Antiplatelet agents for preventing pre-eclampsia and its complications (Review)

Duley L, Henderson-Smart DJ, Meher S, King JF

This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2007, Issue 4

http://www.thecochranelibrary.com

TABLE OF CONTENTS

Antiplatelet agents for preventing pre-eclampsia and its complications (Review)

Duley L, Henderson-Smart DJ, Meher S, King JF

Status: *Commented*

This record should be cited as:
Duley L, Henderson-Smart DJ, Meher S, King JF. Antiplatelet agents for preventing pre-eclampsia and its complications. *Cochrane Database of Systematic Reviews* 2007, Issue 2. Art. No.: CD004659. DOI: 10.1002/14651858.CD004659.pub2.

This version first published online: 18 April 2007 in Issue 2, 2007.
Date of most recent substantive amendment: 07 February 2007

ABSTRACT

Background
Pre-eclampsia is associated with deficient intravascular production of prostacyclin, a vasodilator, and excessive production of thromboxane, a vasoconstrictor and stimulant of platelet aggregation. These observations led to the hypotheses that antiplatelet agents, low-dose aspirin in particular, might prevent or delay development of pre-eclampsia.

Objectives
To assess the effectiveness and safety of antiplatelet agents for women at risk of developing pre-eclampsia.

Search strategy
We searched the Cochrane Pregnancy and Childbirth Group's Trials Register (July 2006), the Cochrane Central Register of Controlled Trials (*The Cochrane Library* 2005, Issue 1), EMBASE (1994 to November 2005) and handsearched congress proceedings of the International and European Societies for the Study of Hypertension in Pregnancy.

Selection criteria
All randomised trials comparing antiplatelet agents with either placebo or no antiplatelet agent were included. Quasi-random studies were excluded. Participants were pregnant women at risk of developing pre-eclampsia. Interventions were any comparisons of an antiplatelet agent (such as low-dose aspirin or dipyridamole) with either placebo or no antiplatelet.

Data collection and analysis
Two authors assessed trials for inclusion and extracted data independently.

Main results
Fifty-nine trials (37,560 women) are included. There is a 17% reduction in the risk of pre-eclampsia associated with the use of antiplatelet agents ((46 trials, 32,891 women, relative risk (RR) 0.83, 95% confidence interval (CI) 0.77 to 0.89), number needed to treat (NNT) 72 (52, 119)). Although there is no statistical difference in RR based on maternal risk, there is a significant increase in the absolute risk reduction of pre-eclampsia for high risk (risk difference (RD) -5.2% (-7.5, -2.9), NNT 19 (13, 34)) compared with moderate risk women (RD -0.84 (-1.37, -0.3), NNT 119 (73, 333)).

Antiplatelets were associated with an 8% reduction in the relative risk of preterm birth (29 trials, 31,151 women, RR 0.92, 95% CI 0.88 to 0.97); NNT 72 (52, 119)), a 14% reduction in fetal or neonatal deaths (40 trials, 33,098 women, RR 0.86, 95% CI 0.76 to 0.98); NNT 243 (131, 1,666) and a 10% reduction in small-for-gestational age babies (36 trials, 23,638 women, RR 0.90, 95% CI0.83 to 0.98). There were no statistically significant differences between treatment and control groups for any other outcomes.

Authors' conclusions
Antiplatelet agents, largely low-dose aspirin, have moderate benefits when used for prevention of pre-eclampsia and its consequences. Further information is required to assess which women are most likely to benefit, when treatment is best started, and at what dose.

PLAIN LANGUAGE SUMMARY

Low doses of aspirin do help prevent pre-eclampsia, and some of its complications

Pre-eclampsia is a condition in pregnancy involving high blood pressure and protein in the urine. It can lead to serious complications. As it affects blood clotting, antiplatelets (drugs like aspirin which can prevent blood clots) are used to prevent pre-eclampsia. The review of 59 trials, involving 37,560 women, found low doses of aspirin reduced the risk of pre-eclampsia by about a sixth (17%), with a similar lowering in the risk of the baby dying (14%) and a small lowering in the risk of being born too early (8%). Doses up to 75 mg appear to be safe. Higher doses might be better, but adverse effects may also increase.

BACKGROUND

Pre-eclampsia is defined as high blood pressure associated with proteinuria (Gifford 1990). It occurs in the second half of pregnancy and complicates between 2% to 8% of pregnancies (WHO 1988). Pre-eclampsia can also affect other maternal organs, leading to problems in liver, kidneys and brain, and to abnormalities of the clotting system. As the placenta also is involved, there are increased risks for the baby. The most common are poor growth due to inadequate blood supply through the damaged placenta, and the problems of prematurity (related either to the spontaneous onset of preterm labour or to early delivery to protect the mother or the fetus). Pre-eclampsia is discussed in more detail in the generic protocol of interventions for preventing pre-eclampsia (Generic Protocol 05).

High blood pressure is common during pregnancy, and around 10% of women will have their blood pressure recorded as above normal at some point before delivery. For women who develop raised blood pressure but have no proteinuria or any other complication, pregnancy outcome is very similar to that for women who have normal blood pressure. Raised blood pressure alone occurring for the first time during pregnancy is known as pregnancy-induced hypertension, or gestational hypertension. One of the difficulties in caring for women with pregnancy-induced hypertension is that it is so common, and there is no reliable way of predicting who will progress to more severe disease. Therefore, very large numbers of these women are admitted to hospital or to day-care units for assessment, or receive antenatal care designed for high-risk women. Women with pregnancy-induced hypertension or mild pre-eclampsia usually feel well. It is only when blood pressure is very high (greater than 170 mmHg systolic or greater than 110 mmHg diastolic) or they develop symptoms of severe pre-eclampsia, such as headache, epigastric pain or visual disturbances, that they may feel unwell.

Although the outcome following pre-eclampsia or eclampsia (the rare occurrence of seizures superimposed on pre-eclampsia) is good for most women, particularly in the developed world, these conditions remain major causes of maternal mortality. Over half a million women die each year of pregnancy related causes, and 99% of these deaths occur in the developing world (Mahler 1987; Rosenfield 1985; WHO 2000). An estimated 10% to 15% of the maternal deaths in developing countries are associated with hypertensive disorders of pregnancy (Duley 1992a), as are 15% of the direct obstetric deaths in the UK (DH 2002). Perinatal mortality is also increased (Ananth 1995; Dept of Health 1996). There is little good quality information about morbidity for either mother or baby, but it is likely that this too is high.

The origins of pre-eclampsia are probably in faulty implantation of the placenta early in pregnancy. The primary lesion is thought to be deficient trophoblast invasion of the spiral arteries in the uterus during the second trimester, leading to underperfusion of the circulation between uterus and placenta, with consequent reduction in blood flow through the placenta (placental ischaemia) (Redman 1991). The resulting placental damage is thought to lead to release of factors into the maternal circulation, which are responsible for the maternal syndrome. Activation of platelets and the clotting system may occur early in the course of the disease, before clinical symptoms develop (Janes 1995; Redman 1978). Deficient intravascular production of prostacyclin, a vasodilator, with excessive production of thromboxane, a platelet-derived vasoconstrictor and stimulant of platelet aggregation (Bussolino 1980) have also been demonstrated to occur in pre-eclampsia. These observations led to the hypotheses that antiplatelet agents, and low-dose aspirin in particular, might prevent or delay the development of pre-eclampsia and that, for women who already have the disorder, the risk of adverse events might be reduced.

These hypotheses were first tested in several small randomised trials which reported very striking benefits in terms of reducing the risk of hypertension and proteinuria. The trials were too small to provide reliable information about other more substantive outcomes, such as perinatal mortality, although there were anecdotal reports of women exposed to aspirin which suggested promising benefits. In addition, there was no information about the potential hazards of this therapy, such as a possible increased risk of bleeding for both the woman and her baby, and possible adverse effects on infant and child development. The promising results of early trials of low-dose aspirin led to several large trials being conducted in various parts of the world. Before these results became available, however, the use of low-dose aspirin had already become relatively widespread for women considered to be at increased risk of pre-

eclampsia.

Over 35,000 pregnant women have been entered into randomised trials evaluating low-dose aspirin. In the past, several systematic reviews have attempted to summarise these results (Collins 1995; Imperiale 1991; Leitich 1997; Rey 1996; Sanchez-Ramos 1994; Sharts-Engel 1992), although none of these are complete or up to date. Nevertheless, there has been a reasonable consensus that, while low-dose aspirin appears to be safe, it is not usefully effective at protecting low-moderate risk women from developing pre-eclampsia (BroughtonPipkin 1996). Several issues remain controversial, however. These include whether antiplatelet agents are beneficial for women with a particularly high risk of developing severe pre-eclampsia (those with a history of previous early onset severe disease or with diabetes, for example) and whether dose, type of preparation or starting treatment early in pregnancy are factors that substantially influence effectiveness. Also, there is concern that enthusiasm for the use of low-dose aspirin may have led to speedy publication of small positive trials in high profile journals, with small negative trials taking far longer to appear, and then doing so only in more obscure publications (BroughtonPipkin 1996).

A wide variety of other interventions have been suggested for possible prevention of pre-eclampsia. Other Cochrane reviews cover calcium supplementation (Hofmeyr 2006), magnesium supplementation (Makrides 2001), protein intake (Kramer 2003), nutritional advice (Kramer 2003) salt intake (Duley 1999b) marine oils (Makrides 2006) and antioxidants (Rumbold 2005). Although some of these interventions are promising, to date none have been clearly shown to have clinically worthwhile benefits.

The aims of this review are (i) to identify as many of both the published and unpublished antiplatelet trials as possible and (ii) to estimate the benefits and hazards of antiplatelet agents when used for the prevention of pre-eclampsia.

OBJECTIVES

To assess the effectiveness and safety of antiplatelet agents, such as aspirin and dipyridamole, when given to women at risk of developing pre-eclampsia.

If antiplatelets were effective, our second objective was to determine which of these agents was best and to compare antiplatelet agents with other interventions. These analyses are not currently included in this review.

CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

Types of studies

All randomised trials comparing antiplatelet agents with either placebo or no antiplatelet agent during pregnancy, and trials comparing one antiplatelet agent with another or with other interventions. Quasi-random study designs were excluded.

Types of participants

Pregnant women considered to be at risk of developing pre-eclampsia. This included women with normal blood pressure and those with chronic hypertension, as well as women with pregnancy-induced or gestational hypertension.

Women who were either normotensive, or had chronic hypertension without superimposed pre-eclampsia at trial entry were classified as being at high risk if they had one or more of the following: previous severe pre-eclampsia, diabetes, chronic hypertension, renal disease, or autoimmune disease. Moderate risk was defined as any other risk factors, in particular first pregnancy, a mild rise in blood pressure and no proteinuria, abnormal uterine artery doppler scan, positive roll-over test, multiple pregnancies, a family history of severe pre-eclampsia and being a teenager. When risk was unclear or unspecified women were classified as moderate-low risk.

Types of intervention

Comparisons of any antiplatelet agent (such as low-dose aspirin or dipyridamole) with either placebo or no antiplatelet agent. This was regardless of dose and duration of therapy or mode of administration, and irrespective of whether in combination with another agent.

Comparisons of one antiplatelet agent with another, and of antiplatelets with other interventions, were included in the search strategy but these studies have been excluded from the analyses. They may be included in future updates of the review once sufficient data become available.

Types of outcome measures

For the women

Death, pre-eclampsia, elective delivery (induction of labour or elective caesarean section), caesarean section (emergency plus elective), bleeding episodes (such as abruption of the placenta, antepartum haemorrhage, postpartum haemorrhage, complications of epidural anaesthesia, need for transfusion), measures of serious maternal morbidity (such as eclampsia, liver failure, renal failure, disseminated intravascular coagulation) and rare adverse events (such as temporary blindness, major psychiatric disorders).

For the children

Death (stillbirth, neonatal or infant), gestational age at birth, growth restriction (preferably using below the third centile of weight for gestational age, but otherwise the most extreme centile available), bleeding episodes (such as intraventricular haemorrhage), infant and child development (such as cerebral palsy, cognitive delay, deafness, and blindness).

Use of health service resources

For the woman
Antenatal hospital admission, visits to day care units, use of intensive care, ventilation and dialysis.

For the infant
Admission to special care/intensive care nursery, duration of mechanical ventilation, length of stay in hospital, as well as development and special needs after discharge.

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 (July 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 1) using the terms pregnan* preeclamp* pre-eclamp* aspirin antiplatelet. We searched EMBASE (1994 to November 2005) using the strategy:
1. pregn*
2. aspirin
3. #1 and #2
4. antiplatelet
5. #1 and (#2 or #4)
6. pre-eclam*
7. preeclam*
8. #6 or #7
9. #5 and #8
10. random*
11. controlled-clinical-trial in pt
12. #10 or #11
13. #9 and #12

In addition, we handsearched the congress proceedings of the International Society for the Study of Hypertension in Pregnancy up to 2006 and the congress proceedings of the European Society for the Study of Hypertension in Pregnancy up to 2002.

We did not apply any language restrictions.

METHODS OF THE REVIEW

Selection of studies
Two review authors assessed the trials for inclusion in the review independently and unblinded. For the initial review (CDSR Issue 2, 2000), four review authors (Lelia Duley, David Henderson-Smart, Marian Knight, James King) worked in pairs, each pair assessing half the total citations. Any differences of opinion regarding trials for inclusion were resolved by discussion between the pair of review authors. If differences could not be resolved, the other pair was consulted. For the CDSR Issue 4, 2003 update, two review authors (Lelia Duley, David Henderson-Smart) independently assessed citations for inclusion.

For this update, two review authors (Shireen Meher, Lelia Duley) independently assessed citations for inclusion. Discrepancies were resolved by discussion.

Assessment of study quality
The quality of each included trial was assessed independently by at least two review authors using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2005). Methods used for generation of the randomisation sequence and concealment of allocation are described for each trial, where possible. Each study was assessed for quality of the concealment of allocation, completeness of follow up and blinding using the following criteria.

For allocation concealment
We allocated a grade to each trial on the basis of allocation concealment:
(A) adequate;
(B) unclear; or
(C) clearly inadequate.

Where the method of allocation concealment was unclear, we made attempts to contact authors to provide further details. We excluded trials with inadequate allocation concealment and trials with quasi-randomised designs, such as alternate allocation and use of record numbers.

For completeness of follow up
(A) less than 3% of participants excluded;
(B) 3% to 9.9% of participants excluded;

(C) 10% to 19.9% of participants excluded.

Excluded
If not possible to present the data by intention to treat or if 20% or more of participants excluded.

We included data for long-term follow up of women and children where losses to follow up were greater than 20%, providing that substantive bias between the groups was unlikely. We documented completeness of follow up for these studies alongside any results.

For blinding of assessment of outcome
(A) double blind; both clinician and woman blind to allocation;
(B) single blind; either clinician or women blind to allocation;
(C) no blinding or blinding of allocation not mentioned.

Data extraction and data entry
Two review authors independently extracted data using previously prepared data extraction forms. Again, for the initial review (CDSR Issue 2, 2000) four review authors worked in pairs (Lelia Duley, David Henderson-Smart, Marian Knight, James King), each extracting data from half of the trials. We resolved any discrepancies by discussion. If the review authors could not agree, we excluded the data until further clarification was available from the study authors. For the CDSR Issue 4, 2003 update, two review authors (Lelia Duley, David Henderson-Smart) independently extracted data, and any discrepancies were resolved by discussion with the review authors (Marian Knight, James King). Data presented in graphs and figures were extracted whenever possible, but were only included if two review authors independently had the same result. We double checked all data entry for discrepancies.

For this update, the same procedure was followed by two review authors (Shireen Meher, Lelia Duley).

Statistical analyses
We performed statistical analyses using the Review Manager (RevMan 2003) software, with results presented as summary relative risk, risk difference and number needed to treat. For each of these, the 95% confidence interval is given in brackets. The I^2 statistic was used to assess heterogeneity between trials. In the absence of significant heterogeneity, results were pooled using a fixed-effect model. If substantial heterogeneity was detected (I^2 more than 50%), possible causes were explored and subgroup analyses for the main outcomes performed. Heterogeneity that is not explained by subgroup analyses may be modelled using random-effects analysis, where appropriate.

We described the relationship between size of trial and time of trial publication to assess potential time-lag bias. We also used funnel plots to compare sample size with the direction and size of treatment effect.

Subgroup analyses
For women with either normal blood pressure or chronic hypertension without superimposed pre-eclampsia at trial entry, we planned subgroup analyses for the main outcomes by:
(1) maternal risk of pre-eclampsia at trial entry: moderate-low or high risk (defined under types of participant);
(2) gestation at trial entry: before 20 weeks' gestation, after 20 weeks' gestation, or gestation unclear or unspecified;
(3) type of antiplatelet agent: aspirin, or all other types;
(4) by dose of aspirin: 75 mg or less or greater than 75 mg;
(5) by type of control group intervention: placebo or no placebo.

DESCRIPTION OF STUDIES

Details for each trial are in the 'Characteristics of included studies' table.

There are 59 trials involving 37,560 women included in the review. In 17 trials, data were reported for less than 50 women, 11 trials reported data for 50 to 99 women, 22 trials had 100 to 999 women and nine trials involved 1000 or more women.

There was a wide range in incidence of pre-eclampsia between women in different trials (2% to 60% in the placebo arm) and, in many studies, between women in the same trial. Several trials included women with gestational hypertension, without proteinuria. In some, all women had gestational hypertension (India 1993; India 1994; India 1999; Israel 1990) whilst others included women with or without gestational hypertension (CLASP 1994; Italy 1993; UK 1992).

Interventions varied as to dose of aspirin, gestation at commencement and use of other treatments. In 51 trials, aspirin alone was compared with placebo or no treatment. Of the remainder, five used a combination of aspirin and dipyridamole or dipyridamole alone versus control (EPREDA 1991; France 1985; France 1990; Russia 1993; S Africa 1988), one small trial used heparin and dipyridamole versus control (Australia 1995a), another combined aspirin with vitamins C and E and fish oil (Venezuela 2000) and another compared ozagrel hydrochloride with placebo (Japan 1999).

Most trials reported data for pre-eclampsia, preterm delivery, perinatal death and the infant being small-for-gestational age.

Overall, 64 studies were excluded from the review. The reasons for exclusion are listed in the 'Characteristics of excluded studies' table.

METHODOLOGICAL QUALITY

Details for each trial are in the 'Characteristics of included studies' table.

There is wide variation in study quality. The poorer quality studies were mostly the small early trials, with the more recent large studies tending to be of higher quality. For many of the smaller studies, it is unclear whether concealment of the allocation at trial entry was adequate. Most trials used some form of placebo, however.

None of the small trials without a placebo attempted to blind the assessment of outcome.

RESULTS

Overall, 59 trials involving 37,560 women are included in this review. Of these trials, three (CLASP 1994; Italy 1993; UK 1992) included both primary and secondary (for women with gestational hypertension) prevention arms. Where possible, data have been presented in the appropriate comparison. Where data are largely for primary prevention, but a small proportion for secondary prevention cannot be separated out, data for all women have been included under primary prevention.

A. Antiplatelet agents versus placebo or no treatment for the primary prevention of pre-eclampsia and its complications

Pregnancy-induced hypertension

There is no overall difference in the risk of gestational hypertension in the 34 trials (20,701 women) reporting this outcome (relative risk (RR) 0.95, 95% confidence interval (CI) 0.88 to 1.03). Heterogeneity in this analysis is borderline (I^2 49.5%), and using a random-effects model this result achieves statistical significance (RR 0.81, 95% CI 0.69 to 0.94).

There is a statistically significant reduction in risk in one prespecified subgroup of 838 high-risk women enrolled in 12 small trials that reported gestational hypertension ((RR 0.54, 95% CI 0.41 to 0.70), risk difference (RD) -13% (-18.6, -8.1), NNT 8 (5, 12)). This result is consistent using a random-effects model (RR 0.56, 95% CI 0.40 to 0.78).

Proteinuric pre-eclampsia

Overall there is a 17% reduction in the risk of pre-eclampsia associated with the use of antiplatelet agents ((46 trials with 32,891 women, RR 0.83, 95% CI 0.77 to 0.89), RD -1.39% (-1.94, -0.24), NNT 72 (52, 119)). This reduction in risk is statistically significant regardless of whether the woman was at moderate or high risk, gestation at trial entry, whether or not she was in a placebo controlled trial.

Although there is a trend for the relative risk reduction to be greater in women at high risk of pre-eclampsia at trial entry (RR 0.75, 95% CI 0.66 to 0.85) than those at moderate risk (RR 0.86, 95% CI 0.79 to 0.95), the confidence intervals overlap and there is no clear statistical difference. However, there is a significant increase in the absolute risk reduction and consequent reduction in number needed to treat to prevent one case of pre-eclampsia in the high-risk women (RD -5.2% (-7.5, -2.9), NNT 19 (13, 34)) compared with moderate-risk women (RD -0.84 (-1.37, -0.3), NNT 119 (73, 333)). In the nine trials (1587 women) that were not placebo controlled, the reduction in risk of pre-eclampsia was significantly greater (RR 0.52, 95% CI 0.39 to 0.71) than in the 34 placebo controlled trials (31,003 women) (RR 0.85, 95% CI 0.78 to 0.92).

Compared with trials using 75 mg or less of aspirin, there is a significant reduction in the risk of pre-eclampsia in trials using higher doses of antiplatelet agents. In the 21 trials (26,984 women) that evaluated 75 mg/day or less of aspirin the RR is 0.88 (95% CI 0.81 to 0.95), in the 17 trials (3061 women) evaluating more than 75 mg/day of aspirin the RR is 0.64 (95% CI 0.51 to 0.80) and in the five trials of 506 women evaluating more than 75 mg/day of aspirin plus dipyridamole the RR is 0.30 (95% CI 0.15 to 0.60). No trials make a direct comparison of different doses of aspirin. A few small trials have combined aspirin with dipyridamole. In view of the small numbers, the results in this subgroup should be interpreted with caution.

Placental abruption

There was no overall difference in the risk of placental abruption in the 16 trials (24,982 women) contributing data to the analysis of this outcome (RR 1.10, 95% CI 0.89 to 1.37).

Preterm birth

Overall, in the 29 trials reporting this outcome (31,151 women), there was a small (8%) reduction in the risk of delivery before 37 completed weeks ((RR 0.92, 95% CI 0.88 to 0.97), RD -1.36% (-2.17, -0.53), NNT 74 (46, 185)). The size of this reduction was similar across all the subgroups. There was insufficient evidence for any firm conclusions on the effect on delivery less than 34 weeks or less than 32 weeks' gestation.

Any reported death: stillbirth, neonatal or infant death

Forty trials (33,098 women) reported stillbirths, neonatal deaths or infant deaths. When any reported deaths are analysed together, regardless of when the death occurred, there is a 14% reduction in the risk of death in the antiplatelet group ((RR 0.86, 95% CI 0.76 to 0.98), RD -0.41% (-0.76, -0.06), NNT 243 (131, 1,666)). The size of this reduction was similar across all the subgroups, except for those trials that included women at high risk (20 trials, 4797 women, RR 0.69, 95% CI 0.53 to 0.90), although this does not reach statistical significance. In the 10 trials that did not use a placebo (1605 women), the reduction in risk is statistically significantly greater (RR 0.58, 95% CI 0.36 to 0.94).

Classifying deaths by the time of death (stillbirth, perinatal death, neonatal death), there were no statistically significant differences in the risk of death in any of the categories.

Small-for-gestational age

In 36 trials (23,638 women), there was a 10% reduction in the risk of small-for-gestational age births ((RR 0.90, 95% CI 0.83 to 0.98), RD -0.87% (-1.57, -0.16), NNT 114 (64, 625)). The results were similar in all subgroups.

Other outcomes

There are no significant differences between treatment and control groups in the risk of eclampsia (nine trials, 22,584 women), maternal death (three trials, 12,709 women), caesarean section (24 trials, 31,834 women), induction of labour (five trials, 19,295 women), antenatal admission (three trials, 12,964 women), birth-

weight less than 2500 gm (six trials, 7512 babies), admission to special care baby unit (15 trials, 28,298 babies), intraventricular haemorrhage (10 trials, 26,184 babies) or other neonatal bleeding (eight trials, 27,032 babies).

Two trials assessed the children in early childhood (CLASP 1994; Italy 1993). In one, (CLASP 1994) no difference was apparent between treatment and control groups in any measure of health and development at 12 to 18 months. The other (Italy 1993) reported a higher risk of gross and fine motor problems at 18 months in treatment compared with control children (15/427 versus 26/361, RR 0.49, 95% CI 0.26 to 0.91). This result should be interpreted with caution, however, as the trial was not placebo controlled and so assessment was unblinded, and 27% of children were lost to follow up.

B. Antiplatelet agents versus placebo or no treatment for secondary prevention of pre-eclampsia and its complications in women with gestational hypertension

Proteinuric pre-eclampsia
In five trials (1643 women), there was a 40% reduction in the relative risk of pre-eclampsia (RR 0.60, 95% CI 0.45 to 0.78).

Preterm birth
In three trials (1451 women), there is a 13% reduction in the relative risk of preterm birth at less than 37 weeks (RR 0.87, 95% CI 0.75 to 0.99).

Any reported death: stillbirth, neonatal or infant death
In four trials (1728 women), there is no statistically significant difference in the relative risk of fetal, neonatal or infant death (RR 1.02, 95% CI 0.72 to 1.45).

Small-for-gestational age
Three trials (344 women) reported whether the baby was small-for-gestational age. There was no clear difference between the groups (RR 0.76, 95% CI 0.52 to 1.10).

Low birthweight (less than 2500 gm)
One small trial (100 women) reported a statistically significant reduction in the relative risk of the baby being born with a low birthweight (RR 0.24, 95% CI 0.09 to 0.65).

Caesarean section
One small trial (47 women) reported caesarean section, and there is no clear difference between the groups (RR 0.87, 95% CI 0.31 to 2.46).

DISCUSSION

There continues to be controversy about the role of aspirin for prevention of pre-eclampsia. This review summarises data from 37,560 women from 59 trials. It demonstrates that, although the benefits are not as high as was hoped for in the early 1990s, low-dose aspirin does reduce the risk of pre-eclampsia and its consequences. As these benefits are small-moderate, depending on the outcome. Further research is required to help determine for which women aspirin would be most worthwhile.

Antiplatelet agents (primarily aspirin in this review) are associated with a moderate (17%) reduction in the risk of pre-eclampsia. The confidence intervals (CI) for this point estimate suggest the true effect could be a reduction of as much as 23%, or as little as 11%. For women who were high risk at trial entry, antiplatelet agents are associated with a 25% reduction in the risk of pre-eclampsia (95% CI 34% to 15% reduction). For moderate-risk women, antiplatelet agents are associated with a 14% reduction in the risk of pre-eclampsia (95% CI 21% to 5% reduction). Based on absolute risk reduction, 72 women (95% CI 52 to 119 women) need to be treated to prevent one case of pre-eclampsia. For high-risk women this drops to 19 who need to be treated to prevent one case of pre-eclampsia (95% CI 13 to 34 women) and for moderate-risk women it rises to 119 women (95% CI 73 to 333 women).

The risk of the baby dying, either before or after delivery, is reduced by 14%. There is a small (8%) overall reduction in the risk of preterm birth, but this seems to be a reduction in the risk of any birth before 37 weeks without any clear evidence of a reduction in the risk of being born before 32 weeks. The relative of having a small-for-gestational-age baby is also reduced by 10%.

It has been suggested that the promising early systematic reviews of antiplatelet therapy may have reflected publication bias (BroughtonPipkin 1996). Graphs (called funnel plots) of the effect size against sample size for each trial have been consistently asymmetric, suggesting that small negative trials may be missing. In this review, most of the small positive trials were published in the 1980s and early 1990s. It remains possible that small negative trials conducted at that time have still not been published. Interestingly, the recently conducted small studies added in this update are also largely positive. The funnel plot of the data for pre-eclampsia therefore continues to be asymmetric. The funnel plot for data on stillbirths and neonatal deaths is more symmetric, however. It should be noted that publication bias is not the only cause of funnel plot asymmetry and it can also be due to differences in maternal characteristics in small compared to large trials.

Although the subgroups presented in this review were all prespecified, their results should be interpreted with caution. The large number of subgroups and outcomes means that at least a few of the statistically significant results may merely reflect the play of chance (with a P value of 0.05, one in 20 can be expected to be positive, purely by chance). Where only a proportion of eligible trials reported a particular outcome and large numbers of women are missing, there is also the potential to be misled by bias.

To prevent or delay the onset of pre-eclampsia, aspirin may need to be started before implantation and trophoblast invasion are complete. In this review, data are presented by before and after

20 weeks, and there is little evidence of any clinically worthwhile difference. It may be that the crucial time for administration is before 16 or 12 weeks, but this review provides little to support that hypothesis. There is promising evidence that higher doses of aspirin may be more effective, but this will require careful evaluation as risks may also be increased. The current reassurance about safety applies only to lower doses. As would be expected, trials with no placebo tended to report more positive effects than those that used a placebo.

These trials involved a wide range of maternal risk both within and between trials. In this aggregate data review, it is not possible to assess the effects of antiplatelet agents for women with specific conditions or risk factors. Such an analysis would require a review based on data from individual women. The trialists who conducted the studies in this review have formed a collaborative group (the PARIS Group) to conduct a review based on data from individual women. The protocol for this review has been published (PARIS 2005), and the results are expected to be available in 2007. Future updates of this Cochrane review will therefore incorporate data from individual women.

AUTHORS' CONCLUSIONS

Implications for practice

Overall, administration of antiplatelet agents to women at risk leads to a 17% reduction in the risk of developing pre-eclampsia. Amongst women in the primary prevention trials, for every 72 women treated, one case of pre-eclampsia is prevented. However, for high-risk women only 19 need to treated to prevent one case . There are also smaller reductions in the risk of preterm birth (8%) and of fetal or neonatal death (14%) with larger numbers of women needed to be treated to prevent such outcomes. Overall, adverse effects appear to be low but under reporting makes it difficult to be confident about this, especially where higher doses are used. As most of the evidence relates to low-dose aspirin, this is the antiplatelet agent that should be used in clinical practice for prevention of pre-eclampsia. Starting aspirin before 12 weeks or using higher doses, or both, cannot be recommended for clinical practice until more information is available about safety.

The evidence presented in this review should be summarised and made available to women at risk of pre-eclampsia. The decision about whether to take aspirin during pregnancy should then be made in consultation between the woman and her doctor. As the reductions in risk are small-moderate, relatively large numbers of women will need to be treated to prevent a single adverse outcome. However, from a public health perspective even these moderate benefits may be worthwhile, and low-dose aspirin may be worth considering for more widespread use.

Implications for research

Several questions remain about the role of low-dose aspirin. These include whether there are particular high-risk subgroups of women who might have greater benefit, whether starting treatment before 12 weeks would have additional benefits without any increase in adverse effects, and whether a higher dose would be more effective. Many of these unresolved questions could be most efficiently answered by a review that analysed data from the individual women in the trials presented here, rather than undertaking further trials. As discussed above, results of this review will be available soon.

FEEDBACK

Coomarasamy, February 2001

Summary

[Aspirin has clinically significant benefit in high risk groups - Summary NNT can mislead clinicians and women]

Editor - The systematic review (1;2) of antiplatelet drugs for prevention of pre-eclampsia found statistically significant reduction in pre-eclampsia and other outcomes such as fetal or neonatal death. The authors concluded that the benefit was 'small to moderate' and the implication for practice was that 'relatively large numbers of women will need to be treated to prevent a single adverse outcome'. With the numbers of women needed to be treated to prevent one case of pre-eclampsia reported as 100 (95% CI 59 to 167), clinicians (and women) might not think treatment worthwhile.

However, calculating numbers needed to treat from pooled meta-analysis data may be inappropriate, if it is possible to identify subgroups of patients with substantially differing baseline risks(3). In women with high levels of baseline risk, and assuming constant relative risk from treatment, numbers needed to treat are smaller (4), and both clinicians and women may be much more likely to wish to use aspirin to prevent pre-eclampsia. It has been suggested(1;2) that meta-analysis of individual patient data would be useful both in identifying high-risk subgroups, and estimating the benefit they derive from antiplatelet treatment. However, such meta-analyses generally take a long time to complete(5). What should clinicians do in the mean time?

We can see no reason for thinking that the reduction in relative risk for various risk levels will be substantially different. If high-risk (or low risk) women can be identified, by any means, specific numbers needed to treat can then be generated by using pooled relative risk estimates from reviews of effectiveness(4), making the decision to treat (or not) more appropriate and, in this particular case, probably more clear-cut for most women.

We systematically reviewed the accuracy of uterine artery Doppler in early pregnancy for predicting pre-eclampsia(6). In clinically

high-risk women, a positive Doppler result (abnormal flow velocimetry ratio or the presence diastolic notch) meant a 23.5% (95% CI 18.6 to 29.2) risk of developing pre-eclampsia. With baseline risk elevated to this level and assuming the global estimated relative risk of 0.85 (1), we estimate that 31 (95% CI 18 to 55) patients will be needed to be treated with aspirin to prevent one case of pre-eclampsia. We would thus expect most women with abnormal uterine artery Dopplers, when advised by their clinicians, to request antiplatelet treatment.

1. Duley L, Henderson-Smart DJ, Knight M, King JF. Anteplatelet drugs for prevention of pre-eclampsia and its consequences: systematic review. BMJ 2001;322: 329-333..

2. Knight M, Duley L, Henderson-Smart DJ, King JF. Antiplatelet agents for preventing and treating pre-eclampsia. Cochrane Database.Syst.Rev. 2000;CD000492.

3. Smeeth L, Haines A, Ebrahim S. Numbers needed to treat derived from meta-analyses--sometimes informative, usually misleading. BMJ 1999;318:1548-51.

4. Guyatt GH, Sackett DL, Sinclair JC, Hayward R, Cook DJ, Cook RJ. Users' guides to the medical literature. IX. A method for grading health care recommendations. Evidence-Based Medicine Working Group. JAMA 1995;274:1800-4.

5. Stewart LA,.Clarke MJ. Practical methodology of meta-analyses (overviews) using updated individual patient data. Cochrane Working Group. Stat.Med. 1995;14:2057-79.

6. Chien PF, Arnott N, Gordon A, Owen P, Khan KS. How useful is uterine artery Doppler flow velocimetry in the prediction of pre-eclampsia, intrauterine growth retardation and perinatal death? An overview. BJOG. 2000;107:196-208.

Author's reply

The main aim of our review was to summarise the evidence. We agree the number needed to treat will be more favourable for women at higher risk, nevertheless, women at moderate/low risk do also seem to benefit. The public health benefit of a 15% reduction in pre-eclampsia and a 14% reduction in stillbirth and neonatal death is difficult to quantify, but is likely to be important. Aspirin is the best we have to offer for prevention of pre-eclampsia, with the added advantages of being low cost and reasonable reassurance about safety.

As indicated in our review, we are addressing the issue of potential variations in effect size for women with different baseline risk by undertaking a review based on data from individual women.

[reply from the review team, September 2002]

Contributors

Comments by:

A Coomarasamy
Research Fellow in Obstetrics
Education Resource Centre
Birmingham Women's Hospital
Metchley Park Road, Birmingham B15 2TG
arricoomar@hotmail.com

Harry Gee
Consultant Obstetrician
Birmingham Women's Hospital, B15 2TG

Khalid S Khan
Consultant Obstetrician and Gynaecologist
Birmingham Women's Hospital, B15 2TG

David Braunholtz
Senior Research Fellow
Department of Public Health & Epidemiology
Public Health Building
University of Birmingham, B15 2TT

POTENTIAL CONFLICT OF INTEREST

Lelia Duley was on the steering committee for Barbados 1998, and was a co-author of the report. James King collaborated on CLASP 1994. Lelia Duley, David Henderson-Smart and James King are all chief investigators on a project grant from the NH&MRC (Australia) to support a review of antiplatelet agents for prevention of pre-eclampsia, based on data from individual women (PARIS Collaborative Group).

ACKNOWLEDGEMENTS

Our thanks to Colin Bagent, Caroline Crowther, Michael de Swiet, Adrian Grant, Hein Odendaal, Chris Redman, Jeffrey Robinson, Isabel Walker and Henk Wallenburg for helpful comments on the original protocol for this review, and to Marian Knight and Rory Collins for their work on earlier versions of the review. Thanks also to Robyn North (Australia 1996a) and John Anthony (S Africa 1988) who have provided additional unpublished data; to Arri Coomarasamy who kindly provided an English translation of Russia 1993; and to Karla Soares who helped with translation and data extraction of Brazil 1992a. Finally thanks to members of the PARIS Collaborative Group who have provided additional unpublished data about randomisation and concealment of allocation for some studies.

SOURCES OF SUPPORT

External sources of support

- Health Technology Assessment UK

Internal sources of support

- NSW Centre for Perinatal Health Services Research, School of Public Health, University of Sydney AUSTRALIA
- Department of Neonatal Medicine, Royal Prince Alfred Hospital, Sydney AUSTRALIA
- Department of Perinatal Medicine, Royal Womens Hospital, Melbourne AUSTRALIA
- Medical Research Council UK
- The University of Liverpool UK

REFERENCES

References to studies included in this review

Australia 1988 *{published data only}*

Trudinger BJ, Cook CM, Connelly AJ, Giles WB, Thompson RS. Aspirin improves fetal weight in placental insufficiency. Proceedings of 8th Annual Meeting of the Society of Perinatal Obstetricians; 1988 February 3-6; Las Vegas, Nevada, USA. 1988:10.

* Trudinger BJ, Cook CM, Thompson RS, Giles WB, Connelly AJ. Low-dose aspirin improves fetal weight in umbilical placental insufficiency. *Lancet* 1988;**2**:214–5.

Trudinger BJ, Cook CM, Thompson RS, Giles WB, Connelly AJ. Low-dose aspirin therapy improves fetal weight in umbilical placental insufficiency. *American Journal of Obstetrics and Gynecology* 1988; **159**:681–5.

Australia 1993 *{published and unpublished data}*

Michael CA, Seville P, Wadeisha P, Walters BNJ. Randomised double blind placebo controlled trial of aspirin in the prevention of pre-eclampsia. Proceedings of 7th World Congress of Hypertension in Pregnancy; 1990 October; Perugia, Italy. 1990:73.

* Michael CA, Walters BNJ. Low-dose aspirin in the prevention of pre-eclampsia: current evaluation. In: TeohES, RatnamSS, MacnaughtonMC editor(s). *Maternal physiology and pathology. The current status of gynaecology and obstetrics series*. Carnforth: Parthenon Publishing Group Limited, 1992:183–9.

Australia 1995 *{published data only}*

Newnham JP, Godfrey M, Walters BJN, Philips J, Evans SF. Low dose aspirin for the treatment of fetal growth restriction: a randomised controlled trial. *Australian and New Zealand Journal of Obstetrics and Gynaecology* 1995;**35**:370–4.

Australia 1995a *{published data only}*

* Kincaid Smith P, North RA, Fairley KF, Kloss M, Ihle BU. Prevention of pre-eclampsia in high risk women with renal disease: a prospective randomized trial of heparin and dipyridamole. *Nephrology* 1995;**1**:297–300.

North RA, Fairley KF, Kloss M, Ihle B, Kincaid-Smith P. Prevention of pre-eclampsia in women with renal disease. Proceedings of 7th World Congress of Hypertension in Pregnancy; 1990 October; Perugia, Italy. 1990:75.

North RA, Fairley KF, Kloss M, Ihle B, Kincaid-Smith P. Prevention of preeclampsia in women with renal disease [abstract]. 26th Annual Meeting of the Australasian Society of Nephrology; 1990 March 14-16; Brisbane, Australia. 1990:9.

North RA, Fairley KF, Kloss M, Ihle B, Oats J, Kincaid-Smith P. Prevention of pre-eclampsia in women with renal disease. Proceedings of 6th International Congress of the International Society for the study of Hypertension in Pregnancy; 1988 May 22-26; Montreal, Quebec, Canada. 1988:193.

Australia 1996 *{published and unpublished data}*

Ferrier C, North R, Kincaid-Smith P. Low dose aspirin delays the onset of pre-eclampsia in pregnancies with abnormal uteroplacental circulation. Proceedings of the 10th World Congress of the International Society for the Study of Hypertension in Pregnancy; 1996 August 4-8; Seattle, Washington, USA. 1996:151.

* Kincaid-Smith P. Trial to evaluate the role of aspirin (60mg) in the prevention of idiopathic intrauterine growth retardation and pregnancy induced hypertension in primigravid women with abnormal uterine artery waveforms on Doppler examination at 22-24 weeks gestation. Personal communication October 30 1991.

Australia 1996a *{published data only}*

Morris JM, Fay RA, Ellwood DA, Cook C, Devonald KJ. A randomized controlled trial of aspirin in patients with abnormal uterine artery blood flow. *Obstetrics & Gynecology* 1996;**87**:74–8.

Australia 1997 *{published data only}*

Gallery EDM, Hawkins M, Ross M, Gyory AZ, Leslie G. Low-dose aspirin in high risk pregnancy. Proceedings of 9th International Congress of the International Society for the Study of Hypertension in Pregnancy; 1994 March 15-18; Sydney, Australia. 1994:71.

* Gallery EDM, Ross MR, Hawkins M, Leslie GI, Gyory AZ. Low-dose aspirin in high-risk pregnancy. *Hypertension in Pregnancy* 1997; **16**:229–38.

Leslie GI, Gallery ED, Arnold JD, Ross MR, Gyory AZ. Neonatal outcome in a randomized controlled trial of low-dose aspirin in high-risk pregnancies. *Journal of Paediatrics and Child Health* 1995;**31**: 549–52.

Austria 1992 *{published data only}*

Schrocksnadel H, Sitte B, Alge A, Stechel-Berger G, Schwegel P, Pastner E, et al. Low-dose aspirin in primigravidae with positive roll-over test. *Gynecologic and Obstetric Investigation* 1992;**34**:146–50.

Schrocksnadel H, Sitte B, Alge A, Steckel-Berger G, Daxenbichler G, Dapunt O. Low-dose aspirin in prevention and therapy of hy-

pertension in pregnancy [Low-dose Aspirin in prophylaxe und therapie des schwangerschaftshochdrucks]. *Gynakologisch Geburtshilfliche Rundschau* 1992;**32**:90–1.

Barbados 1998 *{published data only}*

Cruickshank J, Rotchell Y. The Barbados low-dose aspirin study in pregnancy (BLASP). 8th World Congress on Hypertension in Pregnancy; 1992 November 8-12; Buenos Aires, Argentina. 1992:49.

Elder MG, de Swiet M, Sullivan M. A randomised trial of low dose aspirin for primiparae in pregnancy (golding)/barbados low dose aspirin study in pregnancy (blasp) (rotchell et al.) [Letter; comment]. *British Journal of Obstetrics and Gynaecology* 1999;**106**(2):180.

Griffiths J, Rotchell YE, Cruickshank JK, Philips-Gay M, Stewart A, Farrell B, et al. The Barbados Low-dose Aspirin Study in Pregnancy (BLASP): a population-based trial in a developing country with excess pre-eclampsia and perinatal mortality [abstract]. *West Indian Medical Journal* 1996;**45**(2 Suppl):26–7.

Rotchell YE, Cruickshank JK, Griffiths J, Phillips G, Stuart A, Ayers S, et al. Results of the Barbados low dose aspirin study in pregnancy (BLASP): a population-based trial in a developing country with excess pre-eclampsia (PE) and perinatal mortality. 27th British Congress of Obstetrics & Gynaecology; 1995 July 4-7; Dublin, Ireland. 1995: 31.

* Rotchell YE, Cruickshank JK, Phillips Gay M, Griffiths J, Stuart A, Farrell B, et al. Barbados low dose aspirin study in pregnancy (BLASP): a randomized controlled trial for the prevention of pre-eclampsia and its complications. *British Journal of Obstetrics and Gynaecology* 1998;**105**:286–92.

Brazil 1996 *{published data only}*

* Anonymous. ECPPA: randomised trial of low dose aspirin for the prevention of maternal and fetal complications in high risk pregnancies. *British Journal of Obstetrics and Gynaecology* 1996;**103**:39–47.

Atallah AN. ECPPA: randomized trial of low dose aspirin for the prevention of maternal and fetal complications in high risk pregnant women [abstract]. *Journal of Clinical Epidemiology* 1997;**50 Suppl 1**:3S.

Atallah AN, Taborda WC. ECPPA: the Brazilian low-dose aspirin study in high risk pregnant women. Hypertension in Pregnancy 1997; Vol. 16, issue 1:139.

Brazil 1992a *{published data only}*

Essinger S. The use of low dose acetylsalicylic acid in prevention of pregnancy-induced hypertension [Uso do acido acetilsalicilico em baixa dosagem na prevencao da doenca hipertensiva especifica da gestacao (DHEG)]. *Revista do Colegio Brasileiro de Cirurgioes* 1992; **19**(2):58–62.

China 1996 *{published data only}*

* Wang Z, Li W. A prospective randomized placebo-controlled trial of low dose aspirin for prevention of intra uterine growth retardation. *Chinese Medical Journal* 1996;**109**:238–42.

Wang Z, Li W. Prevention of growth retardation by low dose aspirin. *Chung-Hua Fu Chan Ko Tsa Chih [Chinese Journal of Obstetrics and Gynecology]* 1993;**28**:492–5.

China 1996a *{published data only}*

Wu J, Yang WW, Shen WH, He Y. Small dosage aspirin in the prevention of hypertension of pregnancy. *Acta Academiae Medicinae Suzhou* 1996;**16**:551–3.

China 1999 *{published and unpublished data}*

* Rogers MS, Fung HYM, Hung CY. Calcium and low-dose aspirin prophylaxis in women at high risk of pregnancy-induced hypertension. *Hypertension in Pregnancy* 1999;**18**:165–72.

Rogers MS, Hung C, Arumanayagam M. Platelet angiotensin II receptor status during pregnancy in Chinese women at high risk of developing pregnancy-induced hypertension. *Gynecologic and Obstetric Investigation* 1996;**42**:88–94.

CLASP 1994 *{published data only}*

Bar J, Hod M, Pardo J, Fisch B, Rabinerson D, Kaplan B, et al. Effect on fetal circulation of low-dose aspirin for prevention and treatment of pre-eclampsia and intrauterine growth restriction: Doppler flow study. *Ultrasound in Obstetrics & Gynaecology* 1997;**9**:262–5.

Bar J, Padoa A, Hod M, Sullivan MHF, Kaplan B, Kidron D. Decreased pathological placental findings in aspirin-treated pregnant women at risk of hypertensive complications. *Hypertension in Pregnancy* 1997;**16**:435–44.

Bower SJ, Harrington KF, Schuchter K, McGirr C, Campbell S. Prediction of pre-eclampsia by abnormal uterine Doppler ultrasound and modification by aspirin. *British Journal of Obstetrics and Gynaecology* 1996;**103**:625–9.

* CLASP (Collaborative Low-dose Aspirin Study in Pregnancy) Collaborative Group. CLASP: a randomised trial of low-dose aspirin for the prevention and treatment of pre-eclampsia among 9364 pregnant women. *Lancet* 1994;**343**:619–29.

CLASP Collaborative Group. Low dose aspirin in pregnancy and early childhood development: follow up of the collaborative low dose aspirin study in pregnancy. *British Journal of Obstetrics and Gynaecology* 1994;**102**:861–8.

Kyle PM, Buckley D, Kissane J, de Swiet M, Redman CWG. The angiotensin sensitivity test and low-dose aspirin are ineffective methods to predict and prevent hypertensive disorders in nulliparous pregnancy. *American Journal of Obstetrics and Gynecology* 1995;**173**:865–72.

Mathai M. Aspirin for pre-eclampsia. *National Medical Journal of India* 1995;**8**:23–4.

Vikhlyaeva K, Asymbekova GU, Zerdev VP. Aspirin in profilaxis and treatment of placental insufficiency: lessons from Russian aspirin experience. *Hypertension in Pregnancy* 2000;**19**(Suppl 1):68.

Colorado 1993 *{published data only}*

Porreco RP, Hickok DE, Williams MA, Krenning C. Low-dose aspirin and hypertension in pregnancy. *Lancet* 1993;**341**:312.

Egypt 2005 *{published data only}*

Ebrashy A, Ibrahim M, Marzook A, Yousef D. Usefulness of aspirin therapy in high-risk pregnant women with abnormal uterine artery doppler ultrasound at 14-16 weeks pregnancy: randomized controlled clinical trial. *Croatian Medical Journal* 2005;**46**(5):826–31.

EPREDA 1991 *{published data only}*

Beaufils M, Uzan S, Breart G, Bazin B, Paris J. Prevention of preeclampsia with low-dose aspirin: results of the epreda trial. XIth International Congress of Nephrology; 1990 July 15-20; Tokyo, Japan. 1990:319A.

Sureau C. Prevention of perinatal consequences of pre-eclampsia with low-dose aspirin: results of the EPREDA trial. *European Journal of Obstetrics & Gynecology and Reproductive Biology* 1991;**41**:71–3.

Uzan M, Beaufils M, Breart G, Bazin B, Capitant C, Paris J, et al. Prevention of pre-eclampsia with low-dose aspirin: results of the EPREDA trial. *Journal of Perinatal Medicine* 1990;**18 Suppl**:116.

* Uzan S, Beaufils M, Breart G, Bazin B, Capitant C, Paris J. Prevention of fetal growth retardation with low-dose aspirin: findings of the EPREDA trial. *Lancet* 1991;**337**:1427–31.

Uzan S, Beaufils M, Breart G, Bazin B, Capitant C, Paris J. Prevention of pre-eclampsia with low-dose aspirin: results of the EPREDA trial. *European Journal of Obstetrics & Gynecology and Reproductive Biology* 1992;**44**:12.

Uzan S, Beaufils M, Breart G, Bazin B, Paris J. Prevention of pre-eclampsia with low-dose aspirin: results of the EPREDA trial. Proceedings of 7th World Congress of Hypertension in Pregnancy; 1990 October; Perugia, Italy. 1990:34.

Uzan S, Beaufils M, Breart G, Uzan M, Paris J. Prevention of intrauterine growth retardation and pre-eclampsia by small doses of aspirin. Results of the French multicenter trial EPREDA and comparison with data in the literature; value of uterine Doppler [Prevention du retard de croissance intra-uterin et de la preeclampsie par des petites doses d'Aspirine: resultats de l'essai multicentrique francais EPREDA et comparison avec les donnees de la litterature; interet du Doppler uterin]. *Journal de Gynecologie, Obstetrique et Biologie de la Reproduction (Paris)* 1992;**21**(3):315–8.

ERASME 2003 *{published data only}*

ERASME collaborative group. Failure of systematic low dose aspirin to prevent preeclampsia in primigravidae. *Hypertension in Pregnancy* 2000;**19**(Suppl 1):34.

* Subtil D, Goeusse P, Puech F, Lequien P, Biausque S, Breart G, et al. Aspirin (100mg) used for prevention of pre-eclampsia in nulliparous women: the Essai Regional Aspirine Mere-Enfant study (Part 1). *BJOG: an international journal of obstetrics and gynaecology* 2003; **110**:475–84.

Subtil D, Quandalle F, Houfflin-Debarge V, Malek Y, Truffert P, Breart G, et al. Low dose aspirin to prevent preeclampsia: what do we learn from a new "negative" trial? [abstract]. *European Journal Obstetrics & Gynecology and Reproductive Biology* 2002;**104**:179.

Finland 1993 *{published data only}*

* Viinikka L, Hartikainen-Sorri AL, Lumme R, Hiilesmaa V, Ylikorkala O. Low dose aspirin in hypertensive pregnant women: effect on pregnancy outcome and prostacyclin-thromboxane balance in mother and newborn. *British Journal of Obstetrics and Gynaecology* 1993;**100**:809–15.

Viinikka L, Hartikainen-Sorri AL, Lumme R, Hiilesmaa V, Ylikorkala O. The effect of 50mg of ASA daily on pregnancy outcome and maternal and newborn prostacyclin and thromboxane. Proceedings of 2nd European Congress on Prostaglandins in Reproduction; 1991 April 30-May 3; The Hague, Netherlands. 1991:93.

Finland 1997 *{published data only}*

Zimmermann P, Eirio V, Koskinen J, Niemi K, Nyman R, Kujansuu E, et al. Effect of low dose aspirin treatment on vascular resistance in the uterine, uteroplacental, renal and umbilical arteries - a prospective longitudinal study on a high risk population with persistent notch in the uterine arteries. *European Journal of Ultrasound* 1997;**5**:17–30.

Finland 1997a *{published data only}*

Tulppala M, Marttunen M, Soderstrom-Anttila V, Ailus K, Palosuo T, Ylikorkala O. Low dose aspirin in prevention of miscarriage in women with unexplained or autoimmune related recurrent miscarriage: effect on prostacyclin and thromboxane A2. *Human Reproduction* 1997;**12** (1):191.

Tulppala M, Marttunen M, Soderstrom-Anttila V, Foudila T, Ailus K, Palosuo T, et al. Low-dose aspirin in prevention of miscarriage in women with unexplained or autoimmune related recurrent miscarriage: effect on prostacyclin and thromboxane A2. *Human Reproduction* 1997;**12**:1567–72.

Finland 2002 *{published data only}*

* Vainio M, Kujansuu E, Iso-Mustajarvi M, Maenpaa J. Low dose acetylsalicylic acid in prevention of pregnancy-induced hypertension and intrauterine growth retardation in women with bilateral uterine artery notches. *BJOG: an international journal of obstetrics and gynaecology* 2002;**109**:161–7.

Vainio M, Kujansuu E, Riutta A, Maenpaa J. Effect of ASA on the risk of gestational hypertension and prostanoid synthesis in pregnant women screened by Doppler ultrasound. XXXIV Congress of Nordic Federation of Societies of Obstetrics and Gynecology; 2004 June 12-15; Helsinki, Finland. 2004:21.

Vainio M, Riutta A, Koivisto AM, Maenpaa J. 9 alpha,11 beta-prostaglandin f2 in pregnancies at high risk for hypertensive disorders of pregnancy, and the effect of acetylsalicylic acid. *Prostaglandins Leukotrienes & Essential Fatty Acids* 2003;**69**(1):79–83.

Vainio M, Riutta A, Koivisto AM, Maenpaa J. Prostacyclin, thromboxane a2 and the effect of low-dose asa in pregnancies at high risk of hypertensive disorders. *Acta Obstetricia et Gynecologica Scandinavica* 2004;**83**:1119–23.

France 1985 *{published data only}*

Beaufils M, Uzan S, Donsimoni R, Colau JC. A controlled trial of prophylactic treatment of preeclampsia: preliminary results. *Archives des Maladies du Coeur* 1984;**77**:1226–8.

* Beaufils M, Uzan S, Donsimoni R, Colau JC. Prevention of pre-eclampsia by early antiplatelet therapy. *Lancet* 1985;**1**:840–2.

France 1990 *{published data only}*

Azar R, Turpin D. Effect of antiplatelet therapy in women at high risk for pregnancy-induced hypertension. Proceedings of 7th World Congress of Hypertension in Pregnancy; 1990 October; Perugia, Italy. 1990:257.

Germany 2000 *{published data only}*

Erdmann M, Paulus WE, Flock F, Herget I, Terinde R, Grab D. Utero and fetoplacental hemodynamic measurements with low dose aspirin [Utero-und fetoplazentae haemodynamische Messiungen unter low-

dose aspirin]. *Zeitschrift fur Gerburtshilfe und Neonatologie* 1999;**203** (1):18–23.

Grab D, Erdmann M, Paulus W, Oberhoffer R, Lang D. Effects of low dose aspirin on uterine and fetal blood flow during pregnancy: a randomized placebo controlled double blind trial. *Acta Obstetricia et Gynecologica Scandinavica* 1997;**76**:38.

* Grab D, Paulus WE, Erdmann M, Terinde R, Oberhoffer R, Lang D, et al. Effects of low-dose aspirin on uterine and fetal blood flow during pregnancy: results of a randomized, placebo-controlled, double-blind trial. *Ultrasound in Obstetrics & Gynecology* 2000;**15**:19–27.

India 1993 *{published data only}*

Rai U, Chakravorty M, Juneja Y. Role of low dose aspirin in PIH. Journal of Obstetrics and Gynaecology of India 1993:883–6.

India 1994 *{published data only}*

Roy UK, Pan S. A study of low dose aspirin in prevention of pregnancy induced hypertension. *Journal of the Indian Medical Association* 1994;**92**:188–91.

India 1999 *{published data only}*

Shenoy S, Chandrika D, Pisharody R. RCT of low dose aspirin to prevent the progression of pregnancy induced hypertension grade A to B. *Journal of Clinical Epidemiology* 1999;**52 Suppl 1**:28S.

Israel 1989 *{published data only}*

Schiff E, Peleg E, Goldenberg M, Rosenthal T, Ruppin E, Tamarkin M, et al. The use of aspirin to prevent pregnancy-induced hypertension and lower the ratio of thromboxane A2 to prostacyclin in relatively high risk pregnancies. *New England Journal of Medicine* 1989; **321**:351–6.

Israel 1990 *{published data only}*

Schiff E, Barkai G, Ben-Baruch G, Mashiach S. Low-dose aspirin does not influence the clinical course of women with mild pregnancy-induced hypertension. *Obstetrics & Gynecology* 1990;**76**:742–4.

Israel 1994 *{published data only}*

Caspi E, Raziel A, Sherman D, Arieli S, Bukovski I, Weintraub Z. Prevention of pregnancy induced hypertension in twins by early administration of low-dose aspirin: a preliminary report. *American Journal of Reproductive Immunology* 1994;**31**:19–24.

Italy 1989 *{published data only}*

Ballerini S, Valcamonico A, Greorini G, Frusca T, Benigni A, Orisio S, et al. Low dose aspirin (ASA) given to prevent preeclampsia only partially inhibits platelet cyclooxygenase activity. Proceedings of 6th World Congress of Hypertension in Pregnancy; 1988 May 22-26; Montreal, Quebec, Canada. 1988:234.

* Benigni A, Gregorini G, Frusca T, Chiabrando C, Ballerini S, Valcamonico A, et al. Effect of low-dose aspirin on fetal and maternal generation of thromboxane by platelets in women at risk for pregnancy-induced hypertension. *New England Journal of Medicine* 1989; **321**:357–62.

Frusca T, Gregorini G, Ballerini S, Marchesi D, Bruni M. Low dose aspirin in preventing preeclampsia and IUGR. Proceedings of 6th World Congress of Hypertension in Pregnancy; 1988 May 22-26; Montreal, Quebec, Canada. 1988:232.

Italy 1993 *{published data only}*

* Italian Study of Aspirin in Pregnancy. Low-dose aspirin in prevention and treatment of intrauterine growth retardation and pregnancy-induced hypertension. *Lancet* 1993;**341**:396–400.

Parazzini DF. Low-dose aspirin in prevention and treatment of intrauterine growth retardation and pregnancy-induced hypertension. *Geburtshilfe und Frauenheilkunde* 1993;**53**:822.

Parazzini F. Multicenter randomized Italian study of low-dose aspirin for the prevention of pre-eclampsia and intrauterine growth retardation. *Journal of Nephrology* 1991;**4**:127–9.

Parazzini F, Benedetto C, Frusca T, Guaschino S, Romero M. The Italian study on low-dose aspirin for the prevention of pre-eclampsia and intrauterine growth retardation. Proceedings of 7th World Congress of Hypertension in Pregnancy; 1990 October; Perugia, Italy. 1990:32.

Parazzini F, Bortolus R, Chatenoud L, Restelli S, Benedetto C. Follow-up of children in the Italian Study of Aspirin in Pregnancy. *Lancet* 1994;**343**:1235.

Parazzini F, Bortolus R, Chatenoud L, Restelli S, Ricci E, Marozio L, et al. Risk factors for pregnancy-induced hypertension in women at high risk for the condition. *Epidemiology* 1996;**7**(3):306–8.

Italy 1999 *{published data only}*

Volpicelli T, D'Anto V, Faticato A, Galante L, Civitillo RM, Rappa C, et al. Trial prospettico sull'uso profilattico dell'aspirina in donne gravide ad alto rischio di preeclampsia. Gestosi '99. 1999:159–60.

Italy 2004 *{published data only}*

Chiaffarino F, Parazzini F, Paladini D, Acaia B, Ossola W, Marozio L, et al. A small randomised trial of low-dose aspirin in women at high risk of pre-eclampsia. *European Journal of Obstetrics & Gynecology and Reproductive Biology* 2004;**112**:142–4.

Jamaica 1998 *{unpublished data only}*

Elder MG, de Swiet M, Sullivan M. A randomised trial of low dose aspirin for primiparae in pregnancy (golding)/barbados low dose aspirin study in pregnancy (blasp) (rotchell et al.) [Letter; comment]. *British Journal of Obstetrics & Gynaecology* 1999;**106**(2):180.

Forrester TE, Jones D, McCaw-Binns A, Palmer-Levy M, Wilks R, Bernard GW, et al. Low-dose aspirin in pregnancy - are there any benefits? [abstract]. *West Indian Medical Journal* 1996;**45**(2 Suppl): 26.

* Golding J. A randomised trial of low dose aspirin for primiparae in pregnancy. *British Journal of Obstetrics and Gynaecology* 1998;**105**: 293–9.

McCaw-Binns A, Ashley D, Hawkins N, MacGillivray I, Golding J. International variation in the incidence of hypertension in pregnancy among primiparae: the jamaican experience. 10th World Congress of the International Society for the Study of Hypertension in Pregnancy; 1996 August 4-8; Seattle, Washington, USA. 1996:168.

McCaw-Binns A, Jamaica Low-Dose Aspirin Group. Low dose aspirin in pregnancy - are there any benefits?. 10th World Congress of the International Society for the Study of Hypertension in Pregnancy; 1996 August 4-8; Seattle, Washington, USA. 1996:76.

Japan 1999 *{published data only}*

Seki H, Kuromaki K, Takeda S, Kinoshita K, Satoh K. Trial of prophylactic administration of TXA2 synthetase inhibitor, ozagrel hydrochloride, for preeclampsia. *Hypertension in Pregnancy* 1999;**18**: 157–64.

Netherlands 1986 *{published data only}*

Dekker GA. Low dose aspirin prevents pregnancy-induced hypertensive disease in angiotensin-sensitive primigravidae. *Prediction and prevention of pregnancy-induced hypertensive disorders: a clinical and pathophysiologic study. [MD thesis]*. Rotterdam, The Netherlands: University Medical School, 1989:91–102.

* Wallenburg HCS, Dekker GA, Makovitz JW, Rotmans P. Low-dose aspirin prevents pregnancy-induced hypertension and pre-eclampsia in angiotensin-sensitive primigravidae. *Lancet* 1986;**1**:1–3.

Netherlands 1989 *{published data only}*

Dekker GA. *Prediction and prevention of pregnancy-induced hypertensive disorders: a clinical and pathophysiologic study [MD thesis]*. Rotterdam, The Netherlands: University Medical School, 1989.

Netherlands 1991a *{published data only}*

* Wallenburg HCS, Dekker GA, Makovitz JW, Rotmans N. Effect of low-dose aspirin on vascular refractoriness in angiotensin-sensitive primigravid women. *American Journal of Obstetrics and Gynecology* 1991;**164**:1169–73.

Wallenburg HCS, Dekker GA, Makowitz JW. Reversal of elevated vascular angiotensin II responsiveness in pregnancy by low-dose aspirin. Proceedings of 34th Annual Meeting of the Society for Gynecologic Investigation; 1987 March 18-21; Georgia, USA. 1987:22.

Russia 1993 *{published and unpublished data}*

* Rogov V, Tareeva I, Sidorova S, Androsova S. Prevention of pregnancy complications with acetylsalicylic acid (ASA) and dipyridamol (DP) in women with chronic glomerulonephritis (CGN) and essential hypertension (EH). Proceedings of 9th International Congress of the International Society for the Study of Hypertension in Pregnancy; 1994 March 15-18; Sydney, Australia. 1994:280.

Rogov VA, Tareeva I, Sidorova S, Androsova SO, Katamadze KT, Nikiforova OV. Prevention of pregnancy complications in glomerulonephritis and hypertension with acetylsalicylic acid and curantyl. *Terapevticheskii Arkhiv* 1993;**65**:65–8.

S Africa 1988 *{published and unpublished data}*

Railton A, Davey A. Aspirin and dipyridamole in the prevention of pre-eclampsia: effect on plasma prostanoids 6 keto PG1a and TXB2 and clinical outcome of pregnancy. Proceedings of the 6th International Congress of the International Society for the Study of Hypertension in Pregnancy; 1988 May 22-26; Montreal, Quebec, Canada. 1988:60.

Railton A, Davey DA. Aspirin and dipyridamole in the prevention of pre-eclampsia: effect on plasma 6 keto PGF1alpha and TxB2 and clinical outcome of pregnancy. Proceedings of 1st European Congress on Prostaglandins in Reproduction; 1988 July 6-9; Vienna, Austria. 1988:48.

Spain 1997 *{published data only}*

Hermida RC, Ayala DE, Iglesias M, Mojon A, Silva I, Ucieda R, et al. Time-dependant effects of low dose aspirin administration on blood pressure in pregnant women. *Hypertension* 1997;**30**:589–95.

Spain 1999 *{published data only}*

Hermida R, Ayala D, Mojon A, Fernandez J, Alonso I, Silva I, et al. Time dependant effects of low dose aspirin administration on blood pressure in high risk pregnancy. *Hypertension in Pregnancy* 2000;**19** (Suppl 1):81.

Hermida RC, Ayala DE, Fernandez JR, Mojon A, Alonso I, Silva I, et al. Administration time-dependent effects of aspirin in women at differing risk for preeclampsia. *Hypertension* 1999;**33**(4):1079.

* Hermida RC, Ayala DE, Fernandez JR, Mojon A, Alonso I, Silva I, et al. Administration time-dependent effects of aspirin in women at differing risk for preeclampsia. *Hypertension* 1999;**34**(4 Pt 2):1016–23.

Hermida RC, Ayala DE, Fernandez JR, Mojon A, Alonso I, Ucieda R, Silva I, et al. Administration-time dependent effects of aspirin in women at high risk for preeclampsia. *Hypertension in Pregnancy* 2000; **19**(Suppl 1):35.

Hermida RC, Ayala DE, Iglesias M. Administration time-dependant influence of aspirin on blood pressure in pregnant women. *Hypertension* 2003;**41**:651–6.

Hermida RC, Ayala DE, Iglesias M. Administration-time dependent effects of low-dose aspirin on blood pressure in women at high risk for pre-eclampsia. *Hypertension in Pregnancy* 2002;**21**(Suppl 1):47.

Hermida RC, Ayala DE, Iglesias M. Administration-time dependent effects of low dose aspirin on the incidence of complications in women at high risk for preeclampsia. *Hypertension in Pregnancy* 2002;**21**(Suppl 1):20.

Tanzania 1995 *{published data only}*

Ramaiya C, Mgaya H. Low dose aspirin in prevention of pregnancy-induced hypertension in primigravidae at the Muhimbili Medical Centre, Dar Es Salaam. *Acta Obstetricia et Gynecologica Scandinavica* 1997;**76**(167):1.

* Ramaiya C, Mgaya HN. Low dose aspirin in prevention of pregnancy-induced hypertension in primigravidae at the Muhimbili Medical Centre, Dar es Salaam. *East African Medical Journal* 1995; **72**:690–3.

Ramaiya CP. *Low dosage of aspirin in prevention of pregnancy induced hypertension (PIH) in primigravidae at Muhimbili Medical Centre, Dar es Salaam [MD thesis]*. Ethiopia: University of Dar es Salaam, 1992.

UK 1990 *{published data only}*

* McParland, Pearce JM, Chamberlain GVP. Doppler ultrasound and aspirin in recognition and prevention of pregnancy-induced hypertension. *Lancet* 1990;**335**:1552–5.

McParland PJ, Pearce JMP. Low dose aspirin prevents proteinuric hypertension in women with abnormal uteroplacental waveforms. Proceedings of Silver Jubilee Congress of Obstetrics and Gynaecology; 1989 July 4-7; London, UK. 1989:8.

UK 1992 *{published data only}*

Louden KA, Broughton PF, Heptinsall S, Mitchell JRA, Symonds EM. Maternal low-dose aspirin spares the neonate. Proceedings of Silver Jubilee Congress of Obstetrics and Gynaecology; 1989 July 4-7; London, UK. 1989:9.

Louden KA, Broughton PF, Symonds EM, Tuohy P, O'Callaghan C, Heptinstall S, et al. A randomized placebo-controlled study of the effect of low dose aspirin on platelet reactivity and serum thromboxane B2 production in non-pregnant women, in normal pregnancy and in gestational hypertension. *International Journal of Gynecology & Obstetrics* 1993;**40**:186.

Louden KA, Broughton-Pipkin F, Heptinstall S, Fox SC, Tuohy P, O'Callaghan C, et al. Neonatal platelet reactivity and serum thromboxane B2 production in whole blood: the effect of maternal low dose aspirin. *British Journal of Obstetrics and Gynaecology* 1994;**101**: 203–8.

Louden KA, Broughton Pipkin F, Heptinstall S, Mitchell JRA, Symonds EM. Studies of the effect of low-dose aspirin on thromboxane production and platelet reactivity in normal pregnancy, pregnancy-induced hypertension and neonates. Proceedings of 1st European Congress on Prostaglandins in Reproduction; 1988 July 6-9; Vienna, Austria. 1988:30.

Louden KA, Broughton-Pipkin F, Heptinstall S, Mitchell RAM, Symonds EM. Maternal low-dose aspirin spares neonatal platelets. *British Journal of Obstetrics and Gynaecology* 1990;**97**:1162.

* Louden KA, Broughton Pipkin F, Symonds EM, Tuohy P, O'Callaghan C, Heptinstall S, et al. A randomized placebo-controlled study of the effect of low dose aspirin on platelet reactivity and serum thromboxane B2 production in non-pregnant women, in normal pregnancy, and in gestational hypertension. *British Journal of Obstetrics and Gynaecology* 1992;**99**:371–6.

UK 1992b *{published data only}*

Quenby S, Farquharson R, Ramsden G. The obstetric outcome of patients with positive anticardiolipin antibodies: aspirin vs no treatment. Proceedings of 26th British Congress of Obstetrics and Gynaecology; 1992 July 7-10; Manchester, UK. 1992:443.

UK 1995 *{published data only}*

Davies NJ. A study of low dose aspirin for the prevention of hypertensive disorders of pregnancy in primiparous women. Proceedings of 2nd European Congress on Prostaglandins in Reproduction; 1991 April 30-May 3; The Hague, Netherlands. 1991:183.

Davies NJ, Farquharson RG, Walkinshaw SA. Low-dose aspirin and nulliparae. *Lancet* 1991;**338**:324.

* Davies NJ, Gazvani MR, Farquharson RG, Walkinshaw SA. Low-dose aspirin in the prevention of hypertensive disorders of pregnancy in relatively low-risk nulliparous women. *Hypertension in Pregnancy* 1995;**14**:49–55.

UK+others 2003 *{published data only}*

Yu CKH, Papageorghiou AT, Parra M, Palma Dias R, Nicolaides KH. Randomized controlled trial using low-dose aspirin in the prevention of pre-eclampsia in women with abnormal uterine Doppler at 23 weeks gestation. *Ultrasound in Obstetrics & Gynecology* 2003;**22**:233–9.

USA 1993 *{published and unpublished data}*

Copper R, Hauth J, Cutter G, DuBard M, Goldenberg R. Prerandomization compliance testing may predict pregnancy outcome in a randomized clinical trial. *American Journal of Obstetrics and Gynecology* 1993;**168**:414.

Goldenberg RL, Hauth JC, Copper RL, DuBard MB, Cutter GR. The effect of low dose aspirin on fetal growth in low risk primiparas. *American Journal of Obstetrics and Gynecology* 1993;**168**:383.

Goldenberg RL, Hauth JC, DuBard MB, Copper RL, Cutter GR. Fetal growth in women using low-dose aspirin for the prevention of preeclampsia: effect of maternal size. *Journal of Maternal Fetal Medicine* 1995;**4**:218–24.

Hauth J, Goldenberg R, Parker C, DuBard M, Copper R, Cutter G. Maternal serum thromboxane B2 reduction vs pregnancy outcome in a low-dose aspirin trial. *American Journal of Obstetrics and Gynecology* 1993;**168**:316.

Hauth J, Goldenberg R, Philips J, Copper R, DuBard M, Cutter G. Low-dose aspirin therapy to prevent preeclampsia: safety considerations. *American Journal of Obstetrics and Gynecology* 1993;**168**:389.

Hauth JC, Goldenberg RL, DuBard MB, Copper RL, Parker CR. Low-dose asprin does not alter longitudinal maternal blood pressures. *American Journal of Obstetrics and Gynecology* 1995;**172**:377.

Hauth JC, Goldenberg RL, Parker CR, Copper RL, Cutter GR. Maternal serum thromboxane B2 reduction vs pregnancy outcome in a low-dose aspirin trial. *American Journal of Obstetrics and Gynecology* 1995;**173**:578–84.

* Hauth JC, Goldenberg RL, Parker CR Jr, Philips JB 3rd, Copper RL, DuBard MB, et al. Low-dose aspirin therapy to prevent preeclampsia. *American Journal of Obstetrics and Gynecology* 1993; **168**:1083–93.

Hauth JC, Goldenberg RL, Parker R, Philips JB, Copper RL, DuBard MB, et al. Low-dose aspirin therapy to prevent preeclampsia. *International Journal of Gynecology & Obstetrics* 1994;**44**:97.

Maher J, Owen J, Hauth J, Goldenberg R, Parker C. Low dose aspirin: effect on fetal urine output. *American Journal of Obstetrics and Gynecology* 1993;**168**:332.

Maher JE, Owen J, Hauth J, Goldenberg R, Parker CR Jr, Copper RL. The effect of low-dose aspirin on fetal urine output and amniotic fluid volume. *American Journal of Obstetrics and Gynecology* 1993; **169**:885–8.

Owen J, Maher J, Hauth J, Goldenberg R, Parker C. The effect of low dose aspirin on umbilical artery Doppler measurements. *American Journal of Obstetrics and Gynecology* 1993;**168**:357.

Owen J, Maher JE, Hauth JC, Goldenberg RL, Parker CR Jr. The effect of low-dose aspirin on umbilical artery Doppler measurements [published erratum appears in Am J Obstet Gynecol 1994 Jun;170 (6):1841]. *American Journal of Obstetrics and Gynecology* 1993;**169**: 907–11.

Wenstrom KD, Hauth JC, Goldenberg RL, DuBard M, Lea C. The effect of low-dose aspirin on the development of preeclampsia in women with elevated hCG. *American Journal of Obstetrics and Gynecology* 1995;**172**:376.

Wenstrom KD, Hauth JC, Goldenberg RL, DuBard MB, Lea C. The effect of low-dose aspirin on pregnancies complicated by elevated human chorionic gonadotropin levels. *American Journal of Obstetrics and Gynecology* 1995;**173**:1292–6.

USA 1993a *{published data only}*

Caritis S, Sibai B, Thorn E, McLaughlin S, NICHD-MFM Network. Pregnancy effects of non-proteinuric gestational hypertension (GH). *American Journal of Obstetrics and Gynecology* 1995;**172**:376.

Di Sessa TG, Moretti ML, Khoury A, Pulliam DA, Arheart KL, Sibai BM. Cardiac function in fetuses and newborns exposed to low-dose aspirin during pregnancy. *American Journal of Obstetrics and Gynecology* 1994;**171**:892–900.

Sibai B. Low-dose aspirin (60 mg/d) in pregnancy for the prevention of preeclampsia. 8th World Congress on Hypertension in Pregnancy; 1992 November 8-12; Buenos Aires, Argentina 1992. 1992:50.

Sibai B, Caritis S, Phillips E, Klebanoff M, McNellis D, Rocco L. Prevention of preeclampsia: low-dose aspirin in nulliparous women: a double-blind, placebo controlled trial. *American Journal of Obstetrics and Gynecology* 1993;**168**:286.

Sibai B, Caritis S, Phillips E, Klebanoff M, Paul R, Witter F, et al. Safety of low-dose aspirin in healthy nulliparous women: a double-blind, placebo-controlled trial. Proceedings of 40th Annual Meeting Society for Gynecologic Investigation; 1993 March; Toronto, Canada. 1993:S102.

Sibai B, Caritis S, Thom E, Shaw K, McNellis D, NICHD-MFM Network. Low-dose aspirin in nulliparous women: safety of epidural and correlation between bleeding time and maternal-neonatal bleeding complications. *American Journal of Obstetrics and Gynecology* 1994;**170**:293.

Sibai B, Gordon T, Phillips E, McNellis D, Caritis S, Romero R, et al. Risk factors for preeclampsia in healthy nulliparous women: a prospective multicenter study. Proceedings of 41st Annual Clinical Meeting of The American College of Obstetricians and Gynecologists; 1993 May 3-6; Washington DC, USA. 1993:2.

* Sibai BM, Caritis SN, Thom E, Klebanoff M, McNellis D, Rocco L, et al. Prevention of preeclampsia with low-dose aspirin in healthy, nulliparous pregnant women. *New England Journal of Medicine* 1993; **329**:1213–8.

Sibai BM, Caritis SN, Thom E, Shaw K, McNellis D, NICHD-MFM Network. Low dose aspirin in nulliparous women: safety of continuous epidural block and correlation between bleeding time and maternal-neonatal bleeding complications. *American Journal of Obstetrics and Gynecology* 1995;**172**:1533–7.

Sibai BM, Gordon T, Thom E, Caritis SN, Klebanoff M, McNellis D, et al. Risk factors for preeclampsia in healthy nulliparous women: a prospective multicenter study. *American Journal of Obstetrics and Gynecology* 1995;**172**:642–8.

Witten FR. Double-blind, placebo-controlled trial of low-dose aspirin to prevent pre-eclampsia. Personal communication September 6 1991.

Yaffe S. Clinical trial of low dose aspirin (65mg) as a preventative of pre-eclampsia. Personal communication December 3 1991.

USA 1994 *{published data only}*

August P, Helseth G, Edersheim TG, Hutson JM, Druzin M. Sustained release, low-dose aspirin ameliorates but does not prevent preeclampsia (PE) in a high risk population. Proceedings of 9th International Congress, International Society for the Study of Hypertension in Pregnancy; 1994 March 15-18; Sydney, Australia. 1994: 72.

USA 1997 *{published data only}*

Cowchock S, Reece EA. Do low-risk pregnant women with antiphospholipid antibodies need to be treated? Organizing group of the antiphospholipid antibody treatment trial. *American Journal of Obstetrics and Gynecology* 1997;**176**(5):1099–100.

USA 1998 *{published and unpublished data}*

Caritis NS, NICHD-MFMU Network. Impact of preeclampsia on a subsequent pregnancy. *American Journal of Obstetrics and Gynecology* 1998;**178**(1 Pt 2):S120.

Caritis S. Low dose aspirin does not prevent preeclampsia in high risk women. *American Journal of Obstetrics and Gynecology* 1997;**176** (1 Pt 2):S3.

* Caritis S, Sibai B, Hauth J, Lindheimer M, Klebanoff M, Thom E, et al. Low-dose aspirin to prevent preeclampsia in women at high risk. *New England Journal of Medicine* 1998;**338**:701–5.

Hauth J, Sibai B, Caritis S, VanDorsten P, Lindheimer M, Klebanoff M, et al. Maternal serum thromboxane B2 concentrations do not predict improved outcomes in high-risk pregnancies in a low-dose aspirin trial. *American Journal of Obstetrics and Gynecology* 1998;**179**: 1193–9.

Hauth JC, NICHD MFMU Network. Adverse maternal, fetal and neonatal outcomes in a low dose aspirin trial who developed preeclampsia. *American Journal of Obstetrics and Gynecology* 1998;**178** (1 Pt 2):S110.

Hauth JC, NICHD MFMU Network. Maternal serum thromboxane B2 (TxB2) reduction did not predict improved pregnancy outcome in high risk women in a low dose aspirin trial. *American Journal of Obstetrics and Gynecology* 1998;**178**(1 Pt 2):S110.

Hauth JC, NICHD MFMU Network. Safety of low dose aspirin in high risk patients. *American Journal of Obstetrics and Gynecology* 1998;**178**(1 Pt 2):S111.

Sibai B. Low-dose aspirin (60 mg/d) in pregnancy for the prevention of preeclampsia. 8th World Congress on Hypertension in Pregnancy; 1992 November 8-12; Buenos Aires, Argentina. 1992:50.

Venezuela 2000 *{published data only}*

Rivas-Echeverria CA, Echeverria Y, Molina L, Novoa D. Synergic use of aspirin, fish oil and vitamins C and E for the prevention of preeclampsia. *Hypertension in Pregnancy* 2000;**19**:30.

Zimbabwe 1998 *{published data only}*

Byaruhanga RN, Chipato T, Rusakaniko S. A randomized controlled trial of low-dose aspirin in women at risk from pre-eclampsia. *International Journal of Gynecology & Obstetrics* 1998;**60**:129–35.

References to studies excluded from this review

Australia 1989

Robinson JS. Can the genetic risk of pre-eclampsia be reduced by low dose aspirin?. Personal communication March 25 1993.

Australia 1989a

Trudinger BJ, Cook CM, Giles WB, Connelly AJ, Thompson RS. Low-dose aspirin and twin pregnancy. *Lancet* 1989;**2**:1214.

Brazil 1992

Montenegro CAB. The effect of aspirin therapy on the uterine circulation in preeclampsia. Proceedings of the 8th World Congress of the International Society for the Study of Hypertension in Pregnancy; 1992 November 8-12; Buenos Aires, Argentina. 1992:66.

Brazil 1996a

Sass N, Rocha NSC, Callegari AH, Lima PCA, Camano L. The low dose aspirin study in pregnancy with chronic hypertension (AASHAC). Proceedings of the 10th World Congress on Hypertension in Pregnancy; 1996 August 4-8; Seattle, USA. 1996:152.

China 1991

Cheng WW, Zhang ZJ. Low-dose aspirin preventing pregnancy induced hypertension. *Chung Hua Fu Chan Ko Tsa Chih* 1991;**26**(6): 342–5.

Colombia 1996

Hernandez F, Martinez MF, Camero A, Pinzon JA. Low dose aspirin as prophylactic therapy of pregnancy induced hypertension. *Revista Colombiana de Obstetricia y Ginecologia* 1996;**47**:197–201.

East Germany 1986

Peterseim H, Hofmann KD, Wagner F, Peterseim S, Meier P. Inhibition of prostaglandin synthetase by low-dose acetylsalicylic acid - effects on severity of pregnancy induced hypertension and fetal outcome. Proceedings of 10th European Congress of Perinatal Medicine; 1986 August 12-16; Leipzig, Germany. 1986:290.

East Germany 1988

Heinrich J. Prophylactic management of pregnancy induced hypertension (PIH). Proceedings of 11th European Congress of Perinatal Medicine; 1988; Rome, Italy. 1988:274.

Egypt 1991

Toppozada M, Darwish EA, Osman YF, Abd-Rabbo MS. Low dose acetyl salicylic acid in severe pre-eclampsia. *International Journal of Gynecology & Obstetrics* 1991;**35**:311–7.

Egypt 1998

Shalan H, Kurjak A, Lakkany N. The effect of low dose aspirin versus allylestrinol on uterine artery blood flow. *Prenatal and Neonatal Medicine* 1998;**3 Suppl 1**:141.

Equador 1998

Armando CA, Martha CC, Galo EV. Prevention of the development of preeclampsia by means of the administration of low doses of aspirin. Quito 1998:80.

ERASME 2003a

Subtil D, Goeusse P, Houfflin-Debarge V, Puech F, Lequien P, Breart G, et al. Aspirin (100mg) used for prevention of pre-eclampsia in nulliparous women: the Essai Regional Aspirine Mere-Enfant study (Part 2). *BJOG: an international journal of obstetrics and gynaecology* 2003;**110**:485–91.

Finland 1993a

Kaaja R, Julkunen H, Viinikka L, Ylikorkala O. Production of prostacyclin and thromboxane in lupus pregnancies: effect of small dose of aspirin. *Obstetrics & Gynecology* 1993;**81**:327–31.

France 2001

* Goffinet F. Aboulker D, Paris-Llado J, Bucourt M, Uzan M, Papiernik E, et al. Screening with a uterine Doppler in low risk pregnant women followed by low dose aspirin in women with abnormal results: a multicenter randomised controlled trial. *BJOG: an international journal of obstetrics and gynaecology* 2001;**108**:510–8.

Subtil D, Truffert P, Goeusse P, Dufour P, Uzan S, Breart G, et al. Value of systematic doppler +/- low dose aspirin to prevent vascular complications in primigravidae. *Hypertension in Pregnancy* 2000;**19** (Suppl 1):9.

Germany 1986

Niedner W, Beller FK. The influence of ASA on pre-eclampsia. Proceedings of the 5th International Congress of the Society for the Study of Hypertension in Pregnancy; 1986 July 7-10; Nottingham, UK. 1986:101.

India 1986

Bhattacharya N, Chaudhuri N, Ghosh S, Pradhan P, Ghosh CR. Effect of platelet aggregation inhibitor on fetal outcome in EPH gestosis with IUGR. Proceedings of the 5th Congress of the International Society for the Study of Hypertension in Pregnancy; 1986 July 7-10; Nottingham, UK. 1986:82.

India 1991

Grover V, Sachdeva S, Kumari S. Evaluation of dipyridamole and aspirin in prevention and management of intrauterine growth retardation. *Journal of Perinatal Medicine* 1991;**19**(2):104.

India 1993a

Regi A. Randomised controlled trial of low dose aspirin in high risk pregnancy. Personal communication 1993.

India 1997

Tewari S, Kaushish R, Sharma S, Gulati N. Role of low dose aspirin in prevention of pregnancy induced hypertension. *Journal of the Indian Medical Association* 1997;**95**:43-5, 47.

India 1998

Dasari R, Narang A, Vasishta K, Garewal G. Effect of maternal low dose aspirin on neonatal platelet function. *Indian Pediatrics* 1998; **35**:507–11.

India 2001

Sehgal R, Sood M. Role of low dose aspirin for prevention of pregnancy induced hypertension. *Journal of Obstetrics and Gynecology of India* 2001;**51**(5):81–4.

India 2002

Desai P, Rao S. Role of low dose aspirin in mothers registering high serum HCG levels at mid trimester. *Journal of Obstetrics and Gynecology of India* 2002;**52**(5):30–2.

India 2002a

Khanna A, Prabhakar S. Maternal and foetal outcome with low dose aspirin in pregnancy induced hypertension. *Journal of Obstetrics and Gynecology of India* 2002;**52**(3):62–4.

Iran 2002

Taherian A, Taherian A, Shirvani A. Prevention of preeclampsia with low-dose aspirin or calcium supplementation. *Archives of Iranian Medicine* 2002;**5**:151–6.

Ireland 1995

Regan CL, McAdam BF, McParland P, Boylan PC, FitzGerald GA, Fitzgerald DJ. Reduced fetal exposure to aspirin using a novel controlled release preparation in normotensive and hypertensive pregnancies. *British Journal of Obstetrics and Gynaecology* 1998;**105**:732–8.

Regan CL, McAdam BV, McParland P, Boylan P, FitzGerald GA, Fitzgerald DJ. Pharmacology of low dose aspirin in normotensive and hypertensive pregnancies. 27th British Congress of Obstetrics and Gynaecology; 1995 July 4-7; Dublin, Ireland. 1995:301.

Italy 1988

Airoldi ML, Capetta P, Tasca A, Bertulessi C, Rossi E, Polvani F. Role of early prevention with heparin and dipyridamole in the prevention of pre-eclampsia and placental insufficiency. Proceedings of the 6th International Congress of the International Society for the study of Hypertension in Pregnancy; 1988 May 22-26; Montreal, Quebec, Canada. 1988:233.

Capetta P, Airoldi ML, Tasca A, Bertulessi C, Rossi E, Polvani F. Prevention of pre-eclampsia and placental insufficiency. *Lancet* 1986; **1**:919.

Italy 1990

Di Iorio R, Horvath S, Marinoni E, Manzari G, Martinico E, Bresadola M. Use of a thromboxane receptor inhibitor in pregnancy-induced hypertension. Proceedings of 7th World Congress of Hypertension in Pregnancy; 1990 October; Perugia, Italy. 1990:75.

Italy 2002

Frusca T, Lojacono A, Fratelli N, Platto C, Valcamonico A, Bianchi UA. Can low dose aspirin improve perinatal outcome in chronic hypertensive patients [abstract]. *Hypertension in Pregnancy* 2002;**21** (Suppl 1):44.

Italy 2005

Mello G, Parretti E, Fatini C, Riviello C, Gensini F, Marchionni M, et al. Efficacy of LMWH in lowering the recurrence rate of preeclampsia and in restoring the physiological vascular changes in ACE DD genotype women [abstract]. *Hypertension in Pregnancy* 2004;**23**(Suppl 1): 162.

Mello G, Parretti E, Fatini C, Riviello C, Gensini F, Marchionni M, et al. Low-molecular-weight heparin lowers the recurrence rate of preeclampsia and restores the physiological vascular changes in angiotensin-converting enzyme DD women. *Hypertension* 2005;**45** (1):86–91.

Japan 1989

Terao T, Kobayashi T, Imai N, Oda H, Karasawa T. Pathological state of the coagulatory and fibrinolytic system in preeclampsia and the the possibility of its treatment with AT III concentrate. *Asia-Oceania Journal of Obstetrics and Gynaecology* 1989;**15**:25–32.

Libya 2000

Elmahaishi. The uses of low dose aspirin (150mg/day) in primigravida reduces the severity and complications of pregnancy induced hypertension. XVI FIGO World Congress of Obstetrics and Gynaecology; 2000 Sept 3-8; Washington DC, USA (Book 1). 2000:98.

Netherlands 1991

Noort WA, Rotmans N, Keirse MJNC, Wallenburg HCS. Effect of low-dose aspirin with and without dipyridamole on prostanoid biosynthesis in pregnancy. Proceedings of 2nd European Congress on Prostaglandins in Reproduction; 1991 April 30-May 3; The Hague, Netherlands. 1991:182.

Wallenburg HCS, Rotmans N, Noort WA, Keirse MJNC. Effect of low-dose aspirin with and without dipyridamole on prevention of recurrent idiopathic fetal growth retardation. Proceedings of 2nd European Congress on Prostaglandins in Reproduction; 1991 April 30-May 3; The Hague, Netherlands 1991:92.

Netherlands/UK 1994

* Kraavenbrink A, Gans R, van Geijn H, Dekker G. Insulin resistance, vasoactive mediators and preeclampsia. *American Journal of Obstetrics and Gynecology* 1997;**176**(1 Pt 2):S26.

Kraayenbrink AA, Robson M, Dekker GA, Pearce JM, van Geijn HP. Prevention of preeclampsia and fetal growth retardation; allylestrenol vs aspirin, a two centered study. Proceedings of 9th International Congress, International Society for the Study of Hypertension in Pregnancy; 1994 March 15-18; Sydney, Australia 1994:125.

New Zealand 1990

Hutton JD, Wilkinson AM. Poor participation of nulliparous women in a low dose aspirin study to prevent preeclampsia. *New Zealand Medical Journal* 1990;**103**:511–2.

New Zealand 1998

McCowan L, Harding J, Ford C, Barker S, Roberts A, Townend K. Prenatal treatment with low dose aspirin in small for gestational age fetuses with abnormal umbilical doppler: a randomised controlled trial. 2nd Annual Congress of the Perinatal Society of Australia and New Zealand; 1998 March 30-April 4; Alice Springs, Australia. 1998: 135.

McCowan LM, Harding J, Roberts A, Barker S, Ford C, Stewart A. Administration of low dose aspirin to mothers with small for gestational age fetuses and abnormal umbilical Doppler studies to increase birthweight: a randomised double-blind controlled trial. *British Journal of Obstetrics and Gynaecology* 1999;**106**:647–51.

New Zealand 2000

Pattison N, Chamley L, Birdsall M, Zanderigo A, Liddell H, McDougall J. Does aspirin have a role in improving pregnancy outcome for women with the antiphospholipid syndrome? A randomized controlled trial. *American Journal of Obstetrics and Gynecology* 2000;**183**: 1008–12.

Pakistan 1994

Gilani A, Khan Z. Role of aspirin in management of pregnancy induced hypertension. A study in Pakistani population. *Specialist* 1994; **10**:323–5.

Pergar 1987

Uzan S, Beaufils M, Bazin B, Danays T. Idiopathic recurrent fetal growth retardation and aspirin-dipyridamole therapy [letter]. *American Journal of Obstetrics and Gynecology* 1989;**160**:763–4.

Poland 1999

Kalinka J, Sieroszewski P, Hanke W, Laudanski T, Suzin J. Evaluation of the effectiveness of a low dose aspirin in the treatment of intrauterine growth retardation (IUGR). *Ginekologia Polska* 1999;**70**: 126–34.

Russia 1997

Zozulia OV, Rogov VA, Piatakova NV, Tareeva IE. Nitric oxide: its role in the development of pregnancy complications and in their prevention in women with hypertension and chronic glomerulonephritis. *Terapevticheskii Arkhiv* 1997;**69**(6):17–20.

Slovenia 1992

Sajina-Stritar B, Novak-Antolic Z. Antiaggregational therapy in preventing EPH gestosis and its complications. *Journal of Perinatal Medicine* 1992;**20**(Suppl 1):73.

Sajina-Stritar B, Novak-Antolic Z. Antiaggregational therapy in preventing EPH gestosis and its complications. Proceedings of 26th British Congress of Obstetrics and Gynaecology; 1992 July 7-10; Manchester, UK. 1992:454.

Slovenia 1994

Sajina-Stritar B. Prevention of gestational hypertension and its complications with ASA and N-3 fatty acids (comparative study). Proceedings of 14th European Congress of Perinatal Medicine; 1994 June 5-8; Helsinki, Finland. 1994:182.

Slovenia 1998

Sajina-Stritar B. The effect of acetylsalicylic acid and n-3 fatty acids in prevention of complications of hypertension diseases in pregnancy. *Zdravstveni Vestnik* 1998;**67**:489–93.

South Africa 1986

Richards A, Moodley J, Norman R. The use of low dose aspirin in pregnancy induced hypertension. 23rd South African Congress of Obstetrics and Gynaecology; 1986 September 23-26; South Africa. 1986:16.

Spain + others 2000

Cabero L, Bellart J, Bertini A, Althabe O, Bichou C, Bucheli R. Aspirin in early pregnancy to reduce the incidence and/or severity of pregnancy induced hypertension and intrauterine growth retardation in healthy pregnant women. *Hypertension in Pregnancy* 2000;**19**(1): 98.

Switzerland 2000

Ferrier C, Koeferl U, Duerig P, Schneider H. Effects of LMW-heparin and low-dose aspirin on renal uric acid handling in high-risk pregnancies. *Hypertension in Pregnancy* 2000;**19**(Suppl 1):O68.

Ferrier C, Koferl U, Durig P, Schneider H. LMW heparin and low dose aspirin for prevention of preeclampsia: preliminary data of a randomised prospective study [abstract]. *Hypertension in Pregnancy* 2000;**19**(1):82.

Thailand 1996

* Herabutya Y, Jetsawangsri T, Saropala N. The use of low-dose aspirin to prevent preeclampsia. *International Journal of Gynecology & Obstetrics* 1996;**54**:177–8.

Jetsawangsri T, Herabutya Y, Saropala N. The use of low-dose aspirin to prevent pre-eclampsia. Abstracts of 9th Congress of the Federation of the Asia and Oceania Perinatal Societies; 1996 November 10-14; Singapore. 1996:129.

Trinidad 1997

Bassaw B, Roopnarinesingh S, Roopnarinesingh A, Homer H. Prevention of hypertensive disorders of pregnancy. *Journal of Obstetrics and Gynaecology* 1998;**18**:123–6.

Tunisia 1989

Hachicha J, Ammous A, Damak J, Hammami M, Ghorbel A, Rekik S, et al. Prevention of complications of hypertension in pregnancy with antiplatelets. *Presse Medicale* 1989;**18**:767–9.

Hachicha J, Ammous A, Midassi H, Dammak J, Ghorbel A, Chaabouni MN, et al. Place of antiplatelet therapy (APT) in vasculo-renal accidents's (VRA) preventive treatment during pregnancy. 6th International Congress, International Society for the Study of Hypertension in Pregnancy; 1988 May 22-26; Montreal, Quebec, Canada. 1988:185.

Rekik S, Midassi H, Bayoudh H, Mezghani M, Abid R, Ghorbel A. Place of antiplatelet therapy (APT) in vasculorenal accidents (VRA) preventive treatment in pregnancy. World Congress of Gynecology and Obstetrics; 1988 October 23-28; Brazil. 1988:185.

Tunisia 1990

Hachicha J, Bellaj A, Ghorbel L, Abid R, Rekik S, Jarraya A. Aspirin or aspirin and dipyridamole to prevent vasculo-renal accidents in pregnancy. Proceedings of 7th World Congress of Hypertension in Pregnancy; 1990 October; Perugia, Italy. 1990:256.

Tunisia 1994

Hachicha J, Ben Hmida M, Kharrat M, Jarraya F, Rekik S, Jarraya A. Aspirin or aspirin and dipyridamole to prevent pregnancy-induced hypertension [abstract]. *Nephrology, Dialysis, Transplantation* 1994; **9**:926.

Uganda 1992

Lule J. Trial of aspirin and methyldopa for moderate hypertension in pregnancy. Personal communication June 3 1993.

UK 1992a

McParland P, Pearce JM. Effect of low dose aspirin on maternal and fetal flow velocity waveforms. *American Journal of Obstetrics and Gynecology* 1992;**166**:438.

UK 1993

Williams HD, Howard R, O'Donnell N, Findley I. The effect of low dose aspirin on bleeding times. *Anaesthesia* 1993;**48**:331–3.

UK 1994

Hamid R, Robson M, Pearce JM. Low dose aspirin in women with raised maternal serum alpha-fetoprotein and abnormal Doppler waveform patterns from the uteroplacental bed. *British Journal of Obstetrics and Gynaecology* 1994;**101**:481–4.

Hamid R, Robson M, Pearce JM. Low dose aspirin in women with raised maternal serum alpha-fetoprotein and abnormal Doppler waveform patterns from the uteroplacental circulation. *International Journal of Gynecology & Obstetrics* 1995;**48**:348–9.

UK 2000

* Harrington K, Kurdi W, Aquilina J, England P, Campbell S. A prospective management study of slow-release aspirin in the palliation of uteroplacental insufficiency predicted by uterine artery Doppler at 20 weeks. *Ultrasound in Obstetrics & Gynecology* 2000;**15**:13–8.

Kurdi W, Fayyad A, Thakur V, Harrington K. Delayed normalisation of the uterine artery Doppler waveforms is not a benign phenomenon. *European Journal of Obstetrics & Gynecology and Reproductive Biology* 2004;**117**(1):20–3.

USA 1988a

O'Grady JP Wilson B. Effects of low-dose aspirin in improving fetal outcome in high risk pregnancies for intrauterine fetal growth retardation and/or preterm delivery. Personal communication March 19 1991.

USA 1989

Mirro R, Sibai BM, Leffler CW, Chesney CM. Low dose aspirin during pregnancy. *Pediatric Research* 1988;**23**:419A.

Sibai BM, Mirro R, Chesney CM, Leffler C. Low-dose aspirin in pregnancy. *Obstetrics & Gynecology* 1989;**74**:551–7.

USA 1990

Roberts CS, Beeson JH. Low dose aspirin in the prevention of preeclampsia in nulliparas. Preliminary results of a prospective,

placebo-controlled, double blind study. Proceedings of 10th Annual Meeting of Society of Perinatal Obstetricians; 1990 January 23-27; Houston, Texas, USA. 1990:89.

USA 1990a

Carlson NJ. Trial to evaluate the effectiveness of low dose aspirin versus placebo in the prevention of pregnancy induced hypertension in multiparous patients pregnant with multiple gestations. Personal communication September 6 1991.

USA 1993b

* Silver RK, MacGregor SN, Sholl JS, Hobart JM, Neerhof MG, Ragin A. Comparative trial of prednisone plus aspirin vs aspirin alone in the treatment of anticardiolipin antibody-positive obstetric patients. *American Journal of Obstetrics and Gynecology* 1993;**169**:1411–7.

Silver RK, Sholl JS, MacGregor SN, Hobart JH, Neerhof MG, Hickman AH. Prospective evaluation of single (low-dose aspirin) vs combined (aspirin plus prednisone) therapy in the treatment of the antiphospholipid syndrome. Proceedings of 39th Annual Meeting of the Society for Gynecologic Investigation; 1992 March 18-21; San Antonio, Texas, USA. 1992:125.

USA 1993c

O'Brien WF, Krammer J, O'Leary TD, Mastrogiannis DS. The effect of acetaminophen on prostacyclin production in pregnant women. *American Journal of Obstetrics and Gynecology* 1993;**168**:1164–9.

USA 1996

Martin C, Varner MW, Branch DW, Rodgers G, Mitchell MD. Dose-related effects of low dose aspirin on hemostasis parameters and prostacyclin/thromboxane ratios in late pregnancy. *Prostaglandins* 1996;**51**:321–30.

West Germany 1977

Wolfrum R, Bordasch C, Holweg J, Schulz G. The therapy of chronic nutritional placenta disorders - preliminary results of a double blind study. *Archives of Gynecology* 1977;**224**:114.

Additional references

Ananth 1995

Ananth CV, Savitz DA, Bowes WA. Hypertensive disorders of pregnancy and stillbirth in North Carolina, 1988-1991. *Acta Obstetricia et Gynecologica Scandinavica* 1995;**74**:788–93.

BroughtonPipkin 1996

Broughton Pipkin F, Crowther C, de Swiet M, Duley L, Judd A, Lilford RJ, et al. Where next for prophylaxis against pre-eclampsia?. *British Journal of Obstetrics and Gynaecology* 1996;**103**:603–7.

Bussolino 1980

Bussolino F, Benedetto C, Massobrio M, Camussi G. Maternal vascular prostacyclin activity in pre-eclampsia. *Lancet* 1980;**ii**:702.

CDSR Issue 2, 2000

Knight M, Duley L, Henderson-Smart DJ, King JF. Antiplatelet agents for preventing and treating pre-eclampsia. *Cochrane Database of Systematic Reviews* 2000, Issue 2. Art. No.: CD000492. DOI: 10.1002/14651858.CD000492.

CDSR Issue 4, 2003

Duley L, Henderson-Smart DJ, Knight M, King JF. Antiplatelet agents for preventing pre-eclampsia and its complications. *Cochrane Database of Systematic Reviews* 2003, Issue 4. Art. No.: CD004659. DOI:10.1002/14651858.CD004659.

Dept of Health 1996

Department of Health. *Confidential enquiry into stillbirths and deaths in infancy: 3rd annual report*. London: Department of Health, 1996.

DH 2002

Department of Health, Scottish Executive Health Department and Department of Health, Social Services, Public Safety. Northern Ireland. *Why mothers die. The sixth report on confidential enquiries into maternal deaths in the United Kingdom 2000-2002*. London: RCOG Press, 2002.

Duley 1992a

Duley L. Maternal mortality associated with hypertensive disorders of pregnancy in Africa, Asia, Latin America and the Caribbean. *British Journal of Obstetrics and Gynaecology* 1992;**99**:547–53.

Duley 1999b

Duley L, Henderson-Smart D. Reduced salt intake compared to normal dietary salt, or high intake, in pregnancy. *Cochrane Database of Systematic Reviews* 1999, Issue 3. Art. No.: CD001687. DOI: 10.1002/14651858.CD001687.

Generic Protocol 05

Meher S, Duley L, Prevention of Pre-eclampsia Cochrane Review authors. Interventions for prevention of pre-eclampsia and its consequences: generic protocol. *Cochrane Database of Systematic Reviews* 2005, Issue 2.

Gifford 1990

Gifford RW, August P, Chesley LC, Cunningham G, Ferris TF, Lindheimer MD, et al. National high blood pressure education program working group report on high blood pressure in pregnancy. *American Journal of Obstetrics and Gynecology* 1990;**163**:1689–712.

Higgins 2005

Higgins JPT, Green S, editors. Cochrane Handbook for Systematic Reviews of Interventions 4.2.4 [updated March 2005. In: The Cochrane Library, Issue 2, 2005. Chichester, UK: John Wiley & Sons, Ltd.

Hofmeyr 2006

Hofmeyr GJ, Atallah AN, Duley L. Calcium supplementation during pregnancy for preventing hypertensive disorders and related problems. *Cochrane Database of Systematic Reviews* 2006, Issue 3. Art. No.: CD001059. DOI:10.1002/14651858.CD001059.pub2.

Imperiale 1991

Imperiale TF, Petrulis AS. A meta-analysis of low-dose aspirin for the prevention of pregnancy-induced hypertensive disease. *JAMA* 1991; **266**:260–4.

Janes 1995

Janes S, Kyle P, Redman C, Goodall A. Flow cytometric detection of activated platelets in pregnant women prior to the development of pre-eclampsia. *Thrombosis and Haemostasis* 1995;**74**:1059–63.

Kramer 2003

Kramer MS, Kakuma R. Energy and protein intake in pregnancy. *Cochrane Database of Systematic Reviews* 2003, Issue 4. Art. No.: CD000032. DOI:10.1002/14651858.CD000032.

Leitich 1997

Leitich H, Egarter C, Husslein P, Kaider A, Schemper M. A meta-analysis of low dose aspirin for prevention of intrauterine growth retardation. *British Journal of Obstetrics and Gynaecology* 1997;**104**: 450–9.

Mahler 1987
Mahler H. The safe motherhood initiative: a call to action. *Lancet* 1987;**i**:668–70.

Makrides 2001
Makrides M, Crowther CA. Magnesium supplementation in pregnancy. *Cochrane Database of Systematic Reviews* 2001, Issue 4. Art. No.: CD000937. DOI:10.1002/14651858.CD000937.

Makrides 2006
Makrides M, Duley L, Olsen SF. Marine oil, and other prostaglandin precursor, supplementation for pregnancy uncomplicated by pre-eclampsia or intrauterine growth restriction. *Cochrane Database of Systematic Reviews* 2006, Issue 3. Art. No.: CD003402. DOI: 10.1002/14651858.CD003402.pub2.

PARIS 2005
Perinatal Antiplatelet Review of International Studies (PARIS) Collaboration Steering Group on behalf of the PARIS collaboration. Antiplatelet agents for prevention of pre-eclampsia and its consequences: a systematic review and individual patient data meta-analysis. *BMC Pregnancy and Childbirth* 2005;**5**:7.

Redman 1978
Redman C, Bonnar J, Beilin L. Early platelet consumption in pre-eclampsia. *BMJ* 1978;**1**:467–9.

Redman 1991
Redman C. Current topic: pre-eclampsia and the placenta. *Placenta* 1991;**12**:301–8.

RevMan 2003
The Cochrane Collaboration. Review Manager (RevMan). 4.2 for Windows. Oxford, England: The Cochrane Collaboration, 2003.

Rey 1996
Rey E, Derderian F. Efficacite de l'aspirine a faible dose au cours de al grossesse en fonction des facteurs de risque maternels et foetaux. *Journal SOGC: journal of the Society of Obstetricians and Gynaecologists of Canada* 1996;**18**:51–60.

Rosenfield 1985
Rosenfield A, Maine D. Maternal mortality - a neglected tragedy. *Lancet* 1985;**ii**:83–5.

Rumbold 2005
Rumbold A, Duley L, Crowther C, Haslam R. Antioxidants for preventing pre-eclampsia. *Cochrane Database of Systematic Reviews* 2005, Issue 4. Art. No.: CD004227. DOI: 10.1002/14651858.CD004227.pub2.

Sanchez-Ramos 1994
Sanchez-Ramos L, Wears R, Del Valle GO, Gaudier FL, Adair D. Low dose aspirin for the prevention of pregnancy-induced hypertension: a meta-analysis. *American Journal of Obstetrics and Gynecology* 1994; **170**:408.

Sharts-Engel 1992
Sharts-Engel NC. Aspirin for prevention of pregnancy-induced hypertension. *MCN. The American Journal of Maternal Child Nursing* 1992;**17**(3):168.

WHO 1988
World Health Organization International Collaborative Study of Hypertensive Disorders of Pregnancy. Geographic variation in the incidence of hypertension in pregnancy. *American Journal of Obstetrics and Gynecology* 1988;**158**:80–3.

WHO 2000
AbouZahr C, Wardlaw T. Maternal mortality in 2000: estimates developed by WHO, UNICEF, and UNFPA. http://www.who.int/reproductive-health/publications/maternal_mortality_2000/maternal_mortality_2000.pdf (accessed 12 July 2004).

References to other published versions of this review

CDSR 2000
Knight M, Duley L, Henderson-Smart DJ, King JF. Antiplatelet agents for preventing and treating pre-eclampsia. *Cochrane Database of Systematic Reviews* 2000, Issue 2. Art. No.: CD000492. DOI: 10.1002/14651858.CD000492.

CDSR 2003
Duley L, Henderson-Smart DJ, Knight M, King JF. Antiplatelet agents for preventing pre-eclampsia and its complications. *Cochrane Database of Systematic Reviews* 2003, Issue 4. Art. No.: CD004659. DOI:10.1002/14651858.CD004659.

Collins 1995
Collins R. Antiplatelet agents for IUGR and pre-eclampsia. [revised 04 May 1994]. In: Enkin MW, Keirse MJNC, Renfrew MJ, Neilson JP, Crowther C (eds.) Pregnancy and Childbirth Module. In: The Cochrane Pregnancy and Childbirth Database [database on disk and CDROM]. The Cochrane Collaboration; Issue 2, Oxford: Update Software; 1995.

Duley 1999
Duley L. Aspirin for preventing and treating pre-eclampsia. *BMJ* 1999;**318**(7186):751–2.

Duley 2001
Duley L, Henderson-Smart D, Knight M, King J. Antiplatelet drugs for prevention of pre-eclampsia and its consequences: systematic review. *BMJ* 2001;**322**:329–33.

Knight 2000
Knight M, Duley L, Henderson-Smart D, King J. Anitplatelets for prevention of pre-eclampsia and its consequences: a systematic review. *Hypertension in Pregnancy* 2000;**19**(Suppl 1):33.

* *Indicates the major publication for the study*

TABLES

Characteristics of included studies

Study	Australia 1988
Methods	Women given an identification number at trial entry, with randomisation in the hospital pharmacy using a random-number sequence linked to this number.
Participants	46 women with singleton pregnancy at 28-36 weeks and concern about fetal welfare, in whom umbilical artery velocity waveform systolic/diastolic ratio > 95th centile. Excluded if DBP > 110 mmHg or > 90 mmHg with proteinuria, and if maternal condition likely to lead to delivery.
Interventions	Exp: aspirin 150 mg daily. Control: placebo.
Outcomes	Women: caesarean section; induction; placental weight. Babies: stillbirth; neonatal death; ventilation; admission to SCBU; cerebroventricular haemorrhage; birthweight; gestation at delivery; head circumference; Apgar scores.
Notes	Women divided into 2 groups: high umbilical artery systolic/diastolic ratio (> 95th but < 99.5th centile) and extreme umbilical artery systolic/diastolic ratio (> 99.5th centile). Data incomplete for second group, so only included if available for all women. Continuous data only presented for some outcomes.
Allocation concealment	B – Unclear

Study	Australia 1993
Methods	Randomised. Capsules dispensed by pharmacy.
Participants	110 women at 12-24 weeks with either DBP >/= 90 or SBP >/= 140, or a history of PE.
Interventions	Exp: 100 mg aspirin. Control: placebo.
Outcomes	Women: PE.
Notes	
Allocation concealment	B – Unclear

Study	Australia 1995
Methods	Instructions about the tablets in numbered, sealed opaque envelopes. Women shown 5 envelopes and asked to choose 1.
Participants	51 women at 28-36 weeks with ultrasound diagnosis of restricted fetal growth, umbilical artery. Doppler systolic/diastolic ratio > 95 centile. No previous aspirin during pregnancy.
Interventions	Exp: 100 mg aspirin. Control: starch tablets.
Outcomes	Women: none. Babies: mean gestation at birth; birthweight (< 3 and 10 centile); Apgar 5 minutes; admission SCBU; IVH.
Notes	
Allocation concealment	B – Unclear

Study	Australia 1995a
Methods	Randomised by "envelope method", no other information given. 1/21 women (5%) excluded as miscarriage at 20 weeks.

Characteristics of included studies (*Continued*)

Participants	21 women with renal disease. 20 had previous early onset PE.
Interventions	Exp: dipyridamole 75-100 mg x 4/day + subcutaneous heparin 7500 u x 2/day. Control: no treatment.
Outcomes	Women: hypertension; proteinuria; 'complications'; caesarean section. Babies: neonatal death; premature birth (< 37 weeks); IUGR (< 10th centile).
Notes	Trial stopped early on advice of 'ad hoc' committee, due to complications in control group.
Allocation concealment	B – Unclear

Study	**Australia 1996**
Methods	'Double-blind randomised trial'.
Participants	52 primigravid women with abnormal uterine artery waveforms on doppler examination at 22-24 weeks.
Interventions	Exp: aspirin 60 mg/day. Control: placebo.
Outcomes	Women: GH; PE; caesarean section; abruption. Babies: death; preterm birth (< 37 weeks); IUGR (< 10 centile); admission SCBU.
Notes	
Allocation concealment	B – Unclear

Study	**Australia 1996a**
Methods	Randomisation by taking the next in a series of number identical blister packs. 2 women withdrew, 1 from each group.
Participants	104 primiparous women with abnormal uterine doppler flow at 18 weeks (systolic/diastolic ratio > 3.3 or S/D > 3 and early diastolic notch). Selected from 955 women screened, of whom 186 had abnormal waveforms.
Interventions	Exp: aspirin 100 mg/day. Control: placebo.
Outcomes	Women: GH; PE; eclampsia; APH. Babies: preterm birth; SGA.
Notes	
Allocation concealment	A – Adequate

Study	**Australia 1997**
Methods	Allocated by a series of random numbers. 10% (12/120) of women were excluded as they withdrew before starting treatment.
Participants	120 women at high risk of PE because of one of the following: pre-existing hypertension (BP greater >/= 140/90 prior to pregnancy on at least 2 occasions, or on antihypertensive therapy), renal disease, previous early severe PE. Excluded if aspirin allergy, aspirin-sensitive asthma, pre-existing bleeding diathesis or multiple pregnancy.
Interventions	Exp: aspirin 100 mg modified release daily from 17-19 weeks until delivery. Control: placebo.
Outcomes	Women: proteinuria; duration of pregnancy; indications for and mode of delivery; maximum antenatal BP; 'complications'. Babies: perinatal death; birthweight; Apgar scores.
Notes	.
Allocation concealment	B – Unclear

Characteristics of included studies (*Continued*)

Study	**Austria 1992**
Methods	Randomised to coded packages of medication; assessment of primary outcome blinded.
Participants	41 primigravid women with positive roll-over test (increase of 20 mmHg in DBP) at 28-32 weeks. Exclusions: existing hypertension, renal gut lung or heart disease, IUGR, impending preterm birth.
Interventions	Exp: aspirin 80 mg/day until 37 weeks. Control: placebo.
Outcomes	Women: GH; PE; caesarean section; preterm birth (37 weeks). Babies: stillbirths; neonatal death; SGA (< 10th centile); neonatal bleeding; admission to SCBU.
Notes	
Allocation concealment	A – Adequate

Study	**Barbados 1998**
Methods	Single centre, treatment packs randomly numbered by computer in clinic and dispensed by pharmacist. 55/3697 women (1.5%) excluded after randomisation: 42 because of pack labelling errors, 8 not pregnant and 6 lost to follow up.
Participants	3697 women at 12-32 weeks' gestation. Excluded if: increased risk of bleeding, aspirin allergy, high likelihood of immediate delivery, or previous placental abruption.
Interventions	Exp: aspirin 75 mg controlled release daily until delivery. Control: placebo.
Outcomes	Women: PE; APH; PPH; caesarean section; duration of pregnancy; use of antihypertensives and anticonvulsants. Babies: stillbirth; death before hospital discharge; days in SCBU; bleeding problems; birthweight.
Notes	
Allocation concealment	A – Adequate

Study	**Brazil 1996**
Methods	Central telephone randomisation; 39/1009 women (4%) lost to follow up.
Participants	1009 women at 12-32 weeks' gestation (mean 22, 41% = or < 20 weeks) "who the obstetrician thought were at risk" of PE - generally low/moderate risk (primiparous 47%, chronic hypertension 47%, diabetes 6%). Excluded if bleeding risk, asthma, allergy to aspirin, gastric ulcer, placenta praevia.
Interventions	Exp: aspirin 60 mg/day. Control: placebo.
Outcomes	Women: PE; caesarean section; APH. Babies: SGA; perinatal death; preterm birth; neonatal bleeding.
Notes	Conducted in 12 university teaching hospitals and 182 obstetric offices.
Allocation concealment	A – Adequate

Study	**Brazil 1992a**
Methods	Women randomly divided into 2 groups. No further information available. Blinding not reported. Outcome not reported for 4/56 women (7%).
Participants	56 women in 2nd or 3rd quarter of pregnancy who were young primigravidas, or had chronic HT, diabetes, previous PIH, twin pregnancy, or a family history of HT.
Interventions	Exp: acetylsalicylic acid 60 mg/day in a solution of 50% D-lisine. Control: no intervention.
Outcomes	Women: GH.

	Babies: death, birthweight (mean).
Notes	
Allocation concealment	B – Unclear

Study	**CLASP 1994**
Methods	By telephoning a central computerised randomisation service. 0.6% (55/9364) lost to follow up. International study. Follow up of surviving children with GP letter at 12 months in UK (4688 with 4675 alive at 12 months) and parental questionnaire at 18 months in UK and Canada (410 with 407 alive at 18 months). For GP letter, 89% response rate, for parental questionnaire 86% responded.
Participants	9364 women at 12-32 weeks' gestation at risk of PE or IUGR, or women with established PE or IUGR.
Interventions	Exp: aspirin 60 mg daily until delivery. Control: placebo.
Outcomes	Women: death; eclampsia; PE; bleeding complications; caesarean section; induction; problems with epidural analgesia; PPH; transfusion; use of antihypertensives or anticonvulsants; compliance. Babies: stillbirth; neonatal death; mortality at 1 year; birthweight (mean) and centile (< 3rd); gestation at delivery; admission to SCBU; IVH; other neonatal bleeding. Follow up at 12-18 months: developmental delay; congenital malformations; respiratory problems; hospital admissions.
Notes	Compliance: 96% started treatment, 88% took it for at least 80% of the time from entry-delivery. For some outcomes data not presented separately for prophylaxis and treatment. Follow-up data only for centres in the UK and Ottawa, Canada.
Allocation concealment	A – Adequate

Study	**China 1996**
Methods	"Prospective randomised double-blind study".
Participants	84 women with a singleton pregnancy at high risk of IUGR, and 28-34 weeks' gestation.
Interventions	Exp: 75 mg aspirin, from 28-34 weeks for 6-8 weeks. Control: placebo.
Outcomes	Women: PIH; caesarean section; preterm delivery. Babies: neonatal death; IUGR; IVH.
Notes	
Allocation concealment	B – Unclear

Study	**China 1996a**
Methods	Random allocation. No further information. Not blinded and no information on completeness of follow up.
Participants	104 women at 20 to 38 weeks' gestation. Inclusion criteria: older primiparous; multiparous with history of severe PIH; obesity; MAP > 12 kPa; Hb < 8; PCV > 0.37; family history of HT or PIH in mother or sister.
Interventions	Exp: aspirin 50 mg/d for 3 to 5 weeks. Control: no intervention.
Outcomes	Women: GH; oligohydramnios; mode of delivery (numbers not reported); PPH (numbers not reported) biochemical markers. Babies: mean birthweight.
Notes	Single centre.
Allocation concealment	B – Unclear

Characteristics of included studies (*Continued*)

Study	**China 1999**
Methods	Randomisation by offering participant 5 sealed envelopes (2 aspirin, 2 calcium, 1 placebo). 132 women allocated aspirin, 154 calcium and 83 control (total 369). Women allocated calcium excluded from this review. 22 women lost to follow up (14 aspirin, 8 control).
Participants	215 primigravid women with MAP > 80 and < 106 early in 2nd trimester and MAP > 60 at 22-24 weeks.
Interventions	Exp: aspirin 80 mg/day until delivery. Control: unclear, no placebo mentioned.
Outcomes	Women: GH; PE; eclampsia; caesarean section. Babies: gestation at delivery (mean); birthweight; Apgar scores.
Notes	Authors provided additional information.
Allocation concealment	B – Unclear

Study	**Colorado 1993**
Methods	"Randomised" - no further information; completeness of follow up unclear.
Participants	100 nulliparous women with multiple pregnancy in "early pregnancy".
Interventions	Exp: aspirin 81 mg/day. Control: placebo.
Outcomes	Women: GH; PE. Babies: none reported.
Notes	Multicentre trial, stopped early due to slow recruitment.
Allocation concealment	B – Unclear

Study	**EPREDA 1991**
Methods	Randomised by centre with stratification for 1 or 2 previous poor outcomes. 1 woman excluded after randomisation.
Participants	323 women at 15-18 weeks' gestation with poor outcome during previous 2 pregnancies, at least one being IUGR, or IUGR in one previous pregnancy. Excluded: twins, uterine malformation, renal disease, secondary hypertension, diabetes, cardiac disease.
Interventions	Study 1: exp: aspirin 150 mg daily, or aspirin 150 mg plus dipyridamole 225 mg daily. Control: placebo. Study 2: exp: aspirin 150 mg and dipyridamole 225 mg daily. Control: aspirin 150 mg daily.
Outcomes	Women: death; DBP > 90 mmHg; proteinuria; abruption; caesarean section < 34 weeks; "poor outcome". Babies: stillbirth; neonatal death; ventilation; transfer to intensive care; birthweight < 10th centile; duration of hospital stay (mean).
Notes	2 separate comparisons within the 1 study. Only data for study 1 included in the review. Study 1 has 3 arms. Data for 2 antiplatelet arms combined versus control. For comparison of subgroup analysis based on dose, data presented under aspirin > 75 mg plus dipyridamole.
Allocation concealment	B – Unclear

Study	**ERASME 2003**
Methods	Multicentre, 28 centres in France and 1 in Belgium. Computer-generated randomisation codes, stratified by centre in blocks of 8. Allocation via online 24 hour computer.
Participants	3294 primiparous women at 14-20 weeks' gestation. Singleton or multiple pregnancy. Excluded: known HT, indication or contraindication to aspirin.

Characteristics of included studies (*Continued*)

Interventions	Exp: aspirin 100 mg to 34 weeks. Control: placebo.
Outcomes	Women: PIH; PE; placental abruption; caesarean section; induction; HELLP; PPH; hospital admission; side-effects. Babies: stillbirth; neonatal death; SGA (< 10th and < 3rd centile); neonatal IVH; other bleeding; admission SCBU.
Notes	
Allocation concealment	A – Adequate

Study	**Egypt 2005**
Methods	Computer-generated list of random numbers. Numbers then placed in sealed envelopes, and women asked to choose 1 envelope. Randomisation, drug prescription, and allocation key kept by 1 author with no role in participant follow up or outcome assessment. 3 women (2%) lost to follow up (1 aspirin, 2 control).
Participants	139 women at 14-16 weeks' gestation with abnormal uterine artery doppler (diastolic notch or resistance index > 90th percentile) and other risk factors for PE (previous history of PE/IUGR, essential HT, positive family history, underlying vascular disease, age < 20 yr or > 40 yr or gestational diabetes). Excluded: allergy to aspirin, peptic ulcer, other hepatic, renal, cardiovascular or thyroid disorder.
Interventions	Exp: aspirin 75 mg/day. Control: no treatment.
Outcomes	Women: PE (BP >/= 140/90 plus proteinuria > 300 mg/day); PE onset < 37 weeks; severe PE (BP > 160/110, proteinuria > 2 g, urine output < 500 ml/day, platelets < 100000/cmm, elevated liver enzymes); maternal bleeding. Babies: SGA (< 10th percentile); preterm birth; birthweight; neonatal bleeding; Apgar score at 1 and 5 minutes.
Notes	
Allocation concealment	A – Adequate

Study	**Finland 1993**
Methods	Sealed envelopes, no further details. Double-blind. 5.3% (11/208) women excluded. 6 from aspirin group (1 miscarriage, 1 termination for anencephaly, 4 discontinued due to urticaria, raised AST, or prolonged bleeding time), 5 from placebo group (1 miscarriage, 3 discontinued due to raised AST or prolonged bleeding time, 1 lost to follow up).
Participants	208 women with pre-existing hypertension (BP > 140/90 before pregnancy) or previous severe PE (in immediately preceding pregnancy), and 12-18 weeks' gestation. Excluded: women proteinuric before pregnancy.
Interventions	Exp: aspirin 50 mg daily. Control: placebo.
Outcomes	Women: exacerbation of hypertension +/- proteinuria; caesarean section; blood loss at delivery (mean); hospitalisation during pregnancy; bleeding time and DBP at 36 weeks (mean). Babies: perinatal death; admission to SCBU; birthweight (mean); SGA; gestation at delivery.
Notes	3 centres.
Allocation concealment	B – Unclear

Study	**Finland 1997**
Methods	Randomised, no other information.
Participants	26 high-risk women with uterine artery bilateral notches on doppler, at 22-24 weeks.

Characteristics of included studies (*Continued*)

Interventions	Exp: aspirin 50 mg. Control: no treatment.
Outcomes	Women: GH; PE; placental abruption; delivery < 37 weeks. Babies: stillbirth; IUGR (< 10th centile); IVH on ultrasound; gestation at delivery (mean); birthweight (mean).
Notes	
Allocation concealment	B – Unclear

Study	**Finland 1997a**
Methods	'Randomly allocated', code of medication broken once all data available. No further information.
Participants	66 women at around 5 weeks' gestation with a history of recurrent spontaneous miscarriage.
Interventions	Exp: aspirin 50 mg/day, started as soon as pregnancy test positive. Control: placebo.
Outcomes	Women: PE (BP >/= 140/90 plus proteinuria > 0.3 g/day); minor bleeding; abruption; mode of delivery; length of pregnancy; glucose tolerance. Baby: early fetal loss; SGA (< 10th percentile); birthweight.
Notes	Almost one third of women had a miscarriage or ectopic pregnancy (10/33 aspirin vs 10/33 placebo). Therefore denominators for other pregnancy outcomes are based on women whose pregnancy continued beyond 20 weeks.
Allocation concealment	B – Unclear

Study	**Finland 2002**
Methods	Randomisation in pharmacy. Code broken when last woman delivered. 4 women lost to follow up, 2 each group.
Participants	90 women at risk of PE or IUGR with abnormal uterine doppler. 12-14 weeks' gestation.
Interventions	Exp: aspirin 0.5 mg/kg/day. Control: placebo.
Outcomes	Women: GH; PE; caesarean section. Babies: death; gestation at delivery (mean); birthweight < 2500 g; admission SCBU; IVH.
Notes	
Allocation concealment	A – Adequate

Study	**France 1985**
Methods	"Randomly allocated to group A or B", no other information available. 8.8% (9/102) excluded from analysis (2 controls lost to follow up, 4 treatment and 3 controls had a miscarriage before 16 weeks).
Participants	102 women at high risk of PE or IUGR; for example, if several previous complicated pregnancies or vascular risk factors such as essential hypertension (BP > 160/95) or a family history of hypertension. Excluded: women with secondary hypertension or known or suspected renal disease.
Interventions	Exp: aspirin 150 mg and dipyridamole 300 mg daily, from 3 months until delivery. Control: no antiplatelet agent.
Outcomes	Women: PIH (BP at least 140/85 mmHg; PE; caesarean section; abnormal bleeding during delivery or caesarean section; abruption; headache. Babies: stillbirth; neonatal death; fetal malformation; birthweight < 10th and < 3rd centile (livebirths only); haemorrhagic complication (undefined).
Notes	
Allocation concealment	B – Unclear

Characteristics of included studies (*Continued*)

Study	**France 1990**
Methods	"Randomised study", no other information given.
Participants	91 women at high risk of PIH because of previous early onset PE, severe IUGR or fetal death due to placental insufficiency.
Interventions	Exp: aspirin 100 mg and dipyridamole 300 mg daily until delivery. Control: no treatment.
Outcomes	Women: GH +/-; duration of pregnancy (mean). Babies: fetal death; birthweight (mean).
Notes	Published in abstract form only.
Allocation concealment	B – Unclear

Study	**Germany 2000**
Methods	Computer-generated random sequence. Blister packs, and the code held separately from person doing randomisation.
Participants	43 women with singleton pregnancy, < 20 weeks' gestation with early IUGR, impaired uteroplacental flow, chronic HT, or history of IUGR, stillbirth, or PE. Excluded: diabetes, pre-existing HT or proteinuria, fetal malformation.
Interventions	Exp: aspirin 100 mg/day. Control: placebo.
Outcomes	Women: PE. Babies: gestation at birth (mean); birthweight (mean).
Notes	
Allocation concealment	A – Adequate

Study	**India 1993**
Methods	Method of randomisation not specified; assessment of outcome not blinded.
Participants	100 women with PIH at 24-36 weeks' gestation.
Interventions	Exp: aspirin 60 mg/day. Control: 'standard treatments only'.
Outcomes	Women: severe GH (proteinuria not specified); eclampsia; preterm (gestation not specified). Babies: stillbirths; neonatal deaths; SGA.
Notes	Unclear whether aspirin group also had 'standard treatments'.
Allocation concealment	B – Unclear

Study	**India 1994**
Methods	"Randomly allocated", no other information given.
Participants	94 nulliparous women with PIH in the 3rd trimester (SBP at least 140 mmHg, or DBP at least 90 mmHg, or both, on 2 occasions more than 6 hours but less than 24 hours apart).
Interventions	Exp: aspirin 75 mg daily, until 10 days before EDD. Control: no antiplatelet agent.
Outcomes	Women: development of PE; eclampsia or abruption; mean fall in BP; rise in BP. Babies: neonatal death; admission to SCBU; gestational age at delivery (mean); birthweight (mean); Apgar at 1 minute; macroscopic haematuria.
Notes	Exclusion criteria not described.
Allocation concealment	B – Unclear

Characteristics of included studies (*Continued*)

Study	**India 1999**
Methods	Randomised trial, no further details. 2 women allocated aspirin lost to follow up, 1 allocated placebo.
Participants	163 women with PIH at 20-32 weeks.
Interventions	Exp: aspirin 60 mg daily. Control: placebo. Treatment continued to 38 weeks.
Outcomes	Women: PE; eclampsia. Babies: perinatal death; IUGR < 10th centile.
Notes	Available as an abstract only.
Allocation concealment	B – Unclear

Study	**Israel 1989**
Methods	Coded packages of 100 pills allocated according to a computer-generated randomisation list.
Participants	65 women with either twin pregnancy, a history of PE or in first pregnancy, and a positive roll-over test at 28-29 weeks' gestation.
Interventions	Exp: aspirin 100 mg daily. Control: placebo.
Outcomes	Women: GH +/- proteinuria (BP > 140/90 on at least 2 occasions within 24 hours; proteinuria > 1 g/24 h); caesarean section; length of hospitalisation (mean). Babies: stillbirth; neonatal death; gestation at birth (mean); born < 37 weeks; birthweight < 10th centile; Apgar scores; ventilation; admission to SCBU; IVH; haematuria; cephalhaematoma; sepsis workup.
Notes	
Allocation concealment	A – Adequate

Study	**Israel 1990**
Methods	"Divided randomly into 2 groups", no other information given.
Participants	47 nulliparous at 30-36 weeks with mild PIH (BP > 140/90 but < 165/110), no signs of PE, normal platelets and proteinuria < 500 mg/24 h. Excluded if aspirin sensitivity, chronic hypertension, renal disease or antihypertensive drugs.
Interventions	Exp: aspirin 100 mg until 5 days before EDD. Control: placebo.
Outcomes	Women: PE (BP > 165/110 with low platelet count or proteinuria > 500 mg/24 h, or both); caesarean section. Babies: gestation at delivery; birthweight (mean); Apgar score at 5 minutes (mean).
Notes	
Allocation concealment	B – Unclear

Study	**Israel 1994**
Methods	Allocated to a coded package according to randomisation list. 1 woman withdrawn from placebo group because of thrombocytopaenia - outcomes included where possible.
Participants	48 women with twin pregnancies at about 18 weeks.
Interventions	Exp: aspirin 100 mg/day. Control: placebo.
Outcomes	Women: GH; PE; caesarean section; IUGR. Babies: preterm birth; perinatal mortality; birthweight discordancy (15%).

Notes	
Allocation concealment	B – Unclear

Study	**Italy 1989**
Methods	"Randomly assigned", no other information given.
Participants	33 women at risk of hypertension because of essential hypertension or a significant previous obstetric history (placental insufficiency causing fetal death, severe IUGR or PE < 32 weeks). Excluded: if antiphospholipid antibodies.
Interventions	Exp: aspirin 60 mg daily from 12 weeks until delivery. Control: placebo.
Outcomes	Women: GH (BP > 140/90 and BP previously normal); gestation at delivery (mean). Babies: perinatal death; assisted ventilation; haemorrhagic complications; birthweight < 10th centile for gestational age; born < 37 weeks' gestation; Apgar scores (mean) RDS.
Notes	
Allocation concealment	B – Unclear

Study	**Italy 1993**
Methods	Allocation by a telephone call to 1 of 2 randomisation centres. 5.8% (64/1106) of women lost to follow up (18/523 aspirin, 46/583 control). Follow up: postal questionnaire to parents for 1083 children at 18 months (excludes 41 born before follow up started). 1 reminder and up to 3 telephone calls for non-responders. Data for 427 aspirin (72%) and 361 no treatment (73%).
Participants	1106 women at 16-32 weeks' gestation. Prophylactic: age < 18 or > 40 yr, mild-moderate chronic hypertension, nephropathy with normal renal function and BP, PIH or IUGR in previous pregnancy, twin pregnancy). Therapeutic: PIH (DBP 90-110 mmHg) or early IUGR (fetal abdominal circumference >/= 2 standard deviations below mean for gestational age). Excluded: chronic disease, allergy to aspirin, fetal malformation.
Interventions	Exp: aspirin 50 mg daily. Control: no treatment.
Outcomes	Women: PIH +/- proteinuria; abruption; induced or spontaneous abortion; caesarean section. Babies: perinatal mortality; gestation at delivery; birthweight < 10th or < 5th centile; admission to SCBU; IVH; gastric bleed. At 18 months: death; malformations height and weight < 10th centile, and respiratory; motor; sight; hearing or language problems.
Notes	Data not presented separately for prophylaxis and treatment, and so all women included in prophylaxis for this review. For follow up, no difference between responders and non-responders in baseline characteristics and outcome at discharge from hospital. Also, no differences in information collected by post or by telephone.
Allocation concealment	A – Adequate

Study	**Italy 1999**
Methods	"Randomised". 9 women stopped treatment early, 4 aspirin and 5 control.
Participants	216 women aged 18-36 with pre-existing HT or history of severe PE, at 12-26 weeks.
Interventions	Exp: 50 mg aspirin/day. Control: placebo.
Outcomes	Women: PE.
Notes	

Characteristics of included studies (*Continued*)

Allocation concealment	B – Unclear

Study	**Italy 2004**
Methods	Telephone randomisation using computer-generated randomisation list (separate list for each centre). 5 women (12%) lost to follow up (2 aspirin, 3 control)
Participants	40 women at < 14 weeks' gestation with chronic HT +/- nephropathy or history of severe PE or eclampsia or IUGR or stillbirth. Excluded: allergy to aspirin, fetal malformation, current twin pregnancy, chronic disease except renal/HT/DM without hypertensive nephropathy.
Interventions	Exp: 100 mg aspirin/day until delivery. Control: no treatment.
Outcomes	Women: GH (SBP >/= 140 or DBP >/= 90) or PE (as above + proteinuria > 300 mg/24 h or >/= 1+). Babies: miscarriage, mean gestation at birth, mean birthweight, birthweight < 2500 g.
Notes	Trial recruitment 1998-2000, in 2 centres in Italy. Planned sample size 160 women, but trial stopped due to slow recruitment. Data not presented separately for outcomes PIH and PE. Data for the combined outcome is therefore reported under the outcome PIH.
Allocation concealment	A – Adequate

Study	**Jamaica 1998**
Methods	Women given sequential numbers on admission which identified a bottle containing either aspirin or placebo. 179/6275 (3%) lost to follow up. 50 women with multiple pregnancy excluded. Some women entered twice and given aspirin and placebo excluded, but numbers not given.
Participants	6275 primiparous women 12-32 weeks and no contraindication to aspirin. 144 aspirin women and 161 placebo randomised after 32 weeks, but included in analysis.
Interventions	Exp: aspirin 60 mg daily until delivery. Control: placebo.
Outcomes	Women: hypertension (DBP >/= 90 mmHg or SBP >/= 140 mmHg or rise of 25 mmHg DBP or 40 mmHg SBP); PE; eclampsia; caesarean section; antenatal admission; PPH. Baby: perinatal mortality; preterm delivery; birthweight < 2500 g; admission to SCBU; 5 minute Apgar < 5; IVH; other neonatal bleeding.
Notes	
Allocation concealment	B – Unclear

Study	**Japan 1999**
Methods	"Enrolled randomly", no further information.
Participants	40 women with severe PE in previous pregnancy. Enrolled at 6-18 weeks, treatment started at 20 weeks.
Interventions	Exp: ozagrel hydrochloride, 400 mg/day from 20 weeks - delivery. Control: placebo.
Outcomes	Women: PE. Babies: preterm delivery; delivery < 32 weeks; SGA.
Notes	Ozagrel is a thromboxane synthetase inhibitor.
Allocation concealment	B – Unclear

Characteristics of included studies (*Continued*)

Study	**Netherlands 1986**
Methods	Coded packages, allocated according to a randomisation list. 2 women in treatment group excluded because of non-compliance, but data for some clinical outcomes reported.
Participants	46 angiotensin II sensitive primigravid women at 28 weeks' gestation with uncomplicated pregnancies, no history of hypertension, cardiovascular or renal disease, DBP < 80 mmHg and taking no drugs except iron.
Interventions	Exp: aspirin 60 mg daily. Control: placebo.
Outcomes	Women: eclampsia; GH (DBP at least 95 mmHg on 2 or more occasions 6 hours apart); PE (hypertension as above plus proteinuria > 0.5 g/L); preterm delivery (< 37 weeks); caesarean section. Babies: stillbirth; neonatal death; RDS; birthweight for gestational age < 10th or < 3rd centiles.
Notes	
Allocation concealment	B – Unclear

Study	**Netherlands 1989**
Methods	Coded packages containing trial drug allocated according to a randomisation list.
Participants	10 primigravid women with chronic hypertension and a positive angiotensin II sensitivity test at 26 weeks' gestation. No proteinuria, BP < 90 mmHg diastolic, serum creatinine < 70 umol/L and an adequately grown fetus.
Interventions	Exp: aspirin 60 mg. Control: placebo.
Outcomes	Women: GH (rise in DBP of 20 mmHg or more); PE (hypertension as before plus proteinuria >/= 500 mg/L); caesarean section. Babies: birthweight < 10th centile.
Notes	All women had methyl dopa.
Allocation concealment	B – Unclear

Study	**Netherlands 1991a**
Methods	Coded packages allocated according to a randomisation sheet. Code broken at 34 weeks, some women then started aspirin.
Participants	36 women with a positive angiotensin II sensitivity test at 28 weeks.
Interventions	Exp: aspirin 60 mg daily from 28-32 weeks. Control: placebo.
Outcomes	Women: hypertension at 34 weeks. Babies: stillbirths.
Notes	
Allocation concealment	B – Unclear

Study	**Russia 1993**
Methods	Stratified blocked randomisation using sealed opaque numbered envelopes. Blinding not reported. Data not available for 12 women (16%).
Participants	76 women with chronic glomerulonephritis or essential hypertension.
Interventions	Exp: aspirin 125 mg plus dipyridamole 150-225 mg/day from 12-19 weeks' gestation. Control: no treatment.
Outcomes	Women: PE, abruption. Babies: early (upto 15 wks) and late (15 to 27 wks) fetal deaths and perinatal death (28 wks to 1st wk of life); preterm birth (birth between 28 to 36 wks); SGA (body mass < 2 SD for gestational age).

Notes	Abstract published in 1994 reports 76 women recruited, Russian paper published in 1993 reports 64 women recruited. Authors confirmed additional women recruited after publication of the 1993 paper, but data not available. Data for the inital 64 women only included in this review.
Allocation concealment	A – Adequate

Study	**S Africa 1988**
Methods	By computer-generated random numbers, no other information. One woman lost to follow up.
Participants	44 women with elevated mid-trimester BP, 12-28 weeks' gestation, DBP 80-105 mmHg, and otherwise normal.
Interventions	Exp1: aspirin 81 mg daily. Exp2: aspirin 81 mg + dipyridamole 200 mg daily. Control: no antiplatelet agent.
Outcomes	Women: PE. Babies: stillbirth.
Notes	Published only as an abstract. 3 arm study. Data for 2 antiplatelet arms combined for analysis versus control but presented separately in comparison of subgroup analysis based on dose.
Allocation concealment	B – Unclear

Study	**Spain 1997**
Methods	Computer-generated random numbers used to prepare a table for the sequence of allocation. Tablets in identical blister packs. Allocated to 6 groups, according to treatment and timing of administration. 7 women excluded, because poor compliance or incomplete blood pressure assessments.
Participants	107 women aged 18-40 years at < 16 weeks' gestation and at moderate risk of pre-eclampsia. For example, family or own history of PIH, PE, chronic HT, cardiovascular or endocrine problem, bleeding or endocrine disease. Excluded: multiple pregnancy.
Interventions	Exp: 100 mg aspirin. Control: placebo. Each treatment group could also be allocated to 3 different times of the day.
Outcomes	Women: GH; PE; caesarean section; abruption. Baby: death; preterm birth (< 37 weeks); IUGR.
Notes	Testing the hypothesis that aspirin effects are time dependant, being greater in the evening.
Allocation concealment	A – Adequate

Study	**Spain 1999**
Methods	Randomised. Tablets in identical blister packs. Allocated to 6 groups, according to treatment and timing of administration. 15 women excluded, because poor compliance or incomplete blood pressure assessments.
Participants	255 women aged 18-40 years at < 16 weeks' gestation and at moderate risk of pre-eclampsia. For example, family or own history of PIH, PE, chronic HT, cardiovascular or endocrine problem, bleeding or endocrine disease. Excluded: multiple pregnancy.
Interventions	Exp: 100 mg aspirin. Control: placebo.

Characteristics of included studies (*Continued*)

	Each treatment group could also be allocated to 3 different times of the day.
Outcomes	Women: mean 24 hr BP. Baby: IUGR.
Notes	Testing the hypothesis that aspirin effects are time dependant, being greater in the evening. Data entered into the review from the main publication. Data for a total of 341 women have been presented, but in abstract only and incomplete.
Allocation concealment	A – Adequate

Study	**Tanzania 1995**
Methods	Coded packages A and B. No other information.
Participants	127 women with a positive roll-over test. Excluded if hypertension or increased BP before screening or proteinuria > 300 mg.
Interventions	Exp: 80 mg aspirin daily. Control: placebo.
Outcomes	Women: GH; PE. Babies: none.
Notes	
Allocation concealment	B – Unclear

Study	**UK 1990**
Methods	Computer-generated randomisation list. Serially-numbered bottles dispensed by pharmacist. 5.7% (6/106) excluded after randomisation (5 women moved house, 1 withdrew after 3 weeks).
Participants	106 primigravid women with persistently abnormal doppler waveform studies at 24 weeks' gestation. Excluded: aspirin allergy, diabetes, bleeding disorders, peptic ulceration, systemic lupus erythematosus.
Interventions	Exp: aspirin 75 mg daily. Control: placebo.
Outcomes	Women: GH; proteinuria; hypertension < 37 weeks' gestation; caesarean section for complications of hypertension. Babies: perinatal death; birthweight < 5th centile.
Notes	Lancet contacted to confirm this study has not been retracted.
Allocation concealment	A – Adequate

Study	**UK 1992**
Methods	"Simply randomised with block size 4".
Participants	(a) 18 normal primigravidae, 16 weeks' gestation, and (b) 16 primigravidae with gestational hypertension but no proteinuria at > 20 weeks.
Interventions	Exp: aspirin 60 mg daily until delivery. Control: placebo.
Outcomes	Women: duration of labour; blood loss at delivery. Babies: < 36 weeks at delivery; birthweight < 10th centile; minor bruising of newborn.
Notes	Continuous data only presented for some outcomes.
Allocation concealment	B – Unclear

Study	**UK 1992b**
Methods	"Randomly allocated", no other information given.

Characteristics of included studies (*Continued*)

Participants	26 women with history of recurrent miscarriage or connective tissue disorder, and positive anticardiolipin antibodies.
Interventions	Exp: aspirin 75 mg daily. Control: no treatment.
Outcomes	Women: miscarriage. Babies: neonatal death.
Notes	
Allocation concealment	B – Unclear

Study	**UK 1995**
Methods	Computer-generated randomisation list used to produce sealed envelopes. 4/122 women (3%) withdrew after randomisation.
Participants	122 women with no previous pregnancy proceeding beyond 12 weeks, Hb > 13.2 g/dL at 12-19 weeks' gestation, DBP < 90 mmHg and no proteinuria. Excluded if multiple pregnancy, diabetes, recurrent miscarriage or contraindication to aspirin.
Interventions	Exp: aspirin 75 mg from 18 weeks until delivery. Control: placebo.
Outcomes	Women: GH; PE; eclampsia; abruption; caesarean section; induction of labour; side-effects. Babies: perinatal mortality; delivery < 34 weeks' gestation; admission to SCBU; birthweight < 5th centile.
Notes	Trial conducted 1989-92.
Allocation concealment	B – Unclear

Study	**UK+others 2003**
Methods	Computer-generated random number lists, in blocks of 10, created by pharmaceutical company. 'Appropriately numbered drug' dispensed by each hospital pharmacy. 6 women (1%) lost to follow up (4 aspirin, 2 control).
Participants	560 women with singleton pregnancy at 22-24 weeks and doppler pulsatility index > 1.6 (95th percentile). Excluded: pre-existing hypertensive, renal or cardiovascular disease, DM, bleeding disorders, SLE, peptic ulcers, hypersensitivity to aspirin, fetal abnormality or growth restriction at 23 wk scan.
Interventions	Exp: aspirin 150 mg/day. Control: placebo (identical tablets containing lactose).
Outcomes	Women: PE; early PE < 34 weeks; placental abruption; PPH; blood transfusion. Babies: death (stillbirth, perinatal death); preterm birth < 37 weeks; very preterm birth < 34 weeks; SGA (< 5th percentile); admission to SCBU.
Notes	Trial recruitment 2001-2002. Multicentre: 7 centres in UK, 1 in Brazil, 1 in Chile, and 1 in South Africa. Compliance: 95% in both groups.
Allocation concealment	A – Adequate

Study	**USA 1993**
Methods	Efforts were made to conceal randomisation; placebo controlled; < 1% loss; blind assessment of outcome.
Participants	604 primiparous women at 24 weeks, in single antenatal clinic. Exclusions: renal or collagen disease, diabetes, essential hypertension, multiple pregnancy.
Interventions	Exp: aspirin 60 mg/day, from 22 weeks. Control: placebo.
Outcomes	Women: GH; PE; eclampsia; APH; caesarean section; preterm delivery (< 37, < 34, < 32 weeks). Babies: perinatal death; SGA.

Notes	
Allocation concealment	B – Unclear

Study	**USA 1993a**
Methods	"Assigned randomly" no further details. 150/3135 (4.8%) lost to follow up: 85 from aspirin group and 65 from placebo.
Participants	3135 nulliparous women at 13-25 weeks with BP < 135/85 and no proteinuria; out of the 4241 entered into a run-in compliance phase. Exclusions: chronic hypertension, diabetes, renal disease, other medical illness.
Interventions	Exp: aspirin 60 mg/day. Control: placebo.
Outcomes	Women: GH; PE; eclampsia; caesarean section; abruption; preterm delivery; PPH. Babies: stillbirths; neonatal deaths; SGA < 10th centile; bleeding.
Notes	Mean gestation at trial entry 19.8 weeks.
Allocation concealment	B – Unclear

Study	**USA 1994**
Methods	"Randomised", no further details. 5/54 (9%) women lost to follow up.
Participants	54 women with chronic hypertension or previous severe PE, enrolled at 13-15 weeks.
Interventions	Exp: aspirin 100 mg sustained release/day until 37 weeks. Control: placebo.
Outcomes	Women: PE. Babies: stillbirth; SGA.
Notes	Published as abstract only.
Allocation concealment	B – Unclear

Study	**USA 1997**
Methods	'Randomly assigned', no further information.
Participants	19 women with antiphospholipid antibodies and </= 2 previous miscarriages with no other antiphospholipid antibody related complications. Excluded: previous thrombosis, early onset PE, thrombocytopenia.
Interventions	Exp: aspirin 81 mg/day throughout pregnancy. Control: usual care.
Outcomes	Babies: fetal death; SGA (< 5th percentile); fetal distress at term (not defined).
Notes	
Allocation concealment	B – Unclear

Study	**USA 1998**
Methods	Packets prepared using computer-generated random numbers. Opened consecutively in each centre. 36/2539 women (1%) lost to follow up.
Participants	2539 women 13-26 weeks' gestation with insulin treated diabetes, chronic hypertension, multiple pregnancy or PE in a previous pregnancy. Women with multiple pregnancy excluded if also diabetes, chronic hypertension or proteinuria.
Interventions	Exp: aspirin 60 mg daily. Control: placebo.
Outcomes	Women: GH; PE; abruption; preterm delivery; PPH.

Characteristics of included studies (*Continued*)

	Baby: death; IUGR (< 10th centile); IVH; other neonatal bleeding.
Notes	Additional data provided by the authors.
Allocation concealment	A – Adequate

Study	**Venezuela 2000**
Methods	"Randomised" no further information.
Participants	127 nulliparous women < 29 weeks' gestation. At risk of PE because previous PE, obesity, HT, diabetes, nephropathy, MAP > 85, positive roll-over test, family history PE, multiple pregnancy or < 20 years.
Interventions	Exp: aspirin 100 mg x 3/week + vitamin C 500 mg/day + vitamin E 400 IU/day fish oil x 3/day.
Outcomes	Women: PE.
Notes	Abstract only.
Allocation concealment	B – Unclear

Study	**Zimbabwe 1998**
Methods	Randomisation list used to determine the sequence of numbered containers. 20/250 (8%) women lost to follow up.
Participants	250 women at 20-28 weeks with a history of PE in a previous pregnancy, especially if at < 32 weeks, or chronic hypertension. Excluded if hypersensitivity to aspirin, PE this pregnancy, bleeding or peptic disorder.
Interventions	Exp: aspirin 75 mg/day. Control: placebo.
Outcomes	Woman: PE; antihypertensive drug; preterm delivery; PPH; caesarean section. Baby: death; IUGR; admission SCBU.
Notes	
Allocation concealment	B – Unclear

APH: antepartum haemorrhage
AST: aspartate aminotransferase
BP: blood pressure
DBP: diastolic blood pressure
DM: diabetes mellitus
EDD: estimated date of delivery
Exp: experimental group
GH: gestational hypertension
Hb: haemoglobin
HELLP: haemolysis elevated liver enzymes and low platelets
hr: hour
HT: hypertension
IU: international unit
IUGR: intrauterine growth restriction
IVH: intraventricular haemorrhage
MAP: mean arterial pressure
PCV: packed cell volume
PE: pre-eclampsia
PIH: pregnancy-induced hypertension
PPH: postpartum haemorrhage
RDS: respiratory distress syndrome
SBP: systolic blood pressure
SCBU: special care baby unit
SD: standard deviation
SGA: small-for-gestational age
SLE: systemic lupus erythematosus

vs: versus
wk: week
yr: year

Characteristics of excluded studies

Study	Reason for exclusion
Australia 1989	41% of participants (9/16) excluded postrandomisation as refused to take treatment. Trial abandoned. Intervention: aspirin vs placebo.
Australia 1989a	No relevant outcomes reported. Study design: "randomly treated", no other information given. Participants: 27 women with uncomplicated twin pregnancies at 28-30 weeks' gestation. Interventions: aspirin 100 mg daily vs placebo. Outcomes: mean placental weight, mean gestation at delivery, mean birthweight.
Brazil 1992	Method of allocation to treatment group not stated. No clinical outcomes reported. Available as an abstract only. Participants: 67 high-risk women with abnormal doppler at 26 weeks. Interventions: 60 mg aspirin daily vs placebo.
Brazil 1996a	Study discontinued prematurely due to local problems. A few women recruited but no outcome data available. Study design: not known. Participants: women at 12-26 weeks with chronic hypertension. Intervention: aspirin 100 mg daily vs placebo. Outcomes: PE; prematurity; IUGR.
China 1991	Abstract only available in English, no clinical outcomes. Participants: women at risk of PIH. Interventions: aspirin 50 mg vs placebo.
Colombia 1996	200 women included in the study, data only presented for 97 who completed the protocol. Study design: randomised trial, no other information. Participants: 200 high-risk women: primigravidae, with antecedents of PIH or chronic hypertension. Intervention: 100 mg aspirin vs placebo.
ERASME 2003a	Comparison of doppler vs no doppler estimation of uterine artery flow velocities. Study design: randomised trial (2 treatment: 1 control). Participants: 1870 nulliparous women at 14-20 weeks' gestation. Intervention: doppler at 22 to 24 weeks. If abnormal doppler given 100 mg aspirin until 36 weeks.
East Germany 1986	No clinical outcomes, available as abstract only. Study design: "prospective randomised study". Participants: 142 women in the 3rd trimester. Interventions: aspirin (96 women) vs no antiplatelet agent (46 women).
East Germany 1988	Method of allocation not stated, described as "double-blind" but two very different interventions. No outcomes reported. Participants: 100 primigravidae with "normal pregnancies". Interventions: aspirin vs magnesium sulphate vs placebo.
Egypt 1991	Crossover study, women with established pre-eclampsia at trial entry, no relevant clinical outcomes reported. Study design: 'allocated at random', no further information.

	Participants: 20 primigravid women in the 3rd trimester with SBP >/= 160 mmHg, DBP >/= 110 mmHg, lower limb oedema 2+, and proteinuria 3+ or 4+. Interventions: aspirin 75 mg vs conventional therapy (oral methyldopa, diazepam, and 25% glucose infusion). Outcomes: changes in blood pressure and albuminuria; lower limb oedema; and urine volume.
Egypt 1998	Unclear if randomised trial. No data on clinical outcomes reported. Study design: women 'put' into 3 groups (30, 30 and 13). No further information. Participants: 73 women with abnormal uterine artery flow on doppler ultrasound. Intervention: group 1 received aspirin 75 mg/day, group 2 received allylestrenol 5 mg twice daily, and group 3 was control. Outcomes: uterine artery blood flow; pregnancy outcome.
Equador 1998	No data on clinical outcomes reported. Available as abstract only. Study design: 'randomised'. No further information. Participants: pregnant women who met all inclusion criteria. Intervention: aspirin 100 mg/day vs placebo.
Finland 1993a	No clinical outcomes reported. Study design: randomised with sealed numbered opaque envelopes. Participants: 14 women with systemic lupus erythematosus. Intervention: 50 mg aspirin vs placebo.
France 2001	Comparison of doppler with no doppler. Study design: multicentre randomised trial. Numbered sealed envelopes. 184 (6%) lost to follow up. Participants: 3317 women in routine antenatal clinic. Intervention: doppler, with aspirin if results abnormal, vs no doppler.
Germany 1986	Abstract only, no clinical outcomes reported.
India 1986	Unclear whether randomised trial. Likely that participants include women with established pre-eclampsia at trial entry. No relevant clinical outcomes reported. Study design: 'double blind'. Participants: 68 women with IUGR and mild-moderate PE at 28 weeks' gestation. Intervention: dipyridamole 100 mg x 3/day vs placebo. Outcomes: fetal weight.
India 1991	Abstract only, no clinical outcomes available. Study design: "randomised controlled trial", no further information. Participants: 200 women at risk of IUGR or with IUGR in current pregnancy. Intervention: dipyridamole + aspirin vs control.
India 1993a	Trial in progress in 1993, no longer recruiting. No data available. Further information requested from trialists. Study design: randomised trial. Participants: previous fetal loss > 20 weeks or IUGR in previous pregnancy. Interventions: aspirin vs placebo.
India 1997	Quasi-random study, consecutive women allocated treatment or control. 21/71 women (29%) excluded from the analysis. Participants: 71 women with a positive roll-over test at 28-32 weeks, and previous history of essential hypertension or PIH. Interventions: 50 mg aspirin, not stated whether placebo. Outcomes: PIH, gestation at delivery, birthweight.
India 1998	Not a randomised trial. 22 neonates born to women who took aspirin during pregnancy compared to matched controls. Women allocated to aspirin consecutively.

India 2001	10 out of 50 women (20%) excluded from analysis as a result of loss to follow up. Study design: women divided into 2 groups based on random-number sequence obtained from standard tables. Participants: 50 women at 16-32 weeks with history of IUGR or PIH +/- proteinuria in previous pregnancy after 32 weeks or current twin pregnancy. Intervention: aspirin 1 mg/kg/day vs placebo. Outcomes: hypertension, PE; maternal mortality; mode of delivery; perinatal death; prematurity; severe IUGR.
India 2002	Quasi-randomised study. Study design: every alternate woman given aspirin and the others served as controls. Participants: 215 women at 15-16 weeks with history of either recurrent missed abortion or IUGR or unexplained stillbirth or PE/eclampsia remote from term or DVT or chorea gravidarum (B-HCG > 2 multiples of the mean for that gestation). Intervention: aspirin 1.2 mg/kgm/day vs no treatment. Outcomes: early onset PE, miscarriage, preterm birth, IUGR, birthweight.
India 2002a	Unclear whether randomised trial. Study design: not reported. 2 groups: 1 group was given aspirin and the other was given placebo. Participants: 76 high-risk women (not defined). Intervention: aspirin 50 mg/day vs placebo, until 36 weeks. Outcomes: hypertension; mild and severe PIH; eclampsia; duration of pregnancy; duration of labour; mode of delivery; APH; PPH; fetal death; birthweight; Apgar score; neonatal complications.
Iran 2002	Likely inadequate concealment of allocation. Random-number tables for allocation, without any mention of blinding, and imbalances between the groups at trial entry. Study design: allocation using random number tables, no further information. Participants: 990 nulliparous women, < 20 weeks. Intervention: aspirin 75 g vs 500 mg calcium vs no treatment.
Ireland 1995	Comparison of 2 different aspirin preparations. No clinical outcomes. Study design: "randomly assigned in a double-blind fashion". Participants: 18 normotensive women and 18 women with pre-eclampsia. Intervention: aspirin 75 mg/day vs controlled-release aspirin 75 mg/day. Outcomes: no clinical outcomes reported.
Italy 1988	Inadequate allocation concealment. Study design: randomised trial using open random-number tables. Participants: 34 high-risk women. Interventions: heparin 15000 IU/day sc and dipyridamole 300 mg/day, compared with untreated controls.
Italy 1990	Does not seem to have been randomised. Described as 'random selection' of women with PIH, but control group did not have PIH. Participants: 20 women with PIH at < 36 weeks' gestation. Interventions: picotamide vs no treatment. Outcomes: no data reported on clinical outcomes.
Italy 2002	Not a randomised trial. Study design was a retrospective case-control study. Participants: 52 women at 12 weeks with chronic hypertension. Intervention: aspirin 100 mg/day plus antihypertensive treatment vs antihypertensive treatment alone. Outcomes: PIH, PE, severe SGA, gestation at delivery, preterm delivery < 34 weeks, birthweight.
Italy 2005	Comparison of anticoagulant (low molecular weight heparin) with no treatment. Study design: computer-generated random-number sequence. Participants: 85 women with history of PE and DD genotype for angiotensin-converting enzyme.

	Intervention: low molecular weight heparin 5000 IU/day vs no treatment. Outcomes: PE; IUGR; gestation at delivery; birthweight.
Japan 1989	Quasi-random allocation on the basis of odd and even record numbers, women with established pre-eclampsia at trial entry, and no clinical outcomes reported. Participants: 40 women with pre-eclampsia. Interventions: antithrombin III concentrate vs no treatment.
Libya 2000	Abstract only. Large imbalance between the groups in an open study (538 vs 372), no information about concealment of allocation. Study design: "randomised". Participants: 910 primigravid women. Interventions: aspirin 150 mg/day from 20 weeks vs no aspirin.
Netherlands 1991	No outcomes reported. Available as an abstract only. Study design: "randomly allocated", no other information. Participants: 41 women with 2 or more previous pregnancies complicated by severe IUGR and placental infarction, no other complications. Interventions: aspirin 1 mg/kg daily and dipyridamole 75 mg x 3 daily vs aspirin alone. From 12-34 weeks.
Netherlands/UK 1994	No clinical data available. Published as abstract only. Study design: "double-blind randomised". Participants: 193 primiparous women with resistance index 0.58, or more, in one or both arcuate arteries at 24 weeks. Interventions: allylestrenol 25 mg plus aspirin 60 mg/day vs double placebo.
New Zealand 1990	No outcomes reported, this was a feasibility study and the trial was abandoned due to poor recruitment. Study design: "randomised trial" no other information. Participants: 4 nulliparous women < 16 weeks. Interventions: aspirin 100 mg vs placebo.
New Zealand 1998	> 20% of recruited women excluded. 34/99 (34%) women excluded as <14 days on trial treatment. Study design: randomised trial. Participants: 99 women with normal anatomy scan < 20 weeks and ultrasound diagnosis of IUGR at 24-36 weeks, plus abnormal umbilical doppler. Interventions: 100 mg aspirin daily vs placebo. Outcomes: caesarean section, birthweight, baby deaths, days in hospital for the baby.
New Zealand 2000	10 women (20%) excluded because antibody levels had not met eligibility criteria, or second test normal. Study design: computer-generated sequence, sealed numbered opaque envelopes. Participants: 50 women with antiphospholipid syndrome, 3 or more miscarriages and 1 or more antibodies increased. Interventions: aspirin 75 mg vs placebo. Outcomes: PIH, PE, caesarean section, preterm delivery, SGA.
Pakistan 1994	Comparison of aspirin with antihypertensive drugs. Method of allocation unclear, but the description implies quasi-randomisation. Study design: consecutive women randomly divided into two treatment groups. Participants: 200 women with either a previous history of PE or eclampsia, or BP 140/90 x 2 15 days apart or mild essential hypertension. Intervention: 75 mg aspirin x 2/day vs routine antihypertensive drugs if BP > 100 mmHg.
Pergar 1987	Method of allocation not stated and no clinical outcomes reported. Participants: 300 women with IUGR in the previous pregnancy or 2 previous consecutive pregnancies, 15-17 weeks' gestation.

	Interventions: dipyridamole 225 mg/day, until delivery, vs placebo.
Poland 1999	Comparison of aspirin with another therapy. Abstract only. Large imbalance between groups (22 vs 9) in an open study with no information about concealment of allocation. Study design: "randomly assigned" in 2 to 1 ratio. No further details. Participants: 31 women with IUGR. Interventions: aspirin (1.5 mg/kg) versus 'standard treatment' with sadamin, partusisten, infusion of amino acids and glucose. Outcomes: gestational age at delivery, birthweight, IUGR.
Russia 1997	Comparison of aspirin plus dipyridamole with glyceryl trinitrate. Randomisation: 'blinded randomisation' stratified by essential hypertension or chronic glomerulonephritis. No further information. Participants: 76 women at 16-20 weeks with mild-moderate hypertension, with either essential hypertension or CGN. Intervention: glyceryl trinitrate skin patch 5 mg, increasing to 20 mg if tolerated for 12 hrs/day vs aspirin 125 mg/day and dipyridamole 150-225 mg/day. Outcomes: progressive gestational hypertension; increase in proteinuria; development or progression of renal failure; abruption; pregnancy complications; side-effects; miscarriage or stillbirth; preterm birth; IUGR.
Slovenia 1992	No clinical outcomes reported. Available as an abstract only. Study design: "randomly allocated", no other information. Participants: 43 women at risk of PE on the basis of their obstetric history. Interventions: aspirin 150 mg + dipyridamole 225 mg daily from 16 weeks until delivery vs no treatment.
Slovenia 1994	Abstract only with no data reported. Study design: "randomly allocated". Participants: 20 women at high risk for gestational hypertension. Interventions: aspirin 100 mg/day vs n-3 fatty acids 3 g/day.
Slovenia 1998	Quasi-random study. Study design: "randomly allocated" into 3 groups with odd and even numbers. Participants: 48 women at high risk for gestational hypertension. Interventions: aspirin 100 mg/day vs n-3 fatty acids 300 mg/day vs no treatment.
South Africa 1986	Published in abstract only, no data available. Study design: sealed numbered envelopes, no other information provided. Participants: 152 primigravid women with normal BP and pregnancy at first antenatal hospital visit. Interventions: 75 mg aspirin daily vs placebo.
Spain + others 2000	172/768 (22%) women lost to follow up. Abstract only. Study design: randomisation by sealed opaque numbered envelopes. Multicentre randomised trial in Spain, Portugal, Ecuador, Argentina and Brazil. Participants: women at 12-16 weeks' gestation, BP < 135/85 and no proteinuria. Interventions: aspirin 100 mg vs placebo.
Switzerland 2000	Compared aspirin (100 mg/day) with aspirin plus low molecular weight heparin. Available as an abstract only. Study design: randomly assigned, no other information.
Thailand 1996	Quasi-randomised study. Study design: randomisation by odd and even numbers based on last 2 digits of MRN.
Trinidad 1997	Not a randomised comparison of aspirin with placebo. Study design: alternate allocation to supplemented or control group, and the supplemented group randomised using random-number tables to 3 intervention groups.

	Participants: 510 women, primigravid or with previous PE. Interventions: 1200 mg calcium versus 60 mg calcium + 80 mg aspirin vs 80 mg aspirin vs control.
Tunisia 1989	Not a randomised trial. Concurrent controls. Participants: 60 women with previous hypertension in pregnancy. Interventions: aspirin 250 mg 2nd daily and dipyridamole 300 mg daily if < 12 weeks' gestation or standard treatment if 12-20 weeks.
Tunisia 1990	Compared aspirin with aspirin plus dipyridamole. Available as an abstract only. Study design: 'randomised'. No further information. Participants: 29 women with previous hypertension in pregnancy. Intervention: aspirin (200 mg every other day) vs aspirin plus dipyridamole (300 mg/day) from 3rd month. Outcomes: normal/abnormal pregnancy; hypertension; proteinuria; duration of pregnancy; severe complications; birthweight; fetal death.
Tunisia 1994	Compared aspirin with aspirin plus dipyridamole. Available as an abstract only. Study design: 'randomised'. No further information. Participants: 51 women with previous hypertension in pregnancy. Intervention: aspirin (100 mg every 2 days) vs aspirin plus dipyridamole (300 mg/day) from 3rd month. Outcomes: normal/abnormal pregnancy; hypertension; proteinuria; duration of pregnancy; severe complications; birthweight; fetal death.
UK 1992a	No clinical outcomes reported. Study design: "randomised trial" no further information. Participants: 52 high-risk women > 24 weeks' gestation. Interventions: aspirin 75 mg/day vs placebo.
UK 1993	Study of bleeding times in a subgroup of a larger trial. No clinical outcomes reported. The full trial report does not appear to have been published. Participants: 30 women. Intervention: aspirin vs placebo.
UK 1994	Paper retracted by journal editors, suspected fraud.
UK 2000	Concern about potential for major bias: concealment of allocation not adequate, no placebo, active group had different care to control group (see below). Study design: sealed envelopes, no further details. Participants: 116 women at 19-21 weeks with abnormal uterine artery doppler. Intervention: aspirin 100 mg. Doppler repeated at 24 weeks, if normal aspirin stopped. If persistent notching aspirin continued and further scans every 4 weeks. Control group, no aspirin, no routine doppler. Usual antenatal care.
USA 1988a	No clinical data available. Trial registered as planned in 1988, but no data published. Study design: coded drugs. Participants: women with a history of previous stillbirth or IUGR but negative for systemic lupus and lupus anticoagulant. Interventions: aspirin vs placebo.
USA 1989	Participants were 40 normal pregnant women in the 3rd trimester, not women with PE or considered to be at risk of PE. Study design: allocation by sealed opaque numbered envelopes. Interventions: aspirin 20 mg, or 60 mg or 80 mg daily vs placebo (4 groups). Outcomes: APH, PPH, stillbirth, mean birthweight, Apgar scores.
USA 1990	Interim report of 20 women from a study with a planned sample size of 160. Percentages only reported, with no denominators. Published as an abstract only.

Characteristics of excluded studies (*Continued*)

	Study design: "prospective, placebo-controlled, double-blind study", no other information given. Participants: primiparous women, ultrasound confirmation of dates < 20 weeks' gestation. Intervention: aspirin 80 mg daily vs placebo.
USA 1990a	Registered as a planned trial in 1990. Recruitment due to start in November 1990, but no further information available. Participants: multiparous women with a multiple pregnancy. Interventions: aspirin vs placebo.
USA 1993b	Comparison of prednisone + aspirin with aspirin alone. Study design: sequential opaque envelopes. Participants: 39 antiphospholipid antibody positive women.
USA 1993c	No clinical outcomes reported. Study design: "randomised double-blind crossover". Participants: 24 women with hypertension or other complications. Intervention: acetaminophen vs indomethacin versus control.
USA 1996	Women with uncomplicated pregnancy. No relevant outcomes. Study design: randomised, no other information. Participants: 12 women with uncomplicated pregnancy at 28-34 weeks. Intervention: 4 groups. Aspirin 20 mg vs 40 mg vs 80 mg vs placebo. Outcomes: haematological measures only.
Uganda 1992	Planned in 1992. No further information.
West Germany 1977	No clinical outcomes reported, published in abstract only. Study design: "double-blind trial". Participants: 40 women with suspected early IUGR, 30-33 weeks. Intervention: dipyridamole vs placebo.

APH: antepartum haemorrhage
BP: blood pressure
CGN: chronic glomerulonephritis
DPB: diastolic blood pressure
DVT: deep vein thrombosis
HCG: human chorionic gonadotrophin
hr: hour
IU: international unit
IUGR: intrauterine growth restriction
MRN: medical record number
PE: pre-eclampsia
PIH: pregnancy-induced hypertension
PPH: postpartum haemorrhage
SBP: systolic blood pressure
sc: subcutaneous
SGA: small-for-gestational age
vs: versus

Characteristics of ongoing studies

ANALYSES

Comparison 01. Antiplatelet agents versus placebo/no antiplatelet for primary prevention (subgrouped by maternal risk)

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Gestational hypertension	34	20701	Relative Risk (Fixed) 95% CI	0.95 [0.88, 1.03]
02 Proteinuric pre-eclampsia	43	32590	Relative Risk (Fixed) 95% CI	0.83 [0.77, 0.89]
03 Eclampsia	9	22584	Relative Risk (Fixed) 95% CI	0.94 [0.59, 1.48]
04 Maternal death	3	12709	Relative Risk (Fixed) 95% CI	2.57 [0.39, 17.06]
05 Placental abruption	16	24982	Relative Risk (Fixed) 95% CI	1.10 [0.89, 1.37]
06 Caesarean section	24	31834	Relative Risk (Fixed) 95% CI	1.02 [0.98, 1.06]
07 Induction of labour	5	19295	Relative Risk (Fixed) 95% CI	1.03 [0.98, 1.08]
08 Hospital admission for the woman during pregnancy	3	12964	Relative Risk (Fixed) 95% CI	1.03 [0.97, 1.10]
09 Preterm birth (< 37 weeks)	29	31151	Relative Risk (Fixed) 95% CI	0.92 [0.88, 0.97]
10 Preterm birth (subgroups by gestational age)			Relative Risk (Fixed) 95% CI	Subtotals only
11 Fetal and neonatal deaths	40	33098	Relative Risk (Fixed) 95% CI	0.86 [0.76, 0.98]
12 Fetal, neonatal, infant and childhood deaths (subgroups by time of death)			Relative Risk (Fixed) 95% CI	Subtotals only
13 Deaths after discharge from hospital	3	5886	Relative Risk (Fixed) 95% CI	0.53 [0.21, 1.34]
14 Small-for-gestational age (any definition)	36	23638	Relative Risk (Fixed) 95% CI	0.90 [0.83, 0.98]
15 Small-for-gestational age (subgroups by severity)	32	24333	Relative Risk (Fixed) 95% CI	0.91 [0.84, 0.99]
16 Birthweight < 2500 g	6	7512	Relative Risk (Fixed) 95% CI	0.93 [0.83, 1.05]
17 Admission to a special care baby unit	15	28298	Relative Risk (Fixed) 95% CI	0.95 [0.90, 1.01]
18 Intraventricular haemorrhage	10	26184	Relative Risk (Fixed) 95% CI	0.88 [0.63, 1.22]
19 Other neonatal bleed	8	27032	Relative Risk (Fixed) 95% CI	1.13 [0.83, 1.52]
20 Non-routine GP consultation for child			Relative Risk (Fixed) 95% CI	Subtotals only
21 Child admitted to hospital			Relative Risk (Fixed) 95% CI	Subtotals only
22 Developmental problems at 18 months			Relative Risk (Fixed) 95% CI	Subtotals only
23 Behaviour problems at 18 months	1	4365	Relative Risk (Fixed) 95% CI	0.87 [0.75, 1.01]
24 Malformations at 18 months	1	788	Relative Risk (Fixed) 95% CI	0.74 [0.27, 2.02]
25 Growth at 18 months	4	10306	Relative Risk (Fixed) 95% CI	0.94 [0.84, 1.07]

Comparison 02. Antiplatelet agents versus placebo/no antiplatelet for primary prevention (subgrouped by gestation at entry)

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Gestational hypertension	33	20545	Relative Risk (Fixed) 95% CI	0.97 [0.89, 1.05]
02 Proteinuric pre-eclampsia	48	32590	Relative Risk (Fixed) 95% CI	0.83 [0.77, 0.89]
03 Placental abruption	16	24982	Relative Risk (Fixed) 95% CI	1.10 [0.89, 1.37]
04 Preterm birth	34	31151	Relative Risk (Fixed) 95% CI	0.92 [0.88, 0.97]
05 Fetal, neonatal or infant death	44	33046	Relative Risk (Fixed) 95% CI	0.88 [0.77, 1.00]
06 Small-for-gestational age	39	23638	Relative Risk (Fixed) 95% CI	0.91 [0.84, 0.98]

Comparison 03. Antiplatelet agents versus placebo/no treatment for primary prevention (subgrouped by use of placebo)

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Gestational hypertension	33	20597	Relative Risk (Fixed) 95% CI	0.96 [0.89, 1.04]
02 Proteinuric pre-eclampsia	43	32590	Relative Risk (Fixed) 95% CI	0.83 [0.77, 0.89]
03 Placental abruption	16	24982	Relative Risk (Fixed) 95% CI	1.10 [0.89, 1.37]
04 Preterm birth	29	31151	Relative Risk (Fixed) 95% CI	0.92 [0.87, 0.97]
05 Fetal, neonatal or infant death	40	33098	Relative Risk (Fixed) 95% CI	0.87 [0.76, 0.99]
06 Small-for-gestational age	36	23638	Relative Risk (Fixed) 95% CI	0.94 [0.86, 1.01]

Comparison 04. Antiplatet agents versus placebo/no treatment for primary prevention (subgrouped by dose)

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Gestational hypertension			Relative Risk (Fixed) 95% CI	Subtotals only
02 Proteinuric pre-eclampsia			Relative Risk (Fixed) 95% CI	Subtotals only
03 Placental abruption			Relative Risk (Fixed) 95% CI	Subtotals only
04 Preterm birth			Relative Risk (Fixed) 95% CI	Subtotals only
05 Fetal, neonatal or infant death			Relative Risk (Fixed) 95% CI	Subtotals only
06 Small-for-gestational age			Relative Risk (Fixed) 95% CI	Subtotals only

Comparison 05. Antiplatelet agents versus placebo/no antiplatelet for women with gestational hypertension

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Proteinuric pre-eclampsia	5	1643	Relative Risk (Fixed) 95% CI	0.60 [0.45, 0.78]
02 Eclampsia	3	354	Relative Risk (Fixed) 95% CI	0.25 [0.03, 2.24]
03 Placental abruption	1	94	Relative Risk (Fixed) 95% CI	0.35 [0.01, 8.32]
04 Caesarean section	1	47	Relative Risk (Fixed) 95% CI	0.87 [0.31, 2.46]
05 Preterm birth	3	1451	Relative Risk (Fixed) 95% CI	0.87 [0.75, 0.99]
06 Fetal, neonatal or infant death	4	1728	Relative Risk (Fixed) 95% CI	1.02 [0.72, 1.45]
07 Small-for-gestational age	3	344	Relative Risk (Fixed) 95% CI	0.76 [0.52, 1.10]
08 Birthweight < 2500 g	1	100	Relative Risk (Fixed) 95% CI	0.24 [0.09, 0.65]
09 Admission to a special care baby unit	1	94	Relative Risk (Fixed) 95% CI	0.52 [0.05, 5.56]
10 Neonatal haemorrhagic complications	1	94	Relative Risk (Fixed) 95% CI	Not estimable
11 Severe pre-eclampsia	1	94	Relative Risk (Fixed) 95% CI	0.33 [0.14, 0.75]

INDEX TERMS

Medical Subject Headings (MeSH)

Aspirin [therapeutic use]; Fetal Death [prevention & control]; Obstetric Labor, Premature [prevention & control]; Platelet Aggregation Inhibitors [*therapeutic use]; Pre-Eclampsia [*prevention & control]; Randomized Controlled Trials

MeSH check words

Female; Humans; Pregnancy

COVER SHEET

Title	Antiplatelet agents for preventing pre-eclampsia and its complications
Authors	Duley L, Henderson-Smart DJ, Meher S, King JF
Contribution of author(s)	All the review authors contributed to developing the protocol. Marian Knight wrote the first draft of the protocol, which was then modified in discussion with the other authors and following comments from others. Marian Knight and Lelia Duley did the searches, with help from the Cochrane Pregnancy and Childbirth Group, and decided on potentially eligible studies. All the authors helped with data extraction. Data were entered by Marian Knight, Lelia Duley and David Henderson-Smart. All authors contributed to checking the data. All authors have contributed to preparing the final report, which was drafted by Lelia Duley. Lelia Duley assessed the eligible studies and extracted the data. Lelia Duley revised the report of the review, in consultation with David Henderson-Smart. All authors have contributed to the report of the updated review.
Issue protocol first published	1997/4
Review first published	2000/2
Date of most recent amendment	19 February 2007
Date of most recent SUBSTANTIVE amendment	07 February 2007
What's New	July 2006 This version updates two previously published reviews in The Cochrane Library (CDSR 2000 and CDSR 2003). Seven additional trials have been included (Brazil 1992a; China 1996a; Egypt 2005; Finland 1997a; Italy 2004; UK +others 2003; USA 1997), and one study which had previously been excluded (Russia 1994) is now included after additional clarification from trialists. Fifteen additional trials have been assessed and excluded (Brazil 1996a; Egypt 1991; Egypt 1998; Equador 1998; India 1986; India 2001; India 2002; India 2002a; Italy 1990; Italy 2002; Italy 2005; Japan 1989; Russia 1997; Tunisia 1990; Tunisia 1994). These changes have not made a substantive difference to the overall conclusions of this review. Trials previously classified as 'treatment' rather than 'prevention' (India 1993; India 1994; Israel 1990; subgroup of UK 1992; subgroup of CLASP 1994; subgroup of Italy 1993) are now included with this review, but under a different comparison for secondary prevention of pre-eclampsia. The review 'Antiplatelet agents for preventing and treating pre-eclampsia' has therefore been withdrawn from The Cochrane Library.
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	30 July 2006
Date authors' conclusions section amended	14 July 2003
Contact address	Prof Lelia Duley Obstetric Epidemiologist Centre for Epidemiology and Biostatistics University of Leeds Academic Unit, Fieldhouse Bradford Teaching Hospitals Foundation Trust, Bradford Royal Infirmary, Duckworth Lane Bradford West Yorkshire BD9 6RJ UK E-mail: l.duley@leeds.ac.uk Tel: +44 1274 383079
DOI	10.1002/14651858.CD004659.pub2
Cochrane Library number	CD004659
Editorial group	Cochrane Pregnancy and Childbirth Group
Editorial group code	HM-PREG

GRAPHS AND OTHER TABLES

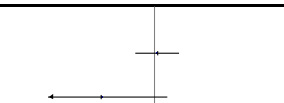
Analysis 01.01. Comparison 01 Antiplatelet agents versus placebo/no antiplatelet for primary prevention (subgrouped by maternal risk), Outcome 01 Gestational hypertension

Review: Antiplatelet agents for preventing pre-eclampsia and its complications

Comparison: 01 Antiplatelet agents versus placebo/no antiplatelet for primary prevention (subgrouped by maternal risk)

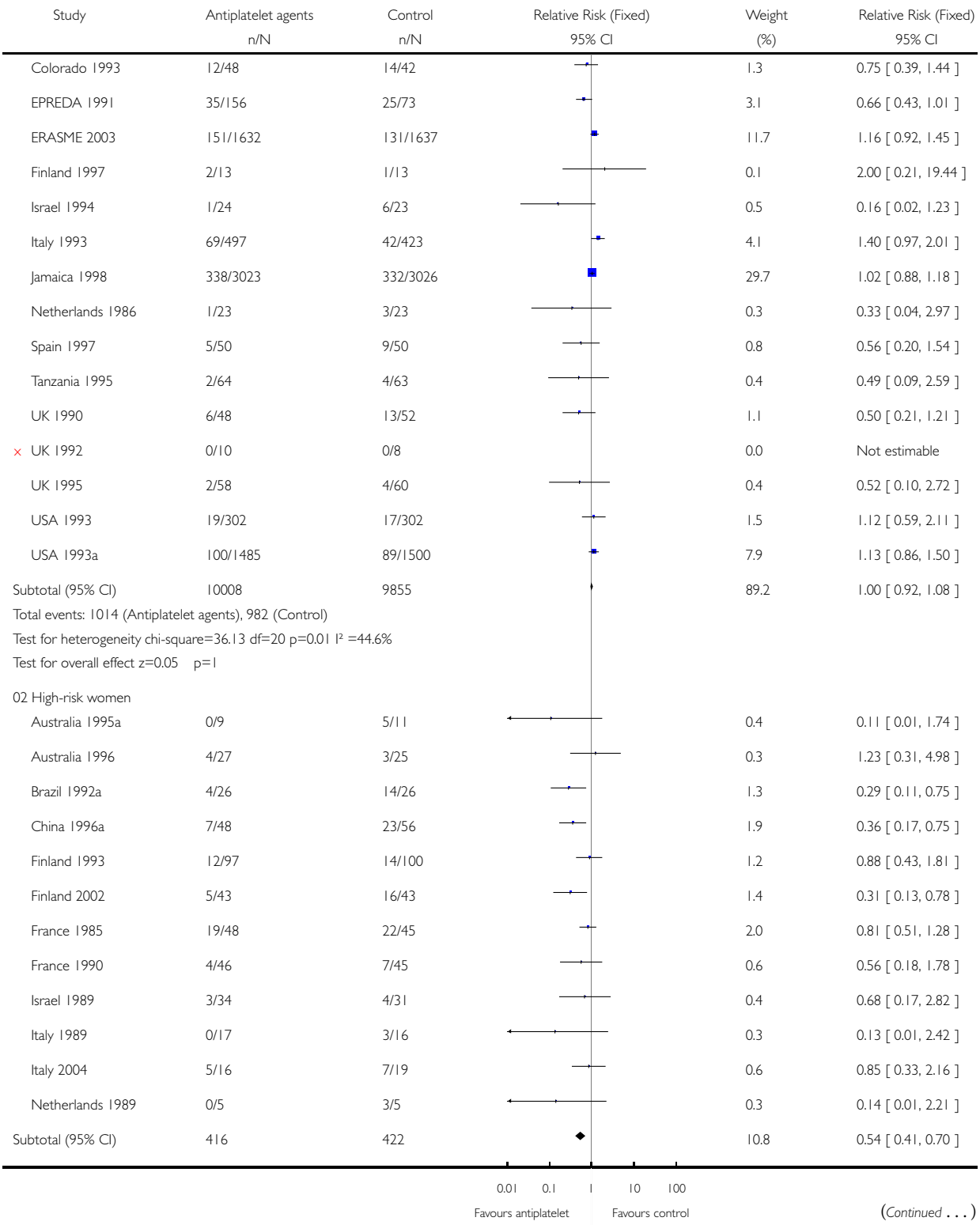
Outcome: 01 Gestational hypertension

Study	Antiplatelet agents n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 Moderate-risk women					
Australia 1996a	8/52	7/50		0.6	1.10 [0.43, 2.81]
Austria 1992	0/22	4/19		0.4	0.10 [0.01, 1.69]
Barbados 1998	162/1819	172/1822		15.4	0.94 [0.77, 1.16]
Brazil 1996	68/476	56/494		4.9	1.26 [0.91, 1.75]
China 1996	4/40	12/44		1.0	0.37 [0.13, 1.05]
China 1996a	7/48	23/56		1.9	0.36 [0.17, 0.75]
China 1999	22/118	18/75		2.0	0.78 [0.45, 1.35]



(*Continued* . . .)

(. . . *Continued*)



Study	Antiplatelet agents n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Colorado 1993	12/48	14/42		1.3	0.75 [0.39, 1.44]
EPREDA 1991	35/156	25/73		3.1	0.66 [0.43, 1.01]
ERASME 2003	151/1632	131/1637		11.7	1.16 [0.92, 1.45]
Finland 1997	2/13	1/13		0.1	2.00 [0.21, 19.44]
Israel 1994	1/24	6/23		0.5	0.16 [0.02, 1.23]
Italy 1993	69/497	42/423		4.1	1.40 [0.97, 2.01]
Jamaica 1998	338/3023	332/3026		29.7	1.02 [0.88, 1.18]
Netherlands 1986	1/23	3/23		0.3	0.33 [0.04, 2.97]
Spain 1997	5/50	9/50		0.8	0.56 [0.20, 1.54]
Tanzania 1995	2/64	4/63		0.4	0.49 [0.09, 2.59]
UK 1990	6/48	13/52		1.1	0.50 [0.21, 1.21]
× UK 1992	0/10	0/8		0.0	Not estimable
UK 1995	2/58	4/60		0.4	0.52 [0.10, 2.72]
USA 1993	19/302	17/302		1.5	1.12 [0.59, 2.11]
USA 1993a	100/1485	89/1500		7.9	1.13 [0.86, 1.50]
Subtotal (95% CI)	10008	9855		89.2	1.00 [0.92, 1.08]
Total events: 1014 (Antiplatelet agents), 982 (Control)					
Test for heterogeneity chi-square=36.13 df=20 p=0.01 I² =44.6%					
Test for overall effect z=0.05 p=1					
02 High-risk women					
Australia 1995a	0/9	5/11		0.4	0.11 [0.01, 1.74]
Australia 1996	4/27	3/25		0.3	1.23 [0.31, 4.98]
Brazil 1992a	4/26	14/26		1.3	0.29 [0.11, 0.75]
China 1996a	7/48	23/56		1.9	0.36 [0.17, 0.75]
Finland 1993	12/97	14/100		1.2	0.88 [0.43, 1.81]
Finland 2002	5/43	16/43		1.4	0.31 [0.13, 0.78]
France 1985	19/48	22/45		2.0	0.81 [0.51, 1.28]
France 1990	4/46	7/45		0.6	0.56 [0.18, 1.78]
Israel 1989	3/34	4/31		0.4	0.68 [0.17, 2.82]
Italy 1989	0/17	3/16		0.3	0.13 [0.01, 2.42]
Italy 2004	5/16	7/19		0.6	0.85 [0.33, 2.16]
Netherlands 1989	0/5	3/5		0.3	0.14 [0.01, 2.21]
Subtotal (95% CI)	416	422		10.8	0.54 [0.41, 0.70]

(*Continued* . . .)

(. . . *Continued*)

Study	Antiplatelet agents n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Total events: 63 (Antiplatelet agents), 121 (Control)					
Test for heterogeneity chi-square=14.51 df=11 p=0.21 I^2 =24.2%					
Test for overall effect z=4.60 p<0.00001					
Total (95% CI)	10424	10277		100.0	0.95 [0.88, 1.03]
Total events: 1077 (Antiplatelet agents), 1103 (Control)					
Test for heterogeneity chi-square=63.38 df=32 p=0.0008 I^2 =49.5%					
Test for overall effect z=1.32 p=0.2					

Analysis 01.02. Comparison 01 Antiplatelet agents versus placebo/no antiplatelet for primary prevention (subgrouped by maternal risk), Outcome 02 Proteinuric pre-eclampsia

Review: Antiplatelet agents for preventing pre-eclampsia and its complications

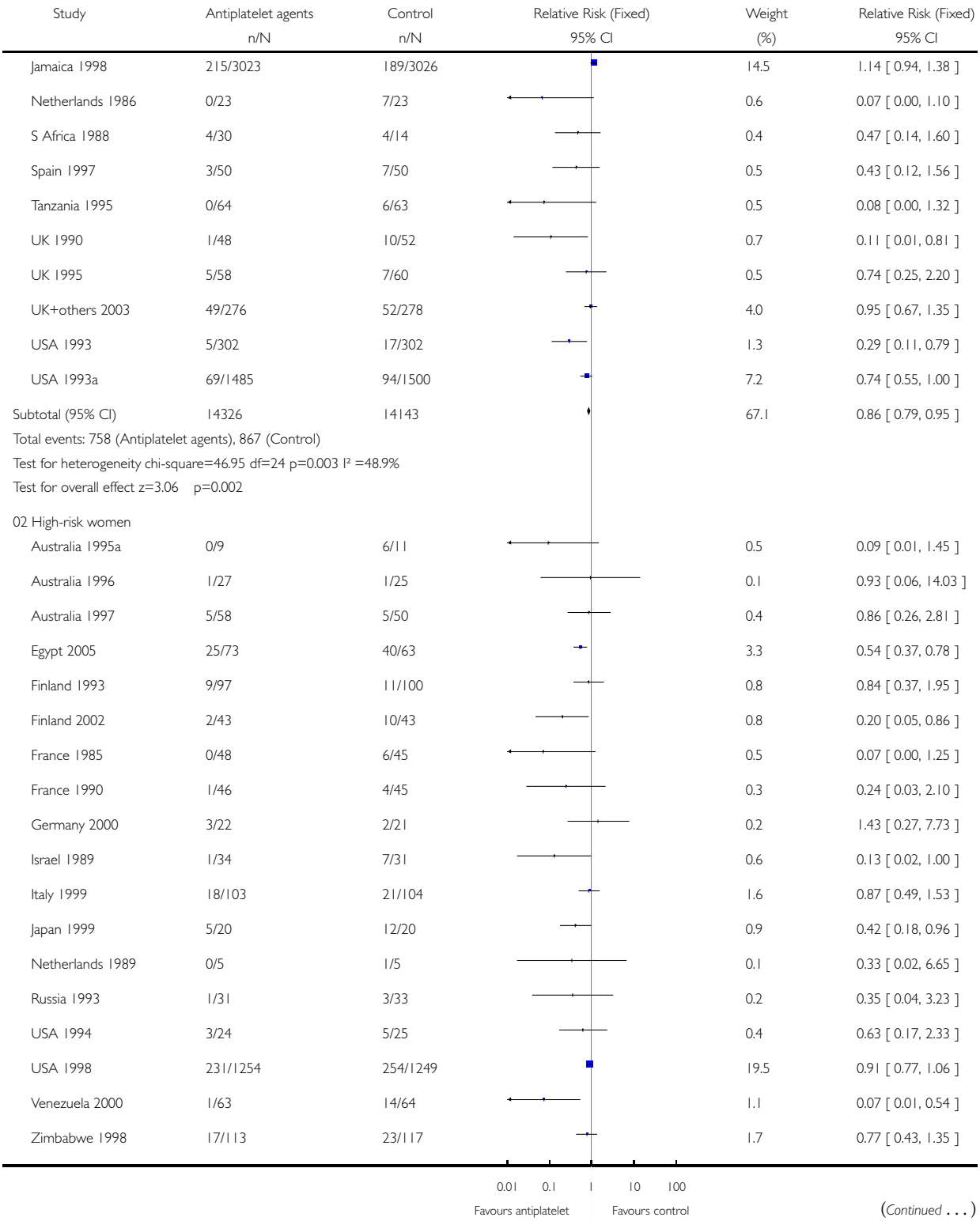
Comparison: 01 Antiplatelet agents versus placebo/no antiplatelet for primary prevention (subgrouped by maternal risk)

Outcome: 02 Proteinuric pre-eclampsia

Study	Antiplatelet agents n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 Moderate-risk women					
Australia 1993	1/55	5/55		0.4	0.20 [0.02, 1.66]
Australia 1996a	4/52	7/50		0.5	0.55 [0.17, 1.76]
Austria 1992	0/22	6/19		0.5	0.07 [0.00, 1.11]
Barbados 1998	40/1819	46/1822		3.5	0.87 [0.57, 1.32]
Brazil 1996	32/476	30/494		2.3	1.11 [0.68, 1.79]
China 1996	4/40	12/44		0.9	0.37 [0.13, 1.05]
China 1999	3/118	7/75		0.7	0.27 [0.07, 1.02]
CLASP 1994	267/3992	302/3982		23.2	0.88 [0.75, 1.03]
Colorado 1993	6/48	9/42		0.7	0.58 [0.23, 1.50]
EPREDA 1991	5/156	8/73		0.8	0.29 [0.10, 0.86]
ERASME 2003	28/1632	26/1637		2.0	1.08 [0.64, 1.83]
Finland 1997	4/13	2/13		0.2	2.00 [0.44, 9.08]
Finland 1997a	1/23	3/23		0.2	0.33 [0.04, 2.97]
Israel 1994	0/24	2/23		0.2	0.19 [0.01, 3.80]
Italy 1993	12/497	9/423		0.7	1.13 [0.48, 2.67]

(*Continued* . . .)

(. . . *Continued*)

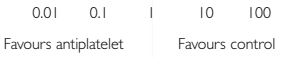


Study	Antiplatelet agents n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Jamaica 1998	215/3023	189/3026		14.5	1.14 [0.94, 1.38]
Netherlands 1986	0/23	7/23		0.6	0.07 [0.00, 1.10]
S Africa 1988	4/30	4/14		0.4	0.47 [0.14, 1.60]
Spain 1997	3/50	7/50		0.5	0.43 [0.12, 1.56]
Tanzania 1995	0/64	6/63		0.5	0.08 [0.00, 1.32]
UK 1990	1/48	10/52		0.7	0.11 [0.01, 0.81]
UK 1995	5/58	7/60		0.5	0.74 [0.25, 2.20]
UK+others 2003	49/276	52/278		4.0	0.95 [0.67, 1.35]
USA 1993	5/302	17/302		1.3	0.29 [0.11, 0.79]
USA 1993a	69/1485	94/1500		7.2	0.74 [0.55, 1.00]
Subtotal (95% CI)	14326	14143		67.1	0.86 [0.79, 0.95]
Total events: 758 (Antiplatelet agents), 867 (Control)					
Test for heterogeneity chi-square=46.95 df=24 p=0.003 I^2 =48.9%					
Test for overall effect z=3.06 p=0.002					
02 High-risk women					
Australia 1995a	0/9	6/11		0.5	0.09 [0.01, 1.45]
Australia 1996	1/27	1/25		0.1	0.93 [0.06, 14.03]
Australia 1997	5/58	5/50		0.4	0.86 [0.26, 2.81]
Egypt 2005	25/73	40/63		3.3	0.54 [0.37, 0.78]
Finland 1993	9/97	11/100		0.8	0.84 [0.37, 1.95]
Finland 2002	2/43	10/43		0.8	0.20 [0.05, 0.86]
France 1985	0/48	6/45		0.5	0.07 [0.00, 1.25]
France 1990	1/46	4/45		0.3	0.24 [0.03, 2.10]
Germany 2000	3/22	2/21		0.2	1.43 [0.27, 7.73]
Israel 1989	1/34	7/31		0.6	0.13 [0.02, 1.00]
Italy 1999	18/103	21/104		1.6	0.87 [0.49, 1.53]
Japan 1999	5/20	12/20		0.9	0.42 [0.18, 0.96]
Netherlands 1989	0/5	1/5		0.1	0.33 [0.02, 6.65]
Russia 1993	1/31	3/33		0.2	0.35 [0.04, 3.23]
USA 1994	3/24	5/25		0.4	0.63 [0.17, 2.33]
USA 1998	231/1254	254/1249		19.5	0.91 [0.77, 1.06]
Venezuela 2000	1/63	14/64		1.1	0.07 [0.01, 0.54]
Zimbabwe 1998	17/113	23/117		1.7	0.77 [0.43, 1.35]

(*Continued* . . .)

(. . . *Continued*)

Study	Antiplatelet agents n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Subtotal (95% CI)	2070	2051		32.9	0.75 [0.66, 0.85]
Total events: 323 (Antiplatelet agents), 425 (Control)					
Test for heterogeneity chi-square=29.14 df=17 p=0.03 I^2 =41.7%					
Test for overall effect z=4.36 p=0.00001					
Total (95% CI)	16396	16194		100.0	0.83 [0.77, 0.89]
Total events: 1081 (Antiplatelet agents), 1292 (Control)					
Test for heterogeneity chi-square=78.31 df=42 p=0.0006 I^2 =46.4%					
Test for overall effect z=4.92 p<0.00001					



Analysis 01.03. Comparison 01 Antiplatelet agents versus placebo/no antiplatelet for primary prevention (subgrouped by maternal risk), Outcome 03 Eclampsia

Review: Antiplatelet agents for preventing pre-eclampsia and its complications

Comparison: 01 Antiplatelet agents versus placebo/no antiplatelet for primary prevention (subgrouped by maternal risk)

Outcome: 03 Eclampsia

Study	Antiplatelet agents n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Australia 1996a	1/52	0/50		1.4	2.89 [0.12, 69.24]
× Austria 1992	0/22	0/19		0.0	Not estimable
Barbados 1998	4/1819	0/1822		1.3	9.01 [0.49, 167.32]
× China 1999	0/118	0/75		0.0	Not estimable
CLASP 1994	7/4659	7/4650		18.6	1.00 [0.35, 2.84]
Jamaica 1998	18/3023	22/3126		57.5	0.85 [0.45, 1.57]
Netherlands 1986	0/23	1/23		4.0	0.33 [0.01, 7.78]
UK 1995	0/58	1/60		3.9	0.34 [0.01, 8.29]
USA 1993a	3/1485	5/1500		13.2	0.61 [0.15, 2.53]
Total (95% CI)	11259	11325		100.0	0.94 [0.59, 1.48]
Total events: 33 (Antiplatelet agents), 36 (Control)					
Test for heterogeneity chi-square=4.06 df=6 p=0.67 I^2 =0.0%					
Test for overall effect z=0.27 p=0.8					

Analysis 01.04. Comparison 01 Antiplatelet agents versus placebo/no antiplatelet for primary prevention (subgrouped by maternal risk), Outcome 04 Maternal death

Review: Antiplatelet agents for preventing pre-eclampsia and its complications

Comparison: 01 Antiplatelet agents versus placebo/no antiplatelet for primary prevention (subgrouped by maternal risk)

Outcome: 04 Maternal death

Study	Antiplatelet agents n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
CLASP 1994	2/4659	1/4650		69.7	2.00 [0.18, 22.01]
EPREDA 1991	1/56	0/73		30.3	3.89 [0.16, 93.84]
× ERASME 2003	0/1634	0/1637		0.0	Not estimable
Total (95% CI)	6349	6360		100.0	2.57 [0.39, 17.06]

Total events: 3 (Antiplatelet agents), 1 (Control)

Test for heterogeneity chi-square=0.11 df=1 p=0.74 I^2 =0.0%

Test for overall effect z=0.98 p=0.3

Analysis 01.05. Comparison 01 Antiplatelet agents versus placebo/no antiplatelet for primary prevention (subgrouped by maternal risk), Outcome 05 Placental abruption

Review: Antiplatelet agents for preventing pre-eclampsia and its complications

Comparison: 01 Antiplatelet agents versus placebo/no antiplatelet for primary prevention (subgrouped by maternal risk)

Outcome: 05 Placental abruption

Study	Antiplatelet agents n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 Moderate-risk women					
Barbados 1998	9/1819	14/1822		9.1	0.64 [0.28, 1.48]
Brazil 1996	5/476	7/494		4.5	0.74 [0.24, 2.32]
CLASP 1994	86/4659	71/4650		46.3	1.21 [0.89, 1.65]
EPREDA 1991	7/156	6/73		5.3	0.55 [0.19, 1.57]
ERASME 2003	13/1623	9/1628		5.9	1.45 [0.62, 3.38]
Finland 1997	2/13	0/13		0.3	5.00 [0.26, 95.02]
× Israel 1994	0/24	0/23		0.0	Not estimable
Italy 1993	7/565	9/477		6.4	0.66 [0.25, 1.75]
× Spain 1997	0/50	0/50		0.0	Not estimable
UK 1995	2/58	1/60		0.6	2.07 [0.19, 22.20]
UK+others 2003	10/276	5/278		3.2	2.01 [0.70, 5.82]

(*Continued . . .*)

(. . . *Continued*)

Study	Antiplatelet agents n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
USA 1993a	11/1485	2/1500		1.3	5.56 [1.23, 25.02]
Subtotal (95% CI)	11204	11068		82.9	1.17 [0.93, 1.48]
Total events: 152 (Antiplatelet agents), 124 (Control)					
Test for heterogeneity chi-square=12.50 df=9 p=0.19 I^2 =28.0%					
Test for overall effect z=1.35 p=0.2					
02 High-risk women					
Australia 1996	1/27	2/25		1.4	0.46 [0.04, 4.80]
Australia 1997	3/58	1/50		0.7	2.59 [0.28, 24.08]
Russia 1993	1/31	1/33		0.6	1.06 [0.07, 16.29]
USA 1998	15/1247	22/1239		14.4	0.68 [0.35, 1.30]
Subtotal (95% CI)	1363	1347		17.1	0.75 [0.42, 1.34]
Total events: 20 (Antiplatelet agents), 26 (Control)					
Test for heterogeneity chi-square=1.50 df=3 p=0.68 I^2 =0.0%					
Test for overall effect z=0.96 p=0.3					
Total (95% CI)	12567	12415		100.0	1.10 [0.89, 1.37]
Total events: 172 (Antiplatelet agents), 150 (Control)					
Test for heterogeneity chi-square=15.77 df=13 p=0.26 I^2 =17.6%					
Test for overall effect z=0.89 p=0.4					

Analysis 01.06. Comparison 01 Antiplatelet agents versus placebo/no antiplatelet for primary prevention (subgrouped by maternal risk), Outcome 06 Caesarean section

Review: Antiplatelet agents for preventing pre-eclampsia and its complications

Comparison: 01 Antiplatelet agents versus placebo/no antiplatelet for primary prevention (subgrouped by maternal risk)

Outcome: 06 Caesarean section

Study	Antiplatelet agents n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Australia 1995a	5/9	9/11		0.2	0.68 [0.36, 1.30]
Australia 1996	5/27	3/25		0.1	1.54 [0.41, 5.80]
Austria 1992	4/22	0/19		0.0	7.83 [0.45, 136.60]
Barbados 1998	246/1819	252/1822		6.9	0.98 [0.83, 1.15]
Brazil 1996	291/476	301/494		8.1	1.00 [0.91, 1.11]
China 1996	16/40	17/44		0.4	1.04 [0.61, 1.76]
China 1999	25/118	12/75		0.4	1.32 [0.71, 2.47]
CLASP 1994	1383/4659	1410/4650		38.6	0.98 [0.92, 1.04]
Egypt 2005	13/73	12/63		0.4	0.93 [0.46, 1.90]
ERASME 2003	274/1634	275/1640		7.5	1.00 [0.86, 1.16]
Finland 1997a	4/23	3/23		0.1	1.33 [0.34, 5.30]
Finland 2002	7/43	4/43		0.1	1.75 [0.55, 5.55]
France 1985	24/48	33/45		0.9	0.68 [0.49, 0.95]
Israel 1989	5/34	9/31		0.3	0.51 [0.19, 1.35]
Israel 1994	10/24	7/23		0.2	1.37 [0.63, 2.98]
Italy 1993	274/565	203/477		6.0	1.14 [1.00, 1.30]
Jamaica 1998	236/3023	200/3126		5.4	1.22 [1.02, 1.46]
Netherlands 1986	1/23	7/23		0.2	0.14 [0.02, 1.07]
Spain 1997	12/50	10/50		0.3	1.20 [0.57, 2.52]
UK 1995	14/58	13/60		0.3	1.11 [0.57, 2.16]
USA 1993	72/302	66/302		1.8	1.09 [0.81, 1.46]
USA 1993a	251/1485	258/1500		7.0	0.98 [0.84, 1.15]
USA 1998	525/1254	488/1249		13.4	1.07 [0.97, 1.18]
Zimbabwe 1998	47/113	49/117		1.3	0.99 [0.73, 1.35]
Total (95% CI)	15922	15912		100.0	1.02 [0.98, 1.06]

Total events: 3744 (Antiplatelet agents), 3641 (Control)

Test for heterogeneity chi-square=27.52 df=23 p=0.23 I^2 =16.4%

Test for overall effect z=1.00 p=0.3

Analysis 01.07. Comparison 01 Antiplatelet agents versus placebo/no antiplatelet for primary prevention (subgrouped by maternal risk), Outcome 07 Induction of labour

Review: Antiplatelet agents for preventing pre-eclampsia and its complications

Comparison: 01 Antiplatelet agents versus placebo/no antiplatelet for primary prevention (subgrouped by maternal risk)

Outcome: 07 Induction of labour

Study	Antiplatelet agents n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Barbados 1998	330/1819	307/1822		12.9	1.08 [0.93, 1.24]
CLASP 1994	1460/4659	1406/4650		59.1	1.04 [0.98, 1.10]
ERASME 2003	397/1634	401/1640		16.8	0.99 [0.88, 1.12]
Finland 2002	16/43	18/43		0.8	0.89 [0.53, 1.50]
USA 1993a	246/1485	250/1500		10.4	0.99 [0.85, 1.17]
Total (95% CI)	9640	9655		100.0	1.03 [0.98, 1.08]
Total events: 2449 (Antiplatelet agents), 2382 (Control)					
Test for heterogeneity chi-square=1.25 df=4 p=0.87 I^2 =0.0%					
Test for overall effect z=1.15 p=0.2					

Analysis 01.08. Comparison 01 Antiplatelet agents versus placebo/no antiplatelet for primary prevention (subgrouped by maternal risk), Outcome 08 Hospital admission for the woman during pregnancy

Review: Antiplatelet agents for preventing pre-eclampsia and its complications

Comparison: 01 Antiplatelet agents versus placebo/no antiplatelet for primary prevention (subgrouped by maternal risk)

Outcome: 08 Hospital admission for the woman during pregnancy

Study	Antiplatelet agents n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Barbados 1998	609/1819	610/1822		39.3	1.00 [0.91, 1.10]
ERASME 2003	450/1634	439/1640		28.2	1.03 [0.92, 1.15]
Jamaica 1998	540/3023	504/3026		32.5	1.07 [0.96, 1.20]
Total (95% CI)	6476	6488		100.0	1.03 [0.97, 1.10]
Total events: 1599 (Antiplatelet agents), 1553 (Control)					
Test for heterogeneity chi-square=0.92 df=2 p=0.63 I^2 =0.0%					
Test for overall effect z=1.02 p=0.3					

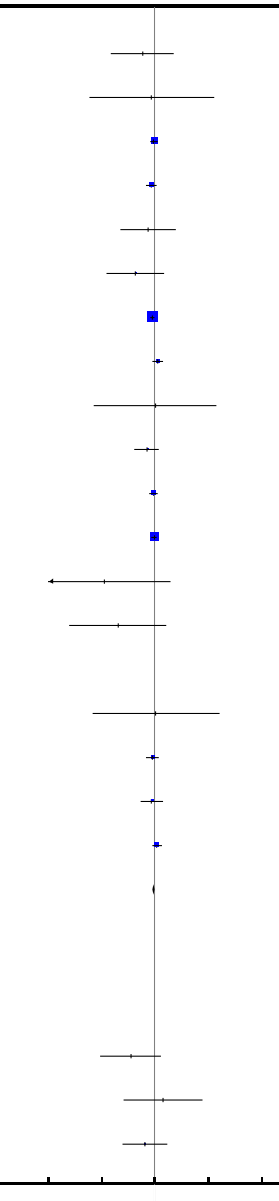
Analysis 01.09. Comparison 01 Antiplatelet agents versus placebo/no antiplatelet for primary prevention (subgrouped by maternal risk), Outcome 09 Preterm birth (< 37 weeks)

Review: Antiplatelet agents for preventing pre-eclampsia and its complications

Comparison: 01 Antiplatelet agents versus placebo/no antiplatelet for primary prevention (subgrouped by maternal risk)

Outcome: 09 Preterm birth (< 37 weeks)

Study	Antiplatelet agents n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 Moderate-risk women					
Australia 1996a	3/52	5/50		0.2	0.58 [0.15, 2.29]
Austria 1992	1/22	1/19		0.0	0.86 [0.06, 12.89]
Barbados 1998	255/1819	270/1822		9.6	0.95 [0.81, 1.11]
Brazil 1996	106/476	129/494		4.5	0.85 [0.68, 1.07]
China 1996	4/40	6/44		0.2	0.73 [0.22, 2.41]
China 1999	4/118	6/75		0.3	0.42 [0.12, 1.45]
CLASP 1994	686/3992	761/3982		27.1	0.90 [0.82, 0.99]
ERASME 2003	120/1645	108/1660		3.8	1.12 [0.87, 1.44]
Finland 1997	1/13	1/13		0.0	1.00 [0.07, 14.34]
Israel 1994	11/24	15/23		0.5	0.70 [0.41, 1.19]
Italy 1993	171/565	154/477		5.9	0.94 [0.78, 1.12]
Jamaica 1998	447/3023	463/3026		16.5	0.97 [0.86, 1.09]
Netherlands 1986	0/23	4/23		0.2	0.11 [0.01, 1.95]
Spain 1997	1/50	5/50		0.2	0.20 [0.02, 1.65]
× UK 1992	0/10	0/8		0.0	Not estimable
UK 1995	1/58	1/60		0.0	1.03 [0.07, 16.15]
UK+others 2003	67/276	75/278		2.7	0.90 [0.68, 1.20]
USA 1993	26/302	30/302		1.1	0.87 [0.53, 1.43]
USA 1993a	157/1485	147/1500		5.2	1.08 [0.87, 1.34]
Subtotal (95% CI)	13993	13906		78.0	0.93 [0.88, 0.99]
Total events: 2061 (Antiplatelet agents), 2181 (Control)					
Test for heterogeneity chi-square=13.06 df=17 p=0.73 I^2 =0.0%					
Test for overall effect z=2.42 p=0.02					
02 High-risk women					
Australia 1995a	2/9	7/11		0.2	0.35 [0.10, 1.28]
Australia 1996	3/27	2/25		0.1	1.39 [0.25, 7.64]
Australia 1997	6/58	8/50		0.3	0.65 [0.24, 1.74]



(*Continued . . .*)

(. . . *Continued*)

Study	Antiplatelet agents n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Egypt 2005	2/73	9/63		0.3	0.19 [0.04, 0.85]
Israel 1989	2/34	6/32		0.2	0.31 [0.07, 1.44]
Italy 1989	2/17	5/16		0.2	0.38 [0.08, 1.67]
Japan 1999	6/20	11/20		0.4	0.55 [0.25, 1.19]
Russia 1993	5/31	6/33		0.2	0.89 [0.30, 2.61]
USA 1998	502/1254	532/1249		19.0	0.94 [0.86, 1.03]
Zimbabwe 1998	21/113	30/117		1.0	0.72 [0.44, 1.19]
Subtotal (95% CI)	1636	1616		22.0	0.89 [0.81, 0.97]
Total events: 551 (Antiplatelet agents), 616 (Control)					
Test for heterogeneity chi-square=13.25 df=9 p=0.15 I^2 =32.1%					
Test for overall effect z=2.52 p=0.01					
Total (95% CI)	15629	15522		100.0	0.92 [0.88, 0.97]
Total events: 2612 (Antiplatelet agents), 2797 (Control)					
Test for heterogeneity chi-square=26.43 df=27 p=0.49 I^2 =0.0%					
Test for overall effect z=3.25 p=0.001					

Analysis 01.10. Comparison 01 Antiplatelet agents versus placebo/no antiplatelet for primary prevention (subgrouped by maternal risk), Outcome 10 Preterm birth (subgroups by gestational age)

Review: Antiplatelet agents for preventing pre-eclampsia and its complications

Comparison: 01 Antiplatelet agents versus placebo/no antiplatelet for primary prevention (subgrouped by maternal risk)

Outcome: 10 Preterm birth (subgroups by gestational age)

Study	Antiplatelet agents n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 Delivery < 37 completed weeks					
Australia 1995a	2/9	7/11		0.2	0.35 [0.10, 1.28]
Australia 1996	3/27	2/25		0.1	1.39 [0.25, 7.64]
Australia 1996a	3/52	5/50		0.2	0.58 [0.15, 2.29]
Australia 1997	6/58	8/50		0.3	0.65 [0.24, 1.74]
Austria 1992	1/22	1/19		0.0	0.86 [0.06, 12.89]
Barbados 1998	255/1819	270/1822		9.7	0.95 [0.81, 1.11]
Brazil 1996	106/476	129/494		4.6	0.85 [0.68, 1.07]

(*Continued* . . .)

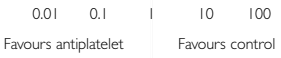
(. . . *Continued*)

Study	Antiplatelet agents n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
China 1999	4/118	6/75		0.3	0.42 [0.12, 1.45]
CLASP 1994	686/3992	761/3982		27.4	0.90 [0.82, 0.99]
Egypt 2005	2/73	9/63		0.3	0.19 [0.04, 0.85]
ERASME 2003	120/1645	108/1660		3.9	1.12 [0.87, 1.44]
Finland 1997	1/13	1/13		0.0	1.00 [0.07, 14.34]
Israel 1989	2/34	6/32		0.2	0.31 [0.07, 1.44]
Israel 1994	11/24	15/24		0.5	0.73 [0.43, 1.25]
Italy 1989	2/17	5/16		0.2	0.38 [0.08, 1.67]
Italy 1993	171/565	154/477		6.0	0.94 [0.78, 1.12]
Jamaica 1998	447/3023	463/3026		16.6	0.97 [0.86, 1.09]
Netherlands 1986	0/23	4/23		0.2	0.11 [0.01, 1.95]
× UK 1992	0/10	0/8		0.0	Not estimable
UK 1995	1/58	1/60		0.0	1.03 [0.07, 16.15]
UK+others 2003	67/276	75/278		2.7	0.90 [0.68, 1.20]
USA 1993	24/302	30/302		1.1	0.80 [0.48, 1.34]
USA 1993a	157/1485	147/1500		5.3	1.08 [0.87, 1.34]
USA 1998	502/1254	532/1249		19.2	0.94 [0.86, 1.03]
Zimbabwe 1998	21/113	30/117		1.1	0.72 [0.44, 1.19]
Subtotal (95% CI)	15488	15376		100.0	0.93 [0.88, 0.97]
Total events: 2594 (Antiplatelet agents), 2769 (Control)					
Test for heterogeneity chi-square=22.39 df=23 p=0.50 I^2 =0.0%					
Test for overall effect z=3.11 p=0.002					
02 Delivery < 34 completed weeks					
China 1999	2/118	2/75		2.3	0.64 [0.09, 4.42]
UK 1995	1/58	1/60		0.9	1.03 [0.07, 16.15]
UK+others 2003	30/276	32/278		30.1	0.94 [0.59, 1.51]
USA 1993	9/302	9/302		8.5	1.00 [0.40, 2.48]
USA 1993a	56/1485	62/1500		58.2	0.91 [0.64, 1.30]
Subtotal (95% CI)	2239	2215		100.0	0.92 [0.71, 1.21]
Total events: 98 (Antiplatelet agents), 106 (Control)					
Test for heterogeneity chi-square=0.19 df=4 p=1.00 I^2 =0.0%					
Test for overall effect z=0.58 p=0.6					
03 Delivery < 32 completed weeks					
Barbados 1998	74/1819	76/1822		32.0	0.98 [0.71, 1.33]

(*Continued* . . .)

(. . . *Continued*)

Study	Antiplatelet agents n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
China 1999	1/118	1/75		0.5	0.64 [0.04, 10.01]
ERASME 2003	21/1645	25/1660		10.5	0.85 [0.48, 1.51]
Jamaica 1998	129/3023	125/3026		52.6	1.03 [0.81, 1.31]
Japan 1999	0/20	3/20		1.5	0.14 [0.01, 2.60]
USA 1993	5/302	7/302		2.9	0.71 [0.23, 2.23]
Subtotal (95% CI)	6927	6905		100.0	0.97 [0.81, 1.16]
Total events: 230 (Antiplatelet agents), 237 (Control)					
Test for heterogeneity chi-square=2.52 df=5 p=0.77 I^2 =0.0%					
Test for overall effect z=0.33 p=0.7					



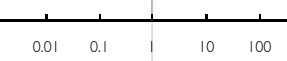
Analysis 01.11. Comparison 01 Antiplatelet agents versus placebo/no antiplatelet for primary prevention (subgrouped by maternal risk), Outcome 11 Fetal and neonatal deaths

Review: Antiplatelet agents for preventing pre-eclampsia and its complications

Comparison: 01 Antiplatelet agents versus placebo/no antiplatelet for primary prevention (subgrouped by maternal risk)

Outcome: 11 Fetal and neonatal deaths

Study	Antiplatelet agents n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 Moderate-risk women					
× Australia 1988	0/22	0/24		0.0	Not estimable
Austria 1992	0/22	1/19		0.3	0.29 [0.01, 6.72]
Barbados 1998	44/1834	38/1841		7.9	1.16 [0.76, 1.79]
Brazil 1996	35/482	30/503		6.1	1.22 [0.76, 1.95]
China 1996	0/40	4/44		0.9	0.12 [0.01, 2.20]
CLASP 1994	77/4123	97/4134		20.1	0.80 [0.59, 1.07]
EPREDA 1991	7/156	6/73		1.7	0.55 [0.19, 1.57]
ERASME 2003	12/1645	11/1660		2.3	1.10 [0.49, 2.49]
Finland 1997	0/13	1/13		0.3	0.33 [0.01, 7.50]
Finland 1997a	10/33	10/33		2.1	1.00 [0.48, 2.08]
Israel 1994	2/48	2/48		0.4	1.00 [0.15, 6.81]
Italy 1993	18/629	19/532		4.3	0.80 [0.42, 1.51]



(*Continued* . . .)

(. . . *Continued*)

Study	Antiplatelet agents n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Jamaica 1998	86/3023	103/3026		21.3	0.84 [0.63, 1.11]
Netherlands 1986	1/23	1/23		0.2	1.00 [0.07, 15.04]
S Africa 1988	2/30	1/14		0.3	0.93 [0.09, 9.45]
× Spain 1997	0/50	0/50		0.0	Not estimable
UK 1990	1/48	3/52		0.6	0.36 [0.04, 3.35]
UK 1992b	0/10	1/16		0.2	0.52 [0.02, 11.54]
× UK 1995	0/58	0/60		0.0	Not estimable
UK+others 2003	7/276	4/278		0.8	1.76 [0.52, 5.95]
USA 1993	1/302	1/302		0.2	1.00 [0.06, 15.91]
USA 1993a	22/1505	14/1519		2.9	1.59 [0.81, 3.09]
USA 1997	1/11	0/8		0.1	2.25 [0.10, 49.04]
Subtotal (95% CI)	14383	14272		73.0	0.92 [0.80, 1.07]
Total events: 326 (Antiplatelet agents), 347 (Control)					
Test for heterogeneity chi-square=12.83 df=19 p=0.85 I^2 =0.0%					
Test for overall effect z=1.07 p=0.3					
02 High-risk women					
Australia 1995a	0/9	2/11		0.5	0.24 [0.01, 4.44]
× Australia 1996	0/27	0/25		0.0	Not estimable
Australia 1997	4/58	2/50		0.4	1.72 [0.33, 9.02]
Brazil 1992a	0/26	2/26		0.5	0.20 [0.01, 3.97]
Finland 1993	2/97	0/100		0.1	5.15 [0.25, 105.98]
× Finland 2002	0/43	0/43		0.0	Not estimable
France 1985	0/48	5/45		1.2	0.09 [0.00, 1.50]
France 1990	2/46	2/45		0.4	0.98 [0.14, 6.65]
× Israel 1989	0/34	0/32		0.0	Not estimable
Italy 1989	0/17	1/16		0.3	0.31 [0.01, 7.21]
Italy 2004	1/16	2/19		0.4	0.59 [0.06, 5.96]
× Netherlands 1989	0/5	0/5		0.0	Not estimable
× Netherlands 1991a	0/17	0/18		0.0	Not estimable
Russia 1993	1/31	5/33		1.0	0.21 [0.03, 1.72]
USA 1994	1/24	1/25		0.2	1.04 [0.07, 15.73]
USA 1998	72/1612	93/1604		19.3	0.77 [0.57, 1.04]
Zimbabwe 1998	5/114	13/122		2.6	0.41 [0.15, 1.12]

(*Continued* . . .)

(. . . *Continued*)

Study	Antiplatelet agents n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Subtotal (95% CI)	2224	2219	◆	27.0	0.69 [0.53, 0.90]
Total events: 88 (Antiplatelet agents), 128 (Control)					
Test for heterogeneity chi-square=9.29 df=11 p=0.60 I^2 =0.0%					
Test for overall effect z=2.73 p=0.006					
Total (95% CI)	16607	16491	◆	100.0	0.86 [0.76, 0.98]
Total events: 414 (Antiplatelet agents), 475 (Control)					
Test for heterogeneity chi-square=24.83 df=31 p=0.78 I^2 =0.0%					
Test for overall effect z=2.28 p=0.02					

Analysis 01.12. Comparison 01 Antiplatelet agents versus placebo/no antiplatelet for primary prevention (subgrouped by maternal risk), Outcome 12 Fetal, neonatal, infant and childhood deaths (subgroups by time of death)

Review: Antiplatelet agents for preventing pre-eclampsia and its complications

Comparison: 01 Antiplatelet agents versus placebo/no antiplatelet for primary prevention (subgrouped by maternal risk)

Outcome: 12 Fetal, neonatal, infant and childhood deaths (subgroups by time of death)

Study	Antiplatelet agents n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 Stillbirths or miscarriages					
× Australia 1996	0/27	0/25		0.0	Not estimable
Australia 1997	4/58	0/50		0.3	7.78 [0.43, 141.05]
Austria 1992	0/22	1/19		0.9	0.29 [0.01, 6.72]
Barbados 1998	29/1834	27/1841		15.2	1.08 [0.64, 1.81]
Brazil 1996	28/482	23/503		12.7	1.27 [0.74, 2.17]
EPREDA 1991	2/156	2/73		1.5	0.47 [0.07, 3.26]
ERASME 2003	9/1645	8/1660		4.5	1.14 [0.44, 2.94]
Finland 1993	1/97	0/100		0.3	3.09 [0.13, 74.98]
Finland 1997	0/13	1/13		0.8	0.33 [0.01, 7.50]
Finland 1997a	10/33	10/33		5.6	1.00 [0.48, 2.08]
× Finland 2002	0/43	0/43		0.0	Not estimable
France 1985	0/48	4/45		2.6	0.10 [0.01, 1.88]
France 1990	2/46	2/45		1.1	0.98 [0.14, 6.65]

(*Continued* . . .)

(. . . *Continued*)

Study	Antiplatelet agents n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
× Israel 1989	0/34	0/32		0.0	Not estimable
Israel 1994	0/48	2/48		1.4	0.20 [0.01, 4.06]
Italy 1993	13/634	14/538		8.6	0.79 [0.37, 1.66]
Italy 2004	1/16	2/19		1.0	0.59 [0.06, 5.96]
Netherlands 1986	1/23	0/23		0.3	3.00 [0.13, 70.02]
× Netherlands 1989	0/5	0/5		0.0	Not estimable
× Netherlands 1991a	0/17	0/18		0.0	Not estimable
Russia 1993	1/31	4/33		2.2	0.27 [0.03, 2.25]
S Africa 1988	2/30	1/14		0.8	0.93 [0.09, 9.45]
UK 1990	1/48	2/52		1.1	0.54 [0.05, 5.78]
UK+others 2003	6/276	4/278		2.2	1.51 [0.43, 5.30]
USA 1993	1/302	1/302		0.6	1.00 [0.06, 15.91]
USA 1993a	17/1505	7/1519		3.9	2.45 [1.02, 5.89]
USA 1994	1/24	1/25		0.6	1.04 [0.07, 15.73]
USA 1998	40/1612	56/1604		31.7	0.71 [0.48, 1.06]
Subtotal (95% CI)	9109	8960		100.0	0.96 [0.78, 1.18]
Total events: 169 (Antiplatelet agents), 172 (Control)					
Test for heterogeneity chi-square=18.33 df=22 p=0.69 I^2 =0.0%					
Test for overall effect z=0.37 p=0.7					
02 Perinatal deaths					
× Australia 1996	0/27	0/25		0.0	Not estimable
Australia 1997	4/58	2/50		1.0	1.72 [0.33, 9.02]
Austria 1992	0/22	1/19		0.8	0.29 [0.01, 6.72]
Brazil 1996	35/482	30/503		13.8	1.22 [0.76, 1.95]
ERASME 2003	3/1645	3/1660		1.4	1.01 [0.20, 4.99]
Israel 1994	2/48	2/48		0.9	1.00 [0.15, 6.81]
Italy 1993	18/634	19/538		9.6	0.80 [0.43, 1.52]
Jamaica 1998	86/3023	103/3026		48.3	0.84 [0.63, 1.11]
Russia 1993	0/31	4/33		2.0	0.12 [0.01, 2.11]
UK 1990	1/48	3/52		1.4	0.36 [0.04, 3.35]
UK 1995	6/79	13/81		6.0	0.47 [0.19, 1.18]
UK+others 2003	7/276	4/278		1.9	1.76 [0.52, 5.95]
USA 1993	1/302	1/302		0.5	1.00 [0.06, 15.91]

(*Continued* . . .)

(. . . *Continued*)

Study	Antiplatelet agents n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
USA 1993a	22/1505	14/1519		6.5	1.59 [0.81, 3.09]
Zimbabwe 1998	5/114	13/122		5.9	0.41 [0.15, 1.12]
Subtotal (95% CI)	8294	8256		100.0	0.89 [0.74, 1.08]
Total events: 190 (Antiplatelet agents), 212 (Control)					
Test for heterogeneity chi-square=13.85 df=13 p=0.38 I^2 =6.2%					
Test for overall effect z=1.15 p=0.2					
03 Neonatal deaths					
Australia 1997	0/58	2/50		3.4	0.17 [0.01, 3.52]
× Austria 1992	0/22	0/19		0.0	Not estimable
Barbados 1998	14/1834	11/1841		13.9	1.28 [0.58, 2.81]
Brazil 1996	7/482	7/503		8.7	1.04 [0.37, 2.95]
China 1996	0/40	4/44		5.4	0.12 [0.01, 2.20]
EPREDA 1991	5/156	2/73		3.5	1.17 [0.23, 5.89]
Finland 1993	1/97	0/100		0.6	3.09 [0.13, 74.98]
× Finland 2002	0/43	0/43		0.0	Not estimable
France 1985	0/48	1/45		2.0	0.31 [0.01, 7.49]
× Israel 1989	0/34	0/32		0.0	Not estimable
Israel 1994	2/48	0/46		0.6	4.80 [0.24, 97.28]
Netherlands 1986	0/23	1/23		1.9	0.33 [0.01, 7.78]
× Spain 1997	0/50	0/50		0.0	Not estimable
UK 1990	0/48	1/52		1.8	0.36 [0.02, 8.64]
UK 1992b	0/10	1/16		1.5	0.52 [0.02, 11.54]
UK+others 2003	1/276	0/278		0.6	3.02 [0.12, 73.85]
× USA 1993	0/302	0/302		0.0	Not estimable
USA 1993a	5/1505	7/1519		8.8	0.72 [0.23, 2.27]
USA 1998	32/1612	37/1604		47.1	0.86 [0.54, 1.37]
Subtotal (95% CI)	6688	6640		100.0	0.89 [0.64, 1.22]
Total events: 67 (Antiplatelet agents), 74 (Control)					
Test for heterogeneity chi-square=7.69 df=13 p=0.86 I^2 =0.0%					
Test for overall effect z=0.73 p=0.5					

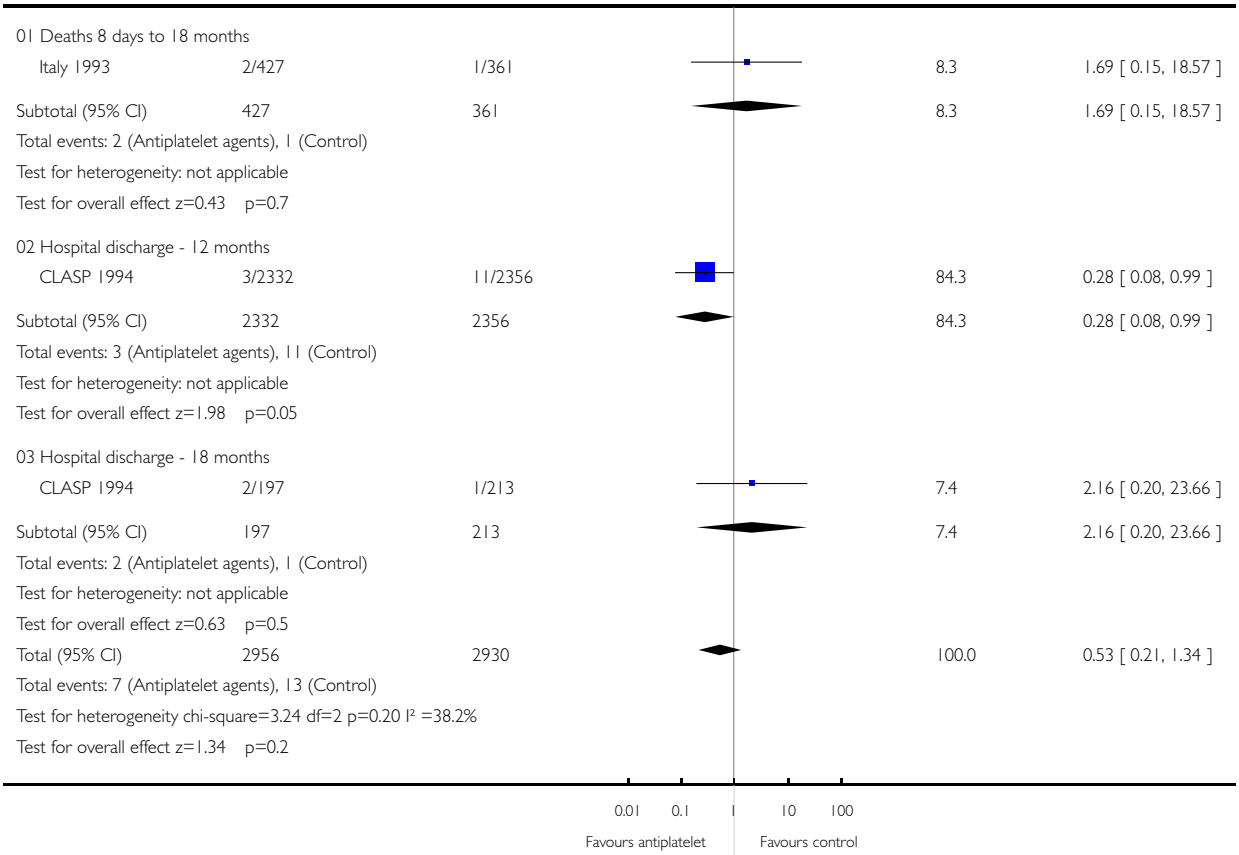
Analysis 01.13. Comparison 01 Antiplatelet agents versus placebo/no antiplatelet for primary prevention (subgrouped by maternal risk), Outcome 13 Deaths after discharge from hospital

Review: Antiplatelet agents for preventing pre-eclampsia and its complications

Comparison: 01 Antiplatelet agents versus placebo/no antiplatelet for primary prevention (subgrouped by maternal risk)

Outcome: 13 Deaths after discharge from hospital

Study	Antiplatelet agents n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 Deaths 8 days to 18 months					
Italy 1993	2/427	1/361		8.3	1.69 [0.15, 18.57]
Subtotal (95% CI)	427	361		8.3	1.69 [0.15, 18.57]
Total events: 2 (Antiplatelet agents), 1 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.43 p=0.7					
02 Hospital discharge - 12 months					
CLASP 1994	3/2332	11/2356		84.3	0.28 [0.08, 0.99]
Subtotal (95% CI)	2332	2356		84.3	0.28 [0.08, 0.99]
Total events: 3 (Antiplatelet agents), 11 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.98 p=0.05					
03 Hospital discharge - 18 months					
CLASP 1994	2/197	1/213		7.4	2.16 [0.20, 23.66]
Subtotal (95% CI)	197	213		7.4	2.16 [0.20, 23.66]
Total events: 2 (Antiplatelet agents), 1 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.63 p=0.5					
Total (95% CI)	2956	2930		100.0	0.53 [0.21, 1.34]
Total events: 7 (Antiplatelet agents), 13 (Control)					
Test for heterogeneity chi-square=3.24 df=2 p=0.20 I^2 =38.2%					
Test for overall effect z=1.34 p=0.2					



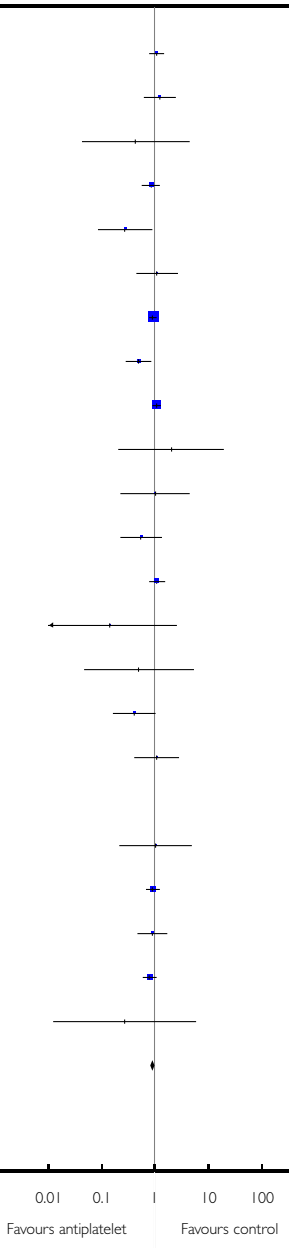
Analysis 01.14. Comparison 01 Antiplatelet agents versus placebo/no antiplatelet for primary prevention (subgrouped by maternal risk), Outcome 14 Small-for-gestational age (any definition)

Review: Antiplatelet agents for preventing pre-eclampsia and its complications

Comparison: 01 Antiplatelet agents versus placebo/no antiplatelet for primary prevention (subgrouped by maternal risk)

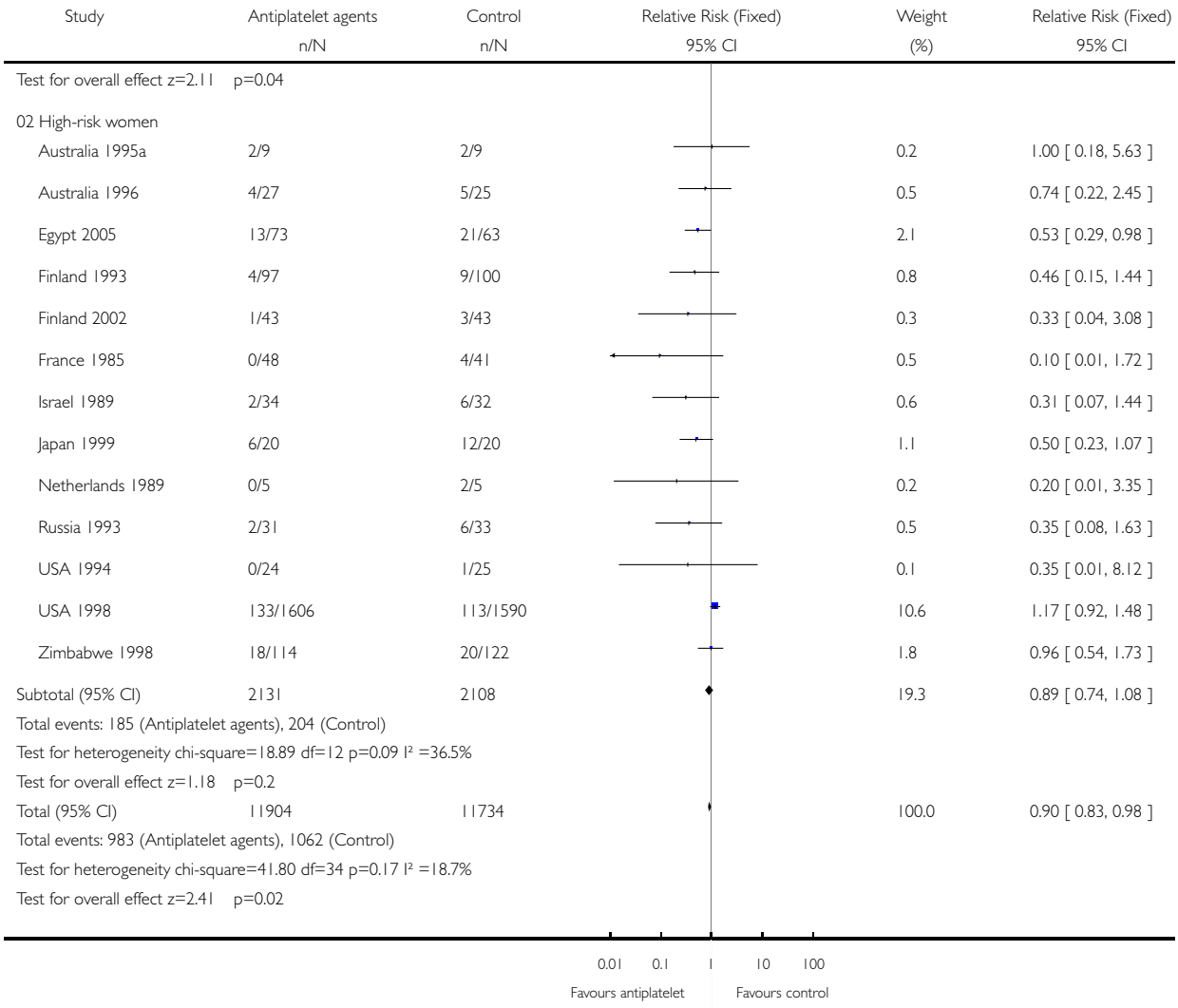
Outcome: 14 Small-for-gestational age (any definition)

Study	Antiplatelet agents n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 Moderate-risk women					
Australia 1995	22/29	21/30		1.9	1.08 [0.79, 1.48]
Australia 1996a	14/52	11/50		1.0	1.22 [0.62, 2.43]
Austria 1992	1/22	2/19		0.2	0.43 [0.04, 4.40]
Brazil 1996	41/482	51/503		4.6	0.84 [0.57, 1.24]
China 1996	3/40	12/44		1.1	0.28 [0.08, 0.90]
China 1999	12/118	7/75		0.8	1.09 [0.45, 2.64]
CLASP 1994	244/4123	272/4134		25.3	0.90 [0.76, 1.06]
EPREDA 1991	20/156	19/73		2.4	0.49 [0.28, 0.86]
ERASME 2003	199/1645	189/1660		17.5	1.06 [0.88, 1.28]
Finland 1997	2/13	1/13		0.1	2.00 [0.21, 19.44]
Finland 1997a	3/23	3/23		0.3	1.00 [0.22, 4.45]
Israel 1994	6/48	11/48		1.0	0.55 [0.22, 1.36]
Italy 1993	67/616	54/538		5.4	1.08 [0.77, 1.52]
Netherlands 1986	0/23	3/23		0.3	0.14 [0.01, 2.62]
Spain 1997	1/50	2/50		0.2	0.50 [0.05, 5.34]
Spain 1999	6/124	14/116		1.3	0.40 [0.16, 1.01]
UK 1990	7/48	7/52		0.6	1.08 [0.41, 2.86]
× UK 1992	0/10	0/8		0.0	Not estimable
UK 1995	3/58	3/60		0.3	1.03 [0.22, 4.92]
UK+others 2003	61/276	68/278		6.3	0.90 [0.67, 1.22]
USA 1993	17/302	19/302		1.8	0.89 [0.47, 1.69]
USA 1993a	69/1505	88/1519		8.1	0.79 [0.58, 1.08]
USA 1997	0/10	1/8		0.2	0.27 [0.01, 5.92]
Subtotal (95% CI)	9773	9626		80.7	0.91 [0.83, 0.99]
Total events: 798 (Antiplatelet agents), 858 (Control)					
Test for heterogeneity chi-square=22.87 df=21 p=0.35 I^2 =8.2%					



(*Continued . . .*)

(. . . *Continued*)



Analysis 01.15. Comparison 01 Antiplatelet agents versus placebo/no antiplatelet for primary prevention (subgrouped by maternal risk), Outcome 15 Small-for-gestational age (subgroups by severity)

Review: Antiplatelet agents for preventing pre-eclampsia and its complications

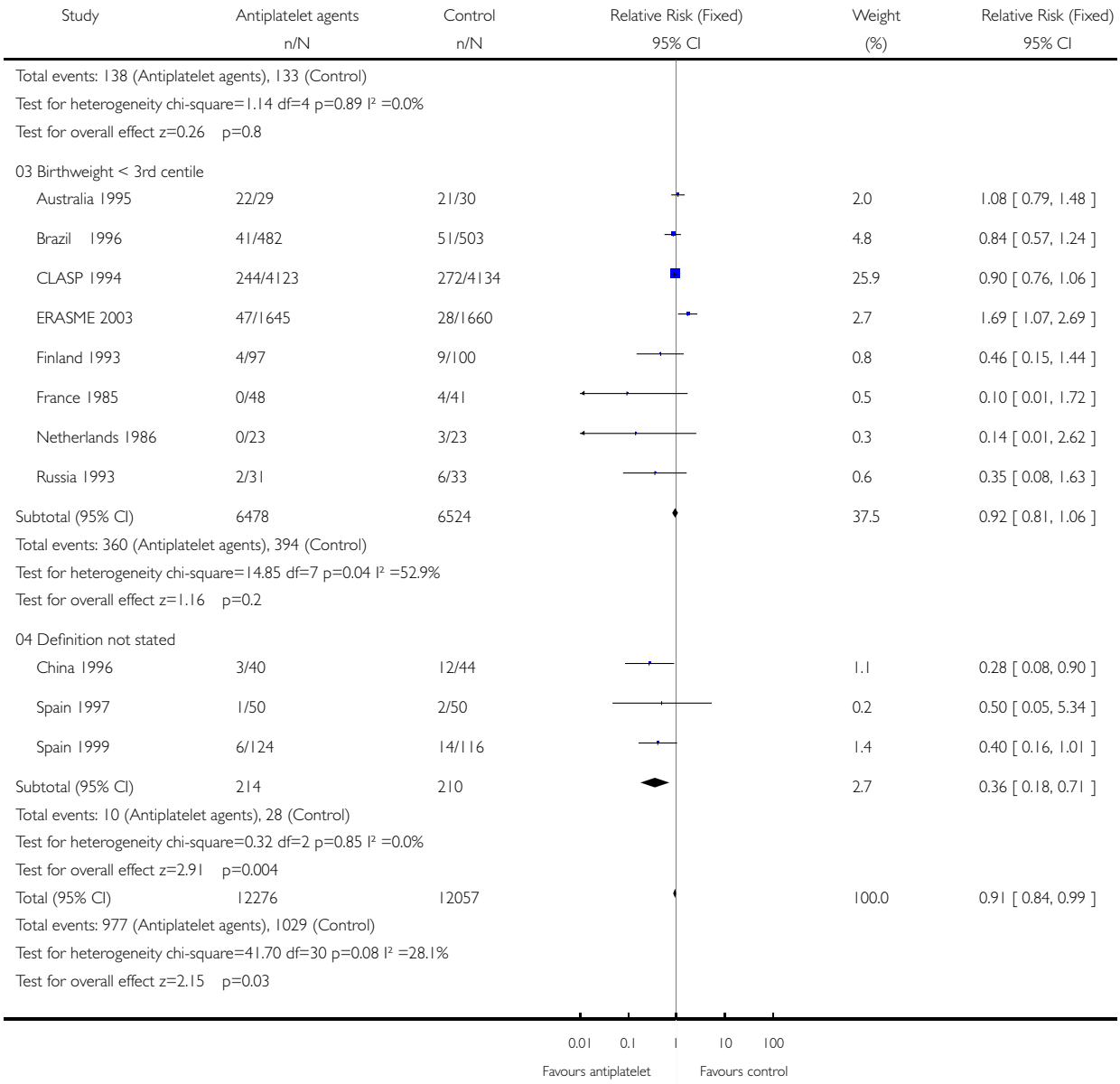
Comparison: 01 Antiplatelet agents versus placebo/no antiplatelet for primary prevention (subgrouped by maternal risk)

Outcome: 15 Small-for-gestational age (subgroups by severity)

Study	Antiplatelet agents n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 Birthweight < 10th centile					
Australia 1995a	2/9	2/9		0.2	1.00 [0.18, 5.63]
Australia 1996	4/27	5/25		0.5	0.74 [0.22, 2.45]
Australia 1996a	14/52	11/50		1.1	1.22 [0.62, 2.43]
Austria 1992	1/22	2/19		0.2	0.43 [0.04, 4.40]
Egypt 2005	13/73	21/63		2.1	0.53 [0.29, 0.98]
EPREDA 1991	20/156	19/73		2.5	0.49 [0.28, 0.86]
ERASME 2003	199/1645	189/1660		17.9	1.06 [0.88, 1.28]
Finland 1997	2/13	1/13		0.1	2.00 [0.21, 19.44]
Finland 1997a	3/23	3/23		0.3	1.00 [0.22, 4.45]
Israel 1989	2/34	6/32		0.6	0.31 [0.07, 1.44]
Israel 1994	6/48	11/48		1.0	0.55 [0.22, 1.36]
Italy 1993	117/634	95/538		9.8	1.05 [0.82, 1.34]
Netherlands 1989	0/5	2/5		0.2	0.20 [0.01, 3.35]
× UK 1992	0/10	0/8		0.0	Not estimable
USA 1993	17/302	19/302		1.8	0.89 [0.47, 1.69]
USA 1993a	69/1505	88/1519		8.4	0.79 [0.58, 1.08]
Subtotal (95% CI)	4558	4387		46.7	0.92 [0.82, 1.04]
Total events: 469 (Antiplatelet agents), 474 (Control)					
Test for heterogeneity chi-square=18.05 df=14 p=0.20 I^2 =22.4%					
Test for overall effect z=1.32 p=0.2					
02 Birthweight < 5th centile					
Italy 1993	67/634	54/538		5.6	1.05 [0.75, 1.48]
UK 1990	7/48	7/52		0.6	1.08 [0.41, 2.86]
UK 1995	3/58	3/60		0.3	1.03 [0.22, 4.92]
UK+others 2003	61/276	68/278		6.5	0.90 [0.67, 1.22]
USA 1997	0/10	1/8		0.2	0.27 [0.01, 5.92]
Subtotal (95% CI)	1026	936		13.1	0.97 [0.78, 1.21]

(*Continued . . .*)

(. . . *Continued*)



Analysis 01.16. Comparison 01 Antiplatelet agents versus placebo/no antiplatelet for primary prevention (subgrouped by maternal risk), Outcome 16 Birthweight < 2500 g

Review: Antiplatelet agents for preventing pre-eclampsia and its complications

Comparison: 01 Antiplatelet agents versus placebo/no antiplatelet for primary prevention (subgrouped by maternal risk)

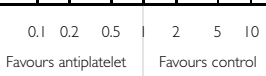
Outcome: 16 Birthweight < 2500 g

Study	Antiplatelet agents n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Australia 1997	7/58	10/50		2.1	0.60 [0.25, 1.47]
Finland 1997	3/43	4/43		0.8	0.75 [0.18, 3.15]
Italy 1993	169/616	142/518		30.2	1.00 [0.83, 1.21]
Italy 2004	2/16	5/19		0.9	0.48 [0.11, 2.13]
Jamaica 1998	303/3023	325/3026		63.6	0.93 [0.80, 1.08]
UK 1990	7/48	13/52		2.4	0.58 [0.25, 1.34]
Total (95% CI)	3804	3708		100.0	0.93 [0.83, 1.05]

Total events: 491 (Antiplatelet agents), 499 (Control)

Test for heterogeneity chi-square=3.54 df=5 p=0.62 I^2 =0.0%

Test for overall effect z=1.19 p=0.2



Analysis 01.17. Comparison 01 Antiplatelet agents versus placebo/no antiplatelet for primary prevention (subgrouped by maternal risk), Outcome 17 Admission to a special care baby unit

Review: Antiplatelet agents for preventing pre-eclampsia and its complications

Comparison: 01 Antiplatelet agents versus placebo/no antiplatelet for primary prevention (subgrouped by maternal risk)

Outcome: 17 Admission to a special care baby unit

Study	Antiplatelet agents n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Australia 1995	13/29	7/30		0.3	1.92 [0.89, 4.12]
Australia 1996	5/27	3/25		0.1	1.54 [0.41, 5.80]
Australia 1997	9/54	13/50		0.6	0.64 [0.30, 1.37]
Barbados 1998	272/1834	293/1841		13.9	0.93 [0.80, 1.08]
CLASP 1994	946/4810	1016/4821		48.1	0.93 [0.86, 1.01]
ERASME 2003	116/1645	111/1660		5.2	1.05 [0.82, 1.36]
Finland 1993	10/97	21/100		1.0	0.49 [0.24, 0.99]
India 1994	1/46	2/48		0.1	0.52 [0.05, 5.56]
Israel 1989	2/34	7/32		0.3	0.27 [0.06, 1.20]

(*Continued . . .*)

(... *Continued*)

Study	Antiplatelet agents n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Italy 1993	181/616	157/518		8.1	0.97 [0.81, 1.16]
Jamaica 1998	285/3023	263/3026		12.5	1.08 [0.92, 1.27]
UK 1995	1/58	2/60		0.1	0.52 [0.05, 5.55]
UK+others 2003	35/276	52/278		2.5	0.68 [0.46, 1.01]
USA 1993a	132/1505	142/1519		6.7	0.94 [0.75, 1.18]
Zimbabwe 1998	17/114	12/122		0.5	1.52 [0.76, 3.03]
Total (95% CI)	14168	14130		100.0	0.95 [0.90, 1.01]
Total events: 2025 (Antiplatelet agents), 2101 (Control)					
Test for heterogeneity chi-square=19.64 df=14 p=0.14 I^2 =28.7%					
Test for overall effect z=1.69 p=0.09					

Analysis 01.18. Comparison 01 Antiplatelet agents versus placebo/no antiplatelet for primary prevention (subgrouped by maternal risk), Outcome 18 Intraventricular haemorrhage

Review: Antiplatelet agents for preventing pre-eclampsia and its complications

Comparison: 01 Antiplatelet agents versus placebo/no antiplatelet for primary prevention (subgrouped by maternal risk)

Outcome: 18 Intraventricular haemorrhage

Study	Antiplatelet agents n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Australia 1995	2/29	3/30		3.9	0.69 [0.12, 3.83]
Barbados 1998	0/1834	1/1841		2.0	0.33 [0.01, 8.21]
× China 1996	0/40	0/44		0.0	Not estimable
CLASP 1994	33/4810	45/4821		60.0	0.74 [0.47, 1.15]
ERASME 2003	1/1645	6/1660		8.0	0.17 [0.02, 1.40]
× Finland 1997	0/13	0/13		0.0	Not estimable
× Finland 2002	0/43	0/43		0.0	Not estimable
× Israel 1989	0/34	0/32		0.0	Not estimable
Jamaica 1998	1/3023	0/3026		0.7	3.00 [0.12, 73.69]
USA 1998	28/1608	19/1595		25.5	1.46 [0.82, 2.61]
Total (95% CI)	13079	13105		100.0	0.88 [0.63, 1.22]
Total events: 65 (Antiplatelet agents), 74 (Control)					
Test for heterogeneity chi-square=6.92 df=5 p=0.23 I^2 =27.8%					
Test for overall effect z=0.76 p=0.4					

Analysis 01.19. Comparison 01 Antiplatelet agents versus placebo/no antiplatelet for primary prevention (subgrouped by maternal risk), Outcome 19 Other neonatal bleed

Review: Antiplatelet agents for preventing pre-eclampsia and its complications

Comparison: 01 Antiplatelet agents versus placebo/no antiplatelet for primary prevention (subgrouped by maternal risk)

Outcome: 19 Other neonatal bleed

Study	Antiplatelet agents n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Austria 1992	2/22	2/19		2.7	0.86 [0.13, 5.56]
Barbados 1998	9/1834	9/1841		11.2	1.00 [0.40, 2.52]
Brazil 1996	9/482	5/503		6.1	1.88 [0.63, 5.56]
CLASP 1994	47/4810	45/4821		56.2	1.05 [0.70, 1.57]
× Egypt 2005	0/73	0/63		0.0	Not estimable
ERASME 2003	4/1645	3/1660		3.7	1.35 [0.30, 6.00]
Jamaica 1998	3/3023	2/3026		2.5	1.50 [0.25, 8.98]
USA 1998	16/1610	14/1600		17.6	1.14 [0.56, 2.32]
Total (95% CI)	13499	13533		100.0	1.13 [0.83, 1.52]

Total events: 90 (Antiplatelet agents), 80 (Control)

Test for heterogeneity chi-square=1.27 df=6 p=0.97 I^2 =0.0%

Test for overall effect z=0.78 p=0.4

Analysis 01.20. Comparison 01 Antiplatelet agents versus placebo/no antiplatelet for primary prevention (subgrouped by maternal risk), Outcome 20 Non-routine GP consultation for child

Review: Antiplatelet agents for preventing pre-eclampsia and its complications

Comparison: 01 Antiplatelet agents versus placebo/no antiplatelet for primary prevention (subgrouped by maternal risk)

Outcome: 20 Non-routine GP consultation for child

Study	Antiplatelet agents n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 At 12 months					
CLASP 1994	1985/2069	2008/2099		100.0	1.00 [0.99, 1.02]
Subtotal (95% CI)	2069	2099		100.0	1.00 [0.99, 1.02]
Total events: 1985 (Antiplatelet agents), 2008 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.44 p=0.7					
02 At 18 months					
CLASP 1994	1449/2146	1502/2219		100.0	1.00 [0.96, 1.04]
Subtotal (95% CI)	2146	2219		100.0	1.00 [0.96, 1.04]
Total events: 1449 (Antiplatelet agents), 1502 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.12 p=0.9					

Analysis 01.21. Comparison 01 Antiplatelet agents versus placebo/no antiplatelet for primary prevention (subgrouped by maternal risk), Outcome 21 Child admitted to hospital

Review: Antiplatelet agents for preventing pre-eclampsia and its complications

Comparison: 01 Antiplatelet agents versus placebo/no antiplatelet for primary prevention (subgrouped by maternal risk)

Outcome: 21 Child admitted to hospital

Study	Antiplatelet agents n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 At 12 months					
CLASP 1994	338/2069	363/2099		100.0	0.94 [0.83, 1.08]
Subtotal (95% CI)	2069	2099		100.0	0.94 [0.83, 1.08]
Total events: 338 (Antiplatelet agents), 363 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.83 p=0.4					
02 At 18 months					
CLASP 1994	483/2146	503/2219		100.0	0.99 [0.89, 1.11]
Subtotal (95% CI)	2146	2219		100.0	0.99 [0.89, 1.11]
Total events: 483 (Antiplatelet agents), 503 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.13 p=0.9					

Analysis 01.22. Comparison 01 Antiplatelet agents versus placebo/no antiplatelet for primary prevention (subgrouped by maternal risk), Outcome 22 Developmental problems at 18 months

Review: Antiplatelet agents for preventing pre-eclampsia and its complications

Comparison: 01 Antiplatelet agents versus placebo/no antiplatelet for primary prevention (subgrouped by maternal risk)

Outcome: 22 Developmental problems at 18 months

Study	Antiplatelet agents n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 Poor gross motor function					
CLASP 1994	53/2146	67/2219		100.0	0.82 [0.57, 1.17]
Subtotal (95% CI)	2146	2219		100.0	0.82 [0.57, 1.17]
Total events: 53 (Antiplatelet agents), 67 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.11 p=0.3					
02 Poor fine motor function					
CLASP 1994	273/2146	288/2219		100.0	0.98 [0.84, 1.14]
Subtotal (95% CI)	2146	2219		100.0	0.98 [0.84, 1.14]
Total events: 273 (Antiplatelet agents), 288 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.25 p=0.8					
03 Poor gross or fine motor function					
Italy 1993	15/427	26/361		100.0	0.49 [0.26, 0.91]
Subtotal (95% CI)	427	361		100.0	0.49 [0.26, 0.91]
Total events: 15 (Antiplatelet agents), 26 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=2.27 p=0.02					
04 Respiratory problems					
Italy 1993	56/427	32/361		100.0	1.48 [0.98, 2.23]
Subtotal (95% CI)	427	361		100.0	1.48 [0.98, 2.23]
Total events: 56 (Antiplatelet agents), 32 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.87 p=0.06					
05 Poor language expression					
CLASP 1994	124/2146	136/2219		100.0	0.94 [0.74, 1.19]
Subtotal (95% CI)	2146	2219		100.0	0.94 [0.74, 1.19]
Total events: 124 (Antiplatelet agents), 136 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.49 p=0.6					
06 Poor language comprehension					
CLASP 1994	229/2146	249/2219		100.0	0.95 [0.80, 1.13]

(*Continued . . .*)

(. . . *Continued*)

Study	Antiplatelet agents n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Subtotal (95% CI)	2146	2219		100.0	0.95 [0.80, 1.13]
Total events: 229 (Antiplatelet agents), 249 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.58 p=0.6					
07 Language problems - undefined					
Italy 1993	55/427	47/361		100.0	0.99 [0.69, 1.42]
Subtotal (95% CI)	427	361		100.0	0.99 [0.69, 1.42]
Total events: 55 (Antiplatelet agents), 47 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.06 p=1					
08 Hearing problems					
Italy 1993	1/427	0/361		100.0	2.54 [0.10, 62.10]
Subtotal (95% CI)	427	361		100.0	2.54 [0.10, 62.10]
Total events: 1 (Antiplatelet agents), 0 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.57 p=0.6					
09 Sight problems					
Italy 1993	5/427	5/361		100.0	0.85 [0.25, 2.90]
Subtotal (95% CI)	427	361		100.0	0.85 [0.25, 2.90]
Total events: 5 (Antiplatelet agents), 5 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.27 p=0.8					

Analysis 01.23. Comparison 01 Antiplatelet agents versus placebo/no antiplatelet for primary prevention (subgrouped by maternal risk), Outcome 23 Behaviour problems at 18 months

Review: Antiplatelet agents for preventing pre-eclampsia and its complications

Comparison: 01 Antiplatelet agents versus placebo/no antiplatelet for primary prevention (subgrouped by maternal risk)

Outcome: 23 Behaviour problems at 18 months

Study	Antiplatelet agents n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 Poor sleep pattern					
CLASP 1994	273/2146	325/2219		100.0	0.87 [0.75, 1.01]
Total (95% CI)	2146	2219		100.0	0.87 [0.75, 1.01]
Total events: 273 (Antiplatelet agents), 325 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.85 p=0.06					

Analysis 01.24. Comparison 01 Antiplatelet agents versus placebo/no antiplatelet for primary prevention (subgrouped by maternal risk), Outcome 24 Malformations at 18 months

Review: Antiplatelet agents for preventing pre-eclampsia and its complications

Comparison: 01 Antiplatelet agents versus placebo/no antiplatelet for primary prevention (subgrouped by maternal risk)

Outcome: 24 Malformations at 18 months

Study	Antiplatelet agents n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Italy 1993	7/427	8/361		100.0	0.74 [0.27, 2.02]
Total (95% CI)	427	361		100.0	0.74 [0.27, 2.02]
Total events: 7 (Antiplatelet agents), 8 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.59 p=0.6					

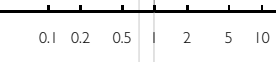
Analysis 01.25. Comparison 01 Antiplatelet agents versus placebo/no antiplatelet for primary prevention (subgrouped by maternal risk), Outcome 25 Growth at 18 months

Review: Antiplatelet agents for preventing pre-eclampsia and its complications

Comparison: 01 Antiplatelet agents versus placebo/no antiplatelet for primary prevention (subgrouped by maternal risk)

Outcome: 25 Growth at 18 months

Study	Antiplatelet agents n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 Height < 3rd or 10th centile					
CLASP 1994	236/2146	248/2219		50.4	0.98 [0.83, 1.16]
Italy 1993	36/427	44/361		9.9	0.69 [0.46, 1.05]
Subtotal (95% CI)	2573	2580		60.3	0.94 [0.80, 1.09]
Total events: 272 (Antiplatelet agents), 292 (Control)					
Test for heterogeneity chi-square=2.35 df=1 p=0.12 I^2 =57.5%					
Test for overall effect z=0.83 p=0.4					
02 Weight < 3rd or 10th centile					
CLASP 1994	112/2146	129/2219		26.2	0.90 [0.70, 1.15]
Italy 1993	76/427	60/361		13.5	1.07 [0.79, 1.46]
Subtotal (95% CI)	2573	2580		39.7	0.96 [0.79, 1.16]
Total events: 188 (Antiplatelet agents), 189 (Control)					
Test for heterogeneity chi-square=0.77 df=1 p=0.38 I^2 =0.0%					
Test for overall effect z=0.45 p=0.7					
Total (95% CI)	5146	5160		100.0	0.94 [0.84, 1.07]
Total events: 460 (Antiplatelet agents), 481 (Control)					
Test for heterogeneity chi-square=3.17 df=3 p=0.37 I^2 =5.3%					
Test for overall effect z=0.93 p=0.4					



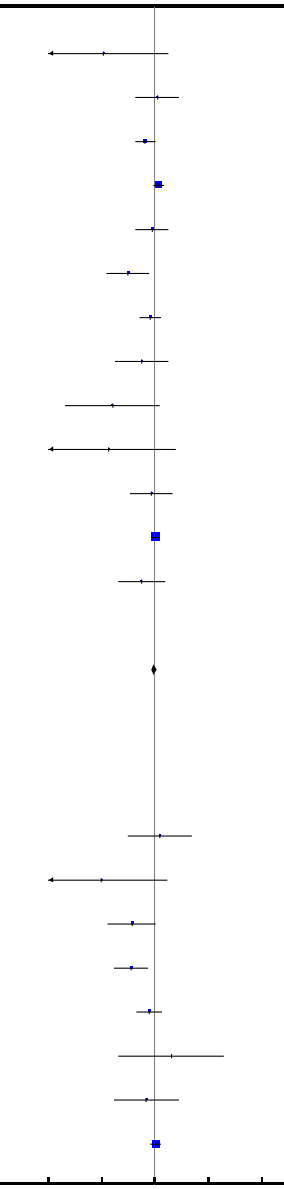
Analysis 02.01. Comparison 02 Antiplatelet agents versus placebo/no antiplatelet for primary prevention (subgrouped by gestation at entry), Outcome 01 Gestational hypertension

Review: Antiplatelet agents for preventing pre-eclampsia and its complications

Comparison: 02 Antiplatelet agents versus placebo/no antiplatelet for primary prevention (subgrouped by gestation at entry)

Outcome: 01 Gestational hypertension

Study	Antiplatelet agents n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 Entered into the study < 20 weeks					
Australia 1995a	0/9	5/11		0.5	0.11 [0.01, 1.74]
Australia 1996a	8/52	7/50		0.7	1.10 [0.43, 2.81]
EPREDA 1991	35/156	25/73		3.2	0.66 [0.43, 1.01]
ERASME 2003	151/1632	131/1637		12.1	1.16 [0.92, 1.45]
Finland 1993	12/97	14/100		1.3	0.88 [0.43, 1.81]
Finland 2002	5/43	16/43		1.5	0.31 [0.13, 0.78]
France 1985	19/48	22/45		2.1	0.81 [0.51, 1.28]
France 1990	4/46	7/45		0.7	0.56 [0.18, 1.78]
Israel 1994	1/24	6/23		0.6	0.16 [0.02, 1.23]
Italy 1989	0/17	3/16		0.3	0.13 [0.01, 2.42]
Italy 2004	5/16	7/19		0.6	0.85 [0.33, 2.16]
Jamaica 1998	203/1770	194/1732		18.1	1.02 [0.85, 1.23]
Spain 1997	5/50	9/50		0.8	0.56 [0.20, 1.54]
× UK 1992	0/10	0/8		0.0	Not estimable
Subtotal (95% CI)	3970	3852		42.4	0.95 [0.84, 1.07]
Total events: 448 (Antiplatelet agents), 446 (Control)					
Test for heterogeneity chi-square=21.72 df=12 p=0.04 I^2 =44.8%					
Test for overall effect z=0.85 p=0.4					
02 Entered into the study > 20 weeks					
Australia 1996	4/27	3/25		0.3	1.23 [0.31, 4.98]
Austria 1992	0/22	4/19		0.4	0.10 [0.01, 1.69]
China 1996	4/40	12/44		1.1	0.37 [0.13, 1.05]
China 1996a	7/48	23/56		2.0	0.36 [0.17, 0.75]
China 1999	22/118	18/75		2.0	0.78 [0.45, 1.35]
Finland 1997	2/13	1/13		0.1	2.00 [0.21, 19.44]
Israel 1989	3/34	4/31		0.4	0.68 [0.17, 2.82]
Jamaica 1998	135/1253	138/1294		12.6	1.01 [0.81, 1.26]



(*Continued . . .*)

(. . . *Continued*)

Study	Antiplatelet agents n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Netherlands 1986	1/23	3/23		0.3	0.33 [0.04, 2.97]
Netherlands 1989	0/5	3/5		0.3	0.14 [0.01, 2.21]
UK 1990	6/48	13/52		1.2	0.50 [0.21, 1.21]
UK 1995	2/58	4/60		0.4	0.52 [0.10, 2.72]
USA 1993	19/302	17/302		1.6	1.12 [0.59, 2.11]
Subtotal (95% CI)	1991	1999		22.5	0.84 [0.70, 1.00]
Total events: 205 (Antiplatelet agents), 243 (Control)					
Test for heterogeneity chi-square=17.97 df=12 p=0.12 I^2 =33.2%					
Test for overall effect z=1.99 p=0.05					
03 Unclassified					
Barbados 1998	162/1819	172/1822		15.9	0.94 [0.77, 1.16]
Brazil 1996	68/476	56/494		5.1	1.26 [0.91, 1.75]
Colorado 1993	12/48	14/42		1.4	0.75 [0.39, 1.44]
Italy 1993	69/497	42/423		4.2	1.40 [0.97, 2.01]
Tanzania 1995	2/64	4/63		0.4	0.49 [0.09, 2.59]
USA 1993a	100/1485	89/1500		8.2	1.13 [0.86, 1.50]
Subtotal (95% CI)	4389	4344		35.1	1.08 [0.94, 1.23]
Total events: 413 (Antiplatelet agents), 377 (Control)					
Test for heterogeneity chi-square=6.67 df=5 p=0.25 I^2 =25.0%					
Test for overall effect z=1.08 p=0.3					
Total (95% CI)	10350	10195		100.0	0.97 [0.89, 1.05]
Total events: 1066 (Antiplatelet agents), 1066 (Control)					
Test for heterogeneity chi-square=50.57 df=31 p=0.01 I^2 =38.7%					
Test for overall effect z=0.79 p=0.4					

Analysis 02.02. Comparison 02 Antiplatelet agents versus placebo/no antiplatelet for primary prevention (subgrouped by gestation at entry), Outcome 02 Proteinuric pre-eclampsia

Review: Antiplatelet agents for preventing pre-eclampsia and its complications

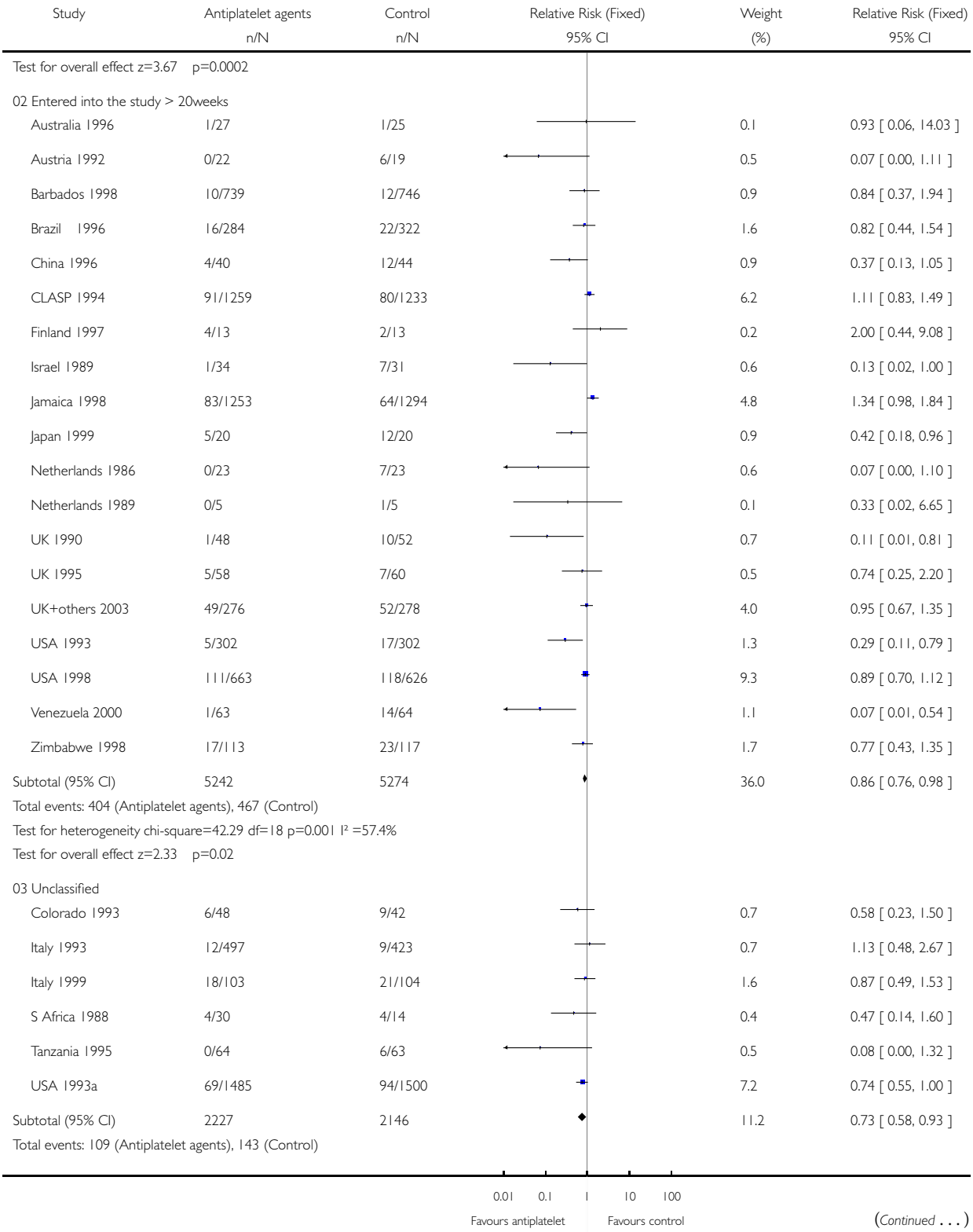
Comparison: 02 Antiplatelet agents versus placebo/no antiplatelet for primary prevention (subgrouped by gestation at entry)

Outcome: 02 Proteinuric pre-eclampsia

Study	Antiplatelet agents n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 Entered into the study < 20 weeks					
Australia 1993	1/55	5/55		0.4	0.20 [0.02, 1.66]
Australia 1995a	0/9	6/11		0.5	0.09 [0.01, 1.45]
Australia 1996a	4/52	7/50		0.5	0.55 [0.17, 1.76]
Australia 1997	5/58	5/50		0.4	0.86 [0.26, 2.81]
Barbados 1998	30/1080	34/1076		2.6	0.88 [0.54, 1.43]
Brazil 1996	16/192	8/172		0.6	1.79 [0.79, 4.08]
China 1999	3/118	7/75		0.7	0.27 [0.07, 1.02]
CLASP 1994	176/2733	222/2749		17.0	0.80 [0.66, 0.96]
Egypt 2005	25/73	40/63		3.3	0.54 [0.37, 0.78]
EPREDA 1991	5/156	8/73		0.8	0.29 [0.10, 0.86]
ERASME 2003	28/1632	26/1637		2.0	1.08 [0.64, 1.83]
Finland 1993	9/97	11/100		0.8	0.84 [0.37, 1.95]
Finland 1997a	1/23	3/23		0.2	0.33 [0.04, 2.97]
Finland 2002	2/43	10/43		0.8	0.20 [0.05, 0.86]
France 1985	0/48	6/45		0.5	0.07 [0.00, 1.25]
France 1990	1/46	4/45		0.3	0.24 [0.03, 2.10]
Germany 2000	3/22	2/21		0.2	1.43 [0.27, 7.73]
Israel 1994	0/24	2/23		0.2	0.19 [0.01, 3.80]
Jamaica 1998	132/1770	125/1732		9.7	1.03 [0.82, 1.31]
Russia 1993	1/31	3/33		0.2	0.35 [0.04, 3.23]
Spain 1997	3/50	7/50		0.5	0.43 [0.12, 1.56]
USA 1994	3/24	5/25		0.4	0.63 [0.17, 2.33]
USA 1998	120/591	136/623		10.2	0.93 [0.75, 1.16]
Subtotal (95% CI)	8927	8774		52.8	0.82 [0.74, 0.91]
Total events: 568 (Antiplatelet agents), 682 (Control)					
Test for heterogeneity chi-square=36.60 df=22 p=0.03 I^2 =39.9%					

(*Continued . . .*)

(. . . *Continued*)



Study	Antiplatelet agents n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Test for overall effect z=3.67 p=0.0002					
02 Entered into the study > 20weeks					
Australia 1996	1/27	1/25		0.1	0.93 [0.06, 14.03]
Austria 1992	0/22	6/19		0.5	0.07 [0.00, 1.11]
Barbados 1998	10/739	12/746		0.9	0.84 [0.37, 1.94]
Brazil 1996	16/284	22/322		1.6	0.82 [0.44, 1.54]
China 1996	4/40	12/44		0.9	0.37 [0.13, 1.05]
CLASP 1994	91/1259	80/1233		6.2	1.11 [0.83, 1.49]
Finland 1997	4/13	2/13		0.2	2.00 [0.44, 9.08]
Israel 1989	1/34	7/31		0.6	0.13 [0.02, 1.00]
Jamaica 1998	83/1253	64/1294		4.8	1.34 [0.98, 1.84]
Japan 1999	5/20	12/20		0.9	0.42 [0.18, 0.96]
Netherlands 1986	0/23	7/23		0.6	0.07 [0.00, 1.10]
Netherlands 1989	0/5	1/5		0.1	0.33 [0.02, 6.65]
UK 1990	1/48	10/52		0.7	0.11 [0.01, 0.81]
UK 1995	5/58	7/60		0.5	0.74 [0.25, 2.20]
UK+others 2003	49/276	52/278		4.0	0.95 [0.67, 1.35]
USA 1993	5/302	17/302		1.3	0.29 [0.11, 0.79]
USA 1998	111/663	118/626		9.3	0.89 [0.70, 1.12]
Venezuela 2000	1/63	14/64		1.1	0.07 [0.01, 0.54]
Zimbabwe 1998	17/113	23/117		1.7	0.77 [0.43, 1.35]
Subtotal (95% CI)	5242	5274		36.0	0.86 [0.76, 0.98]
Total events: 404 (Antiplatelet agents), 467 (Control)					
Test for heterogeneity chi-square=42.29 df=18 p=0.001 I^2 =57.4%					
Test for overall effect z=2.33 p=0.02					
03 Unclassified					
Colorado 1993	6/48	9/42		0.7	0.58 [0.23, 1.50]
Italy 1993	12/497	9/423		0.7	1.13 [0.48, 2.67]
Italy 1999	18/103	21/104		1.6	0.87 [0.49, 1.53]
S Africa 1988	4/30	4/14		0.4	0.47 [0.14, 1.60]
Tanzania 1995	0/64	6/63		0.5	0.08 [0.00, 1.32]
USA 1993a	69/1485	94/1500		7.2	0.74 [0.55, 1.00]
Subtotal (95% CI)	2227	2146		11.2	0.73 [0.58, 0.93]
Total events: 109 (Antiplatelet agents), 143 (Control)					

(*Continued* . . .)

(. . . *Continued*)

Study	Antiplatelet agents n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Test for heterogeneity chi-square=4.50 df=5 p=0.48 I^2 =0.0%					
Test for overall effect z=2.53 p=0.01					
Total (95% CI)	16396	16194		100.0	0.83 [0.77, 0.89]
Total events: 1081 (Antiplatelet agents), 1292 (Control)					
Test for heterogeneity chi-square=85.40 df=47 p=0.0005 I^2 =45.0%					
Test for overall effect z=4.91 p<0.00001					

Analysis 02.03. Comparison 02 Antiplatelet agents versus placebo/no antiplatelet for primary prevention (subgrouped by gestation at entry), Outcome 03 Placental abruption

Review: Antiplatelet agents for preventing pre-eclampsia and its complications

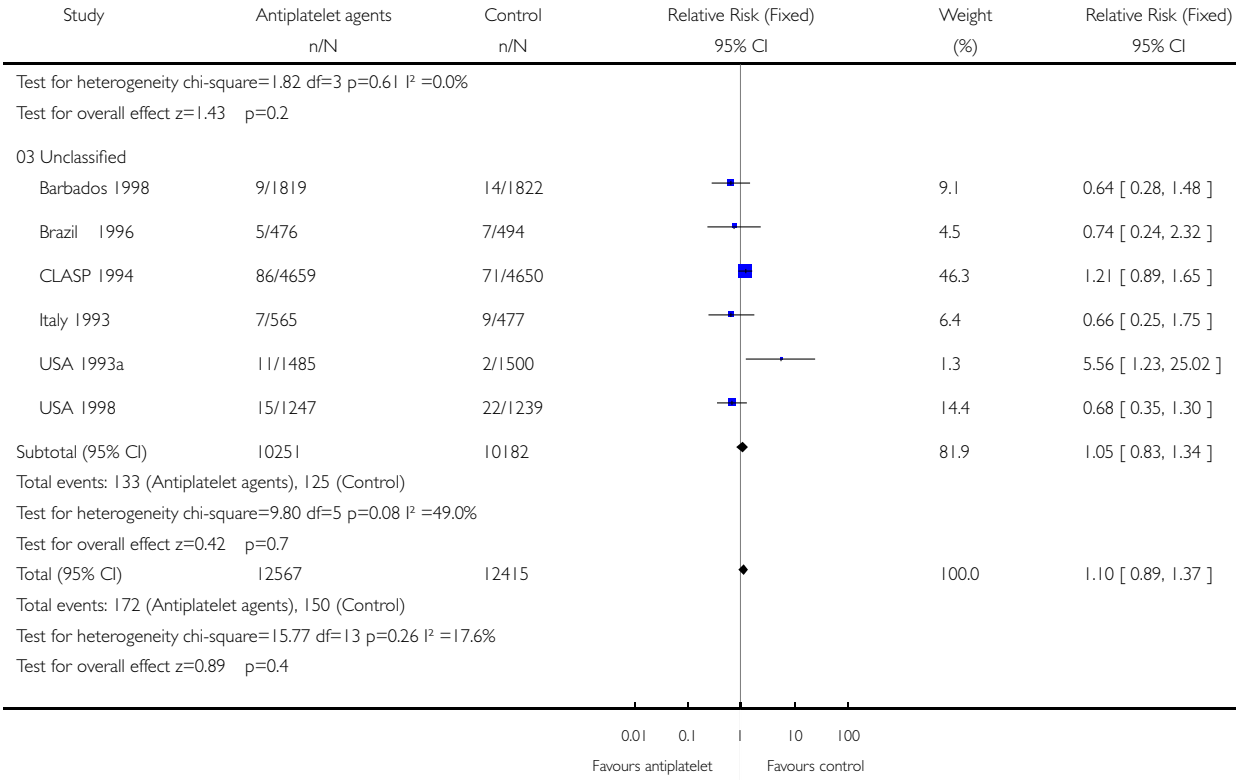
Comparison: 02 Antiplatelet agents versus placebo/no antiplatelet for primary prevention (subgrouped by gestation at entry)

Outcome: 03 Placental abruption

Study	Antiplatelet agents n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 Entered into study at < 20 weeks					
Australia 1997	3/58	1/50		0.7	2.59 [0.28, 24.08]
EPREDA 1991	7/156	6/73		5.3	0.55 [0.19, 1.57]
ERASME 2003	13/1623	9/1628		5.9	1.45 [0.62, 3.38]
× Israel 1994	0/24	0/23		0.0	Not estimable
Russia 1993	1/31	1/33		0.6	1.06 [0.07, 16.29]
× Spain 1997	0/50	0/50		0.0	Not estimable
Subtotal (95% CI)	1942	1857		12.5	1.11 [0.61, 2.02]
Total events: 24 (Antiplatelet agents), 17 (Control)					
Test for heterogeneity chi-square=2.67 df=3 p=0.45 I^2 =0.0%					
Test for overall effect z=0.34 p=0.7					
02 Entered into study at > 20 weeks					
Australia 1996	1/27	2/25		1.4	0.46 [0.04, 4.80]
Finland 1997	2/13	0/13		0.3	5.00 [0.26, 95.02]
UK 1995	2/58	1/60		0.6	2.07 [0.19, 22.20]
UK+others 2003	10/276	5/278		3.2	2.01 [0.70, 5.82]
Subtotal (95% CI)	374	376		5.6	1.82 [0.80, 4.13]
Total events: 15 (Antiplatelet agents), 8 (Control)					

(*Continued* . . .)

(. . . *Continued*)



Analysis 02.04. Comparison 02 Antiplatelet agents versus placebo/no antiplatelet for primary prevention (subgrouped by gestation at entry), Outcome 04 Preterm birth

Review: Antiplatelet agents for preventing pre-eclampsia and its complications

Comparison: 02 Antiplatelet agents versus placebo/no antiplatelet for primary prevention (subgrouped by gestation at entry)

Outcome: 04 Preterm birth

Study	Antiplatelet agents n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 Entered into the study < 20 weeks					
Australia 1995a	2/9	7/11		0.2	0.35 [0.10, 1.28]
Australia 1996a	3/52	5/50		0.2	0.58 [0.15, 2.29]
Australia 1997	6/58	8/50		0.3	0.65 [0.24, 1.74]
Barbados 1998	163/1080	161/1076		5.7	1.01 [0.83, 1.23]
Brazil 1996	53/192	49/172		1.8	0.97 [0.70, 1.35]
China 1999	4/118	6/75		0.3	0.42 [0.12, 1.45]
CLASP 1994	477/2733	497/2749		17.6	0.97 [0.86, 1.08]
Egypt 2005	2/73	9/63		0.3	0.19 [0.04, 0.85]
ERASME 2003	120/1645	108/1660		3.8	1.12 [0.87, 1.44]
Israel 1994	11/24	15/23		0.5	0.70 [0.41, 1.19]
Italy 1989	2/17	5/16		0.2	0.38 [0.08, 1.67]
Jamaica 1998	253/1770	275/1732		9.9	0.90 [0.77, 1.05]
Russia 1993	5/31	6/33		0.2	0.89 [0.30, 2.61]
Spain 1997	1/50	5/50		0.2	0.20 [0.02, 1.65]
× UK 1992	0/10	0/8		0.0	Not estimable
USA 1998	222/591	260/623		9.0	0.90 [0.78, 1.03]
Subtotal (95% CI)	8453	8391		50.4	0.94 [0.88, 1.00]
Total events: 1324 (Antiplatelet agents), 1416 (Control)					
Test for heterogeneity chi-square=17.14 df=14 p=0.25 I^2 =18.3%					
Test for overall effect z=1.95 p=0.05					
02 Entered into the study > 20 weeks					
Australia 1996	3/27	2/25		0.1	1.39 [0.25, 7.64]
Austria 1992	1/22	1/19		0.0	0.86 [0.06, 12.89]
Barbados 1998	92/739	109/746		3.9	0.85 [0.66, 1.10]
Brazil 1996	53/284	80/322		2.7	0.75 [0.55, 1.02]
China 1996	4/40	6/44		0.2	0.73 [0.22, 2.41]
CLASP 1994	209/1259	264/1233		9.5	0.78 [0.66, 0.91]

(*Continued . . .*)

(. . . *Continued*)

Study	Antiplatelet agents n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Finland 1997	1/13	1/13		0.0	1.00 [0.07, 14.34]
Israel 1989	2/34	6/32		0.2	0.31 [0.07, 1.44]
Jamaica 1998	194/1253	188/1294		6.6	1.07 [0.89, 1.28]
Japan 1999	6/20	11/20		0.4	0.55 [0.25, 1.19]
Netherlands 1986	0/23	4/23		0.2	0.11 [0.01, 1.95]
UK+others 2003	67/276	75/278		2.7	0.90 [0.68, 1.20]
USA 1993	26/302	30/302		1.1	0.87 [0.53, 1.43]
USA 1998	280/663	272/626		10.0	0.97 [0.86, 1.10]
Zimbabwe 1998	21/113	30/117		1.0	0.72 [0.44, 1.19]
Subtotal (95% CI)	5068	5094		38.5	0.89 [0.82, 0.95]
Total events: 959 (Antiplatelet agents), 1079 (Control)					
Test for heterogeneity chi-square=15.97 df=14 p=0.32 I^2 =12.3%					
Test for overall effect z=3.16 p=0.002					
03 Unclassified					
Italy 1993	171/565	154/477		5.9	0.94 [0.78, 1.12]
UK 1995	1/58	1/60		0.0	1.03 [0.07, 16.15]
USA 1993a	157/1485	147/1500		5.2	1.08 [0.87, 1.34]
Subtotal (95% CI)	2108	2037		11.2	1.00 [0.87, 1.15]
Total events: 329 (Antiplatelet agents), 302 (Control)					
Test for heterogeneity chi-square=0.99 df=2 p=0.61 I^2 =0.0%					
Test for overall effect z=0.05 p=1					
Total (95% CI)	15629	15522		100.0	0.92 [0.88, 0.97]
Total events: 2612 (Antiplatelet agents), 2797 (Control)					
Test for heterogeneity chi-square=35.92 df=32 p=0.29 I^2 =10.9%					
Test for overall effect z=3.30 p=0.001					

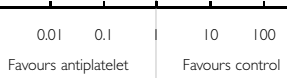
Analysis 02.05. Comparison 02 Antiplatelet agents versus placebo/no antiplatelet for primary prevention (subgrouped by gestation at entry), Outcome 05 Fetal, neonatal or infant death

Review: Antiplatelet agents for preventing pre-eclampsia and its complications

Comparison: 02 Antiplatelet agents versus placebo/no antiplatelet for primary prevention (subgrouped by gestation at entry)

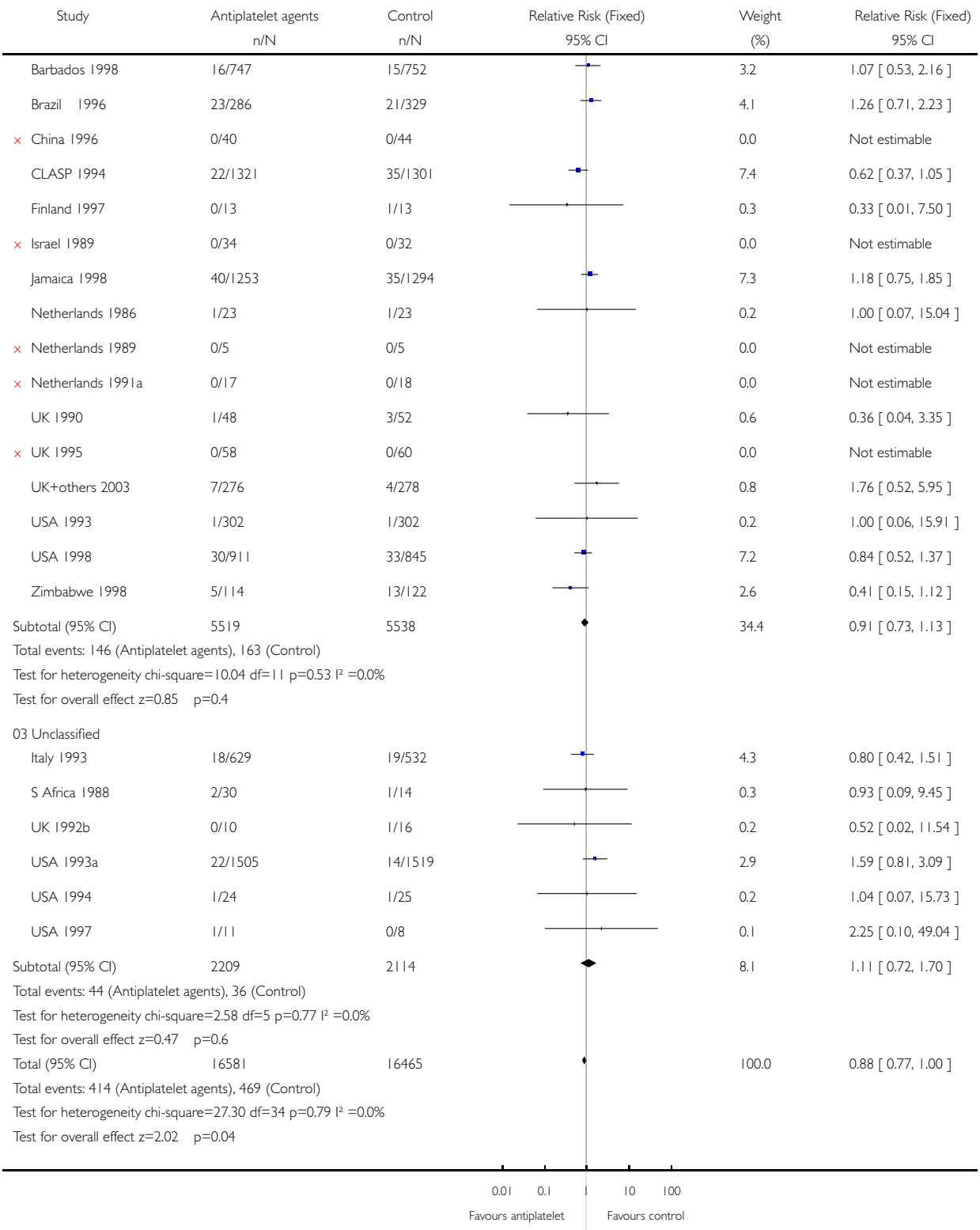
Outcome: 05 Fetal, neonatal or infant death

Study	Antiplatelet agents n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 Entered into the study < 20 weeks					
Australia 1995a	0/9	2/11		0.5	0.24 [0.01, 4.44]
Australia 1997	4/58	2/50		0.5	1.72 [0.33, 9.02]
Barbados 1998	28/1087	23/1089		4.8	1.22 [0.71, 2.10]
Brazil 1996	12/196	9/174		2.0	1.18 [0.51, 2.74]
CLASP 1994	55/2802	62/2833		13.0	0.90 [0.63, 1.28]
EPREDA 1991	7/156	6/73		1.7	0.55 [0.19, 1.57]
ERASME 2003	12/1645	11/1660		2.3	1.10 [0.49, 2.49]
Finland 1993	2/97	0/100		0.1	5.15 [0.25, 105.98]
Finland 1997a	10/33	10/33		2.1	1.00 [0.48, 2.08]
× Finland 2002	0/43	0/43		0.0	Not estimable
France 1985	0/48	5/45		1.2	0.09 [0.00, 1.50]
France 1990	2/46	2/45		0.4	0.98 [0.14, 6.65]
Israel 1994	2/48	2/48		0.4	1.00 [0.15, 6.81]
Italy 1989	0/17	1/16		0.3	0.31 [0.01, 7.21]
Italy 2004	1/16	2/19		0.4	0.59 [0.06, 5.96]
Jamaica 1998	46/1770	68/1732		14.5	0.66 [0.46, 0.96]
Russia 1993	1/31	5/33		1.0	0.21 [0.03, 1.72]
× Spain 1997	0/50	0/50		0.0	Not estimable
USA 1998	42/701	60/759		12.2	0.76 [0.52, 1.11]
Subtotal (95% CI)	8853	8813		57.5	0.82 [0.69, 0.98]
Total events: 224 (Antiplatelet agents), 270 (Control)					
Test for heterogeneity chi-square=13.19 df=16 p=0.66 I^2 =0.0%					
Test for overall effect z=2.22 p=0.03					
02 Entered into the study > 20 weeks					
× Australia 1988	0/22	0/24		0.0	Not estimable
× Australia 1996	0/27	0/25		0.0	Not estimable
Austria 1992	0/22	1/19		0.3	0.29 [0.01, 6.72]



(*Continued . . .*)

(... *Continued*)



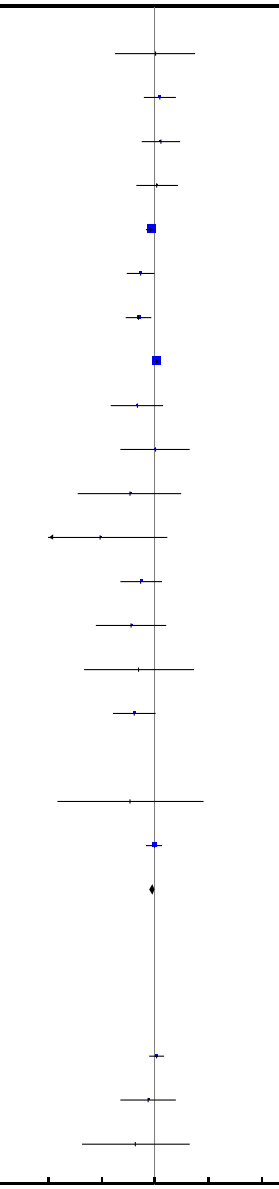
Analysis 02.06. Comparison 02 Antiplatelet agents versus placebo/no antiplatelet for primary prevention (subgrouped by gestation at entry), Outcome 06 Small-for-gestational age

Review: Antiplatelet agents for preventing pre-eclampsia and its complications

Comparison: 02 Antiplatelet agents versus placebo/no antiplatelet for primary prevention (subgrouped by gestation at entry)

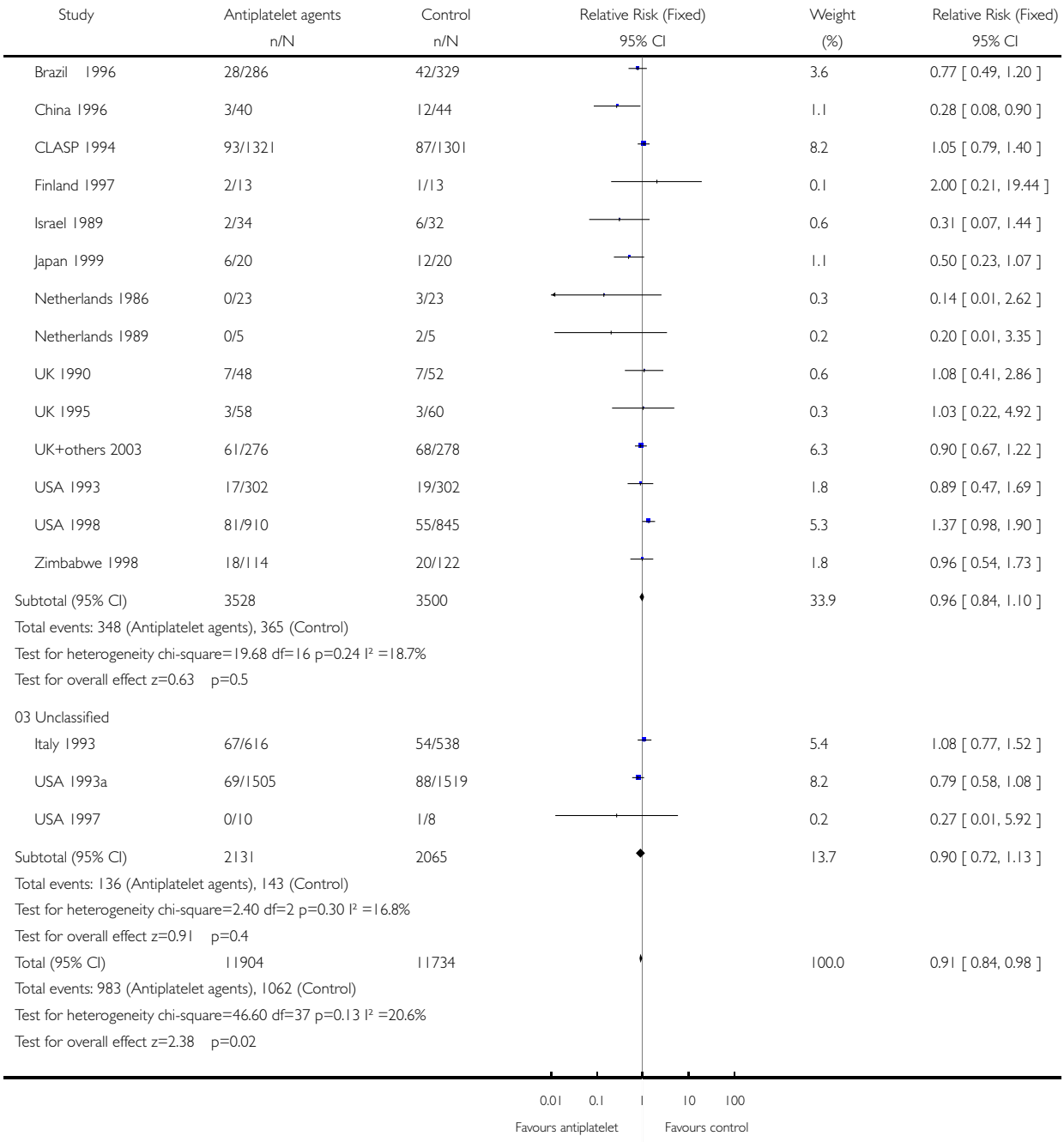
Outcome: 06 Small-for-gestational age

Study	Antiplatelet agents n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 Entered into the study < 20 weeks					
Australia 1995a	2/9	2/9		0.2	1.00 [0.18, 5.63]
Australia 1996a	14/52	11/50		1.0	1.22 [0.62, 2.43]
Brazil 1996	13/196	9/174		0.9	1.28 [0.56, 2.93]
China 1999	12/118	7/75		0.8	1.09 [0.45, 2.64]
CLASP 1994	151/2802	185/2833		17.1	0.83 [0.67, 1.02]
Egypt 2005	13/73	21/63		2.1	0.53 [0.29, 0.98]
EPREDA 1991	20/156	19/73		2.4	0.49 [0.28, 0.86]
ERASME 2003	199/1645	189/1660		17.5	1.06 [0.88, 1.28]
Finland 1993	4/97	9/100		0.8	0.46 [0.15, 1.44]
Finland 1997a	3/23	3/23		0.3	1.00 [0.22, 4.45]
Finland 2002	1/43	3/43		0.3	0.33 [0.04, 3.08]
France 1985	0/48	4/41		0.5	0.10 [0.01, 1.72]
Israel 1994	6/48	11/48		1.0	0.55 [0.22, 1.36]
Russia 1993	2/31	6/33		0.5	0.35 [0.08, 1.63]
Spain 1997	1/50	2/50		0.2	0.50 [0.05, 5.34]
Spain 1999	6/124	14/116		1.3	0.40 [0.16, 1.01]
× UK 1992	0/10	0/8		0.0	Not estimable
USA 1994	0/24	1/25		0.1	0.35 [0.01, 8.12]
USA 1998	52/696	58/745		5.2	0.96 [0.67, 1.38]
Subtotal (95% CI)	6245	6169		52.4	0.87 [0.78, 0.98]
Total events: 499 (Antiplatelet agents), 554 (Control)					
Test for heterogeneity chi-square=23.18 df=17 p=0.14 I² =26.7%					
Test for overall effect z=2.31 p=0.02					
02 Entered into the study > 20 weeks					
Australia 1995	22/29	21/30		1.9	1.08 [0.79, 1.48]
Australia 1996	4/27	5/25		0.5	0.74 [0.22, 2.45]
Austria 1992	1/22	2/19		0.2	0.43 [0.04, 4.40]



(*Continued . . .*)

(. . . *Continued*)



Study	Antiplatelet agents n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Brazil 1996	28/286	42/329		3.6	0.77 [0.49, 1.20]
China 1996	3/40	12/44		1.1	0.28 [0.08, 0.90]
CLASP 1994	93/1321	87/1301		8.2	1.05 [0.79, 1.40]
Finland 1997	2/13	1/13		0.1	2.00 [0.21, 19.44]
Israel 1989	2/34	6/32		0.6	0.31 [0.07, 1.44]
Japan 1999	6/20	12/20		1.1	0.50 [0.23, 1.07]
Netherlands 1986	0/23	3/23		0.3	0.14 [0.01, 2.62]
Netherlands 1989	0/5	2/5		0.2	0.20 [0.01, 3.35]
UK 1990	7/48	7/52		0.6	1.08 [0.41, 2.86]
UK 1995	3/58	3/60		0.3	1.03 [0.22, 4.92]
UK+others 2003	61/276	68/278		6.3	0.90 [0.67, 1.22]
USA 1993	17/302	19/302		1.8	0.89 [0.47, 1.69]
USA 1998	81/910	55/845		5.3	1.37 [0.98, 1.90]
Zimbabwe 1998	18/114	20/122		1.8	0.96 [0.54, 1.73]
Subtotal (95% CI)	3528	3500		33.9	0.96 [0.84, 1.10]
Total events: 348 (Antiplatelet agents), 365 (Control)					
Test for heterogeneity chi-square=19.68 df=16 p=0.24 I^2 =18.7%					
Test for overall effect z=0.63 p=0.5					
03 Unclassified					
Italy 1993	67/616	54/538		5.4	1.08 [0.77, 1.52]
USA 1993a	69/1505	88/1519		8.2	0.79 [0.58, 1.08]
USA 1997	0/10	1/8		0.2	0.27 [0.01, 5.92]
Subtotal (95% CI)	2131	2065		13.7	0.90 [0.72, 1.13]
Total events: 136 (Antiplatelet agents), 143 (Control)					
Test for heterogeneity chi-square=2.40 df=2 p=0.30 I^2 =16.8%					
Test for overall effect z=0.91 p=0.4					
Total (95% CI)	11904	11734		100.0	0.91 [0.84, 0.98]
Total events: 983 (Antiplatelet agents), 1062 (Control)					
Test for heterogeneity chi-square=46.60 df=37 p=0.13 I^2 =20.6%					
Test for overall effect z=2.38 p=0.02					

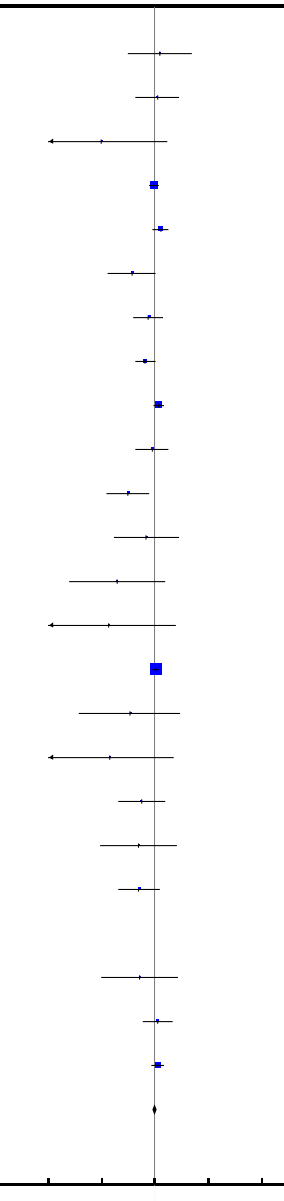
Analysis 03.01. Comparison 03 Antiplatelet agents versus placebo/no treatment for primary prevention (subgrouped by use of placebo), Outcome 01 Gestational hypertension

Review: Antiplatelet agents for preventing pre-eclampsia and its complications

Comparison: 03 Antiplatelet agents versus placebo/no treatment for primary prevention (subgrouped by use of placebo)

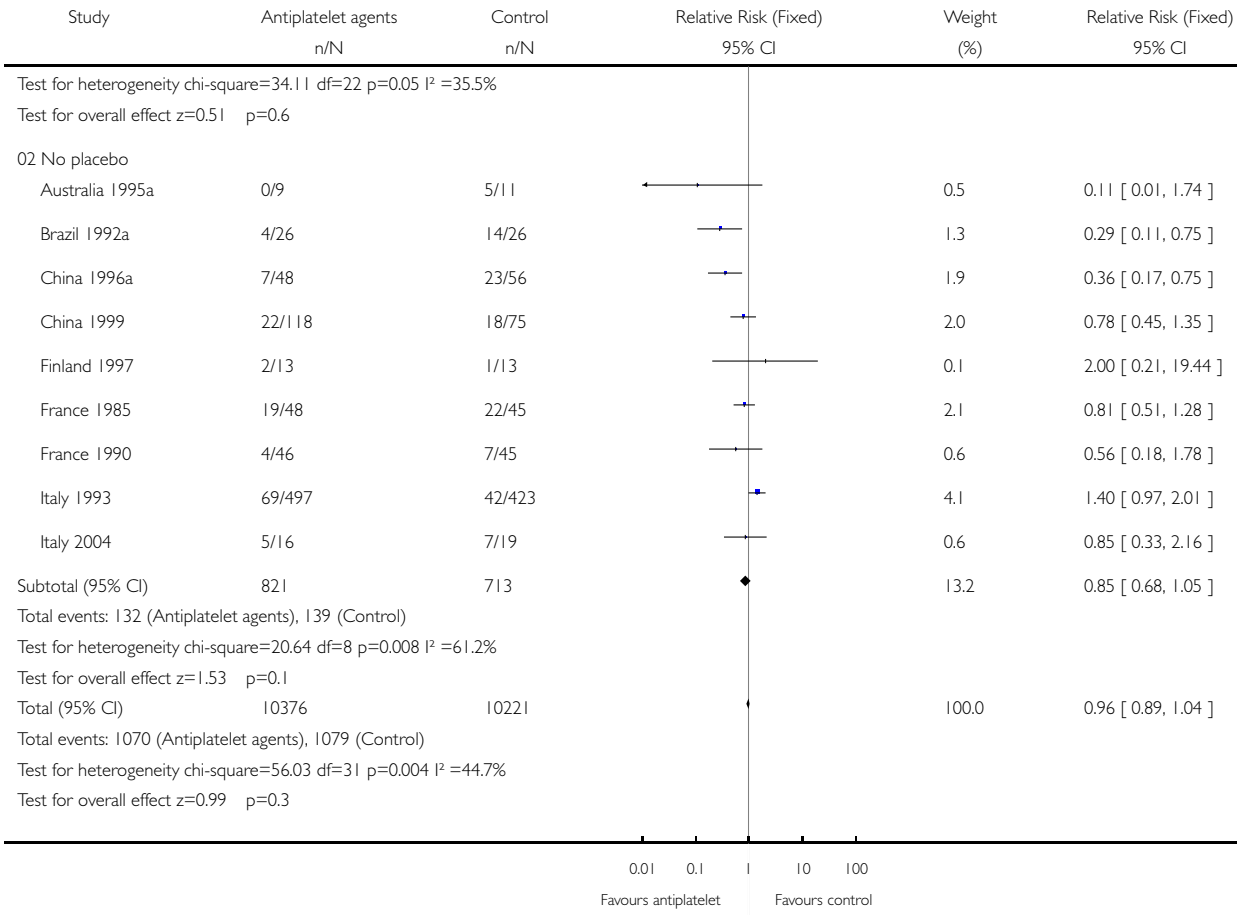
Outcome: 01 Gestational hypertension

Study	Antiplatelet agents n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 Placebo					
Australia 1996	4/27	3/25		0.3	1.23 [0.31, 4.98]
Australia 1996a	8/52	7/50		0.7	1.10 [0.43, 2.81]
Austria 1992	0/22	4/19		0.4	0.10 [0.01, 1.69]
Barbados 1998	162/1819	172/1822		15.7	0.94 [0.77, 1.16]
Brazil 1996	68/476	56/494		5.0	1.26 [0.91, 1.75]
China 1996	4/40	12/44		1.0	0.37 [0.13, 1.05]
Colorado 1993	12/48	14/42		1.4	0.75 [0.39, 1.44]
EPREDA 1991	35/156	25/73		3.1	0.66 [0.43, 1.01]
ERASME 2003	151/1632	131/1637		12.0	1.16 [0.92, 1.45]
Finland 1993	12/97	14/100		1.3	0.88 [0.43, 1.81]
Finland 2002	5/43	16/43		1.5	0.31 [0.13, 0.78]
Israel 1989	3/34	4/31		0.4	0.68 [0.17, 2.82]
Israel 1994	1/24	5/23		0.5	0.19 [0.02, 1.52]
Italy 1989	0/17	3/16		0.3	0.13 [0.01, 2.42]
Jamaica 1998	338/3023	332/3026		30.3	1.02 [0.88, 1.18]
Netherlands 1986	1/23	3/23		0.3	0.33 [0.04, 2.97]
Netherlands 1989	0/5	3/5		0.3	0.14 [0.01, 2.21]
Spain 1997	5/50	9/50		0.8	0.56 [0.20, 1.54]
Tanzania 1995	2/64	4/63		0.4	0.49 [0.09, 2.59]
UK 1990	6/48	13/52		1.1	0.50 [0.21, 1.21]
× UK 1992	0/10	0/8		0.0	Not estimable
UK 1995	2/58	4/60		0.4	0.52 [0.10, 2.72]
USA 1993	19/302	17/302		1.6	1.12 [0.59, 2.11]
USA 1993a	100/1485	89/1500		8.1	1.13 [0.86, 1.50]
Subtotal (95% CI)	9555	9508		86.8	0.98 [0.90, 1.07]
Total events: 938 (Antiplatelet agents), 940 (Control)					



(*Continued . . .*)

(. . . *Continued*)



Analysis 03.02. Comparison 03 Antiplatelet agents versus placebo/no treatment for primary prevention (subgrouped by use of placebo), Outcome 02 Proteinuric pre-eclampsia

Review: Antiplatelet agents for preventing pre-eclampsia and its complications

Comparison: 03 Antiplatelet agents versus placebo/no treatment for primary prevention (subgrouped by use of placebo)

Outcome: 02 Proteinuric pre-eclampsia

Study	Antiplatelet agents n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 Placebo					
Australia 1993	1/55	5/55		0.4	0.20 [0.02, 1.66]
Australia 1996	1/27	1/25		0.1	0.93 [0.06, 14.03]
Australia 1996a	4/52	7/50		0.5	0.55 [0.17, 1.76]
Australia 1997	5/58	5/50		0.4	0.86 [0.26, 2.81]
Austria 1992	0/22	6/19		0.5	0.07 [0.00, 1.11]
Barbados 1998	40/1819	46/1822		3.5	0.87 [0.57, 1.32]
Brazil 1996	32/476	30/494		2.3	1.11 [0.68, 1.79]
China 1996	4/40	12/44		0.9	0.37 [0.13, 1.05]
CLASP 1994	267/3992	302/3982		23.2	0.88 [0.75, 1.03]
Colorado 1993	6/48	9/42		0.7	0.58 [0.23, 1.50]
EPREDA 1991	5/156	8/73		0.8	0.29 [0.10, 0.86]
ERASME 2003	28/1632	26/1637		2.0	1.08 [0.64, 1.83]
Finland 1993	9/97	11/100		0.8	0.84 [0.37, 1.95]
Finland 1997a	1/23	3/23		0.2	0.33 [0.04, 2.97]
Finland 2002	2/43	10/43		0.8	0.20 [0.05, 0.86]
Germany 2000	3/22	2/21		0.2	1.43 [0.27, 7.73]
Israel 1989	1/34	7/31		0.6	0.13 [0.02, 1.00]
Israel 1994	0/24	2/23		0.2	0.19 [0.01, 3.80]
Italy 1999	18/103	21/104		1.6	0.87 [0.49, 1.53]
Jamaica 1998	215/3023	189/3026		14.5	1.14 [0.94, 1.38]
Japan 1999	5/20	12/20		0.9	0.42 [0.18, 0.96]
Netherlands 1986	0/23	7/23		0.6	0.07 [0.00, 1.10]
Netherlands 1989	0/5	1/5		0.1	0.33 [0.02, 6.65]
Spain 1997	3/50	7/50		0.5	0.43 [0.12, 1.56]
Tanzania 1995	0/64	6/63		0.5	0.08 [0.00, 1.32]

(*Continued . . .*)

(. . . *Continued*)

Study	Antiplatelet agents n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
UK 1990	1/48	10/52		0.7	0.11 [0.01, 0.81]
UK 1995	5/58	7/60		0.5	0.74 [0.25, 2.20]
UK+others 2003	49/276	52/278		4.0	0.95 [0.67, 1.35]
USA 1993	5/302	17/302		1.3	0.29 [0.11, 0.79]
USA 1993a	69/1485	94/1500		7.2	0.74 [0.55, 1.00]
USA 1994	3/24	5/25		0.4	0.63 [0.17, 2.33]
USA 1998	231/1254	254/1249		19.5	0.91 [0.77, 1.06]
Venezuela 2000	1/63	14/64		1.1	0.07 [0.01, 0.54]
Zimbabwe 1998	17/113	23/117		1.7	0.77 [0.43, 1.35]
Subtotal (95% CI)	15531	15472		93.2	0.85 [0.78, 0.92]
Total events: 1031 (Antiplatelet agents), 1211 (Control)					
Test for heterogeneity chi-square=59.39 df=33 p=0.003 I^2 =44.4%					
Test for overall effect z=4.10 p=0.00004					
02 No placebo					
Australia 1995a	0/9	6/11		0.5	0.09 [0.01, 1.45]
China 1999	3/118	7/75		0.7	0.27 [0.07, 1.02]
Egypt 2005	25/73	40/63		3.3	0.54 [0.37, 0.78]
Finland 1997	4/13	2/13		0.2	2.00 [0.44, 9.08]
France 1985	0/48	6/45		0.5	0.07 [0.00, 1.25]
France 1990	1/46	4/45		0.3	0.24 [0.03, 2.10]
Italy 1993	12/497	9/423		0.7	1.13 [0.48, 2.67]
Russia 1993	1/31	3/33		0.2	0.35 [0.04, 3.23]
S Africa 1988	4/30	4/14		0.4	0.47 [0.14, 1.60]
Subtotal (95% CI)	865	722		6.8	0.52 [0.39, 0.71]
Total events: 50 (Antiplatelet agents), 81 (Control)					
Test for heterogeneity chi-square=11.16 df=8 p=0.19 I^2 =28.3%					
Test for overall effect z=4.21 p=0.00003					
Total (95% CI)	16396	16194		100.0	0.83 [0.77, 0.89]
Total events: 1081 (Antiplatelet agents), 1292 (Control)					
Test for heterogeneity chi-square=78.31 df=42 p=0.0006 I^2 =46.4%					
Test for overall effect z=4.92 p<0.00001					

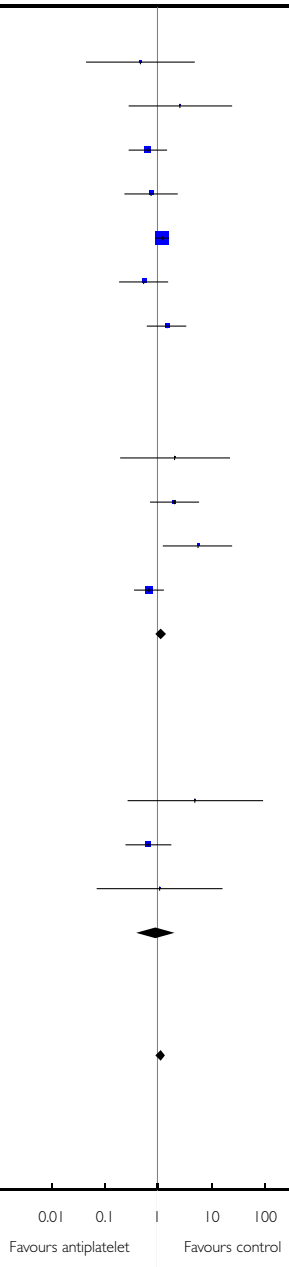
Analysis 03.03. Comparison 03 Antiplatelet agents versus placebo/no treatment for primary prevention (subgrouped by use of placebo), Outcome 03 Placental abruption

Review: Antiplatelet agents for preventing pre-eclampsia and its complications

Comparison: 03 Antiplatelet agents versus placebo/no treatment for primary prevention (subgrouped by use of placebo)

Outcome: 03 Placental abruption

Study	Antiplatelet agents n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 Placebo					
Australia 1996	1/27	2/25		1.4	0.46 [0.04, 4.80]
Australia 1997	3/58	1/50		0.7	2.59 [0.28, 24.08]
Barbados 1998	9/1819	14/1822		9.1	0.64 [0.28, 1.48]
Brazil 1996	5/476	7/494		4.5	0.74 [0.24, 2.32]
CLASP 1994	86/4659	71/4650		46.3	1.21 [0.89, 1.65]
EPREDA 1991	7/156	6/73		5.3	0.55 [0.19, 1.57]
ERASME 2003	13/1623	9/1628		5.9	1.45 [0.62, 3.38]
× Israel 1994	0/24	0/23		0.0	Not estimable
× Spain 1997	0/50	0/50		0.0	Not estimable
UK 1995	2/58	1/60		0.6	2.07 [0.19, 22.20]
UK+others 2003	10/276	5/278		3.2	2.01 [0.70, 5.82]
USA 1993a	11/1485	2/1500		1.3	5.56 [1.23, 25.02]
USA 1998	15/1247	22/1239		14.4	0.68 [0.35, 1.30]
Subtotal (95% CI)	11958	11892		92.7	1.12 [0.90, 1.40]
Total events: 162 (Antiplatelet agents), 140 (Control)					
Test for heterogeneity chi-square=13.72 df=10 p=0.19 I² =27.1%					
Test for overall effect z=0.99 p=0.3					
02 No placebo					
Finland 1997	2/13	0/13		0.3	5.00 [0.26, 95.02]
Italy 1993	7/565	9/477		6.4	0.66 [0.25, 1.75]
Russia 1993	1/31	1/33		0.6	1.06 [0.07, 16.29]
Subtotal (95% CI)	609	523		7.3	0.89 [0.38, 2.05]
Total events: 10 (Antiplatelet agents), 10 (Control)					
Test for heterogeneity chi-square=1.70 df=2 p=0.43 I² =0.0%					
Test for overall effect z=0.29 p=0.8					
Total (95% CI)	12567	12415		100.0	1.10 [0.89, 1.37]
Total events: 172 (Antiplatelet agents), 150 (Control)					
Test for heterogeneity chi-square=15.77 df=13 p=0.26 I² =17.6%					
Test for overall effect z=0.89 p=0.4					



Analysis 03.04. Comparison 03 Antiplatelet agents versus placebo/no treatment for primary prevention (subgrouped by use of placebo), Outcome 04 Preterm birth

Review: Antiplatelet agents for preventing pre-eclampsia and its complications

Comparison: 03 Antiplatelet agents versus placebo/no treatment for primary prevention (subgrouped by use of placebo)

Outcome: 04 Preterm birth

Study	Antiplatelet agents n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 Placebo					
Australia 1996	3/27	2/25		0.1	1.39 [0.25, 7.64]
Australia 1996a	3/52	5/50		0.2	0.58 [0.15, 2.29]
Australia 1997	6/58	8/50		0.4	0.65 [0.24, 1.74]
Austria 1992	1/22	1/19		0.0	0.86 [0.06, 12.89]
Barbados 1998	74/1819	76/1822		3.3	0.98 [0.71, 1.33]
Brazil 1996	106/476	129/494		5.6	0.85 [0.68, 1.07]
China 1996	4/40	6/44		0.3	0.73 [0.22, 2.41]
CLASP 1994	686/3992	761/3982		33.4	0.90 [0.82, 0.99]
ERASME 2003	120/1645	108/1660		4.7	1.12 [0.87, 1.44]
Israel 1989	2/34	6/32		0.3	0.31 [0.07, 1.44]
Israel 1994	11/24	15/23		0.7	0.70 [0.41, 1.19]
Italy 1989	2/17	5/16		0.2	0.38 [0.08, 1.67]
Jamaica 1998	129/3023	125/3026		5.5	1.03 [0.81, 1.31]
Japan 1999	6/20	11/20		0.5	0.55 [0.25, 1.19]
Netherlands 1986	0/23	4/23		0.2	0.11 [0.01, 1.95]
Spain 1997	1/50	5/50		0.2	0.20 [0.02, 1.65]
× UK 1992	0/10	0/8		0.0	Not estimable
UK 1995	1/58	1/60		0.0	1.03 [0.07, 16.15]
UK+others 2003	67/276	75/278		3.3	0.90 [0.68, 1.20]
USA 1993	26/302	30/302		1.3	0.87 [0.53, 1.43]
USA 1993a	157/1485	147/1500		6.4	1.08 [0.87, 1.34]
USA 1998	502/1254	532/1249		23.4	0.94 [0.86, 1.03]
Zimbabwe 1998	21/113	30/117		1.3	0.72 [0.44, 1.19]
Subtotal (95% CI)	14820	14850		91.3	0.93 [0.88, 0.98]
Total events: 1928 (Antiplatelet agents), 2082 (Control)					
Test for heterogeneity chi-square=18.78 df=21 p=0.60 I² =0.0%					

(*Continued . . .*)

(. . . *Continued*)

Study	Antiplatelet agents n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Test for overall effect z=2.71 p=0.007					
02 No placebo					
Australia 1995a	2/9	7/11		0.3	0.35 [0.10, 1.28]
China 1999	4/118	6/75		0.3	0.42 [0.12, 1.45]
Egypt 2005	2/73	9/63		0.4	0.19 [0.04, 0.85]
Finland 1997	1/13	1/13		0.0	1.00 [0.07, 14.34]
Italy 1993	171/565	154/477		7.3	0.94 [0.78, 1.12]
Russia 1993	5/31	6/33		0.3	0.89 [0.30, 2.61]
Subtotal (95% CI)	809	672		8.7	0.86 [0.73, 1.02]
Total events: 185 (Antiplatelet agents), 183 (Control)					
Test for heterogeneity chi-square=7.86 df=5 p=0.16 I^2 =36.4%					
Test for overall effect z=1.69 p=0.09					
Total (95% CI)	15629	15522		100.0	0.92 [0.87, 0.97]
Total events: 2113 (Antiplatelet agents), 2265 (Control)					
Test for heterogeneity chi-square=26.75 df=27 p=0.48 I^2 =0.0%					
Test for overall effect z=3.07 p=0.002					

Analysis 03.05. Comparison 03 Antiplatelet agents versus placebo/no treatment for primary prevention (subgrouped by use of placebo), Outcome 05 Fetal, neonatal or infant death

Review: Antiplatelet agents for preventing pre-eclampsia and its complications

Comparison: 03 Antiplatelet agents versus placebo/no treatment for primary prevention (subgrouped by use of placebo)

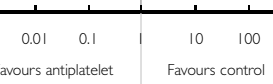
Outcome: 05 Fetal, neonatal or infant death

Study	Antiplatelet agents n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 Placebo					
× Australia 1988	0/22	0/24		0.0	Not estimable
× Australia 1996	0/27	0/25		0.0	Not estimable
Australia 1997	4/58	2/50		0.4	1.72 [0.33, 9.02]
Austria 1992	0/22	1/19		0.3	0.29 [0.01, 6.72]
Barbados 1998	44/1834	38/1841		7.9	1.16 [0.76, 1.79]
Brazil 1996	35/482	30/503		6.1	1.22 [0.76, 1.95]
× China 1996	0/40	0/44		0.0	Not estimable
CLASP 1994	77/4123	97/4134		20.3	0.80 [0.59, 1.07]
EPREDA 1991	7/156	6/73		1.7	0.55 [0.19, 1.57]
ERASME 2003	12/1645	11/1660		2.3	1.10 [0.49, 2.49]
Finland 1993	2/97	0/100		0.1	5.15 [0.25, 105.98]
Finland 1997a	10/33	10/33		2.1	1.00 [0.48, 2.08]
× Finland 2002	0/43	0/43		0.0	Not estimable
× Israel 1989	0/34	0/32		0.0	Not estimable
Israel 1994	2/48	2/48		0.4	1.00 [0.15, 6.81]
Italy 1989	0/17	1/16		0.3	0.31 [0.01, 7.21]
Jamaica 1998	86/3023	103/3026		21.5	0.84 [0.63, 1.11]
Netherlands 1986	1/23	1/23		0.2	1.00 [0.07, 15.04]
× Netherlands 1989	0/5	0/5		0.0	Not estimable
× Netherlands 1991a	0/17	0/18		0.0	Not estimable
× Spain 1997	0/50	0/50		0.0	Not estimable
UK 1990	1/48	3/52		0.6	0.36 [0.04, 3.35]
UK 1992b	0/10	1/16		0.2	0.52 [0.02, 11.54]
× UK 1995	0/58	0/60		0.0	Not estimable
UK+others 2003	7/276	4/278		0.8	1.76 [0.52, 5.95]

(*Continued . . .*)

(. . . *Continued*)

Study	Antiplatelet agents n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
USA 1993	1/302	1/302		0.2	1.00 [0.06, 15.91]
USA 1993a	22/1505	14/1519		2.9	1.59 [0.81, 3.09]
USA 1994	1/24	1/25		0.2	1.04 [0.07, 15.73]
USA 1998	72/1612	93/1604		19.5	0.77 [0.57, 1.04]
Zimbabwe 1998	5/114	13/122		2.6	0.41 [0.15, 1.12]
Subtotal (95% CI)	15748	15745		91.0	0.90 [0.78, 1.02]
Total events: 389 (Antiplatelet agents), 432 (Control)					
Test for heterogeneity chi-square=15.99 df=20 p=0.72 I^2 =0.0%					
Test for overall effect z=1.61 p=0.1					
02 No placebo					
Australia 1995a	0/9	2/11		0.5	0.24 [0.01, 4.44]
Brazil 1992a	0/26	2/26		0.5	0.20 [0.01, 3.97]
Finland 1997	0/13	1/13		0.3	0.33 [0.01, 7.50]
France 1985	0/48	5/45		1.2	0.09 [0.00, 1.50]
France 1990	2/46	2/45		0.4	0.98 [0.14, 6.65]
Italy 1993	18/629	19/532		4.3	0.80 [0.42, 1.51]
Italy 2004	1/16	2/19		0.4	0.59 [0.06, 5.96]
Russia 1993	1/31	5/33		1.0	0.21 [0.03, 1.72]
S Africa 1988	2/30	1/14		0.3	0.93 [0.09, 9.45]
USA 1997	1/11	0/8		0.1	2.25 [0.10, 49.04]
Subtotal (95% CI)	859	746		9.0	0.58 [0.36, 0.94]
Total events: 25 (Antiplatelet agents), 39 (Control)					
Test for heterogeneity chi-square=5.73 df=9 p=0.77 I^2 =0.0%					
Test for overall effect z=2.20 p=0.03					
Total (95% CI)	16607	16491		100.0	0.87 [0.76, 0.99]
Total events: 414 (Antiplatelet agents), 471 (Control)					
Test for heterogeneity chi-square=23.03 df=30 p=0.81 I^2 =0.0%					
Test for overall effect z=2.16 p=0.03					



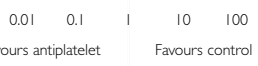
Analysis 03.06. Comparison 03 Antiplatelet agents versus placebo/no treatment for primary prevention (subgrouped by use of placebo), Outcome 06 Small-for-gestational age

Review: Antiplatelet agents for preventing pre-eclampsia and its complications

Comparison: 03 Antiplatelet agents versus placebo/no treatment for primary prevention (subgrouped by use of placebo)

Outcome: 06 Small-for-gestational age

Study	Antiplatelet agents n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 Placebo					
Australia 1995	22/29	21/30		1.9	1.08 [0.79, 1.48]
Australia 1996	4/27	5/25		0.5	0.74 [0.22, 2.45]
Australia 1996a	14/52	11/50		1.0	1.22 [0.62, 2.43]
Austria 1992	1/22	2/19		0.2	0.43 [0.04, 4.40]
Brazil 1996	41/482	51/503		4.6	0.84 [0.57, 1.24]
China 1996	3/40	12/44		1.0	0.28 [0.08, 0.90]
CLASP 1994	244/4123	272/4134		24.9	0.90 [0.76, 1.06]
EPREDA 1991	20/156	19/73		2.4	0.49 [0.28, 0.86]
ERASME 2003	199/1645	189/1660		17.3	1.06 [0.88, 1.28]
Finland 1993	4/97	9/100		0.8	0.46 [0.15, 1.44]
Finland 1997a	3/23	3/23		0.3	1.00 [0.22, 4.45]
Finland 2002	1/43	3/43		0.3	0.33 [0.04, 3.08]
Israel 1989	2/34	6/32		0.6	0.31 [0.07, 1.44]
Israel 1994	6/48	11/48		1.0	0.55 [0.22, 1.36]
Japan 1999	6/20	12/20		1.1	0.50 [0.23, 1.07]
Netherlands 1986	0/23	3/23		0.3	0.14 [0.01, 2.62]
Netherlands 1989	0/5	2/5		0.2	0.20 [0.01, 3.35]
Spain 1997	1/50	2/50		0.2	0.50 [0.05, 5.34]
Spain 1999	6/124	14/116		1.3	0.40 [0.16, 1.01]
UK 1990	7/48	7/52		0.6	1.08 [0.41, 2.86]
× UK 1992	0/10	0/8		0.0	Not estimable
UK 1995	3/58	3/60		0.3	1.03 [0.22, 4.92]
UK+others 2003	61/276	68/278		6.2	0.90 [0.67, 1.22]
USA 1993	17/302	19/302		1.7	0.89 [0.47, 1.69]
USA 1993a	69/1505	58/1519		5.3	1.20 [0.85, 1.69]



(*Continued . . .*)

(. . . *Continued*)

Study	Antiplatelet agents n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
USA 1994	0/24	1/25		0.1	0.35 [0.01, 8.12]
USA 1998	133/1606	113/1590		10.4	1.17 [0.92, 1.48]
Zimbabwe 1998	18/114	20/122		1.8	0.96 [0.54, 1.73]
Subtotal (95% CI)	10986	10954		86.4	0.94 [0.86, 1.02]
Total events: 885 (Antiplatelet agents), 936 (Control)					
Test for heterogeneity chi-square=33.67 df=26 p=0.14 I^2 =22.8%					
Test for overall effect z=1.48 p=0.1					
02 No placebo					
Australia 1995a	2/9	2/9		0.2	1.00 [0.18, 5.63]
China 1999	12/118	7/75		0.8	1.09 [0.45, 2.64]
Egypt 2005	13/73	21/63		2.1	0.53 [0.29, 0.98]
Finland 1997	2/13	1/13		0.1	2.00 [0.21, 19.44]
France 1985	0/48	4/41		0.4	0.10 [0.01, 1.72]
Italy 1993	117/616	95/538		9.3	1.08 [0.84, 1.37]
Russia 1993	2/31	6/33		0.5	0.35 [0.08, 1.63]
USA 1997	0/10	1/8		0.2	0.27 [0.01, 5.92]
Subtotal (95% CI)	918	780		13.6	0.93 [0.75, 1.15]
Total events: 148 (Antiplatelet agents), 137 (Control)					
Test for heterogeneity chi-square=9.69 df=7 p=0.21 I^2 =27.8%					
Test for overall effect z=0.68 p=0.5					
Total (95% CI)	11904	11734		100.0	0.94 [0.86, 1.01]
Total events: 1033 (Antiplatelet agents), 1073 (Control)					
Test for heterogeneity chi-square=43.35 df=34 p=0.13 I^2 =21.6%					
Test for overall effect z=1.62 p=0.1					

Analysis 04.01. Comparison 04 Antiplatet agents versus placebo/no treatment for primary prevention (subgrouped by dose), Outcome 01 Gestational hypertension

Review: Antiplatelet agents for preventing pre-eclampsia and its complications

Comparison: 04 Antiplatet agents versus placebo/no treatment for primary prevention (subgrouped by dose)

Outcome: 01 Gestational hypertension

Study	Antiplatelet agents n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 75 mg or less aspirin					
Australia 1996	4/27	3/25		0.4	1.23 [0.31, 4.98]
Barbados 1998	162/1819	172/1822		21.0	0.94 [0.77, 1.16]
Brazil 1996	68/476	56/494		6.7	1.26 [0.91, 1.75]
Brazil 1992a	4/26	14/26		1.7	0.29 [0.11, 0.75]
China 1996	4/40	12/44		1.4	0.37 [0.13, 1.05]
China 1996a	7/48	23/56		2.6	0.36 [0.17, 0.75]
Finland 1993	12/97	14/100		1.7	0.88 [0.43, 1.81]
Finland 1997	2/13	1/13		0.1	2.00 [0.21, 19.44]
Finland 2002	5/43	16/43		2.0	0.31 [0.13, 0.78]
Italy 1989	0/17	3/16		0.4	0.13 [0.01, 2.42]
Italy 1993	69/497	42/423		5.6	1.40 [0.97, 2.01]
Jamaica 1998	338/3023	332/3026		40.6	1.02 [0.88, 1.18]
Netherlands 1986	1/23	3/23		0.4	0.33 [0.04, 2.97]
Netherlands 1989	0/5	3/5		0.4	0.14 [0.01, 2.21]
UK 1990	6/48	13/52		1.5	0.50 [0.21, 1.21]
× UK 1992	0/10	0/8		0.0	Not estimable
UK 1995	2/58	4/60		0.5	0.52 [0.10, 2.72]
USA 1993	19/302	17/302		2.1	1.12 [0.59, 2.11]
USA 1993a	100/1485	89/1500		10.8	1.13 [0.86, 1.50]
Subtotal (95% CI)	8057	8038		100.0	0.98 [0.90, 1.08]
Total events: 803 (Antiplatelet agents), 817 (Control)					
Test for heterogeneity chi-square=38.23 df=17 p=0.002 I^2 =55.5%					
Test for overall effect z=0.40 p=0.7					
02 > 75 mg aspirin					
Australia 1996a	8/52	7/50		9.1	1.10 [0.43, 2.81]
Austria 1992	0/22	4/19		6.1	0.10 [0.01, 1.69]
China 1999	22/118	18/75		28.0	0.78 [0.45, 1.35]

(*Continued . . .*)

(. . . *Continued*)

Study	Antiplatelet agents n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Colorado 1993	12/48	14/42		19.0	0.75 [0.39, 1.44]
Israel 1989	3/34	4/31		5.3	0.68 [0.17, 2.82]
Israel 1994	1/24	6/23		7.8	0.16 [0.02, 1.23]
Italy 2004	5/16	7/19		8.1	0.85 [0.33, 2.16]
Spain 1997	5/50	9/50		11.4	0.56 [0.20, 1.54]
Tanzania 1995	2/64	4/63		5.1	0.49 [0.09, 2.59]
Subtotal (95% CI)	428	372		100.0	0.67 [0.49, 0.92]
Total events: 58 (Antiplatelet agents), 73 (Control)					
Test for heterogeneity chi-square=5.61 df=8 p=0.69 I^2 =0.0%					
Test for overall effect z=2.51 p=0.01					
03 Aspirin > 75 mg + dipyridamole					
EPREDA 1991	35/156	25/73		53.3	0.66 [0.43, 1.01]
France 1985	19/48	22/45		35.6	0.81 [0.51, 1.28]
France 1990	4/46	7/45		11.1	0.56 [0.18, 1.78]
Subtotal (95% CI)	250	163		100.0	0.70 [0.51, 0.95]
Total events: 58 (Antiplatelet agents), 54 (Control)					
Test for heterogeneity chi-square=0.62 df=2 p=0.73 I^2 =0.0%					
Test for overall effect z=2.29 p=0.02					

Analysis 04.02. Comparison 04 Antiplatet agents versus placebo/no treatment for primary prevention (subgrouped by dose), Outcome 02 Proteinuric pre-eclampsia

Review: Antiplatelet agents for preventing pre-eclampsia and its complications

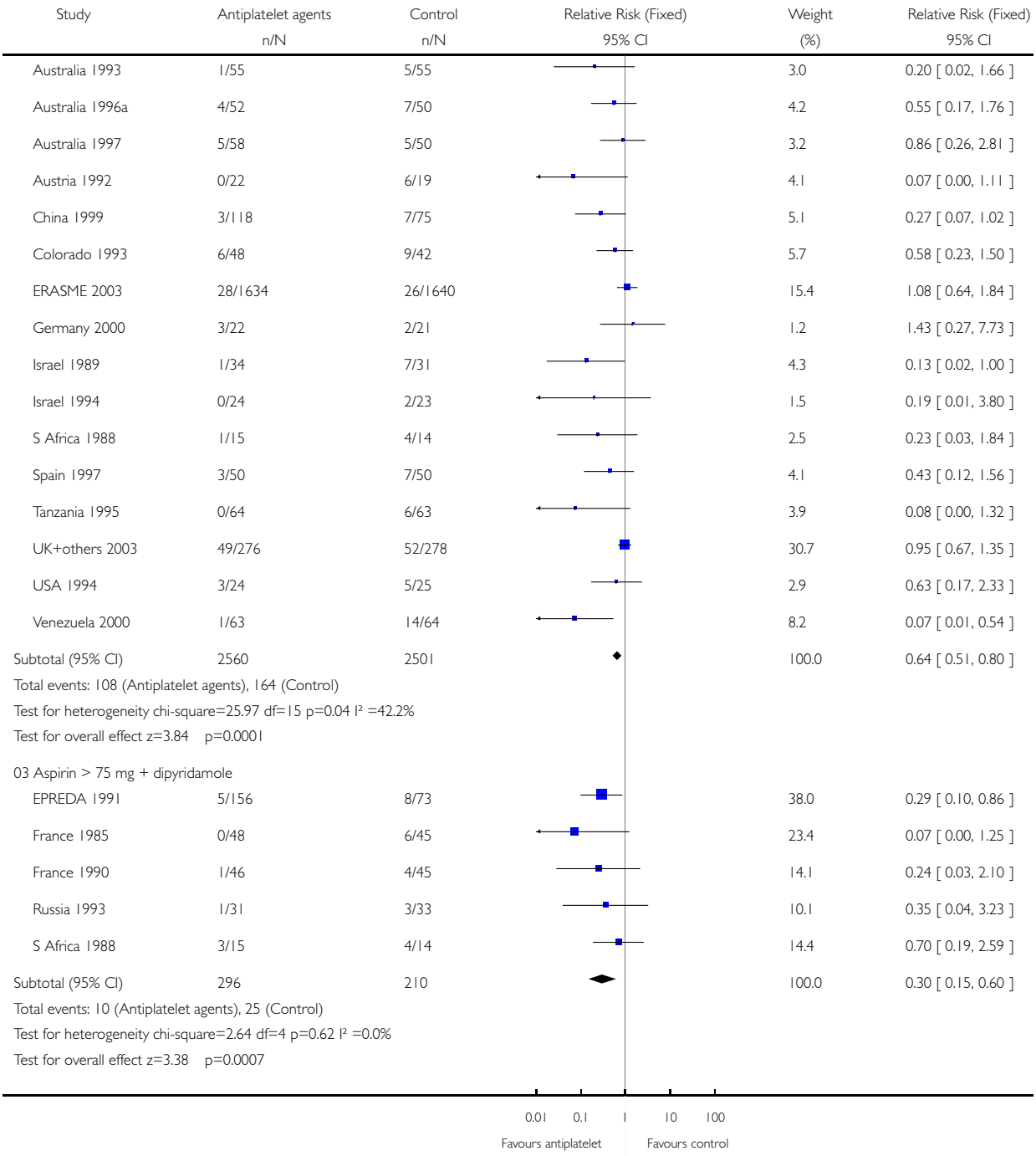
Comparison: 04 Antiplatet agents versus placebo/no treatment for primary prevention (subgrouped by dose)

Outcome: 02 Proteinuric pre-eclampsia

Study	Antiplatelet agents n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 75 mg or less aspirin					
Australia 1996	1/27	1/25		0.1	0.93 [0.06, 14.03]
Barbados 1998	40/1819	46/1822		4.2	0.87 [0.57, 1.32]
Brazil 1996	32/476	30/494		2.7	1.11 [0.68, 1.79]
China 1996	4/40	12/44		1.0	0.37 [0.13, 1.05]
CLASP 1994	267/3992	302/3982		27.7	0.88 [0.75, 1.03]
Egypt 2005	25/73	40/63		3.9	0.54 [0.37, 0.78]
Finland 1993	9/97	11/100		1.0	0.84 [0.37, 1.95]
Finland 1997	4/13	2/13		0.2	2.00 [0.44, 9.08]
Finland 1997a	1/23	3/23		0.3	0.33 [0.04, 2.97]
Finland 2002	2/43	10/43		0.9	0.20 [0.05, 0.86]
Italy 1993	12/497	9/423		0.9	1.13 [0.48, 2.67]
Italy 1999	18/103	21/104		1.9	0.87 [0.49, 1.53]
Jamaica 1998	215/3023	189/3026		17.3	1.14 [0.94, 1.38]
Netherlands 1986	0/23	7/23		0.7	0.07 [0.00, 1.10]
Netherlands 1989	0/5	1/5		0.1	0.33 [0.02, 6.65]
UK 1990	1/48	10/52		0.9	0.11 [0.01, 0.81]
UK 1995	5/58	7/60		0.6	0.74 [0.25, 2.20]
USA 1993	5/302	17/302		1.6	0.29 [0.11, 0.79]
USA 1993a	69/1485	94/1500		8.6	0.74 [0.55, 1.00]
USA 1998	231/1254	254/1249		23.3	0.91 [0.77, 1.06]
Zimbabwe 1998	17/113	23/117		2.1	0.77 [0.43, 1.35]
Subtotal (95% CI)	13514	13470		100.0	0.88 [0.81, 0.95]
Total events: 958 (Antiplatelet agents), 1089 (Control)					
Test for heterogeneity chi-square=37.94 df=20 p=0.009 I^2 =47.3%					
Test for overall effect z=3.15 p=0.002					
02 > 75 mg aspirin					
× Australia 1988	0/1	0/1		0.0	Not estimable

(*Continued . . .*)

(. . . *Continued*)



Analysis 04.03. Comparison 04 Antiplatet agents versus placebo/no treatment for primary prevention (subgrouped by dose), Outcome 03 Placental abruption

Review: Antiplatelet agents for preventing pre-eclampsia and its complications

Comparison: 04 Antiplatet agents versus placebo/no treatment for primary prevention (subgrouped by dose)

Outcome: 03 Placental abruption

Study	Antiplatelet agents n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 75 mg or less aspirin					
Australia 1996	1/27	2/25		1.6	0.46 [0.04, 4.80]
Barbados 1998	9/1819	14/1822		10.8	0.64 [0.28, 1.48]
Brazil 1996	5/476	7/494		5.3	0.74 [0.24, 2.32]
CLASP 1994	86/4659	71/4650		55.0	1.21 [0.89, 1.65]
Finland 1997	2/13	0/13		0.4	5.00 [0.26, 95.02]
Italy 1993	7/565	9/477		7.5	0.66 [0.25, 1.75]
UK 1995	2/58	1/60		0.8	2.07 [0.19, 22.20]
USA 1993a	11/1485	2/1500		1.5	5.56 [1.23, 25.02]
USA 1998	15/1247	22/1239		17.1	0.68 [0.35, 1.30]
Subtotal (95% CI)	10349	10280		100.0	1.07 [0.84, 1.35]
Total events: 138 (Antiplatelet agents), 128 (Control)					
Test for heterogeneity chi-square=11.69 df=8 p=0.17 I^2 =31.5%					
Test for overall effect z=0.53 p=0.6					
02 > 75 mg aspirin					
Australia 1997	3/58	1/50		6.7	2.59 [0.28, 24.08]
ERASME 2003	13/1623	9/1628		56.1	1.45 [0.62, 3.38]
× Israel 1994	0/24	0/23		0.0	Not estimable
Russia 1993	1/31	1/33		6.1	1.06 [0.07, 16.29]
× Spain 1997	0/50	0/50		0.0	Not estimable
UK+others 2003	10/276	5/278		31.1	2.01 [0.70, 5.82]
Subtotal (95% CI)	2062	2062		100.0	1.68 [0.91, 3.10]
Total events: 27 (Antiplatelet agents), 16 (Control)					
Test for heterogeneity chi-square=0.48 df=3 p=0.92 I^2 =0.0%					
Test for overall effect z=1.65 p=0.1					
03 > 75 mg aspirin + dipyridamole					
EPREDA 1991	7/156	6/73		89.4	0.55 [0.19, 1.57]
Russia 1993	1/31	1/33		10.6	1.06 [0.07, 16.29]
Subtotal (95% CI)	187	106		100.0	0.60 [0.23, 1.60]

(*Continued . . .*)

(. . . *Continued*)

Study	Antiplatelet agents n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Total events: 8 (Antiplatelet agents), 7 (Control)					
Test for heterogeneity chi-square=0.20 df=1 p=0.65 I^2 =0.0%					
Test for overall effect z=1.02 p=0.3					

Analysis 04.04. Comparison 04 Antiplatet agents versus placebo/no treatment for primary prevention (subgrouped by dose), Outcome 04 Preterm birth

Review: Antiplatelet agents for preventing pre-eclampsia and its complications

Comparison: 04 Antiplatet agents versus placebo/no treatment for primary prevention (subgrouped by dose)

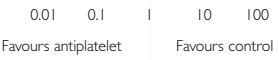
Outcome: 04 Preterm birth

Study	Antiplatelet agents n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 75 mg or less aspirin					
Australia 1996	3/27	2/25		0.1	1.39 [0.25, 7.64]
Barbados 1998	74/1819	76/1822		3.9	0.98 [0.71, 1.33]
Brazil 1996	106/476	129/494		6.5	0.85 [0.68, 1.07]
China 1996	4/40	6/44		0.3	0.73 [0.22, 2.41]
CLASP 1994	686/3992	761/3982		38.9	0.90 [0.82, 0.99]
Egypt 2005	2/73	9/63		0.5	0.19 [0.04, 0.85]
Finland 1997	1/13	1/13		0.1	1.00 [0.07, 14.34]
Italy 1989	2/17	5/16		0.3	0.38 [0.08, 1.67]
Italy 1993	117/565	94/477		5.2	1.05 [0.82, 1.34]
Jamaica 1998	129/3023	125/3026		6.4	1.03 [0.81, 1.31]
Netherlands 1986	0/23	4/23		0.2	0.11 [0.01, 1.95]
× UK 1992	0/10	0/8		0.0	Not estimable
UK 1995	1/58	1/60		0.1	1.03 [0.07, 16.15]
USA 1993	26/302	30/302		1.5	0.87 [0.53, 1.43]
USA 1993a	157/1485	147/1500		7.5	1.08 [0.87, 1.34]
USA 1998	502/1254	532/1249		27.2	0.94 [0.86, 1.03]
Zimbabwe 1998	21/113	30/117		1.5	0.72 [0.44, 1.19]

(*Continued* . . .)

(. . . *Continued*)

Study	Antiplatelet agents n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Subtotal (95% CI)	13290	13221		100.0	0.93 [0.88, 0.98]
Total events: 1831 (Antiplatelet agents), 1952 (Control)					
Test for heterogeneity chi-square=14.02 df=15 p=0.52 I^2 =0.0%					
Test for overall effect z=2.52 p=0.01					
02 > 75 mg aspirin					
× Australia 1988	0/1	0/1		0.0	Not estimable
Australia 1996a	3/52	5/50		2.2	0.58 [0.15, 2.29]
Australia 1997	6/58	8/50		3.6	0.65 [0.24, 1.74]
Austria 1992	1/22	1/19		0.5	0.86 [0.06, 12.89]
China 1999	4/118	6/75		3.1	0.42 [0.12, 1.45]
ERASME 2003	120/1645	108/1660		45.4	1.12 [0.87, 1.44]
Israel 1989	2/34	6/32		2.6	0.31 [0.07, 1.44]
Israel 1994	11/24	15/23		6.5	0.70 [0.41, 1.19]
Russia 1993	5/31	6/33		2.5	0.89 [0.30, 2.61]
Spain 1997	1/50	5/50		2.1	0.20 [0.02, 1.65]
UK+others 2003	67/276	75/278		31.6	0.90 [0.68, 1.20]
Subtotal (95% CI)	2311	2271		100.0	0.93 [0.78, 1.10]
Total events: 220 (Antiplatelet agents), 235 (Control)					
Test for heterogeneity chi-square=9.80 df=9 p=0.37 I^2 =8.2%					
Test for overall effect z=0.89 p=0.4					
03 Aspirin > 75 mg plus dipyridamole					
Russia 1993	5/31	6/33		100.0	0.89 [0.30, 2.61]
Subtotal (95% CI)	31	33		100.0	0.89 [0.30, 2.61]
Total events: 5 (Antiplatelet agents), 6 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.22 p=0.8					



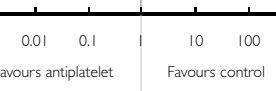
Analysis 04.05. Comparison 04 Antiplatet agents versus placebo/no treatment for primary prevention (subgrouped by dose), Outcome 05 Fetal, neonatal or infant death

Review: Antiplatelet agents for preventing pre-eclampsia and its complications

Comparison: 04 Antiplatet agents versus placebo/no treatment for primary prevention (subgrouped by dose)

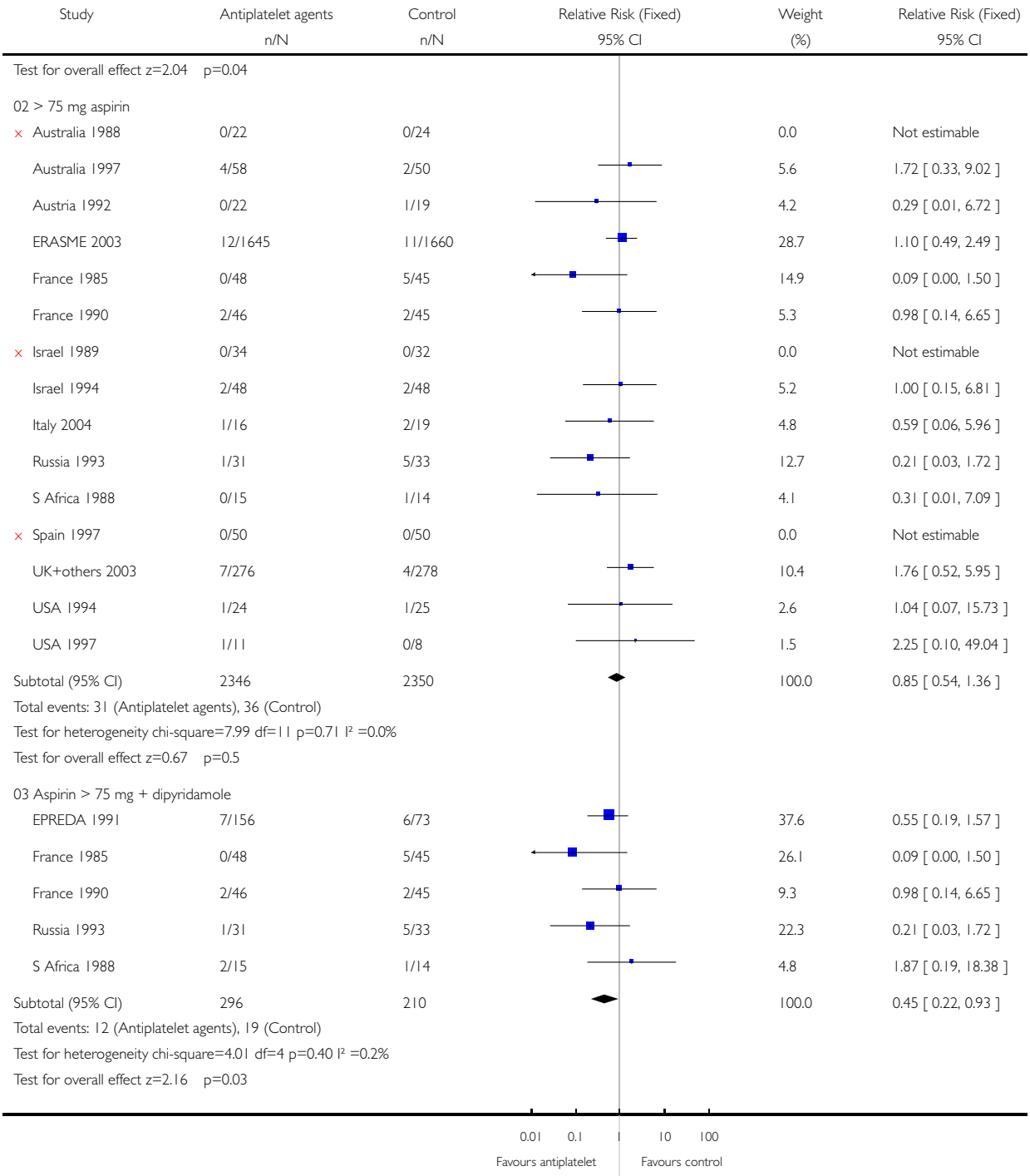
Outcome: 05 Fetal, neonatal or infant death

Study	Antiplatelet agents n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 75 mg or less aspirin					
× Australia 1996	0/27	0/25		0.0	Not estimable
Barbados 1998	44/1834	38/1841		8.7	1.16 [0.76, 1.79]
Brazil 1996	35/482	30/503		6.8	1.22 [0.76, 1.95]
Brazil 1992a	0/26	2/26		0.6	0.20 [0.01, 3.97]
China 1996	0/40	4/44		1.0	0.12 [0.01, 2.20]
CLASP 1994	77/4123	97/4134		22.3	0.80 [0.59, 1.07]
Finland 1993	2/97	0/100		0.1	5.15 [0.25, 105.98]
Finland 1997	0/13	1/13		0.3	0.33 [0.01, 7.50]
Finland 1997a	10/33	10/33		2.3	1.00 [0.48, 2.08]
× Finland 2002	0/43	0/43		0.0	Not estimable
Italy 1989	0/17	1/16		0.4	0.31 [0.01, 7.21]
Italy 1993	18/629	19/532		4.7	0.80 [0.42, 1.51]
Jamaica 1998	86/3023	103/3026		23.7	0.84 [0.63, 1.11]
Netherlands 1986	1/23	1/23		0.2	1.00 [0.07, 15.04]
× Netherlands 1989	0/5	0/5		0.0	Not estimable
× Netherlands 1991a	0/17	0/18		0.0	Not estimable
UK 1990	1/48	3/52		0.7	0.36 [0.04, 3.35]
UK 1992b	0/10	1/16		0.3	0.52 [0.02, 11.54]
× UK 1995	0/58	0/60		0.0	Not estimable
USA 1993	1/302	1/302		0.2	1.00 [0.06, 15.91]
USA 1993a	22/1505	14/1519		3.2	1.59 [0.81, 3.09]
USA 1998	72/1612	93/1604		21.5	0.77 [0.57, 1.04]
Zimbabwe 1998	5/114	13/122		2.9	0.41 [0.15, 1.12]
Subtotal (95% CI)	14081	14057		100.0	0.87 [0.76, 0.99]
Total events: 374 (Antiplatelet agents), 431 (Control)					
Test for heterogeneity chi-square=15.77 df=17 p=0.54 I^2 =0.0%					



(*Continued . . .*)

(... *Continued*)



Analysis 04.06. Comparison 04 Antiplatet agents versus placebo/no treatment for primary prevention (subgrouped by dose), Outcome 06 Small-for-gestational age

Review: Antiplatelet agents for preventing pre-eclampsia and its complications

Comparison: 04 Antiplatet agents versus placebo/no treatment for primary prevention (subgrouped by dose)

Outcome: 06 Small-for-gestational age

Study	Antiplatelet agents n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 75 mg or less aspirin					
Australia 1996	4/27	5/25		0.8	0.74 [0.22, 2.45]
Brazil 1996	41/482	51/503		7.2	0.84 [0.57, 1.24]
China 1996	3/40	12/44		1.7	0.28 [0.08, 0.90]
CLASP 1994	244/4123	272/4134		39.3	0.90 [0.76, 1.06]
Egypt 2005	13/73	21/63		3.3	0.53 [0.29, 0.98]
Finland 1993	4/97	9/100		1.3	0.46 [0.15, 1.44]
Finland 1997	2/13	1/13		0.1	2.00 [0.21, 19.44]
Finland 1997a	3/23	3/23		0.4	1.00 [0.22, 4.45]
Finland 2002	1/43	3/43		0.4	0.33 [0.04, 3.08]
Italy 1993	67/616	54/518		8.5	1.04 [0.74, 1.46]
Netherlands 1986	0/23	3/23		0.5	0.14 [0.01, 2.62]
Netherlands 1989	0/5	2/5		0.4	0.20 [0.01, 3.35]
UK 1990	7/48	7/52		1.0	1.08 [0.41, 2.86]
× UK 1992	0/10	0/8		0.0	Not estimable
UK 1995	3/58	3/60		0.4	1.03 [0.22, 4.92]
USA 1993	17/302	19/302		2.8	0.89 [0.47, 1.69]
USA 1993a	69/1505	88/1519		12.7	0.79 [0.58, 1.08]
USA 1998	133/1606	113/1590		16.4	1.17 [0.92, 1.48]
Zimbabwe 1998	18/114	20/122		2.8	0.96 [0.54, 1.73]
Subtotal (95% CI)	9208	9147		100.0	0.91 [0.82, 1.00]
Total events: 629 (Antiplatelet agents), 686 (Control)					
Test for heterogeneity chi-square=18.14 df=17 p=0.38 I^2 =6.3%					
Test for overall effect z=1.88 p=0.06					
02 > 75 mg aspirin					
Australia 1995	22/39	21/30		6.8	0.81 [0.56, 1.16]
Australia 1996a	14/52	11/50		3.2	1.22 [0.62, 2.43]
Austria 1992	1/22	2/19		0.6	0.43 [0.04, 4.40]

(*Continued . . .*)

(. . . *Continued*)

Study	Antiplatelet agents n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
China 1999	12/118	7/75		2.5	1.09 [0.45, 2.64]
ERASME 2003	199/1645	189/1660		53.9	1.06 [0.88, 1.28]
France 1985	0/48	4/41		1.4	0.10 [0.01, 1.72]
Israel 1989	2/34	6/32		1.8	0.31 [0.07, 1.44]
Israel 1994	6/48	11/48		3.2	0.55 [0.22, 1.36]
Russia 1993	2/31	6/33		1.7	0.35 [0.08, 1.63]
Spain 1997	1/50	2/50		0.6	0.50 [0.05, 5.34]
Spain 1999	6/124	14/116		4.1	0.40 [0.16, 1.01]
UK+others 2003	61/276	68/278		19.4	0.90 [0.67, 1.22]
USA 1994	0/24	1/25		0.4	0.35 [0.01, 8.12]
USA 1997	0/10	1/8		0.5	0.27 [0.01, 5.92]
Subtotal (95% CI)	2521	2465		100.0	0.92 [0.81, 1.06]
Total events: 326 (Antiplatelet agents), 343 (Control)					
Test for heterogeneity chi-square=15.38 df=13 p=0.28 I^2 =15.5%					
Test for overall effect z=1.13 p=0.3					
03 Aspirin > 75 mg + dipyridamole					
EPREDA 1991	20/156	19/73		70.8	0.49 [0.28, 0.86]
France 1985	0/48	4/41		13.3	0.10 [0.01, 1.72]
Russia 1993	2/31	6/33		15.9	0.35 [0.08, 1.63]
Subtotal (95% CI)	235	147		100.0	0.42 [0.25, 0.70]
Total events: 22 (Antiplatelet agents), 29 (Control)					
Test for heterogeneity chi-square=1.38 df=2 p=0.50 I^2 =0.0%					
Test for overall effect z=3.29 p=0.001					

Analysis 05.01. Comparison 05 Antiplatelet agents versus placebo/no antiplatelet for women with gestational hypertension, Outcome 01 Proteinuric pre-eclampsia

Review: Antiplatelet agents for preventing pre-eclampsia and its complications

Comparison: 05 Antiplatelet agents versus placebo/no antiplatelet for women with gestational hypertension

Outcome: 01 Proteinuric pre-eclampsia

Study	Antiplatelet agents n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
CLASP 1994	46/667	50/668		41.3	0.92 [0.63, 1.36]
India 1994	5/41	26/44		20.7	0.21 [0.09, 0.49]
India 1999	14/79	36/81		29.4	0.40 [0.23, 0.68]
Israel 1990	6/23	6/24		4.9	1.04 [0.39, 2.77]
UK 1992	0/8	4/8		3.7	0.11 [0.01, 1.78]
Total (95% CI)	818	825		100.0	0.60 [0.45, 0.78]

Total events: 71 (Antiplatelet agents), 122 (Control)

Test for heterogeneity chi-square=15.63 df=4 p=0.004 I^2 =74.4%

Test for overall effect z=3.77 p=0.0002

Analysis 05.02. Comparison 05 Antiplatelet agents versus placebo/no antiplatelet for women with gestational hypertension, Outcome 02 Eclampsia

Review: Antiplatelet agents for preventing pre-eclampsia and its complications

Comparison: 05 Antiplatelet agents versus placebo/no antiplatelet for women with gestational hypertension

Outcome: 02 Eclampsia

Study	Antiplatelet agents n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
India 1993	0/50	1/50		37.8	0.33 [0.01, 7.99]
× India 1994	0/46	0/48		0.0	Not estimable
India 1999	0/79	2/81		62.2	0.21 [0.01, 4.20]
Total (95% CI)	175	179		100.0	0.25 [0.03, 2.24]

Total events: 0 (Antiplatelet agents), 3 (Control)

Test for heterogeneity chi-square=0.05 df=1 p=0.83 I^2 =0.0%

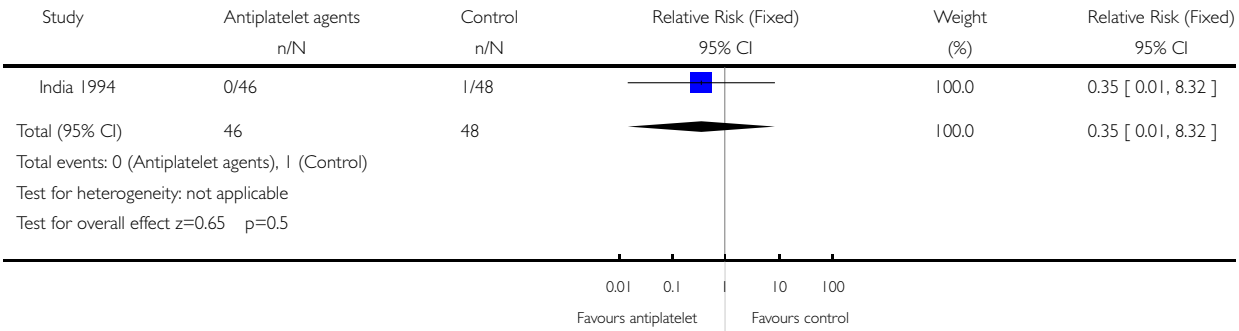
Test for overall effect z=1.23 p=0.2

Analysis 05.03. Comparison 05 Antiplatelet agents versus placebo/no antiplatelet for women with gestational hypertension, Outcome 03 Placental abruption

Review: Antiplatelet agents for preventing pre-eclampsia and its complications

Comparison: 05 Antiplatelet agents versus placebo/no antiplatelet for women with gestational hypertension

Outcome: 03 Placental abruption

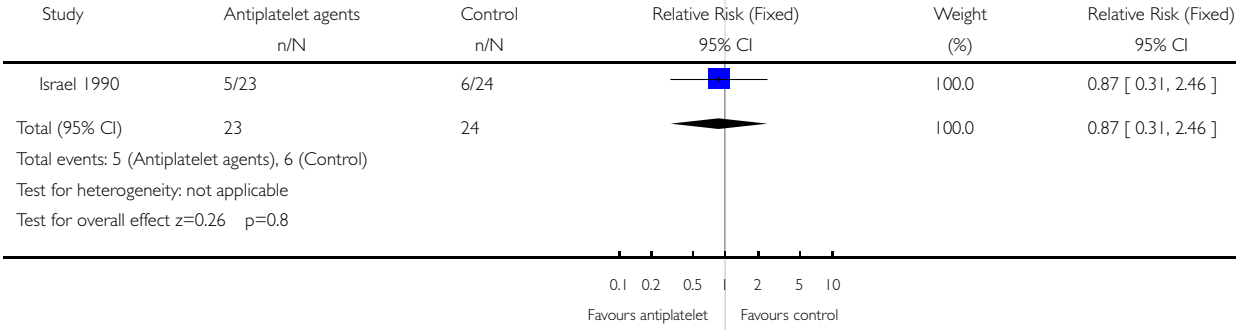


Analysis 05.04. Comparison 05 Antiplatelet agents versus placebo/no antiplatelet for women with gestational hypertension, Outcome 04 Caesarean section

Review: Antiplatelet agents for preventing pre-eclampsia and its complications

Comparison: 05 Antiplatelet agents versus placebo/no antiplatelet for women with gestational hypertension

Outcome: 04 Caesarean section



Analysis 05.05. Comparison 05 Antiplatelet agents versus placebo/no antiplatelet for women with gestational hypertension, Outcome 05 Preterm birth

Review: Antiplatelet agents for preventing pre-eclampsia and its complications

Comparison: 05 Antiplatelet agents versus placebo/no antiplatelet for women with gestational hypertension

Outcome: 05 Preterm birth

Study	Antiplatelet agents n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
CLASP 1994	234/667	272/668		99.8	0.86 [0.75, 0.99]
India 1993	1/50	0/50		0.2	3.00 [0.13, 71.92]
× UK 1992	0/8	0/8		0.0	Not estimable
Total (95% CI)	725	726		100.0	0.87 [0.75, 0.99]

Total events: 235 (Antiplatelet agents), 272 (Control)

Test for heterogeneity chi-square=0.59 df=1 p=0.44 I^2 =0.0%

Test for overall effect z=2.05 p=0.04

Analysis 05.06. Comparison 05 Antiplatelet agents versus placebo/no antiplatelet for women with gestational hypertension, Outcome 06 Fetal, neonatal or infant death

Review: Antiplatelet agents for preventing pre-eclampsia and its complications

Comparison: 05 Antiplatelet agents versus placebo/no antiplatelet for women with gestational hypertension

Outcome: 06 Fetal, neonatal or infant death

Study	Antiplatelet agents n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
CLASP 1994	52/687	39/687		68.0	1.33 [0.89, 1.99]
India 1993	0/50	5/50		9.6	0.09 [0.01, 1.60]
× India 1994	0/46	0/48		0.0	Not estimable
India 1999	6/79	13/81		22.4	0.47 [0.19, 1.18]
Total (95% CI)	862	866		100.0	1.02 [0.72, 1.45]

Total events: 58 (Antiplatelet agents), 57 (Control)

Test for heterogeneity chi-square=7.13 df=2 p=0.03 I^2 =72.0%

Test for overall effect z=0.12 p=0.9

Analysis 05.07. Comparison 05 Antiplatelet agents versus placebo/no antiplatelet for women with gestational hypertension, Outcome 07 Small-for-gestational age

Review: Antiplatelet agents for preventing pre-eclampsia and its complications

Comparison: 05 Antiplatelet agents versus placebo/no antiplatelet for women with gestational hypertension

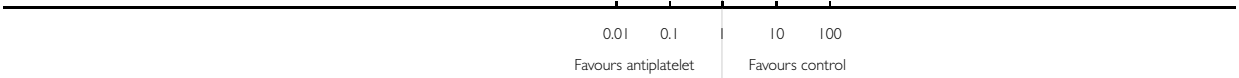
Outcome: 07 Small-for-gestational age

Study	Antiplatelet agents n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
India 1999	16/79	29/81		58.6	0.57 [0.33, 0.96]
Italy 1993	20/85	19/83		39.3	1.03 [0.59, 1.78]
UK 1992	1/8	1/8		2.0	1.00 [0.07, 13.37]
Total (95% CI)	172	172		100.0	0.76 [0.52, 1.10]

Total events: 37 (Antiplatelet agents), 49 (Control)

Test for heterogeneity chi-square=2.41 df=2 p=0.30 I^2 =17.0%

Test for overall effect z=1.47 p=0.1



Analysis 05.08. Comparison 05 Antiplatelet agents versus placebo/no antiplatelet for women with gestational hypertension, Outcome 08 Birthweight < 2500 g

Review: Antiplatelet agents for preventing pre-eclampsia and its complications

Comparison: 05 Antiplatelet agents versus placebo/no antiplatelet for women with gestational hypertension

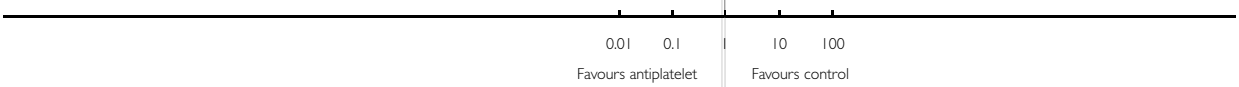
Outcome: 08 Birthweight < 2500 g

Study	Antiplatelet agents n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
India 1993	4/50	17/50		100.0	0.24 [0.09, 0.65]
Total (95% CI)	50	50		100.0	0.24 [0.09, 0.65]

Total events: 4 (Antiplatelet agents), 17 (Control)

Test for heterogeneity: not applicable

Test for overall effect z=2.79 p=0.005



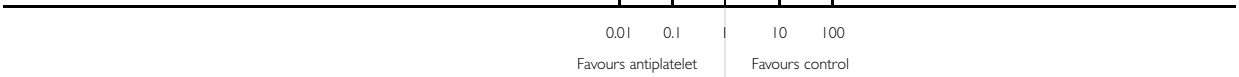
Analysis 05.09. Comparison 05 Antiplatelet agents versus placebo/no antiplatelet for women with gestational hypertension, Outcome 09 Admission to a special care baby unit

Review: Antiplatelet agents for preventing pre-eclampsia and its complications

Comparison: 05 Antiplatelet agents versus placebo/no antiplatelet for women with gestational hypertension

Outcome: 09 Admission to a special care baby unit

Study	Antiplatelet agents n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
India 1994	1/46	2/48		100.0	0.52 [0.05, 5.56]
Total (95% CI)	46	48		100.0	0.52 [0.05, 5.56]
Total events: 1 (Antiplatelet agents), 2 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.54 p=0.6					



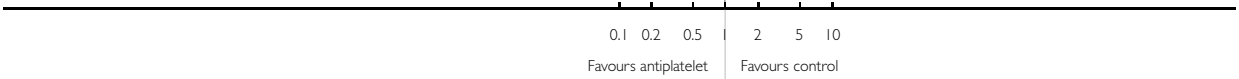
Analysis 05.10. Comparison 05 Antiplatelet agents versus placebo/no antiplatelet for women with gestational hypertension, Outcome 10 Neonatal haemorrhagic complications

Review: Antiplatelet agents for preventing pre-eclampsia and its complications

Comparison: 05 Antiplatelet agents versus placebo/no antiplatelet for women with gestational hypertension

Outcome: 10 Neonatal haemorrhagic complications

Study	Antiplatelet agents n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
× India 1994	0/46	0/48		0.0	Not estimable
Total (95% CI)	46	48		0.0	Not estimable
Total events: 0 (Antiplatelet agents), 0 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					



Analysis 05.11. Comparison 05 Antiplatelet agents versus placebo/no antiplatelet for women with gestational hypertension, Outcome 11 Severe pre-eclampsia

Review: Antiplatelet agents for preventing pre-eclampsia and its complications

Comparison: 05 Antiplatelet agents versus placebo/no antiplatelet for women with gestational hypertension

Outcome: 11 Severe pre-eclampsia

Study	Antiplatelet agents n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
India 1994	6/46	19/48		100.0	0.33 [0.14, 0.75]
Total (95% CI)	46	48		100.0	0.33 [0.14, 0.75]

Total events: 6 (Antiplatelet agents), 19 (Control)

Test for heterogeneity: not applicable

Test for overall effect z=2.64 p=0.008