

Massive Haemorrhage, the Role of the Laboratory and Coagulation Support

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Massive Haemorrhage

INTRODUCTION

ROLE of Laboratory

? **Supply Blood and Blood Products**

- Quickly and effectively
- Within the required timescale

? **Produce results –haematology and clinical chemistry**

? **Give advice on appropriate blood products to be given**

? **Ensure products are available at all times including re-stocking**

Massive Haemorrhage

DEFINITION

? Massive Haemorrhage

=loss of one Mean Normal BV* within 24 hours

=loss of 50% Mean Normal BV* within 3 hours

=blood loss rate 150mls/min

? Massive Transfusion

> 40% Mean Normal BV*: absolute red cell requirement

>150% Mean Normal BV*: plasma products and platelets

[*Mean Normal Blood Volume =70ml/kg]

Massive Haemorrhage

GUIDELINES

- ? BCSH, Clin Lab Haemat 10 1988 Guidelines for transfusion for massive blood loss
- ? Stainsby, Br J Anaesth 85 2000 Management of massive blood loss: a template guideline
- ? BCSH, Br J Haematol 122 2003 Guidelines for the use of platelet transfusions
- ? BCSH, Br J Haematol 126 2004 Guidelines for the use of fresh-frozen plasma, cryoprecipitate and cryosupernatant
- ? GHNHSFT Guidelines for Massive Transfusion (TRPOL004)
www.glos.nhs.uk/ACUTEPathology/Cheltenham/BloodTransfusion
- ? GHNHSFT Guidelines for Obstetric Haemorrhage (DSG15)

Massive Haemorrhage

PRINCIPLES

- ? arrest bleeding
- ? **contact key personnel**
- ? restore circulating volume
- ? **request laboratory investigations**
- ? request suitable red cells
- ? consider use of platelet concentrates
- ? consider use of FFP and/or cryoprecipitate
- ? suspect disseminated intravascular coagulation

Massive Haemorrhage

PRINCIPLES: contact key personnel

- ? prompt and effective communication
- ? use of a clinical co-ordinator
- ? The following should always be involved
 - surgical team
 - duty anaesthetist
 - blood transfusion BMS
 - consultant haematologist

Massive Haemorrhage

PRINCIPLES: laboratory investigations

- ? take samples at earliest opportunity and lab must process ASAP
- ? ensure correct sample identity (for transfusion samples)
- ? remember we may need to give platelets or plasma before results available (following 100% Mean Normal BV loss)
- ? laboratory parameters are essential to guide the selection of optimal products to transfuse- but may show whole picture
- ? repeat FBC, PT, APTT, fibrinogen: every 4 hours, or after 1/3 blood volume replacement, or after blood component infusion
- ? liaise with clinical haematologist and blood transfusion BMS's to guide appropriate and effective replacement therapy
- ? Lab MUST communicate results to those at the patients side ASAP

Massive Transfusion

COMPONENT: Red Cells

- ? blood needed **immediately**: **emergency** group O Rh D negative
- ? blood needed in **15-60 minutes**: **uncrossmatched** ABO group specific will be provided when blood group known
- ? blood needed in **>60 minutes**: fully **crossmatched** blood will be provided
- ? **consider red cell salvage**

Massive Transfusion

COMPONENT: platelets

- ? **anticipate** platelet count $<50 \times 10^9/l$ after 150 -200% Mean Normal BV replacement get platelets ordered and ready
- ? target platelet count (recommendation grade C, level IV)
 - $>50 \times 10^9/l$ for acute bleeding
 - $>100 \times 10^9/l$ for multiple trauma or CNS injury
- ? Dose (10^9) = $PI \times BV (=70ml/kg) \times 3/2$
 - $<20kg$: 10-15ml/kg body weight
 - $>20kg$: one 'adult therapeutic dose'

BCSH, Br J Haematol 122 2003 Guidelines for the use of platelet transfusions

Massive Transfusion

COMPONENT: plasma

- ? **anticipate** coagulation factor deficiency after blood loss of 150% Mean Normal Blood Volume
- ? PT/APTT $>1.5 \times$ mean control correlates with increased risk of surgical bleeding
- ? replacement therapy guided by **timely** coagulation tests (recommendation grade B, level IIb)
- ? dose: 12-15 ml/kg body weight = approx 1 litre or 4 units for an adult (aim for PT and APTT $< 1.5 \times$ mean control)

BCSH, Br J Haematol 126 2004 Guidelines for the use of fresh-frozen plasma, cryoprecipitate and cryosupernatant

Massive Transfusion

COMPONENT: cryoprecipitate

- ? aim to replace fibrinogen, von Willebrands factor and factor VIII
- ? fibrinogen $<0.5\text{g/l}$ strongly associated with microvascular bleeding
- ? commonly associated with massive transfusion and disseminated intravascular coagulation
- ? replacement therapy guided by **timely** coagulation tests
- ? dose: 2 packs for an adult (aim for fibrinogen $>1.0\text{g/l}$)

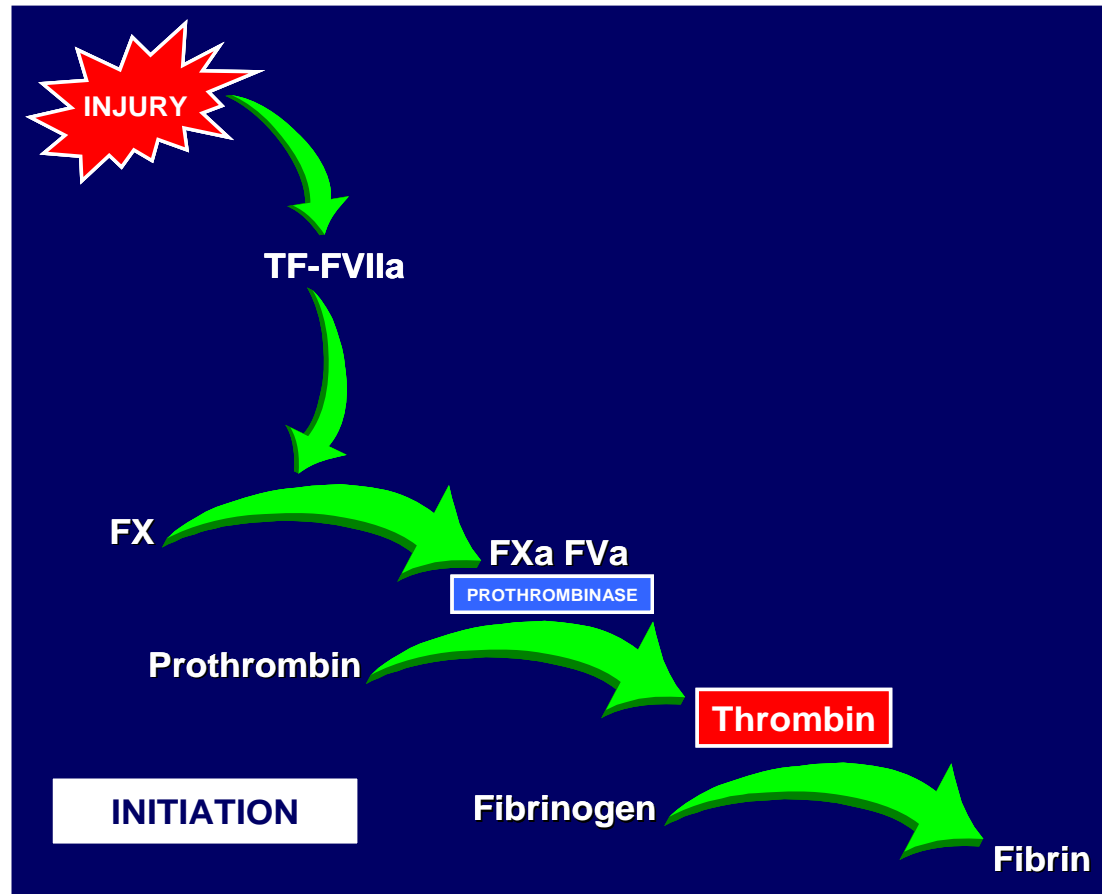
BCSH, Br J Haematol 126 2004 Guidelines for the use of fresh-frozen plasma, cryoprecipitate and cryosupernatant

Massive Transfusion

DISSEMINATED INTRAVASCULAR COAGULATION

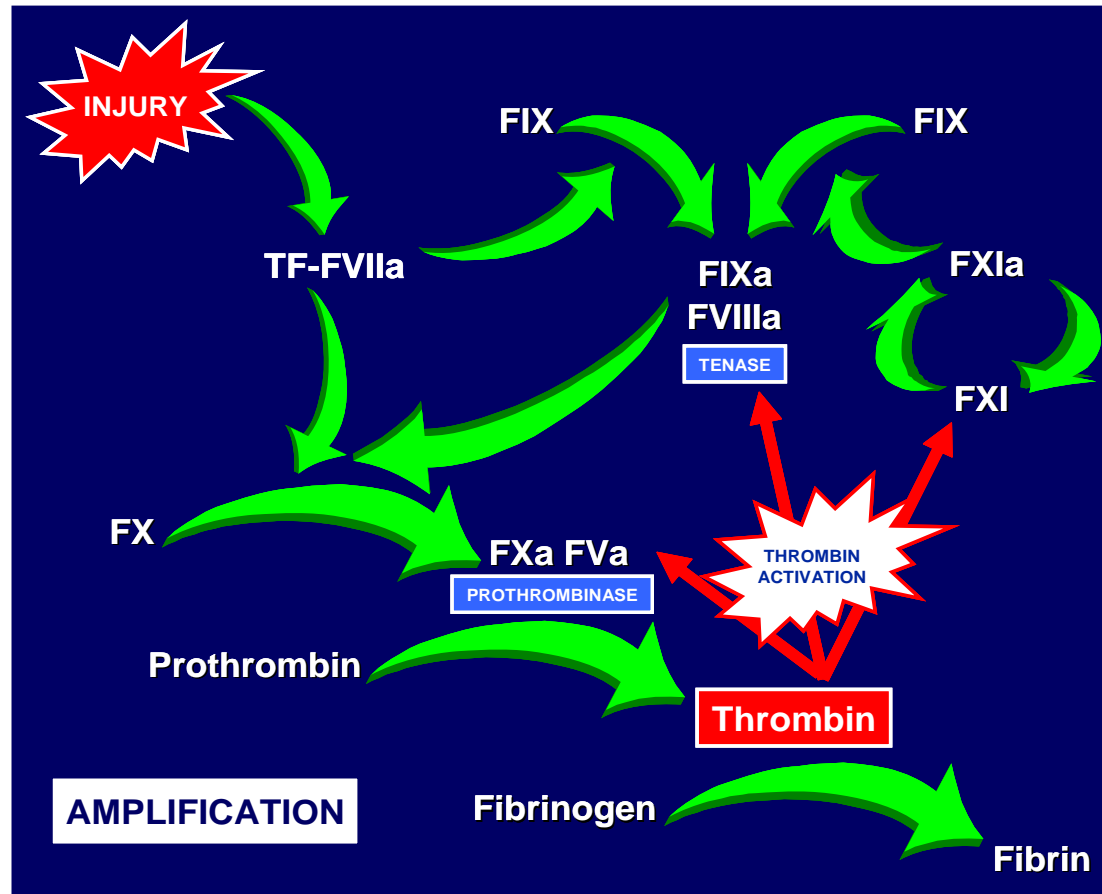
- ? dilutional coagulopathy: crystalloid/packed cell resuscitation dilutes normal clotting proteins and platelets and may impair platelet function
- ? hypothermia: inhibits coagulation protein and platelet function and slows fibrin formation
- ? metabolic derangements: acidosis and hypocalcaemia are common in shock/resuscitation -both compromise clotting
- ? consumptive coagulopathy: depletion of coagulation factors in microangiopathic clot formation

Coagulation Pathway



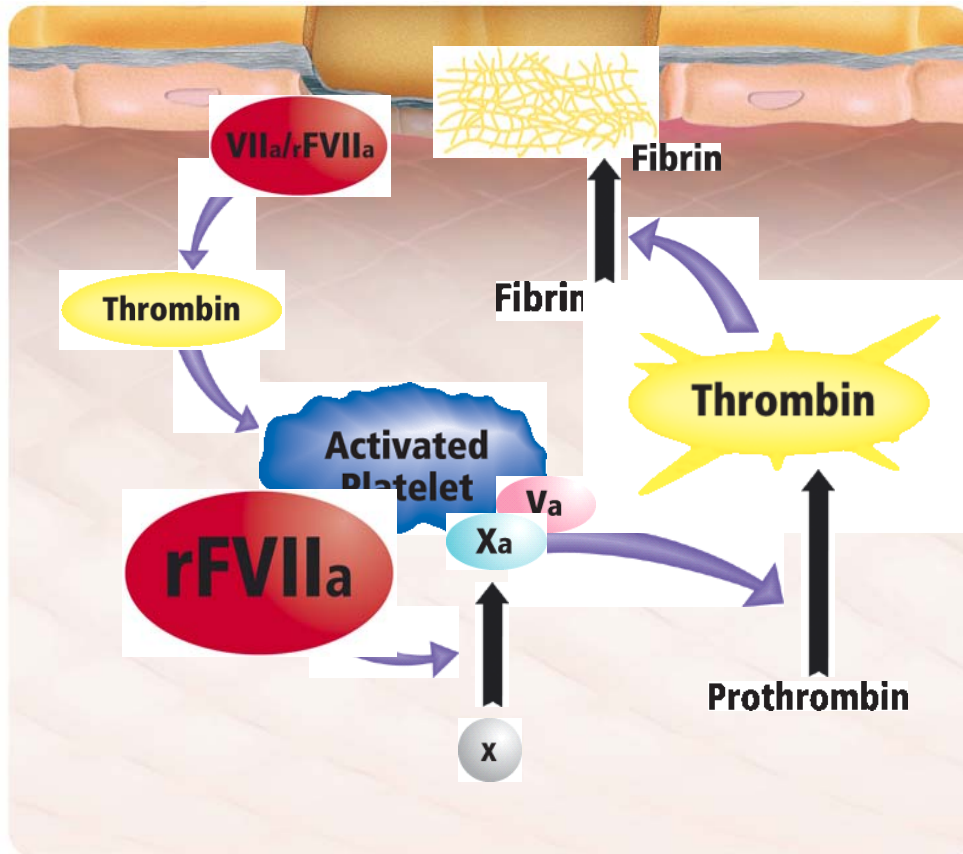
Hoffman, Thromb Haemost 85 2001

Coagulation Pathway



Hoffman, Thromb Haemost 85 2001

Recombinant FVIIa



rFVIIa binds to the surface of the locally activated platelets where it leads to the generation of a **THROMBIN BURST**

mechanism **INDEPENDENT** of the amplification of thrombin production by FVIIIa and FIXa

Recombinant FVIIa

APPLICATIONS

- ? licensed for surgical prophylaxis and treatment of bleeding episodes in patients with inherited or acquired haemophilia with inhibitors to coagulation factors VIII or IX
- ? increasing off license experience for treatment of bleeding patients with thrombocytopenia and defined platelet function defects
- ? increasing off license experience for patients undergoing liver transplantation and following **traumatic, surgical and obstetric haemorrhage refractory to the transfusion of blood products**
- ? may reduce perioperative blood loss and transfusion requirement if given pre-operatively

Recombinant FVIIa

EVIDENCE: critical bleeding

- ? case reports, anecdotal experience, and limited clinical trials describe these uses whilst data from randomised clinical trials are limited
- ? recent trends in rFVIIa usage in non-approved settings raises concern about its safety, efficacy, and cost
- ? rFVIIa dosing for these broad clinical applications is not standardized
- ? industry and clinical registries may enhance indications, limitations, optimal dose schedule and prognostic scoring systems



**Announcing the launch of the
Northern Europe Factor VIIa in Obstetric
Haemorrhage (NEFOH) Registry**



Recombinant FVIIa

EVIDENCE: critical bleeding

Treatment of traumatic bleeding with recombinant factor VIIa

Gili Kenet, Raphael Walden, Arie 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

Kenet, Lancet 354 1999

Recombinant FVIIa

EVIDENCE: critical bleeding

ORIGINAL PAPER

Vox Sanguinis (2004) 87, 34 - 40

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Recombinant activated factor VII (NovoSeven™): addition to replacement therapy in acute, uncontrolled and life-threatening bleeding

A. Mayo,^{1,2} M. Misgav,³ Y. Kluger,^{1,2} R. Geenberg,⁴ D. Pauzner,⁵ J. Klausner² & O. Ben-Tal^{3,6}

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Recombinant FVIIa

EVIDENCE: critical bleeding

- ? 13 patients (surgical, trauma and obstetric)
- ? prospective protocol driven trial
- ? dose range 90-120 g/kg
- ? outcome measures
 - bleeding response
 - survival at 48 h and 15 days
 - blood product use
- ? scoring system for coagulopathy

Mayo, Vox Sang 87 2004

Recombinant FVIIa

EVIDENCE: critical bleeding

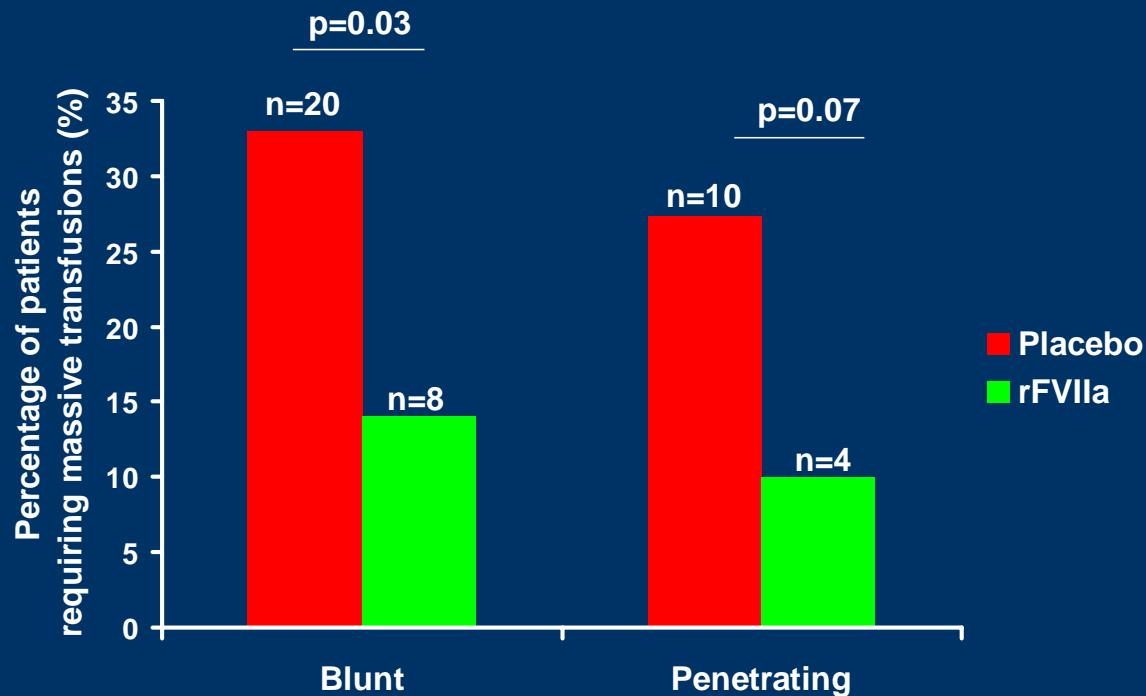
Recombinant Factor VIIa as Adjunctive Therapy for Bleeding Control in Severely Injured Trauma Patients: Two Parallel Randomized Placebo Controlled Double-Blind Clinical Trials

- ? severely bleeding blunt or penetrating trauma patients randomized to rFVIIa or placebo in addition to standard treatment
- ? n =301 patients: 143 blunt trauma and 134 penetrating trauma patients eligible for analysis
- ? significant reduction in RBC transfusion in severe blunt trauma (similar trends in penetrating trauma)
- ? safety of rFVIIa was established in these trauma populations within the investigated dose range

Boffard, Journal of Trauma 59 2005

Recombinant FVIIa

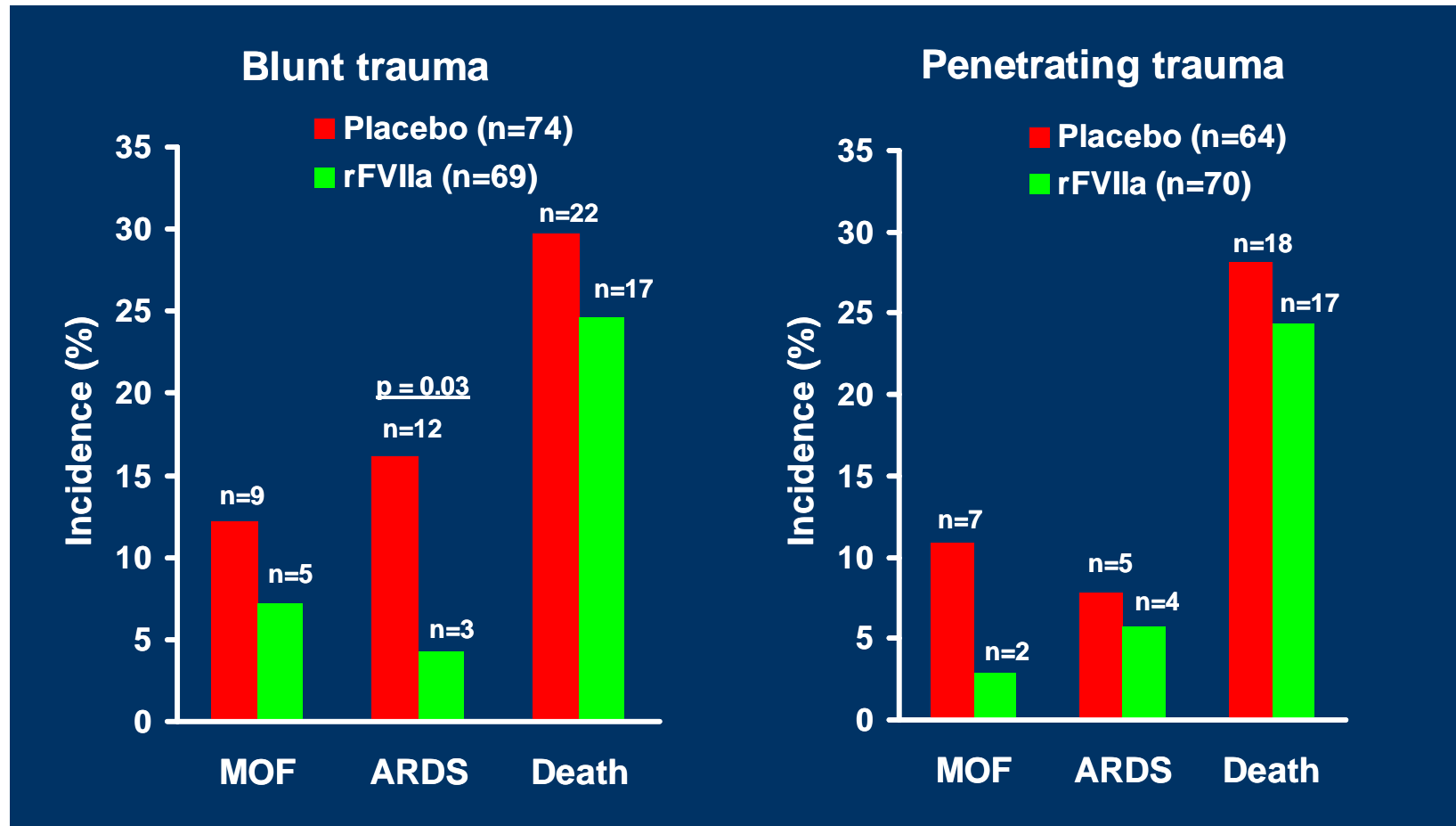
massive transfusion* requirements in the first 48 hours



* massive transfusion defined as >20 units of RBC (>12 units after trial drug initiation in addition to ≥ 8 units given before trial drug initiation)

Boffard, Journal of Trauma 59 2005

Recombinant FVIIa



Boffard, Journal of Trauma 59 2005

Recombinant FVIIa

INDICATIONS

failure of surgical intervention and/or blood component therapy and

- ① **massive haemorrhage**: continued life threatening bleeding following correction of clotting times to 1.5x control mean and resuscitation of fibrinogen levels to >1.0g/L
- ② **haemorrhage in a patient with severe thrombocytopenia** (platelet count <10x10⁹/L) which is refractory to platelet transfusion
- ③ uncontrolled bleeding in **Jehovah's Witnesses** who have explicitly stated that they do not wish to receive blood products

Recombinant FVIIa

CONTRAINDICATIONS

- ① age <16 years

The use of rFVIIa in non-haemophilia bleeding conditions in paediatrics

Mathew, Thromb Haemost 92 2004

- ② thrombotic tendency (venous thrombosis, thrombotic thrombocytopenic purpura) or a history of a recent atherosclerotic event (stroke, myocardial infarction, peripheral vascular disease)
- ③ evidence of sepsis and/or disseminated intravascular coagulation

Recombinant FVIIa

DOSING

- ? rVIIA WILL BE ISSUED FROM BLOOD TRANSFUSION AFTER DISCUSSION WITH CLINICAL HAEMATOLOGIST
- ? initial standard dose 90µg/kg body weight (haemophiliac license)

Body Weight (kg)	Dose micrograms/kg			
	30	60	90	120
10	0.30	0.60	0.90	1.20
15	0.45	0.90	1.35	1.80
20	0.60	1.20	1.80	2.40
25	0.75	1.50	2.25	3.00
30	0.90	1.80	2.70	3.60
35	1.05	2.10	3.15	4.20
40	1.20	2.40	3.60	4.80
45	1.35	2.70	4.05	5.40
50	1.50	3.00	4.50	6.00
55	1.65	3.30	4.95	6.60
60	1.80	3.60	5.40	7.20
65	1.95	3.90	5.85	7.80
70	2.10	4.20	6.30	8.40
75	2.25	4.50	6.75	9.00
80	2.40	4.80	7.20	9.60
85	2.55	5.10	7.65	10.20
90	2.70	5.40	8.10	10.80
95	2.85	5.70	8.55	11.40
100	3.00	6.00	9.00	12.00

Total dose in milligrams
Vial sizes are 1.2mg, 2.4mg and 4.8mg

Recombinant FVIIa

COST

- ? NovoSeven 1.2mg (60 KIU): £664.72 (May 2003)
- ? Standard Dosing 90µg (4.5KIU)/kg
- ? Average Dose 70x90/1200 (6 vials) = £3988.32

Haemostatic Agents

ANTICOAGULANT REVERSAL

Clinical Event	Action
INR above therapeutic range but <8.0 and no bleeding	Stop Warfarin Restart Warfarin when INR in therapeutic range
INR >8.0 and no bleeding or minor bleeding	Stop Warfarin Give Vitamin K 1 - 2 mg orally * Restart Warfarin when INR in the therapeutic range
Major Bleeding	Admit patient Stop Warfarin Give Beriplex (prothrombin complex concentrate) 50 iu/kg iv <u>OR</u> Fresh Frozen Plasma 15 ml/kg ** Give Vitamin K (Konakion MM) 5 mg iv ***

* Draw up 0.1 - 0.2 ml of Konakion MM in 1 ml graduated syringe and squirt into patients mouth (taste is very bitter)

** Discuss with Consultant Haematologist

*** Draw up 0.5 ml of Konakion MM and add to a 50 ml bag of Dextrose. Infuse over 20 minutes

Haemostatic Agents

OTHER

- ? antifibrinolytics
 - tranexamic acid
 - aprotinin
- ? desmopressin (DDAVP)
- ? thrombin (topical)

Massive Haemorrhage

PRINCIPLES

- ? arrest bleeding
- ? **contact key personnel**
- ? **laboratory to react quickly**
- ? restore circulating volume
- ? **appropriate laboratory investigations carried out ASAP**
- ? request suitable red cells and ensure adequate supplies
- ? consider use of platelet concentrates
- ? consider use of FFP and/or cryoprecipitate
- ? suspect disseminated intravascular coagulation
- ? consider use of pharmacological haemostatic agents



Major Obstetric Haemorrhage Drill

? April 05 GRH and April 06 CGH

? Main issues

- Clinical co-ordinator required
- Clear communication with transfusion requirements and problems
- 1 person who is able to have dialogue about situation and make decisions about blood and blood product support ?? Anaesthetist
- Be able to view blood results in clinical area
- Hands free phone
- Clear instructions about emergency blood use e.g. location and communication when used