PCCs, Novoseven and Fibrinogen in Liver Disease - Literature Review and Single Centre Experience

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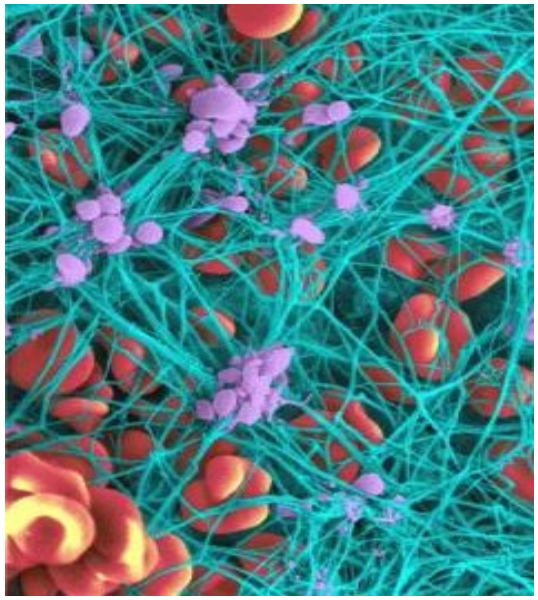
Normal haemostatic response



(Credit: Yuri Veklich and John W. Weisel, University of Pennsylvania School of Medicine)

- Complex
  - multiple pathways (procoagulant & regulatory)
- Triggered
  - Tissue injury
- Magnitude of response
  - appropriate to the injury
- Contained (spatially and temporally)

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Haemostatic interventions - Indications

- Prophylactic – prevent bleeding
  - Identification of patients for intervention
  - No validated global test to predict bleeding tendency
  - No universal haemostatic agent
- Therapeutic – treat bleeding
  - Multitude of tests employed to identify deficiencies
  - Tailored replacement therapy, aimed at normalisation of various parameters
  - Shot gun approach

Haemostatic Therapies – Aim and methods

- Facilitate clot formation through adequate thrombin generation **AND/OR**
- Stabilise the formed clot, through inhibition of clot lysis

- Increase the deficient coagulation factors
  - Fresh frozen plasma
  - Prothrombin complex concentrates
  - Cryoprecipitate
  - Fibrinogen concentrate

- Alter and improve platelet function
  - DDAVP
  - Platelet transfusions
- Inhibit clot lysis
  - Tranexamic acid/ Aprotinin
- Activate the coagulation through alternate pathways
  - Novoseven
  - FEIBA (Factor Eight Inhibitor Bypassing Agent) – VII, IX, X, II, both zymogens and active factors

(Credit: Yuri Veklich and John W. Weisel, University of Pennsylvania School of Medicine)

Coagulopathy of Liver Disease - The Balance

Procoagulants

Anticoagulants

- The balance is in part related to the underlying liver function
- The balance between hypercoagulability and haemorrhagic tendency is dependant in part on the clinical scenario
- Spontaneous bleeding is uncommon
- The risk of bleeding with procedures is difficult to assess in individual patients

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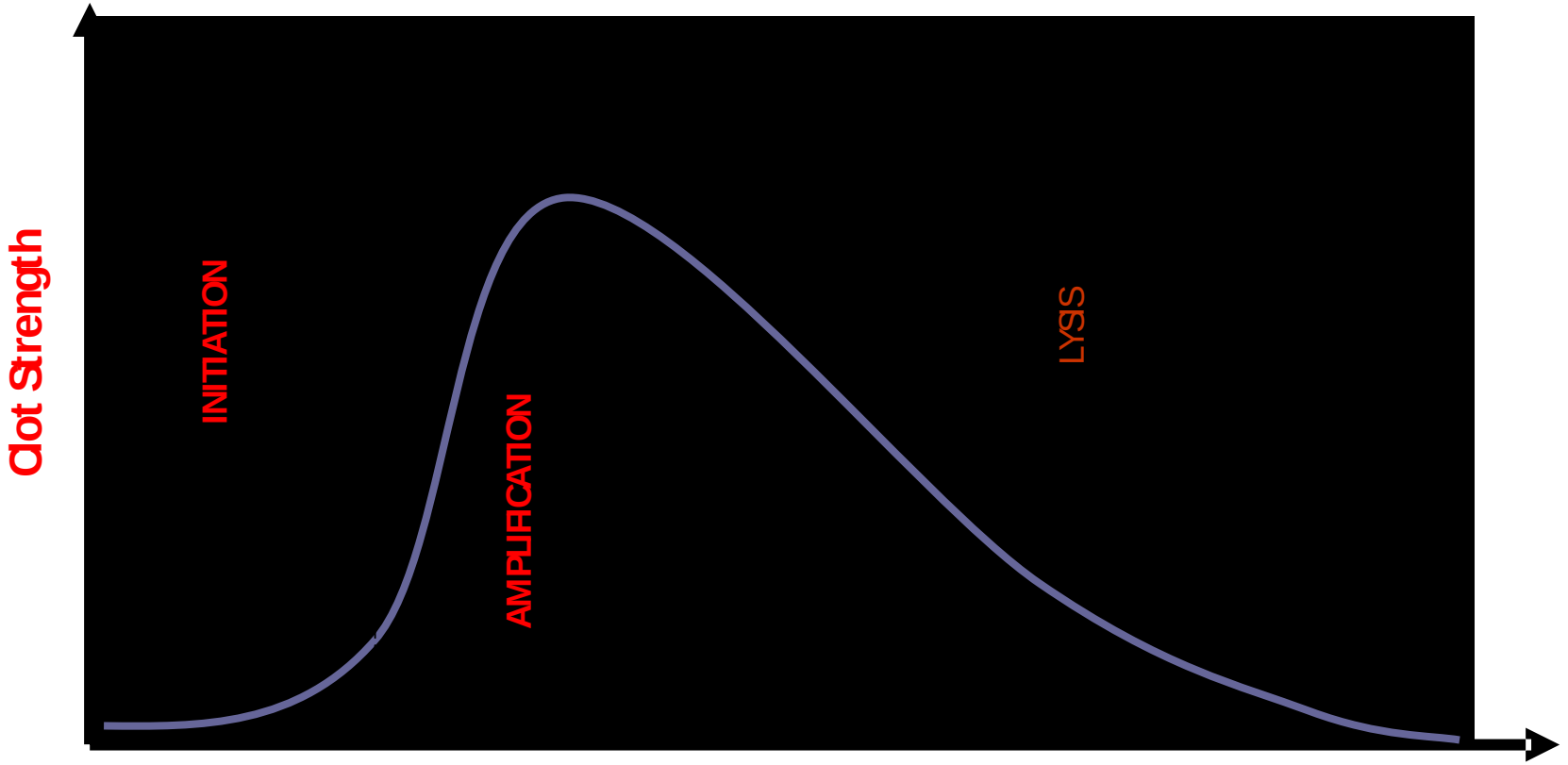
Clot-based assays (PT and APTT)

- Incubate plasma with reagents necessary for coagulation
  - Phospholipid, co-factors
  - Trigger or activator
  - Calcium
- Measure time taken to form fibrin strands
- Beginnings of a clot formation are visible after < 5% of prothrombin has been converted to thrombin
- Surrogates for thrombin generation

Limitations of ‘Clotting Time’



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Thrombin generation tests

- In vitro test that reflects the 'potential' of thrombin generation in a plasma sample
- Has been shown to predict for thrombosis
- More 'physiological' tissue factor (TF)
- TF + Ca+ Fluorogenic substrate + Patient Plasma
- Various assays available

  CAT (Thrombinoscope)

  Technothrombin TGA (Technoclone)

  Thrombopath (IL)

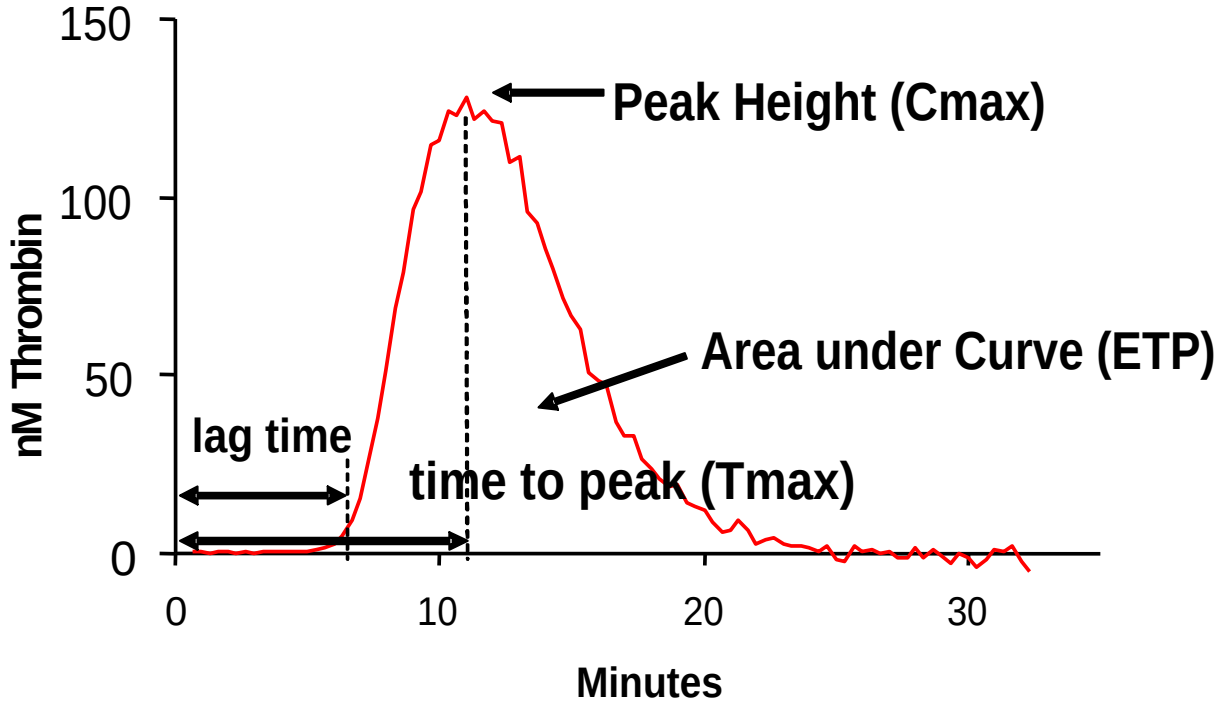
Hron G et al JAMA. 2006 Jul 26;296(4):397-402

Tripodi et al J Thromb Haemost. 2008 Aug;6(8):1327-33

Besser M et al J Thromb Haemost. 2008 Oct;6(10):1720-5

Thrombin generation curve

- Thrombin appears and disappears during blood clotting
- Research tool that allows us to measure the time course of thrombin generation



(from www.thrombinoscope.com)

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Cirrhosis – normal TG, with abnormal conventional tests

- 44 patients with cirrhosis
- All classes of Child pugh
- Maximum PT ratio – 1.8
- Vacutainer
- TF – 1 pmol/L, Phospholipids – 0.5 µ mol/L
- Thrombomodulin – 4 nmol/L
- Automated Flurometer

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Tripodi et. al. Hepatology 2005

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Evidence of Normal Thrombin Generation in Cirrhosis Despite Abnormal Conventional Coagulation Tests

Armando Tripodi, Francesco Salerno, Veena Chantarangkul, Marigrazia Clerici, Massimo Cazzaniga, Massimo Primignani, and Pier Mannuccio Mannucci

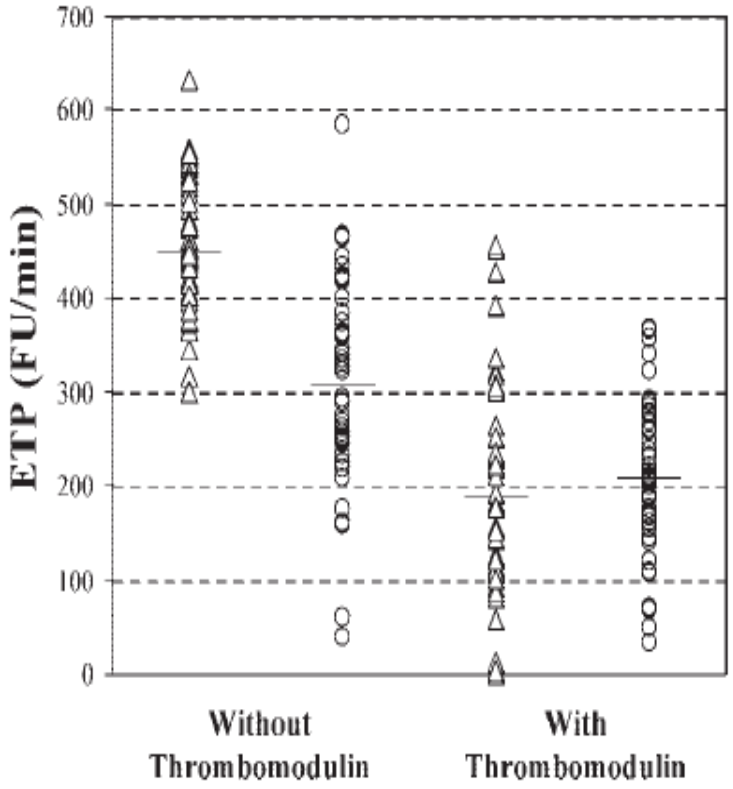

Table 2. Hemostatic Parameters in Patients With Liver Cirrhosis (n = 44) and in Controls (n = 44)

Parameters	Patients	Controls	*P* Value
PT (ratio)*	1.26 (1.02-2.53)	0.99 (0.89-1.18)	< .001
APTT (ratio)*	1.31 (0.95-4.00)	0.99 (0.80-1.19)	< .001
Protein C (%)†	39 (9-77)	105 (79-142)	< .001
Antithrombin (%)†	52 (16-94)	101 (76-112)	< .001
Factor II (%)†	49 (16-81)	105 (84-130)	< .001
Factor II/protein C (ratio)‡	1.28 (0.78-2.43)	1.00 (0.63-1.33)	< .001
Factor VIII (%)†	132 (43-446)	124 (65-223)	.14

Tripodi et. al. Hepatology 2005

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Discussion

- In patients with cirrhosis the reduction of factor II (procoagulant drive) is balanced by the reduction of protein C (anticoagulant drive) thus leaving the coagulation balance unaltered
- Explain the rather mild bleeding tendency seen in patients with cirrhosis compared to patients with inherited bleeding disorders
- PT and APTT do not measure the anticoagulant drive
- Potential role of TGT in predicting bleeding in this group of patients needs to be investigated

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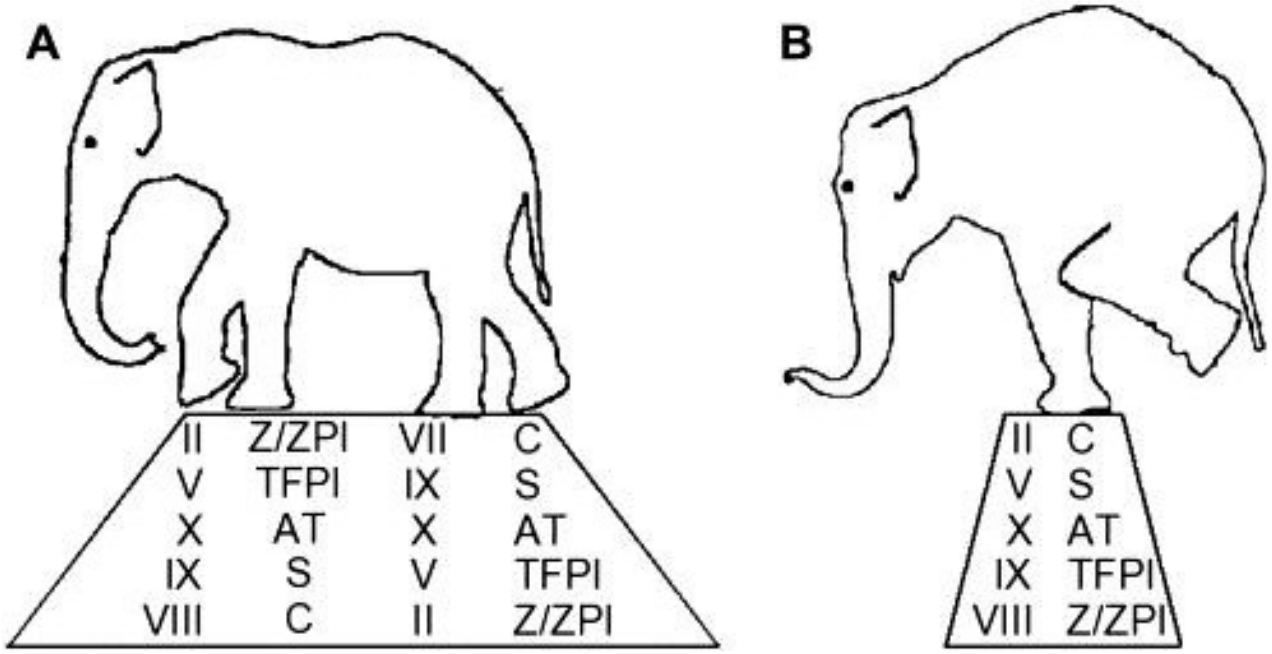
Rebalanced Haemostasis – MAY BE



Dougald M. Monroe, and Maureane Hoffman,
Clinics In Liver Disease 2009; 13:1-9

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Bleeding tendency in patients with decompensated chronic liver disease.

Table 2. Underlying Conditions That Explain the Bleeding Tendency in Patients with Decompensated Chronic Liver Disease.

Hemodynamic alterations owing to portal hypertension[20,28,29]
Endothelial dysfunction[20]
Development of endogenous heparin-like substances owing to bacterial infections[20,29,30]
Renal failure[20,31]

Tripodi A, Mannucci PM. N Engl J Med 2011;365:147-156

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Liver Disease Coagulopathy – Early years

- Ebeling *et al*, NEJM, 1956 &
- Finkbiner *et al*, Am J Medicine, 1959
  - The use of fresh blood decreased the bleeding intra operatively and post operatively in patients with liver disease
- Sherlock, 1968
  - The risk of bleeding with a liver biopsy is increased if the prothrombin time is prolonged more than three seconds

Prothrombin complex concentrates in liver disease

- *4 publications between 1975 and 2011 – 3 from UK & 1 from Germany*
- PCCs are a variable mixtures of Vitamin K-dependant proteins
- The Vitamin K-dependant proteins are
  - Factor VII 4 – 6 hrs
  - Factor IX 21 – 30 hrs
  - Factor X 27 – 48 hrs
  - Factor II 42 – 72 hrs
  - Protein C 6 – 8 hrs
  - Protein S 28 – 36 hrs
  - Protein Z
- Three factor concentrates (II, IX & X)
- Four factor concentrates (+ VII)

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The use of fresh frozen plasma or a concentrate of factor IX as replacement therapy before liver biopsy

B. G. GAZZARD, J. M. HENDERSON, AND ROGER WILLIAMS
From the Liver Unit, King's College Hospital and Medical School, London

Gut, 1975, **16**, 621-625

- 30 patients, PT prolonged more than 4 s
- 15/30 - 600 ml of FFP + 300 ml 6 hrs later
- 15/30 - concentrate of 2000 units of factors II, IX, and X, and less than 80 units of factor VII (prothromboplex)

- FFP Group – 20% corrected PT within 3 s of control
- Concentrate group – 47% corrected PT within 3s of control value

- No clinical evidence of bleeding
- 3/30 patients developed Hepatitis B infection

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USE OF FACTOR-VII-RICH PROTHROMBIN COMPLEX CONCENTRATE IN LIVER DISEASE

- Green *et al*, Lancet, 1975
- 13 patients with liver disease and abnormal coagulation
- Prothrombin complex concentrate of factors II, VII, IX, & X produced by the Oxford Haemophilia Centre

- Liver Biopsy, if PT was within 3 s of control value
- Adequate correction of coagulation was achieved immediately after the infusion in all cases.
- Within 4 hours there was some deterioration and by 24 hours the results approximated to pre-infusion values.

CORRECTION OF ABNORMAL COAGULATION IN CHRONIC LIVER DISEASE BY COMBINED USE OF FRESH-FROZEN PLASMA AND PROTHROMBIN COMPLEX CONCENTRATES

- Mannucci *et al* , Lancet 1976
- Compared 3 different modalities of Rx in patients with liver disease
- 10ml/kg of FFP - 11 patients
  - 4/11 normalised PT, 5/11 normalised APTT
- Concentrates - 11 patients
  - 25 units/kg of Prothromboplex (II, IX,X)
  - PT normalised in 5/11
  - 25 units/kg of Factor VII concentrate
  - normalisation of PT in 10/11 patients & abnormal APTT in 9/11
- FFP and Concentrates - 9 patients
  - FFP(8 ml/kg) + Prothromboplex (12u/kg) + factor VII rich concentrate (12u/kg)
  - Normalisation of PT and APTT in 8/9 patients

Efficacy and safety of a prothrombin complex concentrate with two virus-inactivation steps in patients with severe liver damage

- Lorenz *et al*, 2003
- 22 patients with liver disease, pre procedure or for bleeding
- The dosage & duration of the PCC therapy was determined by the intensity of the coagulopathy, degree and localization of the bleeding, and by the clinical picture

Table 1 Demographic and laboratory data of the enrolled patients ($n = 22$) at baseline before the first treatment

Variable	Median	Range
Age (years)	45	(29–65)
Gender (male/female)	15/7	
Height (cm)	172	(154–185)
Weight (kg)	70	(52–106)
Factor II (%)	39.0	(14.0–83.0)
Factor VII (%)	24.0	(9.0–109.0)
Factor IX (%)	56.5	(23.0–119.0)
Factor X (%)	48.0	(20.0–90.0)
Protein C (%)	30.5	(14.0–71.0)
Quick's value (%)	38.5	(23.0–91.0)
Activated partial thromboplastin time (s)	38.0	(24–67)

liver disease

Indications	Number
Bleeding	
Stomach ulcer	2
Gastro-intestinal haemangioma	1
Invasive diagnostic intervention	
Bone marrow biopsy	3
Lymph node biopsy	2
Liver biopsy	9
Pancreas biopsy	1
Colon biopsy	1
Therapeutic intervention	
Operation due to fracture of femur	2
Endoscopic retrograde cholangiopancreatography with stone extraction	1

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Efficacy and safety of a prothrombin complex concentrate with two virus-inactivation steps in patients with severe liver damage

- Initial PCC dosage ranged from 1000 to 4000 IU (median 1500 IU)
- the Quick's test increased from 39% to a maximum of 65%
- The *in vivo* recovery of factor IX and protein C was 1.2–1.4 (IU/dl)/(IU/kg),
- Activation markers
  - an increase in FVIIa, F1 + 2 and TAT values were observed
  - D-dimer values showed a transient increase
  - fibrin monomer remained almost unchanged.
- No clinical evidence of thromboembolic events
- Clinical efficacy was judged as 'very good' in 76% of patients after the first (n 21) treatment

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Safety of Recombinant Activated Factor VII in Randomized Clinical Trials

Marcel Levi, M.D., Jerrold H. Levy, M.D., Henning Friis Andersen, M.Sc., and David Truloff, D.V.M.

- Off label use for prevention and control of bleeding
- 35 RCTs (26 – patients, 9 - healthy volunteers)
- 4468 subjects (4119 patients, 349 healthy volunteers)
- High doses of rVIIa on an off-label basis increased the risk of arterial but not venous thromboembolic events, especially with increasing age (>65 yrs)

Table 2. Odds Ratios for Thromboembolic Events.

Thromboembolic Event	rFVIIa (N=2583)	Placebo (N=1536)	Odds Ratio (95% CI)*	P Value
	number (percent)†			
All events	264 (10.2)	134 (8.7)	1.17 (0.94–1.47)	0.16
Arterial events	141 (5.5)	49 (3.2)	1.68 (1.20–2.36)	0.003
Venous events	137 (5.3)	88 (5.7)	0.93 (0.70–1.23)	0.61

* Odds ratios were calculated by means of logistic regression with adjustment for age and type of bleeding.
† The percentage of thromboembolic events was calculated as the number of patients with events as a proportion of the number of patients who received the assigned study drug.

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Levi M et al. N Engl J Med 2010;363:1791-1800

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All Arterial Thromboembolic Events, According to Cause of Bleeding

Table 5. All Arterial Thromboembolic Events, According to Cause of Bleeding.*

Cause of Bleeding	No. of Studies	rFVIIa	Placebo	Odds Ratio (95% CI)†	P Value	Reference
		no./total no. (%)‡				
Spontaneous central nervous system bleeding	5	84/974 (8.6)	23/423 (5.4)	1.67 (1.03–2.69)	0.04	Mayer et al.[6-9]
Advanced liver disease	7	23/795 (2.9)	6/449 (1.3)	2.19 (0.89–5.42)	0.09	Bosch et al.,[10,11] Carreno et al.,[12] Lodge et al.,[13,14] Planinsic et al.,[15] Shao et al.[16]
Trauma	3	19/409 (4.6)	15/428 (3.5)	1.39 (0.69–2.77)	0.36	Boffard et al.[17]
Cardiac surgery	3	9/153 (5.9)	4/114 (3.5)	1.59 (0.47–5.34)	0.45	Diprose et al.,[18] Ekert et al.,[19] Gill et al.[20]
Traumatic brain injury	1	2/61 (3.3)	1/36 (2.8)			Narayan et al.[21]
Spinal surgery	1	1/36 (2.8)	0/13			Sachs et al.[22]
Other causes	6	3/155 (1.9)	0/73			Chuansumrit et al.,[23] Friederich et al.,[24] Pihusch et al.,[25] Raobaikady et al.[26]

* References are provided for the trials that have been published. The remaining data are provided in the Supplementary Appendix.
† Odds ratios were calculated by means of logistic regression with adjustment for age. Odds ratios were not calculated in instances with very few events.
‡ The percentage of thromboembolic events was calculated as the number of patients with events as a proportion of the number of patients who received a study drug.

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Levi M et al. N Engl J Med 2010;363:1791-1800

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Prophylactic Activated Recombinant Factor VII in Liver Resection and Liver Transplantation: Systematic Review and Meta-Analysis

- 4 RCTs
- The primary outcome measures were:
  - mortality rate
  - transfusion requirements
  - adverse events including thromboembolic complications
- The secondary outcome measures were:
  - reduction of bleeding complications assessed by any scale
  - improvement in coagulation status assessed by any scale
  - Recurrence of bleeding after the surgery;
  - bleeding during the surgery
  - length of hospitalization

Results: Four randomized controlled trials were included. There were no significant differences between rFVIIa and placebo for mortality (OR 0.96; 95% CI 0.35–2.62), red blood cell units (MD 0.32; 95% CI −0.08–0.72) or adverse events (OR 1.55; 95% CI 0.97–2.49).

Anesthesiology 2005; 102:269–75

Lodge et.al

Recombinant Coagulation Factor VIIa in Major Liver Resection

- Placebo, 20 or 80 µg/kg 5 min pre skin incision
- no statistically significant decrease in the red cell transfusion requirements
- Arterial TE only in the treatment group – 1 MI

Table 2. Trial Results

	Placebo	20 µg/kg rFVIIa	80 µg/kg rFVIIa	*P* Value
No. of patients who underwent surgery	63	63	59	
Perioperative* requirements (no. of patients)				
Erythrocytes (primary endpoint)	23 (37%)	26 (41%)	15 (25%)	0.09
Fresh frozen plasma	10 (16%)	17 (27%)	16 (27%)	0.13
Platelet concentrate	2 (3%)	3 (5%)	0	
Systemic hemostatic drug	3 (5%)	3 (5%)	4 (7%)	0.76
Amount of red blood cells transfused, ml†	1,024 ± 1,001	1,354 ± 989	1,036 ± 904	0.78
Blood loss parameters				
Blood loss during surgery, ml	1,422 ± 1,271	1,372 ± 1,301	1,073 ± 997	0.07
Change in hematocrit during surgery, %	−6.7 ± 5.7	−6.4 ± 6.7	−3.7 ± 5.0	0.04
Drain volume 0–24 h after surgery, ml	409 ± 322	451 ± 698	346 ± 209	0.59
Hematocrit of surgical drain volume, %	3.3 ± 4.7	5.1 ± 7.1	2.8 ± 4.8	0.32
Operating time, h	4.06 ± 1.75	4.04 ± 1.84	3.61 ± 1.56	0.21

Safety and hemostatic effect of recombinant activated factor VII in cirrhotic patients undergoing partial hepatectomy: a multicenter, randomized, double-blind, placebo-controlled trial

- Placebo, rFVIIa 50 or 100 µg/kg 10 min pre skin incision
- Doses repeated two hourly till end of surgery, to max of 4 doses
- 98% of patients included had a PT < 4s of control value
- Primary end points – proportion of patients requiring RBC transfusion, and the no. of transfusions
- The differences between the groups – NS
- Arterial TE seen in the treatment group only

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Shao et.al Am J Surgery 2005

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Efficacy and Safety of Repeated Perioperative Doses of Recombinant Factor VIIa in Liver Transplantation

- Placebo, 60 or 120µg/kg 10 min pre skin incision
- Doses x 2 hrly, until 30 min prior to expected reperfusion of the transplanted liver. Final dose at wound closure
- Compared to placebo, rFVIIa was associated with ↓ in RBC transufsion
- 15% (60µg/kg) 23% (120µg/kg) and the study was powered only to show a 40% reduction
- TE – comparable to other studies, not listed

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Lodge. et.al Liver transplantation 2005

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Safety and Efficacy of a Single Bolus Administration of Recombinant Factor VIIa in Liver Transplantation Due to Chronic Liver Disease

- Randomized to 1 of 4 parallel study groups.
- Single intravenous bolus of rFVIIa (20, 40, or 80 µg/kg) or placebo prior to surgery.
- the doses studied did not have any effect on the number of RBC transfusions required
- Arterial thromboembolic events were similar in all the groups

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Planinsic et al. Liver transplantation 2005

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Recombinant Activated Factor VII in Critical Bleeding After Orthotopic Liver Transplantation

S. Busani, G. Semeraro, C. Cantaroni, M. Masetti, M. Marietta, and M. Girardis

- critical bleeding definition
  - Blood loss of more than 200–500 mL/h for at least 2 consecutive hours
  - within 15 days after OLT
  - refractory to standard transfusion protocol
  - No surgical or radiological intervention indicated
  - No congenital coagulation disorders
  - No preoperative anticoagulants or antiplatelet therapy

Transplantation Proceedings, 40, 1989–1990 (2008)

Recombinant Activated Factor VII in Critical Bleeding After Orthotopic Liver Transplantation

S. Busani, G. Semeraro, C. Cantaroni, M. Masetti, M. Marietta, and M. Girardis

- 135 OLTs
- 7 critical bleeding
  - 4 graft primary non-function
  - 1 fulminant liver failure
  - 1 gastric hemorrhage
  - 1 hemothorax after thoracic drain placement

- 90µg / kg of rVIIa
- Rpt 3 hrs later in 2 patients
- Bleeding controlled x 6
- 1 died due to haemorrhage

Table 1. Blood Loss and Need for Transfusion Products Before and After rFVIIa Administration

	Before rFVIIa	After rFVIIa	*P*
Blood loss (mL/h)	400.0 ± 97.2	198.5 ± 201.6	.04
RBC (U)	8.7 ± 6.2	4.5 ± 3.9	NS
FFP (U)	6.1 ± 3.1	3.8 ± 3.7	NS
Platelets (U)	11.4 ± 6.0	4.2 ± 4.2	.02

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PCCs in liver disease – single centre experience

Anja Drebes[1] Andrew Burroughs[2], Alex Gatt[1], Susan Mallett[3], Edward Tuddenham[1], Pratima Chowdary[1]

KD Haemophilia Centre and Thrombosis Unit[1], Dept. of Hepatology[2], Dept. of Anaesthetics3, Royal Free Hospital, London, UK

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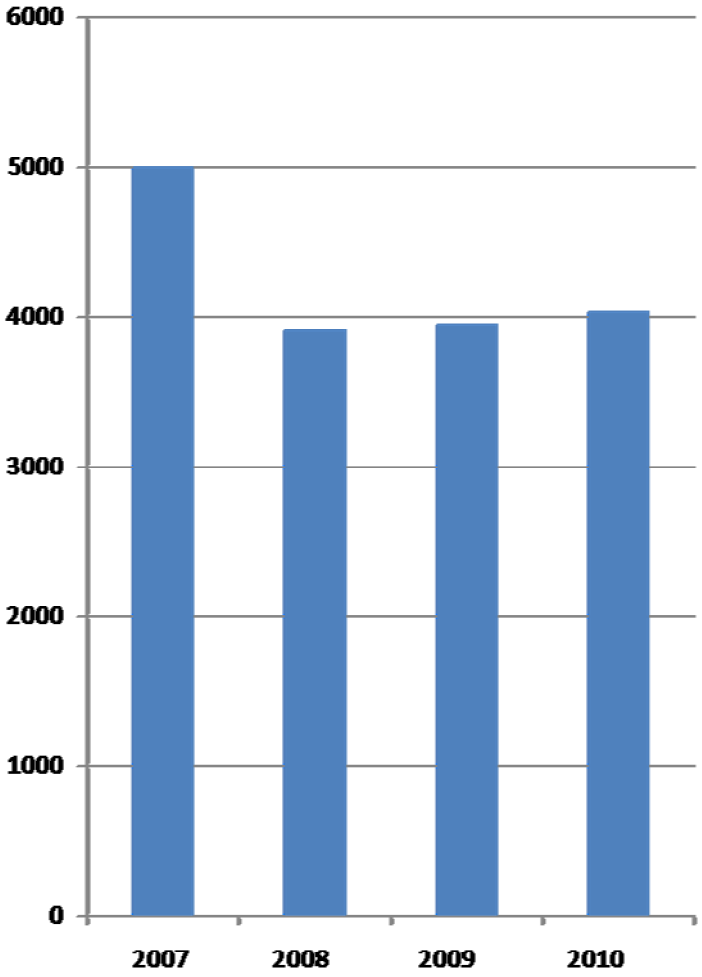
Background, 2005 – Snapshot of clinical practise at RFH

- Massive transfusion protocol – Replacement therapy based on laboratory tests
- One protocol for all specialities
- Novoseven in common use pre-terminally for rescuing patients with bleeding
- Point of care testing for INR and FBC – variable
- Point of care testing with TEG in some instances
- Minimal use of cryoprecipitate
- Very few requests for fibrinogen

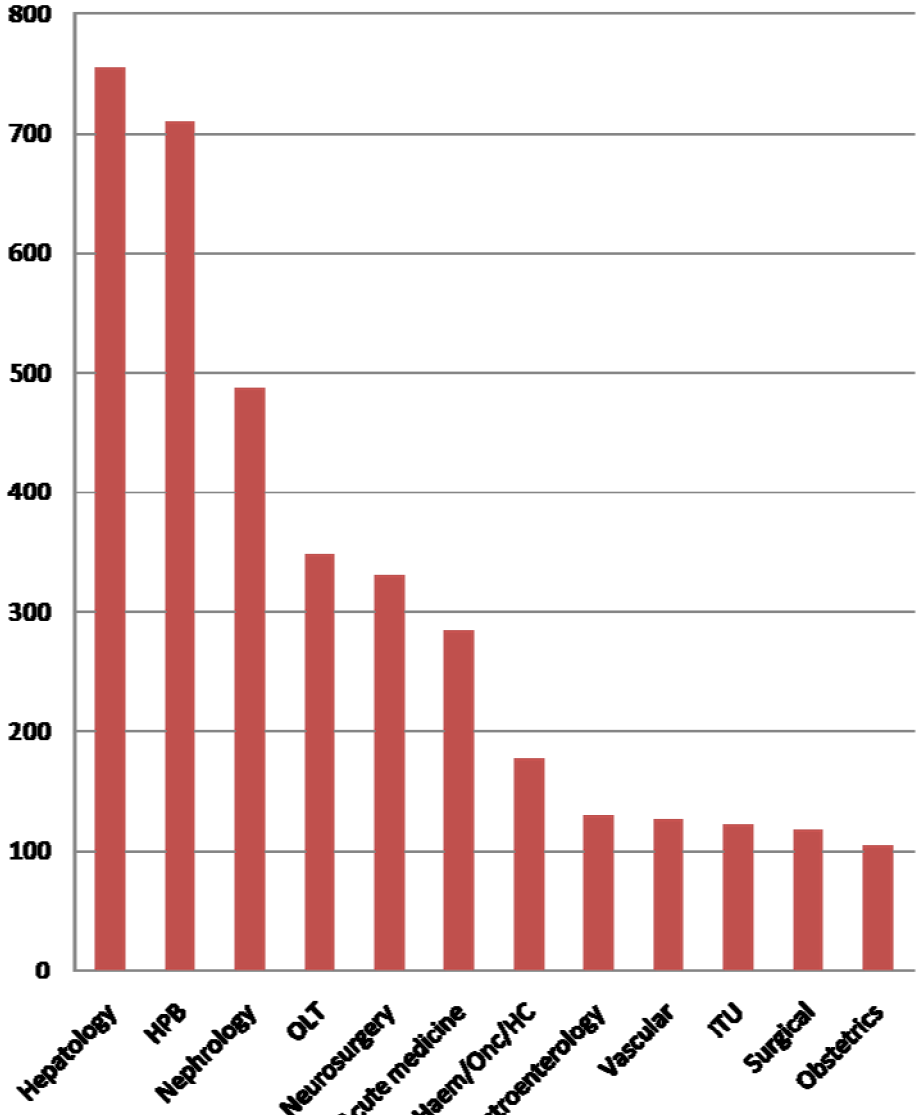
PCCs – Current practise

- For correction of abnormal coagulation
  - Volume is an issue
  - Time is essence – severely bleeding patient in theatre, wards or in ITU
  - Pre-procedure, where an appropriate plan not put in place, for correction of coagulation to prevent cancellation of procedures
  - Pre-terminally to assure anaesthetists and surgeons that all that can be done has been done !

No: of Units of FFP Transfused



FFP by Speciality for 2010



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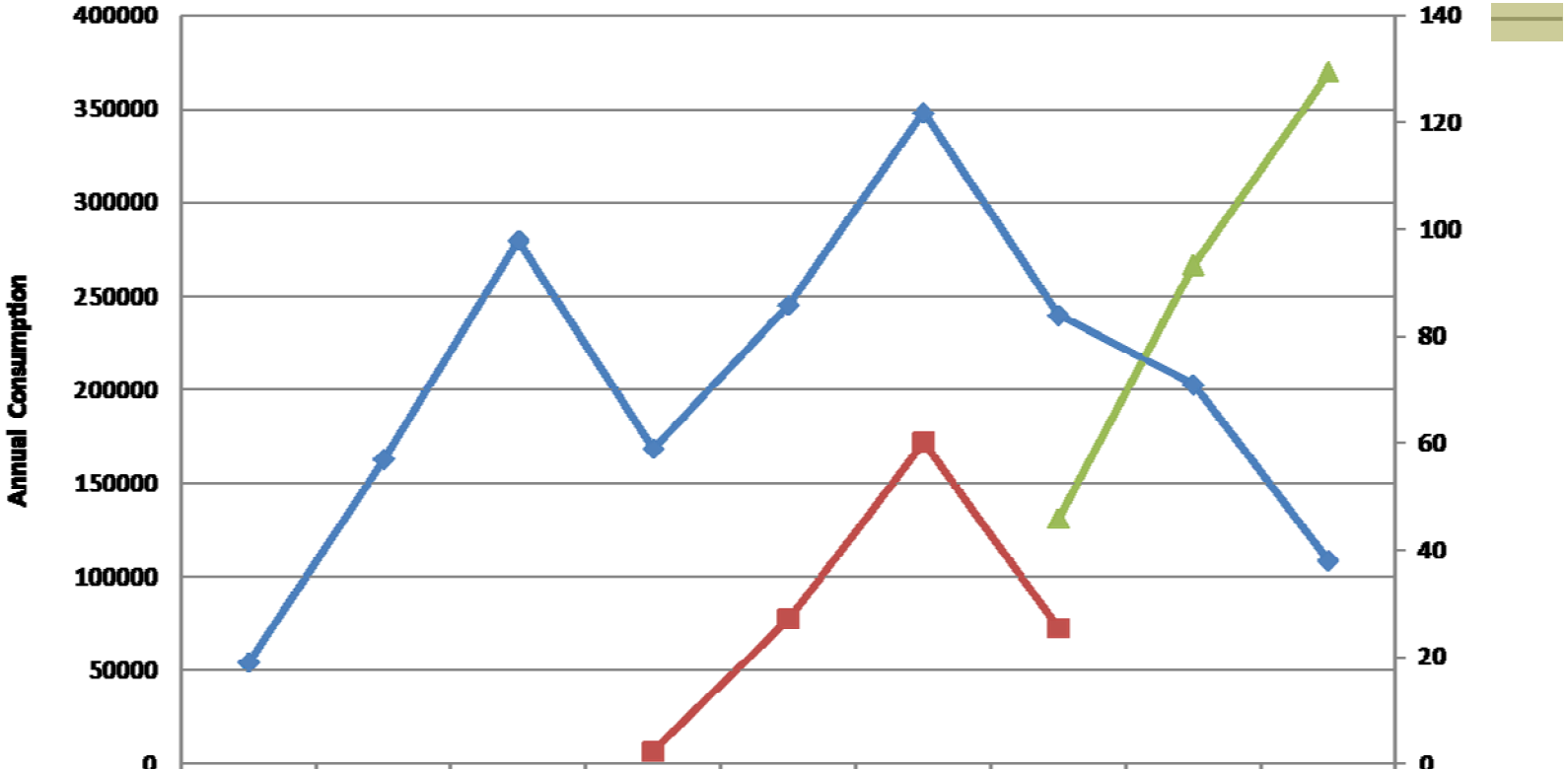
Usage of coagulation factor concentrates for non-haemophilia patients



	2002	2003	2004	2005	2006	2007	2008	2009	2010
octoplex				7000	77500	172000	72500		
Beriplex							131500	267000	370000
novo	19	57	98	59	86	122	84	71	38

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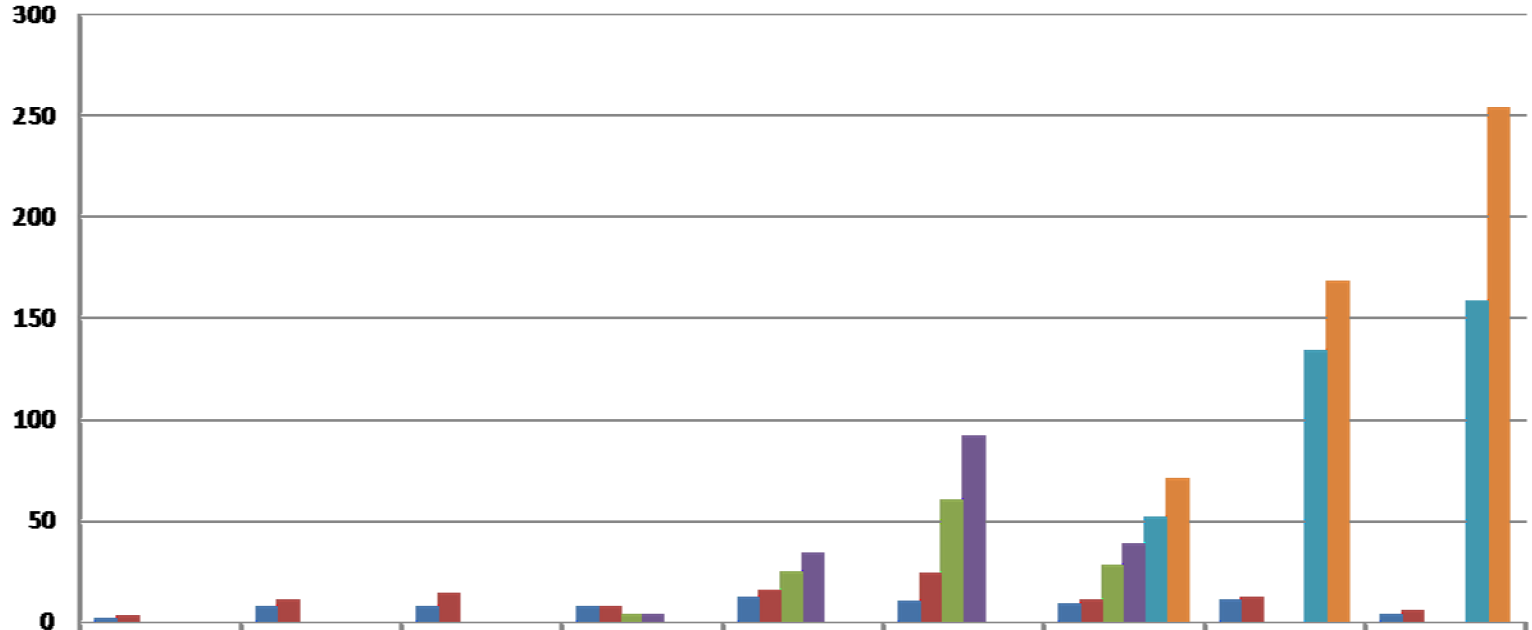
No: of Patients receiving coagulation factor Concentrates and number of episodes of administration



	2002	2003	2004	2005	2006	2007	2008	2009	2010
Novo	2	8	8	8	12	10	9	11	4
Novo.E	3	11	14	8	16	24	11	12	6
Octa				4	25	60	28		
Octa. E				4	34	92	39		
Beri							52	134	159
Beri.E							71	168	254

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PCCs – retrospective case note review

- PCCs (Beriplex P/N, Octaplex)
- 3 year period (Jan 2008 to Dec 2010)
- 123 administration events in 63 patients
- 23 episodes in 10 patients were excluded from data analysis due to data issues

- Data collection
  - Indication
  - Dose
  - Dose / kg
  - Lab results, pre and post PCC
  - Background medical conditions
  - Clinical outcome

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Patients – baseline characteristics

Gender	
Male	39
Female	24
Total	63

Age	
< 40	39
40 - 60	24
> 60 yrs	7
Total	71

Underlying Liver disease	
Chronic liver disease (CLD)	33
Acute liver failure (ALF)	9
Liver transplant for CLD	8
Liver transplant for ALF	4
Partial hepatectomy for underlying malignancy	3
Hepatocellular carcinoma	2
Other	4
Total	63

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Patients – thrombotic risk factors

History of previous venous or arterial thromboembolic events	No: of patients
Prev. DVT or PE	8
Prev. Myocardial infarction or known coronary artery disease	6
Prev. Stroke	2

Number of Cardiovascular risk factors	No: of patients
1	10
2	8
3 or more	5

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PCC administration – Details

Indication	No. of Episodes
Active bleeding	56
Recent bleeding, correction of coagulopathy	14
Pre procedure	53

Products	No. of Episodes
PCCs	123
Beriplex P/N	110
Octaplex	13
Fibrinogen Concentrate + PCC	45
Additional rVIIa	3

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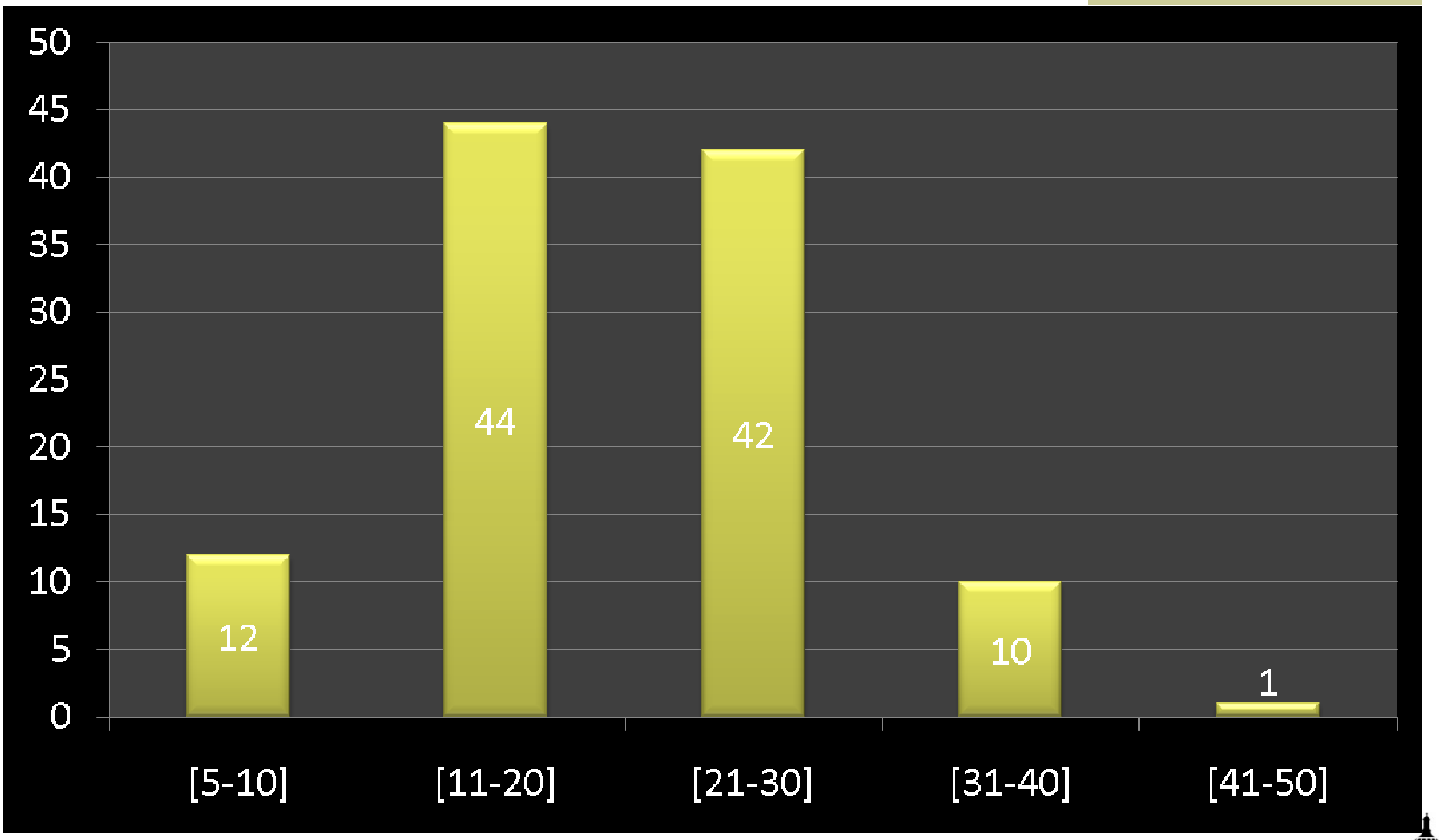
PCC dosing



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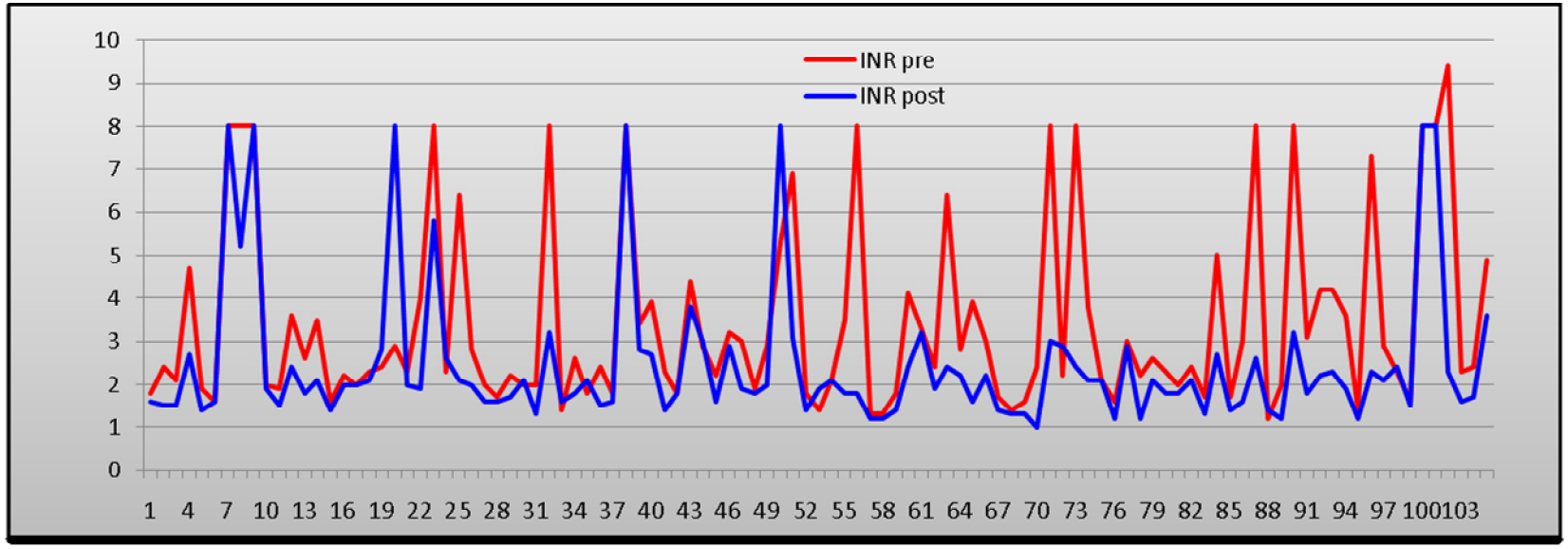
INR – Pre and Post PCCs



INR	Pre	Post
Median	2.4	2
10th Centile	1.6	1.34
90th centile	8	3.44

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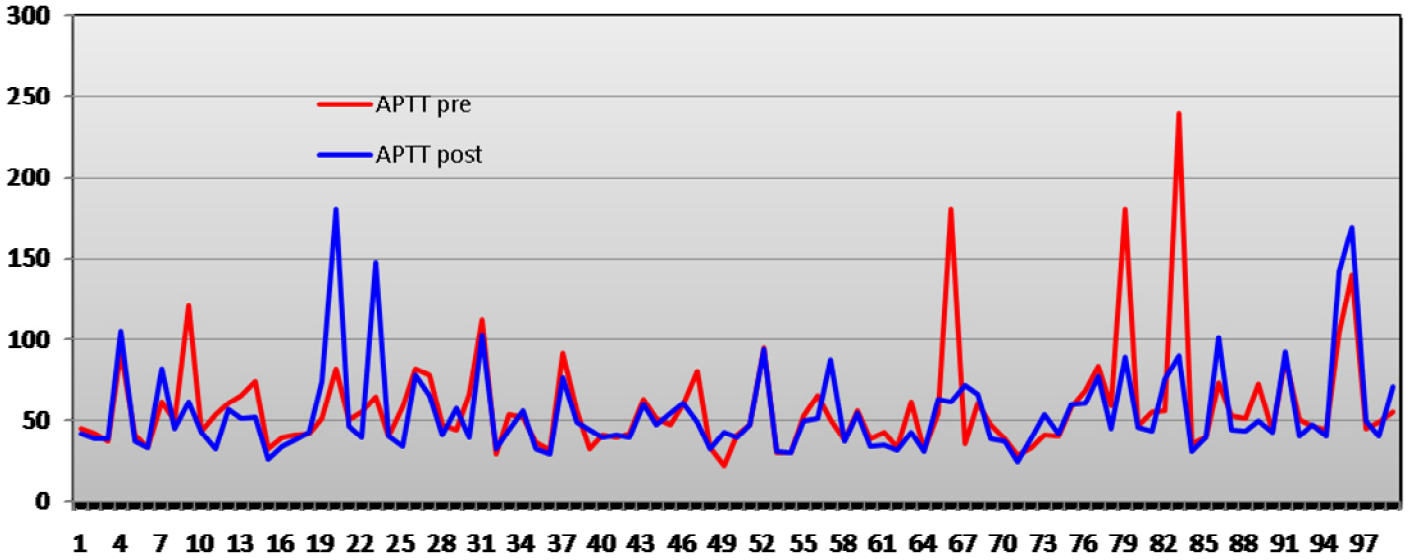
APTT – Pre and Post PCCs



APTT	Pre	Post
Median	50.7	44.6
10th centile	32.86	32.28
90th centile	89.45	89.51

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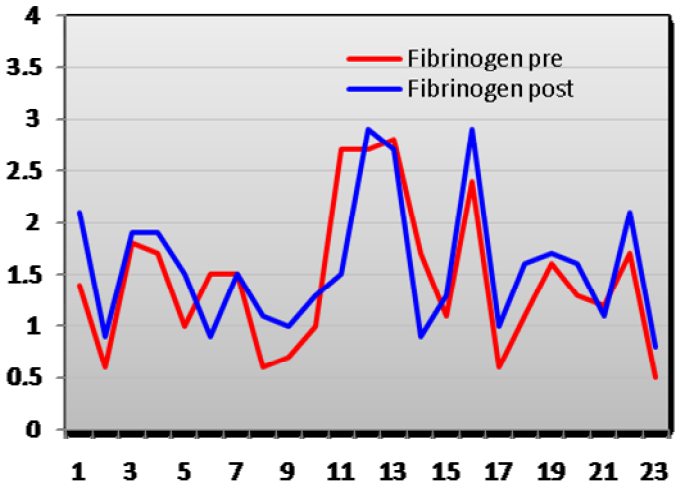
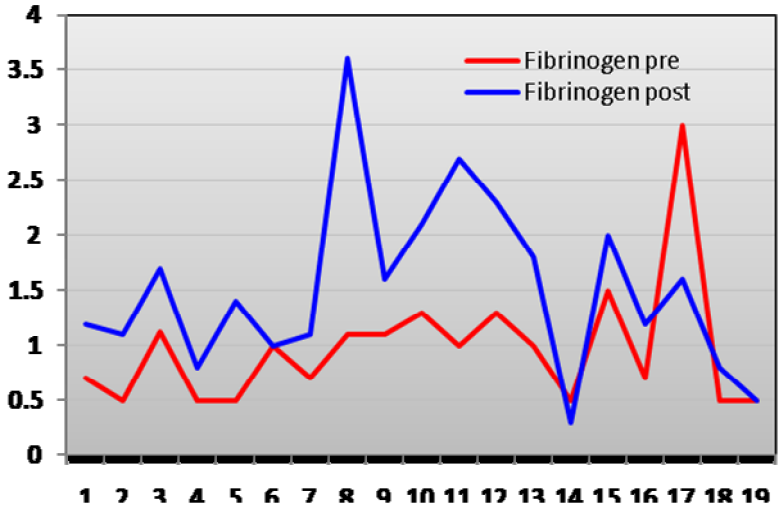
Fibrinogen levels





Fibrinogen	Pre fibrinogen replacement	Post Fibrinogen replacement
Median	1	1.4
10th centile	0.5	0.74
90th centile	1.36	2.42

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Outcomes – Efficacy

- Transfusion of a combination of products was common
- Difficult to evaluate the efficacy
  - INRs were not done in most instances immediately post PCC administration
  - Good proportion of the actively bleeding patients went on to have definitive procedure
- No bleeding complications were recorded for the procedures covered with PCC
- There seems to be more control when concentrates are being administered, the focus shifting to the procedure or otherwise

Outcomes – Thrombotic complications

- No cardiovascular adverse events or strokes were recorded within four weeks after administration of PCC
- A left ventricular thrombus was detected in one patient with fulminant DIC and it was felt that the PCCs did not contribute to the LV thrombus, but might have contributed to an clot extension
- Multiple PE's were an incidental finding on CT-scan in one patient who had PCC 13 days previously during liver transplant.
- One patient developed a proximal DVT in relation to a falling platelet count and positive HIT screen

Clinical outcomes – mortality

- 30 day mortality – 28% (18/ 63)
- 5/ 63 within 24 hrs – 8%
- Day 1 to day 7 – 7/ 63 – 11%
- Day 7 to day 30 – 6/ 63 – 9%

- Cause of death was progression of underlying disease

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PCCs in Liver disease

- The use of PCC can be considered for patients with acute or chronic liver disease:
  - Rapid correction of clotting factors to haemostatic levels is required
  - there is a significant restriction to the volume that can be safely transfused