



Tranexamic acid in Major orthopaedic surgery

V.Ramesh

Consultant Anaesthetist

Royal National Orthopaedic Hospital

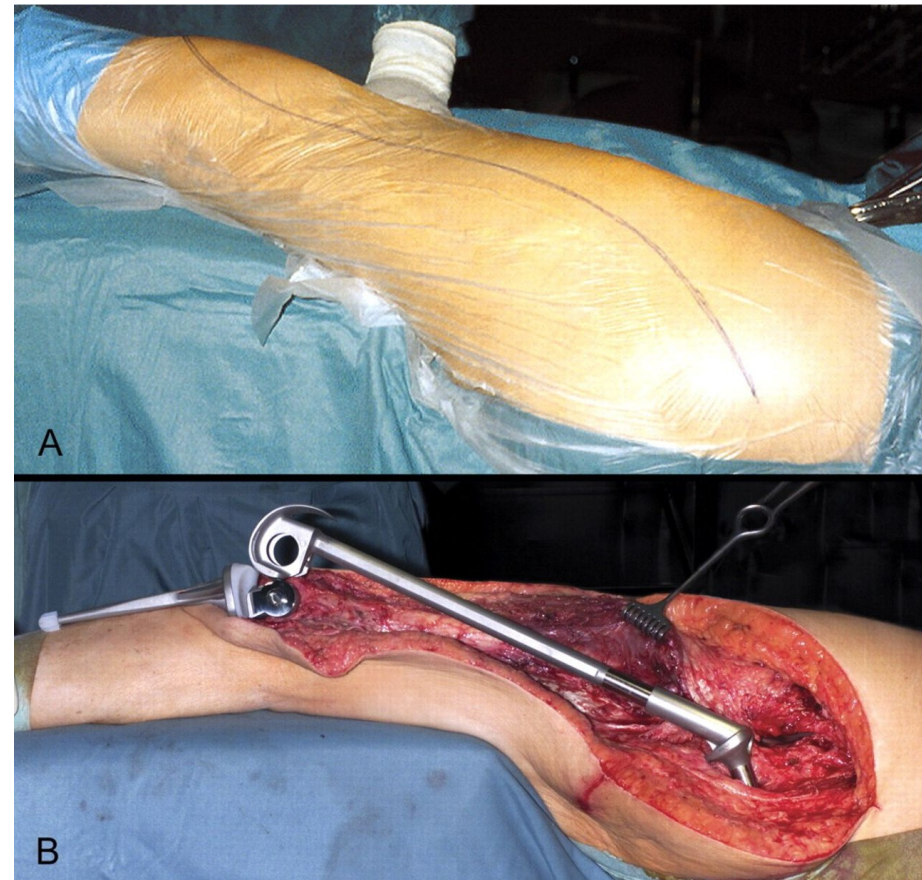
Jan 2015

Definition of major orthopaedic surgery

- Spinal fusion
- Total hip replacements
- Total knee replacements

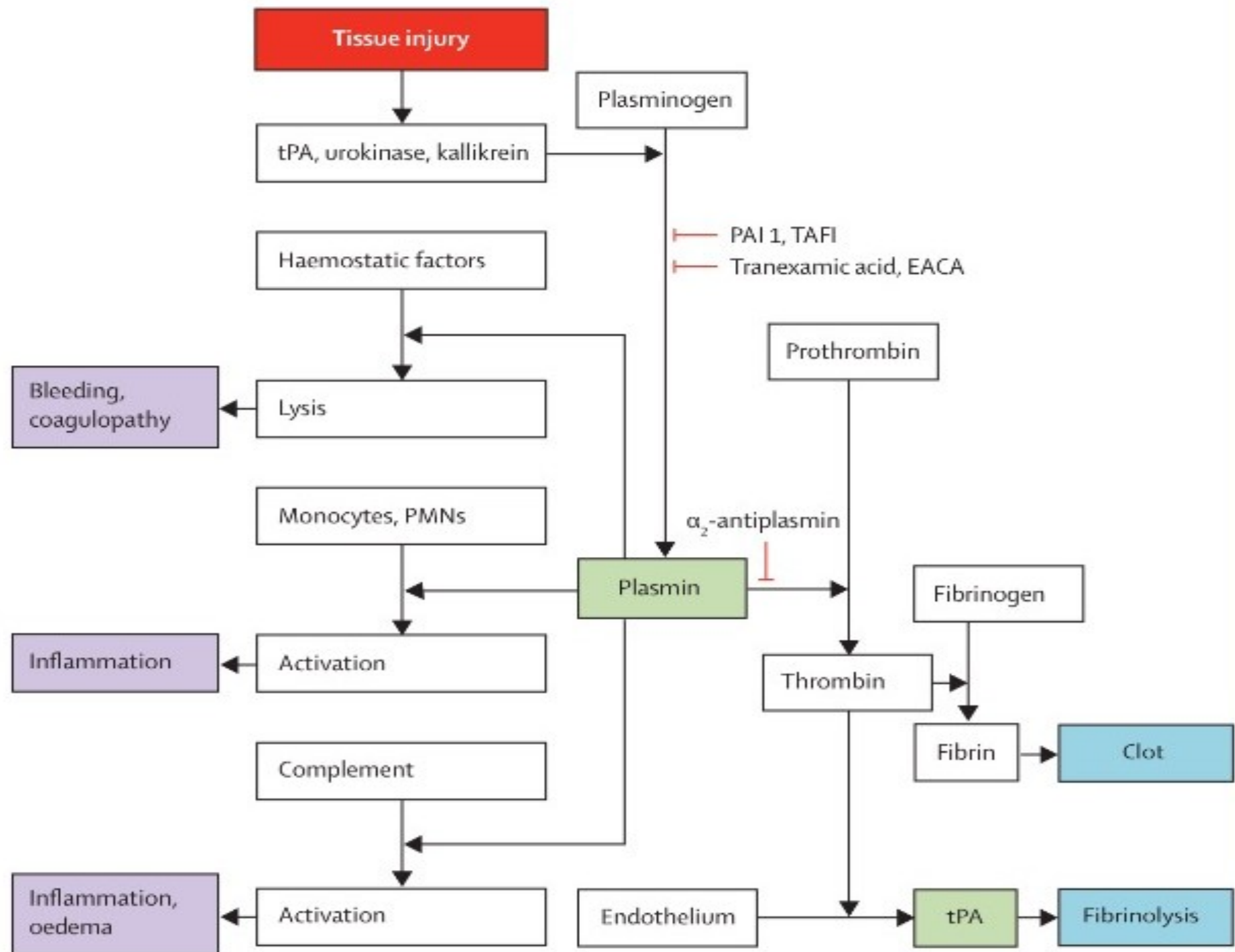
- What about acute trauma and multiple fractures?

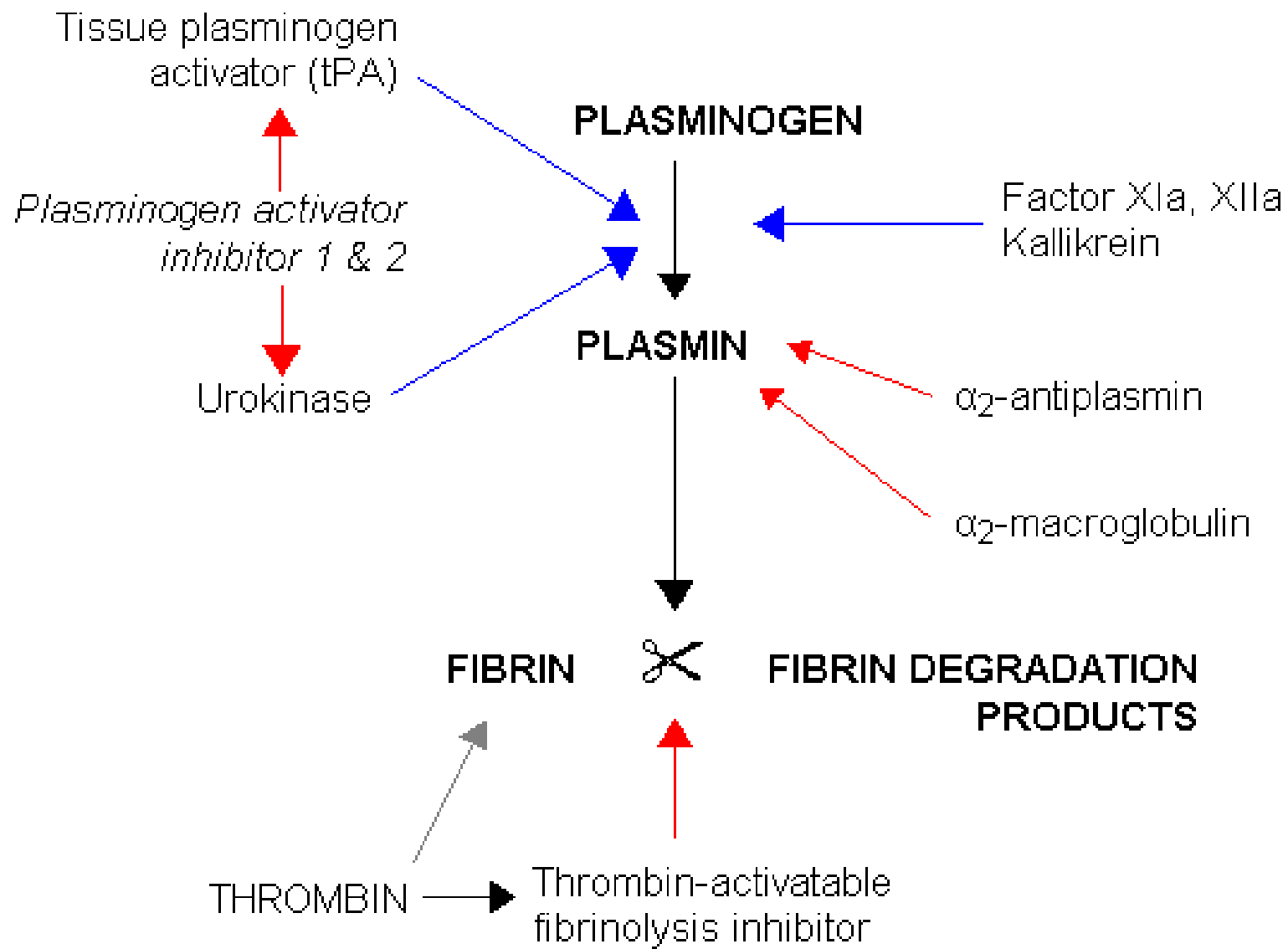
Sacrectomy for osteosarcoma, total femoral replacements



Hoffmann C et al. J Bone Joint Surg Am 2006;88:575-582







Tranexamic Acid

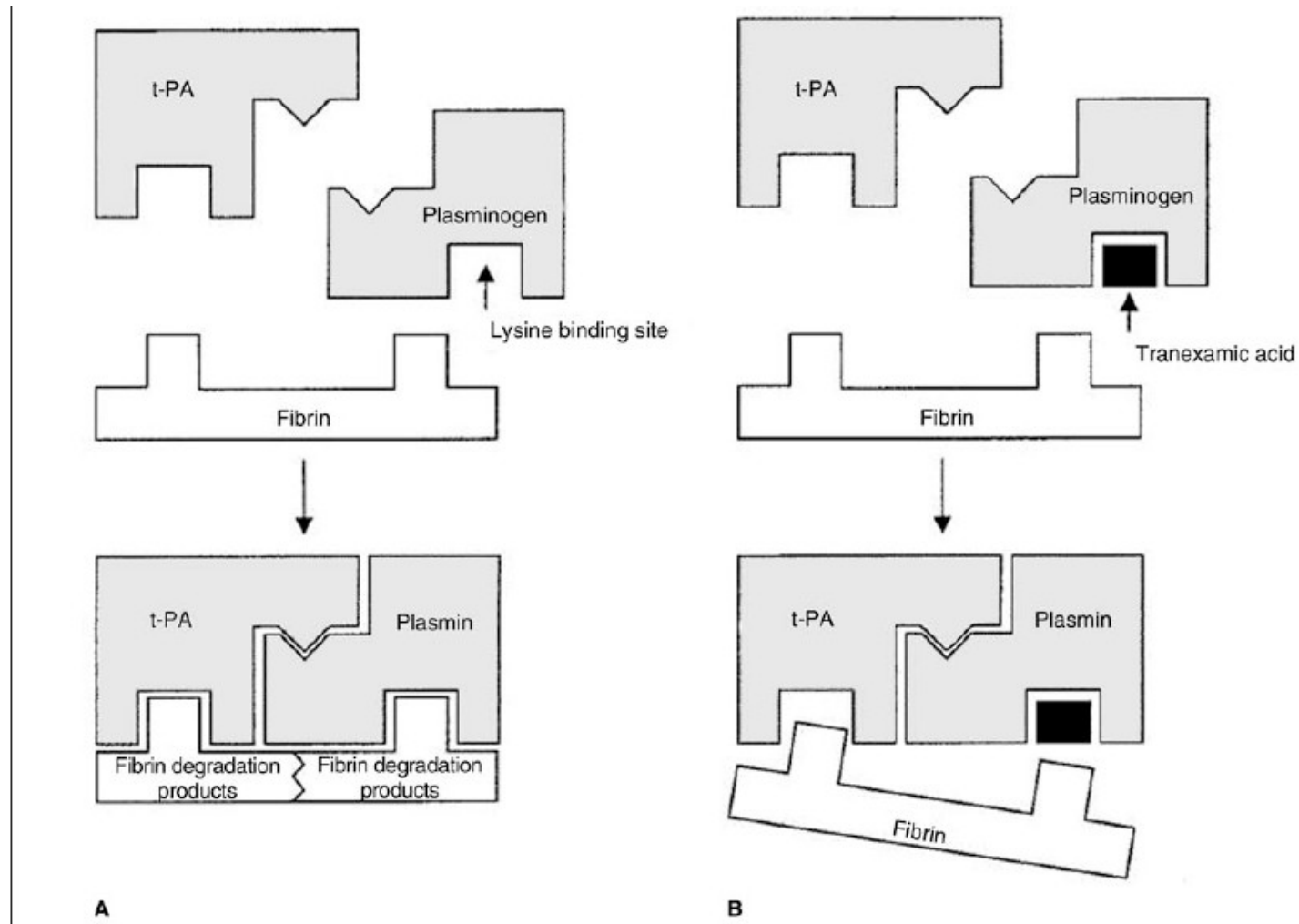
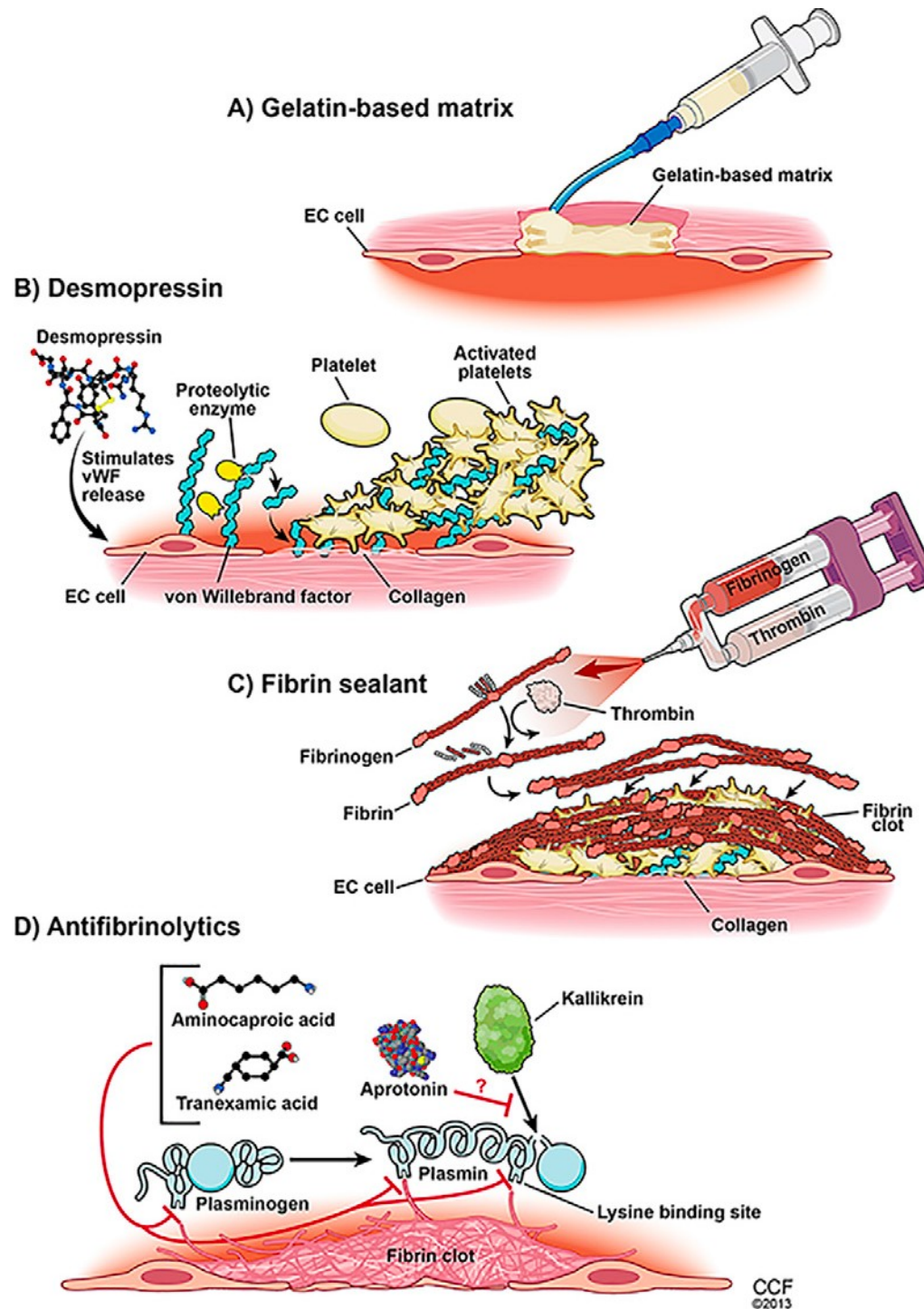


Diagram of the mechanism of action of tranexamic acid. A, Activation of fibrinolysis. B, Inhibition of fibrinolysis. The

Dunn CJ, Goa KL. Drugs. 1999;57:1005-1032

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Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion (Review)

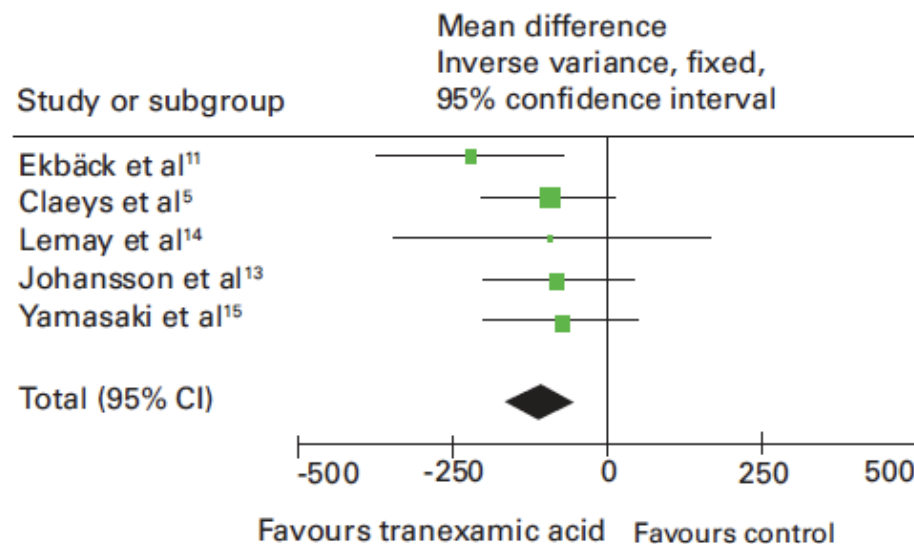
Henry DA, Carless PA, Moxey AJ, O'Connell D, Stokes BJ, Fergusson DA, Ker K



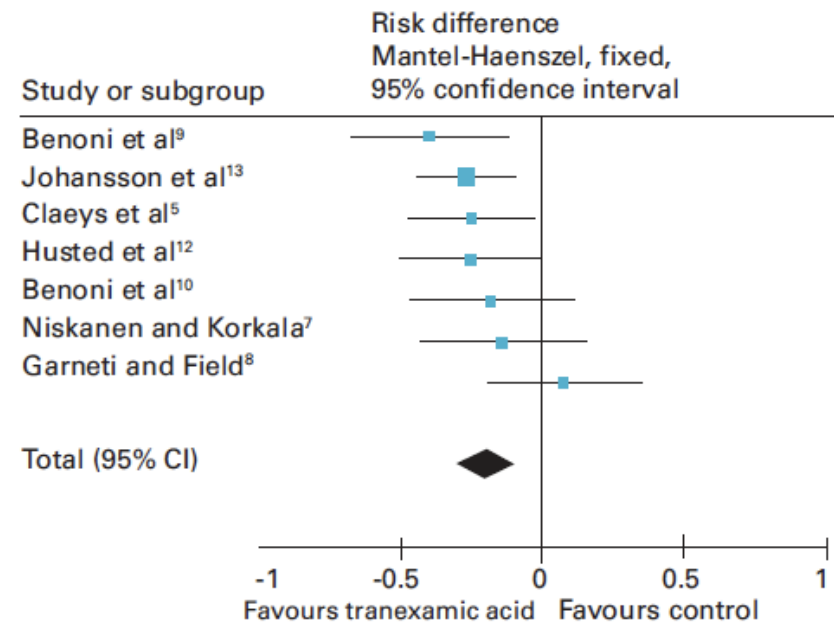
- *Do antifibrinolytics reduce allogenic blood transfusion in orthopedic surgery?- Meta-analysis.*
 - Zufferey et al. Anesthesiology 2006;105:1034-46
- *Use of antifibrinolytic therapy to reduce transfusion in patients undergoing orthopedic surgery: A systematic review of randomized trials.*
 - Kagoma et al. Thrombosis Research. 2009; 123:687-696

Both conclude: TXA reduces bleeding and transfusion

- Systematic review and meta-analysis of the use of tranexamic acid in total hip replacement
 - Sukeik et al. JBJS(Br) 2011;93:39-46



Effect of TXA on intra-operative blood loss



Effect of TXA on blood transfusion

Spine Surgery

- Antifibrinolytic agents for reducing blood loss in scoliosis surgery in children
 - systematic review cochrane database, 2008
- Use of Antifibrinolytic agents in spine surgery-a meta-analysis.
 - Gill JB et al. J bone and Joint Surgery Am. 2008;90:2399-2407
- Tranexamic acid reduces blood loss in adult patients having spinal fusion surgery.
 - Wong et al. Anesth Analg 2008;107:1479-86

Systematic Review and Meta-Analysis of Perioperative Intravenous Tranexamic Acid Use in Spinal Surgery 2013

The blood loss was reduced in spinal surgery patients with perioperative IV TXA treatment.

Also the percentage of spinal surgery patients who required blood transfusion was significantly decreased.

Further evaluation is required to confirm our findings before TXA can be safely used in patients undergoing spine surgery.

The Aprotinin Story



What do we know?

Onset of action : 5-15 minutes

Duration : 3 hours

Protein binding : about 3%

Metabolism : T_{1/2} is 2-3 hours

Excretion : Urine (>95% unchanged).

Suggested Dosage

1g IV over 10-20 mins to avoid hypotension.

Exclusion criteria

DVT/PE within 12 months or on anticoagulants.

Cardiac stent or Ischaemic stroke within 1 yr.

Relative criteria

Renal impairment.

History of seizures.

Thromboembolic or vascular disease.

Side effects

- Ocular – Colour vision loss, blurred vision and/ or vision loss!!
- Seizure – Probably neuronal GABA inhibition
- Renal impairment?

Seizures with TXA

- Sander et al.
 - Critical Care. 2010;14:R148
- Murkin et al.
 - Anesth Analg. 2010;110:350-353
- Keyl et al.
 - Eur. J. Cardiothoracic Surg. 2011;39:114-121
- Martin et al.
 - J. Cardiothoracic and vascular anaesthesia.2011;25(1): 20-25

Seizures with TXA

- Lessons from aprotinin: is the routine use and inconsistent dosing of tranexamic acid prudent? Meta-analysis.

– Ngagge DL, Bland JM. Eur J. of Cardio-thoracic Surgery. 2010;37:1375-1383

Tranexamic acid can cross the BBB when it is compromised.

TXA binds competitively in a dose dependent fashion to GABA type A receptors, which results in reduced inhibitory activity and increased neuronal excitation.

There are reports of TXA causing seizures when in direct contact with the CNS of animals and humans.

Tranexamic acid in trauma?

Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2)

Randomised controlled trial

274 hospitals

40 countries

2011-2012 11 adult trauma patients with, or at risk of, significant bleeding were randomly assigned within 8 h of injury to either tranexamic acid (loading dose 1 g over 10 min then infusion of 1 g over 8 h) or matching placebo.

Both participants and study staff were masked

Tranexamic acid safely reduced the risk of death in bleeding trauma patients in this study. No statistical difference in RBC transfusions between groups.

CRASH-2

The primary outcome was death in hospital within 4 weeks of injury, and was described with the following categories: bleeding, vascular occlusion (myocardial infarction, stroke and pulmonary embolism), multiorgan failure, head injury, and other.

All-cause mortality was significantly reduced with tranexamic acid

The risk of death due to bleeding was significantly reduced

Based on the results of the CRASH-2 Trial,
Tranexamic acid was added to the World Health
Organization list of essential medicines in March
2011.

Negatives of Crash 2

- Only approximately 5% of patients had bleeding as a cause of death.
- No data regarding injury severity of the patient cohort.
- No data regarding shock in the patient cohort (i.e. lactate and base deficit) and there was the inability to determine if the cohorts were similar.
- Small sample size of hypotensive (SBP < 90 mm Hg) (31.5%) and tachycardic (HR > 107) (48%) patients which were the target populations.
- The most common cause of death was traumatic brain injury (TBI).
- TXA did not reduce blood transfusions. Only 50% of study cohort received blood transfusions.
- No adverse events were regarded as serious, unexpected, or suspected to be related to the study treatment..
- Effect size was small. This effect was statistically significant but not a clinically meaningful finding. The study determined a 0.8% absolute reduction in “death caused by bleeding”.

Negatives of Crash 2

Re-examination of the 1063/3076 deaths (35%) that resulted from bleeding found that the benefit from TXA was greatest when it was given early ≤ 1 h, but when given more than 3 hours after injury, an unexpected and unexplained increase in deaths due to bleeding was observed.

Trauma Promise

Home About the Promise Make the Promise! We Promise (Hospital List)
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Tranexamic Acid on TV

Recently the BBC aired a new programme called An Hour to Save Your Life, exploring the life or death decisions facing medical professionals in the first critical hour of emergency care...[more](#)



Click here to register and make the promise!

Are you sure?

You will need to discuss the new information on tranexamic acid with those responsible for the care of trauma patients at your hospital and ...

The Promise

"We promise to consider the new knowledge on tranexamic acid in bleeding trauma patients and to use it to improve trauma care at this hospital."

A Promise to Save 100,000 Trauma Victims

We now know that injury robs humanity of some 300 million years of healthy life per annum, being responsible for 11% of DALYs world-wide. Road traffic crashes are the number one killer for young people and account for nearly one third of the world injury burden, a total of 76 million DALYs in 2010, up from 57 million in 1990. Most of the victims are young, many with families that depend on them... [more](#)

The Evidence for Tranexamic Acid

Download a list of papers, evidence for using tranexamic acid for trauma injuries:

1. [The_CRASH-2_trial_-_tranexamic_acid_in_trauma.pdf](#)
2. [The_CRASH-2_trial_-_importance_of_early_treatment.pdf](#)
3. [Tranexamic_acid_is_highly_cost-effective.pdf](#)

More

Military Application of Tranexamic Acid in Trauma Emergency Resuscitation (MATTERs) Study

- **Patients** A total of 896 consecutive admissions with combat injury, of which 293 received TXA, were identified from prospectively collected UK and US trauma registries.
- **Main Outcome Measures** Mortality at 24 hours, 48 hours, and 30 days and the influence of TXA administration on postoperative coagulopathy and the rate of thromboembolic complications.
- **Results.** The relative reduction in mortality was 6.7% and those who received tranexamic acid had less blood products.
- The NNT was 1:7 but 1:67 in the CRASH-2 trial

Military Application of Tranexamic Acid in Trauma Emergency Resuscitation (MATTERs) Study

This study also showed that the rates of PE and DVT among patients who received tranexamic acid were, respectively, 9 and 12 times the rates amongst those who did not.

What do the others think?

The prospective, observational, multicenter, major trauma transfusion (PROMMTT) study: comparative effectiveness of a time-varying treatment with competing risks. JAMA Surg. 2013 Feb;148(2):127-36.

Pre-hospital Anti-fibrinolytics for Traumatic Coagulopathy and Haemorrhage study (the PATCH-Trauma study), 4-year, 1200-patient, multicentre trial in Australia and New Zealand. Started recruitment in 2013.

Tranexamic acid in Trauma

How Did It Reduce Mortality?

- Is it caused by an attenuated inflammatory response achieved in part through reduction of circulating plasmin levels
- TXA, inhibits plasmin, which is known to induce proinflammatory effects by activation of monocytes, neutrophils, platelets, and endothelial cells and complement releasing lipid mediators and cytokines.

Anti-inflammatory effect

- Casati V, Della Valle P, Benussi S, et al. Effects of tranexamic acid on postoperative bleeding and related hematochemical variables in coronary surgery: comparison between on-pump and off-pump techniques. *J Thorac Cardiovasc Surg.* 2004;128(1):83-91
- Jimenez JJ, Iribarren JL, Lorente L, et al. Tranexamic acid attenuates inflammatory response in cardiopulmonary bypass surgery through blockade of fibrinolysis: a case control study followed by a randomized double-blind controlled trial. *Crit Care.* 2007;11(6):R117

Tranexamic acid attenuates inflammatory response in cardiopulmonary bypass surgery through blockade of fibrinolysis. Crit Care. 2007

In the case control study, 165 patients were studied.

In the TA group, we observed a significant reduction in the incidence of VS ($P = 0.003$), the use of norepinephrine ($P = 0.029$), and time on mechanical ventilation ($P = 0.018$).

Significantly lower D-dimer, plasminogen activator inhibitor 1, and creatine-kinase levels and a trend toward lower levels of soluble tumor necrosis factor receptor and interleukin-6 within the first 24 hours after CPB.

An anti-inflammatory role for tranexamic acid in cardiac surgery?

[Heidi J Robertshaw Crit care 2008](#)

Pro and anti-inflammatory cytokines are elevated after surgery.

The use of tranexamic acid can attenuate this inflammation revealing a glimpse of how the fibrinolytic and inflammatory pathway could be interlinked.

It remains unclear whether the mortality benefit from TXA is from reversal of fibrinolysis or whether an inflammatory or immune modulation is the underlying mechanism.

- How does it act? Why is it different from aprotinin? Does that matter?
- What complications?
- What evidence apart from crash 2?
- What dosage? Bolus and/or infusion
- Does it stop bony bleeding? Soft tissue bleeds
- Should it be given because surgeon requests it?
- Does it change TEG?

- **Future research**
- The relation between age and mortality needs further exploration. A better understanding of the mechanism by which age is associated with increasing mortality could lead to effective interventions to improve the outcome in this vulnerable population. As we were able to validate the model only in patients from high income regions, future studies should also explore its performance in low and middle income countries. Finally, future research should evaluate whether the use of this prognostic model in clinical practice has an effect on the management and outcomes of trauma patients.²⁵

Antifibrinolytic agents in current anaesthetic practice

Table 2

Trauma and orthopaedic surgery. AP, aprotinin; TXA, tranexamic acid; EACA, ε-aminocaproic acid

Author	Year	Study population	Main findings
Shakur and colleagues ⁷⁵	2010	20 211	<i>Multicentre, double-blind, placebo-controlled RCT</i> All-cause mortality and risk of death because of bleeding was significantly reduced in trauma patients with TXA vs placebo; no increased risk of thromboembolic events
Roberts and colleagues ⁷⁶	2011	20 211	<i>Multicentre, double-blind, placebo-controlled RCT; subgroup analysis</i> Risk of death is reduced if TXA is given within 3 h after trauma; later administration is associated with increased risk of death
Roberts and colleagues ⁷⁷	2011	20 548	<i>Cochrane systematic review of four RCTs</i> TXA reduced the risk of death in bleeding trauma patients; no reliable data for AP in trauma
CRASH-2 collaborators ⁷⁸	2011	270	<i>Multicentre double-blind, placebo-controlled RCT, nested into CRASH-2</i> Tranexamic acid did not demonstrate a reduction in intracranial haemorrhage growth or mortality in trauma patients with brain injury
Tzortzopoulou and colleagues ⁸⁰	2008	254	<i>Cochrane systematic review of six RCTs</i> Antifibrinolytic drugs reduced the amount of transfused blood (−327 ml; 95% CI −469.04 to −185.78) and the amount of blood loss (−427 ml; 95% CI −602.51 to −250.56) in paediatric scoliosis surgery
Wong and colleagues ⁸¹	2008	151	<i>Double-blinded, placebo-controlled RCT</i> Estimated blood loss after spinal fusion in adults was reduced by 25% by TXA; no difference for perioperative transfusion and length of hospital stay
Dhawale and colleagues ⁸²	2011	84	<i>Retrospective database analysis</i> Reduced estimated blood loss in children undergoing spinal fusion with prophylactic lysine analogues compared with no treatment
Zufferey and colleagues ⁸⁴	2006	2523	<i>Meta-analysis of 43 RCTs</i> AP (OR 0.43; 95% CI 0.28–0.64) and TXA (OR 0.17; 95% CI 0.11–0.24) led to a reduction in blood transfusion in orthopaedic surgery, whereas EACA did not
Kagoma and colleagues ⁸⁵	2009	2060	<i>Systematic review of 29 RCTs</i> Antifibrinolytic agents are associated with reduced blood transfusion after hip and knee replacement; no increased risk for thromboembolic events with antifibrinolytics

Questions?

- Is there a role in low risk patients routinely for major orthopaedic surgery?
- Should it be given to all trauma patients?
- Bolus dose vs infusion?
- Monitoring and targeting treatment
- Role of topical tranexamic acid

Unanswered questions

Anti-inflammatory action

Age and antifibrinolytics

Dosage, efficacy and safety