
What's good and bad in resuscitation:
CRASH vs CONTROL
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- antifibrinolytic treatment reduces blood loss following surgery…may be effective in trauma
- aprotinin, tranexamic acid, epsilon-aminocaproic acid
- Conclusion: Inadequate data to make a recommendation

Cochrane 2005

http://www.crash2.lshtm.ac.uk/

ESPAÑOL

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CRASH-2

Contributing to global health

Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage

A large randomised placebo controlled trial among trauma patients with, or at risk of, significant haemorrhage, of the effects of antifibrinolytic treatment on death and transfusion requirement

ISRCTN86750102

	INTRANET FOR COLLABORATORS
	The CRASH-2 trial is scheduled to end by the end of 2009. Therefore we are not looking to recruit any new hospitals to participate. If you would like to receive the trial results when they are published in 2010, you can register your interest here.

Peer reviewed Protocol is available on The Lancet protocol website »»» CLICK HERE

17,537 patients randomised

Last updated Fri 04-Sep-2009 17:08 BST

118 days to go!
2,463 patients to recruit

*** CONGRATULATIONS TO DANIEL KINYURU OJUKA & TEAM IN KAPEN(

CRASH-2

Clinical Trials Unit
LSHTM

Worldwide research and postgraduate education in global health

Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage

A large randomised placebo controlled trial among trauma patients with, or at risk of, significant haemorrhage, of the effects of antifibrinolytic treatment on death and transfusion requirement

ISRCTN86750102

20,000 PATIENTS RANDOMISED

Congratulations to all our 274 collaborating hospitals in 40 countries for completing the randomisation of 20,000 patients!

FINAL RESULTS PUBLISHED ON LANCET ONLINE ON 15 JUNE 2010

pdf-version

Abstract in Spanish - Hindi - Chinese - Japanese

PUBLISHED ON LANCET ONLINE 24 MARCH 2011

CRASH-2 subgroup analysis: The importance of early treatment with tranexamic acid in bleeding trauma patients: an exploratory analysis of the CRASH-2 randomised controlled trial; CRASH-2 Collaborators

Lancet. June 15, 2010

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

*CRASH-2 trial collaborators**

- 274 hospitals in 40 countries
- 20,211 adult trauma patients “with, or at risk of, significant bleeding”
- within 8 h of injury
- either tranexamic acid (loading dose 1 g over 10 min then infusion of 1 g over 8 h) or placebo.
- Double blinded

- The primary outcome = death in hospital within 4 weeks of injury, described by categories: bleeding, vascular occlusion (myocardial infarction, stroke and pulmonary embolism), multiorgan failure, head injury, and other. All analyses were by intention to treat.

PATIENT ENTRY FORM

CRASH-2 PATIENT ENTRY INTERNATIONAL

ALL QUESTIONS BELOW NEED TO BE ANSWERED
BEFORE CALLING THE RANDOMISATION SERVICE

INFORMATION ABOUT YOUR HOSPITAL

1. Country	
2. Name of hospital (or your hospital code)	
3. Name of caller	

INFORMATION ABOUT THE PATIENT

4. Patient sex (please circle)	**Male**	**Female**	5. Patient initials	
6. Patient hospital identification number				
7. Do you know patient's date of birth?				
a. **YES** – date of birth	YEAR	MONTH	DAY	b. **NO** – approximate age

INFORMATION ABOUT THE INJURY

8.	Estimated number of hours since injury	hours
9.	Type of injury (please circle)	**1** Blunt **2** Penetrating **3** Both

FIRST MEASUREMENT IN HOSPITAL OF THE FOLLOWING (IF UNKNOWN GIVE VALUE AT RANDOMISATION)

10.	Systolic BP (mmHg)		11.	Respiratory rate (per min)	
12.	Central capillary refill time (sec)		13.	Heart rate (per min)	
14.	Glasgow Coma Score (max 15)		EYE OPENING 4 Spontaneous 3 To sound 2 To pain 1 None	MOTOR RESPONSE 6 Obeys commands 5 Localising 4 Normal flexion 3 Abnormal flexion 2 Extending 1 None	VERBAL RESPONSE 5 Orientated 4 Confused speech 3 Words 2 Sounds 1 None

Now call **Randomisation Service** with these answers and write down the treatment pack number given at the end of the phone call

Box ☐☐☐☐ **Pack** ☐☐

Get this pack and follow the instructions on it carefully

Or paper randomise as per instructions in site file

OUTCOME FORM

CRASH-2

OUTCOME FORM

COMPLETE AT DISCHARGE FROM THE RANDOMISING HOSPITAL, DEATH IN HOSPITAL OR 28 DAYS AFTER INJURY, WHICHEVER OCCURS FIRST

Attach treatment pack sticker here

1. HOSPITAL (Hospital name or code)

2. PATIENT

Patient Initials		Hospital ID Number		Sex	M	F
Date of Birth	/ /					

3. OUTCOME

3.1 DEATH IN HOSPITAL

Date of death / /

Cause of death

- Bleeding
- Head injury
- Myocardial infarction
- Stroke
- Pulmonary Embolism
- Multi organ failure
- Other – describe

3.2 PATIENT ALIVE

- **Discharged** – Date of discharge / /
- **Still in this hospital now** (28 days after injury) – Date / /

3.3 IF ALIVE TICK ONE BOX THAT BEST DESCRIBES THE PATIENT'S CONDITION (at 28 days or prior discharge)

- No symptoms
- Minor symptoms
- Some restriction in lifestyle but independent
- Dependent, but not requiring constant attention
- Fully dependent, requiring attention day and night

4. MANAGEMENT

a) **Days in Intensive Care Unit** (If not admitted to ICU, write '0' here)		
b) **Significant Head Injury**	YES	NO
c) **Operation site** – Tick one box on every line		
• Neurosurgical	YES	NO
• Chest	YES	NO
• Abdomen	YES	NO
• Pelvis	YES	NO

5. COMPLICATIONS

Tick one box on every line		
• Pulmonary Embolism	YES	NO
• Deep Vein Thrombosis	YES	NO
• Stroke	YES	NO
• Operation for bleeding	YES	NO
• Myocardial Infarction	YES	NO
• Gastrointestinal bleeding	YES	NO

6. TRIAL TREATMENT

a) Complete **loading dose** given	YES	NO
b) Complete **maintenance dose** given	YES	NO

7. TRANSFUSION

a) Blood products transfusion	YES	NO
b) Units transfused in 28 days		
• Red cell products		units
• Fresh frozen plasma		units
• Platelets		units
• Cryoprecipitate		units
• Recombinant Factor VIIa	YES	NO

8. PERSON COMPLETING FORM

NAME	
POSITION	
DATE	

NOW SEND THIS FORM TO THE CO-ORDINATING CENTRE IN ONE OF THE FOLLOWING WAYS:

- SECURE WEBSITE
- ELECTRONIC DATA FORMS / EMAIL
- FAX +44 (0)20 7299 4663

SEE INSTRUCTIONS IN YOUR SITE FILE

ISRCTN86750102

CRASH-2

SERIOUS ADVERSE EVENT REPORT

THIS FORM IS FOR REGISTERING ALL ADVERSE REACTIONS THAT ARE SUSPECTED TO BE RELATED TO THE STUDY MEDICINE.
In the first instance, please telephone immediately +44(0)1865 240972 and provide all the details below.
A written report must be faxed to CRASH Trials Co-ordinating Centre, +44(0)20 7299 4663, within 24 hours.

1. NAME OF RESPONSIBLE CLINICIAN (PLEASE PRINT):

Name | Position | Telephone

Hospital

2. PATIENT DETAILS

Patient initials | Patient ID

Sex (please circle) M F | Date of Birth / / (day/month/year)

Box and treatment pack number allocated at entry: Box | Pack

Date randomised / / (day/month/year)

3. OUTCOME (TICK ONE BOX AND GIVE DATE) Date / /

Resulted in death	Life threatening	Prolongation of hospitalisation	Persistent or significant disability	Other (not covered by categories but, in the investigator's opinion, should be considered serious)

4. ADVERSE EVENT DETAILS

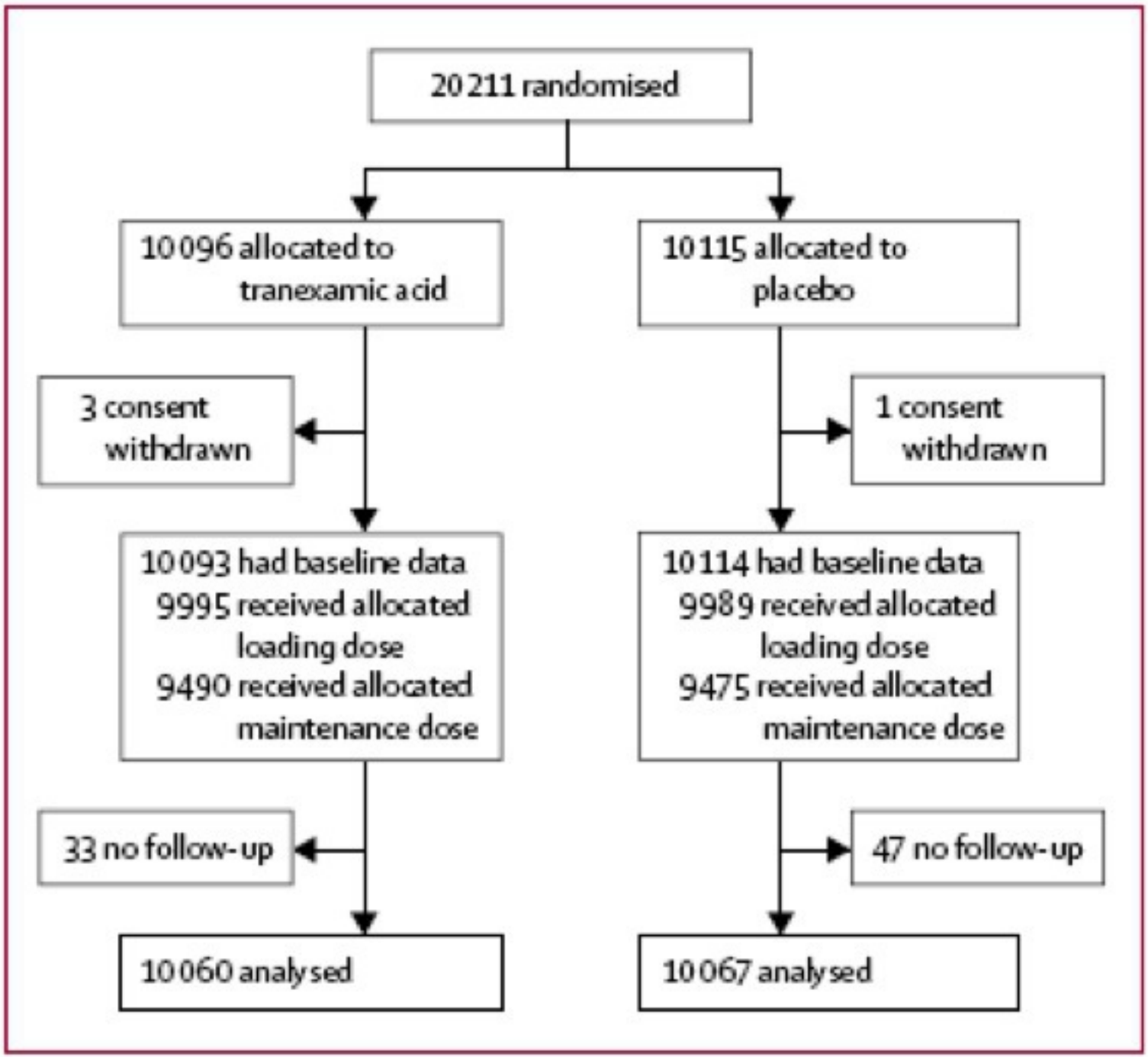
Date of onset / / | Time of onset (24h clock) : | End date / /

Please describe the adverse event:

Please state why you suspect the adverse event to be related to the study drug:

How likely do you think this event was trial drug related? (0 - 100%) %

Signature | Date


20 211 randomised
10 096 allocated to tranexamic acid
10 115 allocated to placebo
3 consent withdrawn
1 consent withdrawn
10 093 had baseline data
9995 received allocated loading dose
9490 received allocated maintenance dose
10 114 had baseline data
9989 received allocated loading dose
9475 received allocated maintenance dose
33 no follow-up
47 no follow-up
10 060 analysed
10 067 analysed

Results

- All-cause mortality was significantly reduced with tranexamic acid (1463 [14·5%] tranexamic acid group *vs* 1613 [16·0%] placebo group; relative risk 0·91, 95% CI 0·85–0·97; p=0·0035).

- The risk of death due to bleeding was significantly reduced (489 [4·9%] *vs* 574 [5·7%]; relative risk 0·85, 95% CI 0·76–0·96; p=0·0077).

- Interpretation Tranexamic acid safely reduced the risk of death in bleeding trauma patients in this study. On the basis of these results, tranexamic acid should be considered for use in bleeding trauma patients.

MP 1. Do you have numbers that were excluded from study because the responsible Dr thought tranexamic acid was definitely indicated or contraindicated?

IR We do not have numbers but in practice the uncertainty principle was largely a theoretical issue given the lack of any prior evidence.

MP 2. Were any patients excluded on the basis of futility i.e. expected to die?

IR Again we don't know but in general it makes no sense to give any trial treatment to a patient certain to die.

MP 3. Why do you think the mortality was only 15% versus your powered estimate of 20%?

IR Sample size calculations are always a guess and being 5% off is within the margin of error.

MP 4. Were patients who died of 'bleeding' equally likely to receive/not receive blood products?

IR Haven't done this analysis but the problem of competing risks always needs to be taken into account. In other words, where there is a 15% reduction in bleeding mortality it becomes very difficult to interpret the blood transfusion data. Because there are substantially fewer deaths in the TXA treated group - there are more patients alive who have the opportunity to receive a blood transfusion. We have done sensitivity analysis assuming that the patients who died in the placebo group as a result of not receiving TXA- had not died and received a blood transfusion - in this case there would be a significant reduction in transfusion.

MP 5. Why do you think the result is the opposite of elective surgical studies that show reduced blood product use but no difference in mortality?

IR Again - competing risks is a big problem. Plus the reasons that we give in the paper.

MP 6. Do you have info to calculate Median ISS?

IR No we don't.

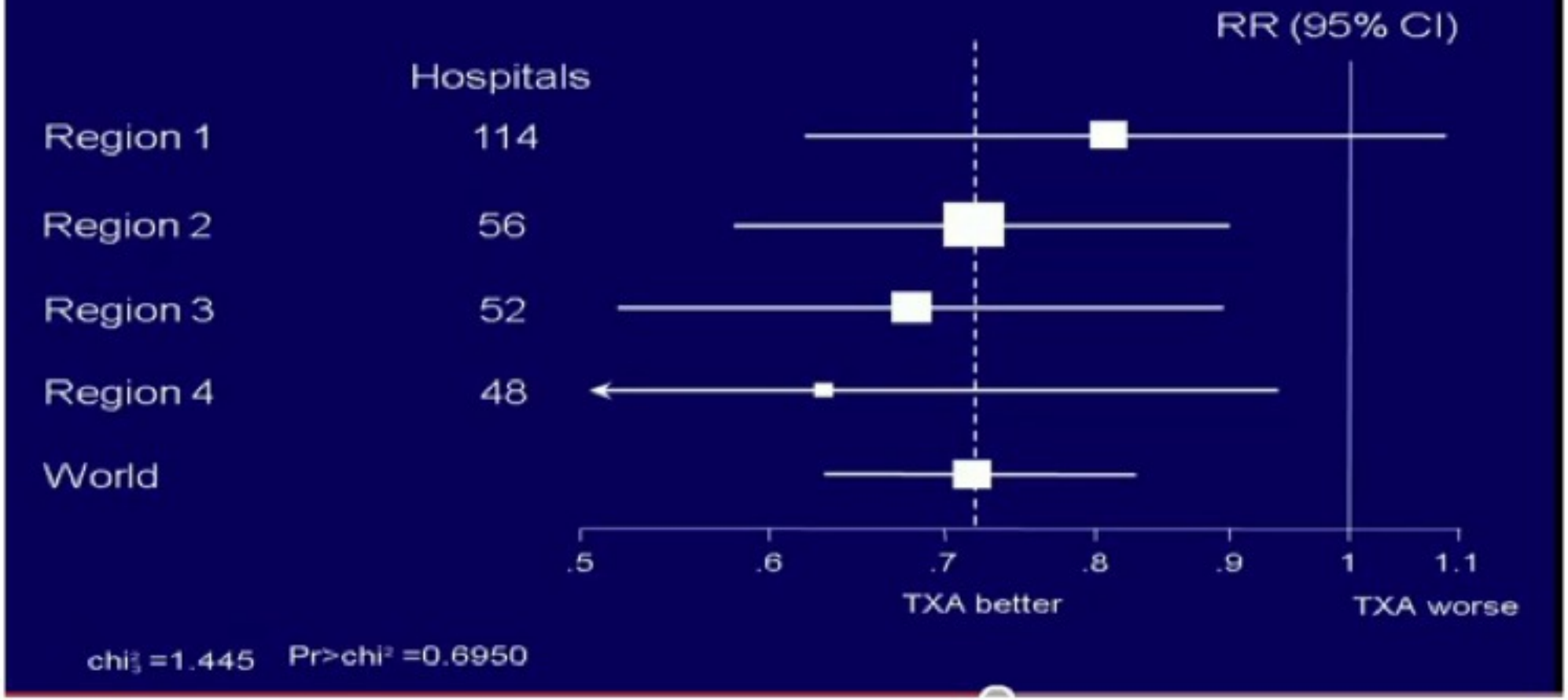
REGION	RR	99% Conf. Interval
Asia	0.92	0.80 – 1.05
Central and South America	0.90	0.76 – 1.06
Africa	0.90	0.75 – 1.08
North America, Europe, Australia	0.90	0.70 – 1.15

Table 1 shows the effect of TXA on mortality by geographic region. There was no significant difference in the effect of TXA by region.

GENDER	RR	99% Conf. Interval
Male	0.92	0.84 – 1.00
Female	0.86	0.70 – 1.06

Table 2 shows the effect of TXA on mortality by sex. There was no significant difference in the effect of TXA by sex.

Bleeding deaths: geographical region



Lancet. March 24, 2011

The importance of early treatment with tranexamic acid in bleeding trauma patients: an exploratory analysis of the CRASH-2 randomised controlled trial

*The CRASH-2 collaborators**

- Because tranexamic acid is thought to exert its effect through inhibition of fibrinolysis, we undertook exploratory analyses of its effect on death due to bleeding.

- We examined the effect of tranexamic acid on death due to bleeding according to time to treatment, severity of haemorrhage as assessed by systolic blood pressure, Glasgow coma score (GCS), and type of injury. All analyses were by intention to treat.

Results:

- Early treatment (≤1 h from injury) significantly reduced the risk of death due to bleeding (198/3747 [5·3%] events in tranexamic acid group *vs* 286/3704 [7·7%] in placebo group; relative risk [RR] 0·68, 95% CI 0·57–0·82; p<0·0001).
- Treatment given between 1 and 3 h also reduced the risk of death due to bleeding (147/3037 [4·8%] *vs* 184/2996 [6·1%]; RR 0·79, 0·64–0·97; p=0·03).
- Treatment given after 3 h seemed to increase the risk of death due to bleeding (144/3272 [4·4%] *vs* 103/3362 [3·1%]; RR 1·44, 1·12–1·84; p=0·004).
- We recorded no evidence that the effect of tranexamic acid on death due to bleeding varied by systolic blood pressure, Glasgow coma score, or type of injury.

Interpretation

- **Tranexamic acid should be given as early as possible to bleeding trauma patients. For trauma patients admitted late after injury, tranexamic acid is less effective and could be harmful.**

OPEN ACCESS Freely available online

PLoS one

Cost-Effectiveness Analysis of Administering Tranexamic Acid to Bleeding Trauma Patients Using Evidence from the CRASH-2 Trial

Carla Guerriero[1]*, John Cairns[1], Pablo Perel[2], Haleema Shakur[2], Ian Roberts[2], on behalf of CRASH 2 trial collaborators

- TXA within 3 hours of injury saved an estimated 372, 315 and 755 LYs per 1,000 trauma patients in Tanzania, India and the UK respectively.
- Cost of TXA/1,000 patients=$17,483 Tanzania, $19,550 India and $30,830 in the UK.
- Incremental cost per LY gained of administering TXA is $48, $66 and $64 in Tanzania, India and the UK respectively.
- Early administration of TXA to bleeding trauma patients is likely to be highly cost effective in low, middle and high income settings.

- Michael Parr was Chairman of an Australian NovoNordisk Advisory Board, member of a NovoNordisk International Trauma Education Advisory Board, and member of the CONTROL trial steering committee

First Case Report

Treatment of traumatic bleeding with recombinant factor VIIa

Gili Kenet, Raphael Walden, Arieh Eldad, Uri Martinowitz

Surgical intervention failed to stop life-threatening bleeding caused by injury complicated by severe coagulopathy. Administration of recombinant factor VIIa immediately corrected the coagulopathy and bleeding stopped.

THE LANCET • Vol 354 • November 27, 1999

The Journal of TRAUMA® Injury, Infection, and Critical Care

Recombinant Factor VIIa as Adjunctive Therapy for Bleeding Control in Severely Injured Trauma Patients: Two Parallel Randomized, Placebo-Controlled, Double-Blind Clinical Trials

Kenneth David Boffard, MD, Bruno Riou, MD, PhD, Brian Warren, MD, Philip Iau Tsau Choong, MD, Sandro Rizoli, MD, Rolf Rossaint, MD, Mads Axelsen, MD, and Yoram Kluger, MD, for the NovoSeven Trauma Study Group

- **Conclusion:**

  rFVIIa resulted in a significant reduction in RBC transfusion in severe blunt trauma.

  The safety of rFVIIa was established in these trauma populations within the investigated dose range.

J Trauma. 2005;59:8 –18.

CONTROL™

CLINICAL TRIAL ON THE EFFECT OF rFVIIa ON TRAUMATIC BLOOD LOSS

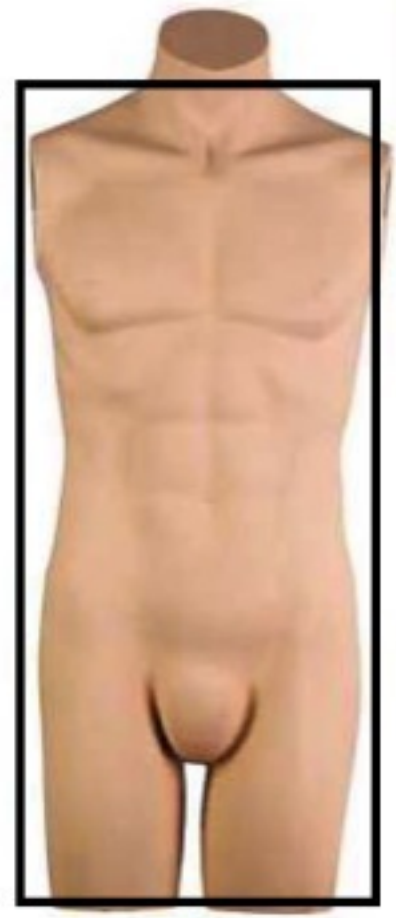
F7Trauma-1711

- Phase III study
- A multi-center, randomized, double-blind, parallel group, placebo controlled trial to evaluate the efficacy and safety of activated recombinant factor VII (rFVIIa/NovoSeven®/ NiaStase®) in severely injured trauma patients with bleeding refractory to standard treatment

CONTROL™

Inclusion Criteria

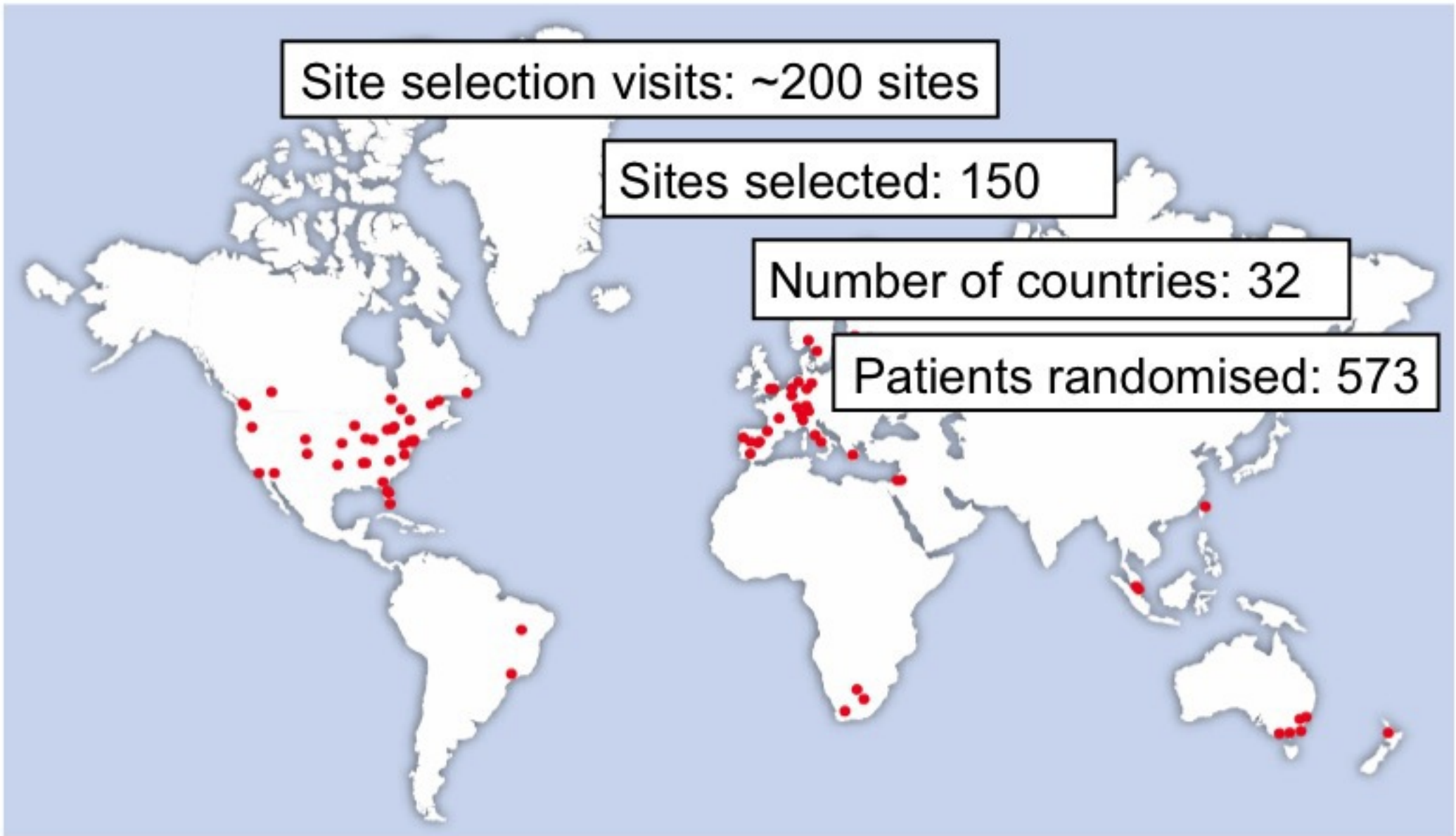
- Aged 18-70
- Blunt/penetrating trauma with evidence of active torso haemorrhage
- Hypotension due to hypovolemia
- Ongoing volume loading
- Acidosis
- Minimum 4U PRBC



CONTROL™

CLINICAL TRIAL ON THE EFFECT OF rFVIIa ON TRAUMATIC BLOOD LOSS

August 2005-Sept 2008



- “Due to an lower mortality than anticipated (around 10% in the phase 3 trial in total compared to more than 25% in the phase 2 trial), a futility analysis was conducted to assess the likelihood of reaching a successful outcome on the primary endpoint.
- The analysis predicted a low likelihood of obtaining a positive trial outcome with the planned study population, and as a consequence, Novo Nordisk has decided to discontinue the trial.
- The decision is not due to safety concerns. The independent Data Monitoring Committee recommended continuation of the study.”

Novo Nordisk press release 2008

Summary

- Mortality and morbidity
  - No significant differences between placebo and rFVIIa
- Transfusion requirements: blunt patients (post-dosing to 24h)
  - Significant reduction in RBC (1.2 units), FFP (2.2 units) and total allogeneic blood (3.6 units)
  - No differences in platelets, fibrinogen concentrate or cryoprecipitate
- Safety
  - No statistical difference for total SAEs

J Trauma. 2011 May 23. [Epub ahead of print]

Recombinant Activated Factor VII Safety in Trauma Patients: Results From the CONTROL Trial.

- Data from 560 patients.
- Subjects were monitored for adverse events (AEs) after rFVIIa or placebo administration. Incidences, timing, and presence of risk factors were reported by site investigators, supported by external study monitors and overseen by an independent Data Monitoring Committee.

J Trauma. 2011 May 23. [Epub ahead of print]

Recombinant Activated Factor VII Safety in Trauma Patients: Results From the CONTROL Trial.

- No differences in overall mortality, organ system failure, or AEs, serious AEs, or medical events of special interest.
- Arterial and venous thromboembolic (TE) events and their risk factors were similar in both groups.
- The greatest risk factor for TE events was a chest injury requiring mechanical ventilation >3 days (86%).
- Four site investigator-reported MIs in the rFVIIa group of which only one met diagnostic criteria pre-established by the Data Monitoring Committee. There were no reported myocardial infarctions in the placebo group. Troponins were increased in 30% of all patients.
- The rate of acute respiratory distress syndrome was lower in the rFVIIa (3.0%) than in the placebo (7.2%) group ($p = 0.022$).

- rFVII associated with an imbalance of investigator-reported AMI/ NSTEMI, but no increased risk for other AEs, including TE complications.

CRASH-2

CONTROL™
CLINICAL TRIAL ON THE EFFECT OF rFVIIa ON TRAUMATIC BLOOD LOSS

- Mortality benefit for at risk of bleeding
- Mechanism?
- Safety as long as given early
- Cheap

- Transfusion benefit in massive transfusion setting
- Known mechanism
- Safety?
- Expensive