

Antiplatelet agents for prevention of pre-eclampsia: a meta-analysis of individual patient data



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Summary

Background Pre-eclampsia is a major cause of mortality and morbidity during pregnancy and childbirth. Antiplatelet agents, especially low-dose aspirin, might prevent or delay pre-eclampsia, and thereby improve outcome. Our aim was to assess the use of antiplatelet agents for the primary prevention of pre-eclampsia, and to explore which women are likely to benefit most.

Methods We did a meta-analysis of individual patient data from 32 217 women, and their 32 819 babies, recruited to 31 randomised trials of pre-eclampsia primary prevention.

Findings For women assigned to receive antiplatelet agents rather than control, the relative risk of developing pre-eclampsia was 0.90 (95% CI 0.84–0.97), of delivering before 34 weeks was 0.90 (0.83–0.98), and of having a pregnancy with a serious adverse outcome was 0.90 (0.85–0.96). Antiplatelet agents had no significant effect on the risk of death of the fetus or baby, having a small for gestational age infant, or bleeding events for either the women or their babies. No particular subgroup of women was substantially more or less likely to benefit from antiplatelet agents than any other.

Interpretation Antiplatelet agents during pregnancy are associated with moderate but consistent reductions in the relative risk of pre-eclampsia, of birth before 34 weeks' gestation, and of having a pregnancy with a serious adverse outcome.

Introduction

Pre-eclampsia is a multisystem disorder of pregnancy that is usually associated with hypertension and proteinuria. The condition complicates 2–8% of pregnancies,¹ and can lead to liver and renal problems, convulsions (eclampsia), and abnormalities of the clotting system. Since the condition adversely affects the placenta, risks for the baby include poor intrauterine growth and premature birth. Worldwide, 10–15% of the half million maternal deaths that occur every year are associated with hypertensive disorders of pregnancy, mainly pre-eclampsia and eclampsia;² 99% of these occur in low-resource countries.^{3,4}

The cause of pre-eclampsia remains unclear. Nevertheless, disordered trophoblast invasion of the maternal spiral arteries in early pregnancy is known to lead to underperfusion of the placenta and, ultimately, placental ischaemia and infarction.⁵ The resultant placental damage is thought to lead to activation of platelets and the clotting system^{6,7} and to an imbalance between prostacyclin, a vasodilator, and thromboxane, a vasoconstrictor and stimulant of platelet aggregation.^{8,9} The hypothesis that antiplatelet agents might prevent or delay pre-eclampsia has been widely tested in randomised trials. The optimism following early trials was later dashed by the results of larger studies.^{10–14} Although systematic reviews of aggregate data show modest reductions in the relative risk of pre-eclampsia, preterm birth, and baby death associated with antiplatelet agent use,¹⁵ controversy remains.^{16,17}

Recent enthusiasm that antioxidants—particularly the combination of vitamins C and E—might prevent

pre-eclampsia has been dampened, because once again the promising results of a small trial were not supported by subsequent larger studies.¹⁸ Although results of further trials are awaited, it now seems unlikely that antioxidants will offer major benefit for women at risk of pre-eclampsia. Thus, better understanding of the effects of antiplatelet agents currently offers the best potential for improving outcomes for women at risk of pre-eclampsia. The PARIS (Perinatal Antiplatelet Review of International Studies) Collaboration was formed to do a systematic review and meta-analysis based on individual patient data to assess the use of antiplatelet agents for the primary prevention of pre-eclampsia and to explore which women are most likely to benefit from such treatment.¹⁹

Methods

Search strategy and selection criteria

We searched the comprehensive register of trials developed and maintained by the Cochrane Pregnancy and Childbirth Review Group. Details of how this register is maintained are available elsewhere,²⁰ but it involves extensive searching of bibliographic databases such as Medline, the database of randomised controlled trials in the Cochrane Library, and searching relevant journals by hand. PARIS trialists were also asked if they knew of any further studies. The search was last updated in December, 2005.

Studies were included if they randomised women at risk of developing pre-eclampsia to receive one or more antiplatelet agents (eg, low-dose aspirin or dipyridamole) versus a placebo or no antiplatelet agent. To reduce the

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See [Comment](#) page 1765

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possibility of bias, quasirandom study designs—eg, those using alternate allocation—were excluded. Methods of treatment assignment and allocation concealment were confirmed with the trialists. Trials that included women who started treatment post partum or had a diagnosis of pre-eclampsia at trial entry were excluded. Each potentially eligible study was assessed independently by at least two members of the steering group, unblinded to authorship. Any differences of opinion regarding the assessment of the inclusion criteria were resolved by discussion.

Primary prevention was defined as antiplatelet agent use for women deemed to be at risk of pre-eclampsia, gestational hypertension, or intra-uterine growth restriction based on either their previous pregnancy history, a pre-existing medical condition (eg, renal disease, diabetes, immune disorder, chronic hypertension), or obstetric risk factors early in their current pregnancy (eg, being a primigravida or a having multiple pregnancy). Trials that recruited women in both primary and secondary prevention settings were divided in such a way that only women enrolled in a primary prevention setting were included in these analyses.

Data collection

Data to be collected were agreed after extensive consultation within the PARIS Collaborative Group. Anonymised data for each of the pre-specified variables were requested for each woman randomised. Data were supplied in a variety of formats, re-coded as necessary, and were checked for internal consistency, consistency with published reports, and for missing items. Information about the trials—eg, randomisation method and antiplatelet dose—were cross-checked with published reports, trial protocols, and data collection sheets. Quality and integrity of the randomisation processes were assessed by reviewing the chronological randomisation sequence and pattern of assignment, as well as the balance of baseline characteristics across treatment groups (taking into account stratification factors). Inconsistencies or missing data were discussed with relevant trialists and corrected when necessary. Finalised data for each study were verified with the relevant trialists.

Four main outcomes were prespecified: pre-eclampsia (hypertension with new onset proteinuria at or beyond 20 weeks' gestation); death in utero or death of the baby before discharge from hospital; preterm birth at less than 34 weeks' gestation; infant small for gestational age at birth (as defined by individual trialists); and pregnancy with serious adverse outcome (pregnancy where the mother dies or develops pre-eclampsia or if any baby is preterm, small for gestational age, or does not survive to discharge from hospital).

Prespecified additional outcomes included: maternal death, ante-partum haemorrhage, placental abruption, early onset proteinuria (before 34 weeks' gestation), serious maternal morbidity (including eclampsia, renal

failure, liver failure, haemolytic anaemia elevated liver enzymes low platelet count [HELLP] syndrome, stroke), non-spontaneous labour (induced labour or pre-labour caesarean), caesarean delivery, post-partum haemorrhage (blood loss ≥ 500 mL if supplied or trialists' definition), infant admission to neonatal special care or intensive care unit, ventilation required by neonate, and neonatal bleeding.

Statistical analysis

Analyses included all women randomised and were based on intention to treat. Each analysis was restricted to those trials that had at least 80% of data available for that particular outcome. The main analysis used a two stage approach: outcomes were analysed in their original trial and then these individual results combined in a meta-analysis to give an overall measure of effect. A fixed effect model was used, and the level of heterogeneity assessed with the I^2 statistic.²¹ Random effects models were also run to test the robustness of results to choice of model. Numbers needed to treat or harm were calculated based on control event rates in the included trials. Analyses were done with SCHARP software, version 4.0.

The main analyses compared the effect of antiplatelet agents versus placebo, or no antiplatelet agent, for each outcome. Subgroup and sensitivity analyses were restricted to the main outcomes. Extra maternal and infant outcomes were also assessed to examine potential benefits and harms.

To explore the effects by trial-level characteristics we prespecified analyses, based on aspirin-only trials, grouped by an intended daily dose of 75 mg or less, or more than 75 mg. Owing to small numbers, a planned third group (≥ 150 mg) was not created and relevant trials were included in the more than 75 mg group.

To explore the effects by participant-level characteristics we prespecified subgroups based on (1) risk factors at trial entry, including whether normotensive, previous hypertensive disorders of pregnancy, diabetes, renal disease, multiple pregnancy, maternal age, previous small for gestational age infant, parity, and by type of hypertension at trial entry, and (2) gestation less than 20 weeks or 20 weeks and greater at trial entry.

Sensitivity analyses were done excluding studies without a placebo and by including studies irrespective of whether data were available for less than 80% of participants. Variations in the definition of pre-eclampsia^{22–24} were also explored. Planned analyses of other quality measures—eg, adequacy of allocation concealment and blinding—were not done because almost all trials (26 of 31 trials, 99% of women) were of good quality.

Role of the funding source

The funding sources had no input into the study design, collection, analysis, or interpretation of the data, report preparation or in the decision to submit the paper for

publication. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

115 trials were identified as potentially eligible for our review. Of these, 50 were ineligible, for several reasons, including an absence of a comparison group or because they recruited women with established pre-eclampsia only. Two further trials were excluded from the analysis after data collection because they were found to have used quasirandom methods of treatment allocation. A full list of ineligible trials is available on request. Thus, 63 trials (with 38 026 women) were eligible for inclusion (webtable). The trials were done in 33 countries over six continents, and published between 1985 and 2005. Of these, we were unable to trace the investigators for seven trials, one trialist refused to participate, data were confirmed as lost or unretrievable for 17 trials, and although available, were not supplied for two small trials. Ultimately, data were therefore available from 36 trials and 34 288 women (90% of randomised women).

This paper presents the results from the 31 trials that recruited women in a primary prevention setting. These trials included 32 217 women and their 32 819 babies.^{10-14,25-50} Depending on the outcome, the minimum and maximum numbers of trials and women or babies available for individual analyses were between nine and 26 trials and between 7413 and 30 822 women or their babies.

Aspirin was given alone in 27 trials, in a dose ranging from 50 to 150 mg per day, accounting for 98% of women in the dataset (n=31 678).^{10-14,25,29,31-36,38-40,43-50} Aspirin was given in combination with dipyridamole in three trials (177 women; two of these trials were three arm trials: aspirin alone vs aspirin and dipyridamole vs control).^{33,37,43} 362 women in three trials received other antiplatelet agents only (dipyridamole and/or heparin, ozagrel).^{26,41,42} 27 trials,^{10-14,25-29,31-36,38-42,44-49} including 97% of women, were done in countries with a low perinatal mortality rate.⁵¹ Randomisation and therapy began before 20 weeks' gestation in 59% of the women enrolled.

Of the 32 217 women who were recruited in a primary prevention setting, 54% (n=17 544) were in their first pregnancy, 92% (29 642) had a singleton pregnancy, 70% (22 657) were aged 20-35 years, and 90% (29 068) had at least one risk factor (which could include primiparity). Overall, 8% (2599) of these women developed pre-eclampsia.

Antiplatelet agents were associated with a significant 10% reduction in the relative risk of both pre-eclampsia (p=0.004) and preterm birth before 34 weeks' gestation (p=0.011) compared with control (figure 1 and figure 2). The data indicated a 10% reduction in the relative risk of the baby being small for gestational age and a 9% reduction in the relative risk of stillbirth or baby death before discharge, although the 95% CI for both crossed the point of no effect (figure 1). Overall, there was a

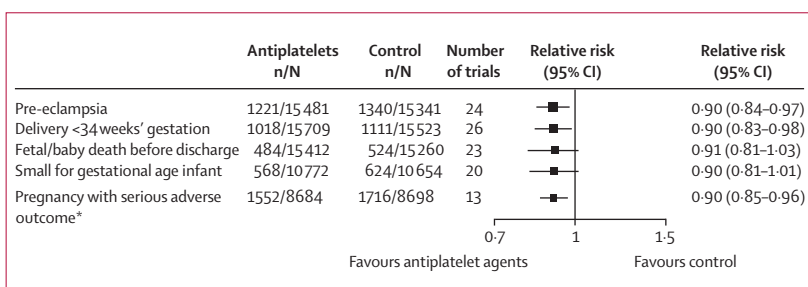


Figure 1: Main outcomes for mother and baby
*Pregnancy with any of four main outcomes above or maternal death. Fixed effect model used to calculate relative risks.

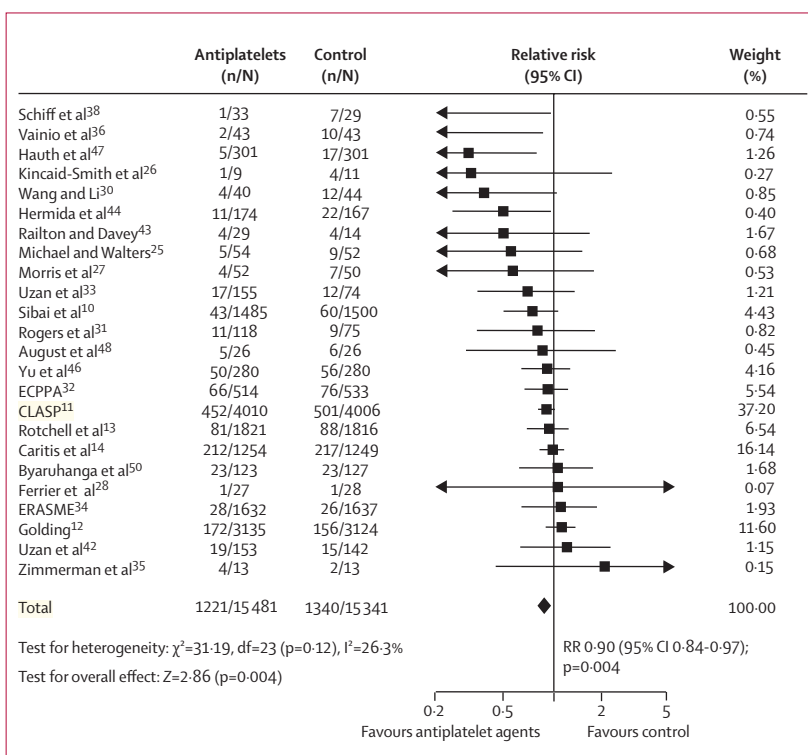


Figure 2: Maternal pre-eclampsia (ordered by effect size)
Fixed effect model used to calculate relative risks.

Outcome	Number of trials	Number of events (%)		Relative risk (95% CI)
		Antiplatelets	Control	
Proteinuria onset <34 weeks	14	332/9338 (4%)	353/9252 (4%)	0.92 (0.80-1.07)
Severe hypertension	21	1669/13 614 (12%)	1719/13 410 (13%)	0.96 (0.90-1.02)
Ante-partum haemorrhage	16	497/12 996 (4%)	480/12 926 (4%)	1.02 (0.90-1.15)
Abruption	16	115/12 213 (1%)	97/12 130 (1%)	1.13 (0.87-1.48)
Induction or non-labour caesarean section	17	4772/14 457 (33%)	4631/14 340 (32%)	1.02 (0.99-1.05)
Caesarean delivery	23	3362/14 652 (23%)	3175/14 464 (22%)	1.03 (0.99-1.08)
Post-partum haemorrhage*	16	1790/11 662 (15%)	1677/11 565 (15%)	1.06 (1.00-1.13)

*Using PARIS definition of blood loss ≥ 500 mL if supplied or trialists definition, but excluding two trials (Sibai et al¹¹ and Caritis et al¹⁴) due to data discrepancies with blood loss data.

Table 1: Other maternal outcomes

	Number of trials	Number of events (%)		Relative risk (95% CI)
		Antiplatelets	Control	
Preterm <37 weeks	26	2649/15749 (17%)	2799/15567 (18%)	0.93 (0.89–0.98)*
Preterm <28 weeks	26	291/15082 (2%)	331/14919 (2%)	0.87 (0.75–1.02)
Infant SCU/NICU	18	2385/15146 (16%)	2456/15015 (16%)	0.96 (0.91–1.01)
Infant ventilated	9	208/3751 (6%)	250/3662 (7%)	0.79 (0.67–0.95)*
Infant bleeding	15	287/14583 (2%)	308/14563 (2%)	0.93 (0.80–1.09)

NICU=neonatal intensive care unit. SCU=special care unit. *Significant difference in relative risk at p=0.05 level.

Table 2: Other infant outcomes

Subgroup	Category	Antiplatelets n/N	Control n/N	Relative risk (95% CI)	Interaction p value
Pregnancy and medical history					
First pregnancy with or without any high risk factor	With	195/1194	212/1176	0.90 (0.76–1.08)	0.71
	Without	287/7335	327/7288	0.87 (0.75–1.02)	
Second or subsequent pregnancy with or without any high risk factor	With	659/5375	720/5281	0.89 (0.81–0.99)	0.56
	Without	79/1545	79/1556	0.98 (0.73–1.33)	
Second or subsequent pregnancy with or without history of HDP	With	449/3116	497/2991	0.86 (0.77–0.97)	0.25
	Without	289/3799	302/3849	0.96 (0.82–1.12)	
Pre-existing renal disease	Yes	21/240	31/210	0.63 (0.38–1.06)	0.23
	No	814/11131	896/11072	0.90 (0.82–0.96)	
Pre-existing diabetes	Yes	60/439	82/466	0.76 (0.56–1.04)	0.26
	No	1053/12707	1138/12601	0.91 (0.84–0.99)	
Pre-existing hypertension	Yes	293/1678	295/1625	0.97 (0.84–1.12)	0.28
	No	849/11641	958/11603	0.88 (0.81–0.96)	
Previous infant small for gestational age	Yes	187/1635	160/1491	1.05 (0.86–1.28)	0.27
	No	308/3419	370/3498	0.85 (0.73–0.98)	
	No previous infant	482/8529	539/8464	0.89 (0.79–0.99)	
Current pregnancy					
Maternal age (years)	<20	158/3593	161/3593	0.97 (0.78–1.20)	0.35
	20–35	924/10935	1038/10777	0.87 (0.80–0.95)	
	>35	139/911	139/927	1.02 (0.83–1.26)	
Pregnancy type	Singleton	1114/14325	1206/14187	0.91 (0.84–0.98)	0.67
	Multiple	57/544	71/577	0.85 (0.61–1.18)	
Trial factors					
Gestation treatment started (weeks)	<20	686/9171	776/9023	0.87 (0.79–0.96)	0.24
	≥20	534/6263	560/6260	0.95 (0.85–1.06)	
Intended aspirin dose* (mg/day)	≤75	1065/12766	1163/12784	0.92 (0.85–0.99)	0.23
	>75	115/2369	142/2316	0.77 (0.61–0.97)	

HDP=hypertensive disorder of pregnancy event including gestational hypertension, pre-eclampsia or eclampsia. There were insufficient data to analyse first pregnancy with family history of HDP (only 20 women with this event). High risk factor=current pregnancy with any of the following: autoimmune disease, renal disease, chronic hypertension, diabetes, abnormal uterine artery doppler flow studies, family history of HDP, multiple pregnancy, or an unspecified risk factor; OR history of any of the following: gestational hypertension, pre-eclampsia, eclampsia, fetal or neonatal death. *Aspirin only trials.

Table 3: Subgroup analyses of pre-eclampsia outcome

significant 10% reduction in the relative risk of our prespecified composite outcome of pregnancy with any serious adverse outcome (any of the four main outcomes or maternal death; p=0.001). These data suggest that, in this population, for every 51 women treated with antiplatelet agents, a serious adverse outcome will be prevented in one pregnancy, and 114 women would need to be treated to prevent one case of pre-eclampsia.

Results for maternal outcomes are shown in table 1. There were no significant differences between the two groups for any of these outcomes. Importantly, potential adverse effects—eg, ante-partum haemorrhage, placental abruption, and post-partum haemorrhage—were not significantly different between the two treatment groups. Additional baby outcomes are shown in table 2. There was a 7% reduction in the relative risk of preterm birth before 37 weeks (p=0.003). Similarly, the data indicate a 13% reduction in the relative risk of preterm birth before 28 weeks, although the 95% CI cross the point of no effect. The reduction in relative risk of admission to a special care baby unit or neonatal intensive care unit associated with antiplatelet use rather than use of controls was small (4%) and not significant. Although data were available for only nine trials (7413 babies), we found a 21% reduction in the likelihood of the baby receiving assisted ventilation (p=0.010), equivalent to an absolute reduction in risk of 1.3%, meaning that in this population, on average, 78 infants would need to be treated with antiplatelet agents (via their mothers) to prevent one from needing assisted ventilation.

For the main outcome of pre-eclampsia, there was no evidence that women in any one of our prespecified subgroups benefited more or less from the use of antiplatelet agents than those in any other subgroup (table 3). There was no evidence that using more than 75 mg of aspirin had more or less effect than a lower dose, or that commencing treatment before 20 weeks' gestation was more or less beneficial than starting later in pregnancy (table 3). Nonetheless, since the absolute benefit derived from antiplatelet agents also depends on the woman's underlying risk, the absolute effects and number needed to treat will vary by risk profile (table 4).

We did the same subgroup analyses for the other four primary outcomes of baby death, preterm birth, small for gestational age infant, and pregnancy with any serious adverse outcome. We found four subgroups with a significant test for interaction (baby death: second or subsequent pregnancy with or without history of hypertensive disorders of pregnancy [p=0.007]; preterm birth less than 34 weeks: second or subsequent pregnancy with or without history of hypertensive disorders of pregnancy [p=0.012]; small for gestational age infant: second or subsequent pregnancy with or without any high risk factor [p=0.032]; pregnancy with serious adverse outcome: single/multiple pregnancy [p=0.046]).

Only the first of these was significant at the 1% level, suggesting a potential greater benefit in women who had a history of hypertensive disorders of pregnancy.

Overall results were similar when analyses were restricted to placebo controlled trials (data not shown), to trials of aspirin alone as the active treatment, and when extended to include trials with less than 80% of data available for a particular outcome (data not shown). Results were also unchanged when analyses of baby outcomes were repeated with numbers of women experiencing events, rather than number of babies experiencing events (data not shown).

For the 26 trials where data were available to allow comparison (webappendix), pooled results did not differ substantially when the trialists' own definition of pre-eclampsia was used (relative risk 0.88, 95% CI 0.81–0.96), compared with the pre-specified PARIS definition¹⁹ (0.90, 0.83–0.97). Both are also consistent with our main analysis of all trials based on the best available definition: recoded to PARIS definition or using trialists' definition if recoding was not possible (0.90, 0.84–0.97).

Discussion

Our results show that antiplatelet agents produce moderate but consistent reductions in the relative risk of pre-eclampsia, preterm birth before 34 weeks' gestation, and having a pregnancy with serious adverse outcome. There is no clear evidence that these agents are any more or less effective in reducing the relative risk for any particular subgroup of women. The effect of antiplatelet agents on pre-eclampsia seen here was much the same as that in the largest individual trial (7974 primary prevention women, relative risk 0.88, 95% CI 0.75–1.03).^{11,52}

Extensive subgroup and sensitivity analyses found no clear evidence that antiplatelet agents are more or less effective in preventing the development of pre-eclampsia for any particular group of women. However, analyses of high-risk categories were based on small numbers of women, reflecting the pattern of recruitment to the original trials, in which most women were at low to moderate risk of developing pre-eclampsia. For example, few women had pre-existing renal disease or diabetes. As a result, our analysis was limited in its power to estimate effects within these high-risk groups and to detect differences, if any exist, between those with and without specific risk factors. Thus, despite having gathered an extremely large dataset, the evidence base for particular groups of high-risk women remains limited and the most appropriate estimate of relative risk reduction remains the overall estimate of 10%.

There was some suggestion that women in their second or subsequent pregnancy with a history of a hypertensive disorder of pregnancy might derive a larger benefit from the use of antiplatelet agents than those in their second or subsequent pregnancy who did not have such a history

	Sample baseline event rate	PARIS relative risk (95%CI)	Number needed-to-treat (95% CI)
Pre-eclampsia	18%	0.90 (0.84–0.97)	56 (35–185)
	6%		167 (104–556)
	2%		500 (313–1667)
Preterm <34 weeks	20%	0.90 (0.83–0.98)	50 (29–250)
	10%		100 (59–500)
	2%		500 (294–2500)
Perinatal death	7%	0.91 (0.81–1.03)	159 (75–476)
	4%		278 (132–833)
	1%		1111 (526–3333)
Small for gestational age baby	15%	0.90 (0.81–1.01)	67 (35–667)
	10%		100 (53–1000)
	1%		1000 (526–10 000)
Pregnancy with serious adverse outcome	25%	0.90 (0.85–0.96)	40 (27–100)
	15%		67 (44–167)
	7%		143 (95–357)

Table 4: PARIS number needed-to-treat with sample baseline event rates

(table 2). Women in this small subgroup seemed to have a larger than average reduction in the relative risk of a stillbirth or baby death before discharge, as well as a possible reduction in the risk of preterm birth when treated with antiplatelet agents rather than control. Although prespecified, these subgroup analyses should, of course, be interpreted cautiously. As always when there are multiple analyses, there is a serious risk of being misled by the play of chance. We note that we did not find similarly significant interactions for pre-eclampsia, small for gestational age infant, or pregnancy with serious adverse outcome in women with a history of hypertensive disorder of pregnancy. Importantly, we found no groups of women for whom there is evidence to justify withholding antiplatelet therapy.

One of the early concerns about the use of antiplatelet agents during pregnancy was the possibility of an increase in bleeding problems for either the woman or her child. This concern has been allayed by results from trials, including two that reported follow-up of the children at around 2 years of age,¹⁵ and the results of a case-control study that indicate that aspirin use in early pregnancy does not result in an increased risk of congenital abnormalities in infants.⁵³ Our analyses showed no change in the risk of post-partum or ante-partum haemorrhage between women who received antiplatelet agents and those who did not, nor was there an effect on infant bleeding (table 1). Our analyses highlight the problem of measuring and defining post-partum haemorrhage. Two trials were excluded from the analysis of this outcome because of discrepancies between the data supplied for the dichotomous definition of post-partum haemorrhage, and for the estimated blood loss. Also, exploratory analyses found the overall results to be sensitive to even small changes in the way we

defined post-partum haemorrhage calculated from estimated blood loss (eg, using greater than or equal to rather than greater than 500 mL; data not shown). Changes in definition had up to a four-fold effect on the estimated effect size, and influenced statistical significance. Data presented here are based on our pre-specified definition. Given the well-known difficulties of accurately estimating blood loss at delivery, this outcome should be interpreted cautiously.

The definition of pre-eclampsia has long been controversial,^{22,23} and it has been argued that differences in the relative risk of pre-eclampsia reported in different trials might merely result from the different definitions of the condition. This argument is also used as a criticism of meta-analyses based on aggregate data. An advantage of using individual patient data was that we were able to do prespecified sensitivity analyses based on alternative definitions of pre-eclampsia. For some studies, the incidence of pre-eclampsia varied considerably depending on whether the trialists' or the PARIS definition was used. For example, the CLASP and ECPPA trials required a minimum rise in diastolic blood pressure in addition to minimum blood pressure values. The PARIS definition did not require this minimum rise because it is no longer included in most international classifications.^{22,24,54–56} The event rate for pre-eclampsia in these two trials in the PARIS analysis is therefore higher than that in the original trial reports, although the relative risks did not alter substantially. Despite differences for individual trials, the overall results across all trials did not change substantially when different definitions were used.

Although well established in cancer and cardiovascular medicine, meta-analyses of individual patient data have rarely been used in other areas of health care.⁵⁷ Advantages of such an approach include the ability to do extensive data checking to ensure the quality of the dataset. The approach could also circumvent the many potential biases associated with publication and published data.⁵⁸ The ability to standardise analyses also improves the robustness of findings, as does the potential to analyse data for a more complete set of outcomes than from the published literature. In our analysis, the trialists provided data for outcomes that have not been consistently reported in trial reports or other systematic reviews—eg, assisted ventilation and post-partum haemorrhage. Collecting individual patient data also permits subgroup analyses that are generally impossible or limited if attempted with aggregate published data. Another advantage, specific to this field, is the ability to link mother and baby outcomes. Furthermore, our dataset will enable risk modelling, further investigation of the effect of different antiplatelet load, and the investigation of the effect of this therapy for women with gestational hypertension. The individual patient data approach thus offers considerable potential in the perinatal field. Those planning and doing trials should ensure that data are

gathered in such a way that sharing for future individual patient data meta-analyses is facilitated.

Despite exhaustive efforts to obtain individual patient data from all eligible trials, several of the early, small, positive trials were unable to retrieve their raw data. Also, fewer small negative trials are included in this review than might be expected.⁵² Although the inclusion of such negative studies would lead to more conservative estimates, the numbers involved are so small that overall estimates would be unlikely to change. Publication bias is one possible explanation for the lack of small negative trials,⁵⁹ but another is a different case mix in small trials compared with large trials. Because we have failed to confirm any clear differences in the effects of antiplatelet agents based on the characteristics of individual women, the true explanation for the lack of small negative trials might be that they remain unpublished and inaccessible. This issue will be explored further in future analyses.

Our data show that antiplatelet agents produce moderate but consistent reductions in pre-eclampsia and its consequences, but there is no clear evidence that such agents are any more or less effective in reducing the relative risk for any particular subgroup. This information should be discussed with women at risk of pre-eclampsia to help them make informed choices about their antenatal care. Whether individual women will choose to take antiplatelet agents might depend on an assessment of their absolute risk. From a public-health perspective, especially for populations with a high risk of pre-eclampsia, even these moderate benefits could make more widespread use of antiplatelet agents worthwhile.

Contributors

LMA participated in protocol development, data collection, data analysis, and interpretation. LD, DJH-S, and LAS participated in protocol development, data analysis and interpretation. All members of the writing committee saw and approved the final version. All active PARIS collaborators were sent the paper as prepared for submission and given the opportunity to comment on the draft manuscript.

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Conflict of interest statement

We declare that we have no conflict of interest.

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