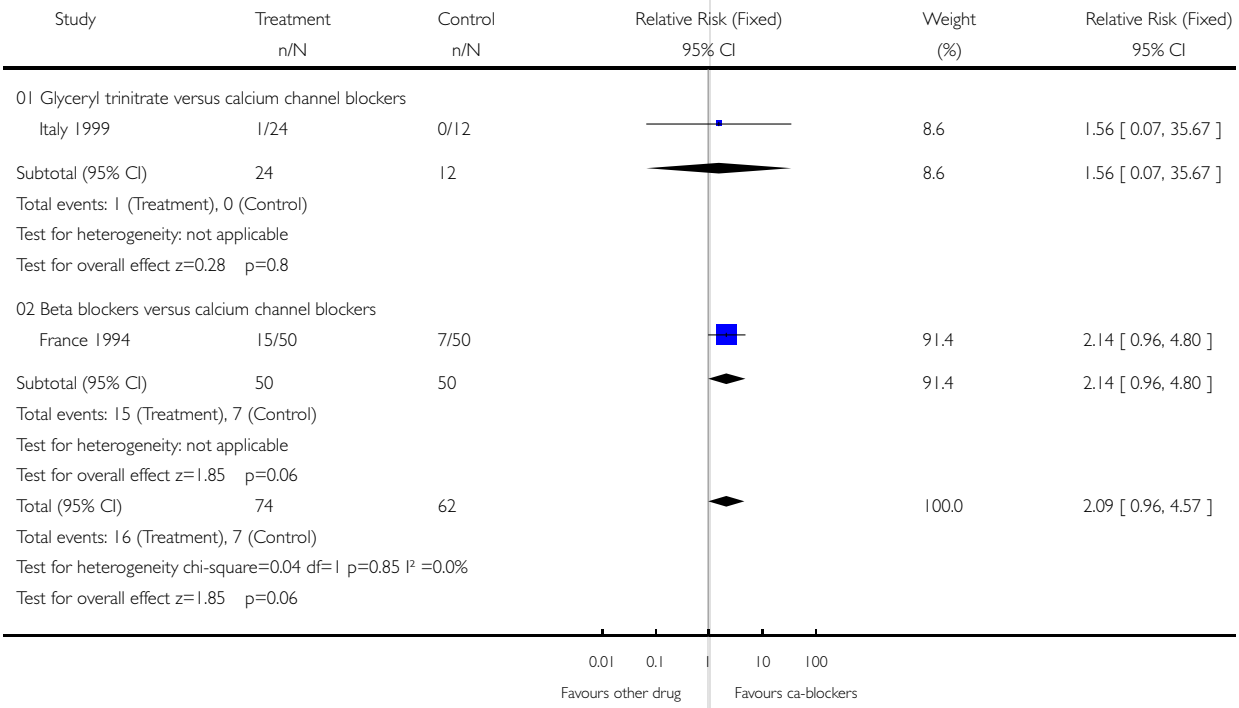


Analysis 06.01. Comparison 06 Any antihypertensive versus calcium channel blocker (subgrouped by class of drug), Outcome 01 Severe hypertension

Review: Antihypertensive drug therapy for mild to moderate hypertension during pregnancy

Comparison: 06 Any antihypertensive versus calcium channel blocker (subgrouped by class of drug)

Outcome: 01 Severe hypertension

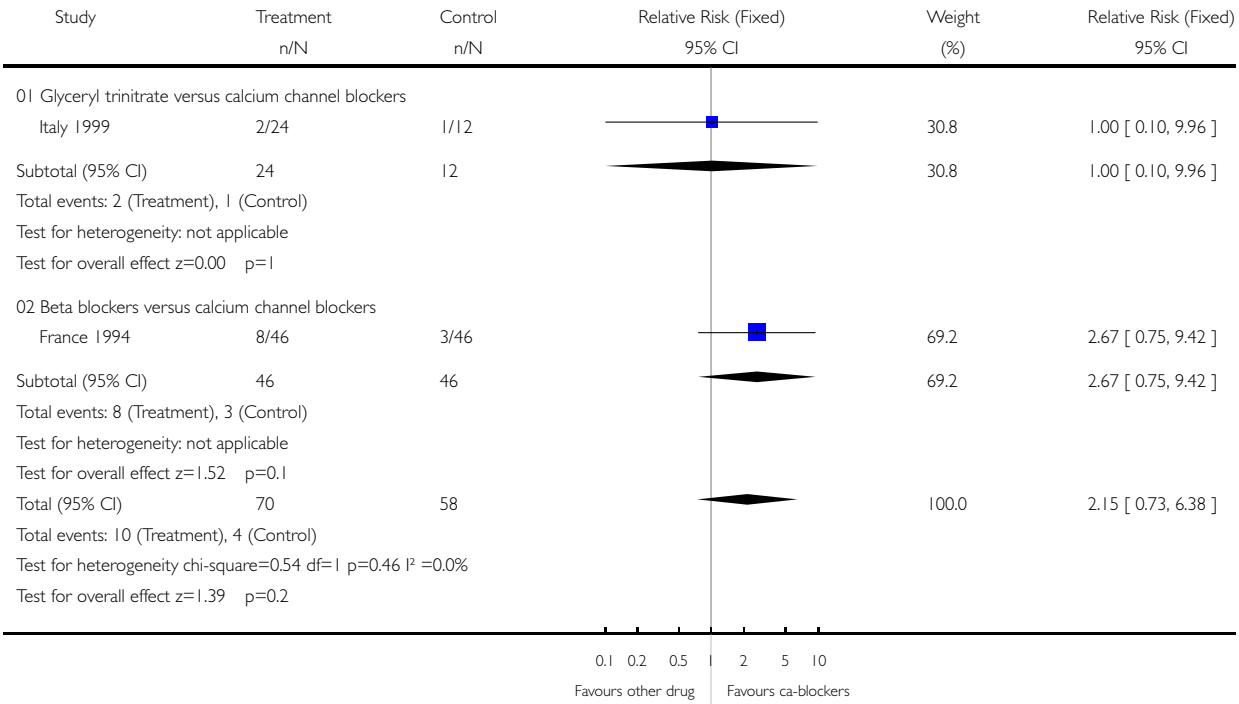


Analysis 06.02. Comparison 06 Any antihypertensive versus calcium channel blocker (subgrouped by class of drug), Outcome 02 Proteinuria/pre-eclampsia

Review: Antihypertensive drug therapy for mild to moderate hypertension during pregnancy

Comparison: 06 Any antihypertensive versus calcium channel blocker (subgrouped by class of drug)

Outcome: 02 Proteinuria/pre-eclampsia

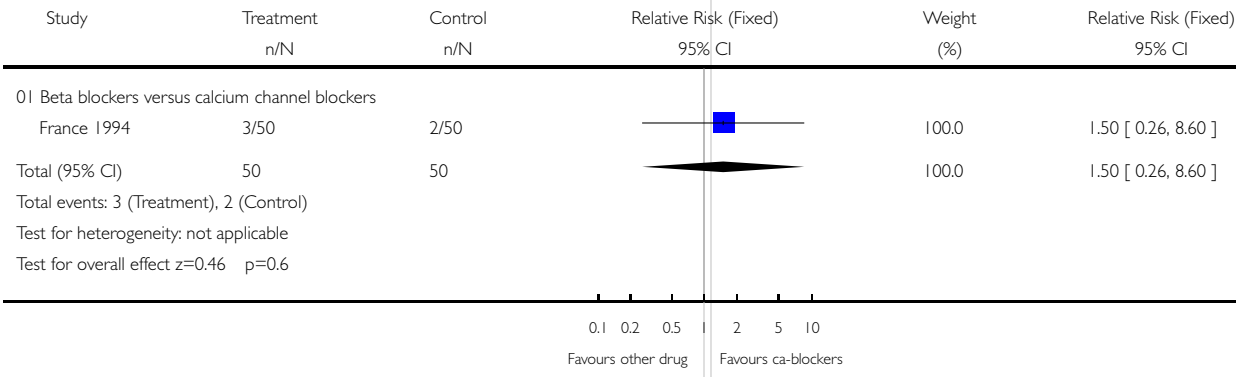


Analysis 06.03. Comparison 06 Any antihypertensive versus calcium channel blocker (subgrouped by class of drug), Outcome 03 HELLP syndrome

Review: Antihypertensive drug therapy for mild to moderate hypertension during pregnancy

Comparison: 06 Any antihypertensive versus calcium channel blocker (subgrouped by class of drug)

Outcome: 03 HELLP syndrome

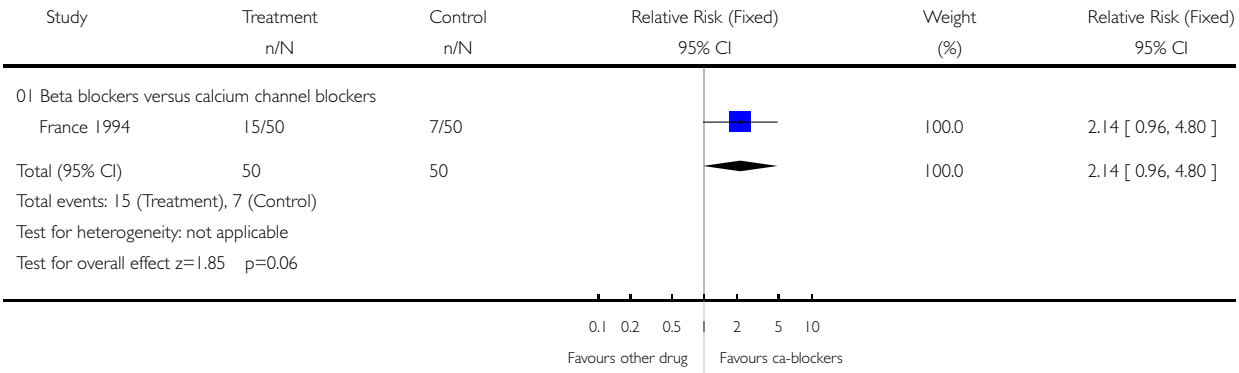


Analysis 06.04. Comparison 06 Any antihypertensive versus calcium channel blocker (subgrouped by class of drug), Outcome 04 Additional antihypertensive

Review: Antihypertensive drug therapy for mild to moderate hypertension during pregnancy

Comparison: 06 Any antihypertensive versus calcium channel blocker (subgrouped by class of drug)

Outcome: 04 Additional antihypertensive

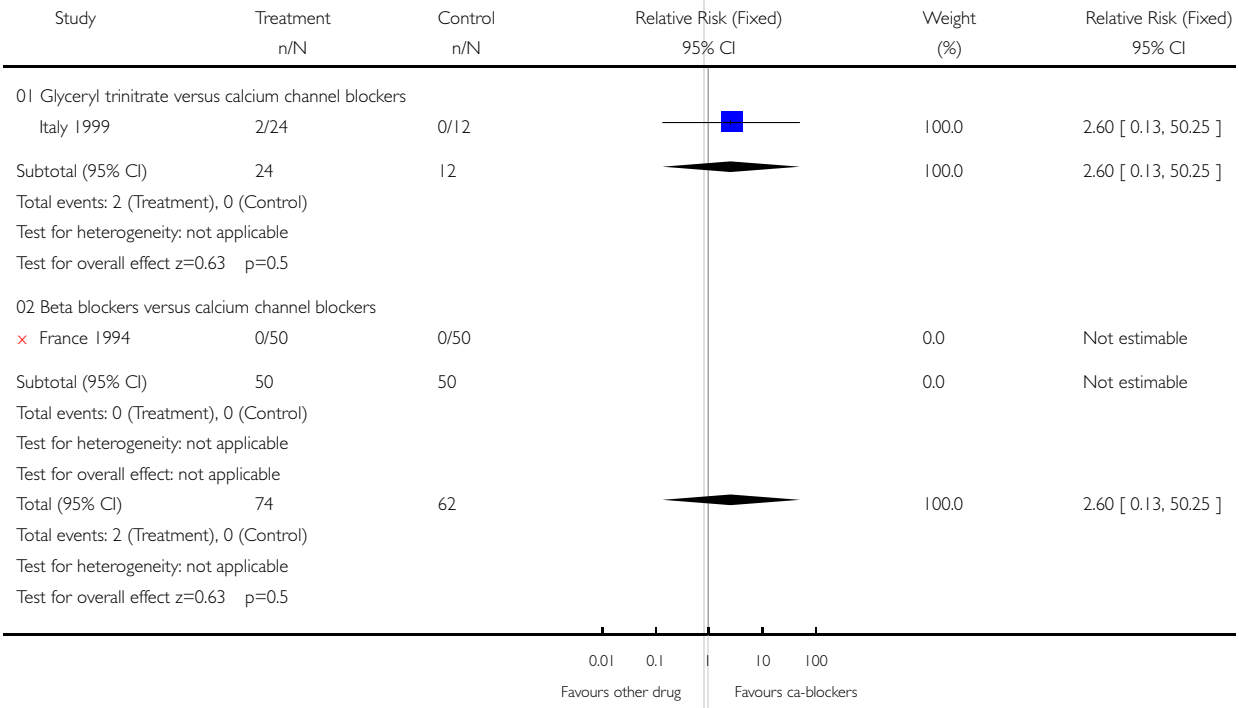


Analysis 06.05. Comparison 06 Any antihypertensive versus calcium channel blocker (subgrouped by class of drug), Outcome 05 Changed/stopped drug due to side-effects

Review: Antihypertensive drug therapy for mild to moderate hypertension during pregnancy

Comparison: 06 Any antihypertensive versus calcium channel blocker (subgrouped by class of drug)

Outcome: 05 Changed/stopped drug due to side-effects

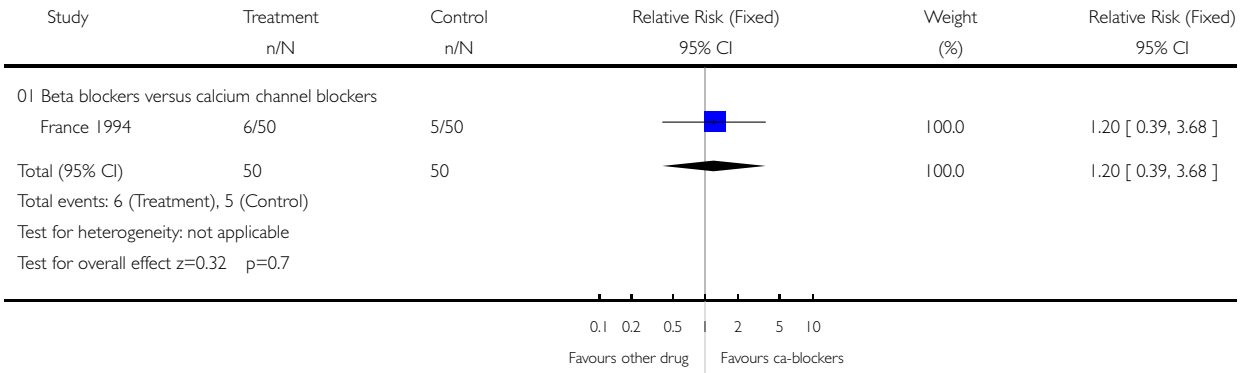


Analysis 06.06. Comparison 06 Any antihypertensive versus calcium channel blocker (subgrouped by class of drug), Outcome 06 Maternal side-effects

Review: Antihypertensive drug therapy for mild to moderate hypertension during pregnancy

Comparison: 06 Any antihypertensive versus calcium channel blocker (subgrouped by class of drug)

Outcome: 06 Maternal side-effects

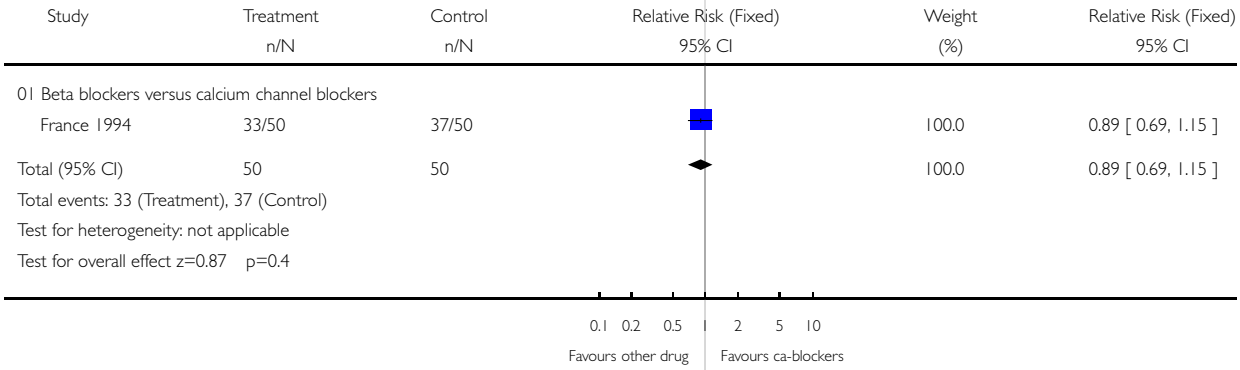


Analysis 06.07. Comparison 06 Any antihypertensive versus calcium channel blocker (subgrouped by class of drug), Outcome 07 Elective delivery (induction of labour + elective caesarean section)

Review: Antihypertensive drug therapy for mild to moderate hypertension during pregnancy

Comparison: 06 Any antihypertensive versus calcium channel blocker (subgrouped by class of drug)

Outcome: 07 Elective delivery (induction of labour + elective caesarean section)

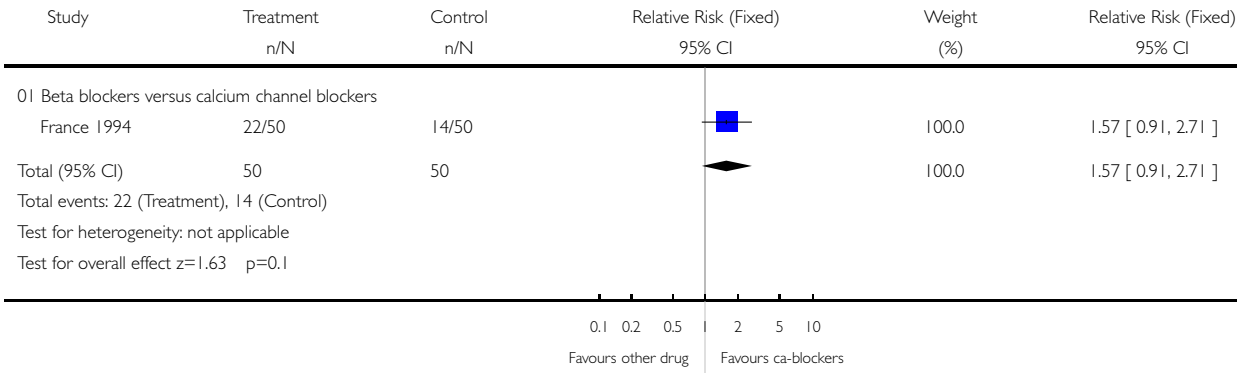


Analysis 06.08. Comparison 06 Any antihypertensive versus calcium channel blocker (subgrouped by class of drug), Outcome 08 Caesarean section

Review: Antihypertensive drug therapy for mild to moderate hypertension during pregnancy

Comparison: 06 Any antihypertensive versus calcium channel blocker (subgrouped by class of drug)

Outcome: 08 Caesarean section

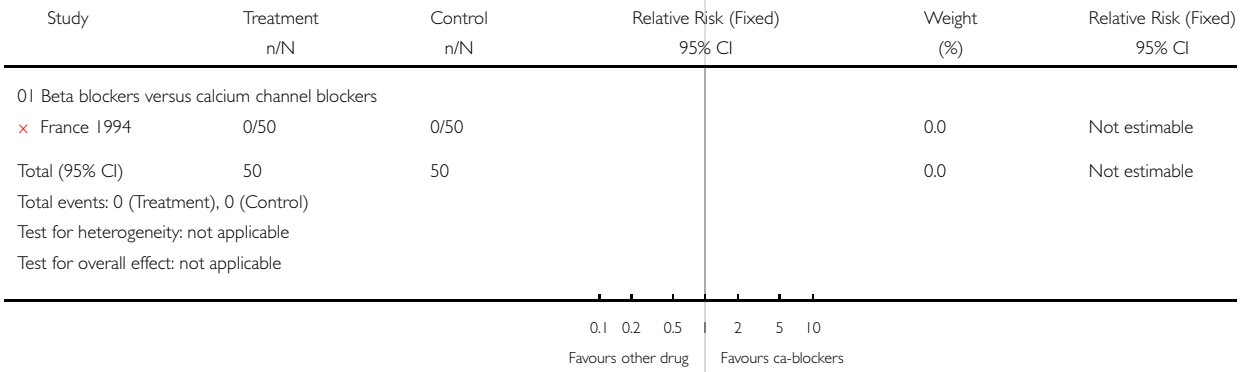


Analysis 06.09. Comparison 06 Any antihypertensive versus calcium channel blocker (subgrouped by class of drug), Outcome 09 Placental abruption

Review: Antihypertensive drug therapy for mild to moderate hypertension during pregnancy

Comparison: 06 Any antihypertensive versus calcium channel blocker (subgrouped by class of drug)

Outcome: 09 Placental abruption

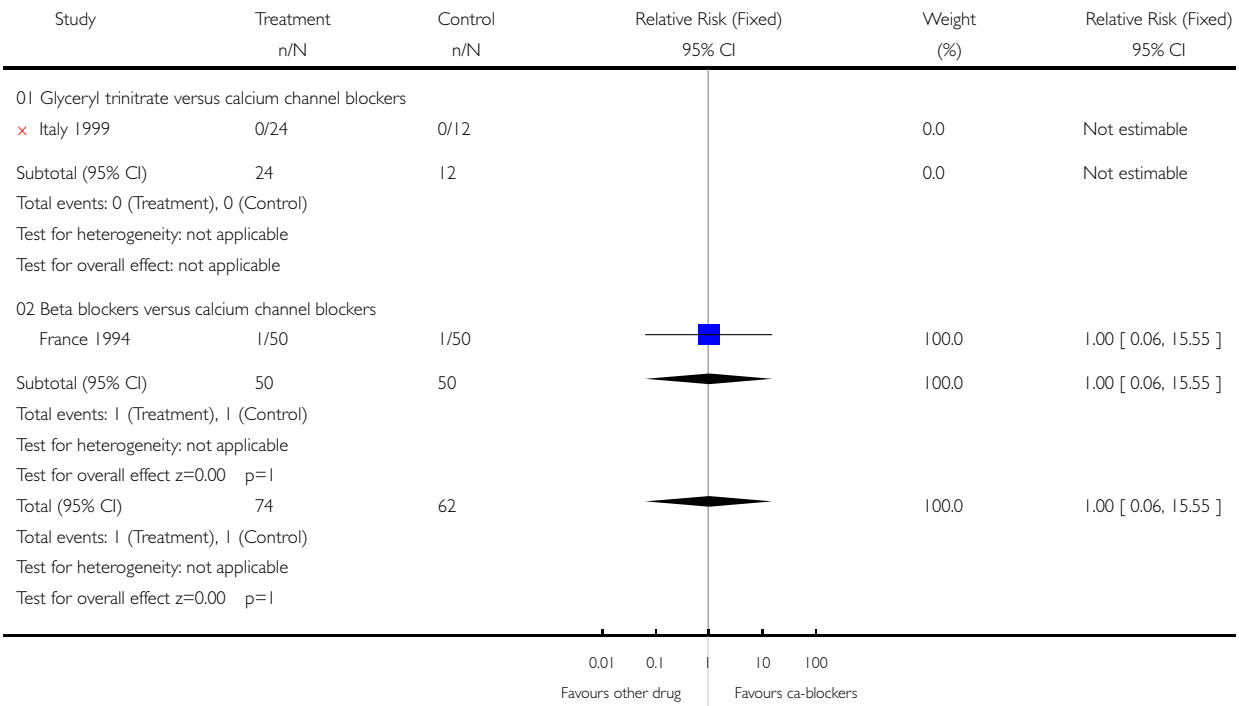


Analysis 06.10. Comparison 06 Any antihypertensive versus calcium channel blocker (subgrouped by class of drug), Outcome 10 Total reported fetal or neonatal death (including miscarriage)

Review: Antihypertensive drug therapy for mild to moderate hypertension during pregnancy

Comparison: 06 Any antihypertensive versus calcium channel blocker (subgrouped by class of drug)

Outcome: 10 Total reported fetal or neonatal death (including miscarriage)

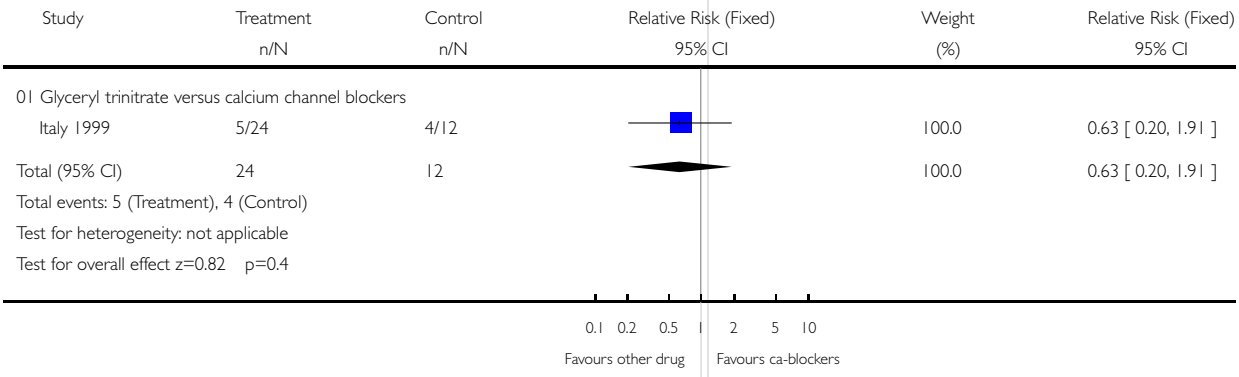


Analysis 06.11. Comparison 06 Any antihypertensive versus calcium channel blocker (subgrouped by class of drug), Outcome 11 Preterm birth (< 37 weeks)

Review: Antihypertensive drug therapy for mild to moderate hypertension during pregnancy

Comparison: 06 Any antihypertensive versus calcium channel blocker (subgrouped by class of drug)

Outcome: 11 Preterm birth (< 37 weeks)

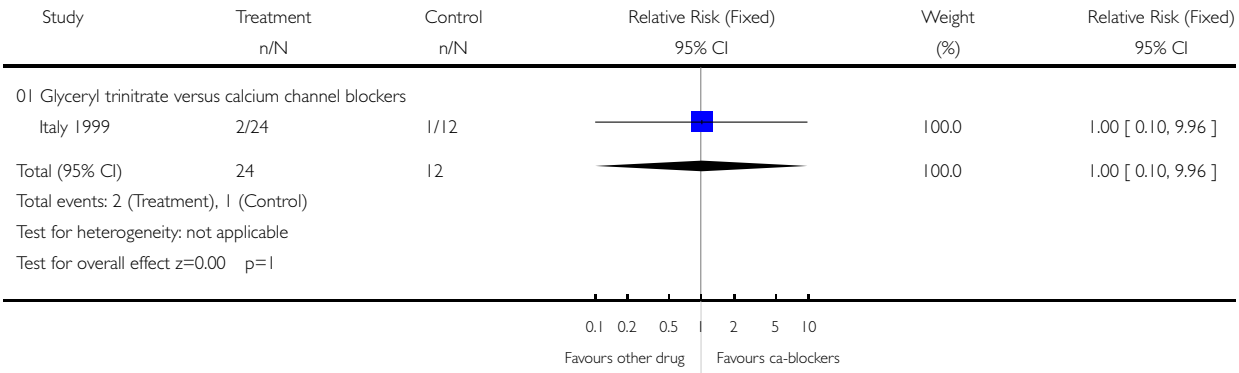


Analysis 06.12. Comparison 06 Any antihypertensive versus calcium channel blocker (subgrouped by class of drug), Outcome 12 Small-for-gestational age

Review: Antihypertensive drug therapy for mild to moderate hypertension during pregnancy

Comparison: 06 Any antihypertensive versus calcium channel blocker (subgrouped by class of drug)

Outcome: 12 Small-for-gestational age



Analysis 06.13. Comparison 06 Any antihypertensive versus calcium channel blocker (subgrouped by class of drug), Outcome 13 Admission to special care baby unit

Review: Antihypertensive drug therapy for mild to moderate hypertension during pregnancy

Comparison: 06 Any antihypertensive versus calcium channel blocker (subgrouped by class of drug)

Outcome: 13 Admission to special care baby unit