ACC.24

Topical Tranexamic Acid to Reduce Seizures in Cardiac Surgery

Dr. Andre Lamy on behalf of DEPOSITION Investigators
Population Health Research Institute
McMaster University, Hamilton, Canada

Canadian Institute of Health Research

Population Health Research Institute
HEALTH THROUGH KNOWLEDGE

AMERICAN COLLEGE of CARDIOLOGY

Disclosure

- None

Background

- Perioperative bleeding in cardiac surgery is associated with morbidity and mortality
- Intravenous antifibrinolytics are standard of care: tranexamic acid (TxA)
- Intravenous TxA increases the risk of seizure (neurotoxic)
- Seizure in ICU: stroke protocol alert

Problem

- Catch 22: Anesthesiologists decrease the dose of TxA to prevent seizures but at risk of more bleeding
- No standard dose: 1 to 10 grams
- Giving TxA directly on the source of bleeding (topical) has been tested in various type of surgery
- Promising alternative in our pilot study

Question

- In patients undergoing on-pump cardiac surgery, does topical tranexamic acid (intra-pericardial) compared to the usual intravenous tranexamic acid administration

  -reduce the risk of in-hospital seizure without increasing red blood cell transfusion?

Design

- Randomized controlled trial
- Double dummy to maintain blinding
- Sample size: 3800 patients
- Funding: Canadian Institute of Health Research

Eligibility criteria

- Included patients
  - ≥18 yrs undergoing cardiac surgery with cardiopulmonary bypass
  - Median sternotomy
- Excluded patients (too low or too high risk of bleeding)
  - Minimally invasive surgery or off-pump CABG
  - Bleeding disorder
  - eGFR <30 ml/min
  - Pre-operative hemoglobin >170 g/L or <110 g/L or thrombocytopenia (<50,000 platelets per µL)
  - Expected circulatory arrest
  - Active endocarditis

Intervention and Follow-up

- Patients randomized to receive
  - TxA 1-10 g IV bolus or placebo at start and during surgery
  - TxA 1-10 g topical or placebo at end of surgery (Protamine)

- Follow-up
  - until discharge or 10 days, whichever occurred first

Outcomes

- Primary outcome
  - Seizure
- Secondary outcome
  - Red blood cell transfusion
- Tertiary outcomes:
  - Blood products transfusion, MACE (death, MI, stroke), reoperation for bleeding or tamponade, ICU length of stay

Enrollment

- Second pre-specified interim analysis by DSMB (75%)
- DSMB recommended to stop the trial for safety
- Operations Committee reviewed the data and stop enrollment in the trial on November 28, 2023
- 3242 patients enrolled out of 3800

Baseline characteristics

	Topical TxA (N=1624)	Intravenous TxA (N=1618)
Age – (mean yrs)	66.3	65.7
Male	77%	78%
History of		
Myocardial infarction	38%	40%
Diabetes	30%	29%
Stroke	4%	4%
Seizure history	0.9%	0.4%
Elective surgery	65%	64%

Surgical characteristics

	Topical TxA (N=1624)	Intravenous TxA (N=1618)
CABG only	69%	70%
Valve only	13%	12%
Ascending aorta only	1%	1%
Mixed	16%	15%
CPB time (mins)	88.7	88.6
Cross-clamp time (mins)	66.2	66.0

Compliance and Follow-up

- In both TxA and placebo groups
  - 96.5% of patients received active treatment allocation
- Follow-up: 100% of participants completed

Primary outcome

	Topical TxA n=1624 no. (%)	Intravenous TxA n=1618 no. (%)	RR (95% CI)	P value
Seizure	4 (0.2)	11 (0.7)	0.36 (0.12-1.14)	0.07

- Fisher's exact test

Post Hoc Primary outcome

	Topical TxA n=1624 no. (%)	Intravenous TxA n=1618 no. (%)	RR (95% CI)	P Value
Seizure	4 (0.2)	11 (0.7)	0.36 (0.12-1.14)	0.07
Any seizure*	4 (0.2)	14 (0.9)	0.29 (0.09-0.86)	0.02

***patients with seizure and stroke were included**

Post Hoc Primary outcome

Stroke	Topical TxA n=22 no. (%)	Intravenous TxA n=12 no. (%)	RR (95% CI)	P value
Any seizure	0 (0)	3 (25%)	-	0.04

Post Hoc Primary outcome

	Close chambers n=2268 no. (%)	Open chambers n=940 no. (%)	RR (95% CI)	P value
Seizure	7 (0.3)	8 (0.9)	0.36 (0.13-0.99)	0.04
Any seizure	8 (0.4)	10 (1.1)	0.33 (0.13-0.84)	0.01

- Chi-square

Secondary outcome

	Topical TxA n=1624 no. (%)	Intravenous TxA n=1618 no. (%)	RR (95% CI)	P value
RBC transfusion	570 (35.1)	433 (26.8)	1.31 (1.18-1.46)	< 0.001

One-side value for non-inferiority P=0.007

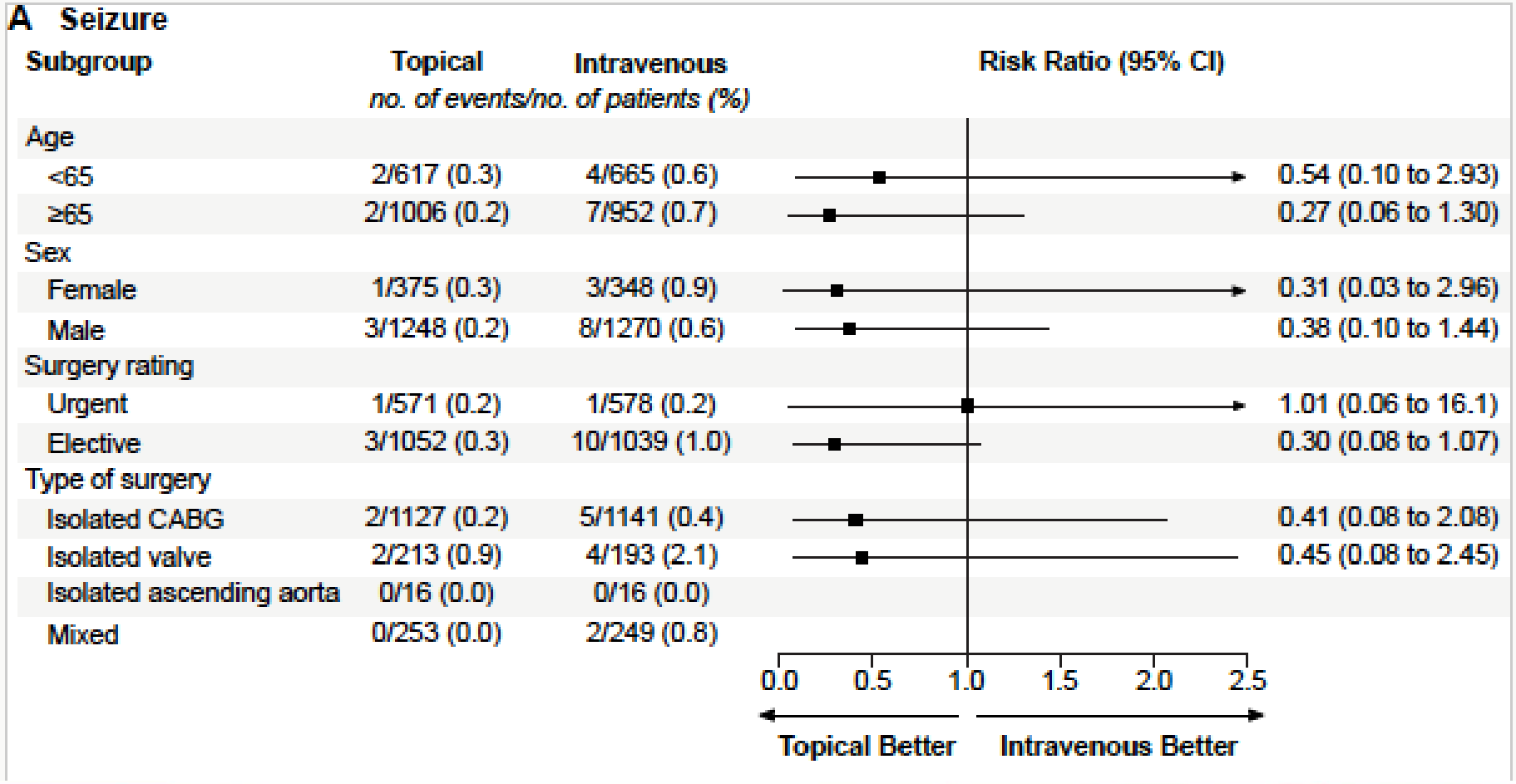
Tertiary outcomes

	Topical TxA n=1624 no. (%)	Intravenous TxA n=1618 no. (%)	RR (95% CI)
Any blood products	756 (46.6)	583 (36.0)	1.29 (1.19-1.40)
Re-op bleeding	63 (3.9)	46 (2.8)	1.37 (0.94-1.98)
ICU LOS (hr) –med	24	24	-
MACE	40 (2.5)	31 (1.9)	1.29 (0.81-2.04)

Intravenous dosage and Outcomes

Intravenous TxA n=1618	Group n=	Seizure no. (%)	Any Seizure no. (%)	RBC transfusion no. (%)
0 to 36mg/kg	612	5 (0.8)	5 (0.8)	164 (26.8)
36.1 to 60mg/kg	621	4 (0.6)	5 (0.8)	154 (24.8)
>60.1 mg/kg	355	2 (0.6)	4 (1.1)	110 (31.0)

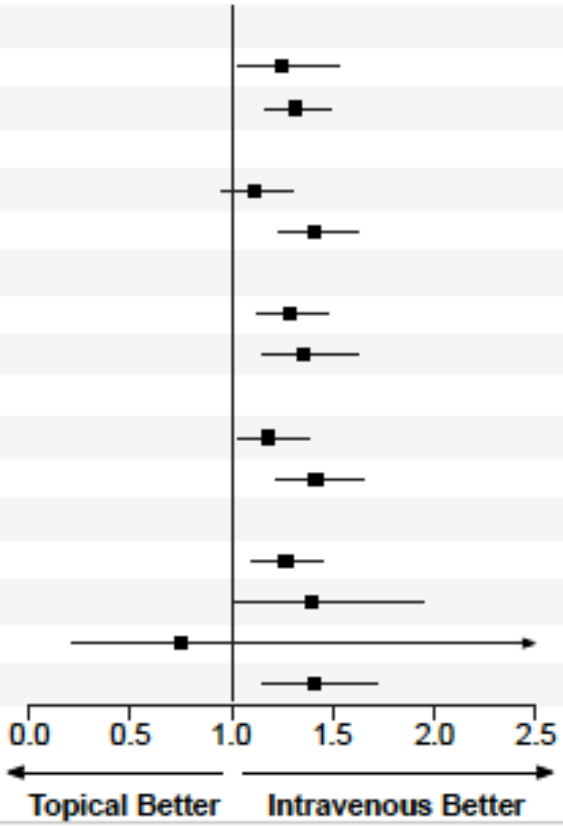
Subgroup Seizure



Subgroup RBC transfusion

B Red Blood Cell Transfusion

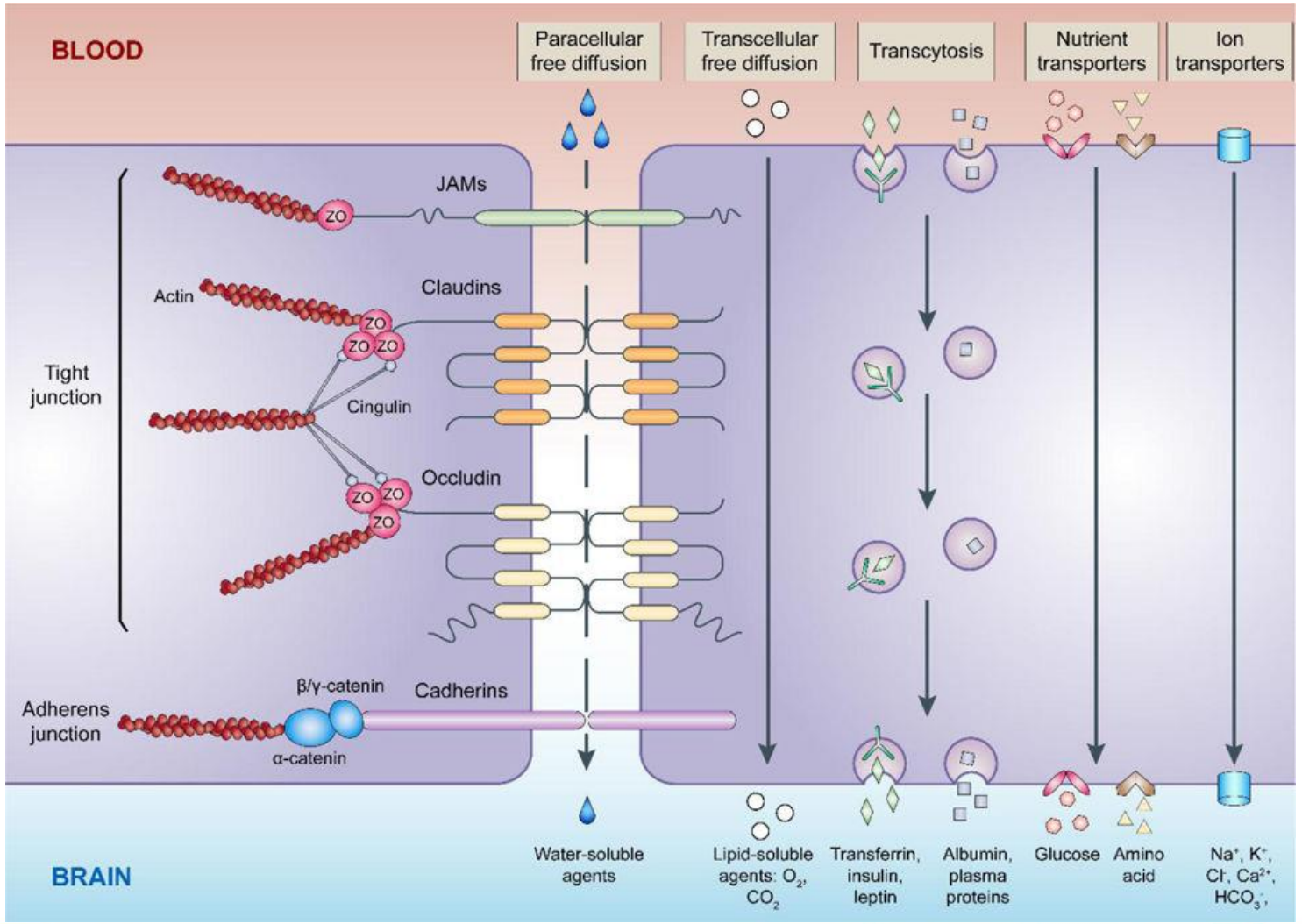
Subgroup	Topical	Intravenous	Risk Ratio (95% CI)
	no. of events/no. of patients (%)		
Age			
<65	168/617 (27.2)	145/665 (21.8)	1.25 (1.03 to 1.52)
≥65	402/1006 (40.0)	288/952 (30.3)	1.32 (1.17 to 1.49)
Sex			
Female	192/375 (51.2)	161/348 (46.3)	1.11 (0.95 to 1.29)
Male	378/1248 (30.3)	272/1270 (21.4)	1.41 (1.24 to 1.62)
Preoperative antiplatelet			
Yes	360/1060 (34.0)	277/1048 (26.4)	1.29 (1.13 to 1.47)
No	210/564 (37.2)	156/570 (27.4)	1.36 (1.15 to 1.62)
Surgery rating			
Urgent	237/571 (41.5)	201/578 (34.8)	1.19 (1.03 to 1.38)
Elective	333/1052 (31.7)	232/1039 (22.3)	1.42 (1.23 to1.64)
Type of surgery			
Isolated CABG	361/1127 (32.0)	288/1141 (25.2)	1.27 (1.11 to 1.45)
Isolated valve	68/213 (31.9)	44/193 (22.8)	1.40 (1.01 to 1.94)
Isolated ascending aorta	3/16 (18.8)	4/16 (25.0)	0.75 (0.20 to 2.83)
Mixed	136/253 (53.8)	95/249 (38.2)	1.41 (1.16 to 1.71)



Conclusions of our trial

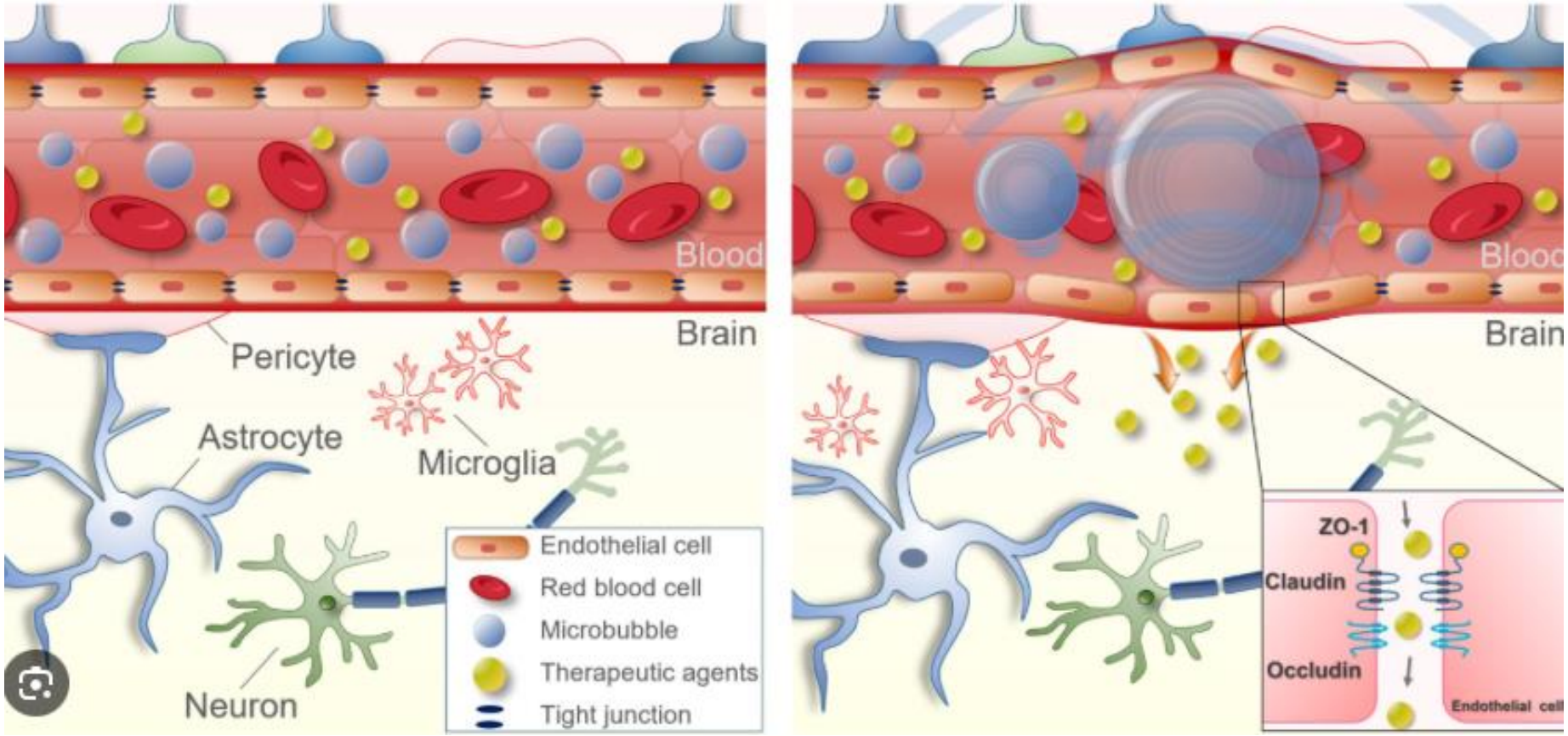
- Topical TxA does not reduce risk of seizure
- Topical TxA increases the risk of transfusion

How does TxA cross the blood-brain barrier?



Jiang X, et al. Prog Neurobiol. 2018

Micro-bubbles and Focused ultrasound



Further hypotheses

- Mechanism of seizure is more complex
  - Not likely related to dose of IV TxA
  - Probably mediated by air embolism or debris
  - Presence or absence of TxA at the time of embolism (X-clamp) could be the mechanism to reduce seizure: timing
  - Need for clinically available tests to measure TxA levels and fibrinolysis to improve bleeding

Circulation

- Circulation. 2024; [published online ahead of print]. DOI: 10.1161/CIRCULATIONAHA.124.069606

• Topical Versus Intravenous Tranexamic Acid in Patients Undergoing Cardiac Surgery: The DEPOSITION Randomized Controlled Trial

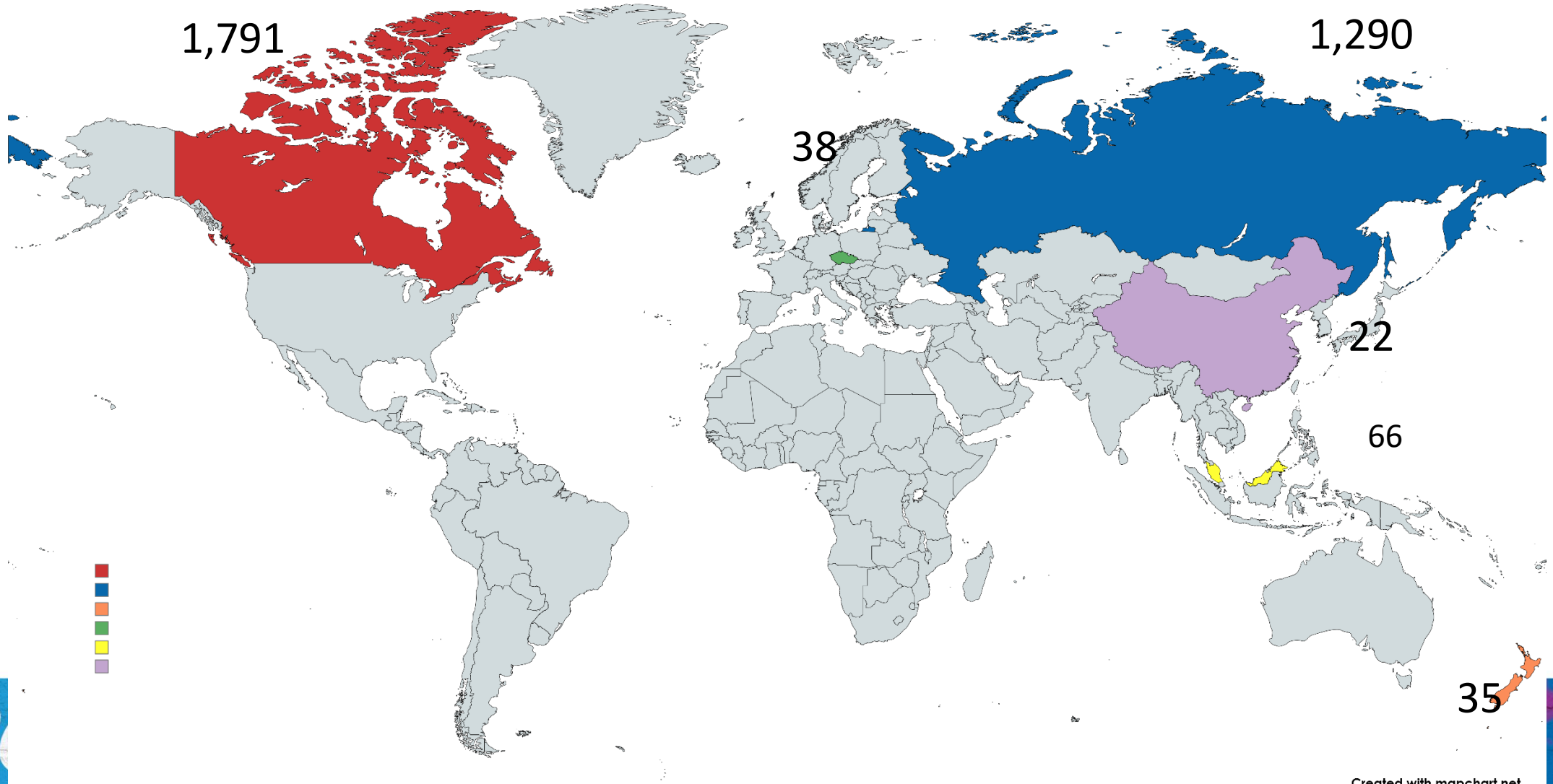
• Andre Lamy, MD,MHSc; Dmitry A. Sirota, MD, PhD; Frederic Jacques, MD, MSc; Ahmad Poostizadeh, MD; Nicolas Noiseux, MD, PhD; Sergey Efremov, MD, PhD; Philippe Demers, MD; Boris Akselrod MD, PhD; Chew Yin Wang, MBChB; Rakesh C. Arora MD, PhD; Piotr Branny, MD; Shay P. McGuinness, MBChB; Craig D. Brown, MD; Hugues Jeanmart, MD; Qiang Zhao, MD; Haibo Zhang, MD, PhD; Emilie P. Belley-Côté, MD, PhD; Richard P. Whitlock, MD, PhD; Austin Browne, MSc, PhD; Ingrid Copland, CCRA; Jessica Vincent, MSc; Rutaba Khatun, MSc; Kumar Balasubramanian, MSc; Shrikant I. Bangdiwala, PhD; Michael H. McGillion, RN, PhD; Alison E. Fox-Robichaud, MD; Jessica Spence, MD, PhD; Salim Yusuf, MD, Dphil; and P.J. Devereaux, MD, PhD for the DEPOSITION Study Group

• ***Circulation***

• https://www.ahajournals.org/DOI: 10.1161/CIRCULATIONAHA.124.069606

- Thank you.

3242 patients randomized
16 centres in 6 countries



Glycine receptors

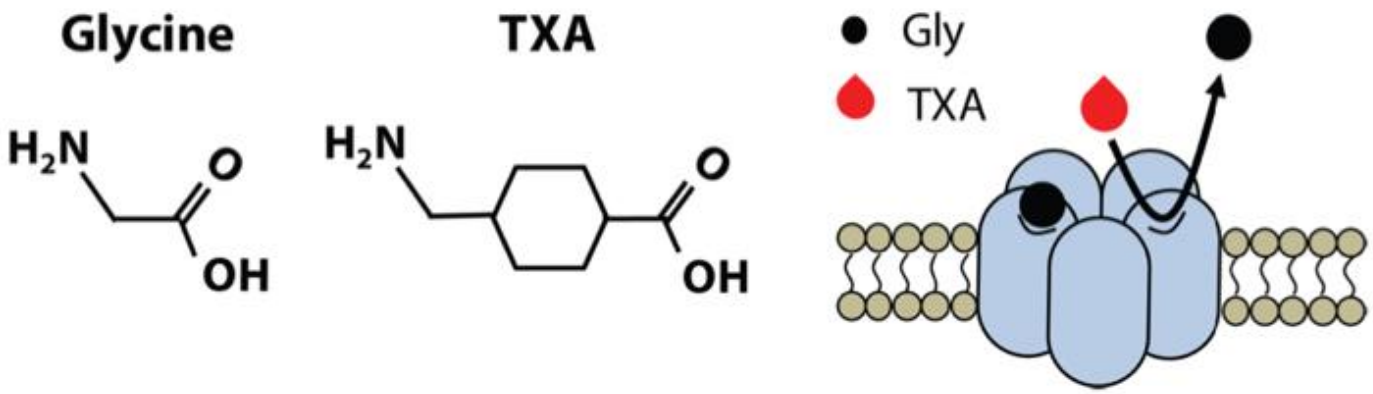
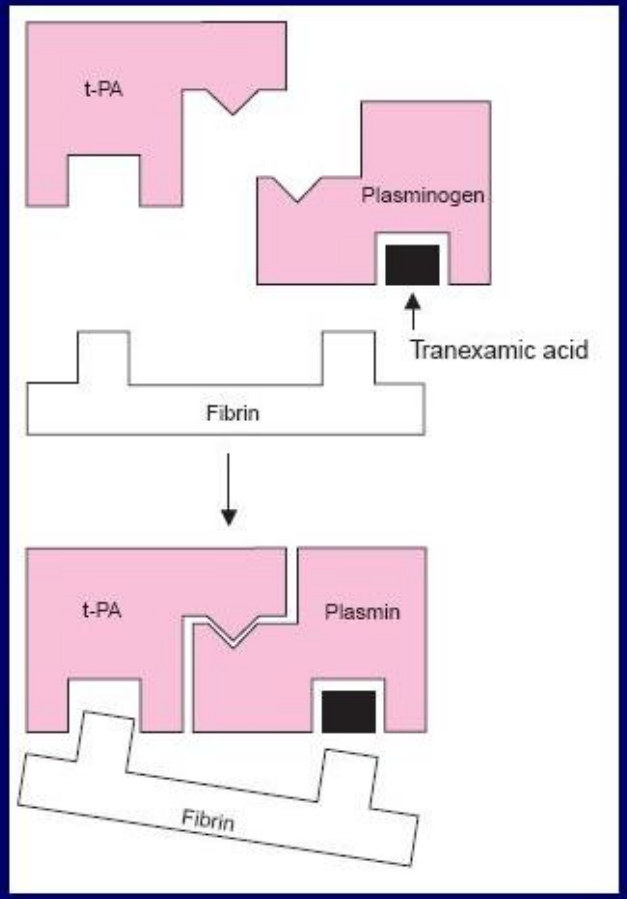


Figure 2.4 TXA is a competitive antagonist of glycine receptors.

Glycine and TXA are structural analogues suggesting that TXA competes for the glycine binding site of the glycine receptor.

Tranexamic acid and bleeding



- **Tranexamic Acid (TXA)** is a synthetic derivative of the amino acid lysine.
  - It has a very high affinity for the lysine binding sites of plasminogen.
  - It blocks these sites and prevents binding of plasmin to the fibrin surface, thus exerting its antifibrinolytic effect.

Statistics

- Primary outcome hypothesis
  - Topical TXA superior to IV TXA for seizure
  - Fisher's exact test with 2-sided P <0.05
- Secondary outcome hypothesis
  - Topical TXA noninferior to IV TXA for red blood cell transfusion
    - upper bound of 1-sided 97.5% CI for HR needed to fall below 1.15
    - 1-sided P <0.025

Post Hoc Tertiary outcome

* Controlled for bleeding

Dialysis	(1.26-7.88)