第49回日本集中治療医学会学術集会 （2022年）

外傷患者へのトラネキサム酸

日本の救急隊員はいかにして人命を救うか

Professor Ian Roberts
Honorary Consultant Royal London Hospital
Director, LSHTM Clinical Trials Unit, University of London

No conflicts of interest

I have no financial conflicts of interest

I receive a salary from the University and from the NHS


FamilyMart
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川崎市消防局
KAWASAKI CITY F.D.
POLICE

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28 May 2019

Prime Minister Shinzō Abe
2-3-1 Nagata-cho,
Chiyoda-ku 100-8968
Tokyo, Japan

Dear Prime Minister Abe

I was saddened to hear about the stabbings today in Kawasaki. My wife is Japanese and the stabbing took place in her home town, in the school she attended as a child. The headmaster who acted so bravely to save the children in his care is a family friend. The purpose of this letter is to raise with you a serious concern about the emergency care of bleeding trauma victims in Japan.

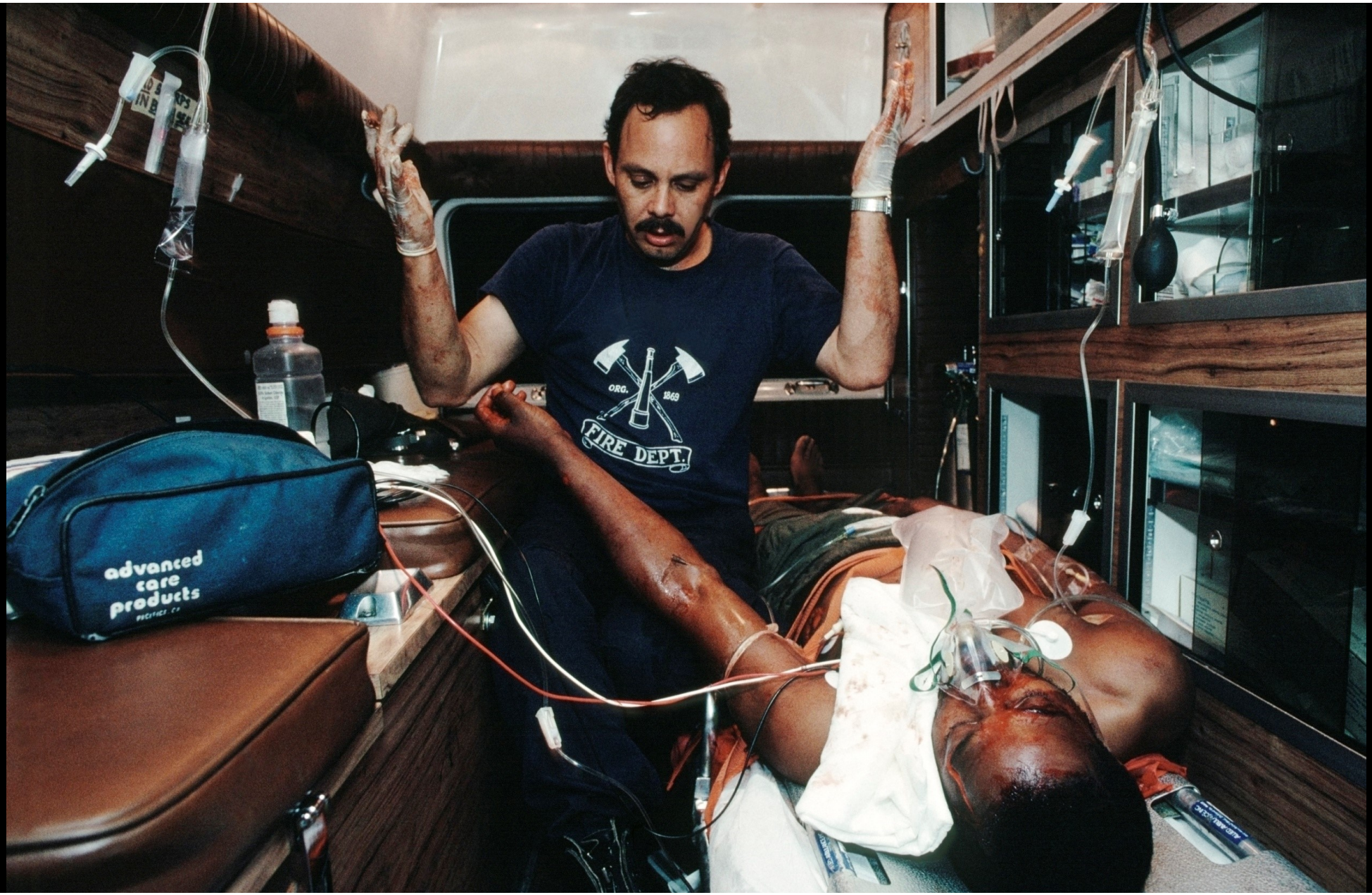
Tranexamic acid is a drug that safely reduces bleeding. It was invented by the Japanese scientists Shosuke and Utako Okamoto in the 1960s. It was mainly used for minor bleeding until 2010 when a large international clinical trial conducted by my team at the London School of Hygiene & Tropical Medicine showed that early administration of tranexamic acid to bleeding trauma victims reduces the risk of bleeding to death by a third. We also showed that treatment is most effective when given soon after injury. For this reason, in the UK, tranexamic acid is given by paramedics at the scene of the injury. **This is not the situation in Japan where Ministry of Health rules do not allow paramedics to give tranexamic acid.** This is regrettable since tranexamic acid is the only drug proven to reduce mortality in bleeding trauma victims.

I have been working with Japanese medical colleagues to make the Japanese Ministry of Health aware of the scientific evidence of the lifesaving benefits of tranexamic acid so that they can change this policy but so far with little success. If any good can come from the awful tragedy today in Kawasaki, it would be a review of the Ministry of Health rules that prevent tranexamic acid being used to save lives in situations like this.

I would be grateful if you could bring this matter to the attention of the appropriate authorities.

Yours sincerely

Professor of Epidemiology and Public Health
Co-Director, LSHTM Clinical Trials Unit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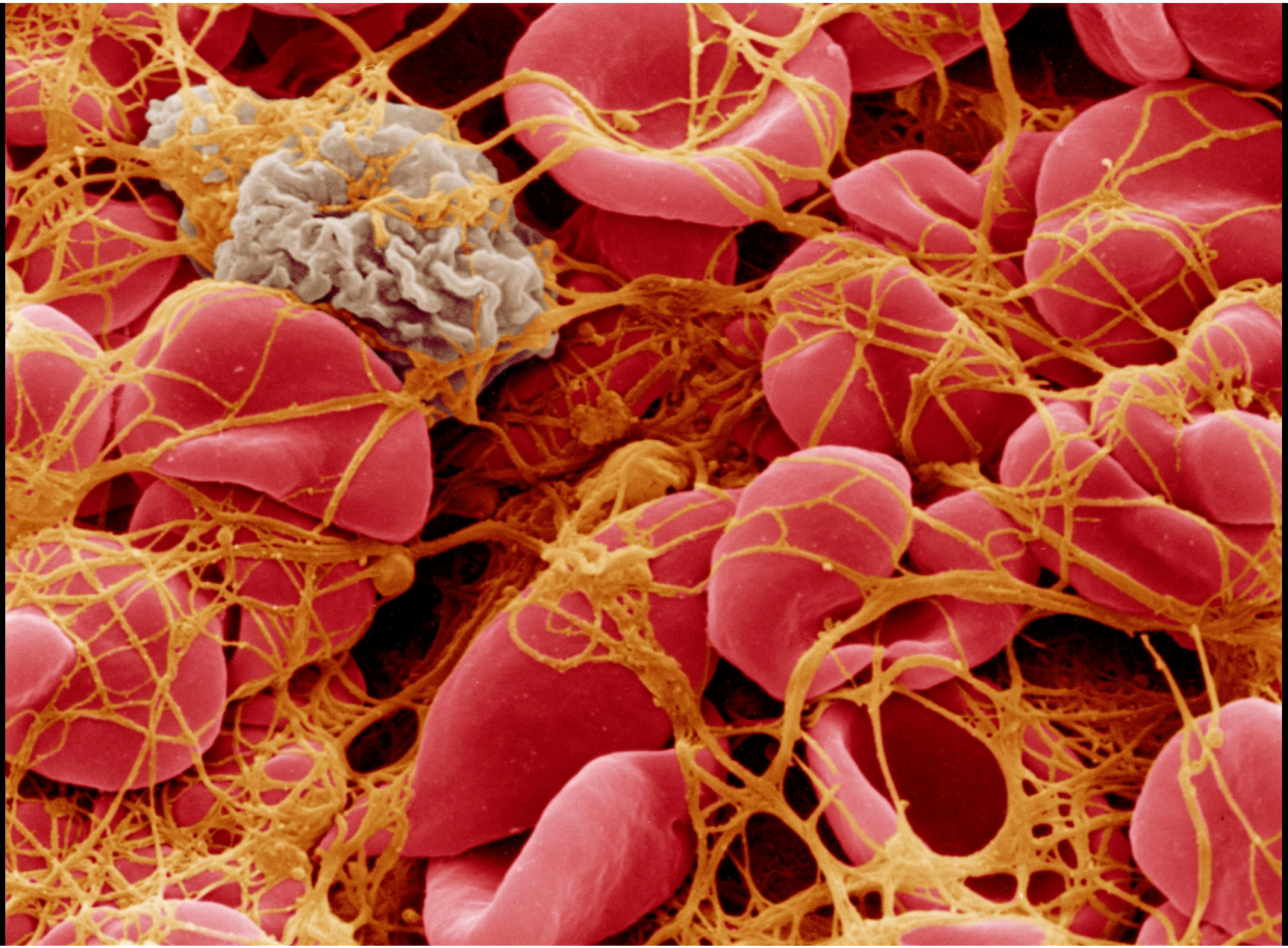
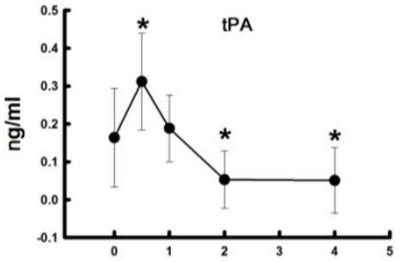
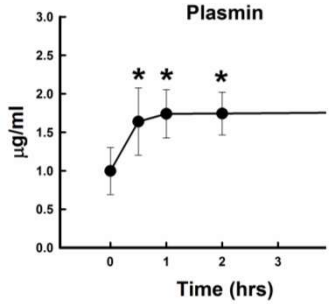
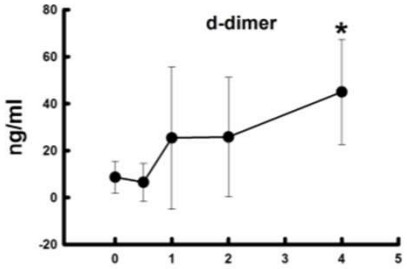


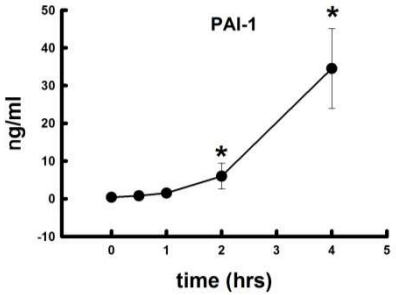


t-PAは外傷直後に放出される



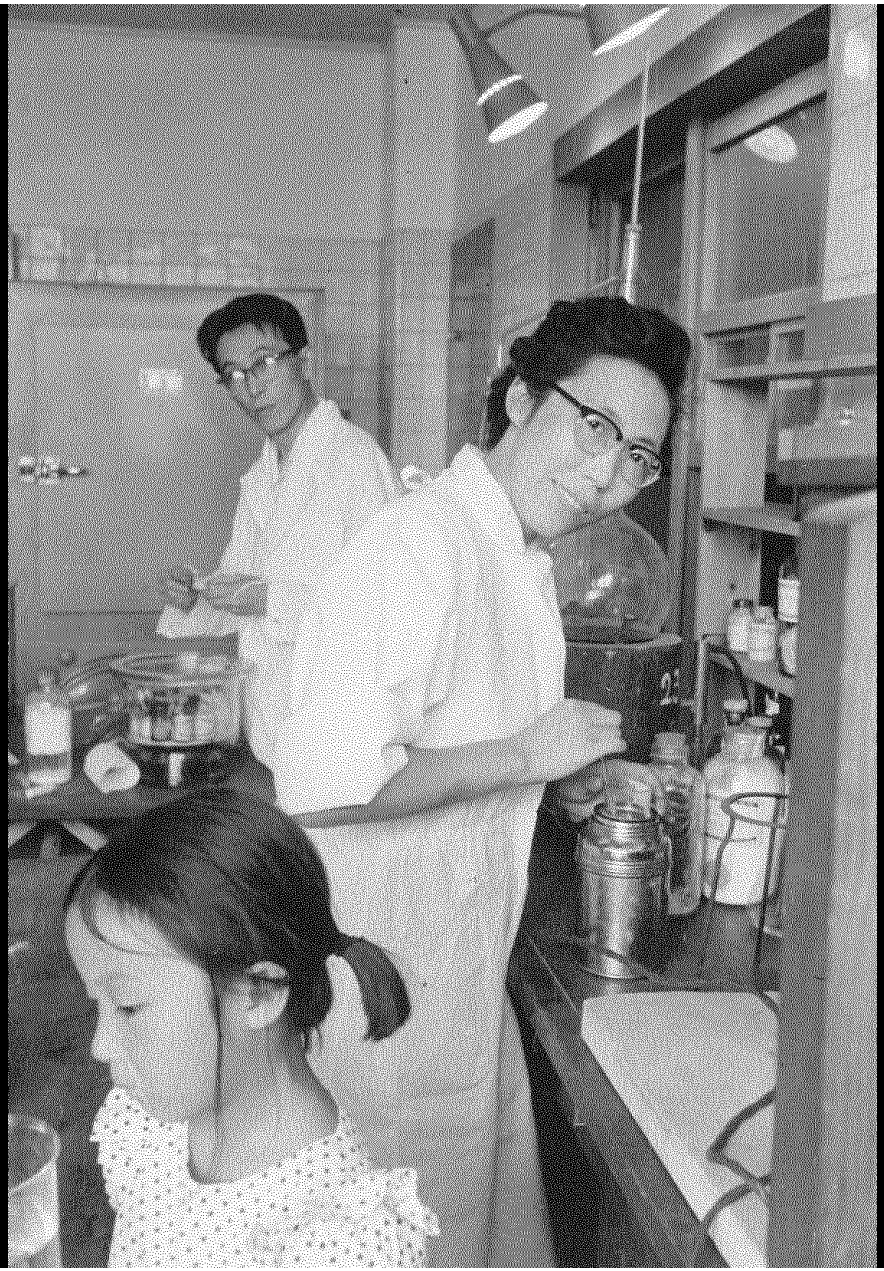


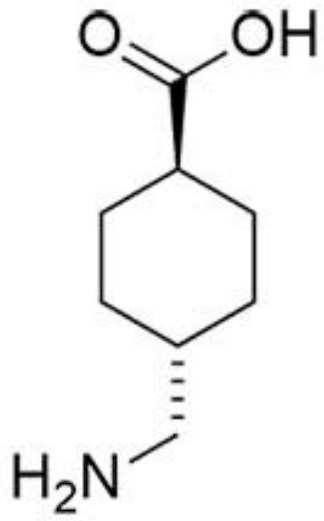
プラスミン活性化と繊維素溶解



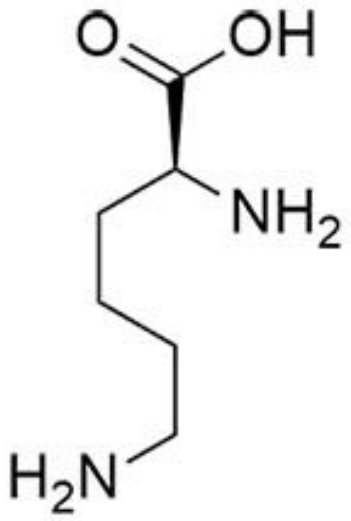
PAI-1は遅れて増加する

Wu X, Darlington D, Cap A. Procoagulant and Fibrinolytic Activity after Polytrauma in Rat.
Am J Physiol Regul Integr Comp Physiol (December 2, 2015). doi:10.1152/ajpregu.00401.2015.





Tranexamic acid



Lysine

トラネキサム酸は手術出血を減少させる

トラネキサム酸は手術部位がどこであれ
手術出血を1/3減らし、血栓性の副作用
を増加させない。

（10万人を超える患者でのランダム試験）

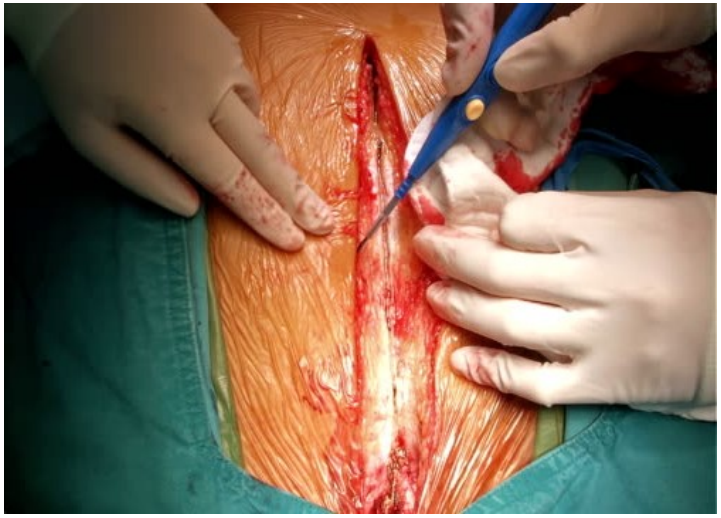
The NEW ENGLAND JOURNAL of MEDICINE

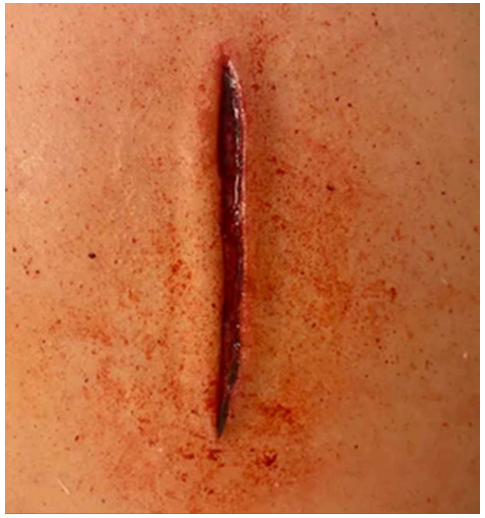
ORIGINAL ARTICLE

冠動脈手術患者におけるトラネキサム酸

Outcome	TXA N=2311	Placebo N=2320	RR (95%CI)	P value
Death	26 (1.1%)	33 (1.4%)	0.79 (0.47-1.32)	0.34
Re-operation	18 (0.8%)	50 (2.2%)	0.36 (0.21–0.62)	<0.001
Transfusion	876 (37.9)	1269 (54.7)		<0.001
MI	269 (11.6)	300 (12.9)	0.90 (0.77–1.05)	0.19
Stroke	32 (1.4)	35 (1.5)	0.92 (0.57–1.48)	0.81
PE	15 (0.6)	15 (0.6)	1.00 (0.49–2.05)	>0.99

外傷性出血と手術性出血は似ている





大出血における抗プラスミン剤の効果についての臨床的ランダム試験

トラネキサム酸は出血だけでなくすべての原因での死亡を減少させる

Bleeding deaths	TXA	Placebo	RR (95%CI)	P value
<1 hour	198 (5.3%)	286 (7.7%)	0.68 (0.57–0.82)	<0.001
1-3 hours	147 (4.8%)	184 (6.1%)	0.79 (0.64-0.97)	0.03

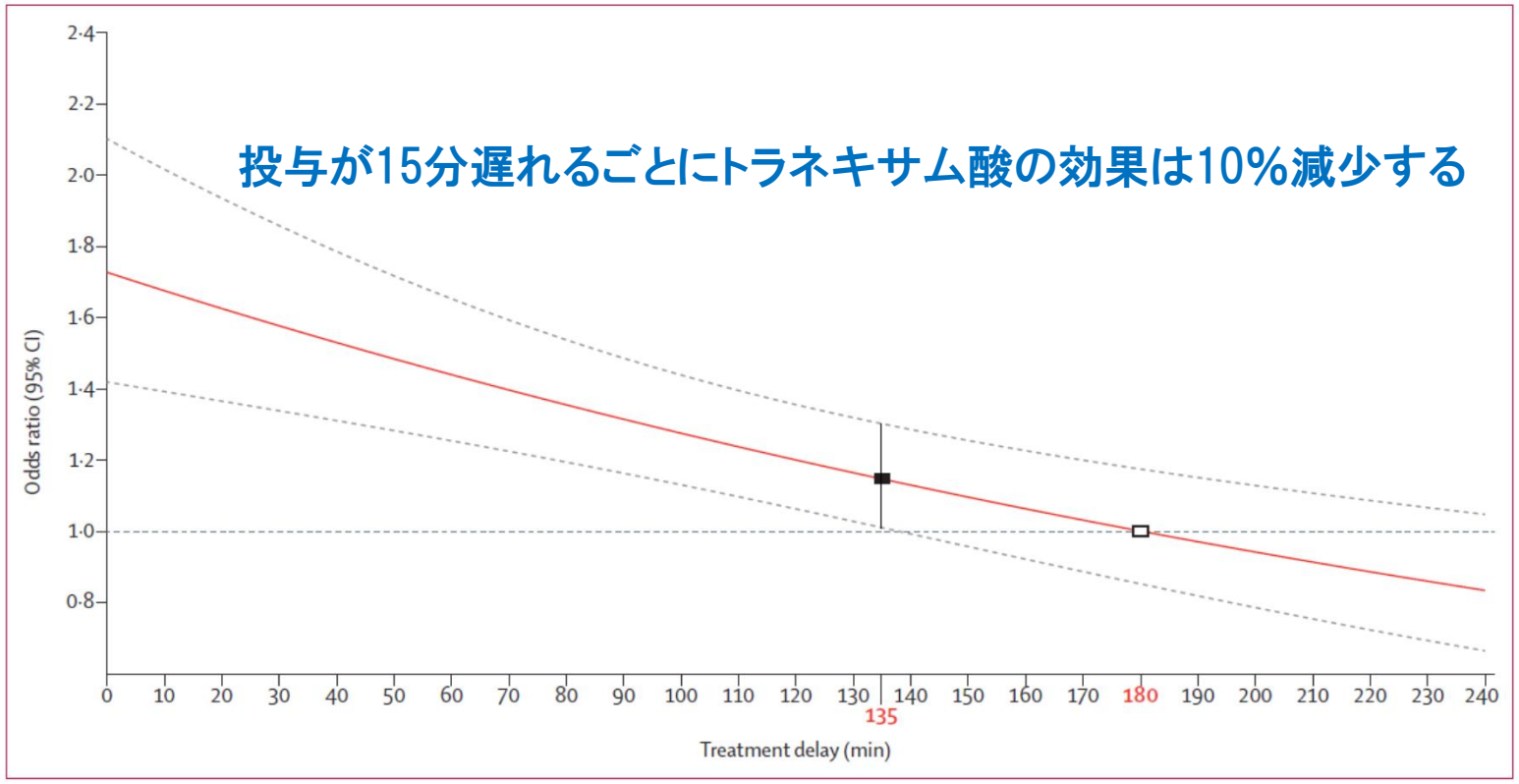
受傷後3時間以内に投与されたトラネキサム酸による致死的および非致死的血流閉塞

Thrombotic events	TXA [n = 6784]	Placebo [n = 6700]	RR (95% CI)	p-value
Any event	98 (1·4%)	141 (2·1%)	0·69 (0·53 – 0·89)	0·004
Any arterial event	47 (0·7%)	81 (1·2%)	0.57 (0·40– 0·82)	0.002
Myocardial infarction	*23 (0·3%)*	*47 (0·7%)*	*0·48 (0·29 – 0·79)*	*0·003*
Stroke	*28 (0·4%)*	*40 (0·6%)*	*0·69 (0·42 – 1·12)*	*0·13*
Any venous event	60 (0·9%)	71 (1·1%)	0.83 (0·59– 1·17)	0.30
Pulmonary embolism	*42 (0·6%)*	*47 (0·7%)*	*0·88 (0·58 – 1·34)*	*0·56*
Deep vein thrombosis	*25 (0·4%)*	*28 (0·4%)*	*0·88 (0·51 – 1·51)*	*0·65*

母体への抗プラスミン剤投与についての世界的検討

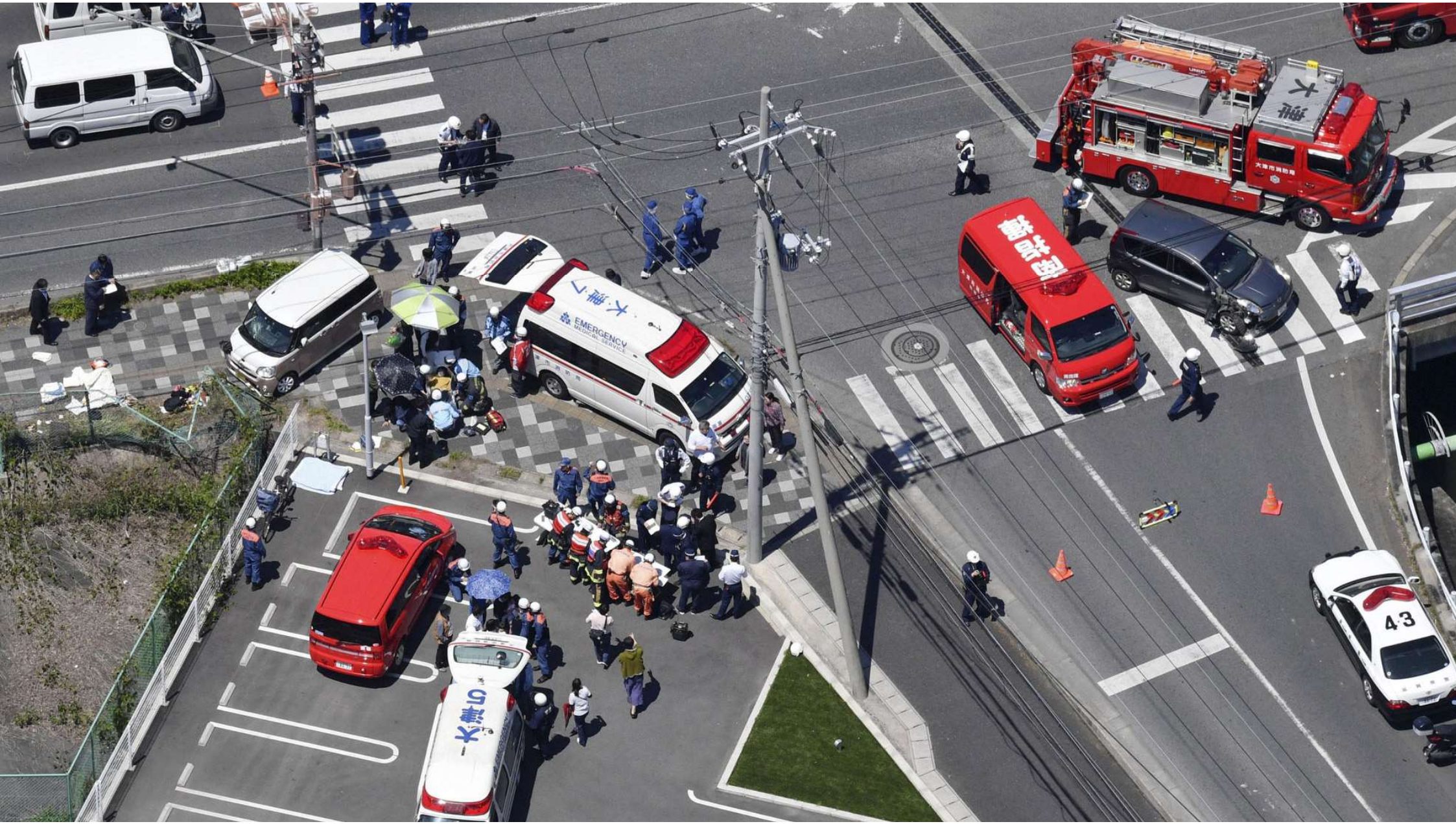
WOMAN Trial Collaborators

早期投与が必須である


投与が15分遅れるごとにトラネキサム酸の効果は10%減少する
Odds ratio (95% CI)
2·4
2·2
2·0
1·8
1·6
1·4
1·2
1·0
0·8
0 10 20 30 40 50 60 70 80 90 100 110 120 130 135 140 150 160 170 180 190 200 210 220 230 240
Treatment delay (min)

Κλεψύδρα (**clepsydra or water clock)**

5th Century BC (2500 years ago)


救急
EMERGENCY
MEDICAL SERVICE
救急
救急
指揮車
43

TARN
THE TRAUMA AUDIT & RESEARCH NETWORK

2017年～2018年

トラネキサム酸投与までの時間（中央値）

病院到着前＝48 分

病院到着後＝148分

事故の犠牲者はたった1回の注射で
数分の内に救命された

Accident victims could be saved in minutes with one simple injection

Kat Lay Health Correspondent

Thousands of lives could be saved each year by giving patients a simple injection to prevent severe bleeding at the scene of accidents, a study has found.

A cheap, widely available drug called tranexamic acid (TXA) encourages the blood to clot and can reduce deaths of injury victims by up to a third when given within an hour. Each 15 minute delay reduces its lifesaving potential by 10 per cent and at present only 3 per cent of trauma victims in the UK get it within the one-hour window.

The study, published in the *British Journal of Anaesthesia*, showed that TXA could be given as a simple intramuscular injection, in the same way as a flujab, rather than via the more complicated intravenous line that is standard.

"Intramuscular TXA is like a vaccine against trauma death," said Dr Ian Roberts, from the London School of Hygiene and Tropical Medicine, who led the study. "An urgent injection of TXA is life-saving after serious injury, but patients are not being treated fast enough. A rapid intramuscular injection given by first responders or paramedics could mean the difference between life and death."

The drug is rapidly absorbed from muscles into the blood, and there were no local side-effects other than some redness and swelling. "I think we can start using it this way immediately," said Dr Roberts.

"If you could just get to the scene of an injury — somebody lying on the floor by the road, or at the foot of a ladder — you just do the basics, sort out airway, breathing, and then you could very quickly give an injection of the intramuscular dose of tranexamic acid, and it's absorbed into the blood so quickly that you get therapeutic effect really, really quickly.

"At the moment in the NHS tranexamic acid is used but patients aren't getting it quick enough. It's most effective when given within an hour of injury, and the hours just disappear so quickly. It takes time for the ambulance to arrive, time for paramedics to orientate themselves to what's going on. It takes a little time to put in an intravenous line — sometimes they just say, well, let's leave that for the hospital.

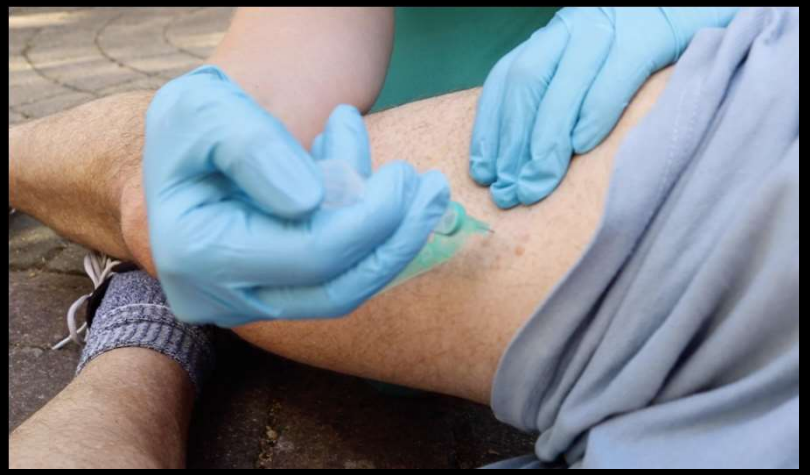
"This way, you can just inject it intramuscularly and forget about it."

The study involved 30 bleeding trauma patients at London hospitals, who were given their first dose of TXA intravenously but the second via intramuscular injection.

Tests showed that TXA was rapidly absorbed from muscle and reached the necessary level to save lives within 15 minutes in all patients.

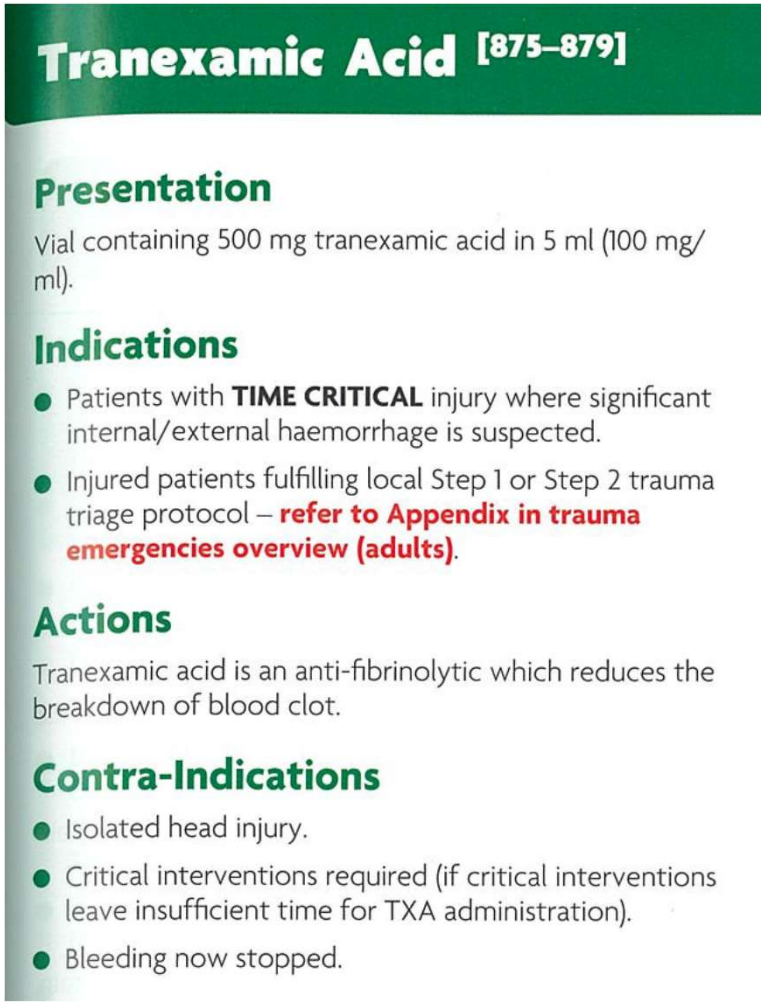
Dr Roberts said that the finding was particularly useful for low and middle-income countries, where first responders are least likely to be able to give intravenous injections. More than 90 per cent of trauma deaths occur in those countries, and up to 80 per cent before the patient arrives at hospital.

The research team is also working with the British military on an Epipen-style autoinjector that could be used on the battlefield. Dr Roberts said the intramuscular injection could be "a game-changer" for a variety of trauma victims. "A simple auto injector device that could be used by lay first responders or police officers — before the ambulance arrives — could save thousands of lives each year," he said. "It could also be used by wounded soldiers either on themselves or a buddy."



トラネキサム酸は単独頭部外傷以外の外傷の治療のガイドラインに載せられた

しかし、なぜ単独頭部外傷を除外するのか？



Tranexamic Acid [875–879]

Presentation

Vial containing 500 mg tranexamic acid in 5 ml (100 mg/ml).

Indications

- Patients with **TIME CRITICAL** injury where significant internal/external haemorrhage is suspected.
- Injured patients fulfilling local Step 1 or Step 2 trauma triage protocol – **refer to Appendix in trauma emergencies overview (adults)**.

Actions

Tranexamic acid is an anti-fibrinolytic which reduces the breakdown of blood clot.

Contra-Indications

- Isolated head injury.
- Critical interventions required (if critical interventions leave insufficient time for TXA administration).
- Bleeding now stopped.

単独頭部外傷におけるトラネキサム酸の効果

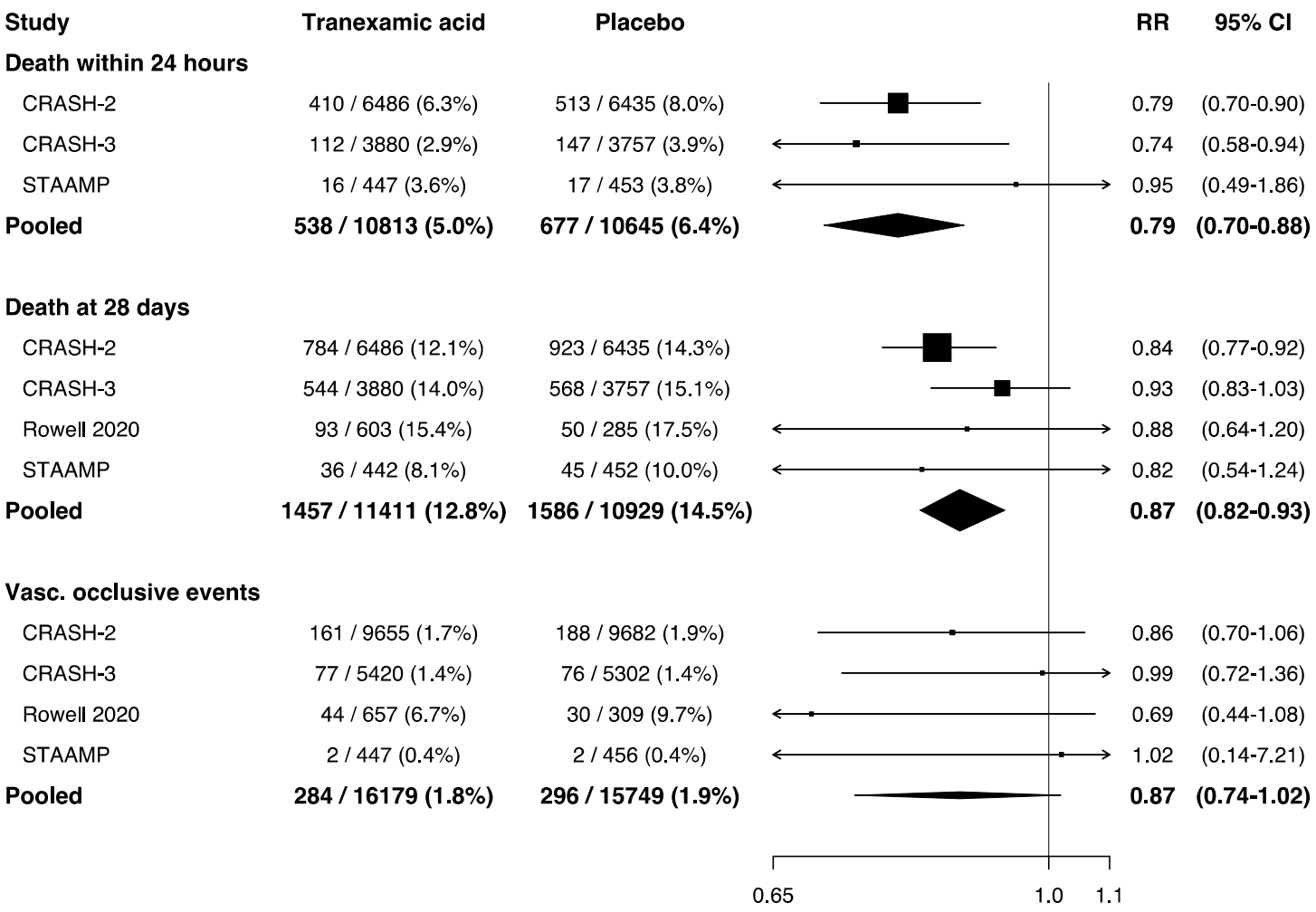
24時間以内および28日以内のすべての原因の死亡に対するトラネキサム酸の効果

＜ベースライン＞到着時にGCS3または両側の対光反射がない患者を除く

	Deaths in TXA group (%)	Deaths in placebo group (%)	Risk ratio (95% CI)
Death within 24 hours			
CRASH-2	6.3	8.0	0.79 (0.70-0.90)
CRASH-3	2.9	3.9	0.74 (0.58-0.94)
Combined	**5.0**	**6.5**	**0.78 (0.70-0.87)**
Death within 28 days			
CRASH-2	12.1	14.3	0.84 (0.77-0.92)
CRASH-3	14.0	15.1	0.93 (0.83-1.03)
Combined	**12.8**	**14.6**	**0.88 (0.82-0.94)**

リスク比が1未満であれば、TXA群での死亡が少ないことを意味する

24時間以内および28日以内のすべての原因の死亡に対するトラネキサム酸の効果



出血患者における血栓性事象と痙攣に対するトラネキサム酸の効果;系統的レビューとメタアナリシス

Murao et al. Crit Care (2021) 25:380
https://doi.org/10.1186/s13054-021-03799-9

Critical Care

RESEARCH Open Access

Effect of tranexamic acid on thrombotic events and seizures in bleeding patients: a systematic review and meta-analysis

Shuhei Murao[1], Hidekazu Nakata[2], Ian Roberts[3] and Kazuma Yamakawa[4*]

Abstract

Background: Tranexamic acid (TXA) reduces surgical bleeding and reduces death from bleeding after trauma and childbirth. However, its effects on thrombotic events and seizures are less clear. We conducted a systematic review and meta-analysis to examine the safety of TXA in bleeding patients.

Methods: For this systematic review and meta-analysis, we searched MEDLINE, EMBASE and the Cochrane Central Register of Controlled trials from inception until June 1, 2020. We included randomized trials comparing intravenous tranexamic acid and placebo or no intervention in bleeding patients. The primary outcomes were thrombotic events, venous thromboembolism, acute coronary syndrome, stroke and seizures. A meta-analysis was performed using a random effects model and meta-regression analysis was performed to evaluate how effects vary by dose. We assessed the certainty of evidence using the grading of recommendations, assessment, development and evaluations (GRADE) approach.

Results: A total of 234 studies with 102,681 patients were included in the meta-analysis. In bleeding patients, there was no evidence that TXA increased the risk of thrombotic events (RR = 1.00 [95% CI 0.93–1.08]), seizures (1.18 [0.91–1.53]), venous thromboembolism (1.04 [0.92–1.17]), acute coronary syndrome (0.88 [0.78–1.00]) or stroke (1.12 [0.98–1.27]). In a dose-by-dose sensitivity analysis, seizures were increased in patients receiving more than 2 g/day of TXA (3.05 [1.01–9.20]). Meta-regression showed an increased risk of seizures with increased dose of TXA ($p = 0.011$).

Conclusion: Tranexamic acid did not appear to increase the risk of thrombotic events in bleeding patients. However, because there may be dose-dependent increase in the risk of seizures, very high doses should be avoided.

Keywords: Tranexamic acid, Bleeding, Surgery, Thrombotic events, Seizure, Meta-analysis

トラネキサム酸は、大量出血が明らかな時だけでなく、
疑われるだけのときにも投与されるべきである

BJA

British Journal of Anaesthesia, 124 (6): 676–683 (2020)

doi: 10.1016/j.bja.2020.01.020
Advance Access Publication Date: 19 March 2020
Cardiovascular

CARDIOVASCULAR

Effect of tranexamic acid by baseline risk of death in acute bleeding patients: a meta-analysis of individual patient-level data from 28 333 patients

Francois-Xavier Ageron[1,2,*], Angele Gayet-Ageron[3], Katharine Ker[1], Timothy J. Coats[4], Haleema Shakur-Still[1] and Ian Roberts[1], for the Antifibrinolytics Trials Collaboration[†]

[1]Clinical Trials Unit, London School of Hygiene and Tropical Medicine, London, UK, [2]Emergency Department, Lausanne University Hospital, CHUV, Lausanne, Switzerland, [3]Division of Clinical Epidemiology, University Hospitals of Geneva, Geneva, Switzerland and [4]Emergency Medicine, University of Leicester, Leicester, UK

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[†]The members of the Antifibrinolytics Trials Collaboration are listed in the Acknowledgments section.

This article is accompanied by an editorial: Tranexamic acid: the king is dead, long live the king! by Lier & Shander, Br J Anaesth 2020:124:659–662, doi: 10.1016/j.bja.2020.02.015

Abstract

Background: Early administration of the antifibrinolytic drug tranexamic acid reduces death from bleeding in trauma and postpartum haemorrhage. We examined how the effectiveness and safety of antifibrinolytic drugs varies by the baseline risk of death as a result of bleeding.

Methods: We performed an individual patient-level data meta-analysis of randomised trials including more than 1000 patients that assessed antifibrinolytics in acute severe bleeding. We identified trials performed between January 1, 1946 and July 5, 2018 (PROSPERO, number 42016052155).

Results: Two randomised trials were selected where 28 333 patients received tranexamic acid treatment within 3 h after the onset of acute bleeding. Baseline characteristics to estimate the risk of death as a result of bleeding were divided into four categories: Low (0–5%), intermediate (6–10%), high (11–20%), and very high (>20%). Most patients had a low baseline risk of death as a result of bleeding (23 008 [81%]). Deaths as a result of bleeding occurred in all baseline risk categories with 240 (1%), 202 (8%), 232 (14%), and 357 (30%) deaths in the low-, intermediate-, high-, and very high-risk categories, respectively. The effectiveness of tranexamic acid did not vary by baseline risk when given within 3 h after bleeding onset ($P=0.51$ for interaction term). There was no increased risk of vascular occlusive events with tranexamic acid and it did not vary by baseline risk categories ($P=0.25$).

Conclusions: Tranexamic acid appears to be safe and effective regardless of baseline risk of death. Because many deaths are in patients at low and intermediate risk, tranexamic acid use should not be restricted to the most severely injured or bleeding patients.

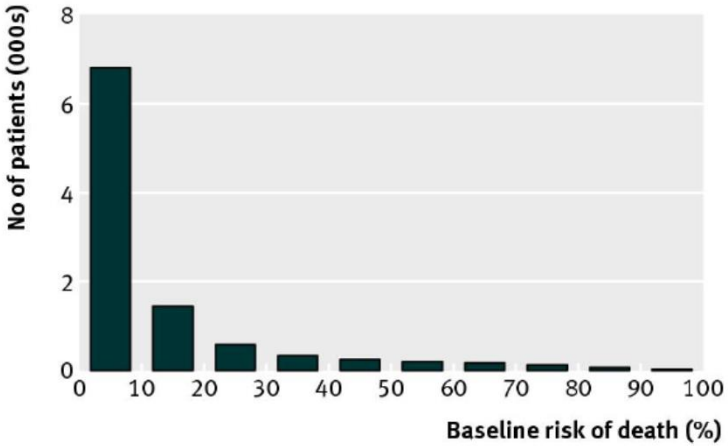
Keywords: antifibrinolytics; bleeding; coagulopathy; mortality; postpartum haemorrhage; trauma

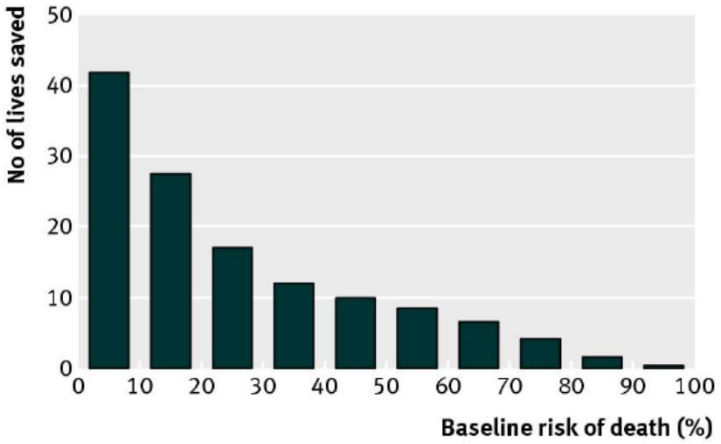
28,000人の出血患者のランダム化試験データにおいて、トラネキサム酸は出血の深刻度にかかわらず安全で効果的であった。

出血による死亡患者の1/4は、出血による死亡の可能性が低いように見えた患者である。

したがって、出血が疑われるだけの患者にも投与するべきである。

出血が明白な患者に限定せず、
全ての外傷患者にトラネキサム酸を投与しよう。






AMBULANCE

明白な治療指針を無視してはいけない

Ageron *et al. Scandinavian Journal of Trauma, Resuscitation and Emergency Medicine* (2021) 29:6
https://doi.org/10.1186/s13049-020-00827-5

Scandinavian Journal of Trauma, Resuscitation and Emergency Medicine

ORIGINAL RESEARCH Open Access

Validation of the BATT score for prehospital risk stratification of traumatic haemorrhagic death: usefulness for tranexamic acid treatment criteria

Francois-Xavier Ageron[1,2*], Timothy J. Coats[3], Vincent Darioli[2] and Ian Roberts[1]

Faculté de biologie et médecine, Service des urgences (URG), UNIL-CHUV, Lausanne

解決法は、EpiPenのエピネフリンのように、外傷患者に迅速に投与できるようにし、出血を減らし、より多くの命を救えるようにしなければならない

Faster Delivery

=

Less Bleeding

=

More Lives Saved