Tranexamic acid in patients undergoing noncardiac surgery

Dr. PJ Devereaux on behalf of POISE-3 Investigators
Population Health Research Institute, Hamilton, Canada

Funding: Canadian Institutes of Health Research, National Health and Medical Research Council (Australia), Research Grant Council (Hong Kong SAR)

Background

- Perioperative bleeding
  - common complication in patients undergoing noncardiac surgery
- Tranexamic acid (TXA)
  - antifibrinolytic drug that may safely decrease such bleeding

Question

- In patients undergoing noncardiac surgery who are at risk of bleeding and vascular events
  - does TXA reduce occurrence of life-threatening, major, and critical organ bleeding
  - is TXA noninferior for occurrence of major vascular complications within 30 days
    - compared with placebo?

Design

- Randomized controlled trial
- Partial 2X2 factorial design
  - patients on antihypertensive medication
    - randomize to hypotension vs hypertension-avoidance strategy
    - BP trial results will be presented separately
- Investigator initiated blinded trial

Eligibility criteria

- Included patients
  - ≥45 yrs undergoing inpatient noncardiac surgery
  - at risk of bleeding and vascular complications
- Excluded patients
  - having intracranial neurosurgery
  - planned administration of systemic non-study TXA during surgery
  - eGFR <30 ml/min or receiving chronic dialysis

Intervention and F/U

- Patients randomized to receive
  - TXA 1 gm IV bolus or placebo at start and end of surgery
- Follow-up
  - troponin on first 3 days after surgery
  - study personnel followed patients throughout hospitalization and contacted patients at 30 days
  - 99.9% of participants completed 30-day follow-up

Outcomes

- Primary efficacy outcome at 30 days after randomization
  - composite of life-threatening, major, and critical organ bleeding
    - referred to as composite bleeding outcome
- Primary safety outcome at 30 days after randomization
  - composite of myocardial injury after noncardiac surgery (MINS), nonhemorrhagic stroke, peripheral arterial thrombosis, and symptomatic proximal venous thromboembolism (VTE)
    - referred to as composite vascular outcome

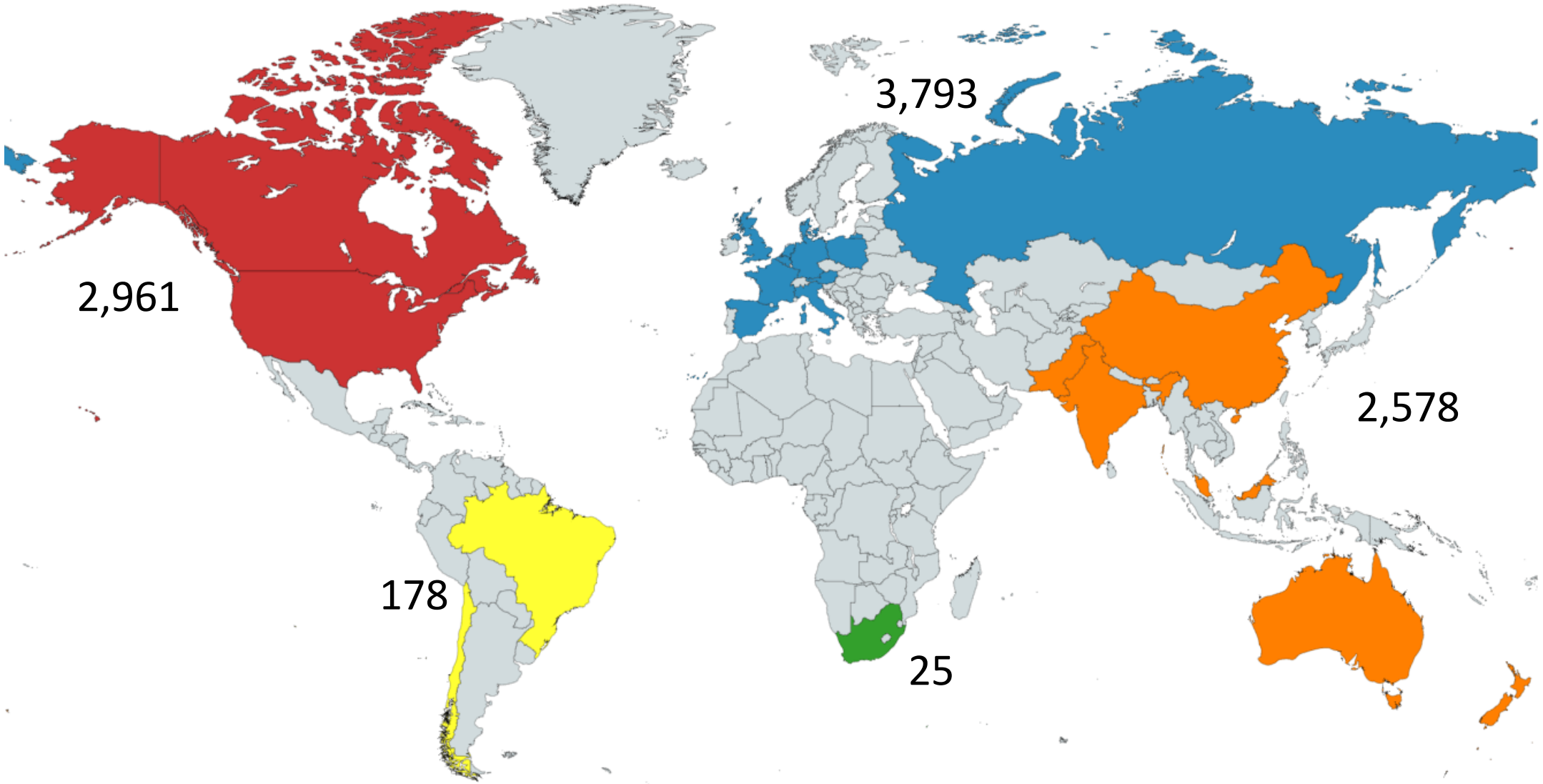
Hypotheses

- Primary efficacy hypothesis
  - TXA superior to placebo for composite bleeding outcome
    - upper bound of 2-sided 95% confidence interval for hazard ratio (HR) needed to fall below 1.0
    - 2-sided P <0.05
- Primary safety hypothesis
  - TXA noninferior to placebo for composite vascular outcome
    - upper bound of 1-sided 97.5% CI for HR needed to fall below 1.125
    - 1-sided P <0.025

Design modification

- Initial design was to randomize 10,000 patient
- Due to financial deficit resulting from slowed recruitment during COVID-19 pandemic, Steering Committee stopped recruitment on July 15, 2021, after at least 9500 patients were randomized
  - decision made without knowledge of trial results but
    - with knowledge that aggregate composite bleeding and vascular outcomes were higher than originally estimated

9535 patients randomized
114 centres in 22 countries



Baseline characteristics

Characteristics	TXA (N=4757)	Placebo (N=4778)
Age – (mean yrs)	70	70
Male	56%	56%
History of		
coronary artery disease	30%	31%
peripheral artery disease	15%	15%
stroke	8%	8%
Undergoing major surgery	79%	80%

Compliance

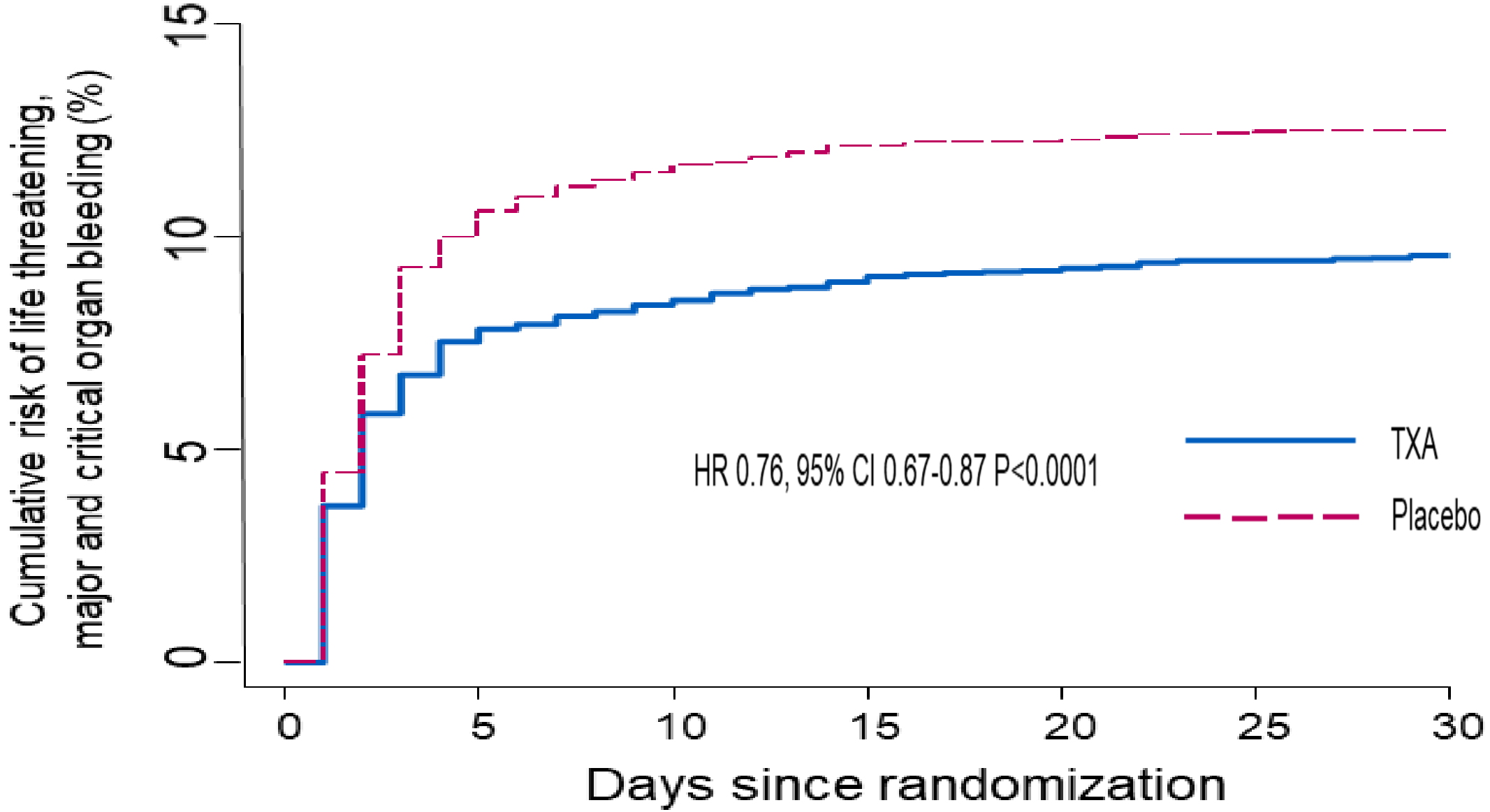
- In both TXA and placebo groups
  - 96.3% of patients received both doses of study drug

Primary efficacy outcome

Outcome	TXA n=4757 no. (%)	Placebo n=4778 no. (%)	HR (95% CI)	P value
Composite bleeding outcome	433 (9.1)	561 (11.7)	0.76 (0.67-0.87)	<0.0001

- No significant effect of blood pressure study interventions on TXA primary efficacy result (interaction P=0.67)

Composite bleeding outcome

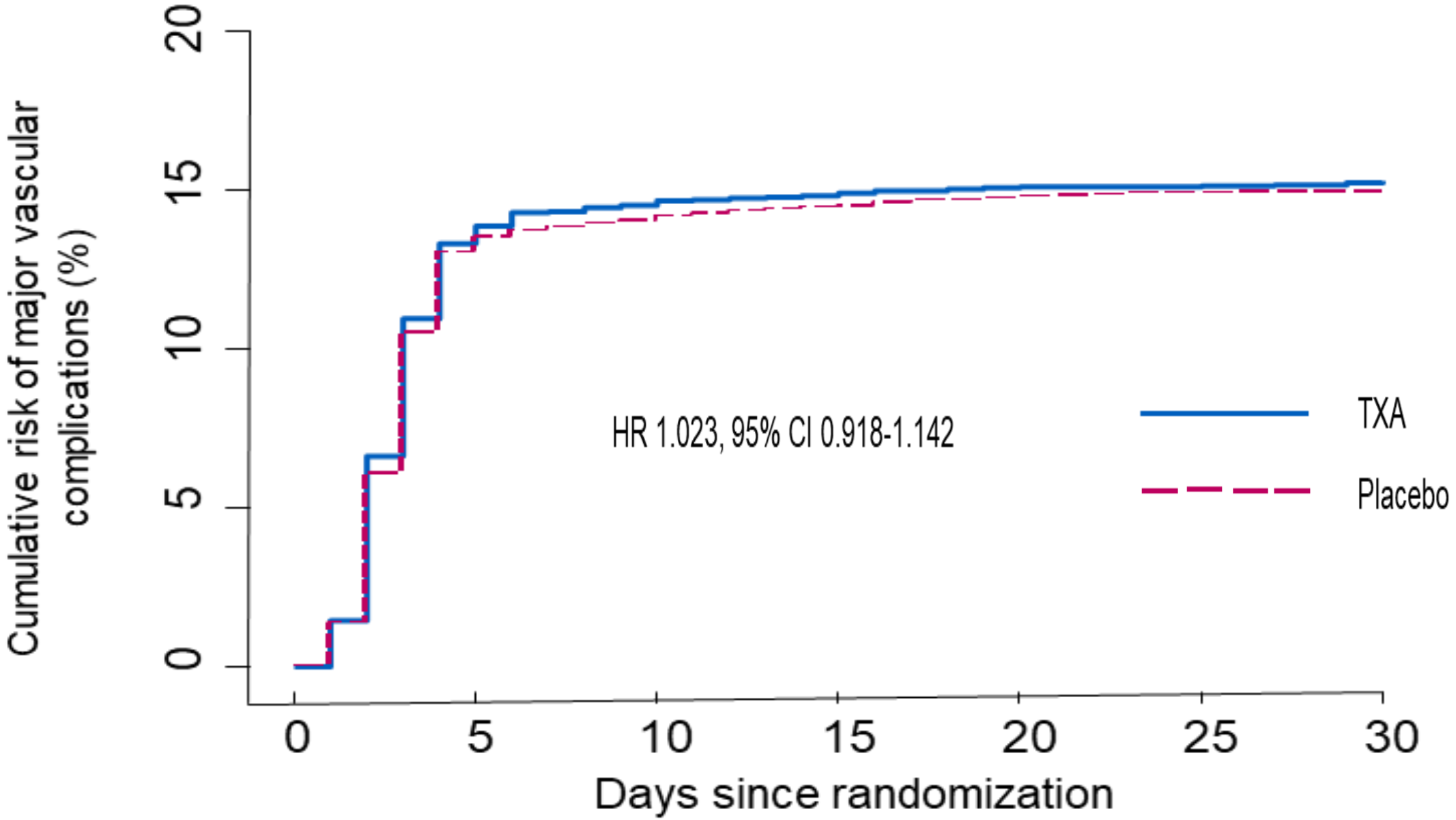


Primary safety outcome

Outcome	TXA n=4757 no. (%)	Placebo n=4778 no. (%)	HR (95% CI)	Non-inferiority P value
Composite vascular outcome	649 (14.2)	639 (13.9)	1.023 (0.918-1.142)	0.04

- No significant effect of blood pressure study interventions on TXA primary safety result (interaction P=0.74)

Composite vascular outcome



Probability that primary safety outcome HR is < or ≥ 1.125

- Based on composite vascular outcome result
  - HR, 1.023; 95% CI, 0.918-1.142
  - there is
    - 95.6% probability that primary safety outcome HR is <1.125 and
    - 4.4% probability that HR is ≥1.125

Secondary bleeding outcomes

Outcome	TXA n=4757 no. (%)	Placebo n=4778 no. (%)	HR (95% CI)	P value
BIMS*	416 (8.7)	541 (11.3)	0.76 (0.67-0.87)	<0.0001
Life-threatening bleeding	78 (1.6)	79 (1.7)	0.99 (0.73-1.36)	0.96
Major bleeding	363 (7.6)	496 (10.4)	0.72 (0.63-0.83)	<0.0001
Critical organ bleeding	12 (0.3)	21 (0.4)	0.57 (0.28-1.16)	0.12

*BIMS - bleeding independently associated with mortality after noncardiac surgery

Secondary vascular and net risk-benefit outcomes

Outcome	TXA n=4757 no. (%)	Placebo n=4778 no. (%)	HR (95% CI)	P value
MINS	608 (12.8)	602 (12.6)	1.02 (0.91-1.14)	0.76
MINS not fulfilling definition of MI	549 (11.5)	549 (11.5)	1.01 (0.89-1.13)	0.91
Myocardial infarction	67 (1.4)	53 (1.1)	1.27 (0.89-1.82)	0.19
Net risk-benefit outcome*	983 (20.7)	1046 (21.9)	0.94 (0.86-1.02)	0.14

*composite of vascular death and nonfatal life-threatening , major, or critical organ bleeding, MINS, stroke, peripheral arterial thrombosis, and symptomatic proximal VTE

Tertiary bleeding outcomes

Outcome	TXA n=4757 no. (%)	Placebo n=4778 no. (%)	HR (95% CI)	P value
ISTH major bleeding*	315 (6.6)	415 (8.7)	0.75 (0.65-0.87)	0.0001
Transfused ≥1 unit of PRBCs	449 (9.4)	574 (12.0)	0.77 (0.68-0.88)	<0.0001

* International society of thrombosis and haemostasis

Tertiary mortality and vascular outcomes

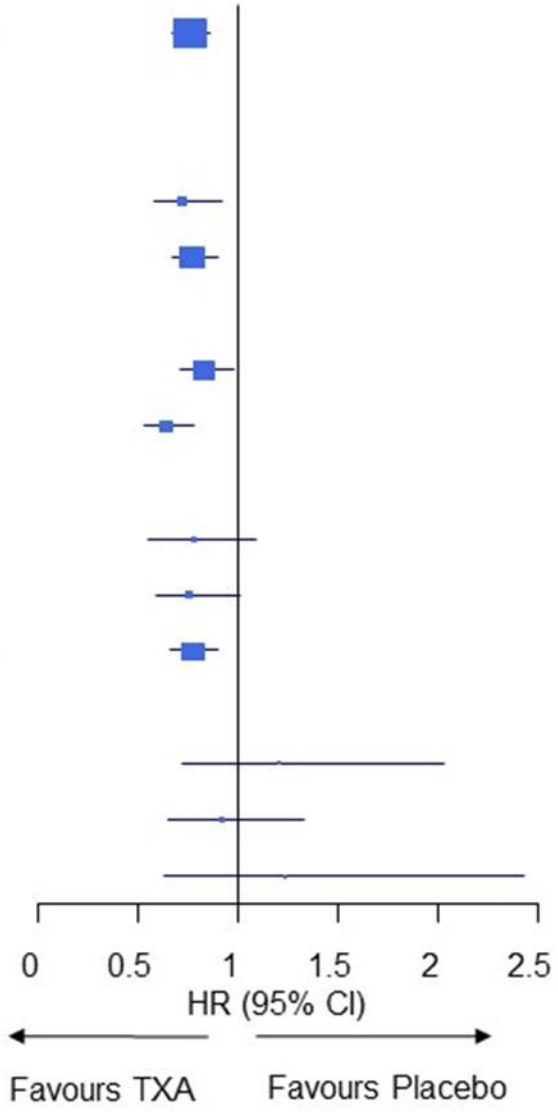
Outcome	TXA n=4757 no. (%)	Placebo n=4778 no. (%)	HR (95% CI)	P value
All-cause mortality	52 (1.1)	57 (1.2)	0.92 (0.63-1.33)	0.65
Vascular mortality	25 (0.5)	30 (0.6)	0.84 (0.49-1.42)	0.51
Hemorrhagic stroke	2 (<0.1)	0 (0)	-	-
Amputation	14 (0.3)	21 (0.4)	0.67 (0.34-1.31)	0.24
Symptomatic PE	24 (0.5)	17 (0.4)	1.42 (0.76-2.64)	0.27
Symptomatic proximal DVT	11 (0.2)	13 (0.3)	0.85 (0.38-1.90)	0.69
Any proximal VTE	32 (0.7)	28 (0.6)	1.15 (0.69-1.91)	0.59
Cardiac revascularization	12 (0.3)	13 (0.3)	0.93 (0.42-2.03)	0.85

Other tertiary outcomes

Outcome	TXA n=4757 no. (%)	Placebo n=4778 no. (%)	HR (95% CI)	P value
Acute kidney injury	672 (14.1)	655 (13.7)	1.03 (0.93-1.15)	0.54
New renal replacement therapy	19 (0.4)	16 (0.3)	1.19 (0.61-2.23)	0.61
Re-hospitalization for vasc reasons	84 (1.8)	75 (1.6)	1.13 (0.82-1.54)	0.46
Seizures	10 (0.2)	3 (<0.1)	3.35 (0.92-12.20)	0.07
Infection	499 (10.5)	487 (10.2)	1.03 (0.91-1.17)	0.64
Sepsis	68 (1.4)	63 (1.3)	1.08 (0.77-1.53)	0.65
Length of hospital stay – median (IQR)	4.0 (2.1-7.1)	4.0 (2.1-7.1)	0 (-0.1 to 0.1)	0.81
Days alive at home – median (IQR)	25 (22-28)	25 (21-28)	0 (-0.4 to <0.1)	1.00
Disability	1408 (31.9)	1407 (31.6)	1.02 (0.92-1.13)	0.74

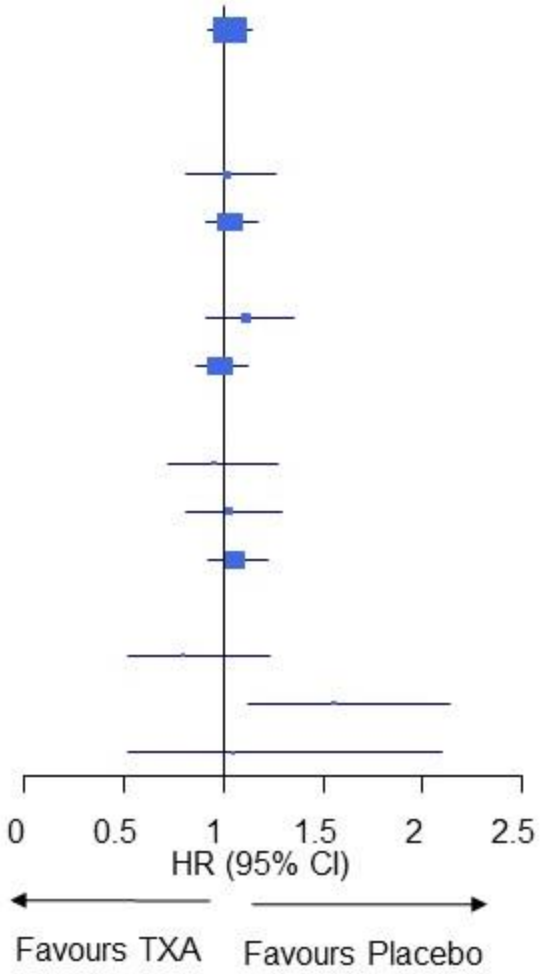
Preplanned subgroup of primary efficacy outcome

	TXA events/Total (%)	Placebo events/Total (%)	Hazard Ratio (95% CI)	P value for Interaction
OVERALL	433 / 4757 (9.1)	561 / 4778 (11.7)	0.76 (0.67 - 0.87)	
Subgroups				
Type of Surgery				
Orthopedic	118 / 1083 (10.9)	156 / 1063 (14.7)	0.72 (0.57-0.92)	0.70
Nonorthopedic	315 / 3645 (8.6)	405 / 3677 (11.0)	0.77 (0.67-0.90)	
Hemoglobin				
<120 g/L	256 / 1185 (21.6)	292 / 1150 (25.4)	0.83 (0.70-0.98)	0.06
≥120 g/L	172 / 3540 (4.9)	266 / 3600 (7.4)	0.65 (0.53-0.78)	
eGFR ml min^{-1} 1.73 m^2				
<45	60 / 401 (15.0)	79 / 424 (18.6)	0.78 (0.55-1.08)	>0.99
45 to <60	91 / 805 (11.3)	122 / 828 (14.7)	0.76 (0.58-1.00)	
≥60	280 / 3520 (8.0)	357 / 3506 (10.2)	0.77 (0.66-0.90)	
NT-proBNP ng/L				
<200	32 / 433 (7.4)	26 / 424 (6.1)	1.20 (0.72-2.02)	0.64
200 to <1500	60 / 499 (12.0)	61 / 474 (12.9)	0.92 (0.65-1.32)	
≥1500	20 / 93 (21.5)	15 / 82 (18.3)	1.24 (0.63-2.43)	



Preplanned subgroup of primary safety outcome

	TXA events/Total (%)	Placebo events/Total (%)	Hazard Ratio (95% CI)	P value for Interaction
OVERALL	649 / 4581 (14.2)	639 / 4601 (13.9)	1.02 (0.92-1.14)	
Subgroups				
Type of Surgery				
Orthopedic	157 / 1042 (15.1)	154 / 1029 (15.0)	1.00 (0.80-1.25)	
Nonorthopedic	492 / 3539 (13.9)	485 / 3572 (13.6)	1.03 (0.91-1.17)	0.88
Hemoglobin				
<120 g/L	207 / 1130 (18.3)	184 / 1108 (16.6)	1.11 (0.91-1.35)	
≥120 g/L	439 / 3423 (12.8)	453 / 3466 (13.1)	0.98 (0.86-1.12)	0.30
eGFR ml min^{-1} 1.73 m^2				
<45	87 / 385 (22.6)	95 / 404 (23.5)	0.95 (0.71-1.27)	
45 to <60	144 / 780 (18.5)	147 / 803 (18.3)	1.02 (0.81-1.29)	0.80
≥60	414 / 3391 (12.2)	394 / 3374 (11.7)	1.05 (0.92-1.21)	
NT-proBNP ng/L				
<200	38 / 421 (9.0)	46 / 405 (11.4)	0.79 (0.52-1.22)	
200 to <1500	94 / 478 (19.7)	61 / 465 (13.1)	1.55 (1.12-2.13)	0.06
≥1500	18 / 84 (21.4)	15 / 77 (19.5)	1.04 (0.52-2.09)	



Additional transfusion data

Outcome	TXA n=4757 no. (%)	Placebo n=4778 no. (%)	OR (95% CI)	P value
Transfusion ≥2 units of PRBC	296 (6.2)	396 (8.3)	0.74 (0.64-0.86)	<0.0001
Transfusion 2-4 units of PRBC	223 (4.7)	312 (6.5)	0.71 (0.60-0.84)	<0.0001

Conclusions

- Among patients undergoing noncardiac surgery
  - TXA reduced risk of composite of life-threatening, major, and critical organ bleeding
  - although TXA had no significant effect on major vascular complications, non-inferiority was not established
  - our results also demonstrated 95.6% probability that primary safety outcome HR is <1.125

Implication

- Healthcare providers and patients will have to weigh
  - clear beneficial reduction in composite bleeding outcome
    - absolute difference, 2.7%; 95% CI, 1.5 to 3.9
  - low probability of small increase in risk of composite vascular outcome
    - absolute difference, 0.3%; 95% CI, -1.1 to 1.7

Implication

- Majority of patients having noncardiac surgery do not receive TXA
- Annual global shortage of 30 million blood product units
  - surgical bleeding accounts for upwards of 40% of all transfusions
- Given that 300 million surgeries occur worldwide annually
- POISE-3 identifies that use of TXA could avoid
  - upwards of 8 million bleeding events resulting in transfusion on annual basis
- Indicating potential for large public health and clinical benefit
  - if TXA becomes standard practice in noncardiac surgery

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Tranexamic Acid in Patients Undergoing Noncardiac Surgery

P.J. Devereaux, M. Marcucci, T.W. Painter, D. Conen, V. Lomivorotov, D.I. Sessler, M.T.V. Chan, F.K. Borges, M.J. Martínez-Zapata, C.-Y. Wang, D. Xavier, S.N. Ofori, M.K. Wang, S. Efremov, G. Landoni, Y.V. Kleinlugtenbelt, W. Szczeklik, D. Schmartz, A.X. Garg, T.G. Short, M. Wittmann, C.S. Meyhoff, M. Amir, D. Torres, A. Patel, E. Duceppe, K. Ruetzler, J.L. Parlow, V. Tandon, E. Fleischmann, C.A. Polanczyk, A. Lamy, S.V. Astrakov, M. Rao, W.K.K. Wu, K. Bhatt, M. de Nadal, V.V. Likhvantsev, P. Paniagua, H.J. Aguado, R.P. Whitlock, M.H. McGillion, M. Prystajecky, J. Vincent, J. Eikelboom, I. Copland, K. Balasubramanian, A. Turan, S.I. Bangdiwala, D. Stillo, P.L. Gross, T. Cafaro, P. Alfonsi, P.S. Roshanov, E.P. Belley-Côté, J. Spence, T. Richards, T. VanHelder, W. McIntyre, G. Guyatt, S. Yusuf, and K. Leslie, for the POISE-3 Investigators*