



*WOMAN Trial Collaborators*

# Aims and objectives

A randomised, double blind, placebo controlled trial among 20,060 women with a clinical diagnosis of postpartum haemorrhage.

## AIMS

To determine the effect of early administration of TXA on mortality, hysterectomy and other morbidities in women with clinically diagnosed PPH.

## OBJECTIVES

To provide reliable evidence as to whether TXA reduces mortality, hysterectomy and other morbidities in women with clinically diagnosed PPH; thromboembolic effects on breastfed babies also assessed.

# Eligibility

Legally adult women with clinically diagnosed PPH following vaginal delivery or caesarean section (minimum age 16 years).

Excluded if

- clear indication for tranexamic acid
- clear contraindication for tranexamic acid

# Consent

- Women given advance information at maternity clinics
- Consent obtained from woman when possible
- If woman unable to provide consent, obtained from Personal or Professional Representative
- If neither available, enrolment by the investigator and a health professional not associated with the trial
- The woman and/or her representative informed as soon as possible and consent sought for continuation in the trial

# Randomisation and treatment

## RANDOMISATION

- Eligibility assessed by completing the Entry form
- The next consecutively numbered treatment pack from a box of eight packs selected

## TREATMENT

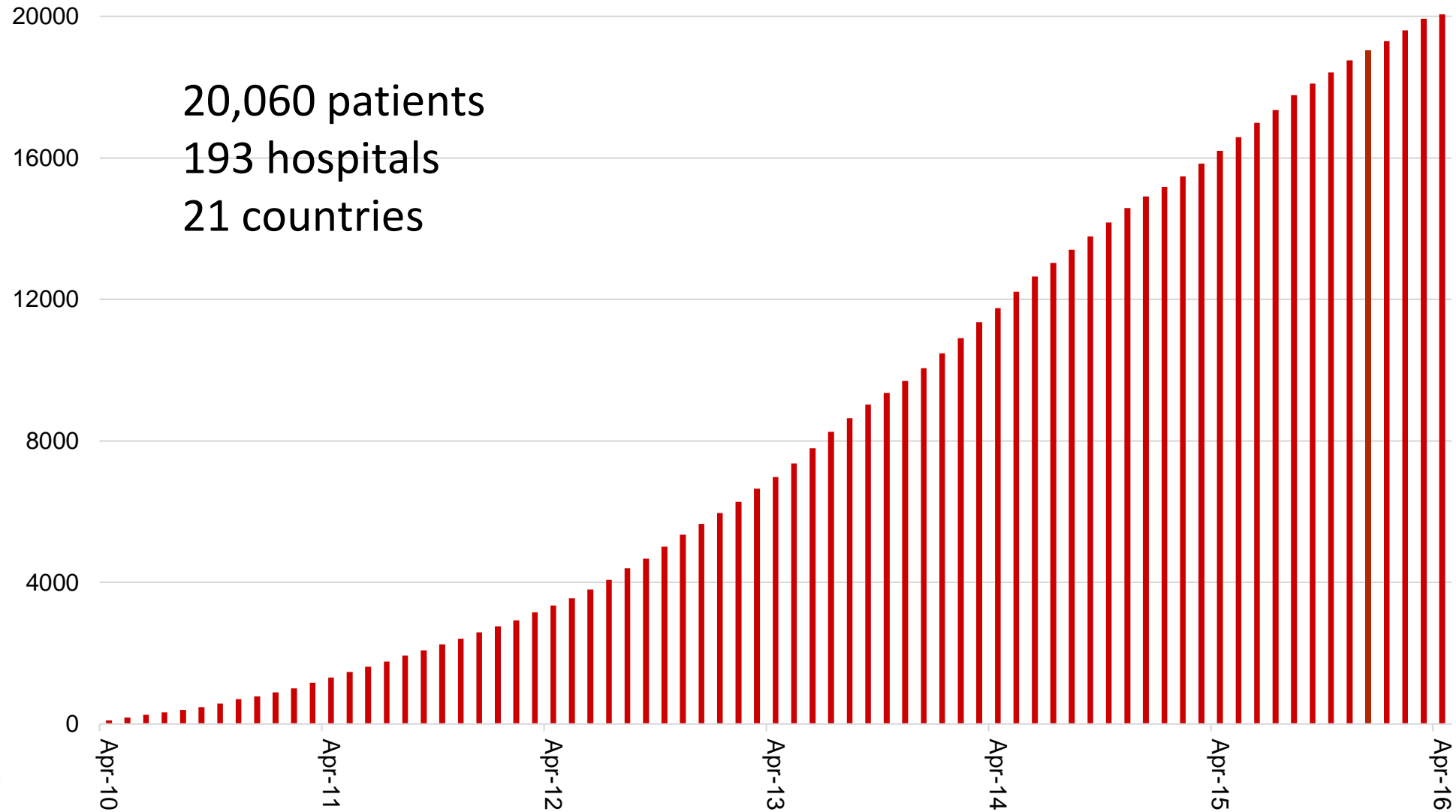
- Dose 1; 1 gram of tranexamic acid by intravenous injection, or placebo (sodium chloride 0.9%)
- Dose 2; if after 30 minutes bleeding continues, or if it stops and restarts within 24 hours after dose 1

# Follow-up

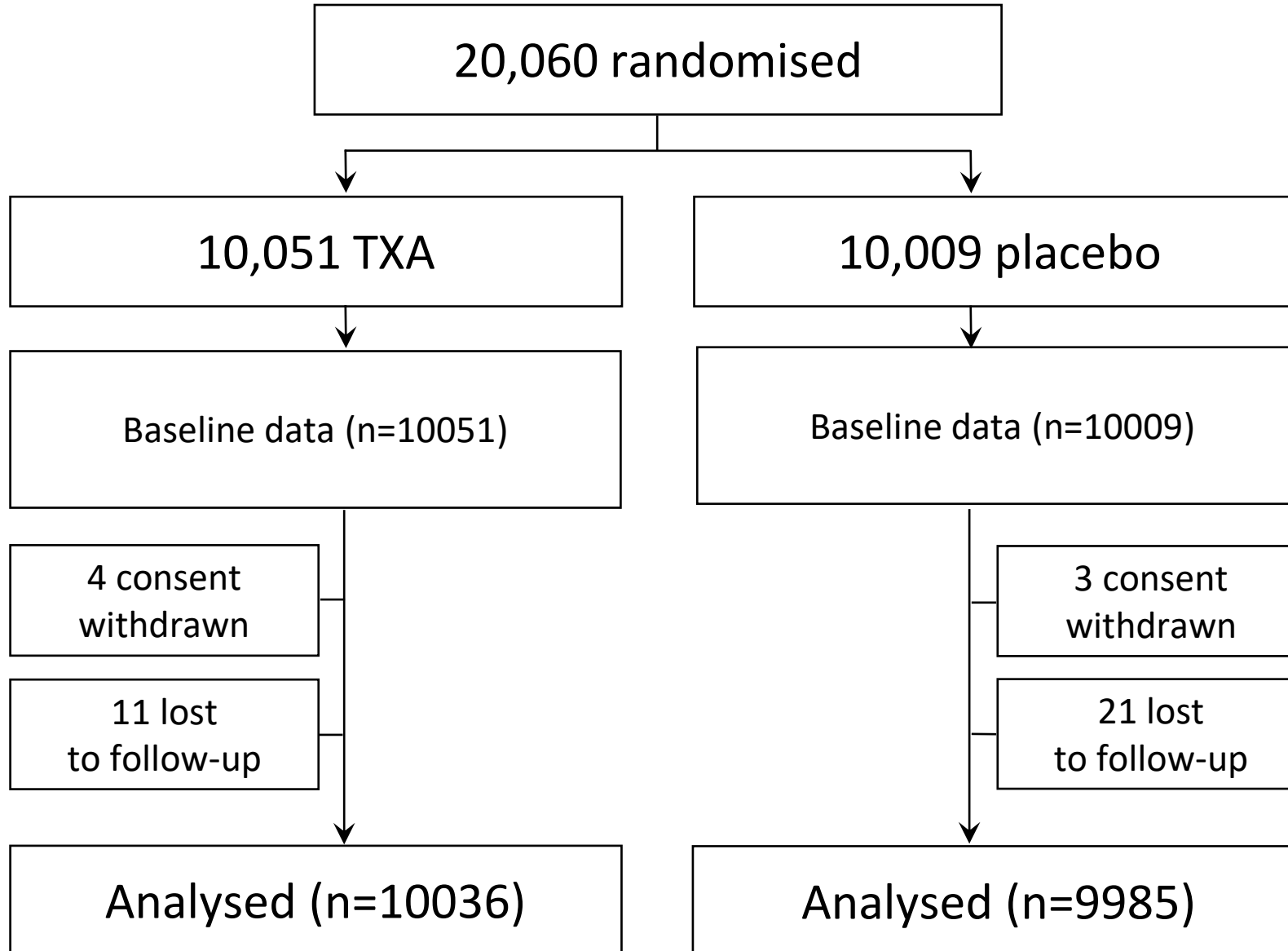
## FOLLOW-UP

- Outcome form completed 42 days after randomisation or at discharge or at death, whichever occurs first
- Adverse events reported up to 42 days after randomisation

# Patient enrolment



# The WOMAN trial





# Baseline characteristics

	TXA n (%)	Placebo n (%)
<b>Age at randomisation</b>		
<16	1 (<1)	3 (<1)
16–25	3445 (34)	3407 (34)
26–33	4580 (46)	4608 (46)
≥34	2022 (20)	1987 (20)
Unknown	3 (<1)	4 (<1)
<b>Baby delivered in the randomising hospital</b>		
Yes	8869 (88)	8756 (88)
No	1181 (12)	1251 (13)
Unknown	1 (<1)	2 (<1)
<b>Type of delivery</b>		
Vaginal	7093 (71)	7126 (71)
Caesarean section	2957 (29)	2879 (29)
Unknown	1 (<1)	4 (<1)

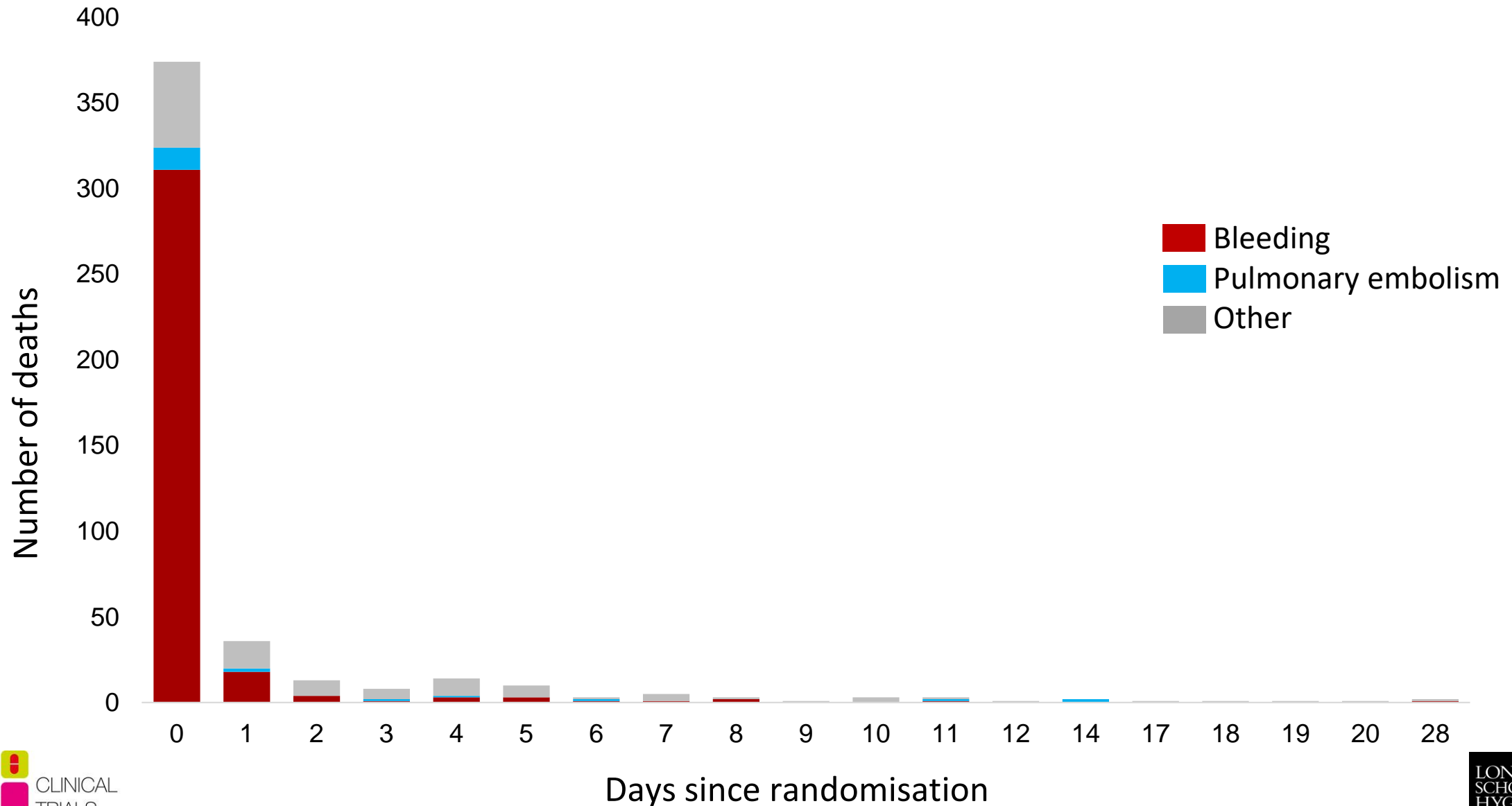
# Baseline characteristics

	TXA n (%)	Placebo n (%)
<b>Time between delivery and randomisation (h)</b>		
≤1	4852 (48)	4733 (47)
>1 to ≤3	2678 (27)	2691 (27)
>3	2517 (25)	2574 (26)
Unknown	4 (<1)	11 (<1)
<b>Placenta fully delivered</b>		
Yes	9089 (90)	9016 (90)
No	962 (10)	990 (10)
<b>Primary cause of haemorrhage</b>		
Uterine atony	6437 (64)	6347 (63)
Placenta praevia or accreta	943 (9)	935 (9)
Surgical trauma or tears	1834 (18)	1857 (19)
Other	720 (7)	737 (7)
Unknown	117 (1)	133 (1)
<b>Systolic blood pressure (mmHg)</b>		
≥90	8138 (81)	8065 (81)
<90	1908 (19)	1929 (19)
Unknown	5 (<1)	15 (<1)

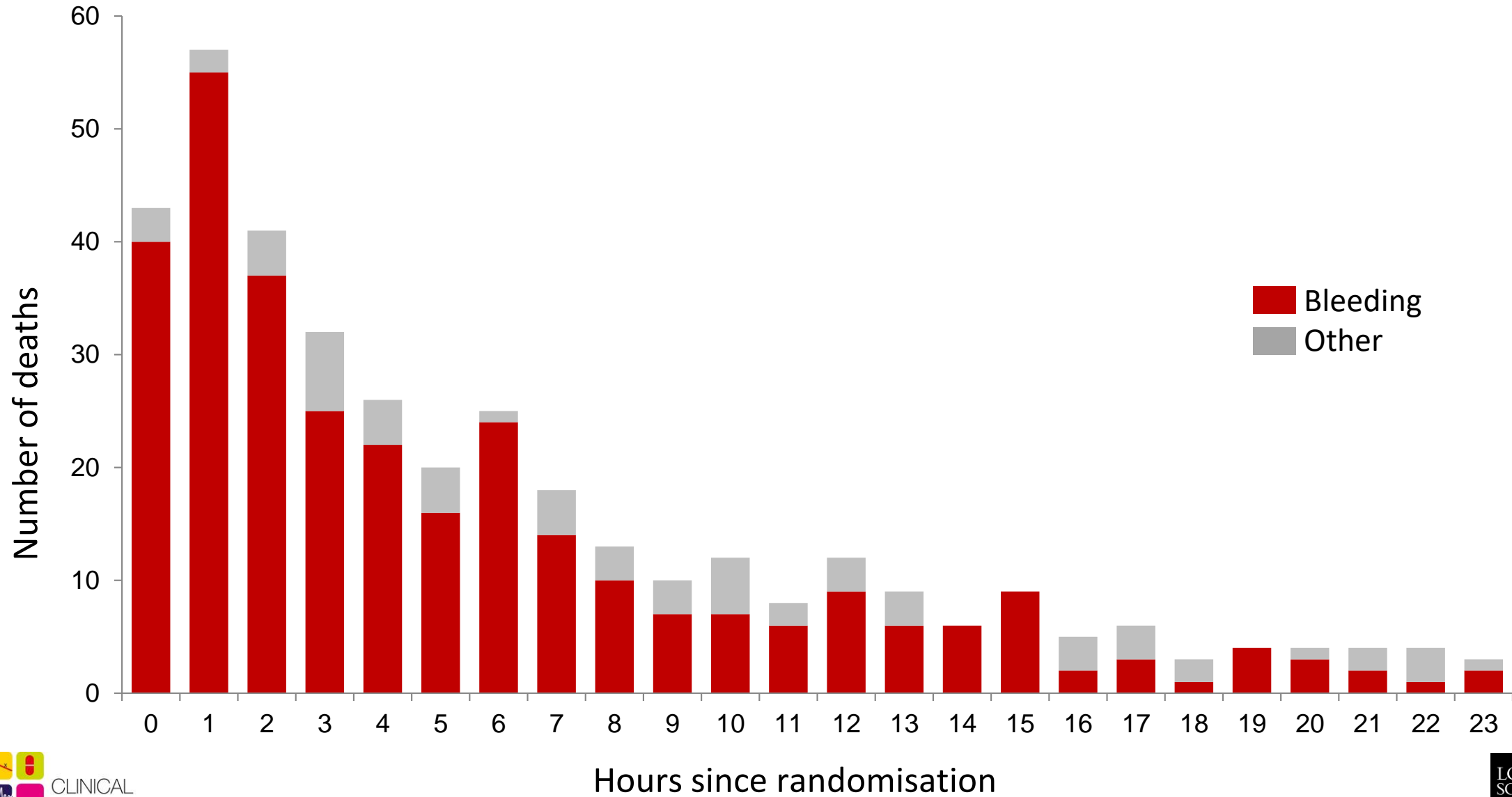
# Baseline characteristics

	TXA n (%)	Placebo n (%)
<b>Estimated volume of blood loss (mL)</b>		
≤500	295 (3)	313 (3)
>500 to ≤1000	4949 (49)	4861 (49)
>1000 to ≤1500	2832 (28)	2882 (29)
>1500	1973 (20)	1953 (20)
Not known	2 (<1)	0
<b>Uterotonic prophylaxis given</b>		
Yes	9687 (96)	9618 (96)
No	131 (1)	139 (1)
Unknown	233 (2)	252 (3)
<b>Clinical signs of haemodynamic instability</b>		
Yes	5961 (59)	5898 (59)
No	4090 (41)	4110 (41)

# Death by days since randomisation



# Death by hours since randomisation



# Death

<b>Cause of death</b>	<b>TXA</b> N=10036 n (%)	<b>Placebo</b> N=9985 n (%)	<b>Risk ratio</b> <b>(95% CI)</b>	<b>P value</b>
Bleeding	155 (1.5)	191 (1.9)	0.81 (0.65–1.00)	0.045
Pulmonary embolism	10 (0.1)	11 (0.1)	0.90 (0.38–2.13)	0.82
Organ failure	25 (0.3)	18 (0.2)	1.38 (0.75–2.53)	0.29
Sepsis	15 (0.2)	8 (0.1)	1.87 (0.79–4.40)	0.15
Eclampsia	2 (0.02)	8 (0.1)	0.25 (0.05–1.17)	0.06
Other	20 (0.2)	20 (0.2)	0.99 (0.54–1.85)	0.99
All causes	227 (2.3)	256 (2.6)	0.88 (0.74–1.05)	0.16

# Effect of TXA on death due to bleeding: subgroups

## Time since delivery

≤1 hour

>1–3 hours

> 3 hours

## Type of delivery

Vaginal

Caesarean section

## Cause of haemorrhage

Uterine atony

Other / unknown

All patients

2-sided p=0.045

RR (95% CI)

0.80 (0.55–1.16)

0.60 (0.41–0.88)

1.07 (0.76–1.51)

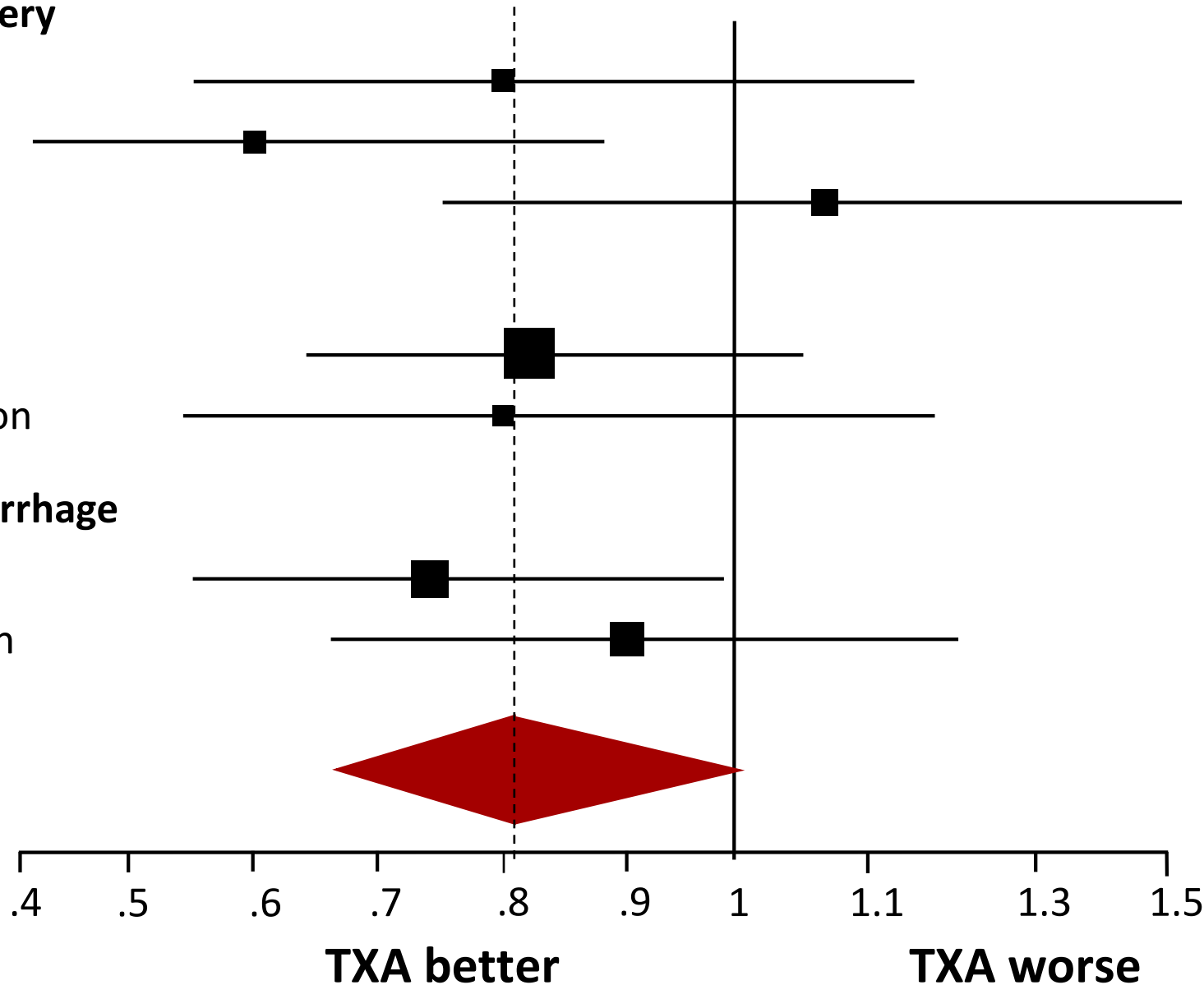
0.82 (0.64–1.05)

0.80 (0.54–1.18)

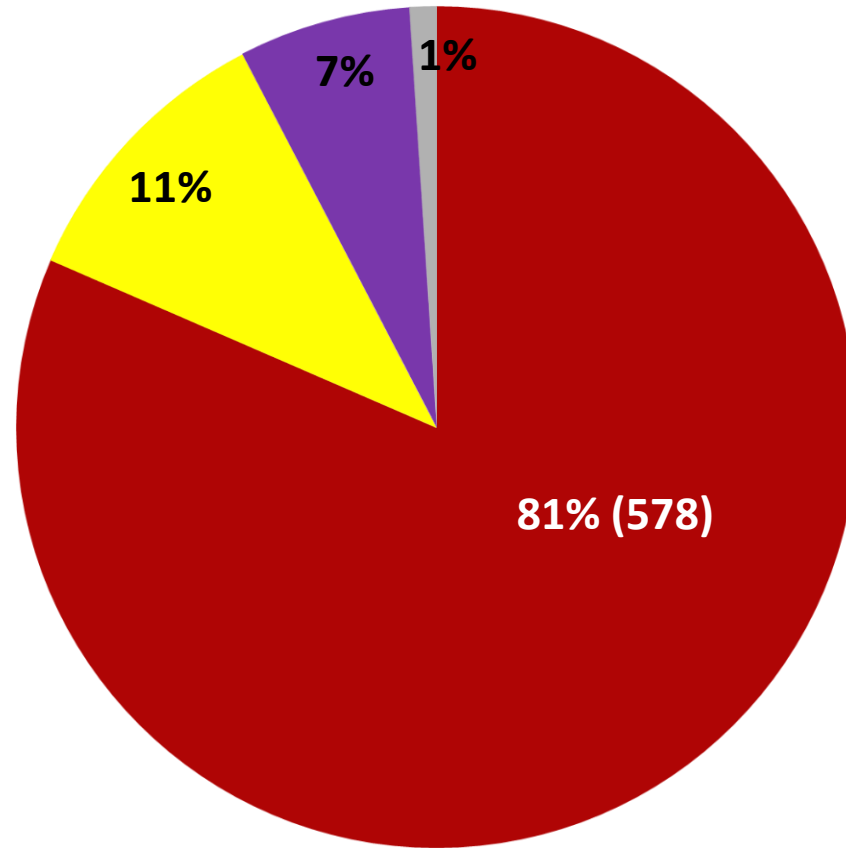
0.74 (0.55–0.99)

0.90 (0.66–1.21)

0.81 (0.65–1.00)



# Cause of hysterectomy

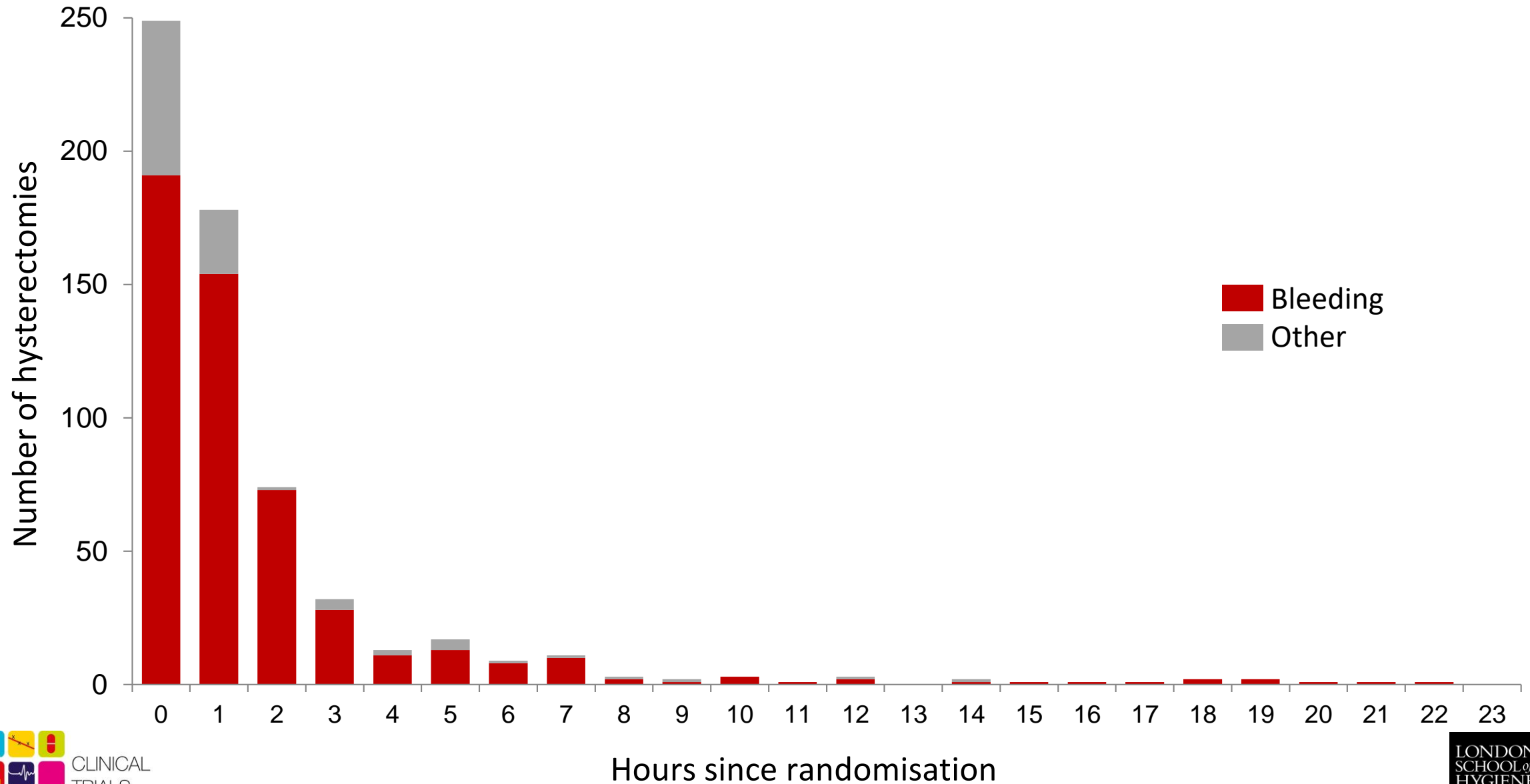


## All causes (n=709)

- Bleeding
- Abnormally adherent placenta
- Ruptured, damaged or infected uterus
- Other



# Hysterectomy by hours since randomisation



# Hysterectomy

Outcome	TXA (N=10036) n (%)	Placebo (N=9985) n (%)	Risk ratio (95% CI)	P-value
Hysterectomy (all causes)	358 (3.6)	351 (3.5)	1.02 (0.88–1.17)	0.84
Hysterectomy (bleeding)	283 (2.8)	295 (3.0)	0.95 (0.81–1.12)	0.57

# Death or hysterectomy

## Time since delivery

≤ 1 hour

>1 to ≤ 3 hours

>3 hours

## Type of delivery

Vaginal

Caesarean

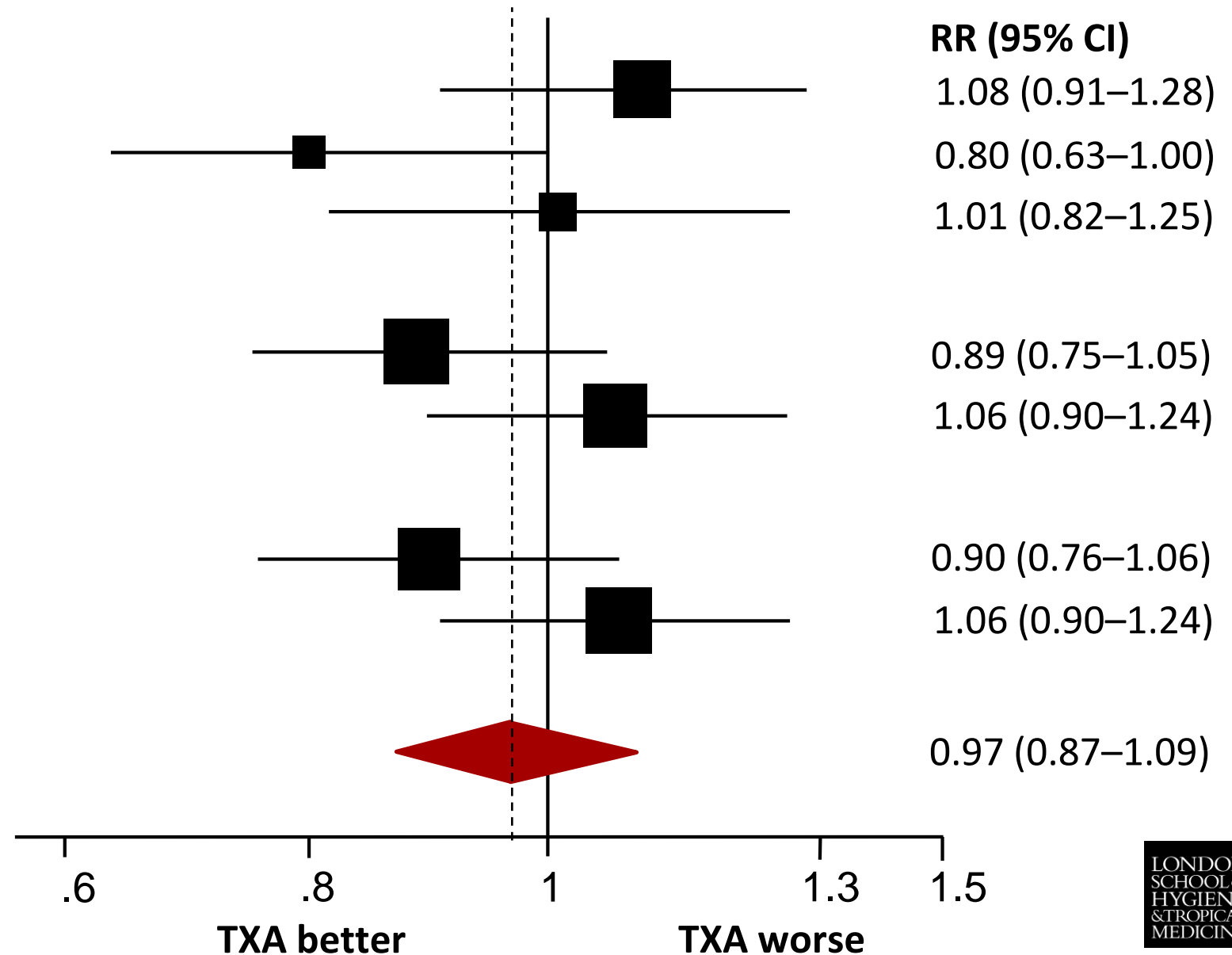
## Cause of haemorrhage

Uterine atony

Other

## All causes

Two-sided p=0.65



# Surgical intervention

<b>Interventions</b>	<b>TXA (N=10036) n (%)</b>	<b>Placebo (N=9985) n (%)</b>	<b>Risk ratio (95% CI)</b>	<b>P-value</b>
Intrauterine tamponade	705 (7.0)	729 (7.3)	0.96 (0.87–1.06)	0.45
Manual removal of placenta	918 (9.2)	961 (9.6)	0.95 (0.87–1.04)	0.25
Embolisation	10 (0.1)	13 (0.1)	0.77 (0.34–1.75)	0.52
Brace sutures of uterus	300 (3.0)	250 (2.5)	1.19 (1.01–1.41)	0.035
Arterial ligation	225 (2.2)	254 (2.5)	0.88 (0.74–1.05)	0.16
Laparotomy for bleeding	82 (0.8)	127 (1.3)	0.64 (0.49–0.85)	0.002

# Surgical intervention [vaginal deliveries]

<b>Interventions</b>	<b>TXA (N=10036) n (%)</b>	<b>Placebo (N=9985) n (%)</b>	<b>Risk ratio (95% CI)</b>	<b>P-value</b>
Intrauterine tamponade	519 (7.3)	547 (7.7)	0.95 (0.85–1.07)	0.41
Manual removal of placenta	745 (10.5)	779 (11.0)	0.96 (0.87–1.06)	0.40
Embolisation	4 (0.06)	7 (0.1)	0.57 (0.17–1.96)	0.37
Brace sutures of uterus	50 (0.7)	50 (0.7)	1.00 (0.68–1.48)	0.98
Arterial ligation	57 (0.8)	65 (0.9)	0.88 (0.62–1.25)	0.48
Laparotomy for bleeding	37 (0.5)	58 (0.8)	0.64 (0.42–0.97)	0.032

# Surgical intervention [caesarean sections]

<b>Interventions</b>	<b>TXA (N=10036) n (%)</b>	<b>Placebo (N=9985) n (%)</b>	<b>Risk ratio (95% CI)</b>	<b>P-value</b>
Intrauterine tamponade	186 (6.3)	182 (6.3)	0.99 (0.82–1.21)	0.96
Manual removal of placenta	173 (5.9)	182 (6.3)	0.93 (0.76–1.13)	0.45
Embolisation	6 (0.2)	6 (0.2)	0.97 (0.31–3.02)	0.96
Brace sutures of uterus	250 (8.5)	200 (7.0)	1.22 (1.02–1.46)	0.031
Arterial ligation	168 (5.7)	189 (6.6)	0.87 (0.71–1.06)	0.16
Laparotomy for bleeding	45 (1.5)	69 (2.4)	0.63 (0.44–0.92)	0.016

# Laparotomy for bleeding

## Time since delivery

≤ 1 hour



RR (95% CI)

0.48 (0.29–0.79)

>1–3 hours



0.54 (0.31–0.95)

>3 hours



0.89 (0.59–1.35)

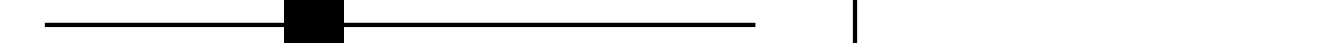
## Type of delivery

Vaginal



0.64 (0.42–0.97)

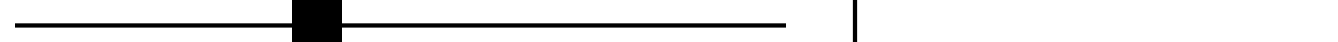
Caesarean section



0.63 (0.44–0.92)

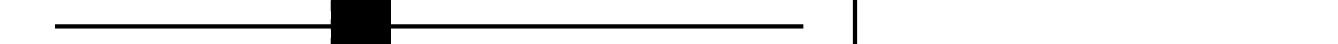
## Cause of haemorrhage

Uterine atony



0.63 (0.42–0.95)

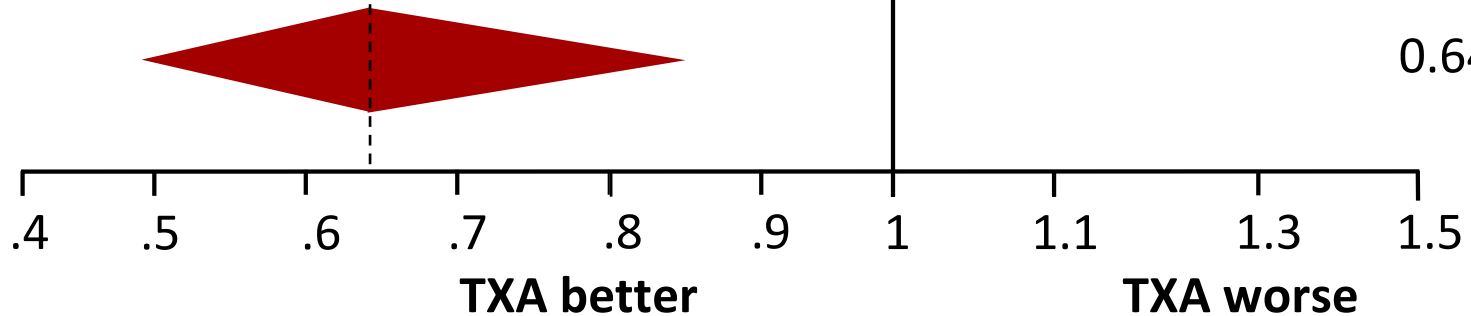
Other



0.66 (0.45–0.96)

## All causes

Two-sided p=0.002



# Thromboembolic events

	<b>TXA (N=10033) n (%)</b>	<b>Placebo (N=9985) n (%)</b>	<b>Risk ratio (95% CI)</b>	<b>P-value</b>
Any event	30 (0.3)	34 (0.3)	0.88 (0.54–1.43)	0.60
Venous events (DVT, PE)	20 (0.2)	25 (0.3)	0.80 (0.44–1.43)	0.45
Deep vein thrombosis	3 (0.03)	7 (0.1)	0.43 (0.11–1.65)	0.20
Pulmonary embolism	17 (0.2)	20 (0.2)	0.85 (0.44–1.61)	0.61
Arterial events (MI, stroke)	10 (0.1)	9 (0.1)	1.11 (0.45–2.72)	0.83
Myocardial infarction	2 (0.02)	3 (0.03)	0.66 (0.11–3.97)	0.65
Stroke	8 (0.1)	6 (0.1)	1.33 (0.46–3.82)	0.60



# Complications

	<b>TXA (N=10033) n (%)</b>	<b>Placebo (N=9985) n (%)</b>	<b>Risk ratio (95% CI)</b>	<b>P-value</b>
Renal failure	129 (1.3)	118 (1.2)	1.09 (0.85–1.39)	0.51
Cardiac failure	110 (1.1)	115 (1.2)	0.95 (0.73–1.23)	0.71
Respiratory failure	108 (1.1)	124 (1.2)	0.87 (0.67–1.12)	0.27
Hepatic failure	29 (0.3)	30 (0.3)	0.96 (0.58–1.60)	0.88
Sepsis	180 (1.8)	185 (1.9)	0.97 (0.79–1.19)	0.76
Seizure	33 (0.3)	43 (0.4)	0.76 (0.49–1.20)	0.24

# Use of uterotonics for PPH treatment

	<b>TXA (N=10034) n (%)</b>	<b>Placebo (N=9984) n (%)</b>	<b>Risk ratio (95% CI)</b>	<b>P-value</b>
Uterotonics administered	9 996 (99.6)	9 930 (99.5)	1.00 (1.00–1.00)	0.090
Oxytocin	9 940 (99.1)	9 865 (98.8)	1.00 (1.00–1.01)	0.079
Ergometrine	4 326 (43.1)	4 314 (43.2)	1.00 (0.97–1.03)	0.891
Misoprostol	6 707 (66.8)	6 717 (67.3)	0.99 (0.97–1.01)	0.513
Prostaglandin	689 (6.9)	722 (7.2)	0.95 (0.86–1.05)	0.313

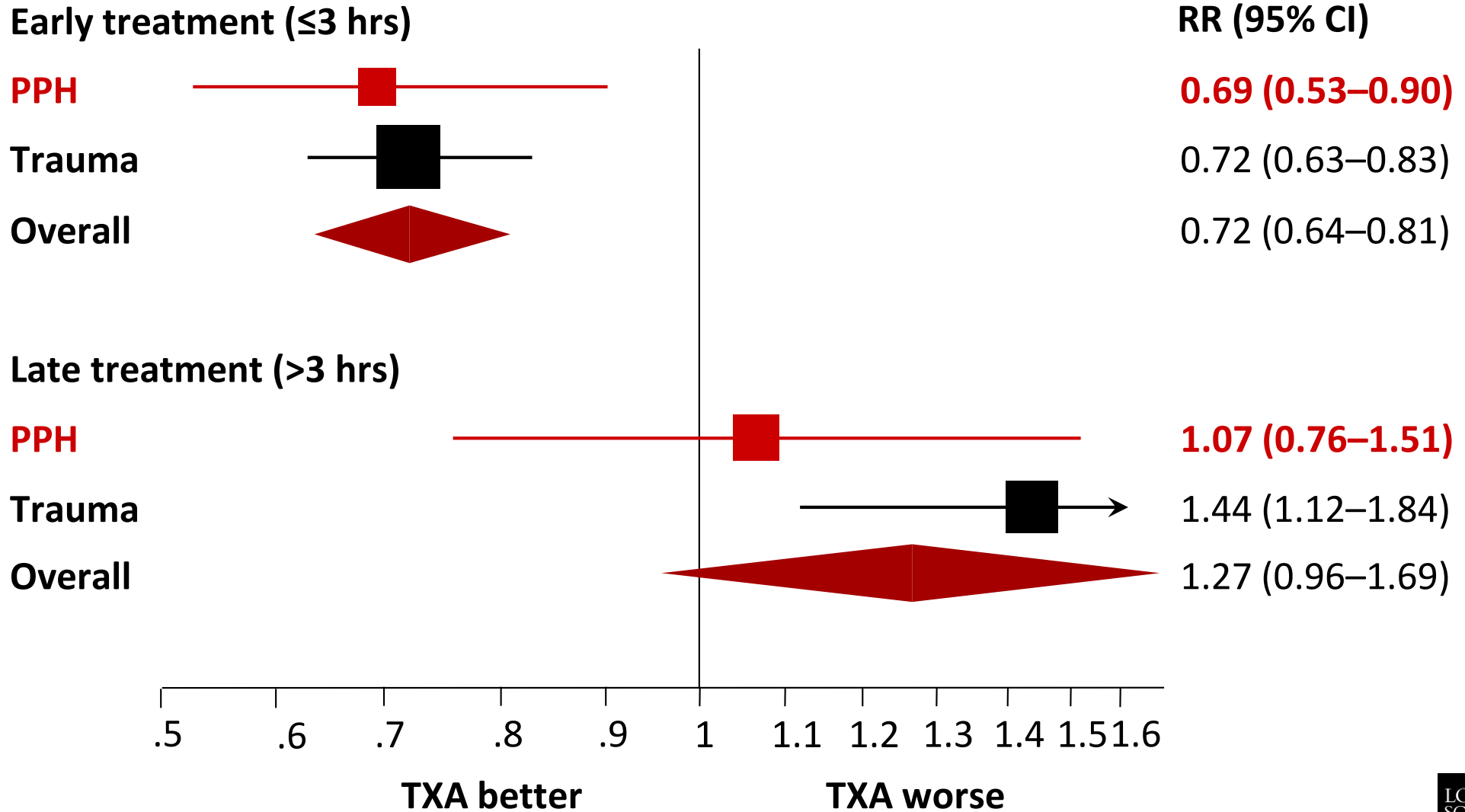
# Quality of life

	<b>TXA (N=9805) n (%)</b>	<b>Placebo (N=9728) n (%)</b>	<b>Risk ratio (95% CI)</b>	<b>P-value</b>
Mobility	30 (0.3)	31 (0.3)	0.96 (0.58–1.58)	0.87
Self-care	39 (0.4)	31 (0.3)	1.25 (0.78–2.00)	0.36
Usual activities	38 (0.4)	44 (0.5)	0.86 (0.56–1.32)	0.48
Pain/discomfort	13 (0.1)	18 (0.2)	0.72 (0.35–1.46)	0.36
Anxiety/depression	30 (0.3)	29 (0.3)	1.03 (0.62–1.71)	0.92

# Death or thromboembolic event in breast-fed babies

<b>Outcome</b>	<b>TXA (N=10033) n (%)</b>	<b>Placebo (N=9985) n (%)</b>	<b>Risk ratio (95% CI)</b>	<b>P-value</b>
Any death	8 (0.1)	7 (0.1)	1.27 (0.47–3.41)	0.63
Any thromboembolic event	0 (0)	0 (0)	-	-

# Death due to bleeding



# Tranexamic acid in PPH

- Reduces death due to bleeding overall by one fifth
- Reduces death due to bleeding within 3 hours by about one third
- No effect on other causes of death
- Did not reduce hysterectomy
- Reduces laparotomy for bleeding by over 35%
- No evidence of adverse effects

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