Tranexamic acid for bleeding: Much more than a treatment for postpartum hemorrhage

Ian Roberts, MD, PhD; Amy Brenner, MSc; Haleema Shakur-Still, MSc

The evidence that early tranexamic acid treatment reduces postpartum hemorrhage deaths has major implications for obstetrical care worldwide. Tranexamic acid may also have a role in the prevention of postpartum hemorrhage, but more evidence is needed on the balance of risks and benefits. Most deaths from postpartum hemorrhage are in low- and middle-income countries where tranexamic acid treatment is often unavailable. Several maternal health organizations including the Reproductive Health Supplies Coalition, Clinton Health Access Initiative, Concept Foundation, International Federation of Gynecology and Obstetrics, and Unitaid are working to increase access. However, a wider view of the evidence on tranexamic acid and bleeding shows that it can improve maternal health in many other ways. An appreciation of these other health benefits could facilitate efforts to increase access. By reducing heavy menstrual bleeding, tranexamic acid could reduce the prevalence of maternal anemia, a common and important risk factor for postpartum hemorrhage and other maternal and neonatal outcomes. Further clinical trials of tranexamic acid for the treatment of menstrual bleeding are needed. By reducing surgical bleeding and the need for blood transfusion, tranexamic acid would increase the availability of blood in countries where there is blood shortage so that more blood is available for use in life-threatening bleeding including postpartum hemorrhage. In countries where there is no blood shortage, tranexamic acid use would reduce healthcare costs and prevent transfusion-transmitted infections and reactions. Trauma affects women and men, and violence is a leading cause of death in pregnancy. Increased use of tranexamic acid in trauma would significantly reduce trauma deaths. Efforts to increase the availability and use of tranexamic acid for obstetrical hemorrhage should acknowledge its other health benefits and aim to increase its use across health services more generally.

Keywords: anemia, bleeding, clinical trials, essential medicines, maternal health, postpartum hemorrhage, surgery, tranexamic acid, trauma, violence

Tranexamic acid for the treatment of postpartum hemorrhage

In 2017, the WOMAN trial showed that early treatment (within 3 hours of birth) with the antifibrinolytic drug tranexamic acid (TXA) reduces postpartum hemorrhage (PPH) deaths and the need for surgical intervention to control bleeding without any increased risk of vascular occlusive events.[1] Within months, TXA was included in the World Health Organization (WHO) guidelines for the treatment of PPH.[2] On the basis of the dosing regimen used in the WOMAN trial, the WHO recommended the intravenous (IV) administration of 1 g of TXA, with a second IV dosage of 1 g if bleeding continues after 30 minutes, or if bleeding restarts within 24 hours. TXA is inexpensive, heat-stable, and has a long shelf life. A major advantage of TXA is that it reduces PPH deaths regardless of the cause of bleeding. A subgroup analysis of the WOMAN trial data found no evidence of heterogeneity in the effect of TXA on deaths due to bleeding according to the cause of the bleeding. When interpreting the results of subgroup analyses, the best working assumption is that the overall result probably applies to everyone unless there is good evidence to the contrary. In this case, the effect of TXA on death due to bleeding was slightly different in the atony and nonatony groups, but the heterogeneity *P* value (*P*=.36) showed that this difference is easily compatible with the play of chance. The WOMAN trial showed that TXA significantly reduces bleeding deaths and the need for laparotomy to control bleeding, even when the primary cause of bleeding was uterine atony. This stands in contrast with uterotonic drugs that should only affect PPH resulting from uterine atony, which is variably estimated to occur in 60% to 70% of PPH cases.

There is strong evidence that TXA is most effective when given as soon as possible after bleeding onset, and the WHO recommended that TXA be given immediately after PPH diagnosis, along with uterotonic drugs. Conversely, the American College of Obstetricians and Gynecologists recommended that TXA be administered when initial therapies fail.[3] Waiting to see if initial therapies fail is likely to lead to delayed administration and reduce the benefits of TXA treatment. Regardless of cause of bleeding, waiting to see if uterotonics fail can only lead to delayed TXA treatment, placing mothers at increased risk of consumptive coagulopathy.

Despite the lifesaving benefits of TXA as a treatment of PPH, in many low- and middle-income countries, where most deaths from PPH occur, TXA is often unavailable. Efforts to scale up global access to TXA for PPH treatment

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From the Department of Population Health, London School of Hygiene and Tropical Medicine, London, United Kingdom.

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Corresponding author: Ian Roberts, MD, PhD. Ian.Roberts@lshtm.ac.uk

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are under way. The Reproductive Health Supplies Coalition, Clinton Health Access Initiative (CHAI), Concept Foundation, International Federation of Gynecology and Obstetrics (FIGO), E-MOTIVE trial, and other organizations are working to bring TXA treatment to all women with PPH. As with any new drug, the barriers to scale-up are bottlenecks in country procurement and distribution, with limited supply forcing up prices. However, it is not widely appreciated that TXA can improve maternal health in many other ways apart from the treatment of PPH, and a more "health systems—oriented" approach to its availability and use could have additional health benefits. Because market forces determine the availability and cost of TXA in many countries, appreciation of its other health benefits could have strategic advantages by increasing its demand for uses beyond PPH treatment. These other health benefits are discussed below.

Tranexamic acid for the prevention of postpartum hemorrhage

The knowledge that TXA treatment of PPH improves outcomes has raised interest in its use for the prevention of severe bleeding. All women bleed after childbirth. As if anticipating this inevitability, the mother's blood becomes increasingly prothrombotic in pregnancy.[4] Levels of clot-forming proteins like fibrinogen and coagulation factor VII increase, whereas the activity of clot-dissolving (fibrinolytic) proteins is reduced because of higher levels of inhibitors. The placenta itself releases potent inhibitors of fibrinolysis (plasminogen activator inhibitor [PAI]-1 and PAI-2). Blood levels peak at the moment of birth, falling away rapidly after placental separation.[5] Given the strong evolutionary links between coagulation and immunity, protection from pathogens might have been one of the selection pressures molding the hemostatic system. Regardless of biological purpose, there are profound changes in the mother's blood around the time of birth.

Despite the prothrombotic tendency, bleeding after childbirth can be severe and sometimes fatal. In parts of sub-Saharan Africa and South Asia, 1 mother dies from bleeding for every 1000 births.[1] In high-income countries, the risk is orders of magnitude lower, with <1 bleeding death per 100,000 births.[6] In these low-risk settings, there are more thrombotic deaths than bleeding deaths. Because of the propensity of the blood to clot and the pressure from the expanding womb, pregnant women have an increased risk of arterial and venous thrombosis. Compared with nonpregnant women, the risk of thromboembolism in pregnant women is 5 times higher, rising to 20 times higher in the postpartum period.[7] To complicate matters, women giving birth are not exposed to one risk (bleeding) or the other (thrombosis) but to both risks simultaneously. Severe bleeding is a risk factor for thrombosis. For this reason, before deciding to use a treatment to prevent bleeding, we must consider the risk of bleeding and thrombosis and the effect of the treatment on both.

The WOMAN trial evaluated the effects of TXA in mothers with severe bleeding after childbirth.[1] All of the included women were bleeding profusely, and most were hemodynamically unstable. Their risk of death from bleeding was extremely high, at approximately 20 deaths per 1000 births. Their risk of death from thrombosis was also high at 1 death per 1000 births, but much lower than the risk of death from bleeding. TXA cut bleeding deaths by a third when given within 3 hours of birth, preventing approximately 6 deaths for every 1000 women treated. There was no apparent effect of TXA on thrombosis deaths, but because there were only 21 thrombotic deaths in this 20,060-patient trial, there is uncertainty about the effects of TXA on this outcome. Nevertheless, this uncertainty does not materially affect the treatment decision. Even if TXA doubled the risk of thrombotic deaths, which seems highly unlikely, in women with severe bleeding the benefit would outweigh the harms. As recommended by the WHO, all women with severe postpartum bleeding should receive TXA.[2]

But does TXA improve outcomes for women without severe bleeding? The WOMAN-2 trial is evaluating the effects of TXA after childbirth in women with moderate or severe anemia.[8] In this trial, women with anemia are treated immediately after birth, as soon as the umbilical cord is clamped. Anemia is a strong risk factor for bleeding after childbirth.[9] The increased heart rate and cardiac output caused by anemia and the reduced viscosity of anemic blood increase blood flow from bleeding vessels.[10–12] Red cells also seem to have a clot-stabilizing effect, and anemic clots are more susceptible to fibrinolysis.[13] Women with severe anemia have elevated D-dimer levels and lower platelet and fibrinogen levels.[14] The risk of death from bleeding in these women is approximately 1 per 1000 births and much higher than the risk of thrombotic death. Because anemia increases the risk of bleeding and decreases the risk of thrombosis, the net effect of TXA should be favorable in women with anemia.

There have also been trials of TXA for PPH prevention in low-risk women in high-income countries.[15–17] Because the risk of death from bleeding is low (approximately 1/100,000 deliveries) and similar to the risk of death from thrombosis, uncertainty about the effect of TXA on thrombosis is far more consequential. If there was an increase in thrombotic events with TXA, this could outweigh the benefits of reduced bleeding. Therefore, it is critical that trials in low-risk women be large enough to assess the effect of TXA on thrombosis. Because fatal events are so rare, we will need to study the effects of TXA on nonfatal thrombosis. However, even then, we would only expect approximately 2 thrombotic events per 1000 births. Trials with just a few thousand low-risk women would be underpowered and almost noninformative. Even the largest trial, which included 11,000 low-risk women giving birth by cesarean delivery, was too small to provide reliable information about safety. We will need larger trials and meta-analyses of these large trials before we can confidently offer TXA treatment to low-risk women.

Are we being overcautious? Could a single injection of TXA to inhibit fibrinolysis for just a few hours, when the

risk of bleeding is greatest, cause a significant increase in the risk of thrombosis? TXA has a short half-life and is almost completely eliminated within 6 to 8 hours. Severe bleeding that requires transfusion or surgery is itself prothrombotic, and thus by preventing bleeding we might even reduce the risk of thrombosis. Without reliable evidence we can only speculate, but with >140 million births each year worldwide, it would be rash to speculate about such an important issue.

Tranexamic acid and heavy menstrual bleeding

Anemia is common and dangerous in women of reproductive age. Worldwide, half a billion women of reproductive age (1 in 3) have anemia, with a particularly high burden in sub-Saharan Africa and South Asia.[18–20] Anemia reduces capacity to benefit from education, to work, and to participate in social and leisure activities.[21] Because it affects educational attainment and work productivity, anemia affects national development. In pregnancy, it increases the risk of low birthweight, preterm birth, and perinatal, neonatal, and maternal mortality.[22–24]

Menstruation is a major cause of anemia in women of reproductive age and affects quality of life. Higher menstrual blood loss (40 mL on average) is correlated with greater losses of iron (1.6 mg on average) and hemoglobin (Hb).[25–27] The presence of anemia strongly suggests that dietary intake of iron, B12, and folate is insufficient to compensate for menstrual losses of iron. In addition to contributing to anemia, menstrual symptoms such as heavy menstrual bleeding affect women's ability to undertake physical, social, and academic activities, which greatly affects quality of life.[28]

New strategies are needed to improve women's health and achieve global anemia targets. The WHO aims to halve anemia prevalence in women of reproductive age by 2025.[29] The prevalence of anemia is falling, but slowly. From 1995 to 2011, global mean Hb increased by just 1 g/L.[20] Interventions to reduce menstrual bleeding have been neglected in anemia control strategies, which largely focus on increasing the dietary intake of iron, B12, and folate, but have had limited success.[30]

By reducing menstrual iron loss, TXA has the potential to reduce anemia regardless of whether it is caused by iron deficiency, underlying diseases, infections, or genetic hemoglobinopathies. Endometrial fibrinolysis in normal menstruation provides the biological basis for using TXA to reduce menstrual losses of iron and Hb in women with anemia.[31] Although the evidence that TXA reduces heavy menstrual bleeding is promising, further high-quality trials are needed in low- and middle-income settings.[32] Such trials could change anemia control policy globally, improve the wellbeing of millions of women, and help achieve the WHO target. Early intervention to reduce the risk of anemia during pregnancy offers the potential to reduce adverse maternal and birth outcomes and to improve maternal wellbeing.

Tranexamic acid and surgical bleeding

Evidence that TXA reduces surgical bleeding and the need for blood transfusion has been available for decades, but uncertainty about the risk of vascular occlusive events has limited its widespread use.[33,34] Recent systematic reviews and meta-analyses of clinical trials of TXA in elective surgery show no increased risk of vascular occlusive events with TXA, but because many of the included trials were small there was still some doubt about the balance of risks and benefits.[35,36] However, to the best of our knowledge, the recent publication of the POISE-3 trial results is a substantive addition to the effects of TXA in surgery and warrants urgent attention.[37] The POISE-3 trial randomly allocated close to 10,000 patients undergoing noncardiac surgery to TXA or placebo and showed that TXA reduced major bleeding by one-quarter and significantly reduced blood transfusion, without increasing the risk of vascular occlusive events. For statistical reasons it is hard to rule out a very small increase in the risk of vascular occlusive events, but because significant bleeding is surprisingly common in surgery, and vascular occlusive events are relatively rare, the balance of benefits and risks will be favorable. As demonstrated previously, the POISE-3 trial showed that TXA reduces bleeding in all types of surgery, including gynecologic surgery. In high-, middle-, and low-income settings, the greater use of TXA in people having in-patient surgery would reduce surgical blood loss, postoperative anemia, and risks of transfusion-transmitted infection. Economic evaluation shows that TXA is a highly cost-effective intervention for reducing the cost and risks associated with surgical procedures requiring blood transfusions in low- and middle-income settings, particularly in sub-Saharan Africa.[38] By increasing the availability of blood, TXA could be lifesaving in countries where there is severe blood shortage. In most low-income countries there is a severely limited supply of safe blood for transfusion. The severe blood shortage is likely to explain the high frequency of single-unit blood transfusions in women with severe postpartum bleeding, despite the need for higher-volume transfusions. Use of TXA would also reduce healthcare costs and prevent transfusion-transmitted infections including HIV, hepatitis B, and hepatitis C in countries where blood is readily available. Given the recent outbreaks of new viral infections (monkeypox and adenovirus causing hepatitis), avoiding unnecessary blood transfusion while improving surgical outcomes should have a high public health profile.

Tranexamic acid and traumatic bleeding

In 2010, results from the global CRASH-2 trial (20,211 polytrauma patients) showed that IV TXA given within 3 hours of injury reduces deaths due to bleeding and all-cause mortality.[39] On the basis of these results TXA was added to the WHO list of essential medicines. In 2019, results from the global CRASH-3 trial (13,000 patients with isolated traumatic brain injury) showed that TXA given within 3 hours of injury also reduces head injury deaths, almost certainly by reducing the extent of traumatic intracranial

TABLE
Established indications for tranexamic acid

PPH: 1-g tranexamic acid as soon as possible after PPH onset (but no later than 3 h from birth) reduces PPH deaths by a third and reduces the need for laparotomy for bleeding.
Surgery: 1-g tranexamic acid just before incision reduces surgical bleeding and the need for blood transfusion by between one-quarter and one-third.
Trauma: 1-g tranexamic acid as soon as possible after injury (but no later than 3 hours) reduces deaths from bleeding by about one-third.

PPH, postpartum hemorrhage.

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bleeding.[40] Early TXA treatment reduces trauma deaths regardless of country income level, although misguided concerns about the generalizability of the trial results have limited the mortality benefits in some settings.[41] The implications for women of the lifesaving benefits of TXA in trauma patients become obvious when considering that violence is the leading cause of death during pregnancy and the postpartum period in the United States. A recent analysis of mortality data from the US National Center for Health Statistics showed that violence during pregnancy or within 42 days of the end of pregnancy exceeded all the leading causes of maternal mortality by more than 2-fold.[42] The pregnancy-associated homicide risk was particularly high in Black women and girls. Unfortunately, there is recent evidence that injured women are much less likely than men to receive TXA treatment.[43] Advocates for women should ensure that when women are victims of injury or violence, they receive evidence-based trauma care including the use of TXA (Table).

Future research priorities

Timely treatment with IV TXA cuts PPH deaths by one-third. To increase access in low- and middle-income countries, WHO has made it a research priority to find different ways to provide TXA treatment. Women die soon after PPH, and thus effective TXA levels must be achieved quickly. Many community health workers cannot give IV drugs, but most are trained to give intramuscular (IM) injections (eg, vaccination). Further research is needed on IM TXA use because this has the potential to take this lifesaving drug out of hospitals and into communities so that more women can be treated and sooner. We will also need larger trials and meta-analyses of large trials before we can offer TXA for the prevention of PPH in low-risk women. Clinical trials of the role of TXA in the treatment of heavy menstrual bleeding and the prevention of anemia are also needed.

Conclusions

The inclusion of TXA into WHO guidelines on the treatment of PPH has led to a profusion of initiatives to increase the availability and use of TXA for this specific indication. However, TXA can improve maternal health in many other ways, and a more "health systems–oriented" approach to TXA availability and use would have major additional health benefits. TXA is a key component of the PPH treatment bundle, and the Reproductive Health Supplies Coalition, CHAI, Concept Foundation, FIGO, and other organizations are working to scale up access to TXA in low- and middle-income countries. Recognizing the other health system uses and benefits of TXA has the potential to expand the hospital demand for TXA, which should lead to increased supply. A health-systems approach to TXA availability and use would have enormous benefits. Anemia owing to heavy menstrual bleeding debilitates millions of young women, reducing their ability to develop to their full potential. Access to TXA could be life-changing for these women. By reducing surgical bleeding, TXA could increase the blood supply for women who need it. Injury and violence kill 5 million men and women each year, and wider use of TXA could save >100,000 lives each year.[44] TXA is an essential medicine for surgical, traumatic, and postpartum bleeding and must be available in hospitals everywhere. ■

REFERENCES

1. 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;389:2105–16.
2. WHO recommendation on tranexamic acid for the treatment of postpartum haemorrhage. Geneva: World Health Organization; 2017. Licence: CC BY-NC-SA 3.0 IGO.
3. American College of Obstetricians and Gynecologists. ACOG expands recommendations to treat postpartum hemorrhage. 2017. Available at: https://www.acog.org/news/news-releases/2017/09/acog-expands-recommendations-to-treat-postpartum-hemorrhage. Accessed May 24, 2022.
4. Hellgren M. Hemostasis during normal pregnancy and puerperium. Semin Thromb Hemost 2003;29:125–30.
5. Kruithof EK, Tran-Thang C, Gudinchet A, et al. Fibrinolysis in pregnancy: a study of plasminogen activator inhibitors. Blood 1987;69:460–6.
6. Knight M, Bunch K, Tuffnell D, et al. Saving lives, improving mothers' care maternal, newborn and infant clinical outcome review programme. 2021. Available at: www.hqip.org.uk/national-programmes. Accessed May 24, 2022.
7. James AH. Venous thromboembolism in pregnancy. Arterioscler Thromb Vasc Biol 2009;29:326–31.
8. Ker K, Roberts I, Chaudhri R, et al. Tranexamic acid for the prevention of postpartum bleeding in women with anaemia: study protocol for an international, randomised, double-blind, placebo-controlled trial. Trials 2018;19:712.
9. Nair M, Choudhury MK, Choudhury SS, et al. Association between maternal anaemia and pregnancy outcomes: a cohort study in Assam, India. BMJ Glob Health 2016;1:e000026.
10. Weiskopf RB, Viele MK, Feiner J, et al. Human cardiovascular and metabolic response to acute, severe isovolemic anemia. JAMA 1998;279:217–21.
11. Whittaker SRF, Winton FR. The apparent viscosity of blood flowing in the isolated hindlimb of the dog, and its variation with corpuscular concentration. J Physiol 1933;78:339–69.
12. Guyton AC, Richardson TQ. Effect of hematocrit on venous return. Circ Res 1961;9:157–64.

13. Wohner N, Sótonyi P, MacHovich R, et al. Lytic resistance of fibrin containing red blood cells. Arterioscler Thromb Vasc Biol 2011;31:2306–13.
14. Nair M, Chhabra S, Choudhury SS, et al. Relationship between anaemia, coagulation parameters during pregnancy and postpartum haemorrhage at childbirth: a prospective cohort study. BMJ Open 2021;11:e050815.
15. Sentilhes L, Winer N, Azria E, et al. Tranexamic acid for the prevention of blood loss after vaginal delivery. N Engl J Med 2018;379:731–42.
16. Sentilhes L, Sénat MV, Le Lous M, et al. Tranexamic acid for the prevention of blood loss after cesarean delivery. N Engl J Med 2021;384:1623–34.
17. Pacheco LD. LB 3: Tranexamic acid for the prevention of obstetrical hemorrhage after cesarean delivery: a randomized controlled trial. Am J Obstet Gynecol 2022;226:S779–80. https://www.ajog.org/article/S0002-9378(21)02663-6/fulltext.
18. Young MF. Maternal anaemia and risk of mortality: a call for action. Lancet Glob Health 2018;6:e479–80.
19. Sunuwar DR, Singh DR, Chaudhary NK, Pradhan PMS, Rai P, Tiwari K. Prevalence and factors associated with anemia among women of reproductive age in seven South and Southeast Asian countries: evidence from nationally representative surveys. PLoS One 2020;15:e0236449.
20. Stevens GA, Finucane MM, De-Regil LM, et al. Global, regional, and national trends in haemoglobin concentration and prevalence of total and severe anaemia in children and pregnant and non-pregnant women for 1995-2011: a systematic analysis of population-representative data. Lancet Glob Health 2013;1:e16–25.
21. Haas JD, Brownlie T 4th. Iron deficiency and reduced work capacity: a critical review of the research to determine a causal relationship. J Nutr 2001;131:676S–88.
22. Rahman MM, Abe SK, Rahman MS, et al. Maternal anemia and risk of adverse birth and health outcomes in low- and middle-income countries: systematic review and meta-analysis. Am J Clin Nutr 2016;103:495–504.
23. Young MF, Oaks BM, Tandon S, Martorell R, Dewey KG, Wendt AS. Maternal hemoglobin concentrations across pregnancy and maternal and child health: a systematic review and meta-analysis. Ann N Y Acad Sci 2019;1450:47–68.
24. Daru J, Zamora J, Fernández-Félix BM, et al. Risk of maternal mortality in women with severe anaemia during pregnancy and post partum: a multilevel analysis. Lancet Glob Health 2018;6:e548–54.
25. Ofojekwu M-JN, Nnanna OU, Okolie CE, Odewumi LA, Isiguzoro IOU, Lugos MD. Hemoglobin and serum iron concentrations in menstruating nulliparous women in Jos, Nigeria. Lab Med 2013;44:121–4.
26. Barr F, Brabin L, Agbaje S, Buseri F, Ikimalo J, Briggs N. Reducing iron deficiency anaemia due to heavy menstrual blood loss in Nigerian rural adolescents. Public Health Nutr 1998;1:249–57.
27. Hallberg L, Högdahl AM, Nilsson L, Rybo G. Menstrual blood loss and iron deficiency. Acta Med Scand 1966;180:639–50.
28. Schoep ME, Nieboer TE, van der Zanden M, Braat DDM, Nap AW. The impact of menstrual symptoms on everyday life: a survey among 42,879 women. Am J Obstet Gynecol 2019;220. 569.e1–7.
29. World Health Organization. Global anaemia reduction efforts among women of reproductive age: impact, achievement of targets and the way forward for optimizing efforts. 2020. Available at: https://www.who.int/publications/i/item/9789240012202. Accessed January 18, 2021.
30. Critchley HOD, Munro MG, Shakur-Still H, Roberts I. Menstruation should not be overlooked in control of anaemia. Lancet 2021;397:26.
31. Gleeson NC, Buggy F, Sheppard BL, Bonnar J. The effect of tranexamic acid on measured menstrual loss and endometrial fibrinolytic enzymes in dysfunctional uterine bleeding. Acta Obstet Gynecol Scand 1994;73:274–7.
32. Bryant-Smith AC, Lethaby A, Farquhar C, Hickey M. Antifibrinolytics for heavy menstrual bleeding. Cochrane Database Syst Rev 2018;4:CD000249.
33. Ker K, Edwards P, Perel P, Shakur H, Roberts I. Effect of tranexamic acid on surgical bleeding: systematic review and cumulative meta-analysis. BMJ 2012;344:e3054.
34. Ker K, Prieto-Merino D, Roberts I. Systematic review, meta-analysis and meta-regression of the effect of tranexamic acid on surgical blood loss. Br J Surg 2013;100:1271–9.
35. Taeuber I, Weibel S, Herrmann E, et al. Association of intravenous tranexamic acid with thromboembolic events and mortality: a systematic review, meta-analysis, and meta-regression. JAMA Surg 2021;156:e210884.
36. Murao S, Nakata H, Roberts I, Yamakawa K. Effect of tranexamic acid on thrombotic events and seizures in bleeding patients: a systematic review and meta-analysis. Crit Care 2021;25:380.
37. Devereaux PJ, Marcucci M, Painter TW, et al. Tranexamic acid in patients undergoing noncardiac surgery. N Engl J Med 2022;386:1986–97.
38. Guerriero C, Cairns J, Jayaraman S, Roberts I, Perel P, Shakur H. Giving tranexamic acid to reduce surgical bleeding in sub-Saharan Africa: an economic evaluation. Cost Eff Resour Alloc 2010;8:1.
39. CRASH-2 trial collaboratorsShakur H, Roberts I, et al. Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomised, placebo-controlled trial. Lancet 2010;376:23–32.
40. CRASH-3 trial collaborators. Effects of tranexamic acid on death, disability, vascular occlusive events and other morbidities in patients with acute traumatic brain injury (CRASH-3): a randomised, placebo-controlled trial. Lancet 2019;394:1713–23.
41. Roberts I, Shakur-Still H. Tranexamic acid for trauma in the USA: is prejudice a barrier to saving lives? Lancet 2022;399:1675–7.
42. Wallace M, Gillispie-Bell V, Cruz K, Davis K, Vilda D. Homicide during pregnancy and the postpartum period in the United States, 2018-2019. Obstet Gynecol 2021;138:762–9.
43. Nutbeam T, Roberts I, Weekes L, Shakur-Still H, Brenner A, Ageron FX. Use of tranexamic acid in major trauma: a sex-disaggregated analysis of the Clinical Randomisation of an antifibrinolytic in Significant haemorrhage (CRASH-2 and CRASH-3) trials and UK trauma registry (Trauma and Audit Research Network) data. Br J Anaesth 2022;129:191–9.
44. Ker K, Kiriya J, Perel P, Edwards P, Shakur H, Roberts I. Avoidable mortality from giving tranexamic acid to bleeding trauma patients: an estimation based on WHO mortality data, a systematic literature review and data from the CRASH-2 trial. BMC Emerg Med 2012;12:3.