WHO recommendation on tranexamic acid for the treatment of postpartum haemorrhage

World Health Organization

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Therese Dowswell and Anna Cuthbert reviewed the scientific evidence, prepared the GRADE tables and drafted the narrative summary of evidence. Joshua Vogel and Olufemi Oladapo revised the narrative summaries and double-checked the corresponding GRADE tables. Joshua Vogel, Olufemi Oladapo, A. Metin Gülmezoglu and Mercedes Bonet commented on the draft document before it was reviewed by participants at the WHO technical consultation. The External Review Group peer-reviewed the final document.

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Acronyms and abbreviations

CI	confidence interval
CRASH-2	Clinical Randomization of an Antifibrinolytic in Significant Haemorrhage trial
DOI	Declaration of Interest
FIGO	International Federation of Gynecology and Obstetrics
FWC	Family, Women's and Children's Health (a WHO cluster)
GDG	Guideline Development Group
GRC	Guideline Review Committee
GRADE	Grading of Recommendations, Assessment, Development, and Evaluation
GSG	Executive Guideline Steering Group
ICM	International Confederation of Midwives
IPD	individual participant data meta-analysis
LMIC	low- and middle-income country
LY	life-year
MCA	WHO Department of Maternal, Newborn, Child and Adolescent Health
MPA	Maternal and Perinatal Health & Preventing Unsafe Abortion (a team in WHO's Department of Reproductive Health and Research)
MPH	maternal and perinatal health
NNT	number needed to treat
PICO	population (P), intervention (I), comparison (C), outcome (O)
PPH	postpartum haemorrhage
RHR	[WHO Department of] Reproductive Health and Research
RR	relative risk
SDG	Sustainable Development Goals
TXA	tranexamic acid
UN	United Nations
UNFPA	United Nations Population Fund
USAID	United States Agency for International Development
WHO	World Health Organization
WOMAN	World Maternal Antifibrinolytics trial

Executive Summary

Introduction

Postpartum haemorrhage (PPH) is commonly defined as a blood loss of 500 ml or more within 24 hours after birth, and it affects about 5% of all women giving birth around the world. Globally, nearly one quarter of all maternal deaths are associated with PPH, and in most low-income countries it is the main cause of maternal mortality.

Improving care for women around the time of childbirth to prevent and treat PPH is a necessary step towards achievement of the health targets of the Sustainable Development Goals (SDGs). Efforts to prevent and reduce PPH-associated morbidity and mortality can reduce the profound inequities in maternal health globally. To achieve this, healthcare providers, health managers, policy makers and other stakeholders need up-to-date and evidence-based recommendations to inform clinical policies and practices.

In 2017, the Executive Guideline Steering Group (GSG) on WHO maternal and perinatal health recommendations prioritized the updating of the existing WHO recommendation on the use of tranexamic acid (TXA) for PPH treatment in response to important new evidence on this intervention. This updated recommendation thus supersedes the previous recommendation on TXA for PPH treatment, which was issued in the 2012 WHO recommendations on prevention and treatment of PPH.

Target audience

The primary audience includes health professionals who are responsible for developing national and local health protocols (particularly those related to PPH) and those directly providing care to pregnant women and their newborns, including midwives, nurses, general medical practitioners, obstetricians, managers of maternal and child health programmes, and relevant staff in ministries of health, in all settings.

Guideline development methods

The updating of this recommendation was guided by standardized operating procedures in accordance with the process described in the *WHO handbook for guideline development.* The recommendation was initially developed using this process, namely (i) identification of the priority question and critical outcomes, (ii) retrieval of the evidence, (iii) assessment and synthesis of evidence, (iv) formulation of the recommendation, and (v) planning for the dissemination, implementation, impact evaluation and updating of the recommendation.

The scientific evidence supporting the recommendation was synthesized using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach. The systematic review was used to prepare evidence profiles for the prioritized question. WHO convened an online technical consultation on 29 August 2017 where an international group of experts – the Guideline Development Group (GDG) – formulated and approved the recommendation.

Recommendation

The WHO technical consultation adopted one recommendation related to the use of TXA for the treatment of PPH. In formulating the recommendation, the GDG reviewed the balance between desirable and undesirable effects of TXA and overall quality of supporting evidence, values and preferences of stakeholders, resource requirements and cost-effectiveness, acceptability, feasibility and equity. To ensure that the recommendation is correctly understood and applied in practice, the contributing experts provided additional remarks. Guideline users should refer to these remarks, as well as to the evidence summary, if there is any doubt as to the basis for the recommendation and how best to implement it. The WHO recommendation on TXA for treatment of PPH is summarized in Table 1 below.

Table 1: Updated WHO recommendation on tranexamic acid for the treatment of postpartum haemorrhage

Early use of intravenous tranexamic acid (within 3 hours of birth) in addition to standard care is recommended for women with clinically diagnosed postpartum haemorrhage following vaginal birth or caesarean section. *(Strong recommendation, moderate quality of evidence)*
Remarks
• Based on the dosing regimen used in the WOMAN trial, the GDG supports the administration of tranexamic acid (TXA) at a fixed dose of 1 g (100 mg/ml) intravenously (IV) at 1 ml per minute (i.e. administered over 10 minutes), with a second dose of 1 g IV if bleeding continues after 30 minutes, or if bleeding restarts within 24 hours of completing the first dose.
• The WOMAN trial defined “clinically diagnosed postpartum haemorrhage” as clinically estimated blood loss of more than 500 ml after a vaginal birth or 1000 ml after caesarean section, or any blood loss sufficient to compromise haemodynamic stability.
• Based on evidence from the WOMAN trial, the reference point for the start of the 3-hour window for starting TXA administration is time of birth. If time of birth is unknown, the best estimate of time of birth should be used as the reference point. As most deaths due to postpartum haemorrhage (PPH) occur within the first 2 to 3 hours after birth, it is critical that TXA is given as soon as possible to achieve clinical benefits.
• Analysis of the effects of timing of administration in the WOMAN trial, as well as an individual participant data (IPD) meta-analysis of 40 138 bleeding patients (including WOMAN trial participants), indicates that TXA administration beyond 3 hours does not confer any clinical benefit. Furthermore, the point estimates of effect of TXA use beyond 3 hours on death for trauma or after PPH were both in the direction of harm, albeit not statistically significant for women with PPH. In view of this evidence, the GDG does not support the use of TXA more than 3 hours after birth.
• Administration of TXA should be considered as part of the standard PPH treatment package. Standard care in the context of this recommendation includes routine care for PPH treatment, including fluid replacement, medical (uterotonics), monitoring of vital signs, nonsurgical (e.g. bimanual compression, intrauterine balloon tamponade, nonpneumatic antishock garment, aortic compression) and surgical interventions (e.g. brace sutures, arterial ligation, or hysterectomy) in accordance with WHO guidelines or adapted local PPH treatment protocols.
• TXA should be used in all cases of PPH, regardless of whether the bleeding is due to genital tract trauma or other causes.
• The use of TXA should be avoided in women with a clear contraindication to antifibrinolytic therapy (including TXA) (e.g. a known thromboembolic event during pregnancy).
• This recommendation applies only to IV use. The evaluation of benefits and potential harms of other routes of TXA administration is a research priority.
• Regardless of the level of health system resources, TXA should be recognized as a life-saving intervention and be made readily available for the management of PPH in settings where emergency obstetric care is provided.

1. Background

PPH is commonly defined as a blood loss of 500 ml or more within 24 hours after birth, and affects about 5% of all women giving birth around the world.[1,2] Globally, nearly one quarter of all maternal deaths are associated with PPH, and in most low-income countries it is the main cause of maternal mortality.[3]

Severe PPH is generally defined as a blood loss of 1000 ml or more after birth. Severe maternal health conditions, such as organ dysfunction or death, generally occur following substantial blood loss that compromises maternal haemodynamic stability. Uterine atony is the most common cause of PPH and a leading cause of maternal mortality worldwide.[3] Genital tract trauma (that is, vaginal or cervical lacerations), uterine rupture, retained placental tissue, or maternal bleeding disorders are frequently associated with PPH. Although the majority of women presenting with PPH have no identifiable risk factor, grandmultiparity, prolonged labour and multiple gestation are obstetric conditions that are associated with an increased risk of bleeding after birth.[4] In addition, anaemia is a common aggravating factor.

The majority of PPH-associated deaths could be avoided by the use of prophylactic uterotonics during the third stage of labour and appropriate treatment. Thus, improving health care for women during childbirth to prevent and treat PPH is a necessary step towards achievement of the health targets of the Sustainable Development Goals (SDGs). Furthermore, 99% of all maternal deaths occur in low- and middle-income countries (LMICs). Efforts to prevent and reduce PPH-associated morbidity and mortality can thus reduce the profound inequities in maternal health globally. In support of this, health workers at all levels of care (particularly in LMICs) need to have access to appropriate medications and training in relevant procedures. Healthcare providers, health managers, policy-makers and other stakeholders also need up-to-date, evidence-based recommendations to inform clinical policies and practices, in order to enable improved healthcare outcomes.

In 2012, WHO published 32 recommendations for the prevention and treatment of PPH, including a recommendation on the use of TXA for treatment of PPH.[5] These recommendations were developed according to WHO guideline development standards, including synthesis of available research evidence, use of the GRADE methodology, and formulation of recommendations by a guideline panel of international experts.

In 2017, the Executive GSG on WHO maternal and perinatal health recommendations prioritized the updating of the existing WHO recommendation on the use of TXA for PPH treatment in response to important new evidence on this question. This updated recommendation thus supersedes the previous recommendation on TXA for PPH treatment, issued in the 2012 WHO recommendations on prevention and treatment of PPH.

Rationale and objectives

TXA is a competitive inhibitor of plasminogen activation, and it can reduce bleeding by inhibiting the enzymatic breakdown of fibrinogen and fibrin clots.[6] It is in routine clinical use for reduction of blood loss in surgery and trauma, and it is listed on the WHO Essential Medicines List for management of anticoagulation.[7] At the time of

the GDG meeting on prevention and treatment of PPH in March 2012, there was no direct evidence on the effectiveness and safety of TXA when used for treatment of PPH. The GDG conditionally recommended the use of TXA for the treatment of PPH only when uterotonics fail to control the bleeding or when the bleeding is thought to be partly due to trauma. The GDG noted that a large, randomized controlled trial – the World Maternal Antifibrinolytic (WOMAN) trial examining the effect of early administration of TXA on mortality, hysterectomy, and other morbidities in women with clinically diagnosed PPH – was ongoing.[8] The WOMAN trial has now concluded, and the primary findings were published in April 2017.[9] In light of this new evidence, the Executive GSG prioritized the updating of the recommendation on TXA use for PPH treatment.

As part of WHO's normative work on supporting evidence-informed policies and practices, the Department of Reproductive Health and Research (RHR) has now updated the recommendation on the use of TXA for treatment of PPH. This recommendation provides a foundation for the sustainable implementation of the intervention globally.

Target audience

The primary audience includes health professionals who are responsible for developing national and local health guidelines and protocols (particularly those related to PPH) and those directly providing care to women during labour and childbirth, including midwives, nurses, general medical practitioners, obstetricians, managers of maternal and child health programmes and relevant staff in ministries of health, in all settings.

This recommendation will also be of interest to professional societies involved in the care of pregnant women, nongovernmental organizations concerned with promotion of people-centred maternal care, and implementers of maternal and child health programmes.

Scope of the recommendation

The question for this recommendation was: in women with PPH (P), does administration of TXA for PPH treatment (I) compared to placebo, no treatment or other treatments (C), improve outcomes (O)? If so, what is the most appropriate period to administer TXA to improve outcomes? The population affected by this recommendation includes women who experience PPH in low-, middle- or high-income settings.

2. Methods

This recommendation is an update of the existing recommendation relating to TXA use for PPH treatment, published in the *WHO recommendations for prevention and treatment of postpartum haemorrhage* (2012).[5]

The recommendation was first developed using standardized operating procedures in accordance with the process described in the *WHO handbook for guideline development*.[10] In summary, the process included: (i) identification of the priority question and critical outcomes, (ii) retrieval of the evidence, (iii) assessment and

synthesis of evidence, (iv) formulation of the recommendation, and (v) planning for the dissemination, implementation, impact evaluation and updating of the recommendation. The WHO recommendation on TXA use for treatment of PPH was identified by the Executive GSG as a high priority for updating in response to new, important evidence on this question.

The updating of this recommendation involved five main groups to guide the process, with their specific roles as described in the following sections.

Contributors to the guideline

Executive Guideline Steering Group (Executive GSG)

The Executive GSG is an independent panel of external experts and relevant stakeholders from the six WHO regions. This group advises WHO on the prioritization of new and existing questions in maternal and perinatal health for recommendation development or updating.

WHO Steering Group

The WHO Steering Group, comprising WHO staff members from the Departments of Reproductive Health and Research (RHR) and Maternal, Newborn, Child and Adolescent Health (MCA), managed the updating process. The Group drafted the key recommendation question in PICO format, identified the systematic review team and guideline methodologist, as well as the guideline development and external review groups. In addition, the WHO Steering Group supervised the retrieval and syntheses of evidence, organized the Guideline Development Group meeting, drafted and finalized the guideline document, and managed the guideline dissemination, implementation and impact assessment. The members of the Steering Group are presented in Annex 1.

Guideline Development Group

The WHO Steering Group identified a pool of approximately 50 experts and relevant stakeholders from the six WHO regions to constitute the WHO Maternal and Perinatal Health Guideline Development Group (MPH-GDG). This is a diverse group of experts who are skilled in critical appraisal of research evidence; implementation of evidence-based recommendations; guideline development methods; and clinical practice, policy and programmes relating to maternal and perinatal health. Members of the MPH-GDG are identified in a way that ensures geographic representation and gender balance, and there were no significant conflicts of interest. Members' expertise cuts across thematic areas within maternal and perinatal health.

From the MPH-GDG pool, 14 external experts and relevant stakeholders were invited to constitute the Guideline Development Group (GDG) for updating this recommendation. This wasis a diverse group of individuals with expertise in PPH research, guideline development methods, and clinical policy and programmes relating to PPH prevention and treatment.

The GDG members convened for this recommendation were selected in a way that ensured geographic representation and gender balance, and there were no important conflicts of interest. The Group appraised the evidence that was used to inform the recommendation, advised on the interpretation of this evidence,

formulated the final recommendation based on the draft prepared by the Steering Group, and reviewed and approved the final document. The members of this Group are presented in Annex 1.

External Review Group

This Group included five technical experts with sufficient interest in the provision of evidence-based obstetric care. None of its members declared a conflict of interest. The Group reviewed the final document to identify any errors of fact and commented on clarity of the language, contextual issues and implications for implementation. The Group ensured that the decision-making processes have considered and incorporated contextual values and preferences of potential users of the recommendations, healthcare professionals and policy makers. They did not change the recommendation that was formulated by the GDG. The members of the External Review Group are presented in Annex 1.

Systematic review team and guideline methodologists

A Cochrane systematic review on this question was initiated, supported by the Cochrane Pregnancy and Childbirth Group. The WHO Steering Group reviewed and provided input into the protocol, and it worked closely with the Cochrane Pregnancy and Childbirth Group to appraise the evidence using the GRADE methodology. A representative of the Cochrane Pregnancy and Childbirth Group attended the GDG meeting to provide an overview of the available evidence and GRADE tables and to respond to technical queries from the GDG.

External partners and observers

Representatives of the United States Agency for International Development (USAID), the Maternal and Child Survival Programme (MCSP)/Jhpiego, the Bill & Melinda Gates Foundation (BMGF), the International Confederation of Midwives (ICM), the International Federation of Gynecology and Obstetrics (FIGO) and Gynuity Health Projects participated in the GDG meeting as observers. These organizations, with a long history of collaboration with the RHR Department in guideline dissemination and implementation, are implementers of the updated recommendation. In addition, one of the WOMAN trial co-ordinators from the London School of Hygiene and Tropical Medicine (LSHTM) provided an overview of the conduct and findings of the WOMAN trial and responded to questions from the GDG, but did not participate in GDG deliberations nor revision of the recommendation. The list of observers who participated in the final technical consultation is presented in Annex 1.

Identification of critical outcomes

The critical and important outcomes were aligned with the prioritized outcomes from the WHO recommendations on prevention and treatment of PPH (2012).[5] These outcomes were initially identified through a search of key sources of relevant, published, systematic reviews and a prioritization of outcomes by the 2012 GDG panel. During the updating of this recommendation, a further two outcomes were identified by the WHO Steering Group and the GDG as critical outcomes for this question: namely, maternal death (all causes) and maternal death due to bleeding. Thus, a total of 13 outcomes were rated as ‘critical’ and nine outcomes were rated as ‘important’ for this question. All outcomes were included in the scope of

this document for evidence searching, retrieval, grading and formulation of the recommendation. The list of critical and important outcomes is provided in Annex 2.

Evidence identification and retrieval

A Cochrane systematic review on the efficacy of TXA for PPH treatment was initiated by the Cochrane Pregnancy and Childbirth Group, as an offshoot of the existing Cochrane review of treatment for PPH.[11] This systematic review[12] was the primary source of evidence for this recommendation.

Randomized, controlled trials relevant to the key question were screened by the review authors, and data on relevant outcomes and comparisons were extracted into Review Manager (RevMan) software. The RevMan file was retrieved from the Cochrane Pregnancy and Childbirth Group and customized to reflect the key comparisons and outcomes (those that were not relevant to the recommendation were excluded). Then the RevMan file was exported to GRADE profiler software (GRADEpro) and GRADE criteria were used to critically appraise the retrieved scientific evidence. Finally, evidence profiles (in the form of GRADE tables) were prepared for comparisons of interest, including the assessment and judgements for each outcome, and the estimated risks.

Quality assessment and grading of the evidence

The quality assessment of the body of evidence for each outcome was performed using the GRADE approach.[13] Using this approach, the quality of evidence for each outcome was rated as 'high', 'moderate', 'low' or 'very low' based on a set of established criteria. The final rating of quality of evidence was dependent on the factors briefly described below.

Study design limitations The risk of bias was first examined at the level of individual study and then across studies contributing to the outcome. For randomized trials, quality was first rated as 'high' and then downgraded by one ('moderate') or two ('low') levels, depending on the minimum quality criteria met by the majority of the studies contributing to the outcome.

Inconsistency of the results The similarity in the results for a given outcome was assessed by exploring the magnitude of differences in the direction and size of effects observed from different studies. The quality of evidence was not downgraded when the directions of the findings were similar and confidence limits overlapped, whereas quality was downgraded when the results were in different directions, and confidence limits showed minimal or no overlap.

Indirectness The quality of evidence was downgraded when there were serious or very serious concerns regarding the directness of the evidence, that is, whether there were important differences between the research reported and the context for which the recommendation was being prepared. Such differences were related, for instance, to populations, interventions, comparisons or outcomes of interest.

Imprecision This assessed the degree of uncertainty around the estimate of effect. As this is often a function of sample size and number of events, studies with relatively few participants or events, and thus wide confidence intervals around effect estimates, were downgraded for imprecision.

Publication bias Quality rating could also be affected by perceived or statistical evidence of bias to underestimate or overestimate the effect of an intervention as a result of selective publication based on study results. We considered downgrading evidence by one level for strong suspicion of publication bias.

Formulation of recommendations

The WHO Steering Group used the evidence profiles to summarise evidence on effects of TXA on the prespecified outcomes. The evidence summary and corresponding GRADE tables, other related documents for assessment of values and preferences, resource requirements and cost-effectiveness, acceptability, feasibility and equity were provided in advance to members of the GDG. The GDG members and other participants were then invited to attend an online technical consultation (see Annex 1 for the list of participants) organized by the Steering Group in Geneva, Switzerland, on 29 August 2017. During the technical consultation, the GDG members reviewed and discussed the balance between desirable and undesirable effects of TXA and the overall quality of supporting evidence, values and preferences of stakeholders, resource requirements and cost-effectiveness, acceptability, feasibility and equity, before finalizing the recommendation and remarks.

Declaration of interests by external contributors

According to WHO regulations, all experts must declare their relevant interests prior to participation in WHO guideline development processes and meetings. All GDG members were therefore required to complete a standard WHO Declaration of Interest (DOI) form before engaging in the guideline development process and before participating in the guideline-related meeting. The WHO Steering Group reviewed all declarations before finalizing the experts' invitations to participate. Where any conflict of interest was declared, the Steering Group determined whether such conflicts were serious enough to affect objective judgement of the expert on the guideline development process and recommendation. To ensure consistency, the Steering Group applied the criteria for assessing the severity of conflict of interests in the *WHO Handbook for Guideline Development* for all experts. All findings from the received DOI statements were managed in accordance with the WHO DOI guidelines on a case-by-case basis and communicated to the experts. Where a conflict of interest was not considered significant enough to pose any risk to the guideline development process or reduce its credibility, the experts were only required to openly declare such conflict at the beginning of the GDG meeting, and no further actions were taken.

Annex 3 shows a summary of the DOI statements, and how declared conflicts of interest were managed by the Steering Group.

Decision-making during the technical consultation

During the technical consultation, the GDG reviewed and discussed the evidence summary and sought clarifications. In addition to evaluating the balance between desirable and undesirable effects of TXA and the overall quality of the evidence, the GDG applied additional criteria based on the GRADE evidence-to-decision framework to determine the direction and strength of the recommendation. These criteria

included values of stakeholders, resource implications, acceptability, feasibility and equity. Considerations were based on the experience and opinions of members of the GDG and supported by evidence from a literature search where available. However, specific systematic reviews of evidence (for example, qualitative evidence synthesis or detailed economic evaluation) were not performed to inform discussions on these criteria. Evidence-to-decision tables were used to describe and synthesize these considerations.

The decision was based on consensus defined as the agreement by three quarters or more of the participants. None of the GDG members expressed opposition to the recommendation.

Document preparation

Prior to the online technical consultation, the WHO Steering Group prepared a draft version of the GRADE evidence profiles, evidence summary and other documents relevant to the deliberation of the GDG. The draft documents were made available to the participants of the technical consultation two weeks before the meeting for their comments. During the meeting, these documents were modified in line with the participants' deliberations and remarks. Following the meeting, members of the WHO Steering Group drafted a full guideline document to accurately reflect the deliberations and decisions of the participants. The draft document was sent electronically to GDG members and the External Review Group for final review and approval.

Peer review

The final document was sent to five external independent experts who were not involved in the guideline panel for peer review. The WHO Steering Group evaluated the inputs of the peer reviewers for inclusion in this document. After the technical consultation and peer review, the modifications made by the WHO Steering Group to the document were limited to correction of factual errors and improvement in language to address any lack of clarity.

3. Evidence and recommendation

The following section outlines the recommendation and the corresponding narrative summary of evidence for the prioritized question. The GRADE table is presented in Annex 5. The evidence-to-decision table, summarizing the balance between desirable and undesirable effects and the overall quality of the supporting evidence, values and preferences of stakeholders, resource requirements, cost-effectiveness, acceptability, feasibility and equity that were considered in determining the strength and direction of the recommendation, is presented in Annex 4.

The following recommendation was adopted by the GDG. Evidence on the effectiveness of the intervention was derived from one systematic review and was summarized in GRADE tables (Annex 5). The quality of the supporting evidence was rated as 'moderate' for most critical outcomes. To ensure that the recommendation is correctly understood and appropriately implemented in practice, additional 'remarks' reflecting the summary of the discussion by GDG are included under the recommendation.

Early use of intravenous tranexamic acid (within 3 hours of birth) in addition to standard care is recommended for women with clinically diagnosed postpartum haemorrhage following vaginal birth or caesarean section. *(Strong recommendation, moderate quality of evidence)*

Remarks

- Based on the dosing regimen used in the WOMAN trial, the GDG supports the administration of tranexamic acid (TXA) at a fixed dose of 1 g (100 mg/ml) intravenously (IV) at 1 ml per minute (i.e. administered over 10 minutes), with a second dose of 1 g IV if bleeding continues after 30 minutes, or if bleeding restarts within 24 hours of completing the first dose.
- The WOMAN Trial defined "clinically diagnosed postpartum haemorrhage" as clinically estimated blood loss of more than 500 ml after a vaginal birth or 1000 ml after caesarean section, or any blood loss sufficient to compromise haemodynamic stability.
- Based on evidence from the WOMAN trial, the reference point for the start of the 3-hour window for starting TXA administration is time of birth. If time of birth is unknown, the best estimate of time of birth should be used as the reference point. As most deaths due to postpartum haemorrhage occur within the first 2 to 3 hours after birth, it is critical that TXA is given as soon as possible to achieve clinical benefits.
- Analysis of the effects of timing of administration in the WOMAN trial, as well as an individual participant data (IPD) meta-analysis of 40 138 bleeding patients (including WOMAN trial participants), indicates that TXA administration beyond 3 hours does not confer any clinical benefit. Furthermore, the point estimates of effect of TXA use beyond 3 hours on death for trauma or after PPH were both in the direction of harm, albeit not statistically significant for women with PPH. In view of this evidence, the GDG does not support the use of TXA more than 3 hours after birth.
- Administration of TXA should be considered as part of the standard postpartum haemorrhage treatment package. Standard care in the context of this recommendation includes routine care for PPH treatment, including fluid replacement, medical (uterotonics), monitoring of vital signs, nonsurgical (e.g. bimanual compression, intrauterine balloon tamponade, nonpneumatic antishock garment, aortic compression) and surgical interventions (e.g. brace sutures, arterial ligation or hysterectomy) in accordance with WHO guidelines or adapted local PPH treatment protocols.
- TXA should be used in all cases of PPH regardless of whether the bleeding is due to genital tract trauma or other causes.
- The use of TXA should be avoided in women with a clear contraindication to antifibrinolytic therapy (including TXA) (e.g. a known thromboembolic event during pregnancy).
- This recommendation applies only to IV use. The evaluation of benefits and potential harms of other routes of TXA administration is a research priority.
- Regardless of the level of health system resources, TXA should be recognized as a life-saving intervention and be made readily available for the management of postpartum haemorrhage in settings where emergency obstetric care is provided.

A. Review Question

- For women with postpartum haemorrhage (P), does administration of tranexamic acid in addition to standard care (I) compared to standard care alone (C), improve outcomes (O)?
  - If so, when is the most appropriate period to administer tranexamic acid to improve outcomes?

B. Assessment

Effects of the intervention

What are the anticipated effects of administration of TXA in addition to standard care for PPH treatment?

Research evidence

Evidence on the use of TXA for treatment of PPH was extracted from a forthcoming Cochrane systematic review of two trials (20 212 women).[12] This review included trials that compared the use of any fibrinolytic drug with no treatment in women with PPH. However, no evidence was identified for interventions other than TXA.

One multicentre trial was conducted in eight obstetric units in France with recruitment between 2005 and 2008.[14] This trial randomized 152 women with PPH > 800 ml after a vaginal birth. The intervention group received a loading dose of 4 g TXA mixed with 50 ml saline, administered IV over 1 hour, followed by a maintenance dose of 1 g/hour for 6 hours. Women in the control group were given standard care only, as per the routine practice in participating facilities. The primary outcome was blood loss between randomization and 6 hours.

The second (WOMAN trial) was a multicountry, multicentre, placebo-controlled randomised trial of 20 060 women in 193 hospitals, across 21 high-, middle- and low-income countries conducted between March 2010 and April 2016.[9] The trial randomized women with clinically diagnosed PPH, defined as clinically estimated blood loss after a vaginal birth of > 500 ml, or > 1000 ml following a caesarean section, or any blood loss sufficient to compromise haemodynamic stability and where the clinician responsible for care was uncertain as to whether or not to use TXA. In addition to usual care, women in the experimental group were initially given 1 g TXA IV in a 10 ml solution, at an approximate rate of 1 ml/minute, as soon as possible after randomization. A second dose was used if bleeding continued after 30 minutes or if it stopped and restarted within 24 hours after the first dose. The control arm received placebo (normal saline) using the same regimen. When the trial protocol was registered, the primary outcome was a composite of death from all causes or hysterectomy within 42 days. During the course of the study (but before results were available or any unblinding), the primary outcome was revised to maternal death due to bleeding, and the sample size increased.

Evidence regarding this intervention is almost entirely derived from the WOMAN trial.

Comparison: TXA (in addition to standard care) versus standard care alone

The effects of TXA on critical outcomes for all women with PPH, regardless of how PPH was defined, the mode of birth or timing of PPH administration, are described below.

- **Maternal mortality (all causes):** Moderate certainty evidence suggests slightly fewer deaths in the group receiving TXA although this difference was not statistically significant (two studies, 20 172 women; 227/10 113 (2.2%) vs 256/10 059 (2.5%); RR 0.88, 95% CI 0.74 to 1.05).

- **Maternal mortality due to PPH:** In both trials, clinicians were asked to record the primary cause of death. Moderate certainty evidence suggests that deaths that were considered to be due to bleeding were probably reduced in the TXA group (two studies, 20 172 women, 155/10 113 (1.5%) vs 191/10 059 (1.9%), RR 0.81, 95% CI 0.65 to 1.00). The number needed to treat (NNT) to prevent one maternal death due to bleeding is 258 (95% CI 133.2 to 4051.8).
- **Severe maternal morbidity:** The French trial reported multiple organ failure; there were no events in either arm and very few admissions to intensive care (one study, 152 women, 3/77 (3.9%) vs 5/74 (6.8%), RR 0.58 (95% CI 0.14 to 2.33). The number of women suffering any severe morbidity was not reported in the WOMAN trial report, but specific morbidities were reported. Moderate certainty evidence suggested little or no difference between groups for any of morbidity outcomes reported (respiratory failure: RR 0.87, 95% CI 0.67 to 1.12; seizure: two studies; RR 0.76, 95% CI 0.49 to 1.20; hepatic failure RR 0.96, 95% CI 0.58 to 1.60; cardiac failure: RR 0.95, 95% CI 0.73 to 1.23; renal failure: two studies; RR 1.09, 95% CI 0.85 to 1.39).
- **Blood products transfusion (all):** Moderate certainty evidence suggests there is very little or no difference between groups for transfusion of blood products, with more than half of the women in both arms of the WOMAN trial receiving a transfusion (two studies; RR 1.00, 95% CI 0.97 to 1.03).
- **Additional blood loss:** The French trial reported additional blood loss > 500 ml or > 1000 ml. Low-quality evidence suggests TXA probably reduces blood loss > 500 ml (RR 0.50, 95% CI 0.27 to 0.93, 151 women). Although the direction of effect was the same for loss > 1000 ml, the study had insufficient power to demonstrate a difference between groups (4/77 women versus 8/74).
- **Additional uterotonics:** The vast majority of women in the WOMAN trial received uterotonics (99.3% vs 99.1%, two studies; RR 1.00, 95% CI 1.0 to 1.0).
- **Surgical interventions:** High or moderate certainty evidence suggests there is probably little difference between groups for most surgical interventions to control bleeding (hysterectomy (all): two studies; RR 1.01, 95% CI 0.88 to 1.17; ligature: RR 0.88, 95% CI 0.74 to 1.05; embolization: RR 0.82, 95% CI 0.42 to 1.62). High certainty evidence suggests laparotomy to control bleeding is reduced for women in the TXA group (0.8% vs 1.3%) (RR 0.64, 95% CI 0.49 to 0.85) while brace sutures are increased (RR 1.19, 95% CI 1.01 to 1.41).
- **Invasive nonsurgical interventions:** High certainty evidence suggests there is probably little or no difference in intrauterine tamponade (one study; RR 0.96, 95% CI 0.87 to 1.06) or manual removal of placenta: (one study; RR 0.95, 95% CI 0.87 to 1.04).
- **Procedure-related complications:** Moderate certainty evidence suggests there is probably little or no difference between groups for thromboembolic events (any maternal thromboembolic event: RR 0.88, 95% CI 0.54 to 1.43; deep venous thrombosis: two studies; RR 0.62 95% CI 0.20 to 1.88; pulmonary embolism RR 0.85, 95% CI 0.44 to 1.61; myocardial infarction: RR 0.66, 95% CI 0.11 to 3.97; stroke: RR 1.33, 95% CI 0.46 to 3.82).
- **Neonatal adverse effects**: Available neonatal outcome data were limited (data from WOMAN trial only). There were no neonatal thromboembolic events and no clear differences in deaths in breastfed neonates (eight deaths with TXA vs seven deaths with placebo) in the WOMAN trial.
- **Longer-term outcomes:** Available data on longer-term outcomes was limited (data from the WOMAN trial only). Outcomes in the WOMAN trial were measured up to hospital discharge or 42 days if still in hospital. There was no information on longer-term outcomes in women or babies.
- Subgroup analysis examining treatment effect by mode of birth (vaginal or caesarean) suggests no clear difference in effect on maternal death (all causes) and maternal death due to PPH for type of birth (moderate certainty of evidence).

Comparison: TXA (in addition to standard care) versus standard care alone, by timing of TXA administration

Evidence for this subgroup comparison was derived from a pre-planned subgroup analysis of the WOMAN trial.

- **Maternal mortality due to PPH:** There are subgroup differences for the timing of drug administration. Women receiving TXA less than 1 hour after birth had reduced risk of death from bleeding, but the confidence interval crossed the line of no effect (less than 1 hour: RR 0.80, 95% CI 0.55 to 1.16). Women receiving TXA 1 to 3 hours after birth were at reduced risk of death from bleeding (1 to 3 hours: RR 0.60, 95% CI 0.41 to 0.88) compared with women where more than 3 hours had elapsed before TXA was administered (more than 3 hours: RR 1.07, 95% CI 0.76 to 1.51).
- **Maternal mortality (all cause):** Compared to the control group, women receiving TXA less than 1 hour after birth had similar risks of death (any cause) (less than 1 hour: RR 0.98, 95% CI 0.72 to 1.33), as did women receiving TXA more than 3 hours after birth (more than 3 hours: RR 1.00, 95% CI 0.75 to 1.33). However, women receiving TXA 1 to 3 hours after birth were at reduced risk of death from all causes (1 to 3 hours: RR 0.69, 95% CI 0.49 to 0.96).
- **Death or hysterectomy:** Compared to the control group, women receiving TXA less than 1 hour after birth had similar risks of death or hysterectomy (less than 1 hour: RR 1.08, 95% CI 0.91 to 1.28), as did women receiving TXA more than 3 hours after birth (more than 3 hours: RR 1.01, 95% CI 0.82 to 1.25). However, women receiving TXA 1 to 3 hours after birth were at reduced risk of death or hysterectomy (1 to 3 hours: RR 0.80, 95% CI 0.63 to 1.00).
- **Laparotomy for bleeding:** Compared to the control group, women receiving TXA less than 1 hour after birth had reduced risk of laparotomy for bleeding (less than 1 hour: RR 0.48, 95% CI 0.29 to 0.79), as did women receiving TXA at 1 to 3 hours after birth (1 to 3 hours: RR 0.54, 95% CI 0.31 to 0.95). Women receiving TXA more than 3 hours after birth were not at reduced risk of laparotomy for bleeding (more than 3 hours: RR 0.89, 95% CI 0.59 to 1.35).

Desirable effects

How substantial are the desirable anticipated effects of TXA + standard care vs standard care alone?

Judgement					
☐ Don't know	☐ Varies	☐ Trivial	☐ Small	☐ Moderate	☒ Large

Undesirable effects

How substantial are the undesirable anticipated effects TXA + standard care vs standard care alone?

Judgement					
☐ Don't know	☐ Varies	☐ Large	☐ Moderate	☐ Small	☒ Trivial

Certainty of the evidence

What is the overall certainty of the evidence of effects?

Judgement				
☐ No included studies	☐ Very low	☐ Low	☒ Moderate	☐ High

Additional considerations
Additional evidence was obtained from a forthcoming individual patient data (IPD) on the impact of treatment delay on the effectiveness and safety of antifibrinolytics in acute, severe haemorrhage.[15] The IPD meta-analysed 40 138 bleeding patients (with 3 558 deaths recorded) who received TXA or placebo from WOMAN and CRASH-2 trials combined. The authors reported that deaths from PPH peaked at 2 to 3 hours after childbirth, and immediate treatment improved bleeding survival. Treatment delay appears to reduce benefit – the benefit appears to decrease by 10% for every 15 minutes' delay, with no benefit seen after 3 hours. The point estimates of effect of TXA use beyond 3 hours on death for trauma or after PPH were both in the direction of harm, albeit not statistically significant for women with PPH.

Values and preferences

Is there important uncertainty about, or variability in, how much women value the main outcomes?

Typically, women, healthcare providers and policy-makers place a higher value on avoiding a maternal death, even when potentially associated with an increase in invasive surgical interventions, such as brace sutures. Therefore, women, healthcare providers and policy-makers in all settings are likely to place a high value on the reduction in the risk of maternal death due to bleeding. The GDG is confident that women, healthcare providers and policy-makers in any setting will invariably place a higher value on this benefit, compared to any inconvenience (or drawbacks) that TXA use might cause to the woman, her baby or the health system. Stakeholders with different values in different contexts are unlikely to make different decisions when presented with these choices.

Judgement			
☐ Important uncertainty or variability	☐ Possibly important uncertainty or variability	☐ Probably no important uncertainty or variability	☒ No important uncertainty or variability

Balance of effects

Does the balance between desirable and undesirable effects favour use of TXA in addition to standard care (intervention) or standard care alone (comparison)?

There is evidence that TXA is probably beneficial in reducing maternal deaths due to bleeding and reducing the need for laparotomy to stop bleeding. Early treatment appears to optimize benefit. There does not appear to be evidence of maternal or newborn harms, or significant side-effects. While no difference in newborn thromboembolic events were seen, in the WOMAN trial most women and babies were followed until discharge from the health facility, thus this evidence is more likely representative of the first few days after birth.

Judgement						
☐ Don't know	☐ Varies	☐ Favours the standard care alone	☐ Probably favours the standard care alone	☐ Does not favour TXA + standard care or standard care alone	☐ Probably favours TXA + standard care	☒ Favours TXA + standard care

Resources required

What are the resource requirements for administering TXA in addition to standard care for PPH treatment?

Research evidence

None of the studies included in the Cochrane systematic review conducted a formal cost-effectiveness analysis.

Main resource requirements

The use of TXA in addition to standard PPH treatment requires the existence of healthcare providers who have been trained in how to administer intravenous drugs.

Resource	Description
Training	2 to 3 day practice-based training/practice drills for PPH management
Supplies	1 to 2 g of TXA (varies between settings, with an approximate range of $1.00 to $5.70 per g) [16] IV infusion set Syringe/needle/swabs = approximately US$0.08 to $0.10
Equipment	None required.
Time	Average time needed is 10 to 15 minutes for gaining IV access and administration of the drug (depending on other factors such as provider skills). However, sufficient time is needed for monitoring the response of the woman to treatment as required for all cases of PPH.
Supervision and monitoring	Regular supervision and review by labour ward lead, especially when first introduced.

Additional considerations

- TXA is relatively cheap in most contexts, easy to administer, and it is often available in healthcare settings due to its use in trauma and surgery. Research evidence on cost-effectiveness can be extrapolated from cost-effectiveness analysis of TXA for bleeding trauma patients.16 The study found that administering TXA to bleeding trauma patients within 3 hours of injury saved an estimated 372, 315 and 755 life-years (LYs) per 1 000 trauma patients in Tanzania, India and the UK respectively. The cost of giving TXA to 1 000 patients was $17 483 in Tanzania, $19 550 in India and $30 830 in the UK. The incremental cost of giving TXA versus not giving TXA was $18 025 in Tanzania, $20 670 in India and $48 002 in the UK. The estimated incremental cost per LY gained of administering TXA is $48, $66 and $64 in Tanzania, India and the UK respectively. Early administration of TXA to bleeding trauma patients is likely to be highly cost-effective in low-, middle- and high-income settings.
- The use of TXA may also reduce subsequent costs related to surgical procedures for PPH treatment (such as laparotomy) as well as any complications associated with surgery.
- Out-of-pocket costs to individual women might be higher when TXA is added to standard care for PPH in settings where women incur financial costs for births.

Resource requirements

How large are the resource requirements for administering TXA in addition to standard care for PPH treatment compared to standard care alone?

Judgement						
☐ Don't know	☐ Varies	☐ Large costs	☐ Moderate costs	☒ Negligible costs or savings	☐ Moderate savings	☐ Large savings

Certainty of evidence on required resources

What is the certainty of the evidence on costs?

Judgement				
☒ No included studies	☐ Very low	☐ Low	☐ Moderate	☐ High

Cost-effectiveness

Does cost-effectiveness favour TXA + standard care or standard care alone?

Judgement						
☐ Don't know	☐ Varies	☐ Favours the standard care alone	☐ Probably favours the standard care alone	☐ Does not favour either the TXA + standard care or the standard care alone	☒ Probably favours TXA + standard care	☐ Favours TXA +standard care

Equity

What would be the impact on health equity of TXA administration in addition to standard care for PPH treatment?

Research evidence

- No direct evidence of the impact of the TXA administration in addition to standard care for PPH treatment on equity was found. However, indirect evidence from a review of barriers and facilitators to facility-based birth indicates that poor quality of care, as evident by poor birth outcomes, is probably a significant barrier to the uptake of facility birth by women in LMICs.[17]

Additional considerations

- The 2015 WHO State of Inequality report indicates that women who are poor, least-educated, and reside in rural areas have lower health intervention coverage and worse health outcomes than more advantaged women.[18] Therefore, reducing maternal deaths due to bleeding through scaling up of TXA for PPH treatment could have a positive impact on health equity and improve outcomes among disadvantaged women, especially in LMICs where these women are at significantly higher risk of PPH-related maternal deaths.
- Reducing the need for expensive, life-saving surgical interventions (such as laparotomy to stop bleeding in women with vaginal birth) through an IV medication would probably reduce inequities, especially in contexts where health services are covered through out-of-pocket means.

Judgement

☐ Don't know	☐ Varies	☐ Reduced	☐ Probably reduced	☐ Probably no impact	☒ Probably increased	☐ Increased

Acceptability

Is TXA (in addition to standard care) acceptable to key stakeholders (women and healthcare providers) for PPH treatment?

The intervention is likely to be acceptable to both women and healthcare providers. TXA is administered in adequately equipped health facilities (providing emergency obstetric care) by a skilled healthcare provider via a standard IV infusion over a short period of time. There is no evidence of adverse maternal or neonatal effects. The balance between benefits and harms suggests that TXA will be acceptable to key stakeholders (women, providers and policy makers) across settings. An incremental cost with substantial benefits in terms of saving lives would be generally acceptable.

Judgement

☐ Don't know	☐ Varies	☐ No	☐ Probably No	☒ Probably Yes	☐ Yes

Feasibility

Is TXA feasible to implement in addition to standard care for PPH treatment?

The use of IV TXA for treatment of PPH in healthcare facilities was regarded by the GDG as feasible. Standard IV infusion equipment is required, as well as healthcare providers with sufficient training to safely administer IV bolus infusions (similar to oxytocin infusion). Many hospitals already have access to TXA due to its common use for trauma and surgery. Available preparations are compatible with recommended dosing regimens for PPH treatment. In many healthcare facilities (including in LMICs) no (or minimal) additional resources, infrastructure or training is required to commence using TXA for this indication. Administration of TXA should be relatively easy to integrate into standard PPH treatment packages. It is listed on the WHO Model List of Essential Medicines under medicines affecting coagulation.

The successful implementation of the WOMAN trial in 193 hospitals in 21 countries, which recruited over 20 000 women, in itself can be considered a potential demonstration of the feasibility of implementing this intervention.[9] The pragmatic nature of the trial, coupled with the variations in the capacities of participating institutions (from low to very high) also supports feasibility across low-, middle- and high-income settings. These hospitals are likely to implement a recommendation of TXA easily.

However, given that evidence currently supports IV TXA for treatment, the intervention may not be feasible in settings where IV administrations are restricted to doctors working in high-level or referral facilities.

Judgement					
☐ Don't know	☐ Varies	☐ No	☐ Probably No	☒ Probably Yes	☐ Yes

4. Research implications

- The GDG identified that further research on the use of TXA for PPH is a priority. While the large, multicountry WOMAN trial has assessed the benefits and harms of IV TXA for PPH treatment, other research priorities include:
- What are the effects of TXA by other routes of administration (for example, oral, intramuscular, topical, buccal) when used for PPH treatment?
- What is the cost-effectiveness of TXA when used for PPH treatment?
- What is the optimal dosing regimen of TXA for PPH treatment?
- What are the longer-term effects (on women and breastfed newborns) of TXA when used for PPH treatment?
- What are the effects of oral or intravenous TXA when used for PPH prevention? [19]

5. Dissemination and implementation of the recommendation

Dissemination and implementation of the recommendation is to be considered by all actors involved in the provision of care for pregnant women at the international, national and local levels. There is a vital need to increase access and strengthen the capacity of health centres to provide high quality services for all women giving birth. It is therefore crucial that this recommendation is translated into PPH treatment packages and programmes at country and health-facility levels.

Recommendation dissemination and evaluation

The recommendation will be disseminated through WHO regional and country offices, ministries of health, professional organizations, WHO collaborating centres, other United Nations agencies and nongovernmental organizations, among others. This recommendation will be also available on the WHO website and in the WHO Reproductive Health Library. To increase awareness of the recommendation, a short commentary will be published in a peer-reviewed journal. The recommendation will be also disseminated during meetings or scientific conferences attended by WHO staff. The executive summary will be translated into the six UN languages and disseminated through the WHO regional offices. Technical assistance will be provided to any WHO regional office willing to translate the full recommendation into any of the six UN languages.

Implementation considerations

The successful introduction of evidence-based policies (related to the prevention and management of PPH) into national programmes and healthcare services depends on well planned and participatory, consensus-driven processes of adaptation and implementation. These processes may include the development or revision of existing national guidelines or protocols based on this document. TXA should be included as part of the standard package for PPH treatment. It should therefore be available at all times in the labour room of facilities providing emergency obstetric care.

Due consideration should be given to any specific manufacturer's instructions on precautions and contraindications. TXA for injection may be mixed with most solutions for infusion, such as electrolyte solutions, carbohydrate solutions, amino acid solutions and dextran solutions.[20] TXA should be administered as a bolus IV injection over 10 minutes, as there is a potential risk of transient lowering of blood pressure. TXA should not be mixed with blood for transfusion, solutions containing penicillin or mannitol.[20] It can be administered via the same IV cannula used for IV hydration or uterotonic administration.

An enabling environment should be created for the use of TXA (for example, by widening its availability) in order to support changes in the behaviour of healthcare practitioners to enable the use of evidence-based practice. This includes technical support for local guideline implementers in the development of training manuals, flowcharts and quality indicators as well as their participation in stakeholders' meetings. Local professional societies play important roles in this process, and an inclusive and participatory process should be encouraged.

Health facilities where emergency obstetric care is provided need to have the necessary supplies and equipment, as well as the necessary training for staff attending births, so that TXA can be administered safely by IV infusion. The shelf life of TXA is generally three years, and can be stored at room temperature (15 to 30 degrees Celsius). The opened product must be used immediately. The manufacturer's instructions on storage and use, however, should always be given precedence.

The recommendation should be adapted into locally appropriate documents that are able to meet the specific needs of each country and health service. Modifications to the recommendation should be justified in an explicit and transparent manner.

6. Applicability issues

Anticipated impact on the organization of care and resources

Implementing this evidence-based recommendation can be achieved without substantive additional resources. The GDG noted that updating training curricula and providing training on the updated recommendation would increase the recommendation's impact and facilitate its implementation. Standardizing PPH treatment by including this recommendation into existing packages of care can encourage healthcare provider behaviour change.

Monitoring and evaluating guideline implementation

Implementation should be monitored at the health-service level as part of broader efforts to monitor and improve the quality of maternal and newborn care. For example, interrupted time series, clinical audits or criterion-based clinical audits can be used to obtain relevant data related to the management of PPH. Clearly defined review criteria and indicators are needed and these could be associated with locally agreed targets. These can be aligned with the standards and indicators described in the WHO document *Standards for improving quality of maternal and newborn care in health facilities*.[21]

In 2012, the GDG of the WHO recommendations on prevention and treatment of PPH strongly recommended the use of coverage of prophylactic uterotonics as a process indicator for the monitoring of PPH prevention.[5] This indicator provides an overall assessment of adherence to a key recommendation within all of WHO's recommendations on PPH prevention and treatment. The use of other locally agreed and more specific indicators (for example, the assessment of the use of specific uterotonics or use of TXA for PPH treatment) may be necessary to obtain a more complete assessment of the quality of care related to the prevention and treatment of PPH. WHO has developed specific guidance for evaluating the quality of care for severe maternal complications (including PPH) based on the near-miss and criterion-based clinical audit concepts.[22]

In collaboration with the WHO RHR and MCA Departments' monitoring and evaluation team, data on country and regional level implementation of the recommendation will be collected and evaluated in the short- to medium-term to evaluate the recommendation's impact on the national policy of individual WHO Member States.

Information on recommended indicators can also be obtained at the local level by interrupted time series or clinical audits.

7. Updating the recommendation

The Executive GSG will convene annually to review WHO's current portfolio of maternal and perinatal health recommendations, and to prioritize new and existing questions for recommendation development and updating. Accordingly, the recommendation on TXA use for the treatment of PPH will be reviewed and prioritized by the Executive GSG. In the event that new evidence (that could potentially impact the current evidence base) is identified, the recommendation may be updated. If no new reports or information is identified, the recommendation may be revalidated.

Following publication and dissemination of the updated recommendation, any concern about validity of the recommendation will be promptly communicated to the guideline implementers, in addition to plans to update the recommendation.

WHO welcomes suggestions regarding additional questions for inclusion in the updated recommendation. Please email your suggestions to mpa-info@who.int.

References

1. Souza JP, Gülmezoglu AM, Vogel J, et al. Moving beyond essential interventions for reduction of maternal mortality (the WHO Multicountry Survey on Maternal and Newborn Health): a cross-sectional study. Lancet. 2013;381(9879):1747-55.
2. Carroli G, Cuesta C, Abalos E, Gulmezoglu AM. Epidemiology of postpartum haemorrhage: a systematic review. Best Pract Res Clin Obstet Gynaecol. 2008;22(6):999-1012.
3. Say L, Chou D, Gemmill A, et al. Global causes of maternal death: a WHO systematic analysis. Lancet Glob Health. 2014;2(6):e323-33.
4. Oyelese Y, Ananth CV. Postpartum hemorrhage: epidemiology, risk factors, and causes. Clin Obstet Gynecol. 2010;53(1):147-56.
5. WHO recommendations for the prevention and treatment of postpartum haemorrhage. Geneva: World Health Organization, 2012.
6. National Center for Biotechnology Information PCD, CID=5526. Tranexamic acid – compound summary for CID 5526. 2017 (https://pubchem.ncbi.nlm.nih.gov/compound/5526, accessed 31 August 2017).
7. Report of the WHO Expert Committee on Selection and Use of Essential Medicines, 2017 (including the 20th WHO Model List of Essential Medicines and the 6th WHO Model List of Essential Medicines for Children). Geneva: World Health Organization, 2017.
8. Shakur H, Elbourne D, Gülmezoglu M, et al. The WOMAN Trial (World Maternal Antifibrinolytic Trial): tranexamic acid for the treatment of postpartum haemorrhage: an international randomised, double blind placebo controlled trial. Trials. 2010:11:40.
9. WOMAN Trial Collaborators. Effect of early tranexamic acid administration on mortality, hysterectomy, and other morbidities in women with post-partum haemorrhage (WOMAN): an international, randomised, double-blind, placebo-controlled trial. Lancet. 2017;389(10084):2105-16.
10. WHO handbook for guideline development (second edition). Geneva: World Health Organization; 2014.
11. Mousa HA, Blum J, Abou El Senoun G, Shakur H, Alfirevic Z. Treatment for primary postpartum haemorrhage. Cochrane Database Syst Rev. 2014;(2):CD003249.
12. Shakur H, Beaumont D, Pavord S, Gayet-Ageron A, Ker K, Dowswell T, Mousa H. Antifibrinolytic drugs for treating primary postpartum haemorrhage. Cochrane Database Syst Rev. 2017;(unpublished).
13. Balshem H, Helfand M, Schünemann HJ, et al. GRADE guidelines: 3. Rating the quality of evidence. J Clin Epidemiol. 2011;64(4):401-6.
14. Ducloy-Bouthors AS, Jude B, Duhamel A, et al. High-dose tranexamic acid reduces blood loss in postpartum haemorrhage. Crit Care. 2011;15(2):R117.

15. Gayet-Ageron A, Prieto-Merino D, Ker K, Shakur H, Ageron F-X, Roberts I. Impact of treatment delay on the effectiveness and safety of anti-fibrinolytics in acute severe haemorrhage: an individual patient data meta-analysis in 40 138 bleeding patients. Lancet. 2017; accepted for publication.

16. Guerriero C, Cairns J, Perel P, Shakur H, Roberts I, collaborators Ct. Cost-effectiveness analysis of administering tranexamic acid to bleeding trauma patients using evidence from the CRASH-2 trial. PLoS One. 2011;6(5):e18987.

17. Bohren MA, Hunter EC, Munthe-Kaas HM, Souza JP, Vogel JP, Gülmezoglu AM. Facilitators and barriers to facility-based delivery in low- and middle-income countries: a qualitative evidence synthesis. Reprod Health. 2014;11(1):71.

18. State of inequality: reproductive, maternal, newborn and child health. Geneva: World Health Organization; 2015.

19. Novikova N, Hofmeyr GJ, Cluver C. Tranexamic acid for preventing postpartum haemorrhage. Cochrane Database Syst Rev. 2015;(6):CD007872.

20. EMC. Cyclokapron Injection. 15 March 2016 (https://www.medicines.org.uk/emc/medicine/1489w5, accessed September 2017).

21. Standards for improving quality of maternal and newborn care in health facilities. Geneva: World Health Organization; 2016.

22. Evaluating the quality of care for severe pregnancy complications: The WHO near-miss approach for maternal health. Geneva: World Health Organization; 2011.

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Annex 2. Critical and important outcomes for decision-making

Key question	Priority Outcomes
For women with postpartum haemorrhage (P), does administration of tranexamic acid in addition to standard care (I) compared to standard care alone (C), improve outcomes (O)?	**Critical outcomes** • Maternal death (all cause)* • Maternal death due to bleeding* • Additional blood loss ≥ 500 ml • Additional blood loss ≥ 1000 ml • Blood transfusion • Additional uterotonics • Invasive nonsurgical interventions • Surgical interventions (including hysterectomy) • Maternal temperature ≥ 40 °C • Procedure-related complications • Infections • Severe morbidity • Maternal transfer • Reduction of time from decision-making to implementation • Availability of drugs and treatment
	Important outcomes • Accuracy in blood loss assessment • Mean blood loss • Postpartum anaemia • Additional nonsurgical interventions (e.g. external aortic compression and compression garments) • Artery embolization • Nausea, vomiting or shivering • Maternal temperature ≥ 38 °C • Delayed initiation of breastfeeding • Prolonged hospitalization

* Maternal death (all cause) and maternal death due to bleeding were added as critical outcomes for the update of this recommendation.

Annex 3: Summary and management of declared interests from GDG members

Name and expertise contributed to the guideline development	Declared interest	Management of conflict of interest
Edgardo Abalos Content expert and end-user	None declared	Not applicable
Yap-Seng Chong Content expert and end-user	None declared	Not applicable
Catherine Deneux-Tharaux Content expert and end-user	None declared	Not applicable
Therese Dowswell Guideline methodologist	None declared	As one of the methodologists for this guideline, Therese Dowswell did not have voting rights at the meeting.
Bukola Fawole Content expert and end-user	Professor Fawole was a country investigator (Nigeria) on the WOMAN trial. He has participated in previous GDGs, including the previous WHO GDG on prevention and treatment of postpartum haemorrhage (2012).	The conflict was not considered serious enough to affect GDG membership or participation in the Technical Consultation. His perspectives on implementation of this intervention (resulting from WOMAN trial) were regarded as important.
Justus Hofmeyr Content expert and end-user	None declared	Not applicable
Caroline Homer Content expert and end-user	Co-Chair of National Antenatal Guidelines Expert Advisory Committee in Australia (2008 onwards)	The conflict was not considered serious enough to affect GDG membership or participation in the Technical Consultation
Pisake Lumbiganon Content expert and end-user	Was a DSMB member of the WOMAN trial	The conflict was not considered serious enough to affect GDG membership or participation in the Technical Consultation
Suellen Miller Content expert and end-user	Prof Miller's employer (University of California, San Francisco) holds the trademark on a nonpneumatic antishock device (NASG) for PPH management	The conflict was not considered serious enough to affect GDG membership or participation in the Technical Consultation
Ashraf Nabhan Content expert and end-user	None declared	Not applicable

Name and expertise contributed to the guideline development	Declared interest	Management of conflict of interest
James Neilson Content expert and end-user	None declared	Not applicable
Hiromi Obara Content expert and implementer	None declared	Not applicable
Zahida Qureshi Content expert and end-user	Professor Qureshi was a country investigator (Kenya) on the WOMAN trial. She has participated in previous GDGs, including the previous WHO GDG on prevention and treatment of postpartum haemorrhage (2012).	The conflict was not considered serious enough to affect GDG membership or participation in the Technical Consultation. Her perspectives on implementation of this intervention (resulting from WOMAN trial) were regarded as important.
Rahat Qureshi Content expert and end-user	None declared	Not applicable
Helen West Consumer representative	None declared	Not applicable

Annex 4. Summary of the considerations related to the strength of the recommendations

Desirable effects	- Don't know	- Varies		- Trivial	- Small	- Moderate	✓ Large
Undesirable effects	- Don't know	- Varies		- Large	- Moderate	- Small	✓ Trivial
Certainty of the evidence	- No included studies			- Very low	- Low	✓ Moderate	- High
Values and preferences				- **Important uncertainty or variability**	- Possibly important uncertainty or variability	- Probably no important uncertainty or variability	✓ No important uncertainty or variability
Balance of effects	- Don't know	- Varies	- Favours the comparison	- Probably favours the comparison	- Does not favour either the intervention or the comparison	- Probably favours the intervention	✓ Favours the intervention
Resources required	- Don't know	- Varies	- Large costs	- Moderate costs	✓ Negligible costs or savings	- Moderate savings	- Large savings
Certainty of evidence of required resources	✓ No included studies			- Very low	- Low	- Moderate	- High
Cost-effectiveness	- Don't know	- Varies	- Favours the comparison	- Probably favours the comparison	- Does not favour either the intervention or the comparison	✓ Probably favours the intervention	- Favours the intervention
Equity	- Don't know	- Varies	- Reduced	- Probably reduced	- Probably no impact	✓ Probably increased	- Increased
Acceptability	- Don't know	- Varies		- No	- Probably No	✓ Probably Yes	- Yes
Feasibility	- Don't know	- Varies		- No	- Probably No	- Probably Yes	✓ Yes

Annex 5. GRADE Tables

Question: Standard care plus tranexamic acid compared to standard care alone for treating primary postpartum haemorrhage

Setting: Data from two studies, one conducted in France (5 tertiary care centres and 3 secondary care obstetric centres: 152 women) and one multicentre RCT with 20 060 women (WOMAN trial).

WOMAN trial: Labour ward settings in high- (United Kingdom: 569 women), and low- and middle-income countries (Nigeria: 5711 women; Pakistan: 5282 women; Uganda: 2235 women; Kenya: 1031 women; Cameroon: 893 women; Sudan: 860 women; Tanzania: 538 women; Nepal: 533 women; Zambia: 496 women; Albania: 485 women; Democratic Republic of Congo: 457 women; Bangladesh: 325 women; Ethiopia: 302 women; Burkina Faso: 142 women; Jamaica: 73 women; Ghana: 41 women; Papua New Guinea: 38 women; Egypt: 33 women; Colombia: 8 women; Côte d'Ivoire: 8 women).

Bibliography: Shakur H, Beaumont D, Pavord S, Gayet-Ageron A, Ker K, Dowswell T, Mousa H. Antifibrinolytic drugs for treating primary postpartum haemorrhage. Cochrane Database Syst Rev. 2017;(unpublished).

Quality assessment							No. of patients		Effect		Certainty	Importance
No. of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other consider-ations**	**Standard care plus tranexamic acid**	**Placebo or standard care alone**	**Relative (95% CI)**	**Absolute (95% CI)**		
Maternal mortality (all causes)												
2	randomised trials	not serious	not serious	not serious	serious [a]	none	227/10113 (2.2%)	256/10059 (2.5%)	**RR 0.88** (0.74 to 1.05)	**3 fewer per 1000** (from 1 more to 7 fewer)	⊕⊕⊕○ MODERATE	CRITICAL
Maternal mortality (due to PPH)												
2	randomised trials	not serious	not serious	not serious	serious [b]	none	155/10113 (1.5%)	191/10059 (1.9%)	**RR 0.81** (0.65 to 1.00)	**4 fewer per 1000** (from 0 fewer to 7 fewer)	⊕⊕⊕○ MODERATE	CRITICAL
Severe maternal morbidity (maternal intensive care admission)												
1	randomised trials	serious [c]	not serious	not serious	very serious [d]	none	3/77 (3.9%)	5/74 (6.8%)	**RR 0.58** (0.14 to 2.33)	**28 fewer per 1000** (from 58 fewer to 90 more)	⊕○○○ VERY LOW	CRITICAL

Quality assessment							No. of patients		Effect		Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other consider-ations	Standard care plus tranexamic acid	Placebo or standard care alone	Relative (95% CI)	Absolute (95% CI)		
Severe maternal morbidity (maternal respiratory failure)												
1	randomised trials	not serious	not serious	not serious	serious [a]	none	108/10033 (1.1%)	124/9985 (1.2%)	**RR 0.87** (0.67 to 1.12)	**2 fewer per 1000** (from 1 more to 4 fewer)	⊕⊕⊕○ MODERATE	CRITICAL
Severe maternal morbidity (maternal seizure)												
2	randomised trials	not serious	not serious	not serious	serious [a]	none	33/10110 (0.3%)	43/10059 (0.4%)	**RR 0.76** (0.49 to 1.20)	**1 fewer per 1000** (from 1 more to 2 fewer)	⊕⊕⊕○ MODERATE	CRITICAL
Severe maternal morbidity (hepatic failure)												
1	randomised trials	not serious	not serious	not serious	serious [a]	none	29/10033 (0.3%)	30/9985 (0.3%)	**RR 0.96** (0.58 to 1.60)	**0 fewer per 1000** (from 1 fewer to 2 more)	⊕⊕⊕○ MODERATE	CRITICAL
Severe maternal morbidity (cardiac failure)												
1	randomised trials	not serious	not serious	not serious	serious [a]	none	110/10033 (1.1%)	115/9985 (1.2%)	**RR 0.95** (0.73 to 1.23)	**1 fewer per 1000** (from 3 fewer to 3 more)	⊕⊕⊕○ MODERATE	CRITICAL
Severe maternal morbidity (maternal renal failure)												
2	randomised trials	not serious	not serious	not serious	serious [a]	none	129/10110 (1.3%)	118/10059 (1.2%)	**RR 1.09** (0.85 to 1.39)	**1 more per 1000** (from 2 fewer to 5 more)	⊕⊕⊕○ MODERATE	CRITICAL
Blood Products transfusion (all)												
2	randomised trials	not serious	serious [e]	not serious	not serious	none	5474/10113 (54.1%)	5446/10059 (54.1%)	**RR 1.00** (0.97 to 1.03)	**0 fewer per 1000** (from 16 fewer to 16 more)	⊕⊕⊕○ MODERATE	CRITICAL

Quality assessment							No. of patients		Effect		Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other consider-ations	Standard care plus tranexamic acid	Placebo or standard care alone	Relative (95% CI)	Absolute (95% CI)		
Additional blood loss > 500 ml												
1	randomised trials	serious [c]	not serious	not serious	serious [f]	none	12/77 (15.6%)	23/74 (31.1%)	**RR 0.50** (0.27 to 0.93)	**155 fewer per 1000** (from 22 fewer to 227 fewer)	⨁⨁◯◯ LOW	CRITICAL
Additional blood loss > 1000 ml												
1	randomised trials	serious [c]	not serious	not serious	very serious [d]	none	4/77 (5.2%)	8/74 (10.8%)	**RR 0.48** (0.15 to 1.53)	**56 fewer per 1000** (from 57 more to 92 fewer)	⨁◯◯◯ VERY LOW	CRITICAL
Additional uterotonics												
2	randomised trials	not serious	not serious	not serious	not serious	none	10032/10106 (99.3%)	9964/10058 (99.1%)	**RR 1** (1 to 1)	**0 fewer per 1000** (from 0 fewer to 0 fewer)	⨁⨁⨁⨁ HIGH	CRITICAL
Surgical intervention (hysterectomy)												
2	randomised trials	not serious	not serious	not serious	not serious	none	358/10109 (3.5%)	352/10059 (3.5%)	**RR 1.01** (0.88 to 1.17)	**0 fewer per 1000** (from 4 fewer to 6 more)	⨁⨁⨁⨁ HIGH	CRITICAL
Surgical intervention (ligature)												
2	randomised trials	not serious	not serious	not serious	serious [a]	none	225/10109 (2.2%)	255/10059 (2.5%)	**RR 0.88** (0.74 to 1.05)	**3 fewer per 1000** (from 1 more to 7 fewer)	⨁⨁⨁◯ MODERATE	CRITICAL
Surgical intervention (embolization)												
2	randomised trials	not serious	not serious	not serious	serious [a]	none	15/10109 (0.1%)	18/10059 (0.2%)	**RR 0.82** (0.42 to 1.62)	**0 fewer per 1000** (from 1 fewer to 1 more)	⨁⨁⨁◯ MODERATE	CRITICAL

Quality assessment							No. of patients		Effect		Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other consider-ations	Standard care plus tranexamic acid	Placebo or standard care alone	Relative (95% CI)	Absolute (95% CI)		
Surgical intervention (laparotomy)												
1	randomised trials	not serious	not serious	not serious	not serious	none	82/10032 (0.8%)	127/9985 (1.3%)	**RR 0.64** (0.49 to 0.85)	**5 fewer per 1000** (from 2 fewer to 6 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
Surgical intervention (brace sutures)												
1	randomised trials	not serious	not serious	not serious	not serious	none	300/10032 (3.0%)	250/9985 (2.5%)	**RR 1.19** (1.01 to 1.41)	**5 more per 1000** (from 0 fewer to 10 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Invasive non-surgical intervention (intrauterine tamponade)												
1	randomised trials	not serious	not serious	not serious	not serious	none	705/10032 (7.0%)	729/9985 (7.3%)	**RR 0.96** (0.87 to 1.06)	**3 fewer per 1000** (from 4 more to 9 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
Invasive non-surgical intervention (manual removal of placenta)												
1	randomised trials	not serious	not serious	not serious	not serious	none	918/10032 (9.2%)	961/9985 (9.6%)	**RR 0.95** (0.87 to 1.04)	**5 fewer per 1000** (from 4 more to 13 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
Procedure-related complication (any maternal thromboembolic event)												
1	randomised trials	not serious	not serious	not serious	serious [a]	none	30/10033 (0.3%)	34/9985 (0.3%)	**RR 0.88** (0.54 to 1.43)	**0 fewer per 1000** (from 1 more to 2 fewer)	⊕⊕⊕○ MODERATE	CRITICAL
Procedure-related complication (deep venous thrombosis)												
2	randomised trials	not serious	not serious	not serious	serious [a]	none	5/10110 (0.0%)	8/10059 (0.1%)	**RR 0.62** (0.20 to 1.88)	**0 fewer per 1000** (from 1 fewer to 1 more)	⊕⊕⊕○ MODERATE	CRITICAL

Quality assessment							No. of patients		Effect		Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other consider-ations	Standard care plus tranexamic acid	Placebo or standard care alone	Relative (95% CI)	Absolute (95% CI)		
Procedure-related complication (pulmonary embolism)												
1	randomised trials	not serious	not serious	not serious	serious [a]	none	17/10033 (0.2%)	20/9985 (0.2%)	**RR 0.85** (0.44 to 1.61)	**0 fewer per 1000** (from 1 fewer to 1 more)	⊕⊕⊕○ MODERATE	CRITICAL
Procedure-related complication (myocardial infarction)												
1	randomised trials	not serious	not serious	not serious	serious [a]	none	2/10033 (0.0%)	3/9985 (0.0%)	**RR 0.66** (0.11 to 3.97)	**0 fewer per 1000** (from 0 fewer to 1 more)	⊕⊕⊕○ MODERATE	CRITICAL
Procedure-related complication (stroke)												
1	randomised trials	not serious	not serious	not serious	serious [a]	none	8/10033 (0.1%)	6/9985 (0.1%)	**RR 1.33** (0.46 to 3.82)	**0 fewer per 1000** (from 0 fewer to 2 more)	⊕⊕⊕○ MODERATE	CRITICAL
Procedure-related complication (neonatal thromboembolic event)												
1	randomised trials	not serious	not serious	not serious	very serious [g]	none	0/10033	0/9985	No events	No events	⊕⊕○○ LOW	CRITICAL
Procedure-related complication (death of breastfed baby)												
1	randomised trials	not serious	not serious	not serious	serious [a]	none	8/10033 (0.1%)	7/9985 (0.1%)	**RR 1.14** (0.41 to 3.14)	**0 fewer per 1000** (from 0 fewer to 2 more)	⊕⊕⊕○ MODERATE	No baby outcomes in WHO but this could be seen as a procedure related complica-tion

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

Explanations

a. Wide confidence interval crossing the line of no effect

b. Wide confidence interval that includes the line of no effect

c. Single study with design limitations (no blinding)

d. Few events, small sample size, and wide confidence interval crossing the line of no effect

e. Moderate statistical heterogeneity and may be clinical heterogeneity

f. Single study with small sample size

g. No events

Question: Standard care plus tranexamic acid compared to placebo or standard care alone for treating primary postpartum haemorrhage (subgroup time from birth)

Setting: Data from one multicentre RCT with 20 060 women (WOMAN trial). Labour ward settings in high- (United Kingdom: 569 women), and low- and middle-income countries (Nigeria: 5711 women; Pakistan: 5282 women; Uganda: 2235 women; Kenya: 1031 women; Cameroon: 893 women; Sudan: 860 women; Tanzania: 538 women; Nepal: 533 women; Zambia: 496 women; Albania: 485 women; Democratic Republic of Congo: 457 women; Bangladesh: 325 women; Ethiopia: 302 women; Burkina Faso: 142 women; Jamaica: 73 women; Ghana: 41 women; Papua New Guinea: 38 women; Egypt: 33 women; Colombia: 8 women; Côte d'Ivoire: 8 women).

Bibliography: Shakur H, Beaumont D, Pavord S, Gayet-Ageron A, Ker K, Dowswell T, Mousa H. Antifibrinolytic drugs for treating primary postpartum haemorrhage. Cochrane Database Syst Rev. 2017;(unpublished).

Quality assessment							No. of patients		Effect		Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other consider-ations	Standard care plus tranexamic acid	Placebo or standard care alone	Relative (95% CI)	Absolute (95% CI)		
Maternal mortality due to bleeding (subgroup time from birth) - less than 1 hour												
1	randomised trials	not serious	not serious	not serious	serious [a]	none	49/4846 (1.0%)	60/4726 (1.3%)	**RR 0.80** (0.55 to 1.16)	**3 fewer per 1000** (from 2 more to 6 fewer)	⨁⨁⨁◯ MODERATE	CRITICAL
Maternal mortality due to bleeding (subgroup time from birth) - 1 to 3 hours												
1	randomised trials	not serious	not serious	not serious	not serious	none	40/2674 (1.5%)	67/2682 (2.5%)	**RR 0.60** (0.41 to 0.88)	**10 fewer per 1000** (from 3 fewer to 15 fewer)	⨁⨁⨁⨁ HIGH	CRITICAL
Maternal mortality due to bleeding (subgroup time from birth) - more than 3 hours												
1	randomised trials	not serious	not serious	not serious	serious [a]	none	66/2514 (2.6%)	63/2569 (2.5%)	**RR 1.07** (0.76 to 1.51)	**2 more per 1000** (from 6 fewer to 13 more)	⨁⨁⨁◯ MODERATE	CRITICAL

Quality assessment							No. of patients		Effect		Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other consider-ations	Standard care plus tranexamic acid	Placebo or standard care alone	Relative (95% CI)	Absolute (95% CI)		
Maternal mortality (all cause) (subgroup time from birth) – less than 1 hour												
1	randomised trials	not serious	not serious	not serious	serious [a]	none	80/4846 (1.7%)	80/4726 (1.7%)	**RR 0.98** (0.72 to 1.33)	**0 fewer per 1000** (from 5 fewer to 6 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Maternal mortality (all cause) (subgroup time from birth) – 1 to 3 hours												
1	randomised trials	not serious	not serious	not serious	not serious	none	57/2674 (2.1%)	83/2682 (3.1%)	**RR 0.69** (0.49 to 0.96)	**10 fewer per 1000** (from 1 fewer to 16 fewer)	⨁⨁⨁⨁ HIGH	CRITICAL
Maternal mortality (all cause) (subgroup time from birth) – more than 3 hours												
1	randomised trials	not serious	not serious	not serious	serious [a]	none	90/2514 (3.6%)	92/2569 (3.6%)	**RR 1.00** (0.75 to 1.33)	**0 fewer per 1000** (from 9 fewer to 12 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Composite outcome: death or hysterectomy by subgroups (timing) – less than 1 hour												
1	randomised trials	not serious	not serious	not serious	serious [a]	none	253/4844 (5.2%)	229/4726 (4.8%)	**RR 1.08** (0.91 to 1.28)	**4 more per 1000** (from 4 fewer to 14 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Composite outcome: death or hysterectomy by subgroups (timing) – 1 to 3 hours												
1	randomised trials	not serious	not serious	not serious	serious [b]	none	122/2672 (4.6%)	154/2682 (5.7%)	**RR 0.80** (0.63 to 1.00)	**11 fewer per 1000** (from 0 fewer to 21 fewer)	⨁⨁⨁◯ MODERATE	CRITICAL
Composite outcome: death or hysterectomy by subgroups (timing) – more than 3 hours												
1	randomised trials	not serious	not serious	not serious	serious [a]	none	159/2514 (6.3%)	161/2569 (6.3%)	**RR 1.01** (0.82 to 1.25)	**1 more per 1000** (from 11 fewer to 16 more)	⨁⨁⨁◯ MODERATE	CRITICAL

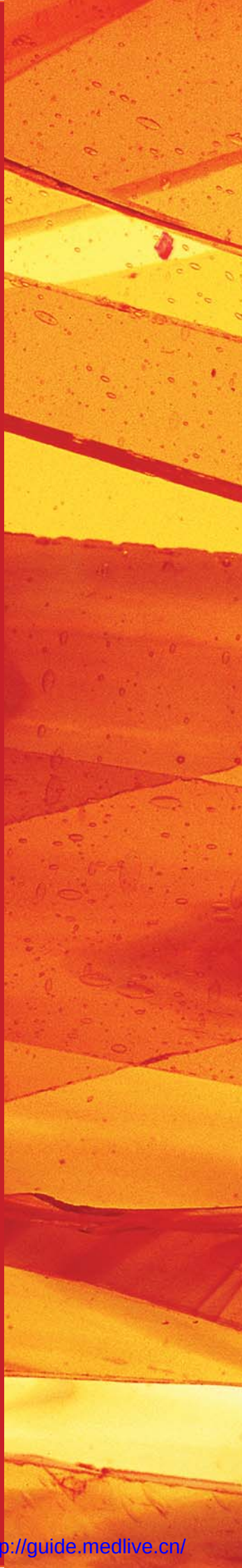
Quality assessment							No. of patients		Effect		Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other consider-ations	Standard care plus tranexamic acid	Placebo or standard care alone	Relative (95% CI)	Absolute (95% CI)		
Laparotomy for bleeding (subgroups by timing) - less than 1 hour												
1	randomised trials	not serious	not serious	not serious	not serious	none	22/4844 (0.5%)	45/4726 (1.0%)	**RR 0.48** (0.29 to 0.79)	**5 fewer per 1000** (from 2 fewer to 7 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
Laparotomy for bleeding (subgroups by timing) - 1 to 3 hours												
1	randomised trials	not serious	not serious	not serious	not serious	none	19/2672 (0.7%)	35/2682 (1.3%)	**RR 0.54** (0.31 to 0.95)	**6 fewer per 1000** (from 1 fewer to 9 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
Laparotomy for bleeding (subgroups by timing) - more than 3 hours												
1	randomised trials	not serious	not serious	not serious	serious [a]	none	41/2514 (1.6%)	47/2569 (1.8%)	**RR 0.89** (0.59 to 1.35)	**2 fewer per 1000** (from 6 more to 8 fewer)	⊕⊕⊕○ MODERATE	CRITICAL

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

Explanations

a. Wide 95% CI crossing the line of no effect

b. Wide 95% CI including the line of no effect



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