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Antifibrinolytic drugs for treating primary postpartum haemorrhage (Review)

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[Intervention Review]

Antifibrinolytic drugs for treating primary postpartum haemorrhage

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ABSTRACT

Background

Postpartum haemorrhage (PPH) - heaving bleeding within the first 24 hours after giving birth - is one of the main causes of death of women after childbirth. Antifibrinolytics, primarily tranexamic acid (TXA), have been shown to reduce bleeding in surgery and safely reduces mortality in trauma patients with bleeding without increasing the risk of adverse events.

An earlier Cochrane review on treatments for primary PPH covered all the various available treatments - that review has now been split by types of treatment. This new review concentrates only on the use of antifibrinolytic drugs for treating primary PPH.

Objectives

To determine the effectiveness and safety of antifibrinolytic drugs for treating primary PPH.

Search methods

We searched Cochrane Pregnancy and Childbirth's Trials Register, ClinicalTrials.gov, the WHO International Clinical Trials Registry Platform (ICTRP) (28 May 2017) and reference lists of retrieved studies.

Selection criteria

Randomised controlled trials (RCTs), including cluster-randomised trials of antifibrinolytic drugs (aprotinin, TXA, epsilon-aminocaproic acid (EACA) and aminomethylbenzoic acid, administered by whatever route) for primary PPH in women.

Participants in the trials were women after birth following a pregnancy of at least 24 weeks' gestation with a diagnosis of PPH, regardless of mode of birth (vaginal or caesarean section) or other aspects of third stage management.

We have not included quasi-randomised trials, or cross-over studies. Studies reported as abstracts have not been included if there was insufficient information to allow assessment of risk of bias.

In this review we only identified studies looking at TXA.

Data collection and analysis

Two review authors independently extracted data from each study using an agreed form. We entered data into Review Manager software and checked for accuracy.

For key review outcomes, we rated the quality of the evidence as 'high', 'moderate', 'low' or 'very low' according to the GRADE approach.

Main results

Three trials (20,412 women) met our inclusion criteria. Two trials (20,212 women) compared intravenous (IV) TXA with placebo or standard care and were conducted in acute hospital settings (labour ward, emergency department) (in high-, middle- and low-income countries).

One other trial (involving 200 women) was conducted in Iran and compared IV TXA with rectal misoprostol, but did not report on any of this review's primary or GRADE outcomes. There were no trials that assessed EACA, aprotinin or aminomethylbenzoic acid.

Standard care plus IV TXA for the treatment of primary PPH compared with placebo or standard care alone

Two trials (20,212 women) assessed the effect of TXA for the treatment of primary PPH compared with placebo or standard care alone. The larger of these (The WOMAN trial) contributed over 99% of the data and was assessed as being at low risk of bias. The quality of the evidence varied for different outcomes, Overall, evidence was mainly graded as *moderate* to *high quality*.

The data show that IV TXA reduces the risk of **maternal death due to bleeding** (risk ratio (RR) 0.81, 95% confidence interval (CI) 0.65 to 1.00; two trials, 20,172 women; *quality of evidence: moderate*). The quality of evidence was rated as moderate due to imprecision of effect estimate. The effect was more evident in women given treatment between one and three hours after giving birth with no apparent reduction when given after three hours (< one hour = RR 0.80, 95% CI 0.55 to 1.16; one to three hours = RR 0.60, 95% CI 0.41 to 0.88; > three hours = RR 1.07, 95% 0.76 to 1.51; test for subgroup differences: $Chi^2 = 4.90$, df = 2 (P = 0.09), $I^2 = 59.2\%$). There was no heterogeneity in the effect by mode of birth (test for subgroup differences: $Chi^2 = 0.01$, df = 1 (P = 0.91), $I^2 = 0\%$). There were fewer **deaths from all causes** in women receiving TXA, although the 95% CI for the effect estimate crosses the line of no effect (RR 0.88, 95% CI 0.74 to 1.05; two trials, 20,172 women, quality of evidence: moderate). Results from one trial with 151 women suggest that **blood loss of ≥ 500 mL** after randomisation may be reduced (RR 0.50, 95% CI 0.27 to 0.93; one trial, 151 women; *quality of evidence: low*). TXA did not reduce the risk of **serious maternal morbidity** (RR 0.99, 95% CI 0.83 to 1.19; one trial, 20,015 women; *quality of evidence: high*), **hysterectomy to control bleeding** (RR 0.95, 95% CI 0.81 to 1.12; one trial, 20,017 women; *quality of evidence: high*) receipt of **blood transfusion (any)** (RR 1.00, 95% CI 0.97 to 1.03; two trials, 20,167 women; *quality of evidence: moderate*) or maternal **vascular occlusive events** (any), although results were imprecise for this latter outcome (RR 0.88, 95% CI 0.54 to 1.43; one trial, 20,018 women; *quality of evidence: moderate)*. There was an increase in the use of brace sutures in the TXA group (RR 1.19, 95% CI 1.01, 1.41) and a reduction in the need for laparotomy for bleeding (RR 0.64, 95% CI 0.49, 0.85).

Authors' conclusions

TXA when administered intravenously reduces mortality due to bleeding in women with primary PPH, irrespective of mode of birth, and without increasing the risk of thromboembolic events. Taken together with the reliable evidence of the effect of TXA in trauma patients, the evidence suggests that TXA is effective if given as early as possible.

Facilities for IV administration may not be available in non-hospital settings therefore, alternative routes to IV administration need to be investigated.

PLAIN LANGUAGE SUMMARY

Antifibrinolytic drugs to treat heavy bleeding after childbirth

What is the issue?

Antifibrinolytic drugs such as tranexamic acid (TXA) reduce breakdown of clots which form to stop bleeding and have been shown to reduce bleeding in surgery and to safely reduce mortality in patients with bleeding following injury without increasing the risk of adverse events. This review assesses the safety and effects of antifibrinolytic drugs in women with primary postpartum haemorrhage (PPH) (heavy bleeding within the first 24 hours after giving birth).

An earlier Cochrane review on treatments for primary PPH covered all the various available treatments; that review has now been split by types of treatment. This new review concentrates only on the use of antifibrinolytic drugs for treating primary PPH.

Why is this important?

Postpartum haemorrhage is one of the main causes of death of women after childbirth and can also cause anaemia and other serious complications.

What evidence did we find?

We searched for evidence on 28 May 2017 and found three trials which met the inclusion criteria for the review. Participants in the trials were women after birth following a pregnancy of at least 24 weeks' gestation with a diagnosis of PPH, regardless of whether they had a vaginal or caesarean section. We identified three trials (involving 20,412 women). However, one of the trials (based in Iran) did not report important outcomes, therefore, our findings are based on two trials (involving 20,212 women) conducted in hospital settings in high-, middle- and

low-income countries. One was a large trial that included more than 20,000 women, and both studies looked at the effectiveness and safety of intravenous (IV) TXA compared with placebo (dummy treatment) or no treatment. In both trials TXA was given in addition to usual care to treat bleeding. The trial contributing most of the information to the review was at low risk of bias.

Our results show that TXA reduces the risk of maternal death due to bleeding (*quality of evidence: moderate*). There were fewer deaths from all causes but the findings were uncertain (*quality of evidence: moderate*). In one trial with a small sample size additional blood loss of 500 mL or more was also reduced (151 women; *quality of evidence: low*). TXA had little or no effect on the risk of serious maternal illness (*quality of evidence: high*), or complications such as stroke or deep venous thrombosis (*quality of evidence: moderate).* Rates of hysterectomy to control bleeding (*quality of evidence: high*) and blood transfusion (*quality of evidence: moderate*) were similar for women receiving TXA versus placebo. There was an increase in one surgical intervention (brace sutures) in the TXA group and a reduction in another (laparotomy to control bleeding) but there were no clear differences between groups for other surgical and invasive procedures.

What does this mean?

TXA when administered intravenously was effective in reducing mortality due to bleeding when given within three hours in women with primary postpartum haemorrhage without increasing the risk of other complications.

Facilities for IV administration is not available in some settings so future research could look at whether TXA is effective and safe if given by other methods.

Summary of findings for the main comparison. Standard care plus IV tranexamic acid compared to placebo or standard care alone for treating primary postpartum haemorrhage

Standard care plus IV tranexamic acid compared to placebo or standard care alone for treating primary postpartum haemorrhage

Patient or population: women with primary postpartum haemorrhage following vaginal or caesarean birth
Setting: acute hospital (labour ward, emergency department) (in high-, middle- and low-income countries)
Intervention: standard care plus tranexamic acid
Comparison: placebo or standard care alone

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with placebo or standard care alone	Risk with standard care plus tranexamic acid				
Maternal mortality due to bleeding	Study population		RR 0.81 (0.65 to 1.00)	20,172 (2 RCTs)	⊕⊕⊕⊖ MODERATE [1]	The estimable data are from a single study with a large sample size
	19 per 1000	15 per 1000 (12 to 19)				
Maternal mortality (all causes)	Study population		RR 0.88 (0.74 to 1.05)	20,172 (2 RCTs)	⊕⊕⊕⊖ MODERATE [2]	The estimable data are from a single study with a large sample size
	25 per 1000	22 per 1000 (19 to 27)				
Serious maternal morbidity (any)	Study population		RR 0.99 (0.83 to 1.19)	20,015 (1 RCT)	⊕⊕⊕⊕ HIGH	
	22 per 1000	22 per 1000 (19 to 27)				
Blood loss 500 mL or more after randomisation	Study population		RR 0.50 (0.27 to 0.93)	151 (1 RCT)	⊕⊕⊖⊖ LOW [3 4]	
	311 per 1000	155 per 1000 (84 to 289)				
Blood transfusion (any)	Study population		RR 1.00 (0.97 to 1.03)	20,167 (2 RCTs)	⊕⊕⊕⊖ MODERATE [5]	Most of the data are from a single study with a large sample size
	542 per 1000	542 per 1000 (525 to 558)				

Surgical intervention to control bleeding: Hysterectomy	Study population		RR 0.95 (0.81 to 1.12)	20,017 (1 RCT)	⊕⊕⊕⊕ HIGH
	30 per 1000	28 per 1000 (24 to 33)			
Side effects of the intervention: Any maternal vascular occlusive event	Study population		RR 0.88 (0.54 to 1.43)	20,018 (1 RCT)	⊕⊕⊕⊖ MODERATE [2]
	3 per 1000	3 per 1000 (2 to 5)			

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] Wide 95% CI that includes the line of no effect (0.65 to 1.00) (-1)
[2] Wide 95% CI crossing the line of no effect (-1)
[3] Single study with design limitations (no blinding) (-1)
[4] Estimate based on small sample size (-1)
[5] Moderate statistical heterogeneity and may be clinical heterogeneity (-1)

BACKGROUND

Description of the condition

Each year, worldwide, over 300,000 women die in childbirth (Alkema 2016). Primary postpartum haemorrhage (PPH) is one of the most common causes with a global prevalence rate of about 6% (Carroli 2008) and accounts for 27% of maternal deaths (Say 2014).

Traditionally, primary PPH is defined as bleeding from the genital tract of 500 mL or more in the first 24 hours following delivery of the baby (Abou Zahr 1991; Cunningham 1993; WHO 2012). Women delivering by caesarean section lose more blood on average than women who have vaginal birth; therefore, 1000 mL is commonly used as a cut-off for significant blood loss after caesarean section. Blood loss up to 500 mL at delivery is regarded as 'physiological', and a healthy pregnant woman can cope with it without difficulty (Gyte 1992; Ripley 1999). However, most deaths from bleeding occur in low-resource settings where anaemia is prevalent and even a small amount of blood loss can affect a woman adversely (Ronsmans 2006). Primary PPH can be caused by inefficient uterine contraction (uterine atony), trauma, retained placenta, retained parts of the placenta, vaginal or cervical tears, uterine rupture, clotting disorders and uterine inversion.

Major primary PPH can lead to significant morbidity including shock, renal failure, respiratory failure and/or liver failure (Bonnar 2000). Lack of easy access to treatment and inadequate intensive care and blood bank facilities are additional contributing factors that lead to high morbidity and mortality rates in low-income countries (Khan 2006; Say 2014; WHO 2015).

Treatment of primary PPH requires a multidisciplinary approach (WHO 2012). Uterotonics are usually given as the first line of treatment. Both surgical and non-surgical techniques including compression devices and radiological measures are also used to control bleeding (WHO 2012). Most deaths occur soon after delivery (Khan 2006; Knight 2007), therefore rapid control of haemorrhage is essential to reduce death and serious complications.

Description of the intervention

Antifibrinolytic drugs, tranexamic acid (TXA), epsilon-aminocaproic acid (EACA), aprotinin and aminomethylbenzoic acid, are used as inhibitors of clot breakdown (fibrinolysis) and may be administered by a variety of routes; intravenous, intramuscular, oral, sublingual, buccal and topical (direct application to the bleeding surfaces).

TXA has been shown to reduce the risk of bleeding in surgery (Ker 2012). It has been shown to reduce death due to bleeding in trauma, with treatment as early as possible being more effective. Treatment after three hours of injury had no effect and could even be harmful (Roberts 2013). TXA is used to reduce blood loss in women with heavy menstrual bleeding (Naoulou 2012). Currently, the use of TXA is recommended for the treatment of primary PPH if oxytocin and other uterotonics fail to stop bleeding, or if it is thought that the bleeding may be partly due to trauma (WHO 2012).

The risk of postpartum venous thromboembolism is highest in the immediate postpartum period (Tepper 2014). Because TXA inhibits fibrinolysis, it carries a potential risk of increasing thromboembolic events.

TXA passes into breast milk in very low concentrations, approximately one hundredth of the concentration in the maternal blood (Nilsson 1980) and risk of vascular occlusive events in breastfed infants is unknown.

How the intervention might work

Antifibrinolytic drugs work through influencing blood coagulation. TXA and EACA are synthetic derivatives of the amino acid lysine, which work by blocking lysine binding sites on plasminogen molecules and can prevent clot breakdown, thereby reducing bleeding (Novikova 2015). TXA is seven to 10 times more potent than EACA (Nilsson 1980). Aminomethylbenzoic acid inhibits fibrinolysis and has antithrombin activity, both of which result in delays of clot resorption (Westlund 1982). Aprotinin is a serine protease inhibitor which acts by inhibiting plasmin and subsequent fibrin clot breakdown (Westaby 1993) There is controversy over the use of aprotinin, whose license has been restricted or withdrawn in some countries.

During the first hours following birth, an increase in fibrinolytic activity has been reported (Gerbasi 1990). Also, an increased fibrinolytic activity is observed in women with PPH. Serum concentration of tissue plasminogen activator (tPA) doubles within one hour of the birth and thereafter, the tPA concentration falls steeply (Kruithof 1987). On the other hand, levels of the plasminogen activator inhibitors (PAI-1 and PAI-2) are increased around the time of birth and remain so for several days. We might therefore expect antifibrinolytics would be most effective when given soon after birth, when tPA levels are highest. Active PPH has been shown to be associated with an early increase in D-dimers and plasmin-anti-plasmin complexes and that D-dimers can be inhibited by the administration of TXA (Ducloy-Bouthors 2016). In PPH, fibrinogen levels decline (Huissoud 2009). This fall may be a reflection of several ongoing processes, including: factor consumption, dilution (from fluid used for resuscitation), fibrinolysis and fibrinogenolysis. We therefore hypothesise that early administration of an antifibrinolytic drug could reduce blood loss by interrupting the vicious circle of fibrinolysis and fibrinogen depletion.

Why it is important to do this review

The last review of treatments for primary PPH in the Cochrane Library was in 2014 (Mousa 2014) and it covered all the various treatment modalities. PPH remains a leading cause of maternal mortality and morbidity especially in poor-resource countries and there is a need to update the knowledge about safe and effective treatments for PPH. Specifically, that a review dedicated to assessing the effectiveness of antifibrinolytic drugs for the treatment of primary PPH is conducted to inform local and national practices and guide clinicians and midwives to understand the role of these drugs when caring for women with primary PPH.

TXA is currently included in the recommendations of the World Health Organization (WHO) for the treatment of primary PPH (WHO 2012) based on the results of its efficacy in trauma patients (CRASH-2 2010; Roberts 2013) and perioperative blood loss(Ker 2013). A review is needed to inform the update of the WHO guidelines on the use of antifibrinolytics for PPH.

OBJECTIVES

To determine the effectiveness and safety of antifibrinolytic drugs for treating primary postpartum haemorrhage.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) including cluster-randomised trials. We have not included quasi-randomised trials, or cross-over studies. Studies reported as abstracts have not been included if there was insufficient information to allow assessment of risk of bias.

Types of participants

Inclusion criteria

Women after birth following a pregnancy of at least 24 weeks' gestation with a diagnosis of primary postpartum haemorrhage (PPH), regardless of mode of birth (vaginal or caesarean section) or other aspects of third stage management.

As it may be difficult to obtain an accurate measurement of blood loss, PPH may be defined in different ways in trials:

- women with blood loss of 500 mL or more and/or
- women with primary PPH requiring blood transfusion and/or blood products and/or
- women with a clinical diagnosis of primary PPH (as defined by trialists).

Exclusion criteria

- Women with PPH with gestational age less than 24 weeks.

Types of interventions

The interventions considered are the antifibrinolytic drugs: aprotinin, tranexamic acid (TXA), epsilon-aminocaproic acid (EACA) and aminomethylbenzoic acid administered by whatever route (e.g. intravenous, oral).

Comparisons

- Aprotinin plus standard care versus placebo, or standard care alone
- TXA plus standard care versus placebo, or standard care alone
- EACA plus standard care versus placebo, or standard care alone
- Aminomethylbenzoic acid plus standard care versus placebo, or standard care alone
- Standard care plus systemic aprotinin, TXA, EACA and aminomethylbenzoic acid versus standard care plus topical antifibrinolytic
- Standard care plus one antifibrinolytic drug therapy versus another

Because PPH is a dynamic process, it is expected that women with primary PPH will have received other interventions to control the bleeding. Due to the random allocation of antifibrinolytic drugs, we anticipated that we would observe a similar proportion of women receiving other interventions in both comparison groups.

Types of outcome measures

Primary outcomes

- Mortality due to bleeding
- All-cause mortality*
- Serious maternal morbidity (renal or respiratory failure, cardiac arrest or multiple organ failure)

Secondary outcomes

- Mortality from causes other than bleeding
- Shock as defined by trialist*
- Coagulopathy as defined by trialist*
- Number of women with total blood loss 500 mL or more after randomisation*
- Number of women with total blood loss 1000 mL or more after randomisation*
- Mean blood loss (mL) (trialist defined)*
- Blood transfusion (red cell or whole blood)*
- Blood product transfusion*
- Post-randomisation additional uterotonic used to control bleeding
- Post-randomisation surgical interventions used to control bleeding (arterial ligation, compressive, uterine sutures, arterial embolisation, laparotomy)
- Post-randomisation non-surgical intervention to control bleeding (uterine packing, bimanual uterine massage, tamponade, external aortic compression and compression garments)
- Admission to higher level of care*
- Hysterectomy (provided it is not part of the intervention under investigation)*
- Post-randomisation additional haemostatic agents used*
- Side effects of intervention (both maternal and neonate); specifically vascular occlusive events (myocardial infarction, stroke, deep vein thrombosis or pulmonary embolism) and renal failure

Other outcomes

- Days in hospital
- Breastfeeding (defined as any breastfeeding at hospital discharge)*
- Maternal satisfaction with therapy (trialist defined)*
- Quality of life, including physiological activity and social and emotional changes (sense of well-being) (trialist defined)*

(*outcomes form part of an outcome set that will be used in all PPH reviews)

NOTE:

- We anticipated that assessment of blood loss could vary between trials. We considered that measurement of blood and blood clots in jars and weighing of linen are likely to be more precise than clinical judgement. The latter is known to underestimate blood loss.
- The way of reporting the amount of loss as 'greater than' or 'greater than or equal to' a certain cut-off level (e.g. greater than

500 mL or greater than or equal to 500 mL) may affect the total reported amount of blood loss.

- Antifibrinolytics such as TXA may be present in breast milk in small quantities. If neonates are breastfed, they are also exposed to the intervention. Side effects of the intervention were assessed in the neonates who were breastfed.

Search methods for identification of studies

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

Electronic searches

We searched Cochrane Pregnancy and Childbirth's Trials Register by contacting their Information Specialist (28 May 2017).

The Register is a database containing over 24,000 reports of controlled trials in the field of pregnancy and childbirth. For full search methods used to populate Pregnancy and Childbirth's Trials Register including the detailed search strategies for CENTRAL, MEDLINE, Embase and CINAHL; the list of handsearched journals and conference proceedings, and the list of journals reviewed via the current awareness service, please follow this link to the editorial information about the Cochrane Pregnancy and Childbirth in the Cochrane Library and select the '***Specialized Register***' section from the options on the left side of the screen.

Briefly, Cochrane Pregnancy and Childbirth's Trials Register is maintained by their Information Specialist and contains trials identified from:

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

Search results are screened by two people and the full text of all relevant trial reports identified through the searching activities described above is reviewed. Based on the intervention described, each trial report is assigned a number that corresponds to a specific Pregnancy and Childbirth review topic (or topics), and is then added to the Register. The Information Specialist searches the Register for each review using this topic number rather than keywords. This results in a more specific search set that has been fully accounted for in the relevant review sections (Included studies; Excluded studies; Studies awaiting classification; Ongoing studies).

In addition, we searched ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform (ICTRP) for unpublished, planned and ongoing trial reports (28 May 2017) using the search methods detailed in Appendix 1.

Searching other resources

We searched the reference lists of retrieved studies.

We did not apply any language or date restrictions.

Data collection and analysis

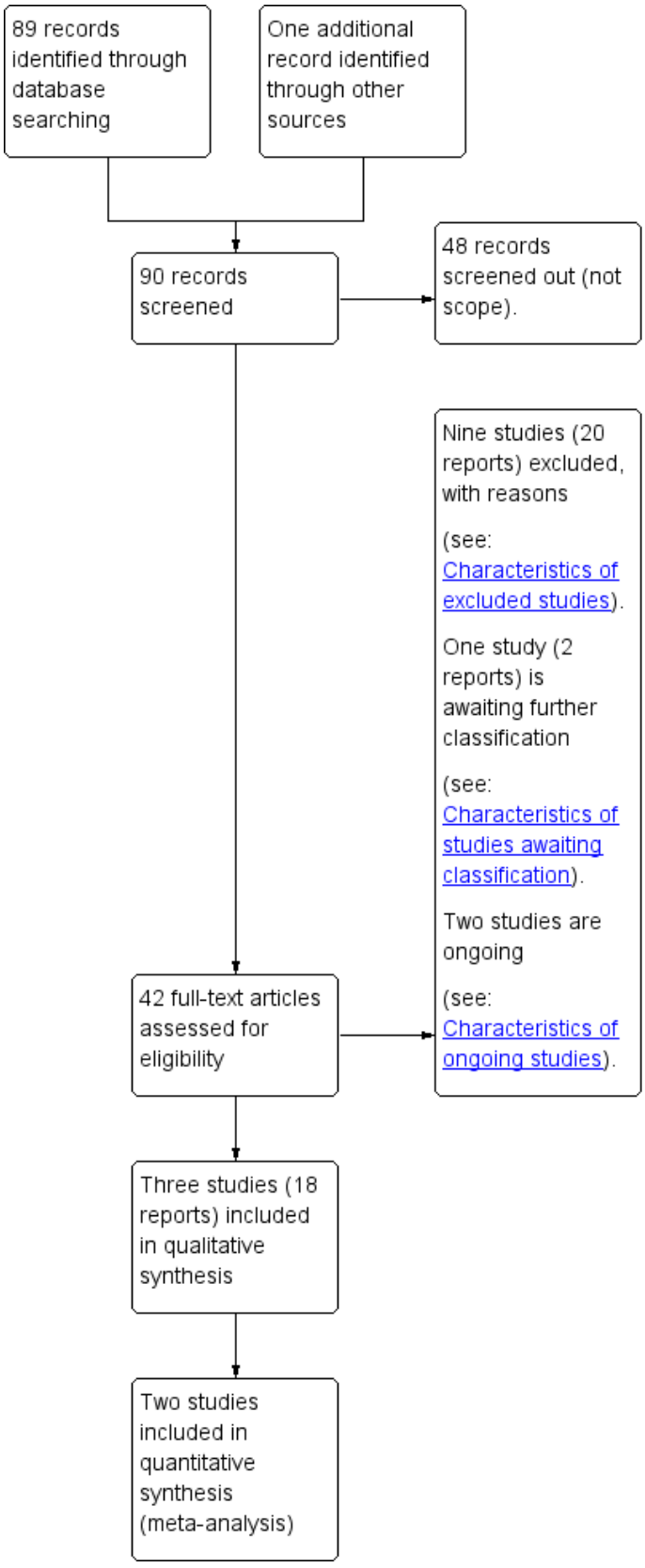
The following methods section of this review is based on a standard template used by Cochrane Pregnancy and Childbirth.

Selection of studies

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

We have included a study flow diagram mapping out the number of records identified, included and excluded (Figure 1).

Figure 1. Study flow diagram.



Data extraction and management

We designed a form to extract data. For eligible studies, two review authors extracted the data using the agreed form. Assessments regarding inclusion and exclusion, GRADE and risk of bias were carried out by review authors not involved in the conduct of included trials. However, review authors involved in one of the included studies were involved in the selection of outcomes and the interpretation of the data. We resolved discrepancies through discussion or, if required, we consulted a third review author. We entered data into Review Manager software (RevMan 2014) and checked for accuracy. When information regarding any of the above was unclear, we attempted to contact authors of the original reports to provide further details.

As part of data extraction we collected information on study design and setting, trial dates, participant characteristics (including information on cause of bleeding and its severity where available), details of routine care provided and the intervention given (drug, route and dose), the outcomes assessed, the source of study funding and any conflicts of interest stated by the investigators.

Assessment of risk of bias in included studies

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

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

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

We assessed the method as:

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

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

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

We assessed the methods as:

- low risk of bias (e.g. telephone or central randomisation; consecutively numbered sealed opaque envelopes);
- high risk of bias (open random allocation; unsealed or non-opaque envelopes, alternation; date of birth);
- unclear risk of bias.

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

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

We assessed the methods as:

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

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

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

We assessed methods used to blind outcome assessment as:

- low, high or unclear risk of bias.

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

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

We assessed methods as:

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

(5) Selective reporting (checking for reporting bias)

We described for each included study how we investigated the possibility of selective outcome reporting bias and what we found. We noted whether or not there was prospective registration, prospective protocol publication, plagiarism, and whether outcome reported matched outcomes pre-specified in trial protocols or registrations.

We assessed the methods as:

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

include results of a key outcome that would have been expected to have been reported);
- unclear risk of bias.

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

We described for each included study any important concerns we have about other possible sources of bias (e.g. baseline imbalance between randomised groups).

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

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

(7) Overall risk of bias

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

Assessment of the quality of the evidence using the GRADE approach

The quality of the evidence was assessed using the GRADE approach as outlined in the GRADE handbook in order to assess the quality of the body of evidence.

Where data were available, we planned to use GRADE to assess the overall quality of the evidence for our main comparisons.

- TXA versus placebo or standard care
- Aprotinin versus placebo or standard of care
- EACA versus placebo or standard of care
- Aminomethylbenzoic acid versus placebo or standard of care
- Standard care plus systemic aprotinin, TXA, EACA and aminomethylbenzoic acid versus standard care plus topical antifibrinolytic
- Standard care plus one antifibrinolytic drug therapy versus another

We assessed the following outcomes.

- Maternal mortality due to bleeding
- Maternal mortality (all causes)
- Serious maternal morbidity (renal or respiratory failure, cardiac arrest or multiple organ failure)
- Surgical intervention to control bleeding (hysterectomy for bleeding)
- Side effects of intervention: specifically maternal vascular occlusive events (any)
- Blood loss equal to or greater than 500 mL after randomisation
- Blood transfusion (any)

(Grade outcomes are included in our review 'Summary of findings' table.)

GRADEpro Guideline Development Tool was used to import data from Review Manager 5.3 (RevMan 2014) in order to create a 'Summary of findings' table. A summary of the intervention effect and a measure of quality for each of the above outcomes was produced using the GRADE approach. The GRADE approach uses five considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias) to assess the quality of the body of evidence for each outcome. The evidence can be downgraded from 'high quality' by one level for serious (or by two levels for very serious) limitations, depending on assessments for risk of bias, indirectness of evidence, serious inconsistency, imprecision of effect estimates or potential publication bias. Evidence was graded by two independent assessors and checked by a third assessor (Therese Dowswell, Lambert Felix (CPC) and Angele Gayet-Ageron)

Measures of treatment effect

Dichotomous data

For dichotomous data, we presented results as summary risk ratio with 95% confidence intervals.

Continuous data

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

Unit of analysis issues

Cluster-randomised trials

We planned to include cluster-randomised trials in the analyses along with individually-randomised trials. No such trials were identified for this version of the review. If such trials are included in future updates we will adjust their sample sizes using the methods described in the *Handbook* using an estimate of the intracluster correlation coefficient (ICC) derived from the trial (if possible), from a similar trial or from a study of a similar population. If we use ICCs from other sources, we will report this and conduct sensitivity analyses to investigate the effect of variation in the ICC. If we identify both cluster-randomised trials and individually-randomised trials, we plan to synthesise the relevant information. We will consider it reasonable to combine the results from both if there is little heterogeneity between the study designs and the interaction between the effect of intervention and the choice of randomisation unit is considered to be unlikely.

We will also acknowledge heterogeneity in the randomisation unit and perform a sensitivity analysis to investigate the effects of the randomisation unit.

Cross-over trials

We have not included cross-over trials.

Other unit of analysis issues

If in future updates we identify trials with more than two treatment groups, we will use methods described in the*Handbook* section 16.4.7. in order to avoid double-counting.

Dealing with missing data

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

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

Assessment of heterogeneity

We planned to assess statistical heterogeneity in each meta-analysis using the Tau^2, I^2 and Chi^2 statistics. The indicator I^2 which reflects the part of variance between studies that is due to factors other than chance, as well as Cochran's Q. We regarded heterogeneity as substantial if I^2 was greater than 30% and either a Tau^2 was greater than zero or a low P value (less than 0.10) was obtained in the Chi^2 test for heterogeneity").

If important heterogeneity was identified (I^2 > 30%), we planned to explore it using pre-defined heterogeneity factors: type of delivery, severity of PPH, time from delivery and route of administration.

Assessment of reporting biases

If, in future updates, there are 10 or more studies in the meta-analysis we will investigate reporting biases (such as publication bias) using funnel plots. We will assess funnel plot asymmetry visually. If asymmetry is suggested by a visual assessment, we will perform exploratory analyses to investigate it.

Data synthesis

We carried out statistical analysis using the Review Manager software (RevMan 2014). We used fixed-effect meta-analysis for combining data where it is reasonable to assume that studies estimate the same underlying treatment effect: i.e. where trials examined the same intervention, and the trials' populations and methods were judged sufficiently similar. If there was clinical heterogeneity sufficient to expect that the underlying treatment effects differed between trials, or if substantial statistical heterogeneity was detected, we planned to use random-effects meta-analysis to produce an overall summary ,if an average treatment effect across trials was considered clinically meaningful.

Subgroup analysis and investigation of heterogeneity

Data permitting, we planned to investigate substantial heterogeneity using subgroup analyses.

To attempt to identify possible factors that may mediate the clinical effect of treatment, where data were available we planned subgroup analysis by:

1. type of delivery (vaginal versus caesarean);
2. severity of haemorrhage at randomisation (blood loss ≤ 1000 mL, > 1000 mL);
3. hours from giving birth to randomisation (< 1, 1 to 3, > 3 hours);
4. route of administration (intravenous, intramuscular, sublingual, buccal, topical, oral).

We carried out subgroup analysis for our primary outcomes only (maternal mortality due to bleeding, all-cause mortality, serious maternal morbidity (renal or respiratory failure, cardiac arrest or multiple organ failure)).

We assessed subgroup differences by interaction tests available within RevMan (RevMan 2014). We reported the results of subgroup analyses quoting the Chi^2 statistic and P value, and the interaction test I^2 value.

Sensitivity analysis

We planned to carry out sensitivity analysis for studies at high risk of bias for attrition (temporarily excluding studies with > 20% loss to follow-up from the analyses). We did not carry out this planned analysis as studies contributing data had low loss to follow-up.

RESULTS

Description of studies

Results of the search

The search retrieved 42 reports relating to 15 trials (*see:* Figure 1). Of the 15 trials, three met the inclusion criteria of the review, nine were excluded, one is awaiting further assessment (pending further information from the trialist - see Characteristics of studies awaiting classification), and there are two ongoing trials. Details of ongoing trials are set out in Characteristics of ongoing studies tables.

Included studies

Design

Three trials (involving 20,412 women) met our inclusion criteria (Ducloy-Bouthors 2011; Sahaf 2014; Woman Trial 2017). One trial (Sahaf 2014) reported results for only one of the review's outcomes: estimated blood loss and does not otherwise contribute to the data and analysis. For all other outcomes two trials have contributed data on 20,212 women to our data and analyses tables (Ducloy-Bouthors 2011; Woman Trial 2017).

Sample sizes

The Woman Trial 2017, a multi-centre trial recruited 20,060 women with little loss to follow-up, contributed the most data to the review. A trial carried out in France (Ducloy-Bouthors 2011) recruited 152 women. The additional trial meeting our inclusion criteria recruited 200 women (Sahaf 2014).

Setting

For most outcomes two trials contributed data to the review. One was a multi-centre randomised controlled trial with 20,060 women (Woman Trial 2017); in this study women were recruited from hospital settings in high- (UK: 569 women), and low- and middle-income countries (Nigeria: 5711; Pakistan: 5282; Uganda: 2235; Kenya: 1031; Cameroon: 893; Sudan: 860; Tanzania: 538; Nepal: 533; Zambia: 496; Albania: 485; Democratic Republic of Congo: 457; Bangladesh: 325; Ethiopia: 302; Burkina Faso: 142; Jamaica: 73; Ghana: 41; Papua New Guinea: 38; Egypt: 33; Colombia: 8; Cote d'Ivoire: 8). Women were recruited to the WOMAN trial between 2010 and 2016. The second trial (Ducloy-Bouthors 2011) was

conducted in France in eight centres (five tertiary care centres and three secondary care obstetric centres: 152 women). This study recruited women between 2005 to 2008.

The remaining trial was carried out in Iran (Sahaf 2014).

Participants

In all trials women were recruited with postpartum haemorrhage (PPH).

The Ducloy-Bouthors 2011trial recruited women with PPH > 800 mL within hours after vaginal birth. Exclusion criteria included women less than 18 years old, no informed consent, caesarean section, known haemostatic abnormality, and history of thrombosis or epilepsy.

The Woman Trial 2017 recruited women aged 16 years or older with clinically diagnosed PPH (estimated blood loss after vaginal birth > 500 mL, or > 1000 mL after caesarean section or estimated blood loss enough to compromise the haemodynamic status of the woman). Women were randomised only if the clinician responsible for their care was "substantially uncertain" as to whether or not to use tranexamic acid (TXA) in a particular woman with PPH. Exclusion criteria included any clear indication or contraindication to TXA (e.g. a known thromboembolic event during pregnancy).

In the Sahaf 2014 trial women were recruited after caesarean or vaginal birth with PPH (500 mL to 1500 mL) after receiving routine therapies for controlling bleeding.

Interventions and comparisons

All trials examined TXA to treat PPH.

In the Ducloy-Bouthors 2011 trial, women in the experimental group were given a loading dose of 4 g TXA mixed with 50 mL saline, administered intravenously (IV) over one hour followed by a maintenance dose of 1 g/hour for six hours (n = 78), while those in the comparison group received usual care (no TXA) (n = 74).

In the Woman Trial 2017, following routine care for PPH, women were randomised. Those in the intervention group were given IV TXA 1 g as an IV bolus over 10 minutes; if after 30 minutes bleeding continued, or had stopped and restarted within 24 hours of the first dose, women were given a second dose (n = 10,051). Women in the control group received placebo (sodium chloride 0.9% contained in ampoules and packaging with identical appearance to active treatment) with the same regimen as that used in the experimental group (n = 10,009).

In the Sahaf 2014 trial, 100 women randomised to the intervention group received 1 g IV TXA repeated after 30 minutes; the comparison group (100 women) received 1000 micrograms (mcg) rectal misoprostol (five 200 mcg tablets). Prostatglandin F2α was administered in case of treatment failure in both groups.

Outcomes

Only one of our included trials, Woman Trial 2017, was sufficiently powered to identify differences between groups for our primary outcomes (mortality and serious maternal morbidity), although mortality was reported in the Ducloy-Bouthors 2011 trial. Cause of death (death due to bleeding and other causes) was reported in the Woman Trial 2017 along with serious maternal complications (renal failure, cardiac failure, respiratory failure, hepatic failure, and seizures). Hysterectomy was reported in two trials (Ducloy-Bouthors 2011; Woman Trial 2017), and other surgical and invasive interventions (including intrauterine tamponade; embolisation; brace sutures (B-Lynch/Cho); artery ligation, to achieve haemostasis; hysterectomy and laparotomy done after randomisation to control bleeding) in the Woman Trial 2017. The number of women experiencing deep venous thrombosis or other vascular occlusive events was reported by Ducloy-Bouthors 2011 and Woman Trial 2017 and less serious side effects in the Ducloy-Bouthors 2011 trial. Blood transfusion or blood product transfusion was reported in two trials (Ducloy-Bouthors 2011; Woman Trial 2017), and estimated blood loss in two trials (Ducloy-Bouthors 2011; Sahaf 2014). Other outcomes reported in the Woman Trial 2017 included maternal quality of life (measured using the EQ5D at hospital discharge or in hospital at 42 days after randomisation) and neonatal outcomes (death in breastfed infants or neonatal thromboembolic events).

Sources of support and conflicts of interest

The Ducloy-Bouthors 2011 trial was funded by the French Ministry of Health. The Woman Trial 2017 was funded by the London School of Hygiene & Tropical Medicine, Pfizer, UK Department of Health, Wellcome Trust, and Bill & Melinda Gates Foundation. The Sahaf 2014 trial was unfunded.

All three trials stated that there were no conflicts of interest.

GIven the sample size of the Woman Trial 2017 this trial dominates our results section.

Excluded studies

Nine trials were excluded from the review; although these studies examined treatments for PPH, these trials did not examine the use of antifibrinolytic drugs (Ahonen 2013; Bruynseels 2016; Ducloy-Bouthors 2016; Lavigne-Lissalde 2015; Paidas 2015; von Beckerath 2016; Wikkelso 2015). One trial (Sadeghipour 2013), examined the treatment of uterine atony. In one study (Wiznitzer 2011), the intervention was a dressing for vaginal tears, however there was no clear evidence from the trial registration that women had PPH. See Characteristics of excluded studies.

Risk of bias in included studies

See Figure 2; Figure 3.

Figure 2. 'Risk of bias' graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

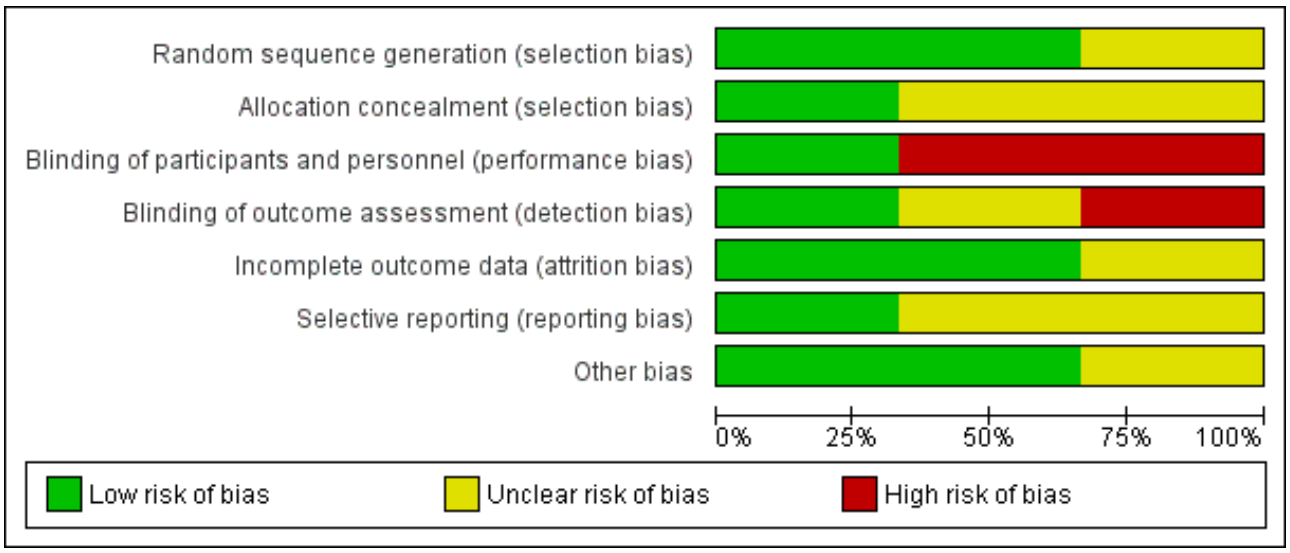
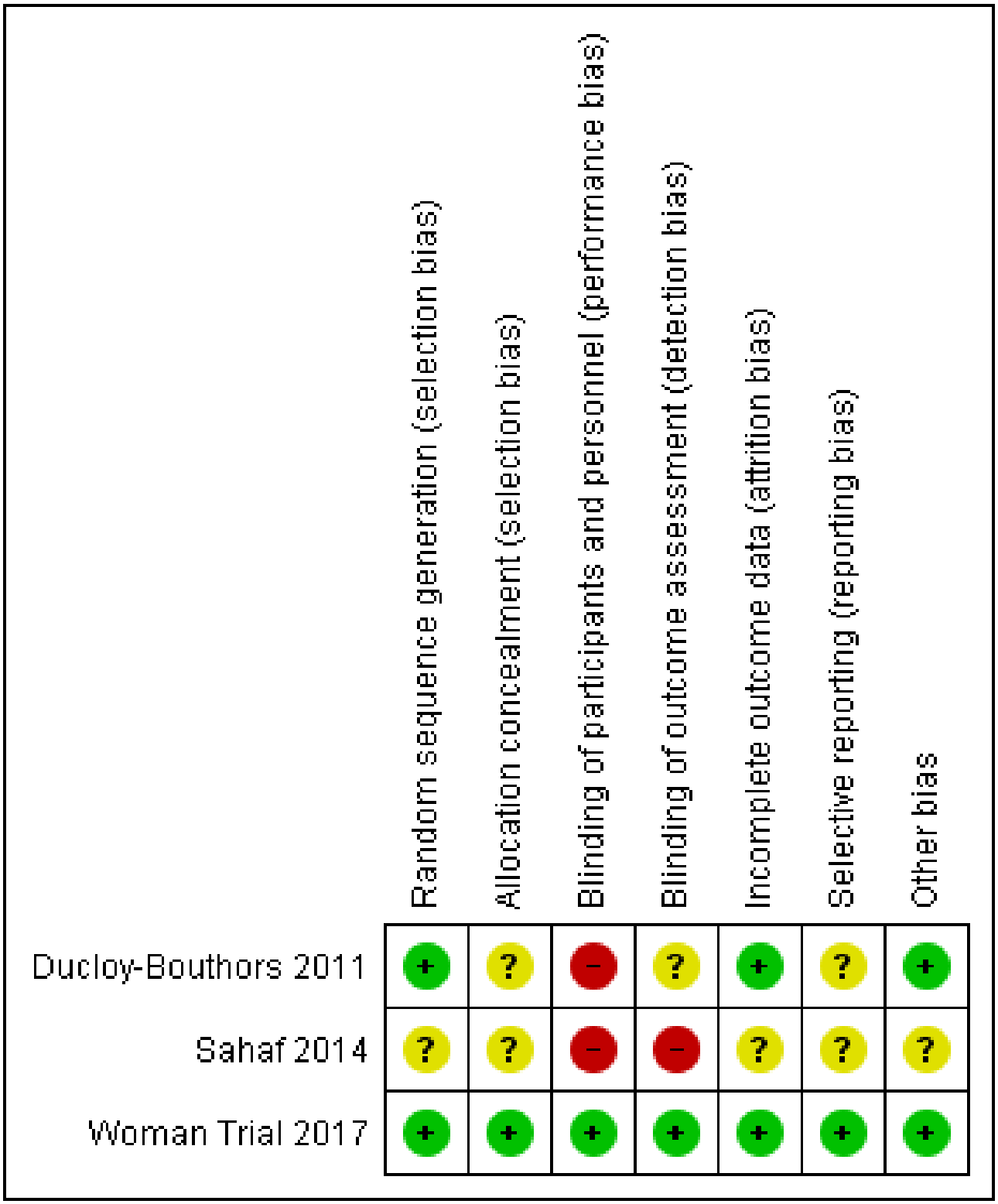


Figure 3. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.



Allocation

In the two trials contributing data to the main comparison in the review, the methods used to generate the randomisation sequence were assessed as low risk of bias. In the Woman Trial 2017 an external randomisation service was used and in the Ducloy-Bouthors 2011 trial a computer-generated sequence was used. In the remaining trial (Sahaf 2014), the method used to generate the randomisation sequence was assessed as unclear. While the report for the Sahaf 2014 trial mentioned a computer programme, it stated

also that the sample was "divided into two equal groups" and we were unable to verify the methods used.

Allocation concealment at the point of randomisation was assessed as low risk of bias in the Woman Trial 2017. In the remaining studies there was insufficient information on methods or methods were unclear.

Blinding

Performance bias: The Woman Trial 2017 was placebo-controlled. In this trial, women and staff providing care were unlikely to be aware of treatment allocation. In the Ducloy-Bouthors 2011 trial there was no placebo, and women and staff would not be blind to treatment. The Sahaf 2014 trial compared different treatments. Both Ducloy-Bouthors 2011 and Sahaf 2014 were assessed as high risk of bias for this domain.

Detection bias: In the Woman Trial 2017, it was stated that the randomisation code was not broken until the end of the trial and all staff and investigators were blind to treatment allocation until that point. In the Ducloy-Bouthors 2011 trial it was stated that staff were unaware of allocation although the women received different treatments so it is not clear whether or not lack of blinding impacted on outcomes. In the remaining trial there was no attempt at blinding and this study was assessed as high risk of bias (Sahaf 2014).

Incomplete outcome data

The two trials contributing data to the main comparison in the review (Ducloy-Bouthors 2011; Woman Trial 2017) had low losses to follow-up (low risk of bias). The remaining trial did not provide information on loss to follow-up or whether or not there were any missing data - we assessed this trial as having an unclear risk of attrition bias (Sahaf 2014).

Selective reporting

For the Woman Trial 2017 selective reporting bias was assessed as low risk of bias. The trial protocol was published before recruitment to the trial, although less emphasis was put on the hysterectomy component of the composite primary outcome, all relevant outcomes were reported in the main trial report or data were provided by the trialists. In the remaining trials (Ducloy-Bouthors 2011; Sahaf 2014), registration did not occur before recruitment or data for all relevant outcomes were not fully reported (both assessed as unclear risk of reporting bias). The author of Ducloy-Bouthors 2011trial kindly provided additional data.

Other potential sources of bias

The two trials contributing data to the main review comparison were assessed as being at low risk of bias for other sources of bias (Ducloy-Bouthors 2011; Woman Trial 2017). The other trial (Sahaf 2014) provided little information on methods and there were baseline differences between groups that may have impacted on outcomes - we assessed this trial as be at unclear risk of other bias.

Effects of interventions

See: **Summary of findings for the main comparison** Standard care plus IV tranexamic acid compared to placebo or standard care alone for treating primary postpartum haemorrhage

Standard care plus IV tranexamic acid (TXA) versus placebo or standard care alone for the treatment of postpartum haemorrhage (PPH) (Comparison 1)

Primary outcomes

Maternal mortality due to bleeding

Two trials were included in this analysis, but in the Ducloy-Bouthors 2011 trial there were no events, therefore all estimable data are from the Woman Trial 2017. TXA probably reduces mortality due to bleeding in women with PPH (risk ratio (RR) 0.81, 95% confidence interval (CI) 0.65 to 1.00; 20,172 women, *moderate-quality evidence*); the reduction in death observed equates to four fewer deaths per 1000 women in the TXA group (19 deaths per 1000 in the placebo group versus 15 deaths per 1000 in the TXA group (95% CI 12 to 19)). Analysis 1.1.

Subgroup analysis

We carried out subgroup analysis by mode of birth and time from birth.

The effect of TXA on death due to bleeding did not differ by the type of birth, with the treatment effect being very similar in women who had given birth vaginally or by caesarean section (test for subgroup differences: $Chi^2 = 0.01$, df = 1 (P = 0.91), $I^2 = 0\%$). Analysis 1.2.

Women receiving treatment with TXA between one and three hours after the birth had a reduced risk of death from bleeding compared with placebo. For women who received treatment in the first hour and after three hours of birth, there was no clear differences between the intervention and control groups (test for subgroup differences: $Chi^2 = 4.90$, df = 2 (P = 0.09), $I^2 = 59.2\%$). Analysis 1.3.

Maternal mortality (all causes)

All estimable data for this analysis are from the Woman Trial 2017. TXA reduced mortality from all causes although the 95% CI for the effect estimate crosses the line of no effect (RR 0.88, 95% CI 0.74 to 1.05; 20,172 women, *moderate-quality evidence*). Analysis 1.4.

Subgroup analysis

Subgroup analysis suggested that mode of birth made little or no difference to the treatment effect (test for subgroup differences: $Chi^2 = 0.14$, df = 1 (P = 0.71), $I^2 = 0\%$). Analysis 1.5. Time from birth did appear to have an impact on the treatment effect with women receiving TXA between one and three hours after the birth having a reduced risk of death compared with placebo, although the subgroup interaction test did not show a clear difference between the three subgroups (test for subgroup differences: $Chi^2 = 3.25$, df = 2 (P = 0.20), $I^2 = 38.5\%$). Analysis 1.6.

Serious maternal morbidity (any)

All estimable data for this analysis are from the Woman Trial 2017. There was little or no difference between TXA and placebo for the number of women with any serious morbidity (renal failure, respiratory failure, cardiac arrest or multiple organ failure) (RR 0.99, 95% CI 0.83 to 1.19; 20,015 women, *high-quality evidence*); 22 women per 1000 suffered a serious morbidity in both arms of the trial. Analysis 1.7.

Subgroup analysis identified no clear differences in treatment effect for women having vaginal or caesarean birth, or by timing of drug administration. Analysis 1.8; Analysis 1.9.

Additional planned subgroup analysis: For primary outcomes, we had planned subgroup analysis by severity of haemorrhage (women with blood loss ≤ 1000 mL versus blood loss > 1000 mL). We were unable to carry out this planned analysis as no separate data were available for women in these two groups. We were also unable to explore the route of administration (e.g. IV versus oral) as in both included trials the method of administration was IV. We will carry out planned additional analysis in updates if data become available.

Serious maternal morbidity (by type)

The number of women experiencing specific types of severe morbidity was also reported.

Multiple organ failure was reported in both trials included in the analysis; the Ducloy-Bouthors 2011 trial reported no events, therefore all estimable data are from the Woman Trial 2017. There was little or no difference between women receiving TXA versus placebo for this outcome, with approximately 1% of women in both arms of the trial suffering multiple organ failure (RR 0.94, 95% CI 0.71 to 1.23; 20,168 women). Analysis 1.10.

Maternal respiratory failure was reported in the Woman Trial 2017 with no clear evidence of difference between the randomised groups (RR 0.87, 95% CI 0.67 to 1.12; 20,018 women). Analysis 1.11.

Similar numbers of women (approximately 1.1%) in both arms of the trial suffered **cardiac arrest** (RR 0.95, 95% CI 0.73 to 1.23; 20,018 women). Analysis 1.12.

Renal failure was reported in both trials; the Ducloy-Bouthors 2011 trial reported no events, so estimable data are from the Woman Trial 2017. There was little or no difference between women receiving TXA versus placebo for this outcome, with approximately 1.3% and 1.2% of women in TXA and control arms of the trial suffering renal failure (RR 1.09, 95% CI 0.85 to 1.39; 20,169 women). Analysis 1.13.

Similar numbers of women (29 versus 30) in the two arms of the Woman Trial 2017 suffered **hepatic failure** (RR 0.96, 95% CI 0.58 to 1.60; 20,018 women). Analysis 1.14.

Maternal seizure was reported in both trials contributing data but all estimable data are from the Woman Trial 2017; the effect estimate was imprecise with no clear evidence of differences between groups (RR 0.76, 95% CI 0.49 to 1.20; 20,169 women). Analysis 1.15.

Ducloy-Bouthors 2011 reported **maternal admission to intensive care** (ICU); 3/77 and 5/74 women in the TXA and control group respectively were admitted to ICU (RR 0.58, 95% CI 0.14 to 2.33; 151 women). Analysis 1.16.

Secondary outcomes

Maternal mortality from causes other than bleeding

This outcome was reported in both trials; the Ducloy-Bouthors 2011 trial reported no events, so all estimable data are from the Woman Trial 2017. There was no clear evidence of difference between women receiving TXA versus placebo (RR 1.10, 95% CI 0.79 to 1.54; 20,172 women). Analysis 1.17.

(Non-prespecified) Maternal death or hysterectomy (composite outcome)

This outcome was reported in the Woman Trial 2017; the risk of death or hysterectomy was similar in both arms of the trial with approximately 5.4% of women experiencing this composite outcome (RR 0.97, 95% CI 0.87 to 1.09; 20,017 women). Analysis 1.18.

Clinical shock and **coagulopathy** were not reported in either trial.

Blood loss

Ducloy-Bouthors 2011 reported additional maternal blood loss following randomisation (measured using a graduated pouch and by weighing all swabs). Women receiving TXA versus usual care alone may be at lower risk of **blood loss of 500 mL or more** following randomisation (RR 0.50, 95% CI 0.27 to 0.93; 151 women; *low-quality evidence*). Analysis 1.19. For additional **blood loss of 1000 mL or more** following randomisation there was no clear difference between TXA and control groups as relatively few women in either group (4/77 versus 8/74) experienced this outcome (RR 0.48, 95% CI 0.15 to 1.53; 151 women). Analysis 1.20. **Mean additional blood loss** was also reported in Ducloy-Bouthors 2011 and results showed blood loss in the TXA group was on average approximately 100 mL less than in the control group the 95% CI crossed the line of no effect (mean difference (MD) -107.00 mL, 95% CI -224.44 to +10.44). Analysis 1.21.

Blood product transfusion

Although slightly fewer women in the TXA arm of the Ducloy-Bouthors 2011 trial required a transfusion of blood or blood products, overall when pooled with results from the Woman Trial 2017 there was very little difference between groups with approximately 55% of women in both arms requiring transfusion (RR 1.00, 95% CI 0.97 to 1.03; 20,167 women; I^2 = 55%,Tau^2 = 0.06; *moderate-quality evidence*). (The I^2 value suggested moderate statistical heterogeneity for this outcome, which is probably explained by clinical differences between the study participants and between study settings, but as Tau^2 was low, and almost all of the data were contributed by the Woman Trial 2017, we used a fixed-effect model.) Analysis 1.22. For blood products transfusion, the Woman Trial 2017 showed very little difference between groups for **transfusion of frozen plasma or other products** (RR 1.03, 95% CI 0.94 to 1.13, and RR 0.93, 95% CI 0.75 to 1.16, respectively). Analysis 1.23.

Additional uterotonics

The number of women receiving uterotonics (any) was reported in both trials included in this comparison. In the Woman Trial 2017, the vast majority of women received these drugs post-randomisation and similar numbers were described in the TXA and placebo arms In the Ducloy-Bouthors 2011 trial, similar numbers received post-randomisation uterotonics in the TXA and placebo arms. Overall, pooled results showed that the use of uterotonics was the same in the TXA and control groups (RR 1.00, 95% CI 1.00 to 1.00; 20,162 women; studies = 2; I^2 = 0%) Analysis 1.24. Trialists also reported comparisons by type of uterotonics women received, and for all types reported (prostaglandins, oxytocin, ergometrine and misoprostol), use in both arms of trials was very similar (prostaglandins: RR 0.96, 95% CI 0.87 to 1.05; oxytocin: RR 1.00, 95% CI 1.00 to 1.01; ergometrine: RR 1.00, 95% CI 0.97 to 1.03; misoprostol: RR 0.99, 95% CI 0.97 to 1.01). Analysis 1.25.

Maternal **admission to a higher level of care** was not reported and nor was **use of other haemostatic agents**.

Surgical interventions to control bleeding

A range of surgical and invasive non-surgical interventions were used to control bleeding.

Hysterectomy

In the Ducloy-Bouthors 2011, only one woman had an hysterectomy, and overall, the number of women undergoing hysterectomy (for any reason) was very similar in the TXA and placebo arms of the Woman Trial 2017 (RR 1.01, 95% CI 0.88 to 1.17; 20,168 women); approximately 3.5% of women had an hysterectomy. Analysis 1.26. The Woman Trial 2017 also reported the number of women undergoing hysterectomy specifically to control bleeding, again, rates were very similar in the two groups (RR 0.95, 95% CI 0.81 to 1.12; 20,017 women, *high-quality evidence*). Analysis 1.27.

There was no clear difference between groups for **arterial ligation**, 2.2% versus 2.5% undergoing this procedure in the TXA and control groups (RR 0.88, 95% CI 0.74 to 1.05; 20,168 women). **Embolisation** was infrequent, and there was no clear difference between groups for this outcome (RR 0.82, 95% CI 0.42 to 1.62; 20,168 women). Late postpartum curettage was carried out in three women in the Ducloy-Bouthors 2011 trial (RR 0.48, 95% CI 0.04 to 5.19; 151 women). The use of intrauterine tamponade was very similar in both arms of the Woman Trial 2017 (RR 0.96, 95% CI 0.87 to 1.06), as was manual removal of the placenta (RR 0.95, 95% CI 0.87 to 1.04; 20,017 women). Analysis 1.28.

In the Woman Trial 2017, the risk of **laparotomy for bleeding** was lower in the TXA group (0.8% versus 1.3% in the placebo group) (RR 0.64, 95% CI 0.49 to 0.85; 20,017 women), while the risk of receiving **brace sutures** was increased (3% in the TXA group versus 2.5% in controls) (RR 1.19, 95% CI 1.01 to 1.41; participants = 20,017). Analysis 1.28.

Maternal vascular occlusive events

The number of women suffering vascular occlusive events was reported in both trials. The Woman Trial 2017 reported the number of women having **any vascular occlusive event** (deep venous thrombosis (DVT), pulmonary embolism (PE), myocardial infarction (MI) or stroke); rates were very similar in women receiving either TXA or placebo (approximately 0.3% in each arm) (RR 0.88, 95% CI 0.54 to 1.43; 20,018 women, moderate-quality evidence). Analysis 1.29.

For each type of vascular occlusive event, rates were generally very low and there were no clear differences for these adverse events between women receiving active treatment or placebo (**DVT**: RR 0.62, 95% CI 0.20 to 1.88; **PE**: RR 0.85, 95% CI 0.44 to 1.61; **MI**: RR 0.66, 95% CI 0.11 to 3.97; **stroke**: RR 1.33, 95% CI 0.46 to 3.82) Analysis 1.30.

Other secondary outcomes were not reported (**length of maternal hospital stay, breastfeeding at hospital discharge, and maternal satisfaction with care**).

Maternal quality of life at hospital discharge or after 42 days were reported in the Woman Trial 2017. Quality of life was measured using the EQ5D for five domains, and the number of women reporting the worst scores for each domain was reported in the trial report. There was no clear difference between groups for any of the EQ5D domains reported (**mobility**: RR 0.96, 95% CI 0.58 to 1.58; **self-care**: RR 1.25, 95% CI 0.78 to 2.00; **usual activities**: RR 0.86, 95% CI 0.56 to 1.32; **pain and discomfort**: RR 0.72, 95% CI 0.35 to 1.46; and, **anxiety/depression**: RR 1.03, 95% CI 0.62 to 1.71; 19,533). Overall rates of very poor quality of life for each domain were low (approximately 0.3% or lower). Analysis 1.31; Analysis 1.32; Analysis 1.33; Analysis 1.34; Analysis 1.35.

Neonatal outcomes

The outcome, **Vascular occlusive events** in neonates was reported in the Woman Trial 2017 but there were no events (Analysis 1.36).

Comparison 2 Tranexamic acid (TXA) versus rectal misoprostol for the treatment of postpartum haemorrhage (PPH)

A single study is included in this comparison and did not report any of the review's primary outcomes. Sahaf 2014 reported no clear difference between intervention and control groups for mean blood loss (MD 0.02 mL, 95% CI -0.09 to 0.13; 200 women). Analysis 2.1.

DISCUSSION

Summary of main results

Our main analysis includes data from two trials, one was a multi-centre trial with a large sample size, and overall 20,212 woman with postpartum haemorrhage (PPH) were recruited to these trials. Both trials examined the use of tranexamic acid (TXA) to treat PPH. Intravenous (IV) TXA when added to standard treatment appears to reduce death from bleeding with an absolute reduction in death from bleeding of four per 1000 and a relative reduction of approximately 19% between the TXA and placebo groups (*moderate-quality evidence*). The reduction in death due to bleeding was primarily in women given treatment within three hours of giving birth with no apparent reduction when given after three hours. Maternal death from all causes was also reduced in the TXA group although the 95% confidence interval crossed the line of no effect for this outcome; the absolute reduction in death from all cause was three per 1000 (from 25 per 1000 to 22 per 1000) (*moderate-quality evidence*). There were no clear differences between groups for some key outcomes; rates of any serious morbidity were similar in intervention and control groups (*high-quality evidence*), as were rates of hysterectomy to control bleeding (*high-quality evidence*), need for blood or blood product transfusion (*moderate-quality evidence*) or maternal vascular occlusive events (*moderate-quality evidence*). Data from a trial with a small sample size suggest additional maternal blood loss of 500 mL or more may be reduced in women receiving TXA (*low-quality evidence*). There was an increase in the use of brace sutures in the TXA group, whereas there was a reduction in the need for laparotomy for bleeding in the TXA treated group.

One study comparing TXA with rectal misoprostol reported on only one outcome (mean blood loss) and identified no clear difference between groups.

Overall completeness and applicability of evidence

We assessed the effect of antifibrinolytic drugs in women with primary PPH. Of the four drugs included for evaluation in this review (aprotinin, TXA, epsilon-aminocaproic acid (EACA) and aminomethylbenzoic acid), only one (TXA) was evaluated in

randomised controlled trials (RCTs). We had also planned to examine the effect of antifibrinolytics by route of administration (oral, IV, intramuscular (IM) and buccal). However, included studies only used the IV route. We had also planned to look at the effects of interventions depending on the severity of haemorrhage at randomisation (blood loss ≤ 1000 mL, > 1000 mL). We were unable to carry out this planned additional analyses as data were not presented separately for women with less or more severe haemorrhage.

TXA was assessed in three included RCTs, of which only two provided data for the main analysis. A total of 20,172 women were included in the two trials with over 99% from one trial. The trials were conducted in high-, middle- and low-income settings. All pre-specified primary outcomes were analysed (mortality due to bleeding, all-cause mortality and serious maternal morbidity (renal or respiratory failure, cardiac arrest or multiple organ failure)). Also, side effects, specifically vascular occlusive events were analysed. There were no data on some secondary outcomes including shock, and coagulopathy. The large sample size of the pooled studies suggest that the use of TXA when added to standard care could reduce mortality from bleeding and overall mortality without increasing the risk of vascular occlusive events. Although the data showed that TXA reduced the number of women who had blood loss of over 500 mL, the quality of this evidence was low.

Quality of the evidence

Two trials contributed data to the main comparison in the review. One was a trial with a relatively small sample size comparing TXA plus usual care with usual care alone; this trial was not blinded and lack of blinding may have increased the risk of both performance and detection bias (Ducloy-Bouthors 2011). The second trial had a large sample size and was placebo-controlled and assessed as at low risk of bias for all domains (Woman Trial 2017). For most outcomes the vast majority of data were from the Woman Trial 2017.

For important outcomes we graded the evidence using Gradepro. Some Grade decisions were difficult to assess. Most of the data from the Woman Trial 2017 was from low- and middle-income settings. We would not expect the biological effects of TXA for women in different settings to vary. We did not downgrade for indirectness**.** Inconsistency between trials was not an important issue in this review as findings were dominated by a single trial. Overall, evidence was mainly graded as moderate to high quality. The main reason for downgrading evidence for some outcomes was imprecision of effect estimates; even with a very large sample size, with rare events such as maternal death, the 95% confidence interval may suggest some uncertainty in findings.

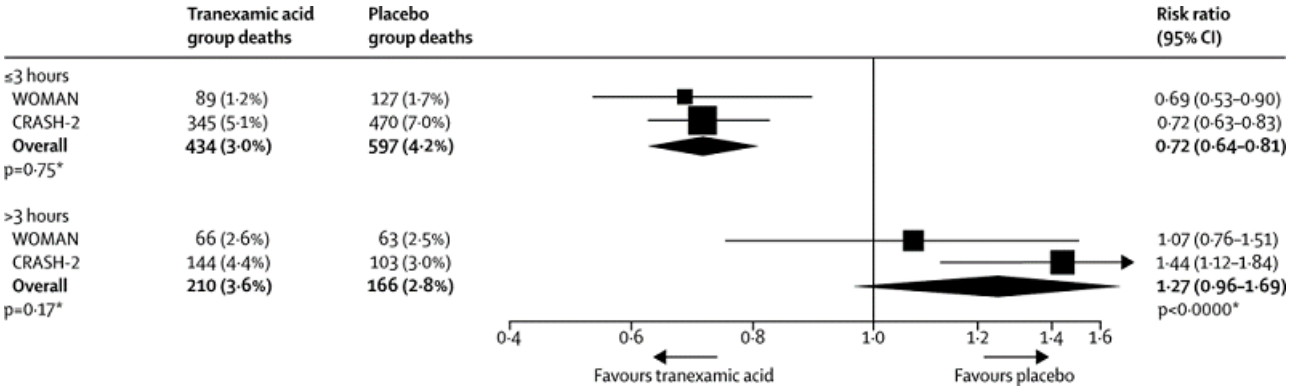
Potential biases in the review process

We followed Cochrane methods to extract data and to assess risk of bias and the certainty of the evidence. Two review authors independently extracted data, and a third review author examined data extraction forms to identify any discrepancies between review authors. The review team includes trialists involved in the Woman Trial 2017. These review authors were not involved in data extraction or assessing risk of bias for this trial. However, review authors involved in one of the included studies were involved in the selection of outcomes and the interpretation of the data. Data entry was double checked. Any discrepancies regarding assessment of risk of bias or grading the evidence were resolved by discussion within the team.

Agreements and disagreements with other studies or reviews

There is evidence from systematic reviews that the antifibrinolytic drug, TXA, reduces blood loss and the need for transfusion in surgery (Henry 2011; McNicol 2016; Perel 2013). In our review, although there was a reduction in blood loss in one small trial, we did not see a reduction in the need for transfusion for the treatment of PPH. TXA did not reduce the use of uterotonics, arterial ligation, embolisation or hysterectomy. One explanation could be that the decision about the need for these interventions is made soon after the onset of PPH and before the trial intervention is given or too soon for TXA to exert its effect. There was an increase in the use of brace sutures in women who gave birth by caesarean section, although the effect of TXA did not differ by mode of giving birth. The review by Henry and colleagues showed a trend towards reduction in the need for re-operation due to bleeding. In our review, there was a significant reduction in the need for laparotomy for bleeding.The results of a systematic review of antifibrinolytics for trauma, that are based largely on the CRASH-2 trial of 20,211 patients, showed that TXA reduces death due to bleeding in trauma by a relative 15% (Ker 2015). In this review, we saw a similar effect on death due to bleeding with a relative reduction of 19%. In trauma, treatment with TXA within one hour of injury was associated with a 32% relative reduction in risk of death due to bleeding, and treatment between one and three hours after injury was associated with a 21% reduction. Treatment after three hours of injury was associated with a 44% relative increase in risk of death due to bleeding. In this review however, where women received treatment with TXA between one and three hours after birth, it was associated with a 40% relative reduction in risk of death due to bleeding. For women who received treatment within one hour of the birth, although we saw less deaths due to bleeding in the treatment group, there were no clear differences between the intervention and control groups. Where women were treated after three hours, there was more deaths due to bleeding, but there was no clear difference between the intervention and control groups. However, there is no reason to believe that the biological action of TXA would differ between bleeding trauma patients and women with PPH. Indeed the results of a pre-specified analysis presented in the final WOMAN trial publication (Woman Trial 2017) shows the consistency of the WOMAN results with the CRASH-2 results (Figure 4). Additionally, a meta-analysis of individual patient-level data from 40 138 bleeding patients showed that deaths from PPH peak at two to three hours after childbirth and every 15 minutes of treatment delay with TXA appears to decrease the benefit by about 10%, with no benefit after three hours (Gayet-Ageron 2017). Taken together, the evidence from these trials strongly indicates that treatment within three hours is the most effective. The recently updated World Health Organization (WHO) guideline on the use of TXA for the treatment of PPH recommends that TXA is given as soon as possible to achieve clinical benefits as most deaths due to PPH occur within the first two to three hours after birth and did not support the use of TXA more than three hours after birth (WHO 2017).

Figure 4. Time to treatment. Effect of TXA on death due to bleeding by time to treatment in the WOMAN and CRASH-2 trials (reproduced from http://dx.doi.org/10.1016/S0140-6736(17)30638-4)



AUTHORS' CONCLUSIONS

Implications for practice

The use of the antifibrinolytic drug tranexamic acid (TXA) appears to reduce the risk of death due to bleeding without increasing the risk of vascular occlusive events. There is evidence from this review and from another major trial that the effect on death due to bleeding depends on the time interval between giving birth and the commencement of treatment, and this would suggest that TXA should be given as early as possible and within three hours of giving birth.

Implications for research

Our review found data for only the antifibrinolytic drug, TXA; we did not identify trials examining the use of other antifibrinolytic drugs. As the use of the antifibrinolytic aprotinin in other bleeding conditions is controversial, trials of this agent in the treatment of postpartum haemorrhage (PPH) are unlikely in the near future.

We identified that only intravenous administration of TXA was evaluated. Many women die from PPH, having delivered at home or in facilities in resource-poor settings where intravenous drugs cannot be administered, there is urgent need for trials of alternative routes of administration.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Ducloy-Bouthors 2011

Methods	Parallel RCT.
Participants	Setting: 8 obstetric units, France. Dates of recruitment: 2005 to 2008.

Ducloy-Bouthors 2011 *(Continued)*

	152 women randomised. **Inclusion criteria:** women with PPH > 800 mL within 2 hours after vaginal delivery. **Exclusion criteria:** age < 18 years, no informed consent, caesarean section, known haemostatic abnormality, history of thrombosis or epilepsy.
Interventions	Experimental intervention: loading dose of 4 g TXA mixed with 50 mL saline, administered intravenously over 1 hour followed by maintenance dose of 1 g/hour for 6 hours (n = 78). Control/Comparison intervention: no TXA (n = 74).
Outcomes	Primary outcome: volume of blood loss between inclusion (T1) and after 6 hours (T4). Secondary outcomes: duration of bleeding; anaemia; need for invasive procedures; need for transfusion; major thrombotic events, renal failure, seizures; minor side effects.
Notes	Funding: French Ministry of Health. Conflict of interest: "The authors declare that they have no competing interests".

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"The randomisation sequence was generated by a centralized computer, and randomisation was balanced by centre."
Allocation concealment (selection bias)	Unclear risk	Not described.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label trial.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	All outcomes: "Although the study was not blinded, obstetrician and midwives were not aware of the treatment group, so the rest of the management, blood loss measurement and transfusion algorithm were conducted regardless of the group allocation". However, as the treatment group would have an IV infusion ongoing for 7 hours and control group none, it would be difficult to blind in this situation. No explanation given as to how this was achieved. Blood loss outcome: "Midwives unaware of the group allocation measure the volume of haemorrhage in the graduated collection bag at each time point". However, as the treatment group would have an IV infusion ongoing for 7 hours and control group none, it would be difficult to blind in this situation. No explanation given as to how this was achieved. Death: ascertainment of death would be unlikely to be biased by lack of blinding.
Incomplete outcome data (attrition bias) All outcomes	Low risk	1 woman assigned to TXA was later found not to be eligible and was excluded from ITT analysis.
Selective reporting (reporting bias)	Unclear risk	Retrospectively registered. Unable to compare reported results to pre-specified outcomes.

Ducloy-Bouthors 2011 *(Continued)*

Other bias	Low risk	Other bias not apparent.

Sahaf 2014

Methods	Described as double-blind randomised trial in Tabriz, Iran.
Participants	200 women after caesarean or vaginal birth with PPH (500 mL to 1500 mL) after routine therapies for controlling bleeding. Study conducted between June 2011 and June 2013.
Interventions	1 g IV TXA repeated after 30 minutes versus 5 200 micrograms rectal misoprostol. Prostatglandin F2α in case of treatment failure in both groups.
Outcomes	Estimation of blood loss (weighing sponges).
Notes	There was no information about how women were randomised. There was limited information on results. Funding: Trial reported stated "nil" under source of funding. Conflict of interest: Trial report stated "none declared".

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Divided into "two equal groups" using computer software.
Allocation concealment (selection bias)	Unclear risk	No information (2 equal groups).
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding.
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	It was not clear if there was any loss to follow-up or missing data. 2 equal-sized groups.
Selective reporting (reporting bias)	Unclear risk	Protocol registered retrospectively.
Other bias	Unclear risk	Some differences between groups at baseline in terms of episiotomy and perineal laceration.

Woman Trial 2017

Methods	Randomised, double-blind, placebo-controlled trial.
Participants	**Number randomised: 20,060 women recruited and randomised** Setting: 193 hospitals or maternal health facilities from 21 high-, middle- or low-income countries in which women have delivered their babies or were secondary hospitalised after delivery due to a diagnosis of PPH (recruitment in high-income countries: UK: 569 women; recruitment in low- and middle-income countries: Nigeria: 5711; Pakistan: 5282; Uganda: 2235; Kenya: 1031; Cameroon: 893; Sudan: 860; Tanzania: 538; Nepal: 533; Zambia: 496; Albania: 485; Democratic Republic of Congo: 457; Bangladesh: 325; Ethiopia: 302; Burkina Faso: 142; Jamaica: 73; Ghana: 41; Papua New Guinea: 38; Egypt: 33; Colombia: 8; Cote d'Ivoire: 8). Dates of recruitment: March 2010 to April 2016. **Inclusion criteria:** • Legally adult women (aged 16 years or older). • With clinically diagnosed PPH (estimated blood loss after vaginal delivery of a baby > 500 mL OR > 1000 mL from caesarean section OR estimated blood loss enough to compromise the haemodynamic status of the woman) following vaginal delivery of a baby or caesarean section. • Women who have delivered their babies at a participating hospital or outside a participating hospital, with hospital admission following delivery. • Responsible clinician is substantially uncertain as to whether or not to use TXA. • Consent has been given following approved procedures. **Exclusion criteria:** • Women for whom the responsible clinician considers there is a clear indication for TXA. • Women for whom the responsible clinician considers there is a clear contraindication for TXA use (e.g. a known thromboembolic event during pregnancy). • If the responsible clinician is certain about the use or the non use of TXA. • Women recruited to the trial received all usual care but were also randomly allocated to receive TXA or placebo.
Interventions	**Experimental intervention** First dose: IV TXA 2 ampoules = 1 g at approximate rate of 1 mL/minute as soon after randomisation followed by second dose of 2 ampoules = 1 g (at approximate rate of 1 mL/minute) if after 30 minutes bleeding continues or if it stops and restarts within the 24 hours after the first dose. Clinicians advised that the trial treatment should not be mixed with blood for transfusion or infusion solutions containing penicillin or mannitol. Each treatment pack contained 4 x 500 mg ampoules of TXA, 2 x sterile 10 mL syringe and 21 FG needle and stickers for attaching to data forms and patient medical records (n = 10,051). **Control intervention**: placebo (sodium chloride 0.9% contained in ampoules and packaging with identical appearance). Same regimen and identical packs as those used in the experimental group (n = 10,009).
Outcomes	**Outcomes:** **(measured at hospital discharge or on day 42 if still in hospital)** **Primary outcome**: composite of death from all causes or hysterectomy within 42 days of randomisation (Participating clinicians were requested to record the immediate cause of death (the final pathophysiological process leading to death) rather than the underlying cause of death and were trained accordingly. In the event that there was more than 1 cause, clinicians were asked to record the main cause.) **Secondary outcomes:**

Woman Trial 2017 *(Continued)*

- Death was assessed separately and immediate main cause of death was also recorded (final pathophysiological process leading to death), death due to bleeding considered as secondary outcome.
- Vascular occlusive events (deep-vein thrombosis, pulmonary embolism, myocardial infarction and stroke).
- Surgical Interventions including intrauterine tamponade; embolisation; brace suture (B-Lynch/Cho); artery ligation, to achieve haemostasis; hysterectomy and laparotomy done after randomisation to control bleeding.
- Complications (renal failure, cardiac failure, respiratory failure, hepatic failure, sepsis and seizures).
- Other untoward medical events (adverse events).
- Quality of life measured using EQ5D at discharge from the randomising hospital or in hospital at 42 days after randomisation.
- Status of any vascular occlusive events in breastfed babies assessed as per normal clinical practice with no special tests done.

Other outcomes reported in the protocol published in 2010 and not listed in final publication:

- Medical events including adult respiratory distress syndrome, hypertensive disorders of pregnancy (including HELLP Syndrome, eclampsia, toxaemia of pregnancy) and other adverse events reported.
- Length of stay at hospital/time spent at an intensive care unit.
- Receipt of mechanical ventilation.

Notes	The sample size was increased from 15,000 to 20,000 woman as the trial was ongoing to allow for sufficient power to detect a reduction in maternal mortality alone. Funding: London School of Hygiene & Tropical Medicine, Pfizer, UK Department of Health, Wellcome Trust, and Bill & Melinda Gates Foundation. Conflict of interest: the trial report stated that there were no conflicts of interest.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was generated and secured by an independent statistical consultant from Sealed Envelope Ltd (UK). The codes were then made available to Brecon Pharmaceuticals Limited (UK) explicitly for the treatment packs to be created in accordance with the randomisation list.
Allocation concealment (selection bias)	Low risk	After eligibility was confirmed and consent procedures completed, baseline information was collected on the entry form. Women were then randomly allocated to TXA or placebo group by selection of the lowest numbered treatment pack form from a box containing eight numbered packs that were identical apart from the pack number. (An emergency un-blinding service was available from the pharmaceutical company.) (No information was provided in the trial report re any verification of whether sequence order was followed or whether any packs were not used.)
Blinding of participants and personnel (performance bias) All outcomes	Low risk	All outcomes: use of TXA versus placebo with ampoules and packaging identical in appearance. Participants, caregivers and study staff (site investigators and trial co-ordinating centre staff) were blinded to treatment allocation. The masking was done by Brecon Pharmaceuticals Limited, Hereford, UK and involved the removal of the original manufacturer's label and replacement with the clinical trial label bearing the randomisation number, which was used as the pack identification. Apart from the randomisation number, all pack label texts were identical for TXA and placebo. Correct masking and coding of

Woman Trial 2017 *(Continued)*

		ampoules was checked by independent random testing of each batch by high-performance liquid chromatography to confirm the contents of the ampoules.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	All outcomes were measured at hospital discharge or on day 42 if still in hospital. Data were sent to the trial co-ordinating centre by direct entry into an electronic database or by using encrypted data forms (which were sent by fax, email, or uploaded to a secure server). Data quality was monitored using a combination of centralised consent monitoring, statistical data checking, and site visits at which patient data forms were compared with clinical case notes. Death is an objective outcome that could not be "manipulated". Cause of death is more subject to be influenced by the knowledge of intervention received but treatment allocation group was blinded so the risk is low.
Incomplete outcome data (attrition bias) All outcomes	Low risk	7 women withdrew their consent after randomisation and data were excluded from the analyses (4 in the TXA group and 3 in the placebo group). 32 women did not have primary outcome data (11 in active group and 21 in control group) and were thus excluded from analyses. Reasons for incompleteness were not described in the trial report. However, overall there were only small numbers missing so unlikely to impact on results.
Selective reporting (reporting bias)	Low risk	Most outcomes pre-specified in the protocol were reported in final publication except length of hospital stay and receipt of mechanical ventilation. Primary outcome: composite of death from all causes or hysterectomy within 42 days of randomisation.
Other bias	Low risk	No other risk of bias identified.

HELLP: haemolysis, elevated liver enzymes, low platelet count
ITT: intention-to-treat
IV: intravenous
PPH: postpartum haemorrhage
RCT: randomised controlled trial
TXA: tranexamic acid

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

Study	Reason for exclusion
Ahonen 2013	This trial looks at treatment for women with severe PPH. It examines prothrombin complex plus fibrinogen versus fresh frozen plasma plus fibrinogen if needed. This comparison is not relevant for this review which focuses on antifibrinolytic drugs.
Bruynseels 2016	This trial looks at treatment for women with severe PPH. It examines fibrinogen concentrate versus placebo. This comparison is not relevant for this review which focuses on antifibrinolytic drugs.
Ducloy-Bouthors 2016	This ongoing trial looks at treatment for women with severe PPH. It examines fibrinogen versus placebo. This comparison is not relevant for this review which focuses on antifibrinolytic drugs.
Lavigne-Lissalde 2015	This trial looks at treatment for women with PPH unresponsive to uterotonics. It examines an infusion of recombinant human factor VIIa versus usual care. This comparison is not relevant for this review which focuses on antifibrinolytic drugs.

Study	Reason for exclusion
Paidas 2015	This ongoing trial looks at treatment for women with PPH and low fibrinogen levels. It examines fibrinogen concentrate versus placebo. This comparison is not relevant for this review which focuses on antifibrinolytic drugs.
Sadeghipour 2013	This study was not clearly about PPH but about the treatment of uterine atony.
von Beckerath 2016	This is a comparison of a topical mechanical agent versus a mechanical device to treat PPH. This comparison is not relevant for this review which focuses on antifibrinolytic drugs.
Wikkelso 2015	This trial looks at treatment for women with severe PPH. It examines fibrinogen concentrate versus placebo. This comparison is not relevant for this review which focuses on antifibrinolytic drugs.
Wiznitzer 2011	The intervention in this study is a dressing for vaginal tears; there was no evidence from the trial registration that women had PPH.

PPH: postpartum haemorrhage

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

Ayedi 2011

Methods	Described as a prospective randomised double-blind placebo-controlled trial.
Participants	74 women following caesarean section with spinal anaesthesia with postpartum bleeding due to uterine atony not controlled by oxytocin. Inclusion criteria: women aged 20-40 years with uterine atony receiving sulprostone. Exclusion: women with abnormal placentation, severe pre-eclampsia, coagulopathy or uterine rupture. Women with contraindication to tranexamic acid. Women with accidental surgical complications (e.g. bladder or colon damage) were not included.
Interventions	Women were divided into 2 groups of 37 women. Tranexamic acid group: 10 mg/kg of tranexamic acid within 12 minutes as an induction dose, followed by a maintenance dose 1 mg/kg/hour during the following 2 hours. Control: placebo with same volumes from identical 20 mL syringes.
Outcomes	Blood loss, blood transfusions, deep vein thrombosis, hysterectomy.
Notes	Results from this study are reported in a brief abstract and in an unpublished manuscript. There was no information about how women were randomised. There was limited information on results. We have tried to contact the author. If further information is available for the next update we will reassess this study for inclusion.

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

Sambou 2015

Trial name or title	Tranexamic acid to reduce blood loss in hemorrhagic caesarean delivery: a multicenter randomised double blind placebo controlled dose ranging study - TRACES.
Methods	Multicentre randomised double-blind placebo-control therapeutic and pharmaco-biological dose-ranging study.

Sambou 2015 *(Continued)*

Participants	Inclusion criteria: Women: • Experiencing a bleeding volume of more than 800 mL • Due to surgery or to atony uterine • During an elective or non-emergeny caesarean section • After complete information and consent signature • Covered by social security. Reference non-haemorrhagic group Exclusion criteria: Women unable to consent (< 18 years old or incapable people and specially protected mentioned in the article L1121-5 to L1121-8) RCP medical contraindication to TXA acid such as • Hypersensibility to the product or excipient • Previous or ongoing arterial or venous thrombosis • Coagulopathy, except DIC associated with a predominant fibrinolytic profile • Renal failure • Previous seizures • Intrathecal or intraventricular administration. Obstetrical contraindication to TXA • Severe HELLP syndrome (platelet count < 50,000/m^3 or renal failure prior to the caesarean. Protocol-related contraindication to inclusion • Emergent caesarean section • Administration of TXA before inclusion • Inherited haemorrhagic diseases or low molecular weight heparin within 24 hours before inclusion • Previous inclusion in an interventional trial since the 2 months before caesarean section
Interventions	Experimental: TXA 1 g or TXA 0.5 g intravenous as bolus over 1 minute. Control: placebo (saline).
Outcomes	Primary outcome measures: bleeding between inclusion and 6 hours after inclusion. Secondary outcomes: • Postpartum anaemia (days 2 and 5) • Postpartum blood loss (day 2) • Maternal morbidity i.e. haemostatic interventions and organ failure and intensive care unit admission up to 42 days • Death up to 42 days • Biological fibrinolysis inhibition (percentage of women for which D Dimers increase is blunted) • Urinary urea and creatinuria on timed diuresis • The number of women developing an oliguria or a renal failure • Deep vein thrombosis or pulmonary embolism • Visual disturbances • Nausea • Peak plasma concentration (Cmax) in venous blood • Area under the plasma concentration versus time curve (AUC) in venous blood • Lagtime between thrombin and plasmin peaks (s) in venous blood • Peak plasma concentration (Cmax) in uterine bleeding • Area under the plasma concentration versus time curve (AUC) in uterine bleeding • Lagtime between thrombin and plasmin peaks (s) in uterine bleeding • TXA plasma concentration

Sambou 2015 *(Continued)*

	• TXA urinary excretion
Starting date	March 2016. Final data collection February 2018.
Contact information	Anne-Sophie Ducloy-Bouthors, MD; anne-sophie.ducloy@chru-lille.fr Hospital Jeanne de Flandre - CHRU de Lille, France.
Notes	Sponsor: University Hospital, Lille. ClinicalTrials.gov identifier: NCT02797119

Winikoff 2016

Trial name or title	Effectiveness of tranexamic acid when used as an adjunct to misoprostol for the treatment of postpartum haemorrhage.
Methods	This study is a randomised, double-blind, placebo-controlled trial that will enrol 250 women (125 per study arm). Phase 4 trial.
Participants	The objective of the study is to determine the efficacy and tolerability of oral TXA when used as an adjunct to misoprostol for treatment of postpartum haemorrhage. Women will be diagnosed with postpartum haemorrhage if blood loss reaches 700 mL in the calibrated receptacle. Inclusion criteria: • Women who delivery vaginally • Women who experience postpartum haemorrhage defined as blood loss ≥ 700 mL • Women capable of giving consent Exclusion criteria: • Clear contraindication for TXA such as known allergy or thromboembolic event during pregnancy • Women delivering via caesarean section • Provider feels that the woman, at presentation for delivery, is not in a position to give appropriate informed consent
Interventions	Women diagnosed with postpartum haemorrhage will be randomised to receive either TXA or placebo, both in tablet form. All participants will receive 800 mcg sublingual misoprostol (4 tablets 200 mcg each).
Outcomes	Primary: proportion of women with bleeding controlled with the study regimens alone, without recourse to further treatment. Secondary: rate of severe postpartum haemorrhage (> 1000 mL total blood loss); mean/median blood loss; proportion of women with bleeding controlled at different time intervals (20, 40, 60, 120 minutes); proportion of women who are given uterotonic agents after initial treatment; serious intervention (defined as blood transfusion, interventions for tissue repair, surgical intervention (including curettage, vacuum aspiration for retained placental tissue, hysterectomy, surgical uterine artery ligature)); proportion of women who receive additional drugs; proportion of women who receive additional interventions (i.e. suturing); proportion of women who experience an adverse event; proportion of women who experience side effects; proportion of women who find the procedure tolerable and acceptable as indicated in an acceptability scale.
Starting date	October 2016. Final data collection October 2017.
Contact information	Centre hospitalier Abass Ndao, Dakar, Sengal. Contact: Marie Antoinette Cmara +221 775376984.

Winikoff 2016 *(Continued)*	Centre hospitalier Regional de Thies, Senegal. Contact: Rachel Sarr +221 776086090. Hung Vuong Hospital, Ho Chi Minh City, Vietnam. Contact: Nguyen Thi Nhu Ngog, MD Principal Investigator: Beverly Winikoff, Gynuity Health Projects
Notes	Sponsored by Gynuity Health Projects.

DIC: disseminated intravascular coagulation
HELLP: haemolysis, elevated liver enzymes, low platelet count
TXA: tranexamic acid

DATA AND ANALYSES

Comparison 1. Standard care plus IV tranexamic acid versus placebo or standard care alone for the treatment of PPH

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Maternal mortality due to bleeding	2	20172	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.65, 1.00]
2 Maternal mortality due to bleeding (subgroup by mode of birth)	1	20014	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.66, 1.00]
2.1 Vaginal delivery	1	14191	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.64, 1.05]
2.2 Caesarean	1	5823	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.54, 1.18]
3 Maternal mortality due to bleeding (subgroup time from birth)	1	20011	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.66, 1.01]
3.1 Less than 1 hour	1	9572	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.55, 1.16]
3.2 1-3 hours	1	5356	Risk Ratio (M-H, Fixed, 95% CI)	0.60 [0.41, 0.88]
3.3 More than 3 hours	1	5083	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.76, 1.51]
4 Maternal mortality (all causes)	2	20172	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.74, 1.05]
5 Maternal mortality (all cause) (subgroup by mode of birth)	1	20016	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.74, 1.06]
5.1 Vaginal delivery	1	14191	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.69, 1.07]
5.2 Caesarean	1	5825	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.68, 1.26]
6 Maternal mortality (all cause) (subgroup time from birth)	1	20011	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.75, 1.06]
6.1 Less than 1 hour	1	9572	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.72, 1.33]
6.2 1-3 hours	1	5356	Risk Ratio (M-H, Fixed, 95% CI)	0.69 [0.49, 0.96]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.3 More than 3 hours	1	5083	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.75, 1.33]
7 Serious maternal morbidity (any)	1	20015	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.83, 1.19]
8 Serious maternal morbidity (any) (subgroup by mode of birth)	1	20013	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.82, 1.19]
8.1 Vaginal birth	1	14189	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.77, 1.21]
8.2 Caesarean	1	5824	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.76, 1.44]
9 Serious maternal morbidity (any) (subgroup by time of drug use from birth)	1	20007	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.83, 1.20]
9.1 Drug intake < 1 hour	1	9570	Risk Ratio (M-H, Fixed, 95% CI)	1.12 [0.81, 1.55]
9.2 Drug intake 1-3 hours	1	5354	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.62, 1.21]
9.3 Drug intake > 3 hours	1	5083	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.75, 1.36]
10 Serious maternal morbidity: multiple organ failure	2	20168	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.71, 1.23]
11 Serious maternal morbidity: maternal respiratory failure	1	20018	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.67, 1.12]
12 Serious maternal morbidity: Cardiac arrest	1	20018	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.73, 1.23]
13 Serious maternal morbidity: Maternal renal failure	2	20169	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [0.85, 1.39]
14 Serious maternal morbidity: Hepatic failure	1	20018	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.58, 1.60]
15 Serious maternal morbidity: Maternal Seizure	2	20169	Risk Ratio (M-H, Fixed, 95% CI)	0.76 [0.49, 1.20]
16 Maternal Intensive care admission	1	151	Risk Ratio (M-H, Fixed, 95% CI)	0.58 [0.14, 2.33]
17 Mortality from causes other than bleeding	2	20172	Risk Ratio (M-H, Fixed, 95% CI)	1.10 [0.79, 1.54]
18 Non-prespecified composite outcome: death or hysterectomy	1	20017	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.87, 1.09]
19 Blood loss 500 mL or more after randomisation	1	151	Risk Ratio (M-H, Fixed, 95% CI)	0.50 [0.27, 0.93]
20 Blood loss 1000 mL or more after randomisation	1	151	Risk Ratio (M-H, Fixed, 95% CI)	0.48 [0.15, 1.53]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
21 Mean blood loss (mL)	1	151	Mean Difference (IV, Fixed, 95% CI)	-107.0 [-224.44, 10.44]
22 Blood transfusion (all)	2	20167	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.97, 1.03]
23 Blood products transfusion	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
23.1 Frozen plasma	1	20013	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.94, 1.13]
23.2 Other product transfusion	1	20013	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.75, 1.16]
23.3 Any transfusion	1	19916	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.97, 1.02]
24 Post randomisation additional uterotonics	2	20162	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [1.00, 1.00]
25 Post randomisation additional uterotonics	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
25.1 Prostaglandin	2	20162	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.87, 1.05]
25.2 Oxytocin	1	20018	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [1.00, 1.01]
25.3 Ergometrine	1	20018	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.97, 1.03]
25.4 Misoprostol	1	20018	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.97, 1.01]
26 Hysterectomy (provided it is not part of the intervention under investigation)	2	20168	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.88, 1.17]
27 Hysterectomy to control bleeding	1	20017	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.81, 1.12]
28 Post randomisation surgical intervention to control bleeding	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
28.1 Arterial ligation	2	20168	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.74, 1.05]
28.2 Embolisation	2	20168	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.42, 1.62]
28.3 Late postpartum curettage (after day 7)	1	151	Risk Ratio (M-H, Fixed, 95% CI)	0.48 [0.04, 5.19]
28.4 Intrauterine tamponade	1	20017	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.87, 1.06]
28.5 Manual removal of placenta	1	20017	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.87, 1.04]
28.6 Laparotomy for bleeding	1	20017	Risk Ratio (M-H, Fixed, 95% CI)	0.64 [0.49, 0.85]
28.7 Brace sutures	1	20017	Risk Ratio (M-H, Fixed, 95% CI)	1.19 [1.01, 1.41]
29 Side effects of the intervention: any maternal vascular occlusive event	1	20018	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.54, 1.43]

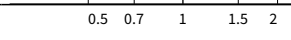
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
30 Side effects of the intervention: maternal vascular occlusive events	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
30.1 DVT	2	20169	Risk Ratio (M-H, Fixed, 95% CI)	0.62 [0.20, 1.88]
30.2 Pulmonary embolism	1	20018	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.44, 1.61]
30.3 Myocardial infarction	1	20018	Risk Ratio (M-H, Fixed, 95% CI)	0.66 [0.11, 3.97]
30.4 Stroke	1	20018	Risk Ratio (M-H, Fixed, 95% CI)	1.33 [0.46, 3.82]
31 Quality of Life: EQ5D Mobility	1	19533	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.58, 1.58]
32 Quality of Life: EQ5D Self care	1	19533	Risk Ratio (M-H, Fixed, 95% CI)	1.25 [0.78, 2.00]
33 Quality of Life: EQ5D Usual activities	1	19533	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.56, 1.32]
34 Quality of Life: EQ5D Pain/discomfort	1	19533	Risk Ratio (M-H, Fixed, 95% CI)	0.72 [0.35, 1.46]
35 Quality of Life: EQ5D Anxiety/depression	1	19533	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.62, 1.71]
36 Side effects of the intervention: neonatal vascular occlusive event	1	20018	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 1.1. Comparison 1 Standard care plus IV tranexamic acid versus placebo or standard care alone for the treatment of PPH, Outcome 1 Maternal mortality due to bleeding.

Study or subgroup	Tranexamic acid n/N	Placebo/std care n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Ducloy-Bouthors 2011	0/77	0/74			Not estimable
Woman Trial 2017	155/10036	191/9985		100%	0.81[0.65,1]
Total (95% CI)	**10113**	**10059**		**100%**	**0.81[0.65,1]**
Total events: 155 (Tranexamic acid), 191 (Placebo/std care)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2(P=0.05)					

Analysis 1.2. Comparison 1 Standard care plus IV tranexamic acid versus placebo or standard care alone for the treatment of PPH, Outcome 2 Maternal mortality due to bleeding (subgroup by mode of birth).

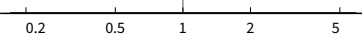
Study or subgroup	Tranexamic acid n/N	Placebo/std care n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.2.1 Vaginal delivery					
Woman Trial 2017	110/7083	135/7108		70.73%	0.82[0.64,1.05]
Subtotal (95% CI)	**7083**	**7108**		**70.73%**	**0.82[0.64,1.05]**
Total events: 110 (Tranexamic acid), 135 (Placebo/std care)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.58(P=0.11)					
1.2.2 Caesarean					
Woman Trial 2017	45/2952	55/2871		29.27%	0.8[0.54,1.18]
Subtotal (95% CI)	**2952**	**2871**		**29.27%**	**0.8[0.54,1.18]**
Total events: 45 (Tranexamic acid), 55 (Placebo/std care)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.15(P=0.25)					
Total (95% CI)	**10035**	**9979**		**100%**	**0.81[0.66,1]**
Total events: 155 (Tranexamic acid), 190 (Placebo/std care)					
Heterogeneity: Tau^2=0; Chi^2=0.01, df=1(P=0.91); I^2=0%					
Test for overall effect: Z=1.95(P=0.05)					
Test for subgroup differences: Chi^2=0.01, df=1 (P=0.91), I^2=0%					



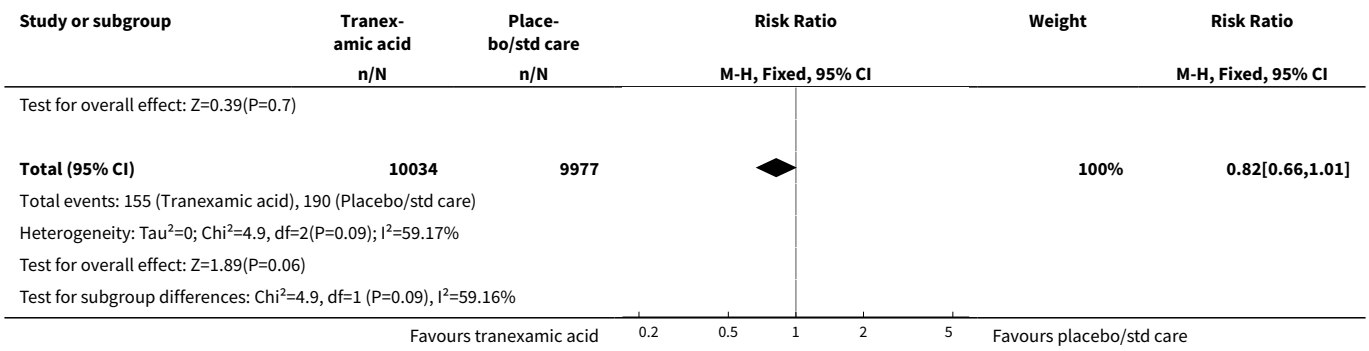
Favours tranexamic acid — Favours placebo/std care

Analysis 1.3. Comparison 1 Standard care plus IV tranexamic acid versus placebo or standard care alone for the treatment of PPH, Outcome 3 Maternal mortality due to bleeding (subgroup time from birth).

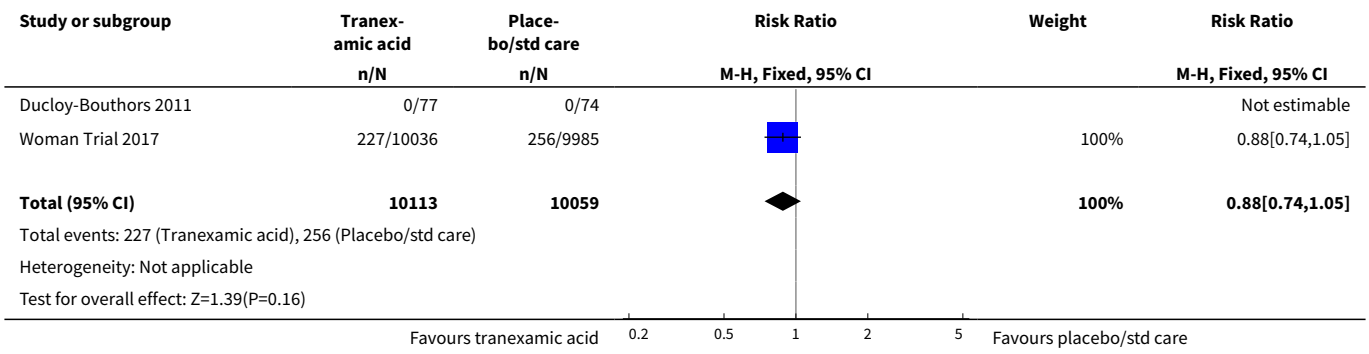
Study or subgroup	Tranexamic acid n/N	Placebo/std care n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.3.1 Less than 1 hour					
Woman Trial 2017	49/4846	60/4726		31.98%	0.8[0.55,1.16]
Subtotal (95% CI)	**4846**	**4726**		**31.98%**	**0.8[0.55,1.16]**
Total events: 49 (Tranexamic acid), 60 (Placebo/std care)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.19(P=0.23)					
1.3.2 1-3 hours					
Woman Trial 2017	40/2674	67/2682		35.22%	0.6[0.41,0.88]
Subtotal (95% CI)	**2674**	**2682**		**35.22%**	**0.6[0.41,0.88]**
Total events: 40 (Tranexamic acid), 67 (Placebo/std care)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.59(P=0.01)					
1.3.3 More than 3 hours					
Woman Trial 2017	66/2514	63/2569		32.8%	1.07[0.76,1.51]
Subtotal (95% CI)	**2514**	**2569**		**32.8%**	**1.07[0.76,1.51]**
Total events: 66 (Tranexamic acid), 63 (Placebo/std care)					
Heterogeneity: Not applicable					



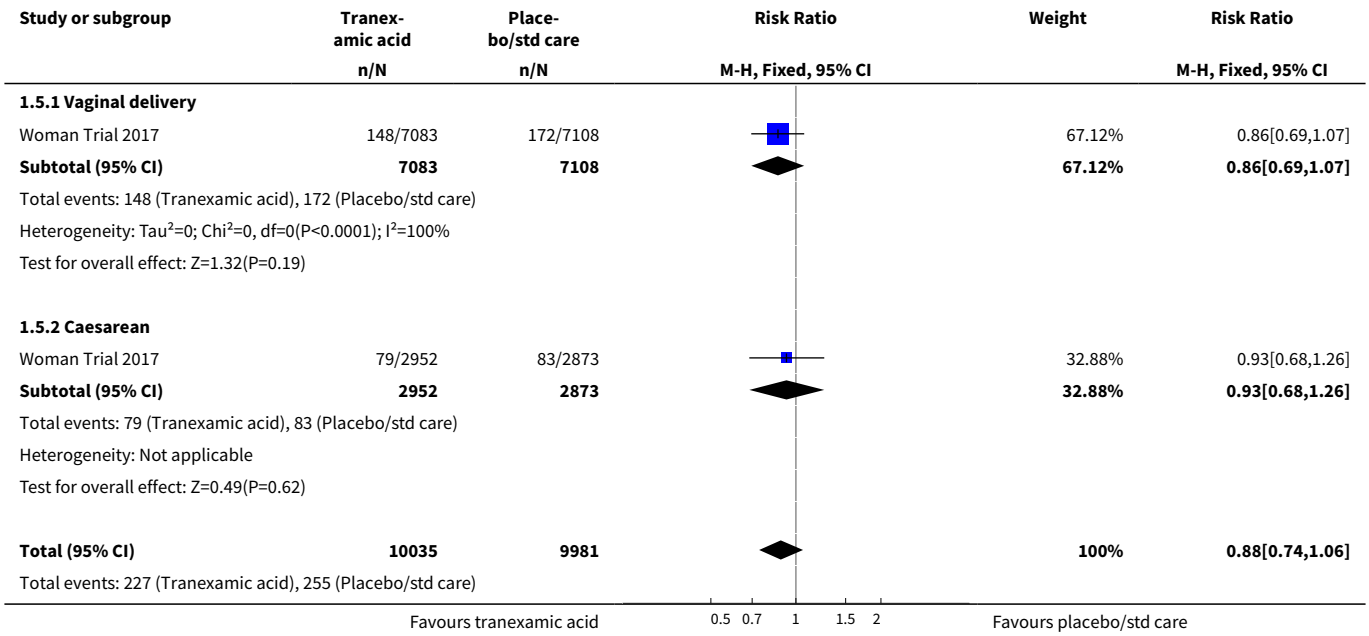
Favours tranexamic acid — Favours placebo/std care

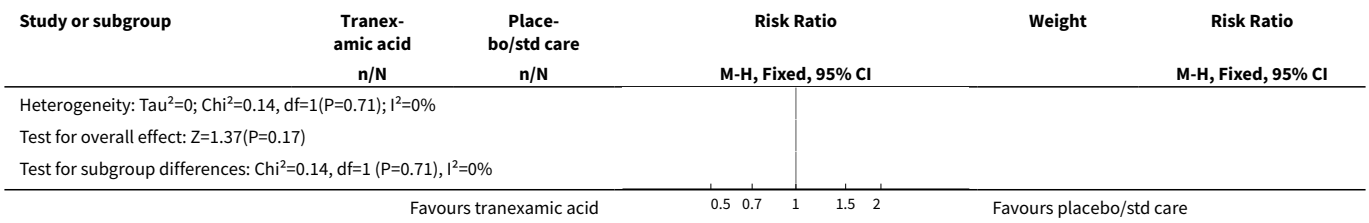


Analysis 1.4. Comparison 1 Standard care plus IV tranexamic acid versus placebo or standard care alone for the treatment of PPH, Outcome 4 Maternal mortality (all causes).

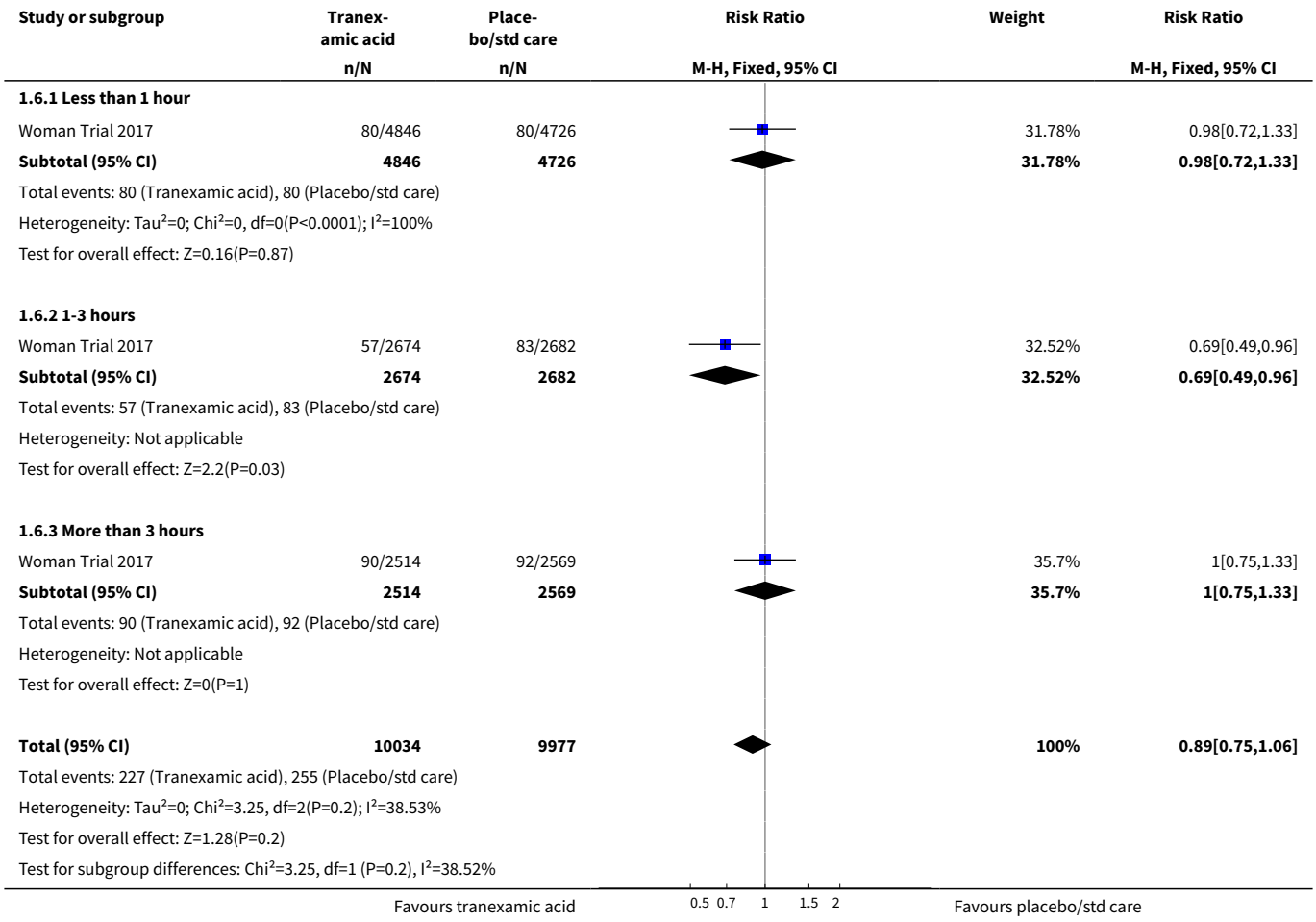


Analysis 1.5. Comparison 1 Standard care plus IV tranexamic acid versus placebo or standard care alone for the treatment of PPH, Outcome 5 Maternal mortality (all cause)(subgroup by mode of birth).

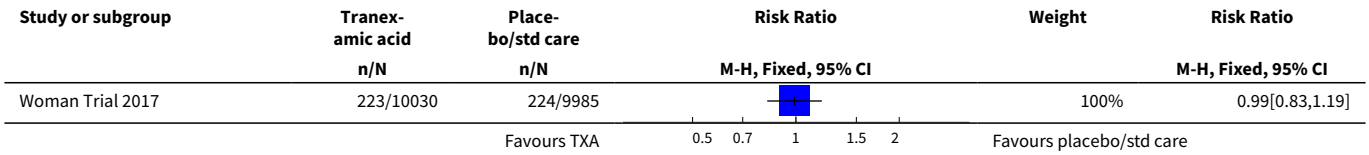


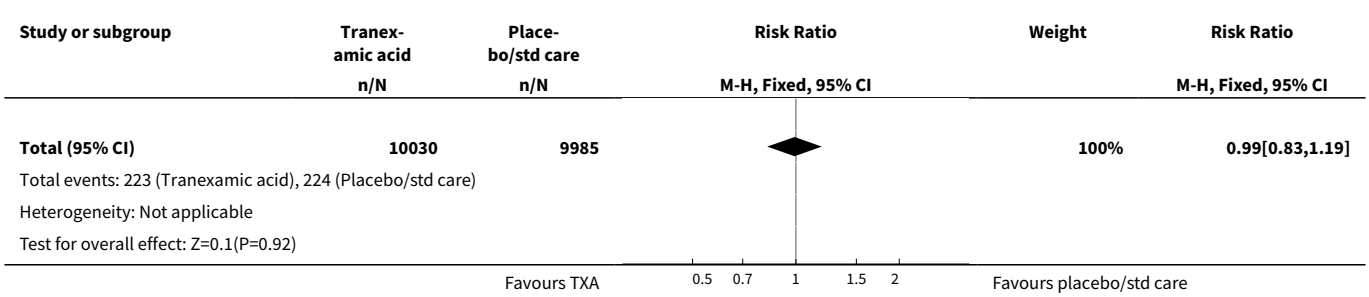


Analysis 1.6. Comparison 1 Standard care plus IV tranexamic acid versus placebo or standard care alone for the treatment of PPH, Outcome 6 Maternal mortality (all cause) (subgroup time from birth).

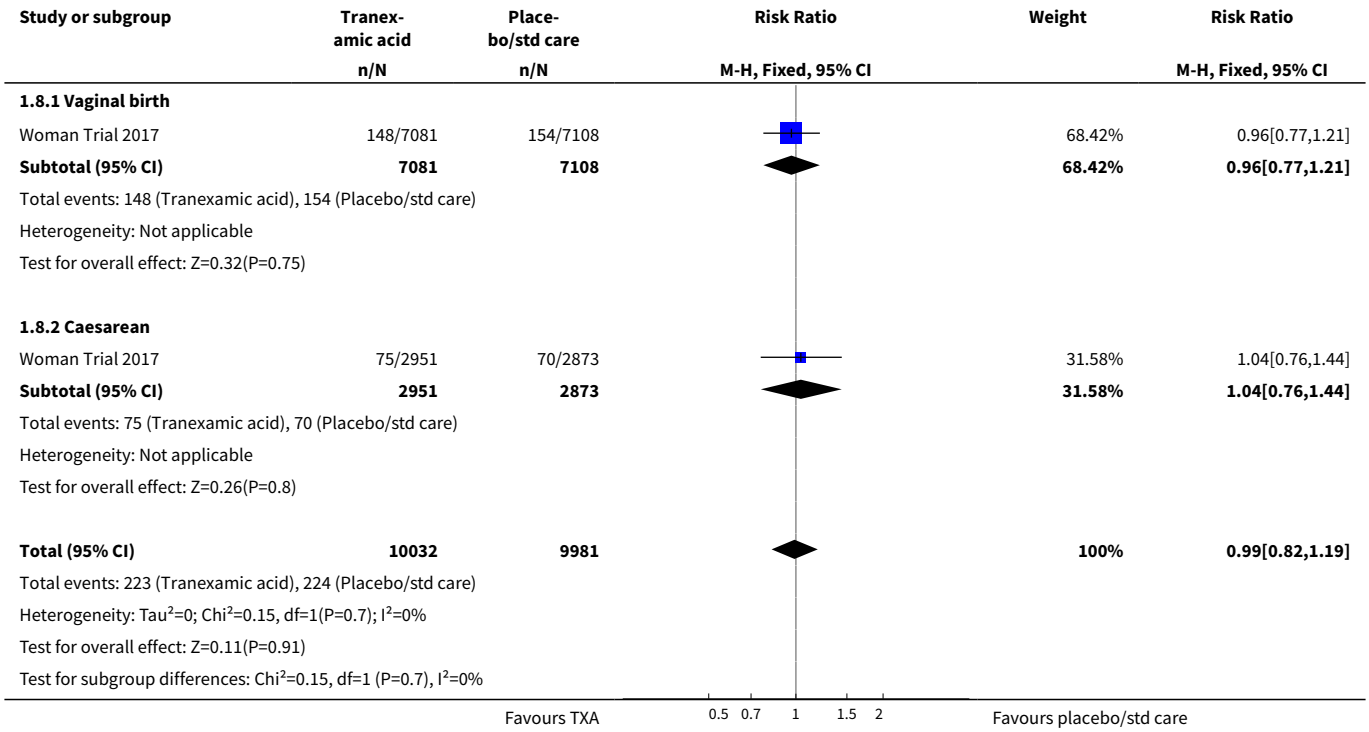


Analysis 1.7. Comparison 1 Standard care plus IV tranexamic acid versus placebo or standard care alone for the treatment of PPH, Outcome 7 Serious maternal morbidity (any).

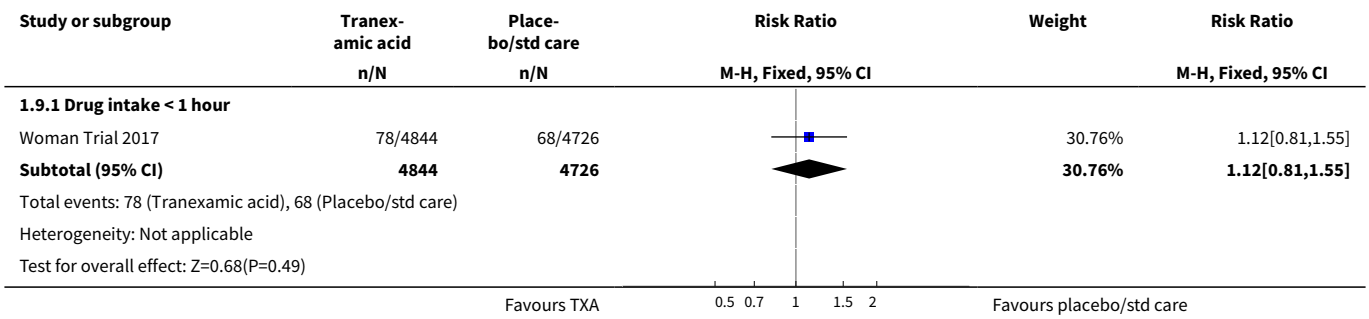


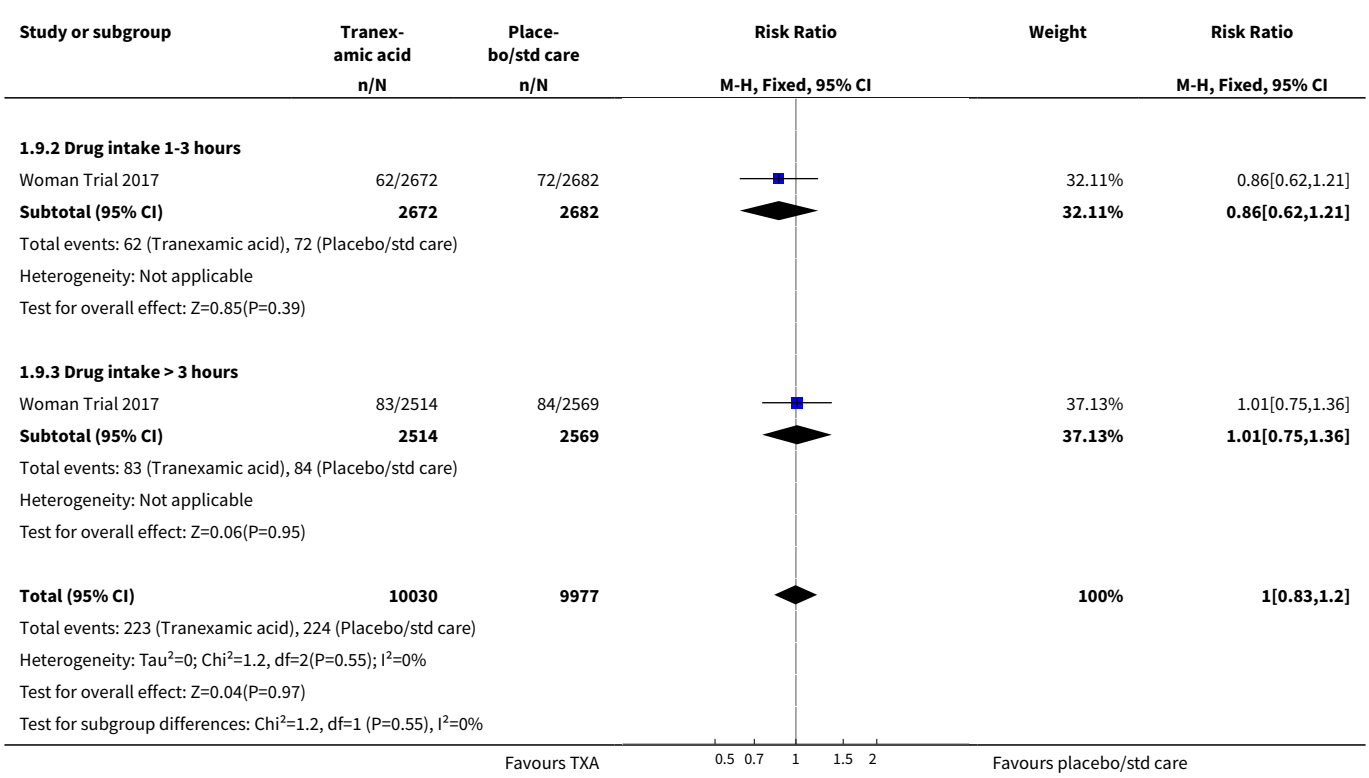


Analysis 1.8. Comparison 1 Standard care plus IV tranexamic acid versus placebo or standard care alone for the treatment of PPH, Outcome 8 Serious maternal morbidity (any) (subgroup by mode of birth).

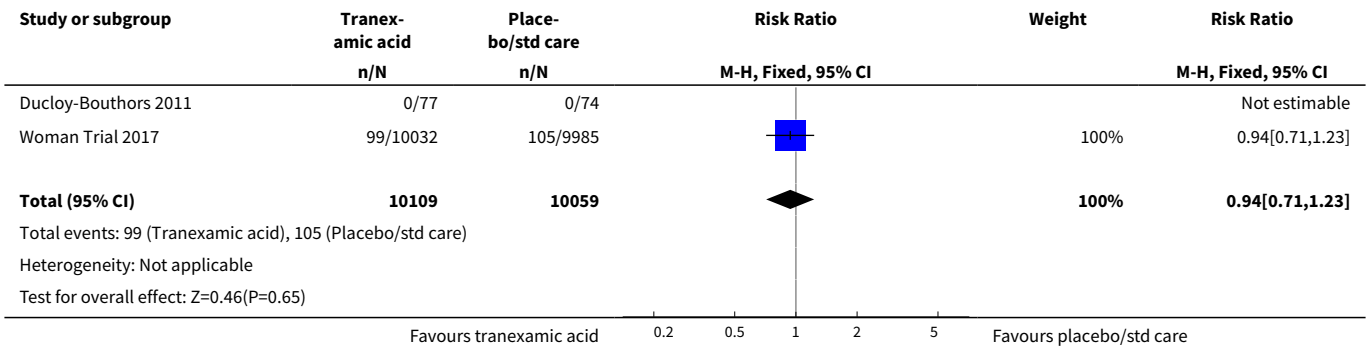


Analysis 1.9. Comparison 1 Standard care plus IV tranexamic acid versus placebo or standard care alone for the treatment of PPH, Outcome 9 Serious maternal morbidity (any) (subgroup by time of drug use from birth).

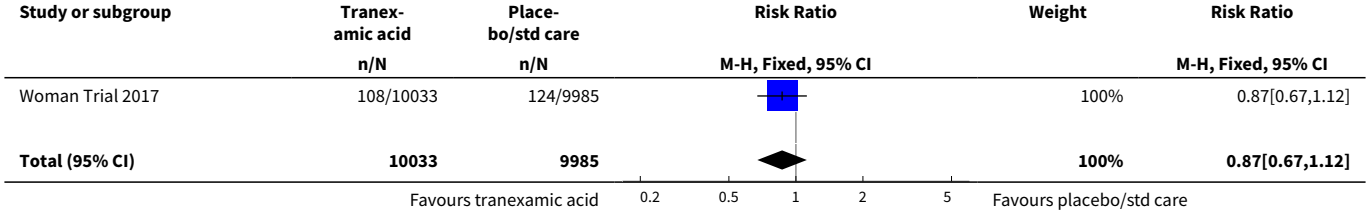


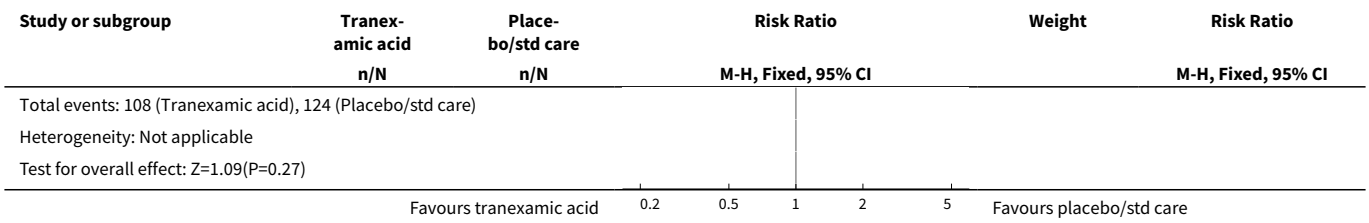


Analysis 1.10. Comparison 1 Standard care plus IV tranexamic acid versus placebo or standard care alone for the treatment of PPH, Outcome 10 Serious maternal morbidity: multiple organ failure.

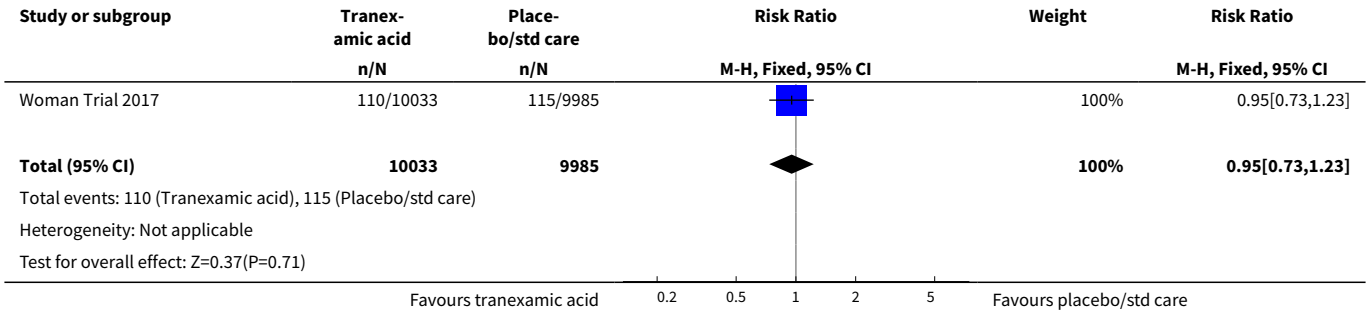


Analysis 1.11. Comparison 1 Standard care plus IV tranexamic acid versus placebo or standard care alone for the treatment of PPH, Outcome 11 Serious maternal morbidity: maternal respiratory failure.

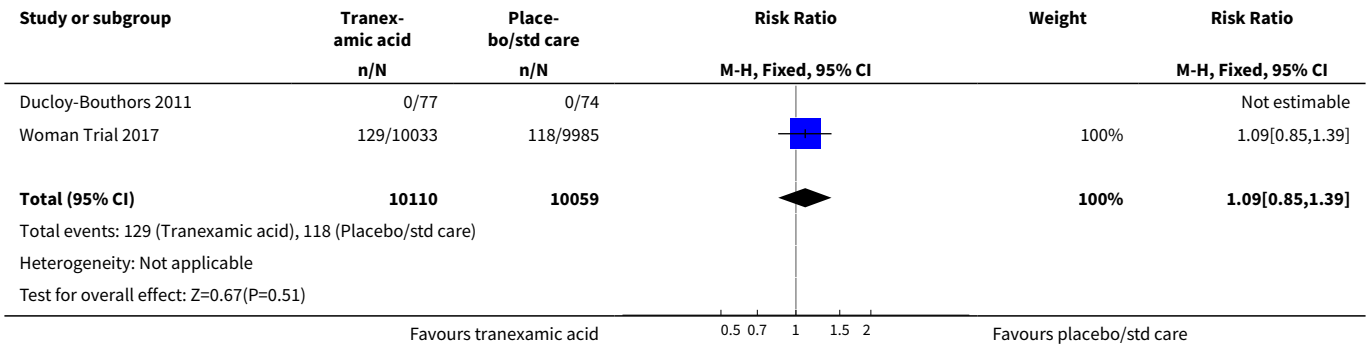




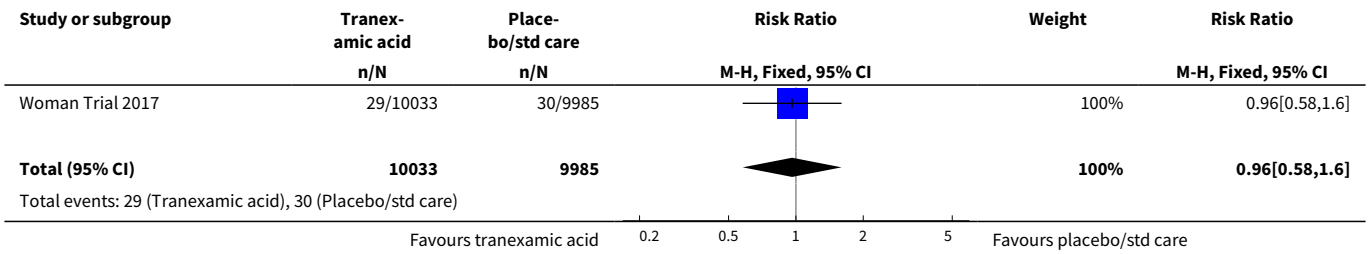
Analysis 1.12. Comparison 1 Standard care plus IV tranexamic acid versus placebo or standard care alone for the treatment of PPH, Outcome 12 Serious maternal morbidity: Cardiac arrest.

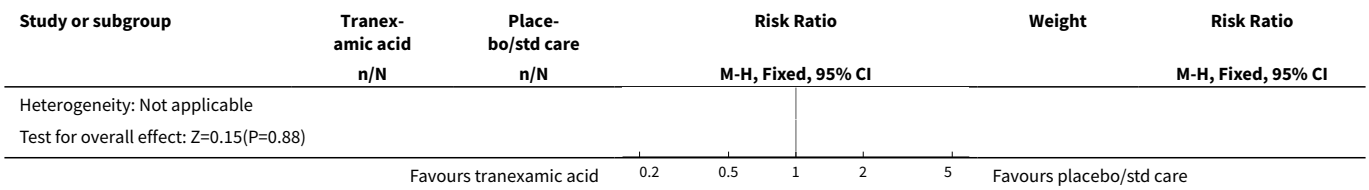


Analysis 1.13. Comparison 1 Standard care plus IV tranexamic acid versus placebo or standard care alone for the treatment of PPH, Outcome 13 Serious maternal morbidity: Maternal renal failure.

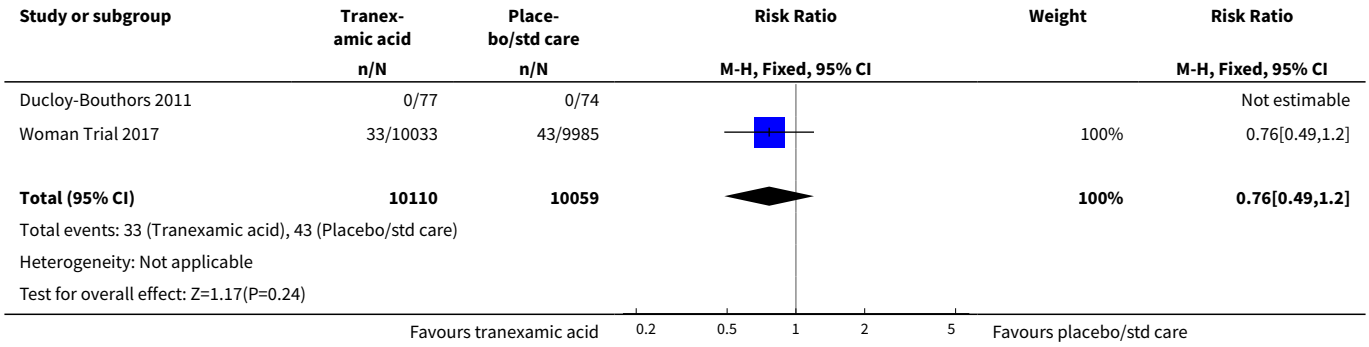


Analysis 1.14. Comparison 1 Standard care plus IV tranexamic acid versus placebo or standard care alone for the treatment of PPH, Outcome 14 Serious maternal morbidity: Hepatic failure.

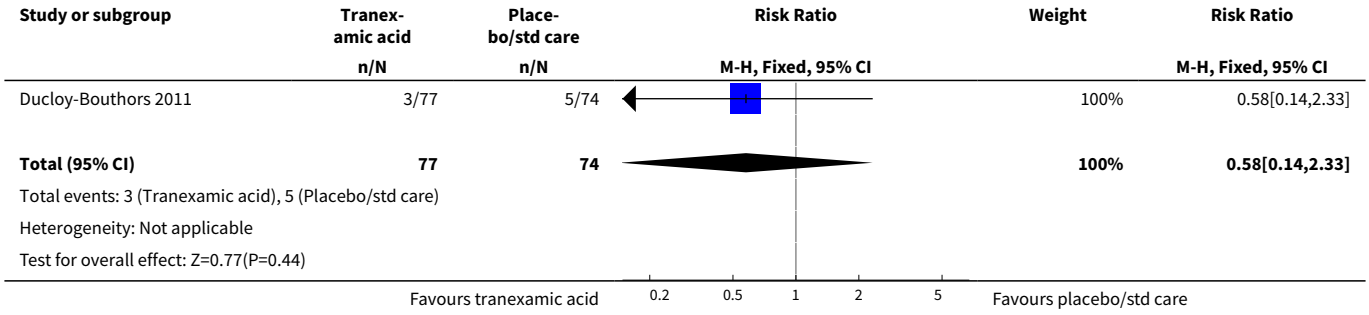




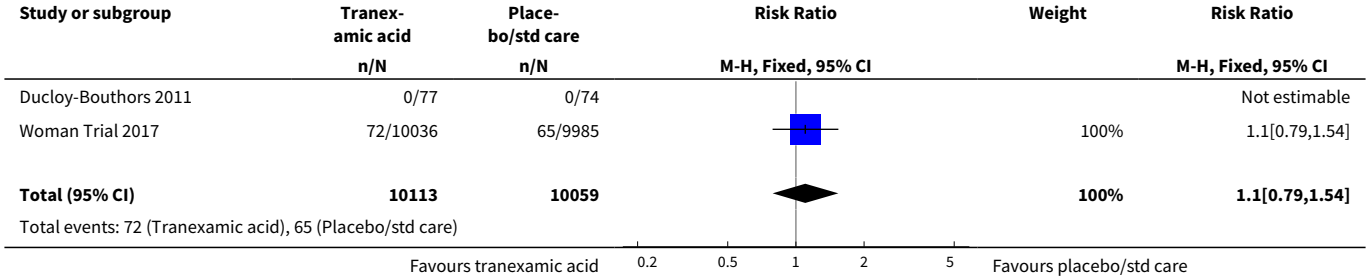
Analysis 1.15. Comparison 1 Standard care plus IV tranexamic acid versus placebo or standard care alone for the treatment of PPH, Outcome 15 Serious maternal morbidity: Maternal Seizure.

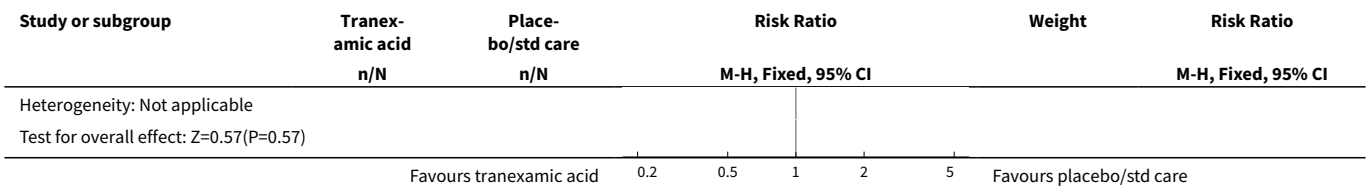


Analysis 1.16. Comparison 1 Standard care plus IV tranexamic acid versus placebo or standard care alone for the treatment of PPH, Outcome 16 Maternal Intensive care admission.

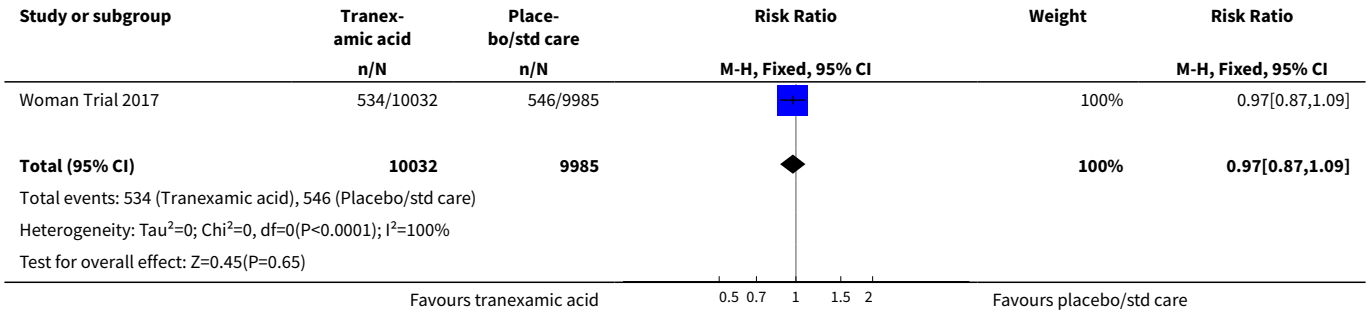


Analysis 1.17. Comparison 1 Standard care plus IV tranexamic acid versus placebo or standard care alone for the treatment of PPH, Outcome 17 Mortality from causes other than bleeding.

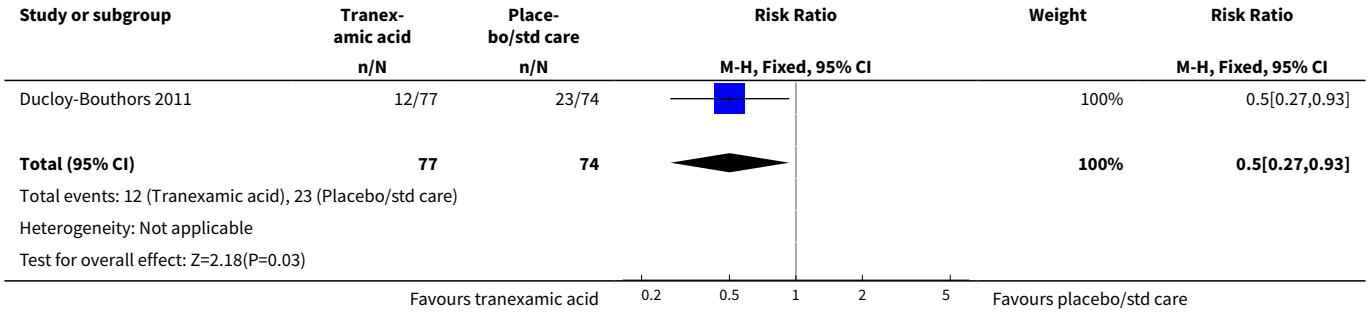




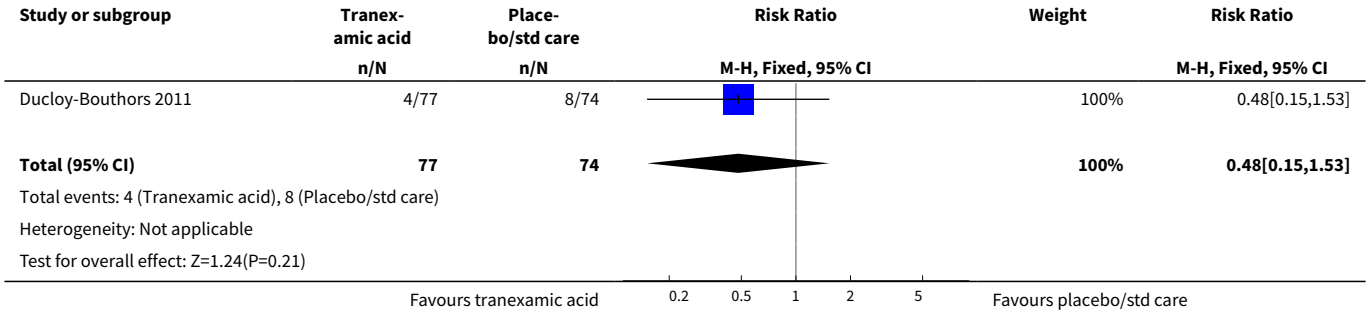
Analysis 1.18. Comparison 1 Standard care plus IV tranexamic acid versus placebo or standard care alone for the treatment of PPH, Outcome 18 Non-prespecified composite outcome: death or hysterectomy.



Analysis 1.19. Comparison 1 Standard care plus IV tranexamic acid versus placebo or standard care alone for the treatment of PPH, Outcome 19 Blood loss 500 mL or more after randomisation.

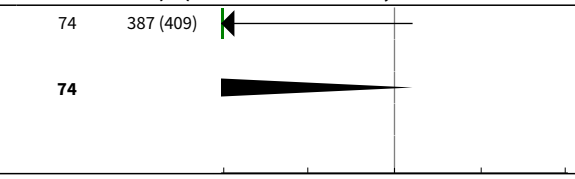


Analysis 1.20. Comparison 1 Standard care plus IV tranexamic acid versus placebo or standard care alone for the treatment of PPH, Outcome 20 Blood loss 1000 mL or more after randomisation.



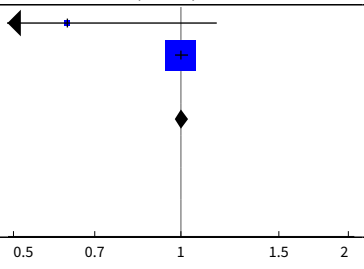
Analysis 1.21. Comparison 1 Standard care plus IV tranexamic acid versus placebo or standard care alone for the treatment of PPH, Outcome 21 Mean blood loss (mL).

Study or subgroup	Tranexamic acid N	Tranexamic acid Mean(SD)	Placebo/std care N	Placebo/std care Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Ducloy-Bouthors 2011	77	280 (320)	74	387 (409)		100%	-107[-224.44,10.44]
Total ***	**77**		**74**			**100%**	**-107[-224.44,10.44]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.79(P=0.07)							



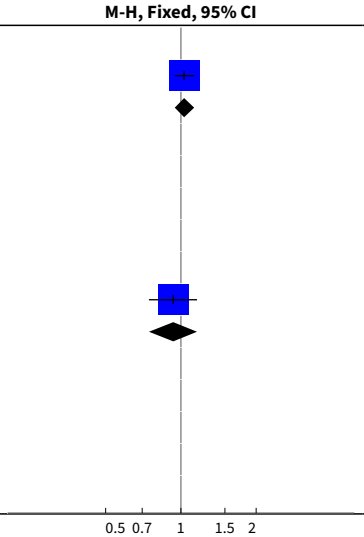
Analysis 1.22. Comparison 1 Standard care plus IV tranexamic acid versus placebo or standard care alone for the treatment of PPH, Outcome 22 Blood transfusion (all).

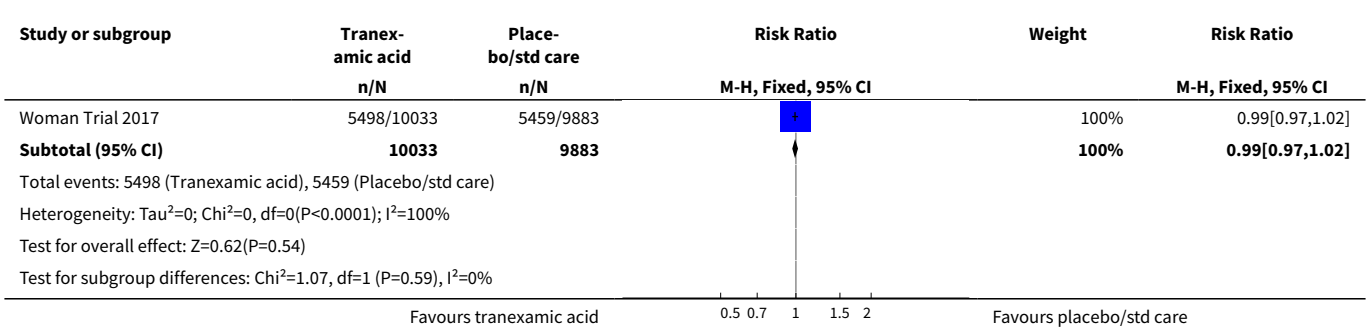
Study or subgroup	Tranexamic acid n/N	Placebo/std care n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Ducloy-Bouthors 2011	13/77	20/74		0.37%	0.62[0.34,1.16]
Woman Trial 2017	5461/10033	5426/9983		99.63%	1[0.98,1.03]
Total (95% CI)	**10110**	**10057**		**100%**	**1[0.97,1.03]**
Total events: 5474 (Tranexamic acid), 5446 (Placebo/std care)					
Heterogeneity: Tau²=0; Chi²=2.22, df=1(P=0.14); I²=54.89%					
Test for overall effect: Z=0(P=1)					



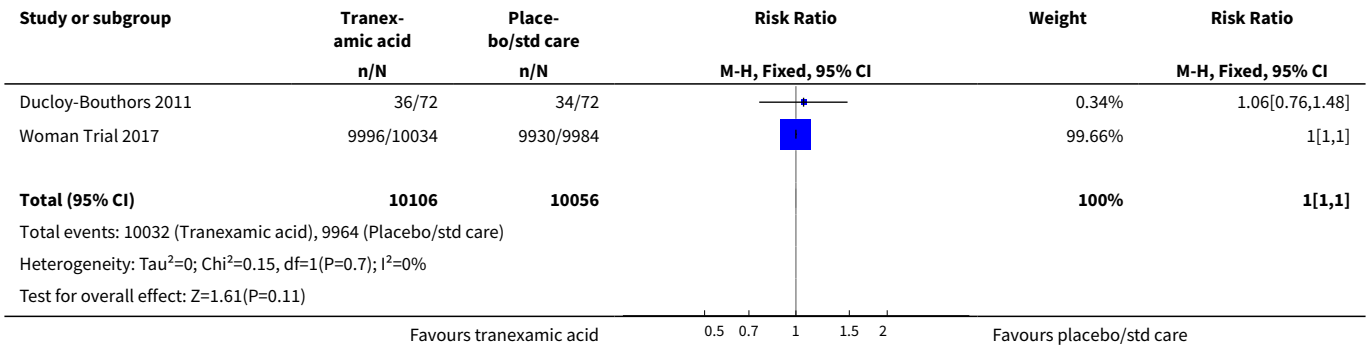
Analysis 1.23. Comparison 1 Standard care plus IV tranexamic acid versus placebo or standard care alone for the treatment of PPH, Outcome 23 Blood products transfusion.

Study or subgroup	Tranexamic acid n/N	Placebo/std care n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.23.1 Frozen plasma					
Woman Trial 2017	889/10031	856/9982		100%	1.03[0.94,1.13]
Subtotal (95% CI)	**10031**	**9982**		**100%**	**1.03[0.94,1.13]**
Total events: 889 (Tranexamic acid), 856 (Placebo/std care)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.72(P=0.47)					
1.23.2 Other product transfusion					
Woman Trial 2017	147/10031	157/9982		100%	0.93[0.75,1.16]
Subtotal (95% CI)	**10031**	**9982**		**100%**	**0.93[0.75,1.16]**
Total events: 147 (Tranexamic acid), 157 (Placebo/std care)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.62(P=0.53)					
1.23.3 Any transfusion					

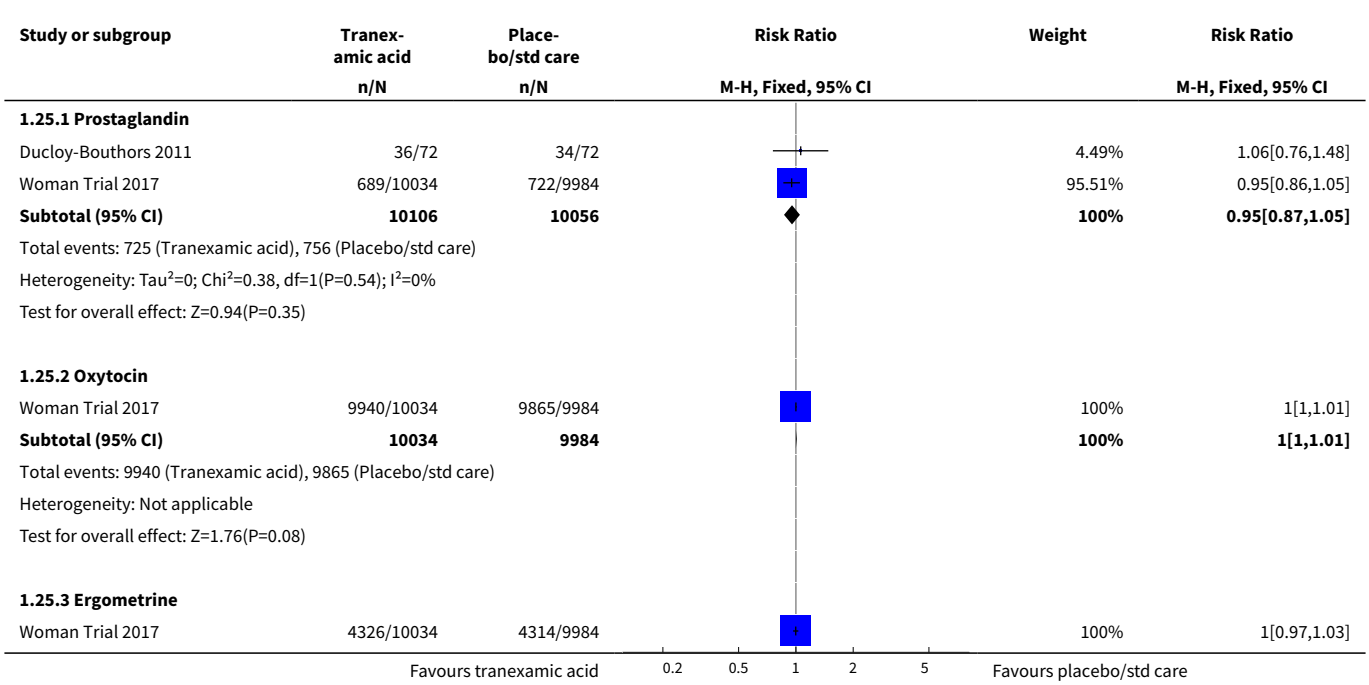


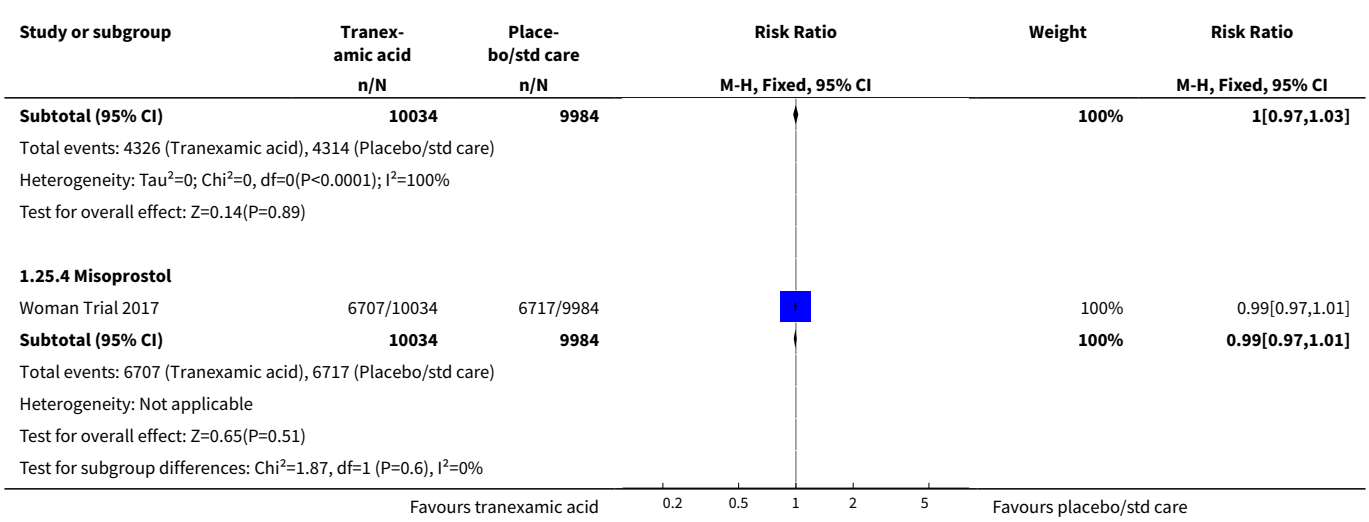


Analysis 1.24. Comparison 1 Standard care plus IV tranexamic acid versus placebo or standard care alone for the treatment of PPH, Outcome 24 Post randomisation additional uterotonics.

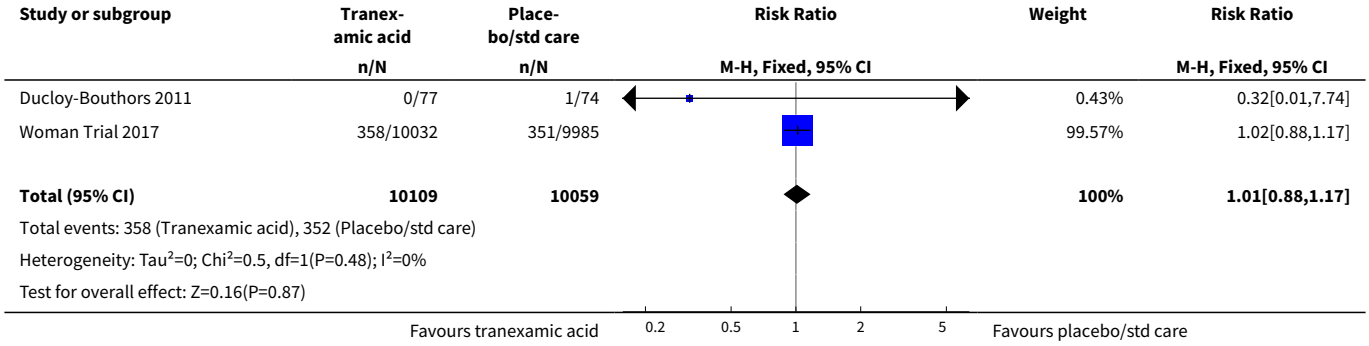


Analysis 1.25. Comparison 1 Standard care plus IV tranexamic acid versus placebo or standard care alone for the treatment of PPH, Outcome 25 Post randomisation additional uterotonics.

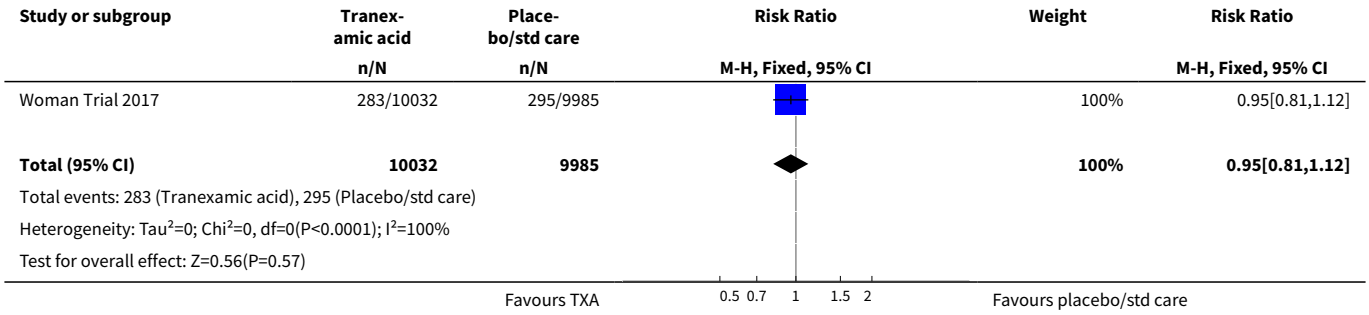




Analysis 1.26. Comparison 1 Standard care plus IV tranexamic acid versus placebo or standard care alone for the treatment of PPH, Outcome 26 Hysterectomy (provided it is not part of the intervention under investigation).

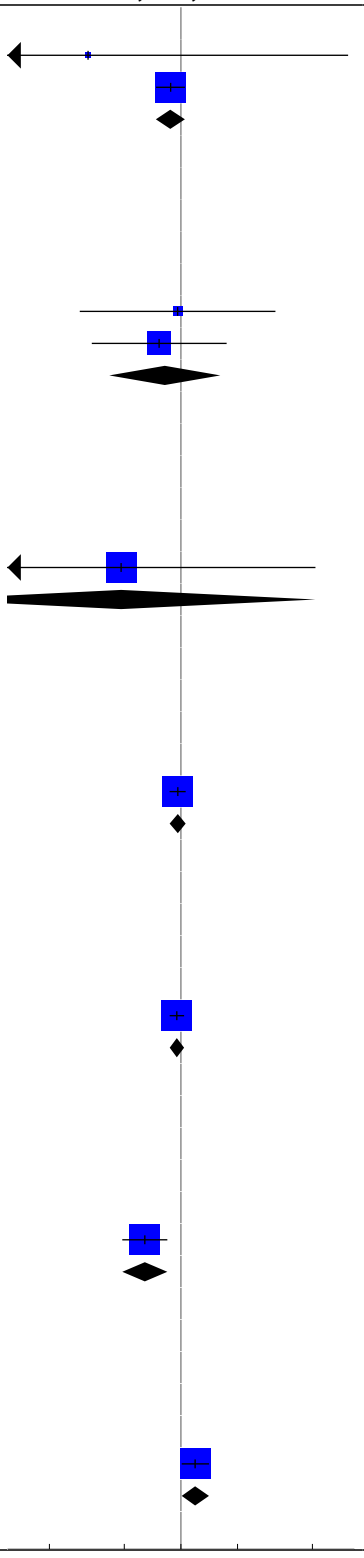


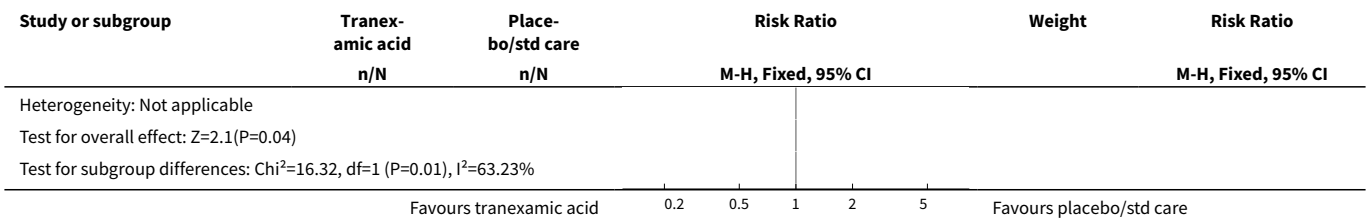
Analysis 1.27. Comparison 1 Standard care plus IV tranexamic acid versus placebo or standard care alone for the treatment of PPH, Outcome 27 Hysterectomy to control bleeding.



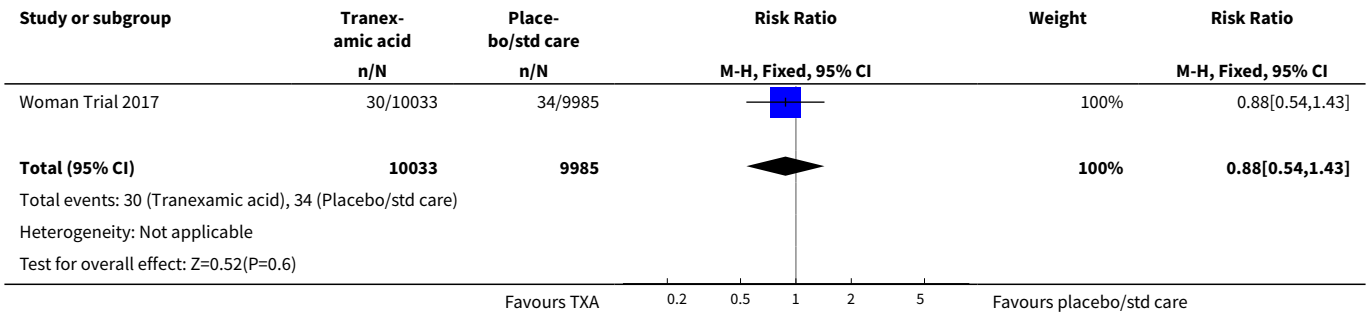
Analysis 1.28. Comparison 1 Standard care plus IV tranexamic acid versus placebo or standard care alone for the treatment of PPH, Outcome 28 Post randomisation surgical intervention to control bleeding.

Study or subgroup	Tranexamic acid n/N	Placebo/std care n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.28.1 Arterial ligation					
Ducloy-Bouthors 2011	0/77	1/74		0.6%	0.32[0.01,7.74]
Woman Trial 2017	225/10032	254/9985		99.4%	0.88[0.74,1.05]
Subtotal (95% CI)	**10109**	**10059**		**100%**	**0.88[0.74,1.05]**
Total events: 225 (Tranexamic acid), 255 (Placebo/std care)					
Heterogeneity: $Tau^2=0$; $Chi^2=0.39$, df=1(P=0.53); $I^2=0\%$					
Test for overall effect: Z=1.44(P=0.15)					
1.28.2 Embolisation					
Ducloy-Bouthors 2011	5/77	5/74		28.13%	0.96[0.29,3.18]
Woman Trial 2017	10/10032	13/9985		71.87%	0.77[0.34,1.75]
Subtotal (95% CI)	**10109**	**10059**		**100%**	**0.82[0.42,1.62]**
Total events: 15 (Tranexamic acid), 18 (Placebo/std care)					
Heterogeneity: $Tau^2=0$; $Chi^2=0.09$, df=1(P=0.76); $I^2=0\%$					
Test for overall effect: Z=0.57(P=0.57)					
1.28.3 Late postpartum curettage (after day 7)					
Ducloy-Bouthors 2011	1/77	2/74		100%	0.48[0.04,5.19]
Subtotal (95% CI)	**77**	**74**		**100%**	**0.48[0.04,5.19]**
Total events: 1 (Tranexamic acid), 2 (Placebo/std care)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.6(P=0.55)					
1.28.4 Intrauterine tamponade					
Woman Trial 2017	705/10032	729/9985		100%	0.96[0.87,1.06]
Subtotal (95% CI)	**10032**	**9985**		**100%**	**0.96[0.87,1.06]**
Total events: 705 (Tranexamic acid), 729 (Placebo/std care)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.75(P=0.45)					
1.28.5 Manual removal of placenta					
Woman Trial 2017	918/10032	961/9985		100%	0.95[0.87,1.04]
Subtotal (95% CI)	**10032**	**9985**		**100%**	**0.95[0.87,1.04]**
Total events: 918 (Tranexamic acid), 961 (Placebo/std care)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.15(P=0.25)					
1.28.6 Laparotomy for bleeding					
Woman Trial 2017	82/10032	127/9985		100%	0.64[0.49,0.85]
Subtotal (95% CI)	**10032**	**9985**		**100%**	**0.64[0.49,0.85]**
Total events: 82 (Tranexamic acid), 127 (Placebo/std care)					
Heterogeneity: Not applicable					
Test for overall effect: Z=3.14(P=0)					
1.28.7 Brace sutures					
Woman Trial 2017	300/10032	250/9985		100%	1.19[1.01,1.41]
Subtotal (95% CI)	**10032**	**9985**		**100%**	**1.19[1.01,1.41]**
Total events: 300 (Tranexamic acid), 250 (Placebo/std care)					

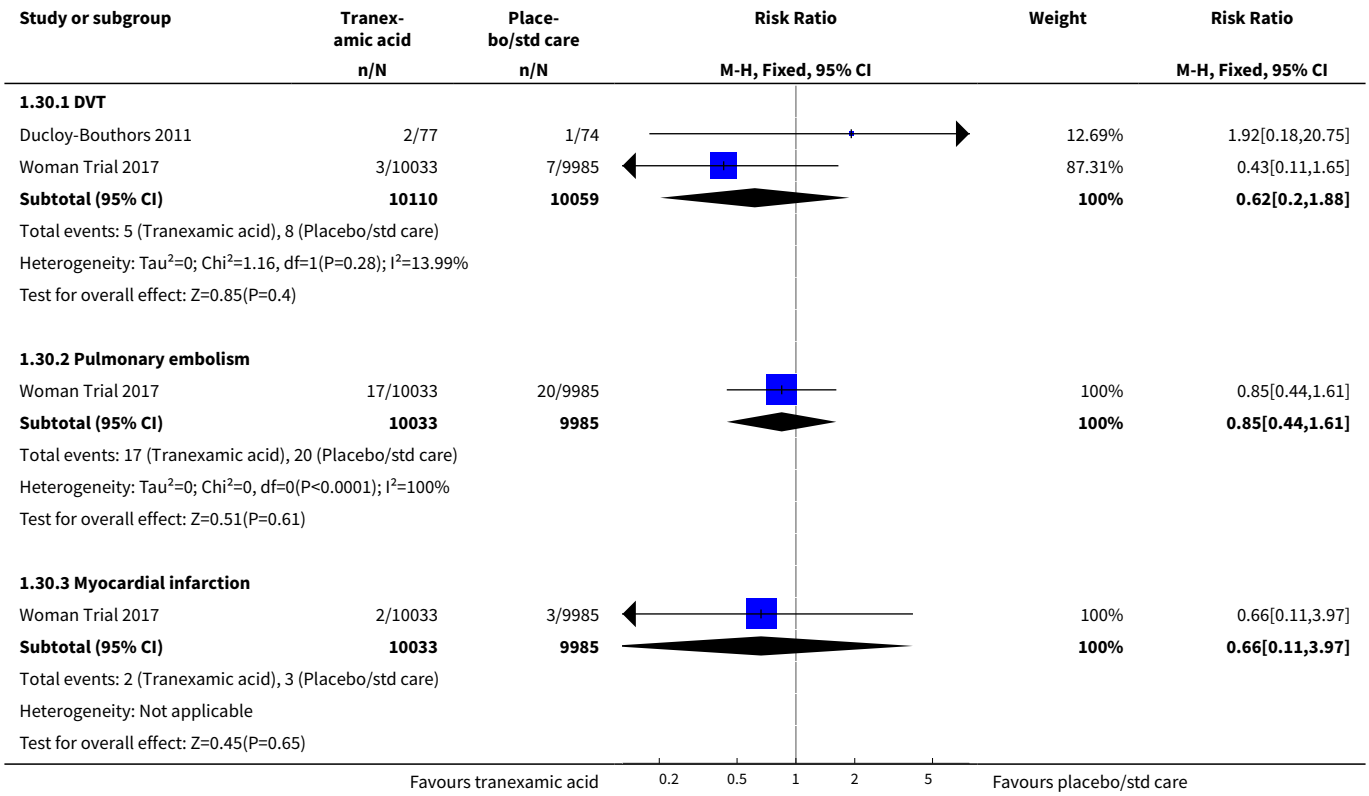


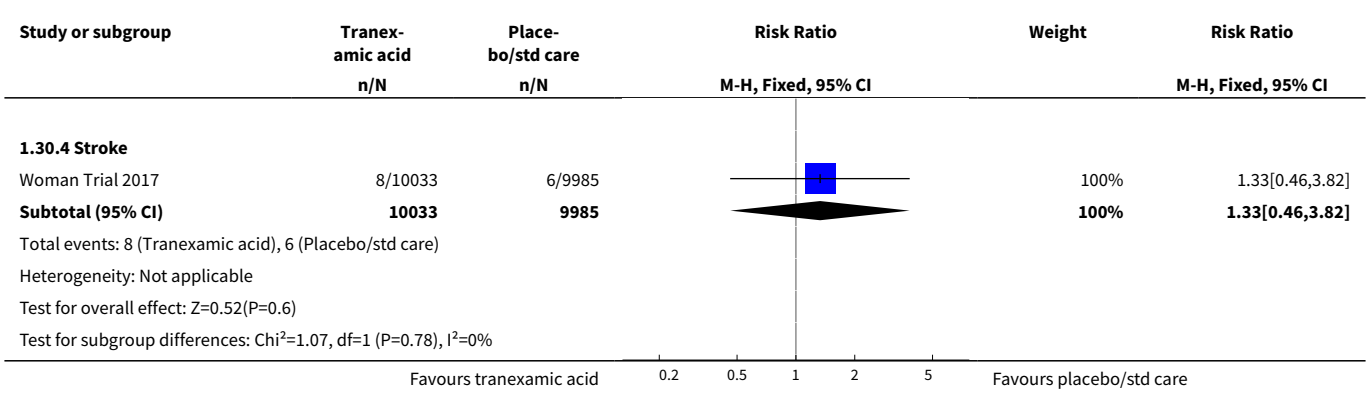


Analysis 1.29. Comparison 1 Standard care plus IV tranexamic acid versus placebo or standard care alone for the treatment of PPH, Outcome 29 Side effects of the intervention: any maternal vascular occlusive event.

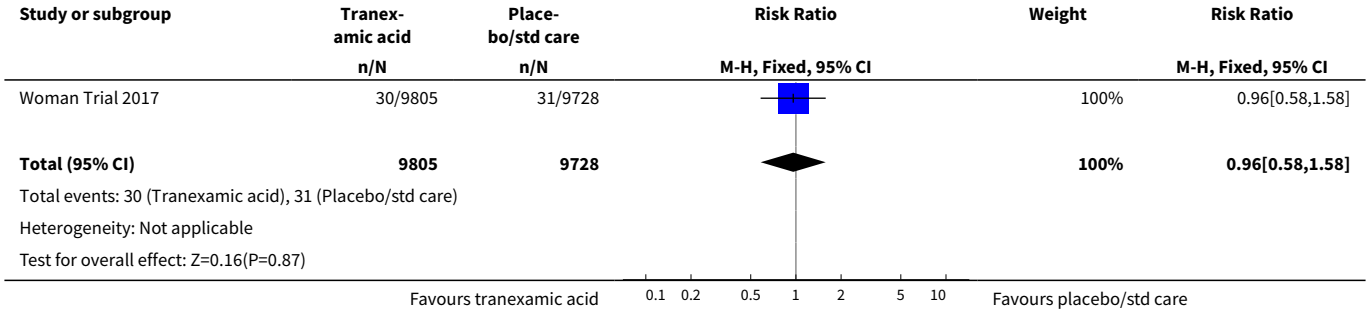


Analysis 1.30. Comparison 1 Standard care plus IV tranexamic acid versus placebo or standard care alone for the treatment of PPH, Outcome 30 Side effects of the intervention: maternal vascular occlusive events.

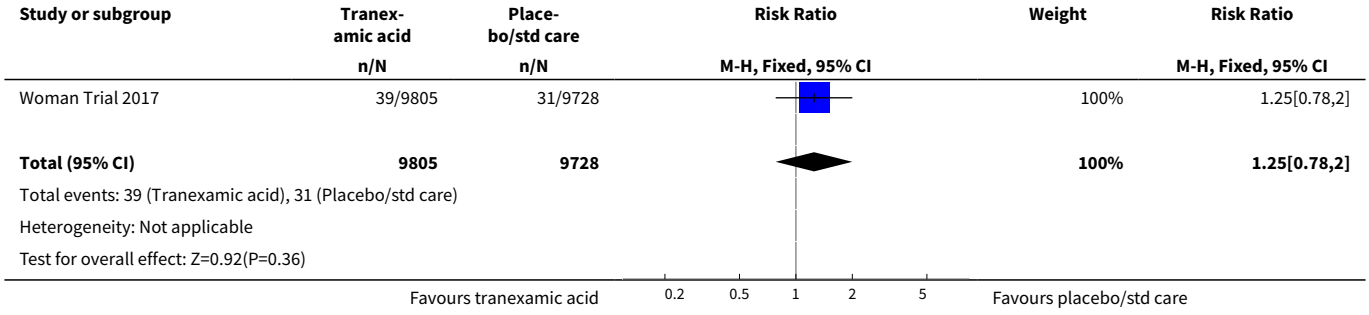




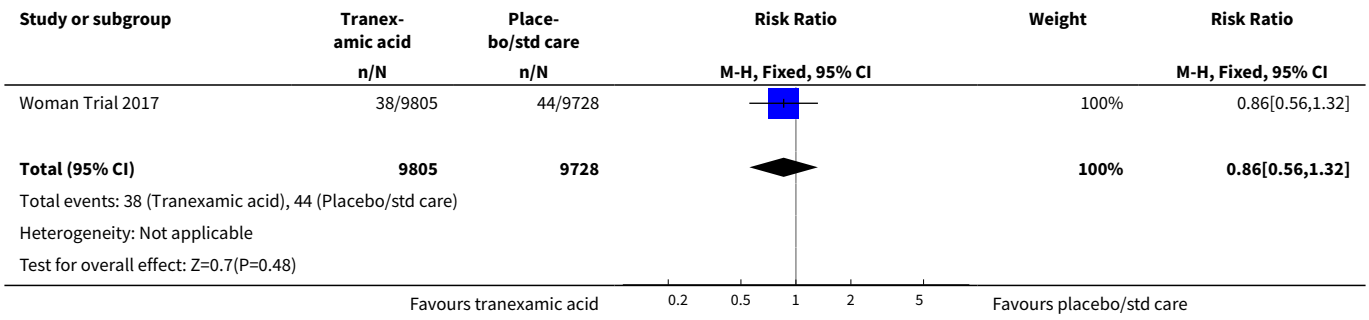
Analysis 1.31. Comparison 1 Standard care plus IV tranexamic acid versus placebo or standard care alone for the treatment of PPH, Outcome 31 Quality of Life: EQ5D Mobility.



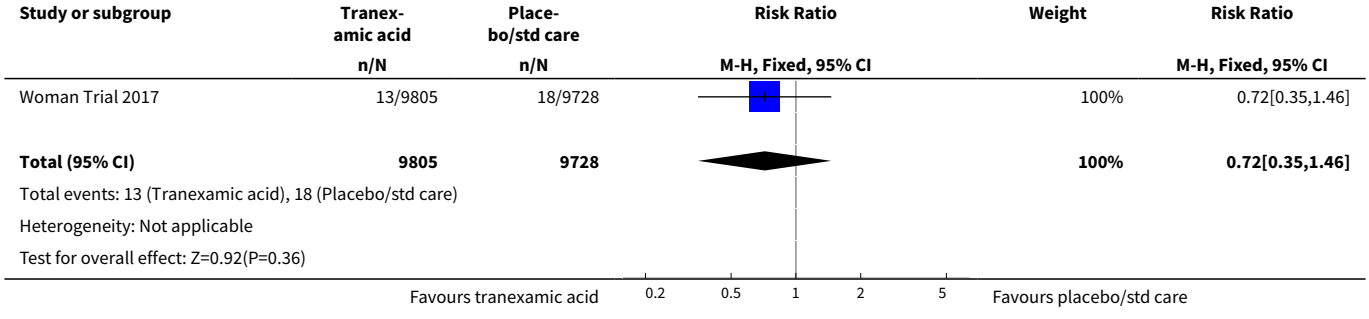
Analysis 1.32. Comparison 1 Standard care plus IV tranexamic acid versus placebo or standard care alone for the treatment of PPH, Outcome 32 Quality of Life: EQ5D Self care.



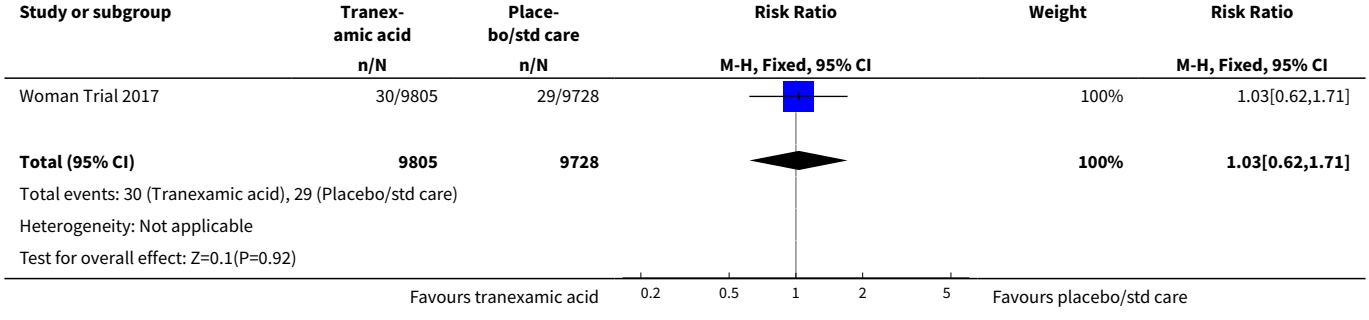
Analysis 1.33. Comparison 1 Standard care plus IV tranexamic acid versus placebo or standard care alone for the treatment of PPH, Outcome 33 Quality of Life: EQ5D Usual activities.



Analysis 1.34. Comparison 1 Standard care plus IV tranexamic acid versus placebo or standard care alone for the treatment of PPH, Outcome 34 Quality of Life: EQ5D Pain/discomfort.

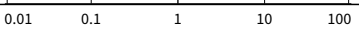


Analysis 1.35. Comparison 1 Standard care plus IV tranexamic acid versus placebo or standard care alone for the treatment of PPH, Outcome 35 Quality of Life: EQ5D Anxiety/depression.



Analysis 1.36. Comparison 1 Standard care plus IV tranexamic acid versus placebo or standard care alone for the treatment of PPH, Outcome 36 Side effects of the intervention: neonatal vascular occlusive event.

Study or subgroup	Tranexamic acid n/N	Placebo/std care n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Woman Trial 2017	0/10033	0/9985			Not estimable
Total (95% CI)	**10033**	**9985**			**Not estimable**
Total events: 0 (Tranexamic acid), 0 (Placebo/std care)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					



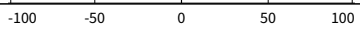
Favours tranexamic acid — Favours placebo/std care

Comparison 2. Tranexamic acid versus rectal misoprostol for the treatment of PPH

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mean blood loss (mL)	1	200	Mean Difference (IV, Fixed, 95% CI)	0.02 [-0.09, 0.13]

Analysis 2.1. Comparison 2 Tranexamic acid versus rectal misoprostol for the treatment of PPH, Outcome 1 Mean blood loss (mL).

Study or subgroup	TXA N	TXA Mean(SD)	Misoprostol N	Misoprostol Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Sahaf 2014	100	1.2 (0.3)	100	1.2 (0.5)		100%	0.02[-0.09,0.13]
Total * **	**100**		**100**			**100%**	**0.02[-0.09,0.13]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.35(P=0.73)							



Favours TXA — Favours misoprostol

APPENDICES

Appendix 1. Search methods used in ICTRP and ClinicalTrials.gov

ICTRP

Each line was run separately

tranexamic AND labo(u)r

TXA AND labo(u)r

aprotinin AND labo(u)r

epsilon-aminocaproic AND labo(u)r

aminomethylbenzoic AND labo(u)r

antifibrinolytic AND labo(u)r

tranexamic AND postpartum AND h(a)emorrhage

TXA AND postpartum AND h(a)emorrhage

aprotinin AND postpartum AND h(a)emorrhage

epsilon-aminocaproic AND postpartum AND h(a)emorrhage

aminomethylbenzoic AND postpartum AND h(a)emorrhage

antifibrinolytic AND postpartum AND h(a)emorrhage

ClinicalTrials.gov

Advanced search, Intervention studies

Intervention/Treatment : antifibrinolytic; aprotinin; tranexamic acid; epsilon-aminocaproic acid; aminomethylbenzoic

Condition: Postpartum hemorrhage

CONTRIBUTIONS OF AUTHORS

Haleema Shakur is guarantor for this review. She helped design the protocol, identified the included trials, extracted data (excluding the WOMAN trial) and drafted the final version of the review.

Danielle Beaumont helped design the protocol, extracted data (excluding the WOMAN trial) and drafted the final version of the review.

Sue Pavord helped design the protocol and drafted the final version of the review.

Angele Gayet-Ageron helped design the protocol, extracted data (for the WOMAN trial) and drafted the final version of the review.

Katharine Ker helped design the protocol, extracted data (excluding the WOMAN trial) and drafted the final version of the review.

Hatem A Mousa helped design the protocol, extracted data (for the WOMAN trial) and drafted the final version of the review.

DECLARATIONS OF INTEREST

Haleema Shakur was one of the principal investigators of the WOMAN trial of tranexamic acid for the treatment of postpartum haemorrhage. The run-in phase of this trial for 2000 patients' recruitment was funded by London School of Hygiene and Tropical Medicine. The funds to support the drug and placebo costs through an Investigator initiated research grant for the run-in phase were provided by Pfizer. The main phase was funded by the Department of Health (UK), grant number HICF-T2-0510-007 and the Wellcome Trust, grant number WT094947. The Bill & Melinda Gates Foundation (grant number OPP1095618) supported the final 5000 patients' recruitment and dissemination activities. The trial was eligible for inclusion in the current review. All decisions relating to this trial (assessment for inclusion, risk of bias, data extraction, GRADE) were carried out by other members of the review team who were not directly involved in the conduct of the WOMAN trial.

Danielle Beaumont was an investigator on the WOMAN trial. She was not involved in any decisions relating to this study (e.g. assessment for inclusion, risk of bias, data extraction). These tasks were carried out by other members of the review team who were not directly involved in the trial.

Sue Pavord - none known.

Angele Gayet -Ageron - none known.

Katharine Ker - was an investigator on the WOMAN trial. She was not involved in any decisions relating to this study (e.g. assessment for inclusion, risk of bias, data extraction). These tasks were carried out by other members of the review team who were not directly involved in the trial.

Hatem A Mousa - none known.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- WHO UNDP-UNFPA-UNICEF-WHO-World Bank Special Programme of Research, Development and Research Training in Human Reproduction (HRP), Department of Reproductive Health and Research (RHR), World Health Organization, Switzerland.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The protocol for this Cochrane review (Shakur 2017) was published in PROSPERO on 18 July 2017 - see https://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42017071200. The protocol was not published in the Cochrane Library.

There are some differences between our published protocol and this full review. These are outlined below.

Assessment of the quality of the evidence using GRADE

Outcomes for use in GRADE

We have edited 'Surgical treatment (hysterectomy, arterial ligation, compressive uterine sutures, arterial embolization)' to 'Surgical intervention to control bleeding' for consistency with the main methods/list of outcomes and for the purposes of GRADE we have restricted the outcome to hysterectomy.

We have removed the following outcomes from the list of outcomes for use in GRADE: non-surgical intervention to control bleeding (uterine packing, bimanual uterine massage, tamponade, external aortic compression and compression garments). Shock and maternal quality of life were also amongst our GRADE outcomes for inclusion in our 'Summary of findings' table. Shock was not reported in either of the trials included in the review; we have therefore presented data for maternal blood transfusion and blood loss ≥500 mL in our 'Summary of findings' table. While maternal quality of life was reported in the WOMAN trial, this was for the five separate domains on the EQ5D; we have therefore reported results in the text rather than as five separate outcomes in the 'Summary of findings' table.

Side effects of the intervention (both maternal and for breastfed neonates); specifically vascular occlusive events (myocardial infarction, stroke, deep vein thrombosis or pulmonary embolism) and renal failure) has been restricted to maternal vascular occlusive events only for the purposes of GRADE.

Main comparisons for use in GRADE

We have also added further main comparisons to be considered using GRADE in future updates of this review: standard care plus systemic aprotinin, tranexamic acid (TXA), epsilon-aminocaproic acid (EACA) and aminomethylbenzoic acid versus standard care plus topic antifibrinolytic; standard care plus one antifibrinolytic drug therapy versus another.

Outcomes

An important outcome in the Woman Trial 2017 was a composite outcome "death or hysterectomy". We have included this non-prespecified outcome in our data and analyses.

We have edited 'Surgical treatment (hysterectomy, arterial ligation, compressive uterine sutures, arterial embolization)' to 'Surgical intervention used to control bleeding (hysterectomy, arterial ligation, compressive uterine sutures, arterial embolisation, laparotomy).

INDEX TERMS

Medical Subject Headings (MeSH)

Antifibrinolytic Agents [administration & dosage] [*therapeutic use]; Cause of Death; Maternal Mortality; Misoprostol [administration & dosage] [*therapeutic use]; Postpartum Hemorrhage [*drug therapy] [mortality]; Randomized Controlled Trials as Topic; Tranexamic Acid [administration & dosage] [*therapeutic use]

MeSH check words

Female; Humans; Pregnancy