

An international view, including the CRASH2 trial

**Professor Tim Coats
Professor of Emergency Medicine
Leicester University, UK**

Conflict of Interest Statement

- **Paid consultancy for Novonordisk**
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The International View - what has changed

- **Changed view of the timing of coagulopathy**
 - **New understanding of coagulation**
 - **New management guidelines**
 - **New approaches to old therapies**
 - **New therapies**
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When does coagulopathy occur?

- **Traditional view**

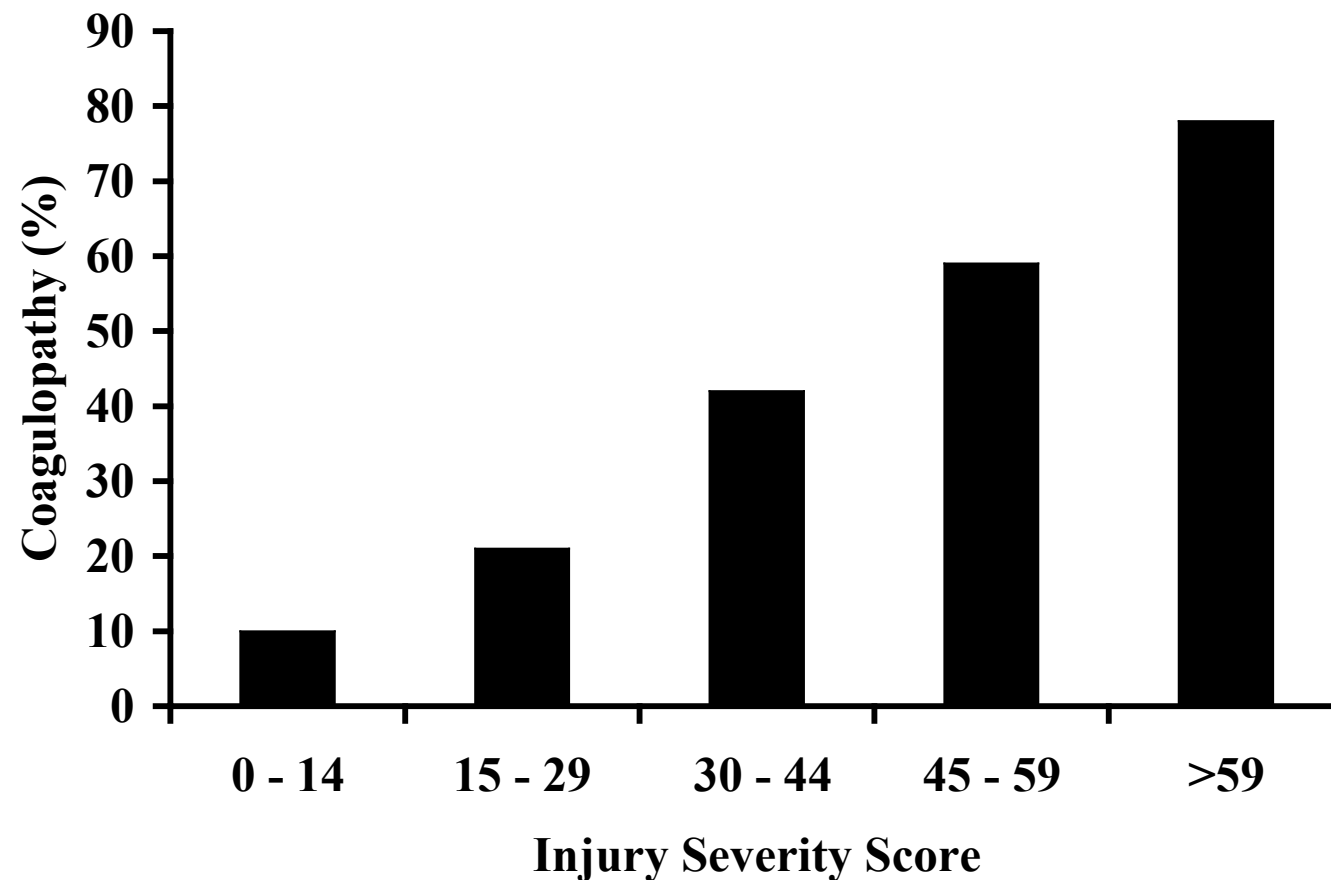
- After cooling / fluids / transfusion etc
- Coagulation not a 'primary survey' concern

- **New view**

- Coagulation changes happen in the first few minutes
- Coagulopathy often established before any intervention
- Coagulopathy on hospital arrival common

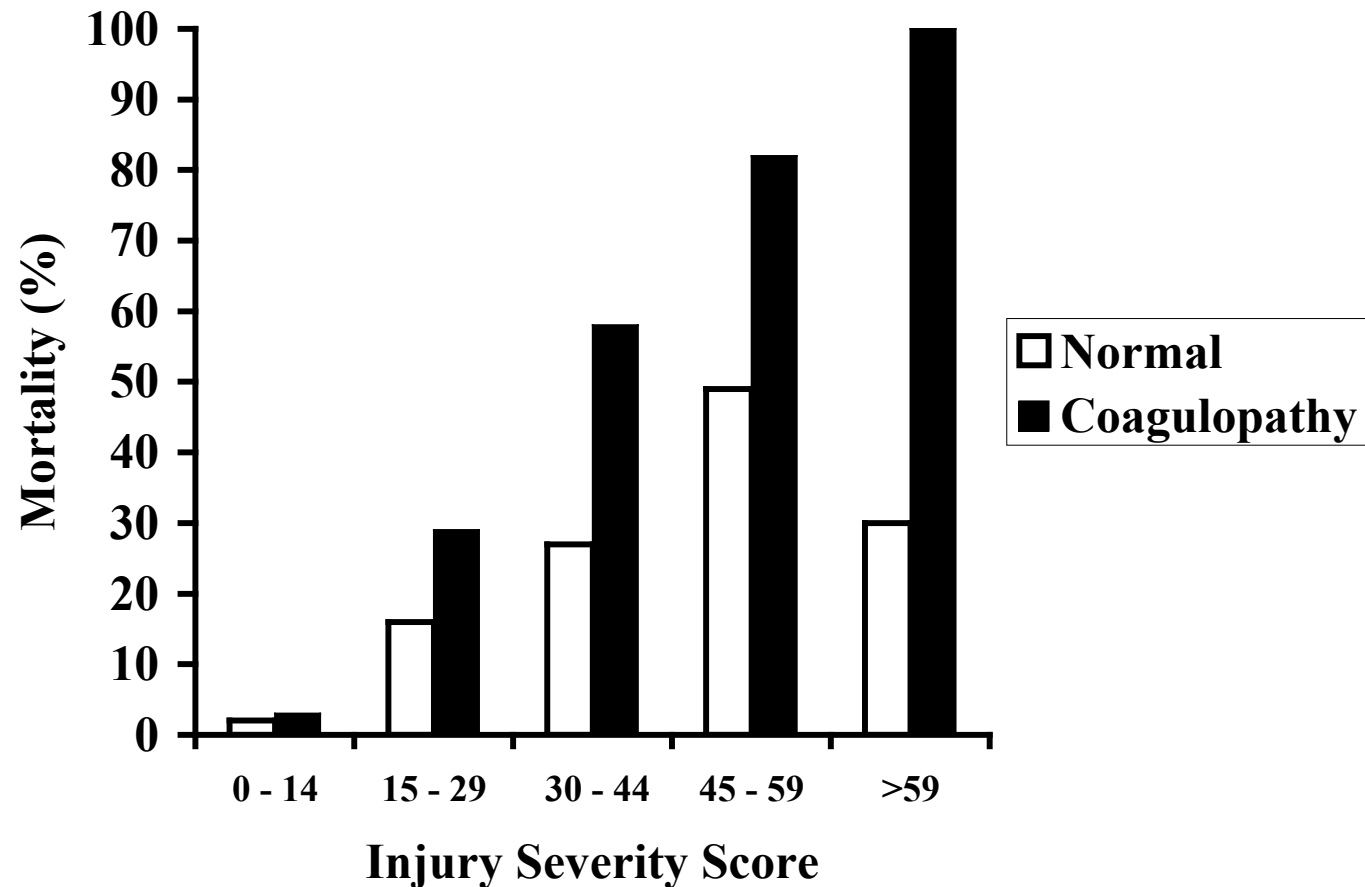
When does coagulopathy occur?

- **Abnormal clotting common**



Coagulation after Injury

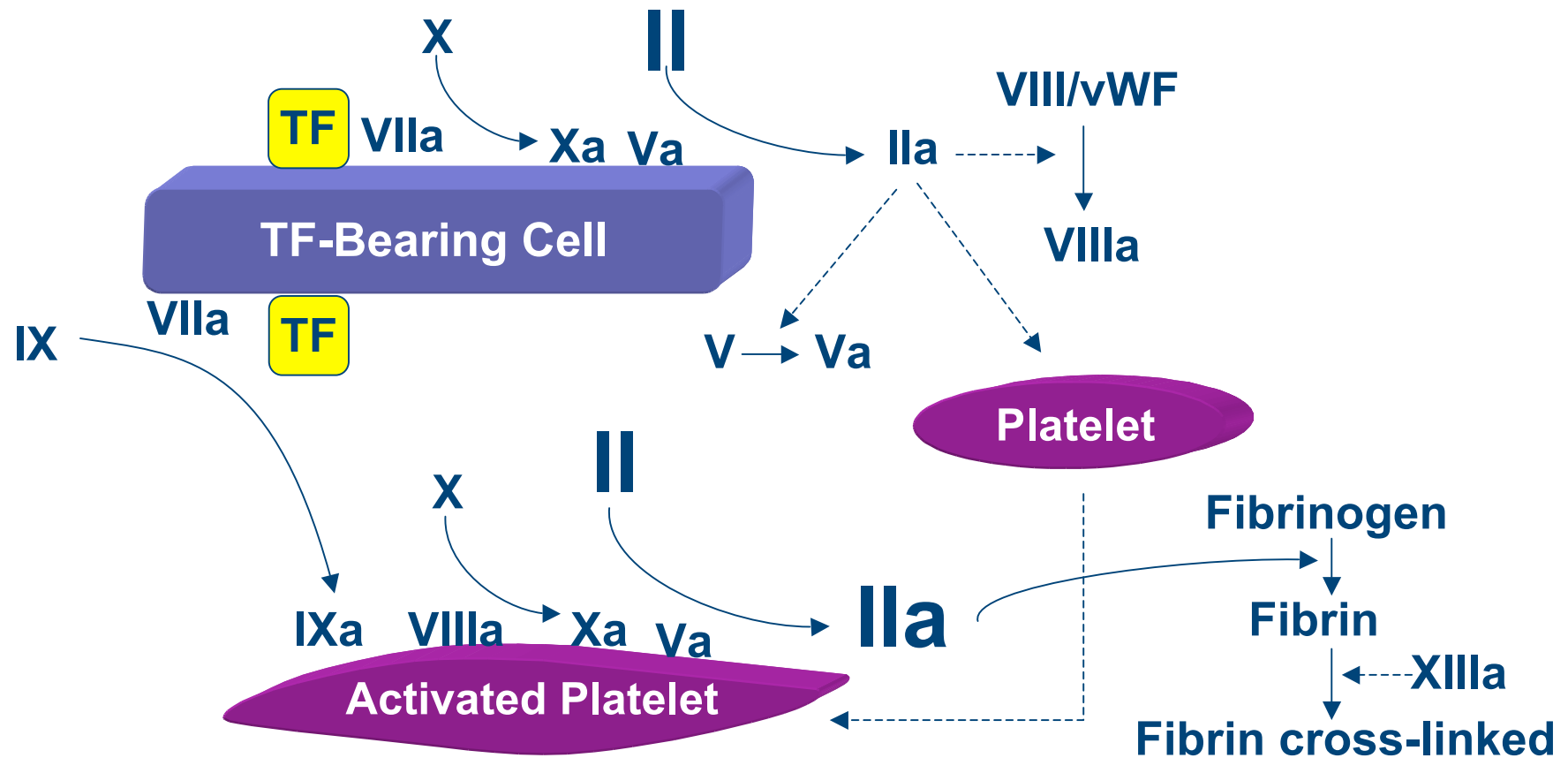
- Abnormal clotting related to death



How does blood clot - a new view

- **Cascades of reactions - extrinsic and intrinsic systems**
 - Long-standing theory
 - Good description of 'test tube' coagulation
 - Not a good description of real life
- **Cell-based model**
 - Better description of the complex interactions
 - Includes cellular as well as plasma components

Coagulation



New Guideline

- **Until recently no comprehensive Guideline**
 - **ABC Trauma Group**
 - **Educational grant from Novonordisk**
 - **Critical Care, February 2007**
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Management of bleeding following major trauma: a European guideline

Donat R Spahn¹, Vladimir Cerny², Timothy J Coats³, Jacques Duranteau⁴, Enrique Fernández-Mondéjar⁵, Giovanni Gordini⁶, Philip F Stahel⁷, Beverley J Hunt⁸, Radko Komadina⁹, Edmund Neugebauer¹⁰, Yves Ozier¹¹, Louis Riddez¹², Arthur Schultz¹³, Jean-Louis Vincent¹⁴ and Rolf Rossaint¹⁵

¹Department of Anesthesiology, University Hospital Zurich, Rämistrasse 100, 8091 Zurich, Switzerland

²Charles University in Prague, Faculty of Medicine in Hradec Králové, Department of Anaesthesiology and Intensive Care Medicine, University Hospital Hradec Králové, Sokolska 581, 50006 Hradec Králové, Czech Republic

³Leicester Royal Infirmary, Accident and Emergency Department, Infirmary Square, Leicester LE1 5WW, UK

⁴Department of Anaesthesia and Intensive Care, University of Paris XI Faculté de Médecine Paris-Sud, 63 rue Gabriel Péri, 94276 Le Kremlin-Bicêtre, France

⁵Department of Emergency and Critical Care Medicine, University Hospital Virgen de las Nieves, ctra de Jaén s/n, 18013 Granada, Spain

⁶Department of Anaesthesia and Intensive Care, Ospedale Maggiore, Largo Nigrisoli 2, 40100 Bologna, Italy

⁷Department of Orthopaedic Surgery, Denver Health Medical Center, University of Colorado Medical School, 777 Bannock Street, Denver, CO 80204, USA

⁸Departments of Haematology, Pathology and Rheumatology, Guy's & St Thomas' Foundation Trust, Lambeth Palace Road, London SE1 7EH, UK

⁹Department of Traumatology, General and Teaching Hospital Celje, 3000 Celje, Slovenia

¹⁰Institute for Research in Operative Medicine, University of Witten/Herdecke, Ostmerheimerstrasse 200, 51109 Köln (Merheim), Germany

¹¹Department of Anaesthesia and Intensive Care, Université René Descartes Paris 5, AP-HP, Hôpital Cochin, 27 rue du Fbg Saint-Jacques, 75014 Paris, France

¹²Department of Surgery and Trauma, Karolinska University Hospital, 171 76 Solna, Sweden

¹³Ludwig-Boltzmann-Institute for Experimental and Clinical Traumatology, Donaueschingenstrasse 13, 1200 Vienna, Austria

¹⁴Department of Intensive Care, Erasme Hospital, University of Brussels, Belgium, route de Lennik 808, 1070 Brussels, Belgium

¹⁵Department of Anaesthesiology, University Hospital Aachen, Pauwelsstraße 30, 52074 Aachen, Germany



Areas covered - ABC Trauma Website

- **Module I** Introduction
- **Module II** Burden of Trauma
- **Module III** Bleeding in Trauma
- **Module IV** Management of Bleeding and Coagulopathy Associated with Trauma
- **Module V** Key Objectives at Each Step of Patient Pathway
- **Module VI** Case Reports

What I learnt from the process

- **A lot of variation in practice within Europe**
 - **Little evidence in trauma care - therapy by extrapolation from haematology patients**
 - **Exciting possibilities for research**
 - **Local discussions with haematologists important**
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New uses for old therapies

- **Tourniquets are back (for the military)**
 - **Much earlier use of blood products**
 - **More Fresh frozen plasma / thawed plasma**
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New Therapies

- **Local haemostatic agents**
 - **Factor 7a**
 - **Antifibrinolytics**
 - **?? DDAVP**
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CRASH₂

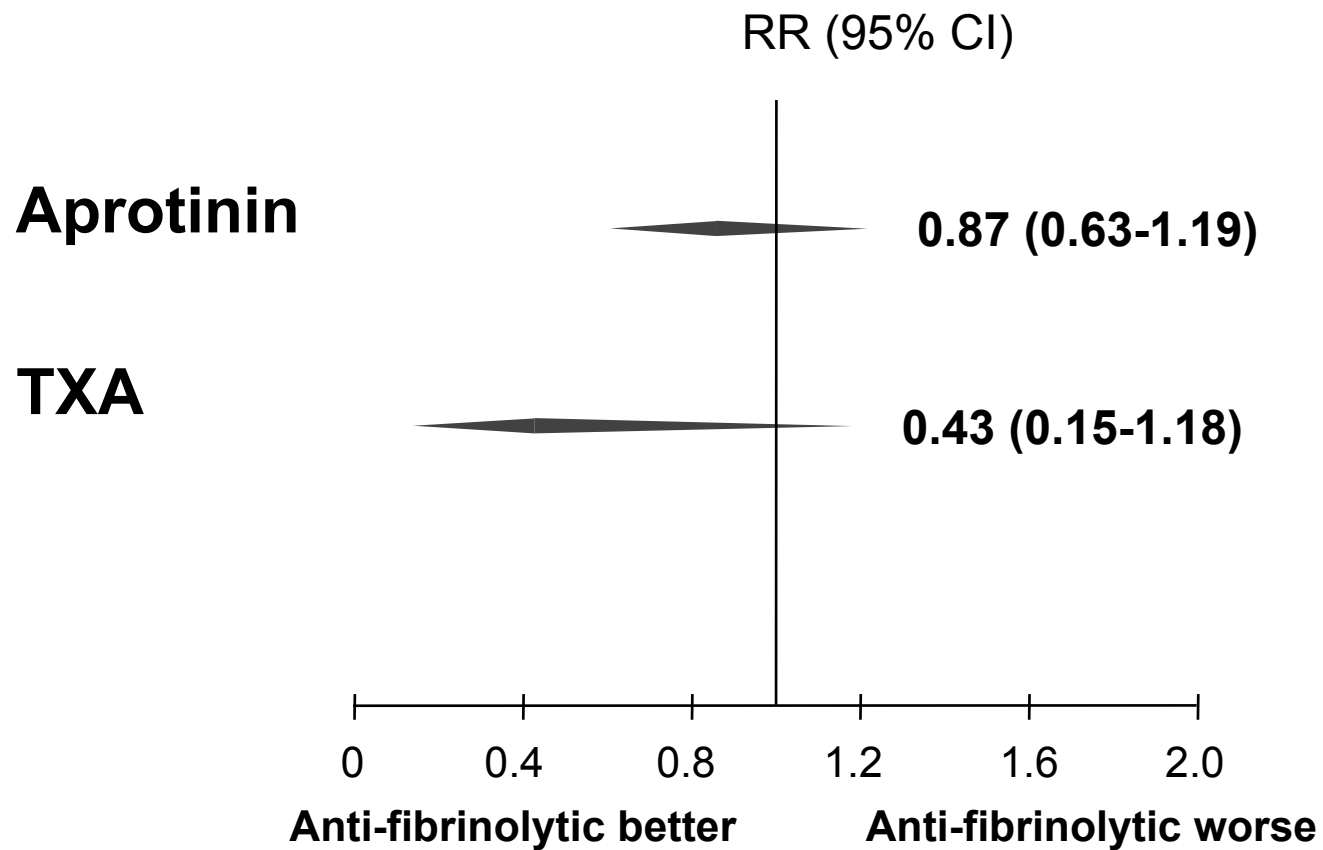
Clinical Randomisation of an
Antifibrinolytic in Significant Haemorrhage 

A large randomised controlled trial among trauma patients with significant haemorrhage, of the effects of anti-fibrinolytic treatment on death and transfusion requirement

www.crash2.lshtm.ac.uk

Anti-fibrinolytic agents in elective surgery

- **Mortality:**



Anti-fibrinolytic agents in trauma

- **Cochrane review:**
 - Coats, Roberts and Shakur 2004
- **1 study. 77 patients randomised.**
- **“Insufficient evidence to either support or refute a clinically important treatment effect”**

Rationale for CRASH2

- 1) Antifibrinolytics reduce blood loss in surgery - Cochrane review.
- 2) Surgery and trauma are similar enough for us to think that the surgical effect might also be true for trauma.
- 3) We don't know if antifibrinolytics improve outcomes following injury - Cochrane review.
- 4) We therefore need to perform a trial

POTENTIALLY ELIGIBLE

Adults with trauma and significant haemorrhage or at risk of significant haemorrhage within 8 hours of injury

DOCTOR IS "REASONABLY CERTAIN"
THAT ANTI-FIBRINOLYTIC AGENTS
ARE INDICATED.

INELIGIBLE

GIVE ANTI-FIBRINOLYTIC AGENTS;
DO NOT RANDOMISE.

DOCTOR IS "REASONABLY CERTAIN"
THAT ANTI-FIBRINOLYTIC AGENTS
ARE CONTRA-INDICATED.

INELIGIBLE

DON'T GIVE ANTI-FIBRINOLYTIC AGENTS;
DO NOT RANDOMISE.

Doctor is "SUBSTANTIALLY UNCERTAIN"
as to the appropriateness of
anti-fibrinolytic agents in this patient

**TELEPHONE FOR RANDOMISATION
OR PAPER RANDOMISE**

TRANEXAMIC ACID

PLACEBO

CRASH₂

Treatment

Treatment	Ampoules	Dose (Tranexamic Acid or placebo)	Infusion rate
Loading	2	1 gram	100 ml over 10 minutes
Maintenance	2	1 gram	120 mg/hr [60 ml/hr] for about 8 hours

- fixed dose more practicable in emergency situation
- dose within range shown to inhibit fibrinolysis and provide haemostatic benefit

Current status - CRASH2

- In progress in 40 Countries. > 250 collaborators
- 5000 patients randomised (need 20 000)
- Your participation is invited

www.crash2.lshtm.ac.uk

Summary

- **New view of when coaguloapthy occurs**
 - Very early effect
 - **New model of coagulation**
 - Cell based
 - **New Guideline - 2007**
 - **New uses for old therapies**
 - Tourniquet, FFP
 - **New therapies**
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