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Supplementary appendix

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Supplement to: The WOMAN-2 Trial Collaborators. The effect of tranexamic acid on postpartum bleeding in women with moderate and severe anaemia (WOMAN-2): an international, randomised, double-blind, placebo-controlled trial. *Lancet* 2024; **404:** 1645–56.

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1. Baseline risk of postpartum haemorrhage (low, intermediate, high)

1.1. Methods S1: Baseline risk of postpartum haemorrhage prognostic model

We used logistic regression to develop a prognostic model to estimate the baseline risk of postpartum haemorrhage after childbirth using the data from the Woman-2 trial. The risk model was developed prior to unblinding and contained the following baseline variables:

1. Country (Pakistan, Nigeria, Tanzania, Zambia)
2. Birth canal trauma (any, none)
3. Number of babies (2+, 1)
4. Antepartum haemorrhage (current, past, none)
5. Haemoglobin (per g/l increase)
6. Hypertensive disease during pregnancy (any, none)
7. Placental abnormality (any, none)
8. Body temperature (per degree C increase)
9. Episiotomy (yes, no)
10. Assisted delivery (any, none)
11. Respiratory rate (per bpm)
12. Gravida (per unit increase)
13. Gestational age (per week increase)
14. Previous PPH (yes, no/unknown)
15. Augmentation (any, none)
16. Pulse rate (per bpm)

To create the three risk groups (low, intermediate, high) we used the 33rd and 66th percentiles of the risk score among women who had PPH in the trial.

2. Secondary outcomes assessed at 24 hours after administration of the trial treatment or at discharge from hospital, whichever is earlier

2.1. Table S1: Haemodynamic instability and shock index

Variable	Statistic	Total (N=15066)	TXA (N=7579)	Placebo (N=7487)
Haemodynamic Instability*	n (%)	480 (3.2)	242 (3.2)	238 (3.2)
Shock Index ≥1 **	n (%)	1284 (8.52%)	622 (8.21%)	662 (8.84%)
Systolic Blood Pressure <100 mmHg	n (%)	263 (1.8%)	133 (1.8%)	130(1.7 %)
Systolic Blood Pressure, mmHg	N	15047	7571	7476
	Mean±SD	110.5±11.22	110.6±11.38	110.3±11.06
	Median (IQR)	110 (102, 117)	110 (102, 118)	110 (102, 117)
	[min, max]	[52, 200]	[54, 184]	[52, 200]
	Missing	19	8	11
Heart rate≥100 bpm	n (%)	1876 (12.5%)	950 (12.5%)	926 (12.4 %)
Heart Rate, bpm	N	15047	7570	7477
	Mean±SD	87.6±11.16	87.5±11.10	87.7±11.23
	Median (IQR)	87 (80, 93)	87 (80, 92)	87 (80, 93)
	[min, max]	[43, 192]	[49, 192]	[43, 174]
	Missing	19	9	10

* based on presence of clinical signs e.g., low blood pressure, tachycardia, reduced urine output requiring intervention (e.g., intravenous fluid).

** Shock index = Heart rate/systolic blood pressure - lowest recorded systolic blood pressure and the corresponding heart rate used

2.2. Table S2: Expected side effects of trial medication

Variable	Statistic	Total (N=15066)	TXA (N=7579)	Placebo (N=7487)
Nausea	n (%)	304 (2.0)	153 (2.0)	151 (2.0)
Vomiting	n (%)	131 (0.9)	66 (0.9)	65 (0.9)
Diarrhoea	n (%)	57 (0.4)	23 (0.3)	34 (0.5)
Dizziness	n (%)	842 (5.6)	413 (5.5)	429 (5.7)

3. Secondary outcomes assessed at death, discharge from hospital or 42 days, whichever is earlier.

3.1. Table S3: Quality of life (overall wellbeing and ability of the woman to care for herself)

Variable	Statistic	Total (N=15066)	TXA (N=7579)	Placebo (N=7487)
Global assessment of pain				
Not at all	n (%)	7515 (50.7)	3785 (50.9)	3730 (50.6)
A little	n (%)	5653 (38.2)	2835 (38.1)	2818 (38.2)
Moderately	n (%)	1464 (9.9)	726 (9.8)	738 (10.0)
Quite a bit	n (%)	138 (0.9)	71 (1.0)	67 (0.9)
Extremely	n (%)	47 (0.3)	22 (0.3)	25 (0.3)
	Missing	249	140	109
Global assessment of pain	N	14817	7439	7378
	Mean±SD	0.6±0.73	0.6±0.72	0.6±0.73
	Median (IQR)	0 (0, 1)	0 (0, 1)	0 (0, 1)
Global assessment of feeling ill				
Not at all	n (%)	9741 (65.7)	4906 (65.9)	4835 (65.5)
A little	n (%)	3790 (25.6)	1884 (25.3)	1906 (25.8)
Moderately	n (%)	1084 (7.3)	537 (7.2)	547 (7.4)
Quite a bit	n (%)	162 (1.1)	89 (1.2)	73 (1.0)
Extremely	n (%)	40 (0.3)	23 (0.3)	17 (0.2)
	Missing	249	140	109
Global assessment of feeling ill	N	14817	7439	7378
	Mean±SD	0.4±0.70	0.4±0.71	0.4±0.69
	Median (IQR)	0 (0, 1)	0 (0, 1)	0 (0, 1)
Multi-Dimensional Fatigue	N	14810	7435	7375
Symptom Inventory	Mean±SD	-5.6±15.14	-5.6±15.15	-5.6±15.13
Total scale score	Median (IQR)	-9 (-16, 1)	-9 (-16, 2)	-9 (-16, 1)
	[min, max]	[-24, 85]	[-24, 79]	[-24, 85]

3.2. Table S4: Symptoms of anaemia, breastfeeding and usual activities

Variable	Statistic	Total (N=15066)	TXA (N=7579)	Placebo (N=7487)
Total score	N	14816	7438	7378
	Mean±SD	2.3±3.05	2.3±3.03	2.3±3.07
	Median (IQR)	1 (0, 3)	1 (0, 3)	1 (0, 3)
	[min, max]	[0, 28]	[0, 28]	[0, 23]
I have felt dizzy				
Not at all	n (%)	9987 (67.4)	5023 (67.5)	4964 (67.3)
A little	n (%)	3849 (26.0)	1932 (26.0)	1917 (26.0)
Moderately	n (%)	750 (5.1)	361 (4.9)	389 (5.3)
Quite a bit	n (%)	166 (1.1)	93 (1.3)	73 (1.0)
Extremely	n (%)	64 (0.4)	29 (0.4)	35 (0.5)
I have had a headache				
Not at all	n (%)	9747 (65.8)	4888 (65.7)	4859 (65.9)
A little	n (%)	3964 (26.8)	1987 (26.7)	1977 (26.8)
Moderately	n (%)	929 (6.3)	477 (6.4)	452 (6.1)
Quite a bit	n (%)	136 (0.9)	68 (0.9)	68 (0.9)
Extremely	n (%)	41 (0.3)	19 (0.3)	22 (0.3)
I have felt my heart beating very fast or strangely				
Not at all	n (%)	11686 (78.9)	5872 (78.9)	5814 (78.8)
A little	n (%)	2291 (15.5)	1150 (15.5)	1141 (15.5)
Moderately	n (%)	663 (4.5)	325 (4.4)	338 (4.6)
Quite a bit	n (%)	142 (1.0)	72 (1.0)	70 (0.9)
Extremely	n (%)	35 (0.2)	20 (0.3)	15 (0.2)
I have felt sleepy				
Not at all	n (%)	8435 (56.9)	4249 (57.1)	4186 (56.7)
A little	n (%)	3864 (26.1)	1927 (25.9)	1937 (26.3)
Moderately	n (%)	1822 (12.3)	919 (12.4)	903 (12.2)
Quite a bit	n (%)	467 (3.2)	230 (3.1)	237 (3.2)
Extremely	n (%)	229 (1.5)	114 (1.5)	115 (1.6)
I have felt numbness in my hands and feet				
Not at all	n (%)	11916 (80.4)	5986 (80.5)	5930 (80.4)
A little	n (%)	2188 (14.8)	1082 (14.5)	1106 (15.0)
Moderately	n (%)	537 (3.6)	277 (3.7)	260 (3.5)
Quite a bit	n (%)	125 (0.8)	68 (0.9)	57 (0.8)
Extremely	n (%)	51 (0.3)	26 (0.3)	25 (0.3)
My hands have felt shaky				
Not at all	n (%)	12723 (85.9)	6395 (86.0)	6328 (85.8)
A little	n (%)	1645 (11.1)	820 (11.0)	825 (11.2)
Moderately	n (%)	346 (2.3)	176 (2.4)	170 (2.3)
Quite a bit	n (%)	77 (0.5)	33 (0.4)	44 (0.6)
Extremely	n (%)	26 (0.2)	15 (0.2)	11 (0.1)
I have had difficulty in breathing				
Not at all	n (%)	13437 (90.7)	6734 (90.5)	6703 (90.9)
A little	n (%)	1146 (7.7)	589 (7.9)	557 (7.5)
Moderately	n (%)	188 (1.3)	90 (1.2)	98 (1.3)
Quite a bit	n (%)	33 (0.2)	16 (0.2)	17 (0.2)
Extremely	n (%)	13 (0.1)	10 (0.1)	3 (<0.1)

I have breastfed my baby				
No	n (%)	1362 (9.2)	705 (9.5)	657 (8.9)
Yes	n (%)	12346 (83.3)	6190 (83.2)	6156 (83.4)
Not applicable	n (%)	1109 (7.5)	544 (7.3)	565 (7.7)
I have had difficulty with breastfeeding my baby				
Not at all	n (%)	9764 (73.1)	4940 (73.5)	4824 (72.7)
A little	n (%)	2491 (18.6)	1247 (18.5)	1244 (18.8)
Moderately	n (%)	800 (6.0)	390 (5.8)	410 (6.2)
Quite a bit	n (%)	223 (1.7)	104 (1.5)	119 (1.8)
Extremely	n (%)	80 (0.6)	44 (0.7)	36 (0.5)
I will have difficulty doing my usual activities				
Not at all	n (%)	8012 (54.1)	4049 (54.4)	3963 (53.7)
A little	n (%)	3898 (26.3)	1958 (26.3)	1940 (26.3)
Moderately	n (%)	2213 (14.9)	1076 (14.5)	1137 (15.4)
Quite a bit	n (%)	544 (3.7)	275 (3.7)	269 (3.6)
Extremely	n (%)	145 (1.0)	79 (1.1)	66 (0.9)

3.3. Table S5: Exercise tolerance assessed using the six-minute walk test

Variable	All N=15066	TXA N=7579	Placebo N=7487
Perceived breathlessness before walk test			
Not at all	13127 (87.1%)	6581 (86.8%)	6546 (87.4%)
A little	1508 (10.0%)	774 (10.2%)	734 (9.8%)
Moderately	153 (1.0%)	69 (0.9%)	84 (1.1%)
Quite a bit	13 (0.1%)	7 (0.1%)	6 (0.1%)
Extremely	3 (0.0%)	3 (0.0%)	0 (0.0%)
Missing	262 (1.7%)	145 (1.9%)	117 (1.6%)
Nasal flaring			
N (%)	60 (0.40%)	32 (0.42%)	28 (0.37%)
Missing (%)	262 (1.74%)	146 (1.93%)	116 (1.55%)
Total walk test distance (m)			
Mean(SD)	212.32 (92.64)	212.43 (93.45)	212.22 (91.83)
Median (IQR)	198.00 (147.00-270.00)	198.00 (146.00-270.00)	199.00 (147.00-270.00)
[Min,Max]	[4.50,830.00]	[4.50,830.00]	[12.00,750.00]
Missing	589	308	281
Perceived breathlessness after walk test			
Not at all	9300 (61.7%)	4673 (61.7%)	4627 (61.8%)
A little	4183 (27.8%)	2095 (27.6%)	2088 (27.9%)
Moderately	899 (6.0%)	465 (6.1%)	434 (5.8%)
Quite a bit	97 (0.6%)	40 (0.5%)	57 (0.8%)
Extremely	21 (0.1%)	11 (0.1%)	10 (0.1%)
Missing	566 (3.8%)	295 (3.9%)	271 (3.6%)

3.4. Table S6: Organ dysfunction

Variable	Statistic	Total (N=15066)	TXA (N=7579)	Placebo (N=7487)
Cardiovascular dysfunction				
Shock	n (%)	34 (0.2)	18 (0.2)	16 (0.2)
Cardiac Arrest	n (%)	14 (0.1)	8 (0.1)	6 (0.1)
Vasoactive drugs	n (%)	12 (0.1)	6 (0.1)	6 (0.1)
Hypoperfusion	n (%)	7 (<0.1)	4 (0.1)	3 (<0.1)
Acidosis	n (%)	6 (<0.1)	3 (<0.1)	3 (<0.1)
Cardiopulmonary resuscitation	n (%)	15 (0.1)	8 (0.1)	7 (0.1)
Cardiovascular dysfunction diagnosed	n (%)	30 (0.2)	13 (0.2)	17 (0.2)
Respiratory dysfunction				
Cyanosis	n (%)	4 (<0.1)	1 (<0.1)	3 (<0.1)
Gasping	n (%)	13 (0.1)	8 (0.1)	5 (0.1)
Tachypnea	n (%)	16 (0.1)	9 (0.1)	7 (0.1)
Bradypnea	n (%)	5 (<0.1)	2 (<0.1)	3 (<0.1)
Intubation/ventilation	n (%)	23 (0.2)	12 (0.2)	11 (0.1)
Hypoxemia	n (%)	19 (0.1)	9 (0.1)	10 (0.1)
Respiratory dysfunction diagnosed	n (%)	24 (0.2)	11 (0.1)	13 (0.2)
Renal dysfunction				
Oliguria	n (%)	28 (0.2)	14 (0.2)	14 (0.2)
Dialysis	n (%)	14 (0.1)	7 (0.1)	7 (0.1)
Azotemia	n (%)	25 (0.2)	17 (0.2)	8 (0.1)
Renal dysfunction diagnosed	n (%)	37 (0.2)	22 (0.3)	15 (0.2)
Coagulation/haematological dysfunction				
Clot failure	n (%)	13 (0.1)	7 (0.1)	6 (0.1)
Transfusion	n (%)	13 (0.1)	10 (0.1)	3 (<0.1)
Thrombocytopenia	n (%)	18 (0.1)	9 (0.1)	9 (0.1)
Coagulation/haematological dysfunction diagnosed	n (%)	28 (0.2)	13 (0.2)	15 (0.2)
Hepatic dysfunction				
Jaundice	n (%)	1 (<0.1)	1 (<0.1)	0 (0.0)
Bilirubinemia	n (%)	2 (<0.1)	1 (<0.1)	1 (<0.1)
Hepatic dysfunction diagnosed	n (%)	3 (<0.1)	2 (<0.1)	1 (<0.1)
Neurological dysfunction				
Paralysis	n (%)	0 (0.0)	0 (0.0)	0 (0.0)
Stroke	n (%)	0 (0.0)	0 (0.0)	0 (0.0)
Unconscious ≥12hrs	n (%)	0 (0.0)	0 (0.0)	0 (0.0)
Seizure	n (%)	12 (0.1)	9 (0.1)	3 (<0.1)
Neurological dysfunction diagnosed	n (%)	6 (<0.1)	5 (0.1)	1 (<0.1)

Cardiovascular dysfunction - shock, cardiac arrest (absence of pulse/heart beat and loss of consciousness), use of continuous vasoactive drugs, cardiopulmonary resuscitation, severe hypoperfusion (lactate >5 mmol/L or >45 mg/dL), severe acidosis (pH <7.1).
Respiratory dysfunction - acute cyanosis, gasping, severe tachypnea (respiratory rate >40 breaths per minute), severe bradypnea (respiratory rate <6 breaths per minute), intubation and ventilation not related to anaesthesia, severe hypoxemia (O2 saturation <90% for ≥60 min or PAO2/FiO2 <200).
Renal dysfunction - Oliguria non-responsive to fluids or diuretics, dialysis for acute renal failure, severe acute azotemia (creatinine ≥300 µmol/mL or ≥3.5 mg/dL).
Coagulation/ haematologic dysfunction - Failure to form clots, massive transfusion of blood or red cells (≥5 units), severe acute thrombocytopenia (<50,000 platelets/mL).
Hepatic dysfunction - jaundice in the presence of eclampsia, severe acute hyper-bilirubinemia (bilirubin >100 µmol/L or >6.0 mg/dL).
Neurologic dysfunction - prolonged unconsciousness (lasting ≥12 hours)/coma (including metabolic coma), stroke, uncontrollable fits/status epilepticus, total paralysis.

3.5. Table S7: Sepsis

Variable	Statistic	Total (N=15066)	TXA (N=7579)	Placebo (N=7487)
Sepsis	n (%)	30 (0.2)	18 (0.2)	12 (0.2)
Infection	n (%)	47 (0.3)	28 (0.4)	19 (0.3)
Body temperature <36 or >38	n (%)	107 (0.7)	54 (0.7)	53 (0.7)
Heart rate >90 beats per minute	n (%)	1523 (10.1)	777 (10.3)	746 (10.0)
White blood cell count abnormal	n (%)	149 (1.0)	87 (1.1)	62 (0.8)
Respiratory rate>20 breaths per minute	n (%)	702 (4.7)	351 (4.6)	351 (4.7)

Sepsis: diagnosis is based on the presence of both infection and a systemic inflammatory response syndrome (SIRS). SIRS requires two or more of the following: a) temperature <36°C or >38°C (b) heart rate >90 beats/min (c) respiratory rate >20 breaths/min (d) white blood cell count <4 x 109/L (<4000/mm³) or >12 x 109/L (>12,000/mm³)

3.6. Table S8: Length of hospital stay

Variable	Statistic	Total (N=15066)	TXA (N=7579)	Placebo (N=7487)
Time to discharge, hours	N	15017	7553	7464
	Mean±SD	21.08 (30.84)	21.27 (30.52)	20.89 (31.16)
	Median (IQR)	13.17 (6.83-24.60)	13.25 (6.88-24.65)	13.02 (6.80-24.55)
	[min, max]	[0.07,799.93]	[0.38,716.10]	[0.07,799.93]
Admission to higher level facility*	n (%)	48 (0.3)	28 (0.4)	20 (0.3)
Time spent in higher level facility*	N	48	28	20
	Mean±SD	2.7±3.25	2.9±2.09	2.5±4.45
	Median (IQR)	1 (1, 4)	2 (1, 4)	1 (1, 2)
	[min, max]	[1, 21]	[1, 8]	[1, 21]

**Admission to a unit that provides 24-hr medical supervision and is able to provide mechanical ventilation and continuous vasoactive drug support. Higher level facilities include high dependency and intensive care units.*

3.7. Table S9: Status of baby/ies after randomisation

Variable	Statistic	Total (N=14604)	TXA (N=7354)	Placebo (N=7250)
Outcome				
Alive	n (%)	14453 (99.0)	7283 (99.0)	7170 (98.9)
Died after randomisation	n (%)	151 (1.0)	71 (1.0)	80 (1.1)
	Missing	0	0	0
Thromboembolic events in breastfed babies				
No	n (%)	14601 (100.0)	7352 (100.0)	7249 (100.0)
	Missing	3	2	1

Thromboembolic events defined as any venous or arterial thrombosis (thrombosis of limb artery/deep veins, renal artery/veins, pulmonary embolism, hepatic veins, caval veins, intracardiac thrombosis, portal vein, mesenteric veins/artery, cerebral veins, retinal vein, ischemic stroke, arteries, aorta, myocardial infarction, microvascular thrombosis from purpura fulminans or disseminated intravascular coagulation).

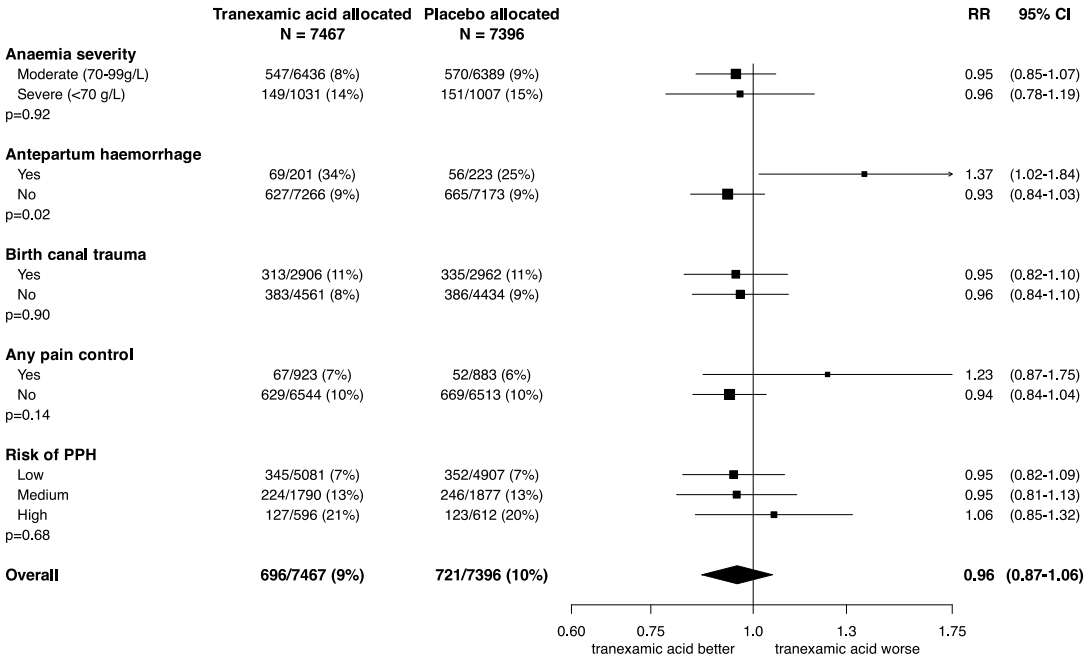
4. Adverse events

4.1. Table S10: Adverse events

	Description	Placebo	Tranexamic acid	Total
Adverse events	Transfusion reaction	3	3	6
	Adverse drug reaction	1	0	1
	Syncope	0	1	1
Serious adverse events	Cardiac failure	1	0	1
	Postpartum haemorrhage	0	1	1
	Puerperal sepsis	0	1	1
	Pulmonary oedema	1	0	1
	TOTAL	**6**	**6**	**12**

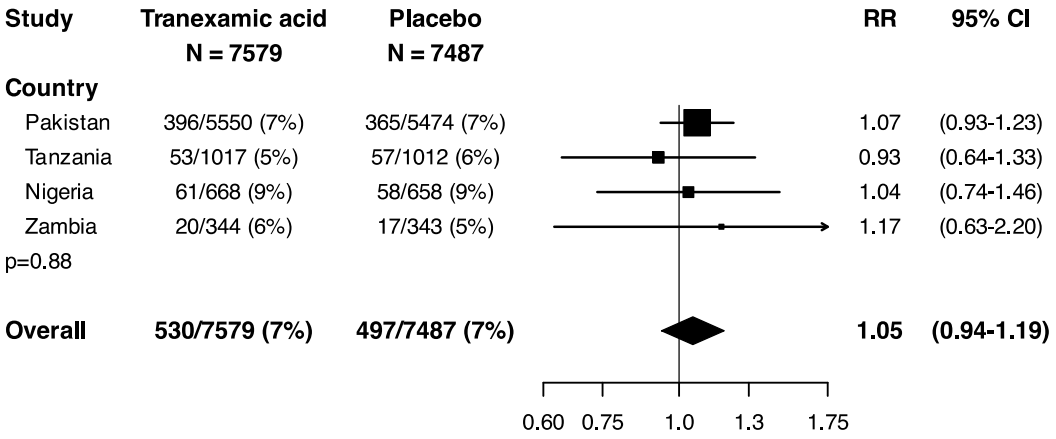
5. Effect of tranexamic acid on postpartum haemorrhage

5.1. Figure S1: Effect of tranexamic acid on calculated postpartum haemorrhage overall and by subgroup.



Birth canal trauma includes episiotomy, vaginal, perineal or cervical tear or uterine rupture.
p–values are for heterogeneity. N=14863.
Calculated PPH is a measure of blood loss based on peripartum haemoglobin concentration. We calculated estimated blood loss as the product of estimated blood volume and relative peripartum change in haemoglobin.
There were 203 women for whom did not have a post birth haemoglobin measurement. So we could not calculated peripartum haemoglobin for these women.
Estimated blood volume (in litres) was obtained by multiplying weight in kg by 0·085. We corrected for the effect of transfusion on postpartum haemoglobin using the method described by Roubinian and colleagues. We classified a woman as having calculated postpartum haemorrhage if her calculated estimated blood loss was 1000 mL or more. Reference: Roubinian NH, Plimier C, Woo JP, et al. Effect of donor, component, and recipient characteristics on haemoglobin increments following red blood cell transfusion. Blood 2019; 134: 1003–13. RR=Relative Risk.

5.2. Figure S2: Effect of tranexamic acid on clinically diagnosed postpartum haemorrhage stratified by the country of recruitment



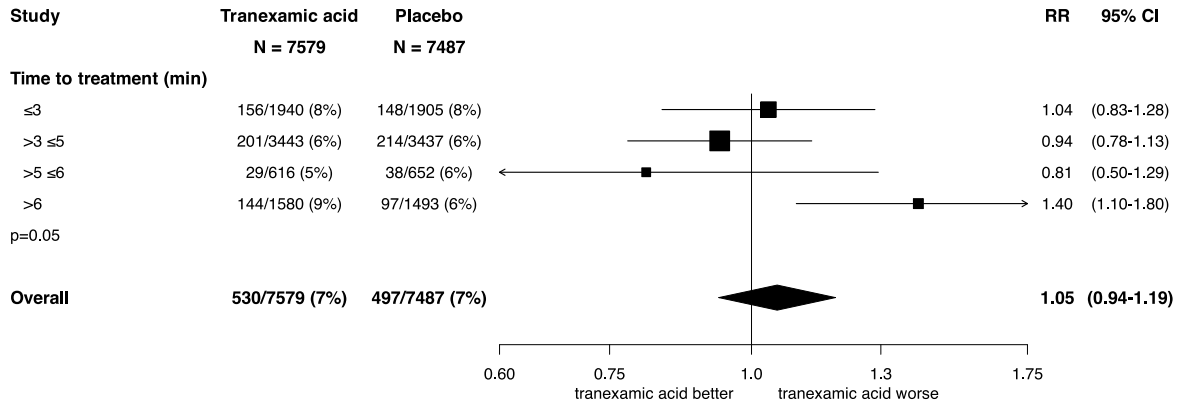
The p-value is for heterogeneity; there was no evidence of country level heterogeneity (P=0.88).

5.3. Figure S3: Effect of tranexamic acid on clinically diagnosed postpartum haemorrhage when women received the trial treatment within five minutes of giving birth

	Tranexamic acid	Placebo	RR	95% CI
Women who received the trial treatment within 5 minutes of giving birth				
N=10 725 (71%)	357/5383 (6.6%)	362/5342 (6.8%)	0.98	0.85-1.13
Women who received the trial treatment after 5 minutes of giving birth				
N=4341 (28%)	173/2196 (7.9%)	135/2145 (6.2%)	1.25	1.01-1.56

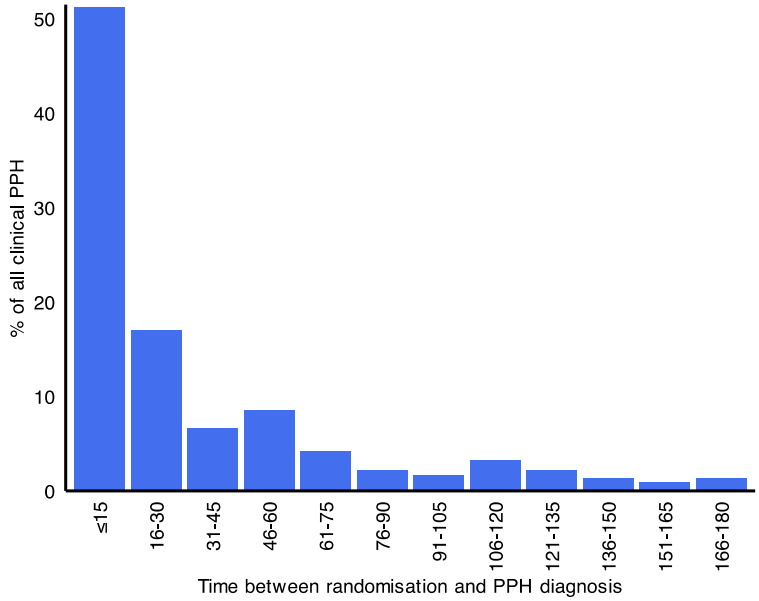
The p-value for treatment effect heterogeneity was p=0.063 which did not meet our prespecified threshold of p<0.001.

5.4. Figure S4: Effect of tranexamic acid on clinically diagnosed postpartum haemorrhage stratified by treatment time



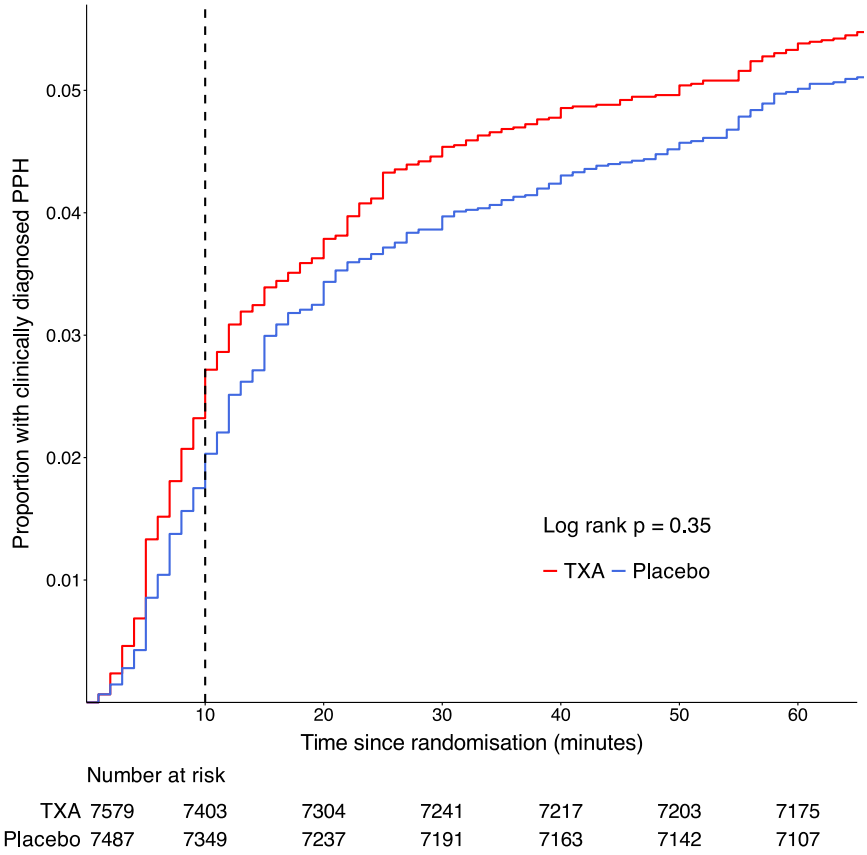
6. Time between randomisation and the diagnosis of postpartum haemorrhage

6.1. Figure S5: Clinically diagnosed postpartum haemorrhage by minutes since randomisation



Time measured in minutes
N=940. 3 women had missing time of PPH diagnosis. The 84 women who were diagnosed after 3 hours of randomisation are omitted from this analysis.

6.2. Figure S6: Cumulative incidence plot of clinically diagnosed postpartum haemorrhage



N=15066. Cumulative hazard for clinically diagnosed PPH. The dashed line indicates the time taken (10-minutes) to intravenously administer tranexamic acid or matching placebo.