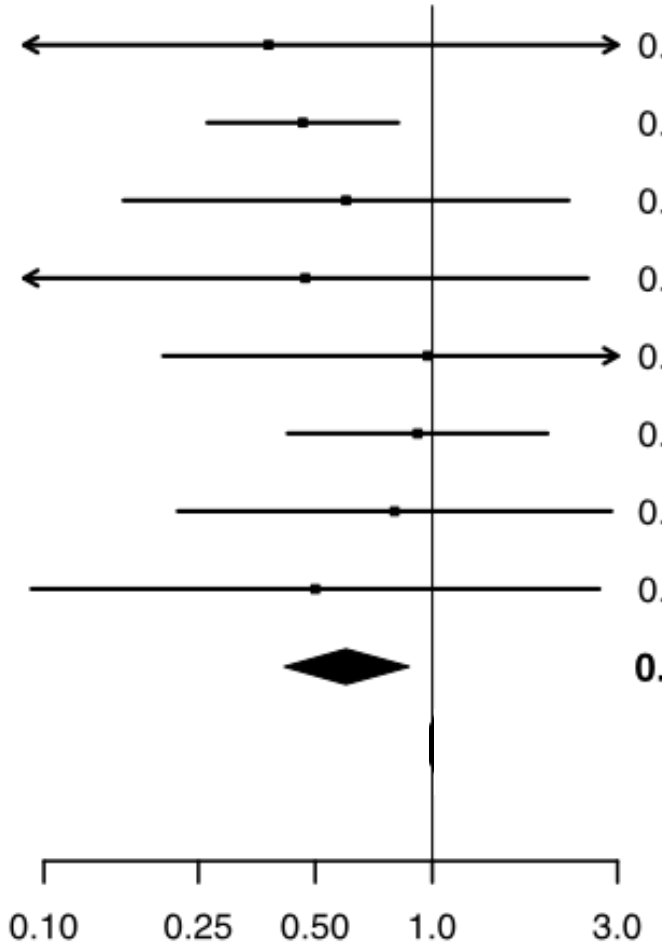
Tranexamic acid for the treatment of gastrointestinal bleeding: an international randomised, double-blind placebo controlled trial

Previous evidence on TXA in GI bleeding - Death

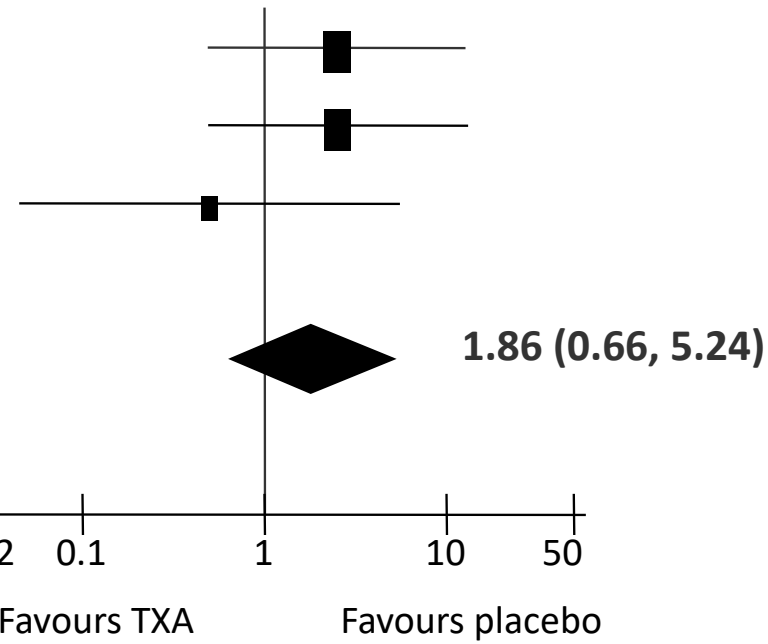
Study	Tranexamic acid	Placebo	RR	95% CI
Bagnenko 2011	1 / 22 (4.5%)	3 / 25 (12.0%)	0.38	(0.04-3.38)
Barer 1983	16 / 256 (6.2%)	35 / 260 (13.5%)	0.46	(0.26-0.82)
Bergqvist 1980	3 / 25 (12.0%)	5 / 25 (20.0%)	0.60	(0.16-2.25)
Biggs 1976	2 / 103 (1.9%)	4 / 97 (4.1%)	0.47	(0.09-2.51)
Cormack 1973	3 / 76 (3.9%)	3 / 74 (4.1%)	0.97	(0.20-4.67)
Engquist 1979	11 / 102 (10.8%)	12 / 102 (11.8%)	0.92	(0.42-1.98)
Hawkey 2001	4 / 103 (3.9%)	5 / 103 (4.9%)	0.80	(0.22-2.89)
Holstein 1987	2 / 164 (1.2%)	4 / 164 (2.4%)	0.50	(0.09-2.69)
Subtotal of 8 trials	**42 / 851 (4.9%)**	**71 / 850 (8.4%)**	**0.60**	**(0.42-0.87)**

Heterogeneity test
χ^2_7 =2.80 p=(0.90) for 8 previous trials



Previous evidence on TXA in GI bleeding - Thromboembolic events

	TXA		Placebo		Risk Ratio (95% CI)
	Events	*Total*	*Events*	*Total*	
Engquist 1979	5	102	2	102	
Barer 1983	5	256	2	260	
von Holstein 1987	1	164	2	164	
Total	11	522	6	526	**1.86 (0.66, 5.24)**



Overview

ELIGIBILITY

- Adults with significant acute upper or lower gastrointestinal bleeding
- Responsible clinician is substantially uncertain as to the appropriateness of tranexamic acid in a patient

↓

Appropriate **CONSENT PROCESS**
(ie patient, representative or waiver)

↓

RANDOMISE (tranexamic acid or placebo)

↓

LOADING DOSE 1g TXA over 10 minutes

↓

MAINTENANCE DOSE 3 g TXA over 24 hours

↓

Complete **OUTCOME FORM** at discharge, death or day 28

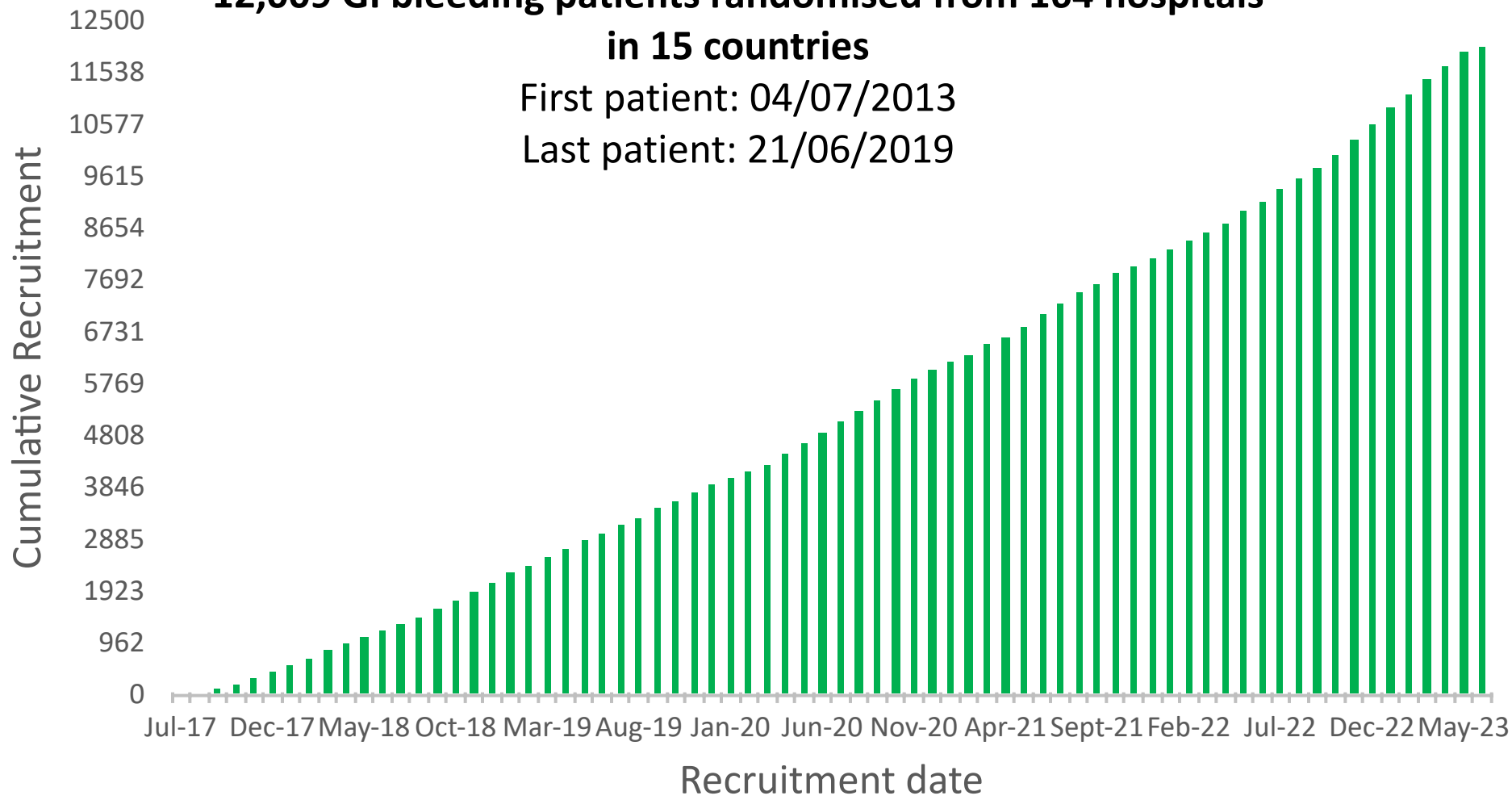
All clinically indicated treatment is given in addition to trial enrolment.

HALT-IT trial recruitment

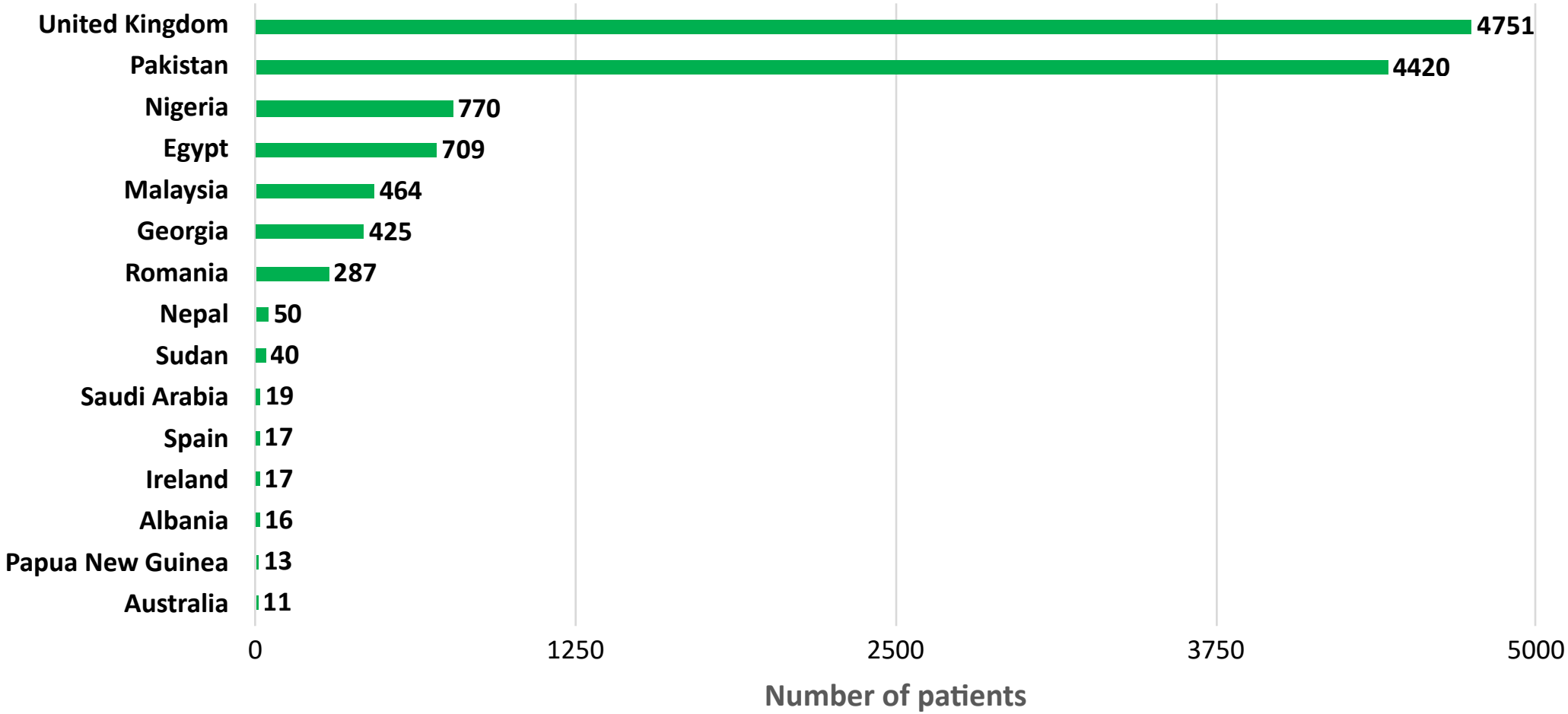
12,009 GI bleeding patients randomised from 164 hospitals in 15 countries

First patient: 04/07/2013

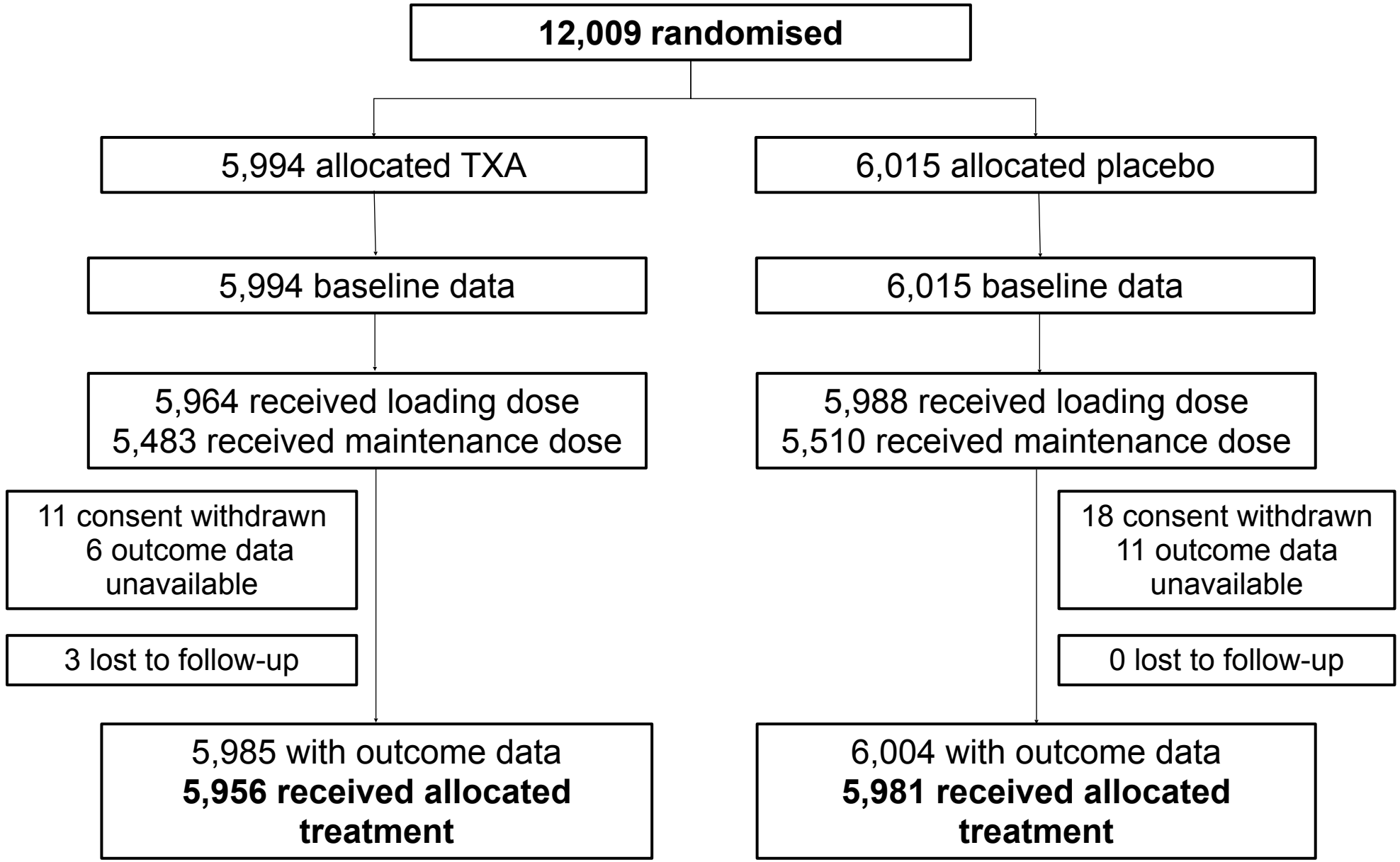
Last patient: 21/06/2019



Trial recruitment by country



Trial profile



Baseline characteristics

	TXA (N=5994)		Placebo (N=6015)	
	n	%	n	%
Age at randomisation (years)				
Mean (SD)	*58.1*	*(17.0)*	*58.1*	*(17.0)*
<40	790	(13)	779	(13)
40-59	2355	(39)	2333	(39)
60-79	2077	(35)	2130	(35)
80+	769	(13)	773	(13)
Sex				
Female	2141	(36)	2124	(35)
Male	3850	(64)	3891	(65)

Baseline characteristics

	TXA (N=5994)		Placebo (N=6015)	
	n	%	n	%
Time from onset to randomisation (hours)				
mean(SD)	*21.4*	*(36.4)*	*22.5*	*(37.8)*
≤3	960	(16)	975	(16)
>3-≤8	1607	(27)	1551	(26)
>8	3424	(57)	3488	(58)
Missing	0	(0)	1	(<1)
Suspected location of bleeding				
Lower	674	(11)	654	(11)
Upper	5317	(89)	5361	(89)

Baseline characteristics

	TXA (N=5994)		Placebo (N=6015)	
	n	%	n	%
Haematemesis				
Yes	4283	(72)	4240	(71)
No	1708	(29)	1775	(30)
Melaena or fresh blood per rectum				
Yes	4571	(76)	4626	(77)
No	1420	(24)	1389	(23)
Suspected variceal bleeding				
Yes	2694	(45)	2739	(46)
No	3297	(55)	3276	(55)
Suspected active bleeding				
Yes	5244	(88)	5226	(87)
No	747	(13)	789	(13)

Baseline characteristics

	TXA (N=5994)		Placebo (N=6015)	
	n	%	n	%
Systolic blood pressure				
≥90	5219	(87)	5216	(87)
76-89	577	(10)	577	(10)
≤75	181	(3)	201	(3)
Missing	14	(<1)	21	(<1)
Heart rate				
<77	811	(14)	756	(13)
77-91	1545	(26)	1644	(27)
92-107	1759	(29)	1720	(29)
>107	1864	(31)	1885	(31)
Missing	12	(<1)	10	(<1)

Baseline characteristics

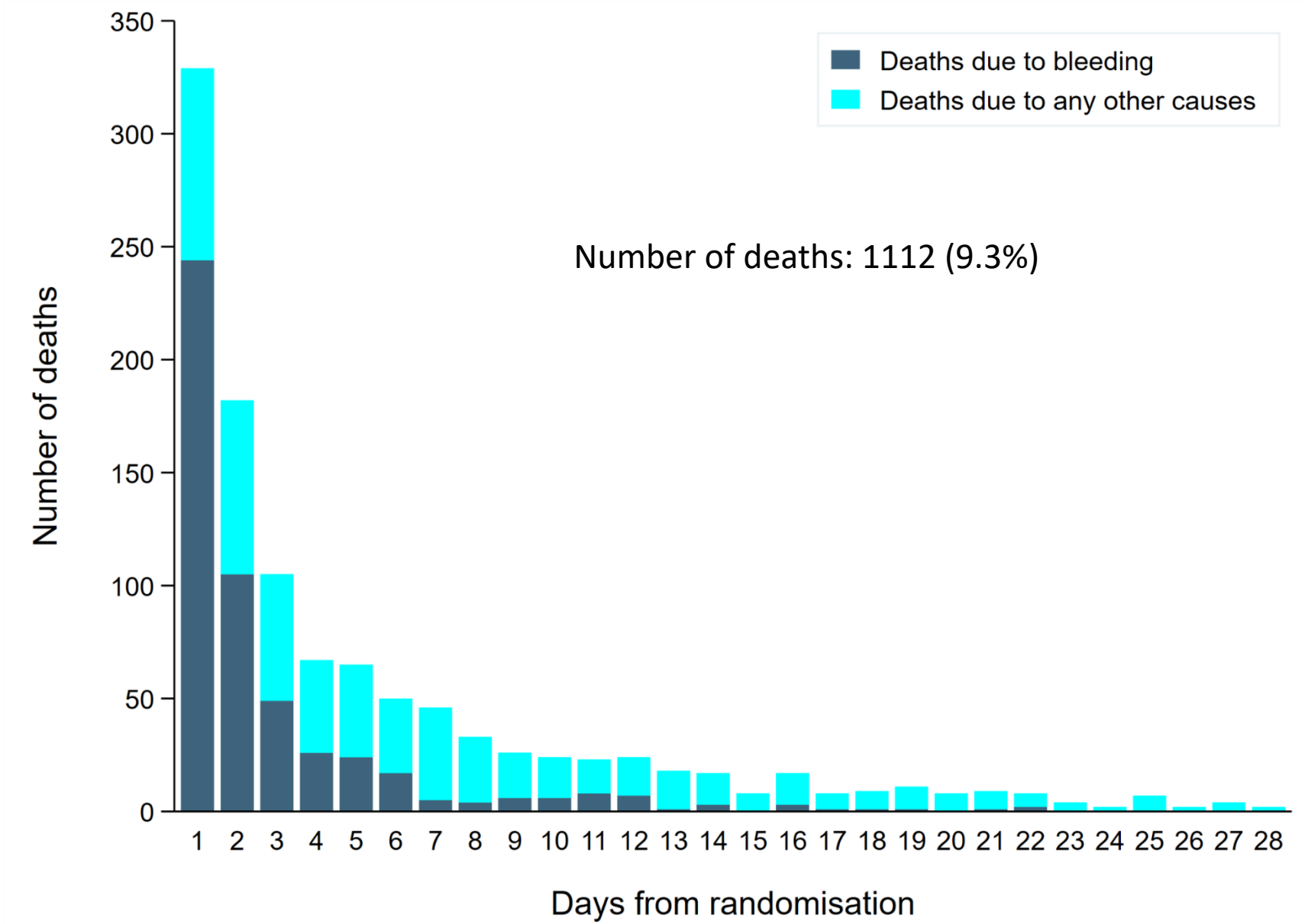
	TXA (N=5994)		Placebo (N=6015)	
	n	%	n	%
Signs of shock				
Yes	2573	(43)	2648	(44)
No	3418	(57)	3367	(56)
Rockall score				
1-2	1416	(24)	1395	(23)
3-4	2306	(39)	2332	(39)
5-7	2269	(38)	2288	(38)
Emergency admission				
Yes	5670	(95)	5687	(95)
No	321	(5)	328	(5)

Baseline characteristics

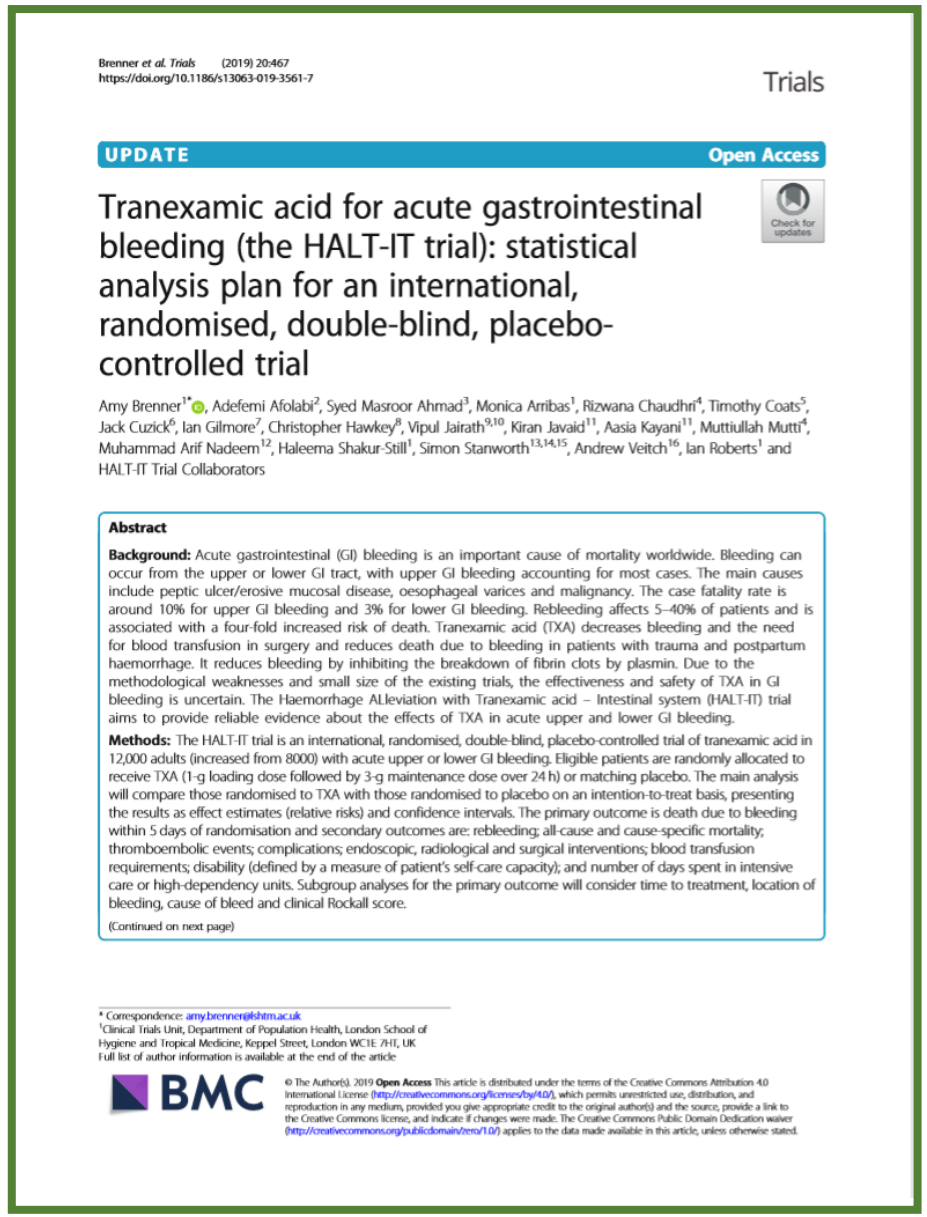
	TXA (N=5994)		Placebo (N=6015)	
	n	**%**	**n**	**%**
Major comorbidities				
Cardiovascular	1108	(19)	1132	(19)
Respiratory	337	(6)	324	(5)
Liver	2432	(41)	2532	(42)
Renal	325	(5)	310	(5)
Malignancy	417	(7)	382	(6)
Other	999	(17)	968	(16)
Any	**4308**	**(72)**	**4329**	**(72)**

Results

Time from randomisation to death



Statistical analysis plan



Brenner et al. Trials (2019) 20:467
https://doi.org/10.1186/s13063-019-3561-7

Trials

UPDATE Open Access

Tranexamic acid for acute gastrointestinal bleeding (the HALT-IT trial): statistical analysis plan for an international, randomised, double-blind, placebo-controlled trial

Amy Brenner[1*], Adefemi Afolabi[2], Syed Masroor Ahmad[3], Monica Arribas[1], Rizwana Chaudhri[4], Timothy Coats[5], Jack Cuzick[6], Ian Gilmore[7], Christopher Hawkey[8], Vipul Jairath[9,10], Kiran Javaid[11], Aasia Kayani[11], Muttiullah Mutti[4], Muhammad Arif Nadeem[12], Haleema Shakur-Still[1], Simon Stanworth[13,14,15], Andrew Veitch[16], Ian Roberts[1] and HALT-IT Trial Collaborators

Abstract

Background: Acute gastrointestinal (GI) bleeding is an important cause of mortality worldwide. Bleeding can occur from the upper or lower GI tract, with upper GI bleeding accounting for most cases. The main causes include peptic ulcer/erosive mucosal disease, oesophageal varices and malignancy. The case fatality rate is around 10% for upper GI bleeding and 3% for lower GI bleeding. Rebleeding affects 5–40% of patients and is associated with a four-fold increased risk of death. Tranexamic acid (TXA) decreases bleeding and the need for blood transfusion in surgery and reduces death due to bleeding in patients with trauma and postpartum haemorrhage. It reduces bleeding by inhibiting the breakdown of fibrin clots by plasmin. Due to the methodological weaknesses and small size of the existing trials, the effectiveness and safety of TXA in GI bleeding is uncertain. The Haemorrhage ALleviation with Tranexamic acid – Intestinal system (HALT-IT) trial aims to provide reliable evidence about the effects of TXA in acute upper and lower GI bleeding.

Methods: The HALT-IT trial is an international, randomised, double-blind, placebo-controlled trial of tranexamic acid in 12,000 adults (increased from 8000) with acute upper or lower GI bleeding. Eligible patients are randomly allocated to receive TXA (1-g loading dose followed by 3-g maintenance dose over 24 h) or matching placebo. The main analysis will compare those randomised to TXA with those randomised to placebo on an intention-to-treat basis, presenting the results as effect estimates (relative risks) and confidence intervals. The primary outcome is death due to bleeding within 5 days of randomisation and secondary outcomes are: rebleeding; all-cause and cause-specific mortality; thromboembolic events; complications; endoscopic, radiological and surgical interventions; blood transfusion requirements; disability (defined by a measure of patient's self-care capacity); and number of days spent in intensive care or high-dependency units. Subgroup analyses for the primary outcome will consider time to treatment, location of bleeding, cause of bleed and clinical Rockall score.

(Continued on next page)

* Correspondence: amy.brenner@lshtm.ac.uk
[1]Clinical Trials Unit, Department of Population Health, London School of Hygiene and Tropical Medicine, Keppel Street, London WC1E 7HT, UK
Full list of author information is available at the end of the article

Statistical analysis plan

Primary outcome:
Death due to bleeding within 5 days of randomisation.

Secondary outcomes:
- Re-bleeding within 24 h, 5 days and 28 days of randomisation.
- Death due to bleeding within 28 days.
- All-cause and cause-specific mortality within 28 days.
- Diagnostic and therapeutic endoscopic and radiological procedures and surgical interventions.
- Blood product transfusion.
- Thromboembolic events (pulmonary embolism, deep vein thrombosis, stroke and myocardial infarction).
- Other complications (renal, hepatic and respiratory failure, cardiac events, sepsis, pneumonia and seizures).
- Self-care capacity.
- Days spent in the intensive care or high-dependency unit.

Subgroup analyses for the primary outcome of death due to bleeding: time to treatment, location of bleeding, cause of bleeding and clinical Rockall score.

Death due to bleeding and re-bleeding

	TXA (n=5956)		Placebo (n=5981)		RR (95% CI)
	n	(%)	n	(%)	
Death due to bleeding within 24 hours	124	(2.1)	120	(2.0)	1.04 (0.81-1.33)
Death due to bleeding within 5 days	**222**	**(3.7)**	**226**	**(3.8)**	**0.99 (0.82-1.18)**
Death due to bleeding within 28 days	253	(4.2)	262	(4.4)	0.97 (0.82-1.15)
Rebleeding within 24 hours*	41	(0.7)	41	(0.7)	1.00 (0.65-1.55)
Rebleeding within 5 days*	287	(4.8)	315	(5.3)	0.91 (0.78-1.07)
Rebleeding within 28 days*	410	(6.8)	448	(7.5)	0.92 (0.81-1.05)

*Excludes 13 patients missing data on rebleed status or rebleed date.
Death or rebleeding in-hospital during follow-up.
CI=confidence interval, RR=risk ratio, TXA=tranexamic acid

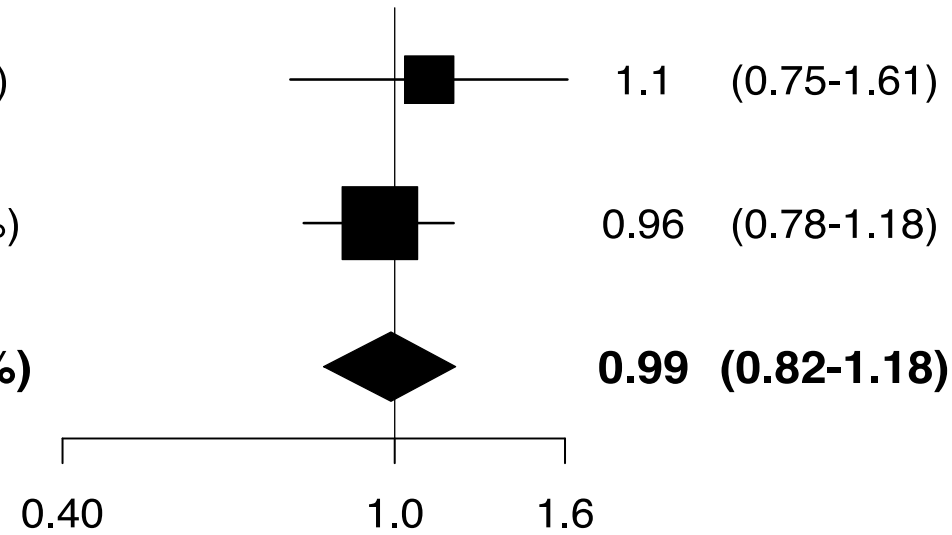
All causes of death

	TXA (N=5956)		Placebo (N=5981)		RR (95% CI)
	n	(%)	n	(%)	
Bleeding	253	(4.2)	262	(4.4)	0.97 (0.82-1.15)
Thromboembolic event	26	(0.4)	17	(0.3)	1.54 (0.83-2.83)
Organ failure	109	(1.8)	114	(1.9)	0.96 (0.74-1.25)
Pneumonia	57	(1.0)	42	(0.7)	1.36 (0.92-2.03)
Sepsis	33	(0.6)	49	(0.8)	0.68 (0.44-1.05)
Malignancy	65	(1.1)	40	(0.7)	1.63 (1.10-2.42)
Other	21	(0.4)	24	(0.4)	0.88 (0.49-1.58)
All cause	564	(9.5)	548	(9.2)	1.03 (0.92-1.16)

Death in-hospital during follow-up.

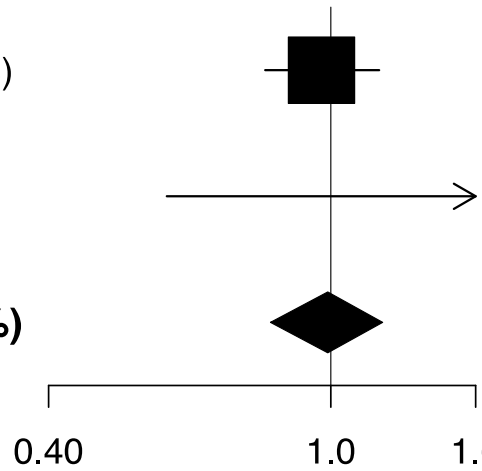
Subgroup analysis – Time since onset

Time since onset	Tranexamic acid N = (5956)	Placebo N = (5980)	RR	95% CI
<3h	52 (5.4%)	48 (4.9%)	1.1	(0.75-1.61)
>3h	170 (3.4%)	178 (3.6%)	0.96	(0.78-1.18)
Total	**222 (3.7%)**	**226 (3.8%)**	**0.99**	**(0.82-1.18)**



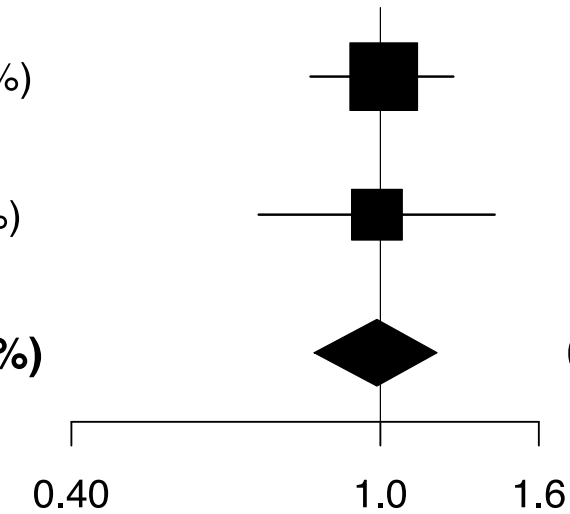
Subgroup analysis – Bleed location

Bleed location	Tranexamic acid N = (5956)	Placebo N = (5981)	RR	95% CI
Upper	212 (4.0%)	220 (4.1%)	0.97	(0.81-1.17)
Lower	10 (1.5%)	6 (0.9%)	1.61	(0.59-4.40)
Total	**222 (3.7%)**	**226 (3.8%)**	**0.99**	**(0.82-1.18)**



Subgroup analysis – Liver disease

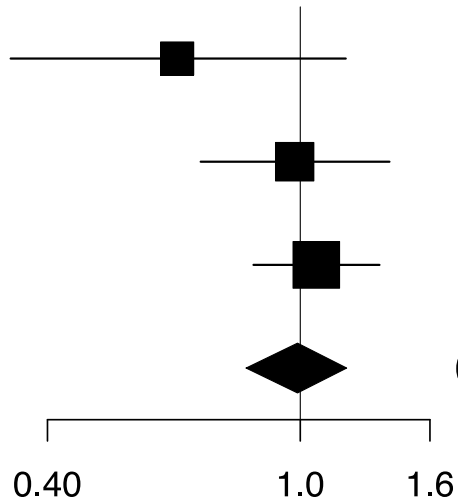
	Tranexamic acid	Placebo	RR	95% CI
Variceal/Liver *	**N = (5956)**	**N = (5981)**		
Yes	160 (5.5%)	165 (5.5%)	1.01	(0.81-1.24)
No/unknown	62 (2.0%)	61 (2.1%)	0.99	(0.70-1.40)
Total	**222 (3.7%)**	**226 (3.8%)**	**0.99**	**(0.82-1.18)**



* Suspected variceal bleeding and comorbid liver disease

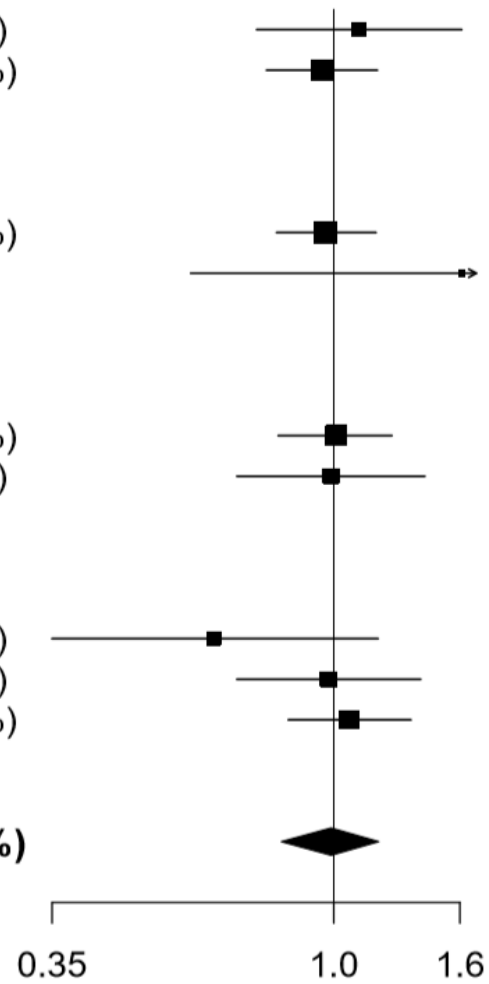
Subgroup analysis – Rockall score

Rockall score	Tranexamic acid N = (5956)	Placebo N = (5981)	RR	95% CI
1-2	17 (1.2%)	26 (1.9%)	0.64	(0.35-1.18)
3-4	63 (2.7%)	65 (2.8%)	0.98	(0.70-1.38)
5-7	142 (6.3%)	135 (5.9%)	1.06	(0.84-1.33)
Total	**222 (3.7%)**	**226 (3.8%)**	**0.99**	**(0.82-1.18)**



Subgroup analysis

	Tranexamic acid N = (5956)	Placebo N = (5981)	RR	95% CI
Time since onset				
<3h	52 (5.4%)	48 (4.9%)	1.10	(0.75-1.61)
>3h	170 (3.4%)	178 (3.6%)	0.96	(0.78-1.18)
p = 0.53				
Bleed location				
Upper	212 (4.0%)	220 (4.1%)	0.97	(0.81-1.17)
Lower	10 (1.5%)	6 (0.9%)	1.61	(0.59-4.40)
p = 0.34				
Variceal/Liver				
Yes	160 (5.5%)	165 (5.5%)	1.01	(0.81-1.24)
No/unknown	62 (2.0%)	61 (2.1%)	0.99	(0.70-1.40)
p = 0.94				
Rockall score				
1-2	17 (1.2%)	26 (1.9%)	0.64	(0.35-1.18)
3-4	63 (2.7%)	65 (2.8%)	0.98	(0.70-1.38)
5-7	142 (6.3%)	135 (5.9%)	1.06	(0.84-1.33)
p = 0.32				
Total	**222 (3.7%)**	**226 (3.8%)**	**0.99**	**(0.82-1.18)**



Subgroup analysis

	TXA (N=5956)			Placebo (N=5981)			RR (95% CI)
	n	%	N	n	%	N	
Time since onset							
≤3h	52	5.4%	956	48	4.9%	970	1.10 (0.75-1.61)
>3h	170	3.4%	5000	178	3.6%	5010	0.96 (0.78-1.18)
(p=0.53)							
Bleed location							
Upper	212	4.0%	5285	220	4.1%	5334	0.97 (0.81-1.17)
Lower	10	1.5%	671	6	0.9%	647	1.61 (0.59-4.40)
(p=0.34)							
Suspected variceal bleeding/liver disease							
No/unknown	62	2.0%	3049	61	2.1%	2968	0.99 (0.70-1.40)
Yes	160	5.5%	2907	165	5.5%	3013	1.01 (0.81-1.24)
(p=0.94)							
Rockall score							
1-2	17	1.2%	1412	26	1.9%	1388	0.64 (0.35-1.18)
3-4	63	2.7%	2291	65	2.8%	2321	0.98 (0.70-1.38)
5-7	142	6.3%	2253	135	5.9%	2272	1.06 (0.84-1.33)
(p=0.32)							

Diagnostic and therapeutic interventions

	TXA			Placebo			RR (95% CI)
	n	N	(%)	n	N	(%)	
Diagnostic endoscopy	4781 /	5953	(80.3)	4729 /	5978	(79.1)	1.02 (1.00-1.03)
Therapeutic endoscopy	2542 /	5952	(42.7)	2658 /	5978	(44.5)	0.96 (0.92-1.00)
Diagnostic radiological procedure	1704 /	5953	(28.6)	1744 /	5978	(29.2)	0.98 (0.93-1.04)
Therapeutic radiological procedure	74 /	5953	(1.2)	89 /	5978	(1.5)	0.83 (0.61-1.13)
Surgical intervention	146 /	5953	(2.5)	158 /	5978	(2.6)	0.93 (0.74-1.16)
Any surgical, endoscopic or radiological intervention	**5216 /**	**5956**	**(87.6)**	**5236 /**	**5981**	**(87.5)**	**1.00 (0.99-1.01)**

Blood products transfusion

	TXA n		N	(%)	Placebo n		N	(%)	RR (95% CI)
Any transfusion	**4076**	**/**	**5951**	**(68.5)**	**4129**	**/**	**5978**	**(69.1)**	**0.99 (0.97-1.02)**
Whole blood/red cells	3984	/	4076	(97.7)	4018	/	4129	(97.3)	1.00 (1.00-1.01)
Frozen plasma	910	/	4076	(22.3)	993	/	4129	(24.0)	0.93 (0.86-1.00)
Any platelets	219	/	4076	(5.4)	255	/	4129	(6.2)	0.87 (0.73-1.04)
Units	**Mean**		**(SD)**		**Mean**		**(SD)**		**Difference in means (95% CI)**
Whole blood/red cells	2.8		(2.4)		2.9		(2.7)		-0.06 (0.05, -0.18)
Frozen plasma	0.9		(2.4)		1.0		(2.6)		-0.05 (-0.01, -0.23)
Any platelets	0.2		(0.9)		0.2		(1.0)		-0.02 (0.02, -0.06)

Thromboembolic events

	TXA			Placebo			RR (95% CI)
	n	N	(%)	n	N	(%)	
Any thromboembolic event	**86 /**	**5952**	**(1.4)**	**72 /**	**5977**	**(1.2)**	**1.20 (0.88-1.64)**
Venous events (DVT, PE)	**48 /**	**5952**	**(0.8)**	**26 /**	**5977**	**(0.4)**	**1.85 (1.15-2.98)**
DVT	23 /	5952	(0.4)	12 /	5977	(0.2)	1.92 (0.96-3.86)
PE	28 /	5952	(0.5)	16 /	5977	(0.3)	1.76 (0.95-3.24)
Arterial events (MI, stroke)	**42 /**	**5952**	**(0.7)**	**46 /**	**5977**	**(0.8)**	**0.92 (0.60-1.39)**
MI	24 /	5952	(0.4)	28 /	5977	(0.5)	0.86 (0.50-1.48)
Stroke	19 /	5952	(0.3)	18 /	5977	(0.3)	1.06 (0.56-2.02)

CI = confidence interval, DVT = deep vein thrombosis, PE = pulmonary embolism, MI = myocardial infarction, RR = risk ratio, TXA = tranexamic acid

Complications and self-care capacity

	TXA			Placebo			RR (95% CI)
	n	N	(%)	n	N	(%)	
Renal failure	142 /	5951	(2.4)	157 /	5978	(2.6)	0.91 (0.73-1.14)
Liver failure	196 /	5952	(3.3)	184 /	5977	(3.1)	1.07 (0.88-1.30)
Respiratory failure	105 /	5952	(1.8)	131 /	5978	(2.2)	0.81 (0.62-1.04)
Cardiac event	100 /	5952	(1.7)	89 /	5977	(1.5)	1.13 (0.85-1.50)
Sepsis	210 /	5952	(3.5)	216 /	5977	(3.6)	0.98 (0.81-1.18)
Pneumonia	193 /	5952	(3.2)	174 /	5978	(2.9)	1.11 (0.91-1.36)
Seizure	38 /	5952	(0.6)	22 /	5977	(0.4)	1.73 (1.03-2.93)
	Mean	**(SD)**		**Mean**	**(SD)**		**Difference in means (95% CI)**
Days in ICU	0.4	(1.8)		0.4	(2.0)		-0.06 (0.01, -0.13)
Katz score	5.5	(1.5)		5.5	(1.4)		-0.03 (0.02, -0.09)

ICU = Intensive Care Unit

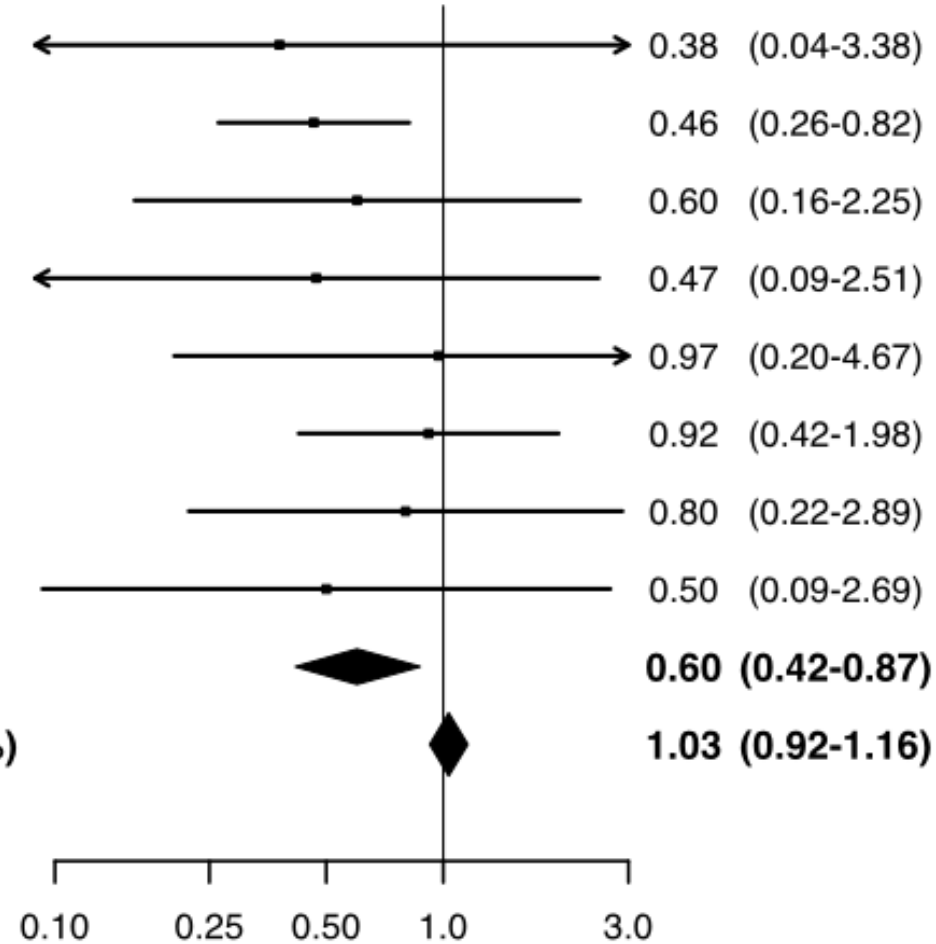
Subgroup analyses – venous events

		TXA			Placebo			RR (95% CI)
		n	N	%	n	N	%	
Suspected variceal bleeding / liver disease *(p=0.035)*	**No**	34 /	3047	1.1%	24 /	2966	0.8%	1.38 (0.82-2.32)
	Yes	14 /	2905	0.5%	2 /	3011	0.1%	7.26 (1.65-31.90)
Location of bleed *(p=0.60)*	**Upper**	39 /	5281	0.7%	20 /	5310	0.4%	1.97 (1.15-3.37)
	Lower	9 /	671	1.3%	6 /	647	0.9%	1.45 (0.52-4.04)
Age *(p=0.036)*	**<60**	12 /	3128	0.4%	5 /	3098	0.2%	2.38 (0.84-6.74)
	60-79	26 /	2066	1.3%	8 /	2114	0.4%	3.33 (1.51-7.33)
	80+	10 /	758	1.3%	13 /	765	1.7%	0.78 (0.34-1.76)
Rockall score *(p=0.51)*	**1-2**	7 /	1412	0.5%	6 /	1382	0.4%	1.15 (0.39-3.40)
	3-4	18 /	2287	0.8%	7 /	2313	0.3%	2.61 (1.09-6.23)
	5-7	23 /	2253	1.0%	13 /	2269	0.6%	1.78 (0.90-3.51)
Time since injury *(p=0.37)*	**<=3h**	10 /	955	1.0%	4 /	969	0.4%	2.54 (0.80-8.06)
	3-8h	10 /	1595	0.6%	9 /	1540	0.6%	1.07 (0.44-2.63)
	>8h	28 /	3402	0.8%	13 /	3467	0.4%	2.19 (1.14-4.23)

Current evidence on TXA in GI bleeding - death

Study	Tranexamic acid	Placebo	RR	95% CI
Bagnenko 2011	1 / 22 (4.5%)	3 / 25 (12.0%)	0.38	(0.04-3.38)
Barer 1983	16 / 256 (6.2%)	35 / 260 (13.5%)	0.46	(0.26-0.82)
Bergqvist 1980	3 / 25 (12.0%)	5 / 25 (20.0%)	0.60	(0.16-2.25)
Biggs 1976	2 / 103 (1.9%)	4 / 97 (4.1%)	0.47	(0.09-2.51)
Cormack 1973	3 / 76 (3.9%)	3 / 74 (4.1%)	0.97	(0.20-4.67)
Engquist 1979	11 / 102 (10.8%)	12 / 102 (11.8%)	0.92	(0.42-1.98)
Hawkey 2001	4 / 103 (3.9%)	5 / 103 (4.9%)	0.80	(0.22-2.89)
Holstein 1987	2 / 164 (1.2%)	4 / 164 (2.4%)	0.50	(0.09-2.69)
Subtotal of 8 trials	**42 / 851 (4.9%)**	**71 / 850 (8.4%)**	**0.60**	**(0.42-0.87)**
HALT-IT 2019	**564 / 5956 (9.5%)**	**548 / 5981 (9.2%)**	**1.03**	**(0.92-1.16)**

Heterogeneity test
χ^2_7 =2.80 p=(0.90) for 8 previous trials
χ^2_1 =7.47 p=(0.006) for HALT-IT versus previous trials



Tranexamic acid did not reduce the deaths from GI bleeding

There was an increased risk of venous thromboembolic events and seizures in patients with GI bleeding

Tranexamic acid should not be used for the treatment of GI bleeding outside the context of a randomised trial.

Haltit

Haemorrhage alleviation with tranexamic acid - Intestinal system

FUNDED BY
NIHR | National Institute for Health Research

Website: http://haltit.lshtm.ac.uk Twitter: @ctu_LSHTM