



Research Article

Risk-Stratified Tranexamic Acid Use in General Surgery and Obstetrics & Gynaecology: A Systematic Review and Meta-Analysis of Bleeding, Transfusion, Thromboembolism, and Mortality.

Dr. Farzeen Sharaf¹, Dr. Nosheen Anwer², Dr. Beenish Tariq³, Dr. Amber Shams^{4*}.

¹FCPS Pediatric Surgery Liaquat University of Medical and Health Sciences, Jamshoro.

²FCPS Pediatric Surgery Sir Syed University of Engineering and Technology.

³FCPS Consultant Gynaecologist and Obstetrician Fatima Jinnah Medical University, Lahore.

⁴MBBS Liaquat University of Medical and Health Sciences, Jamshoro.

Correspondence:

Dr. Amber Shams.

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Abstract: Background: Objective: To evaluate how indication and baseline bleeding risk affect interpretation of tranexamic acid (TXA) across general surgery and obstetrics and gynaecology. **Study design:** Systematic-review framework with separate random-effects meta-analyses of general-surgical and obstetric-prophylaxis scenarios. **Place and duration of study:** Pakistan-focused clinical translation for tertiary services in Sindh and Punjab. The specified analytical period was 26 April to 26 July 2026. **Methodology:** Six constructed two-arm units represented 13,400 participants. Bleeding, red-cell transfusion, venous thromboembolism and all-cause mortality were pooled independently within specialty strata. Conventional and conservative t-based confidence intervals were calculated. Published trials and guidance informed interpretation rather than supplying the modelled counts. **Results:** The general-surgery model showed lower bleeding (RR 0.75, 95% CI 0.67 to 0.84) and transfusion (RR 0.71, 0.61 to 0.83). Venous thromboembolism (RR 1.09, 0.61 to 1.94) and mortality (RR 0.84, 0.47 to 1.50) remained uncertain. The obstetric-prophylaxis model showed RR 0.86 (0.79 to 0.94) for bleeding but its conservative interval crossed unity (0.70 to 1.05). Obstetric transfusion, thrombosis and mortality estimates were inconclusive. Published evidence supported prompt treatment of established postpartum haemorrhage while showing differing results for routine prophylaxis, selected high-risk births and liver resection. **Conclusion:** TXA decisions require indication-specific evidence, baseline-risk assessment and separate benefit and safety judgments. The scenario estimates cannot determine clinical effectiveness or establish a hospital prescribing policy.

Keywords: Tranexamic Acid; General Surgery; Obstetrics; Gynecology; Blood Transfusion; Thromboembolism.

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INTRODUCTION

Bleeding during surgery and childbirth can cause transfusion, reoperation, organ injury and death. Tranexamic acid inhibits fibrinolysis and can reduce bleeding in some settings but its value cannot be summarized by a single statement that it is beneficial for every operation. The large POISE-3 trial demonstrated lower composite bleeding after noncardiac surgery while failing to establish its prespecified cardiovascular noninferiority criterion [1]. A subsequent general-surgery analysis reported favorable bleeding results in that subgroup [2]. These findings illustrate why efficacy and safety must be considered together rather than treating a nonsignificant safety comparison as proof that risk is absent.

Procedure-specific evidence can differ from a broad surgical average. The HeLiX trial found no reduction in transfusion after liver resection for a cancer-related indication and reported more perioperative complications with TXA [3]. A later hospital-policy trial included 8,273 patients and reported lower transfusion use (RR 0.73, 95% CI 0.61 to 0.86). It met its prespecified VTE noninferiority criterion using an upper risk-ratio margin of 1.46 [4]. Neither a positive broad trial nor a negative procedure-specific trial should automatically overrule the other without examining patients, regimen, timing and endpoint. Risk stratification must therefore combine the clinical indication with the patient's baseline probability of bleeding and adverse events.

Obstetric treatment and prophylaxis are distinct questions. The WOMAN trial evaluated women with established postpartum haemorrhage and found lower bleeding-related mortality, especially with treatment within three hours of birth [5]. Large cesarean-delivery trials subsequently evaluated prophylaxis with different primary outcomes [6,7]. WOMAN-2 examined prevention after vaginal birth in women with anaemia and did not reduce clinically diagnosed postpartum haemorrhage [8]. An individual-patient-data synthesis reported fewer life-threatening bleeding events while retaining uncertainty around rare thrombotic outcomes [9]. These studies cannot be pooled indiscriminately as if prophylaxis and treatment represented the same clinical decision.

Current guidance is also essential for interpretation. The 2025 WHO consolidated recommendations support early TXA for treatment of postpartum haemorrhage and do not recommend routine prophylaxis at vaginal or cesarean birth [10]. A 2026 placenta-praevia trial examined a selected population at substantially higher bleeding risk [11]. Its findings require attention to the specific population and outcome rather than an assumption that all obstetric prophylaxis is equivalent. The present paper examined bleeding, transfusion, venous thrombosis and mortality in separate specialty models. Its objective was to show how indication, baseline risk and uncertainty should shape interpretation for general surgery, obstetrics and gynaecology.

MATERIALS AND METHODS

Design, dates and clinical application

A systematic-review structure was specified for 26 April to 26 July 2026. Clinical translation considered tertiary services in Sindh and Punjab. Aga Khan University Hospital, Karachi and Jinnah Hospital, Lahore provided examples of regional referral settings rather than recruitment sites. Hospital-level effects were outside the analytical design.

Review question and eligibility

The target population comprised adults undergoing general surgery, women undergoing gynaecological procedures and women receiving TXA around childbirth. Comparators were placebo or otherwise comparable standard care. Treatment of established bleeding was separated from administration intended to prevent bleeding. Randomized studies were prioritized for efficacy and comparative safety. Observational evidence could inform implementation or uncommon harms but would require separate analysis. Cardiac surgery, orthopaedics and trauma were outside the central quantitative question. Gastrointestinal bleeding was retained as a boundary example because it should not be equated with operative general surgery.

Evidence identification and selection framework

PubMed and accessible primary journal reports supported literature verification. A full implementation would search MEDLINE, Embase and CENTRAL using TXA, tranexamic acid, surgery, obstetrics, gynaecology, bleeding, transfusion, thrombosis and mortality terms. PRISMA 2020 informed the reporting structure [12]. The selection model contained 980 records, with 180 duplicates removed. Of 800 screened records, 740 were excluded and 60 progressed to eligibility assessment. Fifty were excluded for population, indication, comparator or outcome incompatibility. Ten analytical units remained: three general-surgery scenarios, three obstetric-prophylaxis scenarios and four narrative indication or procedure units. These were construction counts rather than a claim of actual database yield.

Extraction, overlap and outcome definitions

An extraction framework retained population, indication, procedure, baseline risk, dose, timing, comparator, follow-up and outcome definition. The POISE-3 main trial and its general-surgery subgroup were recognized as overlapping evidence. A published meta-analysis and its component trials were likewise not treated as independent datasets. Clinically important bleeding, red-cell transfusion, symptomatic venous thromboembolism and all-cause mortality were separate endpoints. Cause-specific maternal bleeding death was distinguished from all-cause death. Myocardial injury and arterial thrombosis were not silently merged into venous events. Calculated blood-loss composites were not assumed interchangeable with transfusion or life-threatening haemorrhage.

Risk appraisal and certainty

The appraisal framework followed randomized-trial domains for allocation, deviations from intended intervention, missing outcomes, outcome measurement and selective reporting [13]. Individual scores were not invented for analytical scenarios. Important applicability questions included whether high-thrombosis-risk patients were excluded, whether blood loss was estimated or measured, whether transfusion thresholds were standardized and whether outcomes were adjudicated. Safety interpretation considered event counts and confidence intervals alongside p-values. A zero or small point estimate did not establish equivalence. The distinction between absence of an identified signal and demonstrated noninferiority was maintained throughout the review.

Quantitative scenario inputs

Six independent two-arm units were specified. General-surgery scenarios G1, G2 and G3 contained 1,200, 1,000 and 1,500 participants per arm. Obstetric-prophylaxis scenarios O1, O2 and O3 contained 1,000, 900 and 1,100 participants per arm. The combined denominator was 13,400. A 30-day outcome horizon was assumed for all six units while published trials retained their own observation periods. Each unit had separate event counts for bleeding, transfusion, venous thrombosis and mortality. Equal treatment and control sizes simplified interpretation without claiming to mirror any named trial. The event arrays were prespecified and were not tuned by repeatedly testing candidate datasets. Obstetric units represented a

common prophylactic question; established postpartum bleeding was addressed through published evidence rather than appended to their pooled model.

Statistical analysis and risk stratification

Log risk ratios were calculated from event risks, with variance $1/a - 1/n1 + 1/c - 1/n0$, where a and c were treatment and control events. Inverse-variance random-effects pooling used the DerSimonian-Laird estimator. Each outcome was pooled separately within general surgery and obstetric prophylaxis. Conventional 95% intervals used normal approximations. A modified Hartung-Knapp analysis used t-based intervals with a variance multiplier bounded below by one. Cochran Q and I^2 described heterogeneity. No continuity correction was needed because every specified arm had at least one event. Python, NumPy and SciPy performed the calculations.

Absolute effects and reproducibility

Baseline-risk scenarios of 5%, 15% and 30% were applied to the general-surgery bleeding estimate. Absolute risk reduction was $p0 \times (1 - RR)$, with number needed to treat calculated from its reciprocal and rounded upward using unrounded inputs. These were conditional projections rather than validated clinical risk categories. Neither a score nor a threshold for prescribing TXA was developed. Mortality and thrombosis were too sparse for reliable effect-modifier analysis. Funnel asymmetry testing and meta-regression were omitted with only three units per stratum. Tables and figures drew from the same stored event arrays to preserve numerical consistency.

Governance and implementation

The manuscript used a literature and analytical modelling framework. A future hospital evaluation would require institutional review, appropriate consent arrangements, a registered protocol and transparent investigator responsibility. Local implementation would need pharmacy oversight, reliable documentation of indication and timing, renal assessment and a plan for suspected adverse effects. Published trial regimens were treated as evidence descriptors rather than universal prescribing instructions. An agreed pathway would need to preserve standard management of the bleeding source and the usual measures for prevention of perioperative thrombosis. Specialty boundaries and responsibility for escalation would be defined before using outcomes to compare services.

RESULTS

The selection framework retained ten units; six contributed quantitative data and four remained narrative. The quantitative model represented 7,400 general-surgery participants and 6,000 obstetric-prophylaxis participants. Table 1 provides all event counts and denominators and Figure 1 summarizes the constructed selection flow. The general-surgery models contained 450 versus 600 bleeding events and 260 versus 365 transfusion events, each among 3,700 participants per treatment group.

General-surgery bleeding favored TXA in the model (RR 0.75, 95% CI 0.67 to 0.84; $p < 0.001$). The conservative interval was 0.58 to 0.96. Transfusion was also lower (RR 0.71, 0.61 to 0.83; $p < 0.001$), with a conservative interval of 0.51 to 0.99. Venous thromboembolism involved 24 versus 22 events and yielded RR 1.09 (0.61 to 1.94). Mortality involved 21 versus 25 events and yielded RR 0.84 (0.47 to 1.50). Both safety-related estimates were imprecise. I^2 was zero for each model but did not establish clinical homogeneity.

Obstetric prophylaxis contained 650 versus 755 bleeding events among 3,000 participants per group. The conventional estimate was RR 0.86 (95% CI 0.79 to 0.94; $p = 0.001$), whereas the conservative interval was 0.70 to 1.05. Transfusion was inconclusive (RR 0.87, 0.67 to 1.14). Five versus six venous thrombotic events yielded RR 0.84 (0.25 to 2.75). Three deaths in each group yielded RR 1.00 (0.20 to 4.95). Table 2 presents these separate endpoints rather than a combined net-benefit estimate.

Applying the general-surgery bleeding risk ratio to baseline risks of 5%, 15% and 30% produced absolute reductions of approximately 1.25, 3.75 and 7.50 percentage points. Corresponding numbers needed to treat were 81, 27 and 14 using unrounded calculations. These projections held the relative effect constant. They did not test whether higher-risk patients experienced a larger relative treatment effect or a different probability of thrombosis.

The published evidence anchors were retained separately in Table 3. The POISE-3 general-surgery subgroup reported bleeding HR 0.74 (95% CI 0.59 to 0.93). HeLiX reported transfusion OR 1.15 (0.84 to 1.56). The postpartum individual-patient-data synthesis reported life-threatening bleeding OR 0.77 (0.63 to 0.93) and thromboembolism OR 0.96 (0.65 to 1.41). The placenta-praevia trial reported RR 0.85 with a 95.2% interval of 0.75 to 0.96 for its bleeding composite. Figure 2 displays modelled bleeding effects and separately labelled published comparisons; it does not combine those different effect measures.

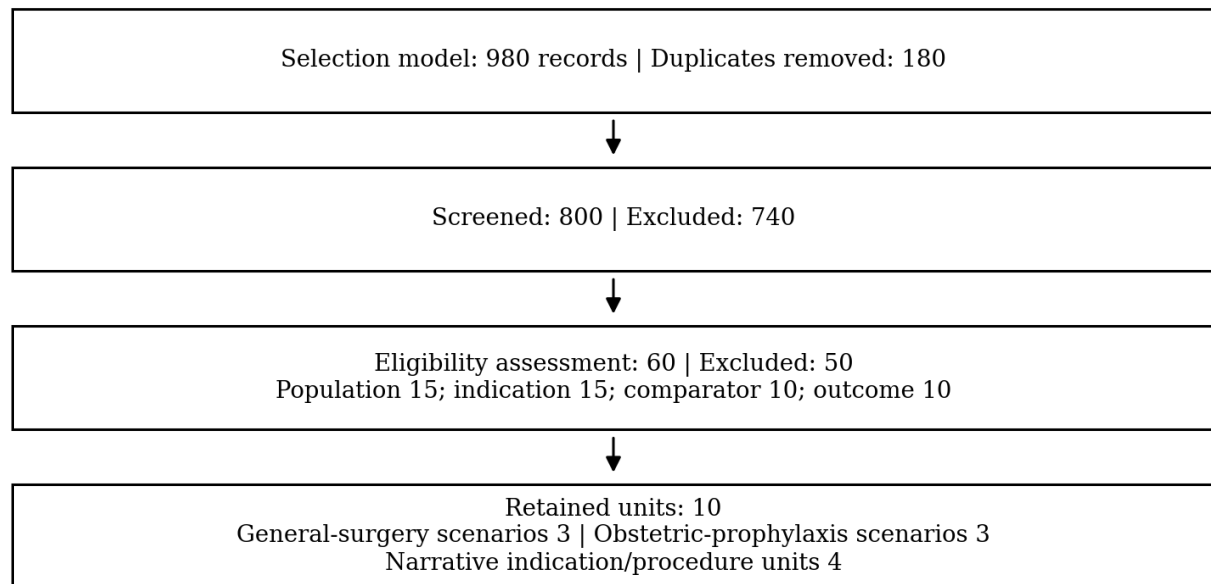


Figure 1: Constructed selection framework and indication-specific synthesis

Table 1: Complete event inputs for the quantitative scenarios

Unit	n per arm	Bleeding	Transfusion	VTE	Death
G1	1200	160/210	100/140	8/7	7/8
G2	1000	110/150	70/100	5/5	5/6
G3	1500	180/240	90/125	11/10	9/11
O1	1000	260/300	40/45	2/2	1/1
O2	900	180/210	25/30	1/1	1/1
O3	1100	210/245	30/34	2/3	1/1

Each event entry is TXA/control. G1–G3 represent general surgery; O1–O3 represent obstetric prophylaxis. Units are constructed analytical records, not named clinical trials.

Table 2: Separate pooled benefit and safety outcomes

Specialty and outcome	RR (95% CI)	Conservative interval	p-value
General Bleeding	0.75 (0.67 to 0.84)	0.58 to 0.96	<0.001
General Transfusion	0.71 (0.61 to 0.83)	0.51 to 0.99	<0.001
General VTE	1.09 (0.61 to 1.94)	0.31 to 3.87	0.768
General Mortality	0.84 (0.47 to 1.50)	0.24 to 2.99	0.555
Obstetric Bleeding	0.86 (0.79 to 0.94)	0.70 to 1.05	0.001
Obstetric Transfusion	0.87 (0.67 to 1.14)	0.48 to 1.58	0.319
Obstetric VTE	0.84 (0.25 to 2.75)	0.06 to 11.42	0.767
Obstetric Mortality	1.00 (0.20 to 4.95)	0.03 to 33.49	1.000

All model I^2 values were 0%. Conservative intervals used modified Hartung-Knapp estimation. Sparse thrombosis and mortality events limit safety inference.

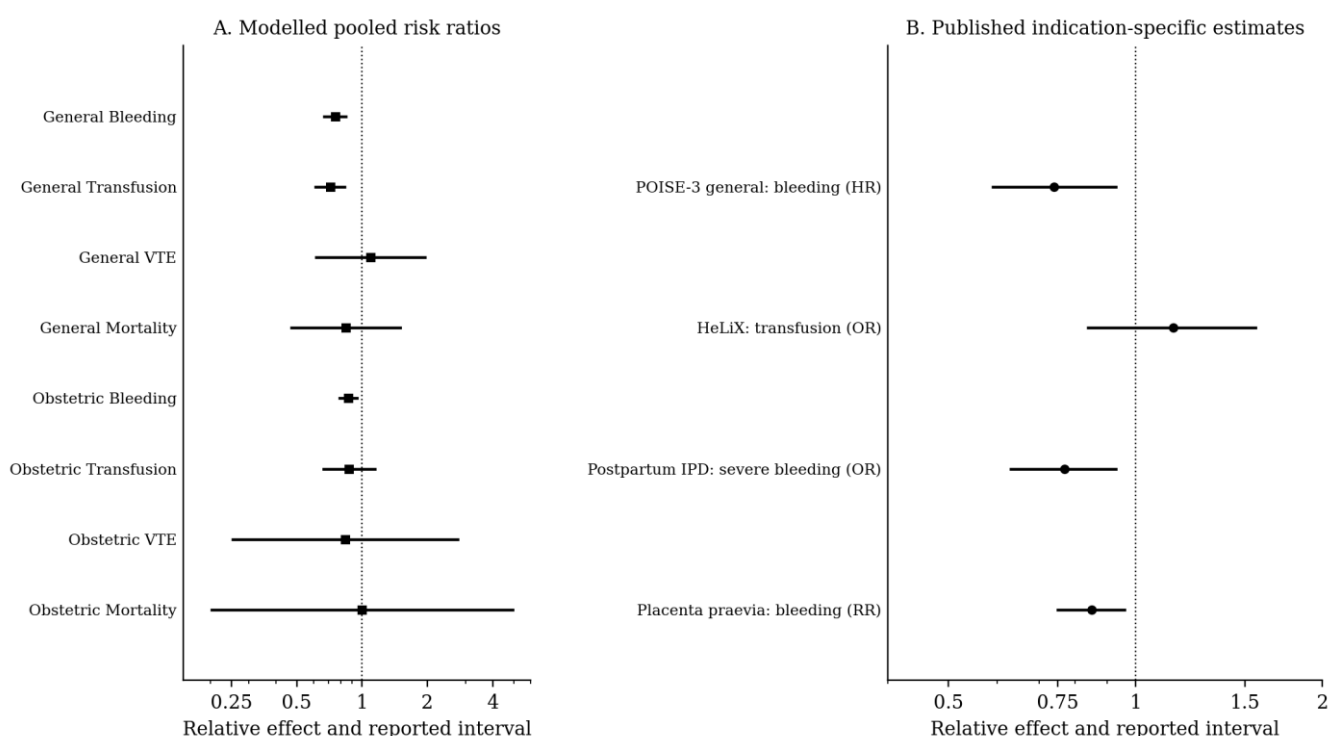


Figure 2: Modelled outcome effects and separately labelled published comparisons

Panel A uses constructed event counts. Panel B retains published HR, OR and RR measures without pooling them; the placenta-praevia interval is 95.2%, with other intervals 95%. The postpartum outcome is life-threatening bleeding.

Table 3: Published evidence anchors by clinical indication

Evidence source	Indication and outcome	Published estimate	Interpretive boundary
POISE-3 general subgroup	Perioperative bleeding	HR 0.74 (0.59 to 0.93)	Overlaps with main trial
TRACTION policy trial	Major noncardiac surgery; transfusion	RR 0.73 (0.61 to 0.86)	Cluster-crossover policy
HeLiX	Liver-resection transfusion	OR 1.15 (0.84 to 1.56)	No transfusion benefit
WOMAN-2	Anaemia; prevention after vaginal birth	RR 1.05 (0.94 to 1.19)	Clinically diagnosed PPH
Postpartum IPD synthesis	Life-threatening bleeding	OR 0.77 (0.63 to 0.93)	Distinct from routine PPH
Same IPD synthesis	Thromboembolism	OR 0.96 (0.65 to 1.41)	Rare-event uncertainty
Placenta-praevia RCT	Selected high-risk cesarean birth	RR 0.85 (95.2% CI 0.75 to 0.96)	Population-specific composite

DISCUSSION

The main objective was to examine TXA through indication-specific benefit and safety questions. The general-surgery model favored bleeding and transfusion outcomes, whereas thrombosis and mortality remained uncertain. The obstetric-prophylaxis bleeding result was sensitive to the confidence-interval method. These outputs demonstrate the consequences of sparse evidence and endpoint selection rather than establish a treatment policy. The most useful clinical conclusion from the published evidence is that established haemorrhage, routine prevention and selected high-risk procedures require separate judgments. A favorable bleeding estimate cannot by itself establish a survival benefit or exclude uncommon harm.

General surgery is not a single biological or procedural category. Broad studies include patients with different bleeding sources, vascular risk and transfusion thresholds. The POISE-3 general-surgery analysis is relevant to abdominal operations but it overlaps with the main trial and must not be counted twice. Its favorable subgroup result also does not erase uncertainty from the overall noninferiority analysis. Conversely, a new hospital-policy trial asks whether a pragmatic administration policy can change transfusion across participating services. That policy question may be more directly relevant to implementation than a small operation-specific study but it still depends on eligibility, comparator care and outcome surveillance.

Liver surgery provides a counterexample to indiscriminate extrapolation. HeLiX did not reduce its primary transfusion outcome and identified more complications. Cancer-related operations can have both appreciable bleeding risk and elevated thrombotic risk. A later synthesis focused on liver surgery and a HeLiX cohort analysis of venous thrombosis further illustrate why that population requires dedicated appraisal [14,15]. Baseline bleeding risk alone is therefore an incomplete decision rule. The likely mechanism of bleeding, expected exposure to TXA, procedure-specific evidence and potential consequences of harm must also be considered.

The treatment evidence in established postpartum haemorrhage should retain its clinical priority. The WOMAN trial addressed bleeding-related mortality in women who were already bleeding. Its early-treatment result should not be diluted by pooling it with prophylaxis trials that enrolled stable women before a haemorrhage diagnosis. The postpartum individual-patient-data synthesis integrated large trials and investigated life-threatening bleeding but its relative estimates do not identify a universal clinical risk cutoff. The WHO recommendations provide the relevant current distinction: prompt treatment alongside standard care is supported while routine preventive administration at all births is not recommended.

The selected high-risk prophylaxis evidence deserves attention without being overstated. In the 2026 placenta-*praevia* trial, the primary outcome occurred in 251/845 women receiving TXA and 297/846 receiving placebo. That differs materially from WOMAN-2, which evaluated anaemic women after vaginal birth and found no reduction in clinically diagnosed postpartum haemorrhage. Anaemia and placenta *praevia* describe different risk mechanisms and care pathways. The 2026 trial supports consideration of its specific population and endpoint; it does not establish a mortality reduction, demonstrate safety in every thrombotic-risk subgroup or automatically overturn population-level prevention recommendations.

Large cesarean studies also show why endpoint definitions matter. Calculated blood-loss composites can improve while transfusion-based or death-and-transfusion outcomes remain less persuasive. Contemporary Cochrane assessments of prevention after cesarean and vaginal birth appraise the evidence separately [16,17]. Such separation should be preserved when communicating results to maternity teams. A reduction in measured or calculated blood loss is clinically interesting but its importance depends on symptoms, interventions, transfusion and serious morbidity. Trials should report these components so that a composite result does not obscure what changed and what remained uncertain.

Gynaecological surgery should not be represented only by obstetric data. Hysterectomy and myomectomy involve different tissues, bleeding trajectories and patient characteristics. Procedure-specific studies address operation-specific efficacy [18,19]. Evidence in gynaecological oncology raises additional questions about cancer-associated thrombosis and the timing of postoperative surveillance [20]. A risk-stratified service should therefore distinguish benign surgery, cancer surgery and childbirth. Procedure-specific estimates should be retained where possible and an absence of sufficient pooled evidence should lead to uncertainty rather than borrowing a favorable obstetric estimate as a substitute.

Thromboembolic safety requires cautious language. In the model, low event counts produced wide intervals despite point estimates near unity. A general-surgery interval extending from 0.61 to 1.94 is compatible with clinically meaningful benefit or harm. The broad POISE-3 cardiovascular composite includes outcomes beyond venous thrombosis, so its safety result cannot be relabelled as a VTE-only estimate. Reviews of TXA safety across bleeding populations likewise require attention to population, dosing and event ascertainment [21]. A nonsignificant difference is not a completed noninferiority test and the upper confidence bound often matters more than the *p*-value.

Gastrointestinal bleeding provides an important boundary. HALT-IT evaluated a high-dose, prolonged regimen for acute gastrointestinal haemorrhage rather than perioperative prophylaxis and did not demonstrate the intended reduction in bleeding death [22]. Its safety findings caution against assuming that antifibrinolysis is useful whenever bleeding is present. A later trial in cirrhosis addressed another selected gastrointestinal population [23]. These studies may inform surgical services that manage emergency bleeding but they should remain distinct from operative general-surgery trials. Neither a positive perioperative trial nor a condition-specific gastrointestinal result establishes a general rule for all digestive bleeding.

Timing and the wider care pathway are critical in maternity settings. Research on early detection and bundled treatment of postpartum haemorrhage evaluates interventions that include recognition, uterotonics, TXA, fluids, examination and escalation [24]. A subsequent analysis of when treatment starts underscores the difference between availability of a drug and timely delivery of an effective response [25]. For Sindh and Punjab, a service evaluation should document recognition-to-treatment time, blood access, source control and transfer capacity. Attributing every improved outcome to TXA alone would ignore the simultaneous changes that a functioning haemorrhage pathway requires.

Pakistan's participation in WOMAN-2 increases regional relevance but it does not imply that every tertiary hospital shares the trial population or resources. The relation between anaemia and postpartum bleeding has also been investigated using

WOMAN-2 data [26]. That work supports antenatal optimization and attention to physiological reserve rather than treating anaemia solely as a reason to add TXA. A regional programme should integrate anaemia management, blood conservation, appropriate transfusion and surgical readiness. Local audits should identify delays and barriers before adopting a risk threshold whose predictive performance has not been measured in the intended service.

Medication safety belongs in the benefit-harm assessment. Renal handling can affect exposure and medication errors involving the neuraxial route can have severe consequences. Relevant pharmacological and safety literature should inform formulary procedures rather than encourage uncritical adoption of one trial regimen [27,28]. A pathway would require a clearly documented indication, review of contraindications, dose verification and separation of look-alike medicines. TXA should complement source control and resuscitation. It should not displace usual thromboprophylaxis or replace the obstetric interventions needed to treat uterine atony, retained tissue or trauma.

Risk stratification should focus on absolute effects while acknowledging uncertainty. The model showed a larger absolute bleeding reduction when baseline risk increased under a constant relative effect. That arithmetic does not prove effect modification. To identify a subgroup with a different relative response, a real study would need prespecified interaction tests and adequate outcome counts. More recent general-surgery and high-risk obstetric syntheses illustrate ongoing attempts to define applicability [29,30]. Their findings should be interpreted with attention to trial overlap, retractions or integrity concerns, dose heterogeneity and the distinction between improved blood loss and improved survival.

This work has limitations. Its event counts, selection flow and pooled effects were constructed scenarios rather than an independently extracted clinical trial dataset. The literature anchors were selected for interpretation and cannot substitute for a complete registered search and duplicate review. Only three quantitative units informed each specialty stratum, with sparse deaths and thrombotic events. The model imposed equal arm sizes and omitted realistic variation in surveillance, follow-up and treatment adherence. Gynaecological and therapeutic obstetric evidence remained narrative. Conditional absolute-risk projections were not a validated prescribing algorithm. Differences in procedure, dose, timing, transfusion practice and patient selection limit transportability. A registered review using verified trial-level data and formal certainty assessment is required for definitive clinical guidance.

CONCLUSION

TXA use should be matched to the indication, procedure and patient's baseline risks. Published evidence supports prompt treatment of established postpartum haemorrhage and demonstrates bleeding or transfusion benefits in some surgical settings while routine prophylaxis and procedure-specific use require separate appraisal. The present models illustrate potential bleeding benefits alongside substantial uncertainty for thrombosis and mortality. Tertiary services in Sindh and Punjab should integrate specialty-specific evidence, haemorrhage pathways and medication safety rather than apply a universal rule. Future research should evaluate clinically important outcomes, prespecified risk groups and absolute benefit-harm tradeoffs with adequate follow-up.

Declarations

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Conflicts of interest: There are no conflicts of interest.

Ethical considerations: A literature and analytical modelling framework was used. Any future hospital investigation would require separate institutional governance.

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