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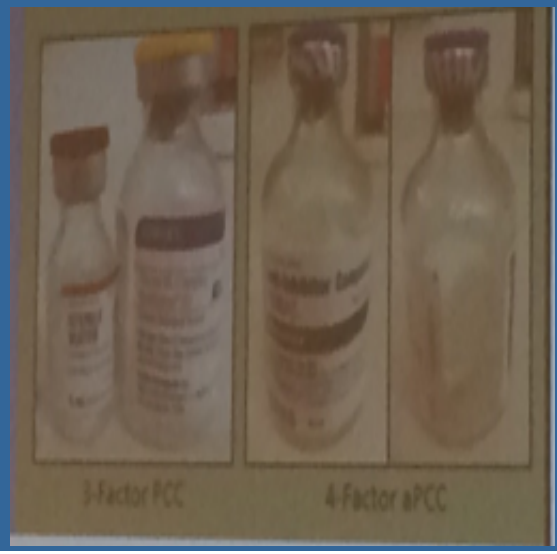
Prothrombin Complex Concentrate- Octaplex

Octaplex

Concentrated Factors

Prothrombin Complex Concentrate (PCC)

- 3- factor (factor II, IX, X)
- 4-factor (factors II, VII, IX, X)
- Activated 4-factor (factors II, VIIa, IX, X)



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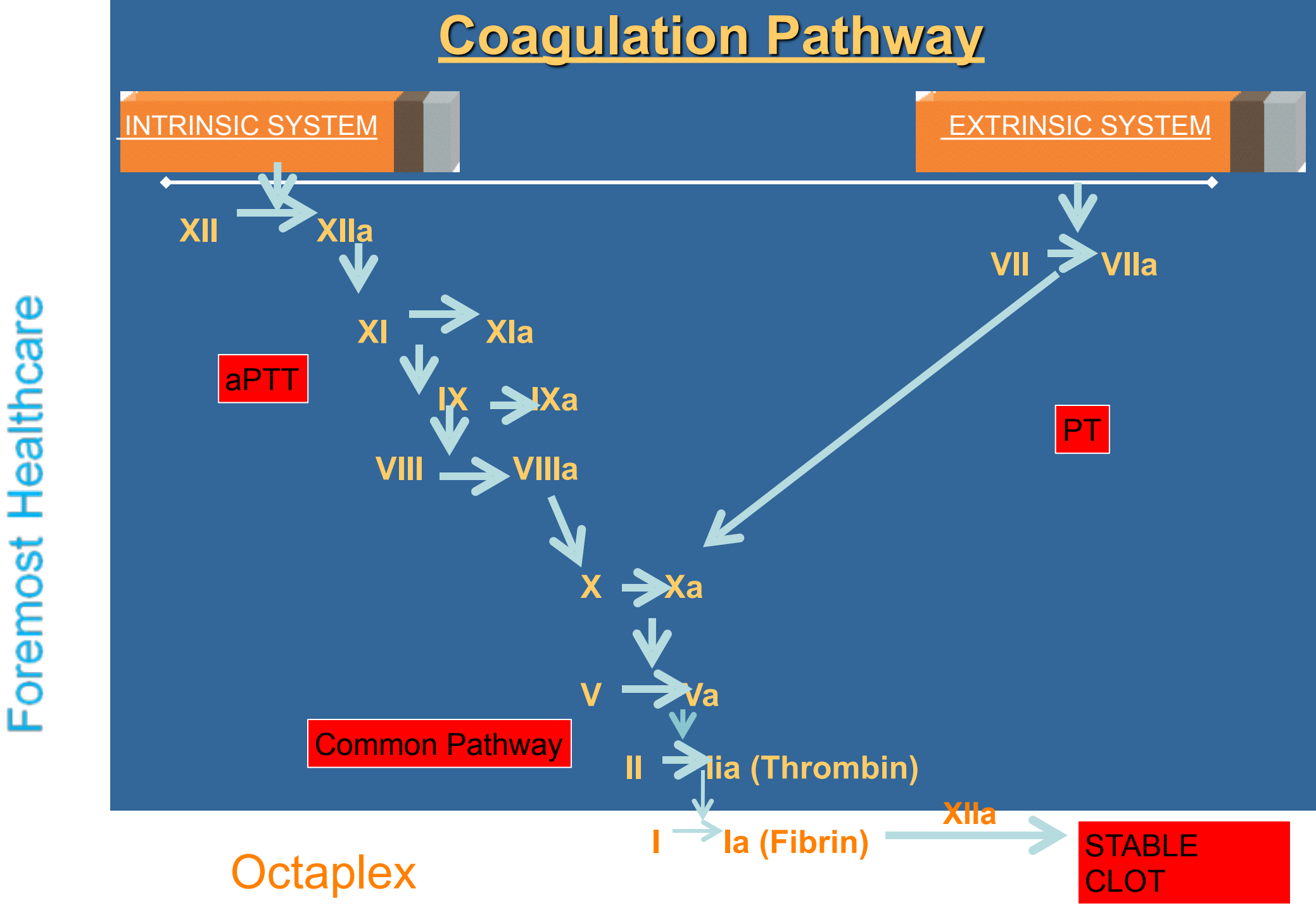
Coagulation Pathway
INTRINSIC SYSTEM
EXTRINSIC SYSTEM
XII
XIIa
XI
XIa
IX
IXa
VIII
VIIIa
VII
VIIa
aPTT
PT
X
Xa
V
Va
Common Pathway
II
IIa (Thrombin)
I
Ia (Fibrin)
XIIa
STABLE CLOT
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PCC Content

One vial of Octaplex for Injection contains:

	Octaplex 500 in 20mL
Human coagulation Factor II	270-760 IU
Human coagulation Factor VII	180-480 IU
Human coagulation Factor IX	**500 IU**
Human coagulation Factor X	360-600 IU
Protein C	260-620 IU
Protein S	240-640 IU

Octaplex Indications

1. Treatment of bleeding and perioperative prophylaxis of bleeding in acquired deficiency of the prothrombin complex coagulation factors.
2. Urgent reversal of warfarin to stop bleeding.
3. Urgent reversal of bleeding in liver failure patients
4. Intracranial haemorrhage on warfarin
5. Haemophillia B- Factor IX Deficiency with bleeding
6. Patient with bleeding during CABG

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FFP vs PCC

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Comparison: PCC and FFP

	PCC	FFP
Clotting Factors	II, VII, IX, X	II, V, VII – XIII; fibrinogen
Anticoagulants	AT, heparin, protein C & S	protein C & S
Preparation	Dilute each vial with 20mL. No ABO cross matching required. Pretested for HBSAG, HIV and HCV. Stable at Room temperature.	Thaw; ABO match required
Volume	Average 40 -100 mL/dose	Average 30 mL/**dose**
Considerations	Less volume & faster administration = faster restoration of factor levels	• Dilutional coagulopathy • Risk of transfusion-related acute lung injury

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PCC Dose VKA Bleeding

Table 1: Approximate Doses of Octaplex Required for Normalization of INR

Initial INR	2-2.5	2.5-3	3-3.5	>3.5
Approximate dose (mL/Kg body weight)	0.9-1.3	1.3-1.6	1.6-1.9	>1.9

The single dose should not exceed 3000 IU (120 ml Octaplex)

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Role of PCC in Vit K Antagonist associated bleeding

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Treatment option for reversal of INR

Vitamin K dependent coagulation factors	Recombinant Factor VIIa	Fresh frozen plasma	Three-factor prothrombin complex concentrate	Four-factor prothrombin complex concentrate
X		✓	✓	✓
IX			✓	✓
VII	✓	✓		✓
II		✓	✓	✓

Correction of INR protocol

Parameters and management

The following table should be used as a guide for the use vitamin K, FFP, and PCCs or recombinant factor VII according to various levels of INR prolongation and evidence of clinically significant bleeding .

Parameters	Management
INR less than 5 with no significant bleeding	**Cessation of warfarin and observation with serial PT / INR**
INR 5-9 with no significant bleeding	Hold warfarin and restart at lower dose once INR therapeutic. vitamin K 1-2.5 mg orally if the patient is at increased bleeding risk
INR greater than 9 with no significant bleeding	Hold warfarin and monitor PT/INR.
INR greater than 20 or clinically significant bleeding	Hold warfarin .FFP1.0-1.5 ML/Kg coagulation factors (typically 3 to 4 units) to restore coagulations factor greater than >30% of normal. Vitamin K 10 mg by slow IV infusion (requires 12-24 hours for full effect).Repeat vitamin K administration every 12 hours for persistent INR elevation.
Life-threatening bleeding (i.e.,intracranial hemorrhage) and elevated INR.	Hold warfarin. Prothrombin complex concentrate (20 mg) that normalize the INR or Vitamin K 10 mg by slow IV infusion , repeated , if necessary, depending on INR.

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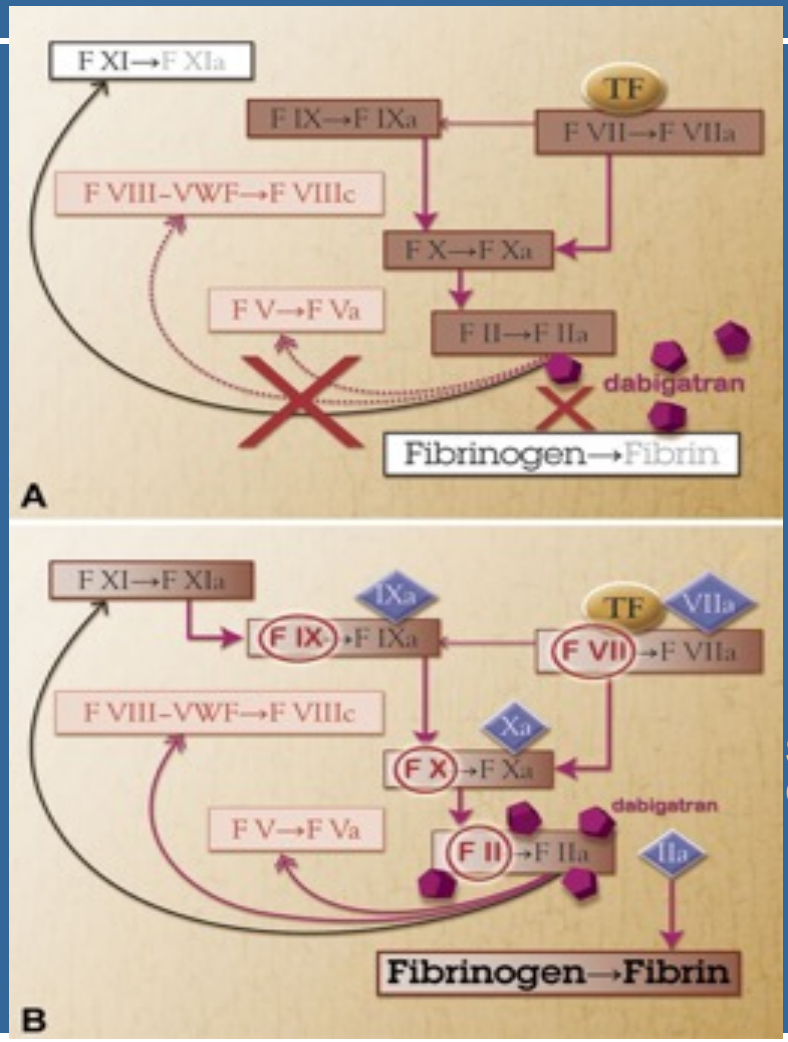
Source- ACEP; Dr Mathew and Dr

Anticoagulant-Specific Reversal

Anticoagulant	Interval Between Last Dose and Procedure	Reversal Agent	NYP Recommended Concentrated Factors	Dose
Warfarin	1-8 days	Vitamin K	4F-PCC	25-50 unit/kg based on INR
Dabigatran	24-48 hours	None	FEIBA	25 units/kg
Rivarexaban	24-48 hours	None	4F-PCC	25 units/kg
Apixaban	24-48 hours	None	4F-PCC	25 units/kg

Possible reversal of dabigatran.



Sam Schulman, and Mark A. Crowther Blood 2012;119:3016-3023

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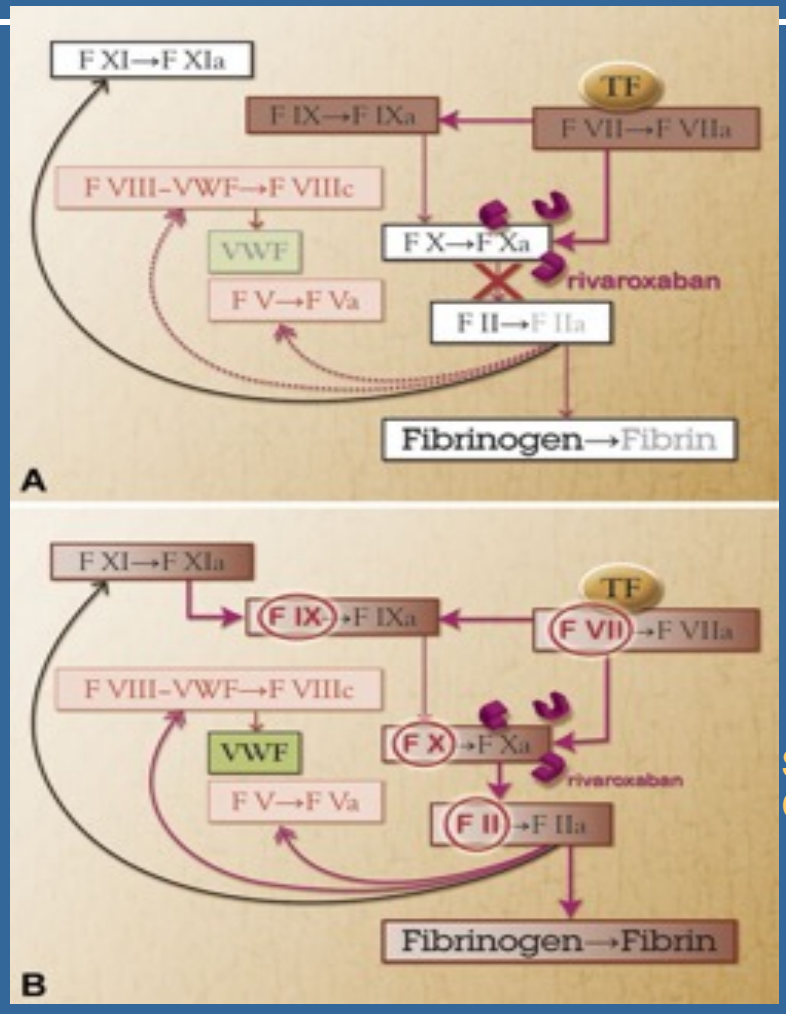
Possible reversal of factor Xa inhibitors.



Sam Schulman, and Mark A. Crowther Blood 2012;119:3016-3023

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ACCP Guidelines

- For patients with VKA-associated major bleeding, we suggest rapid reversal of anticoagulation with
  - Four-factor prothrombin complex concentrate (PCC) rather than with plasma (Grade 2C).
- We suggest the additional use of vitamin K 5 to 10 mg administered by slow IV injection rather than reversal with coagulation factors alone (Grade 2C).

Holbrook A. Chest. 2012 Feb;141(2 Suppl). PMID: 22315259

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PCC in traumatic bleed

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2012 CHEST guidelines22 recommend 4-factor PCC over FFP for VKA-associated bleeding

Dickneite G, et al. Prothrombin complex concentrate vs. fresh frozen plasma for reversal of dilutional coagulopathy in a porcine trauma model. 2009.	
Design	Randomized, placebo-controlled trial in pigs
Population	47 anaesthetized, mildly hypothermic (36° C) pigs
Interventions	• 65-70% of total blood volume substituted in phases with hydroxyethyl starch and pRBCs • Randomized to recieve: 15 mL/kg isotonic saline, 25 units/kg PCC, or standard-dose (15 mL/kg) or high-dose (40 mL/kg) porcine FFP • 4 factor PCC used • Immediately after treatment given, standardized injury inflicted
Endpoints	PT, thrombin generation, time to hemostasis, volume of blood loss
Results	• PCC therapy fully reversed prolonged PT and corrected reduced peak thrombin generation • Compared with 15 mL/kg FFP, PCC shorted time to hemostasis after either bone or spleen trauma, and reduced volume of blood loss .
Take Home Points	**PCC is effective in correcting dilutional coagulopathy and controlling bleeding when administered prior to trauma**

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PCC in Liver Failure

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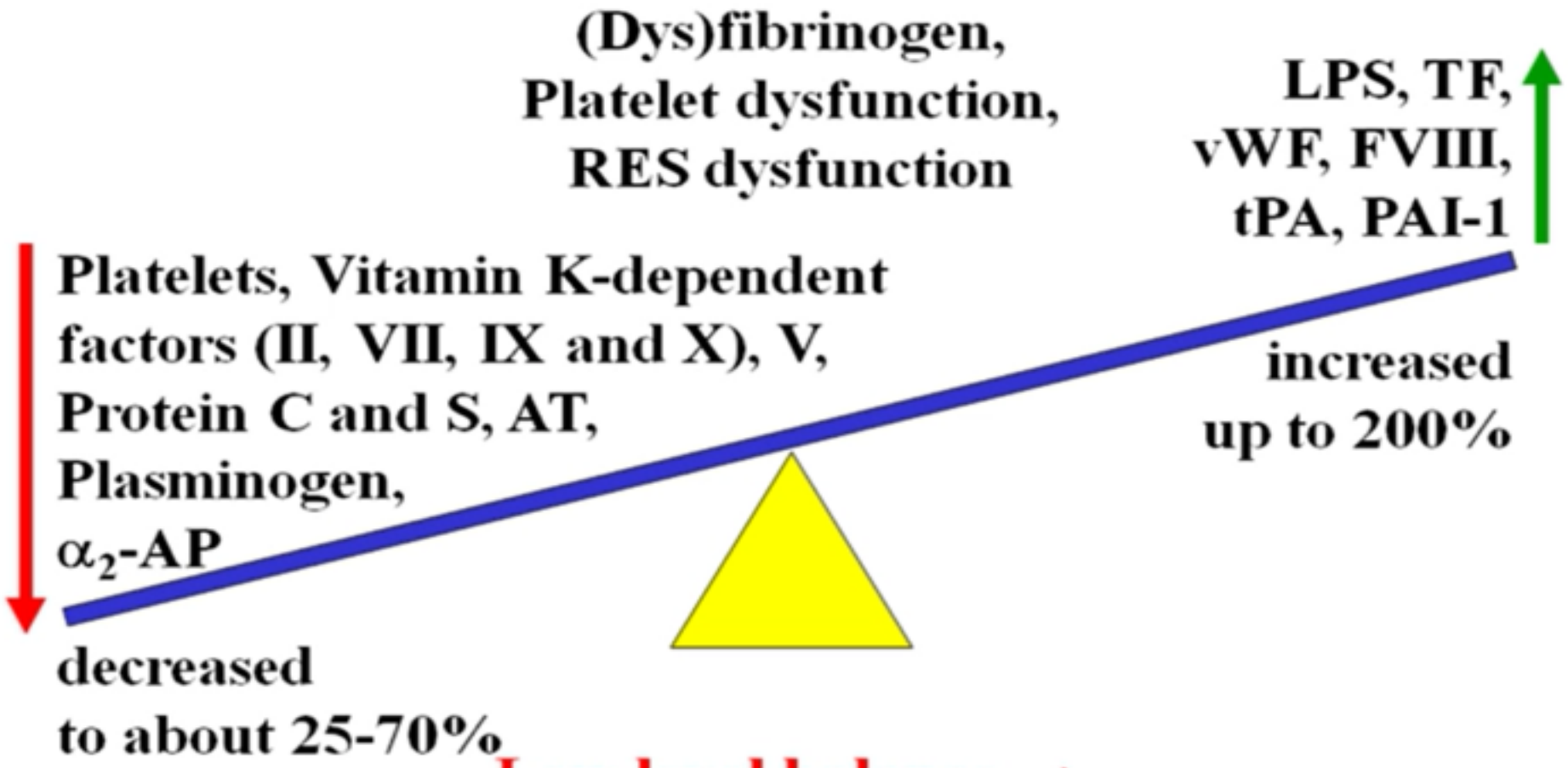
Coagulation system in liver cirrhosis



Low level balance →

high risk of haemostatic disturbances !!!

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

Reinhard Lorenz[a], Joachim Kienast[b], Ulrich Otto[c], Klaus Egger[a], Michael Kiehl[b], Dirk Schreiter[c], Harald Kwasny[d], Sabine Haertel[d] and Monika Barthels[e]

European Journal of Gastroenterology & Hepatology 2003, **15**:1–6

- Median PCC dose of 25.7 IU/kg
  → Quick increases from 39% to 65%
- **1 IU PCC per kg bw → Quick increases by 1%**
- Clinical efficacy was judged as ‚very good‘ in 76% of patients
- **without evidence of any thromboembolic events.**
- There were no changes in serological status (HIV, HAV, HAB and HAC).
- **No PCC-related adverse reactions occurred.**

PCC Dose In liver failure associated bleeding 25 IU/Kg

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PCC in Cardiac Surgery Bleedng

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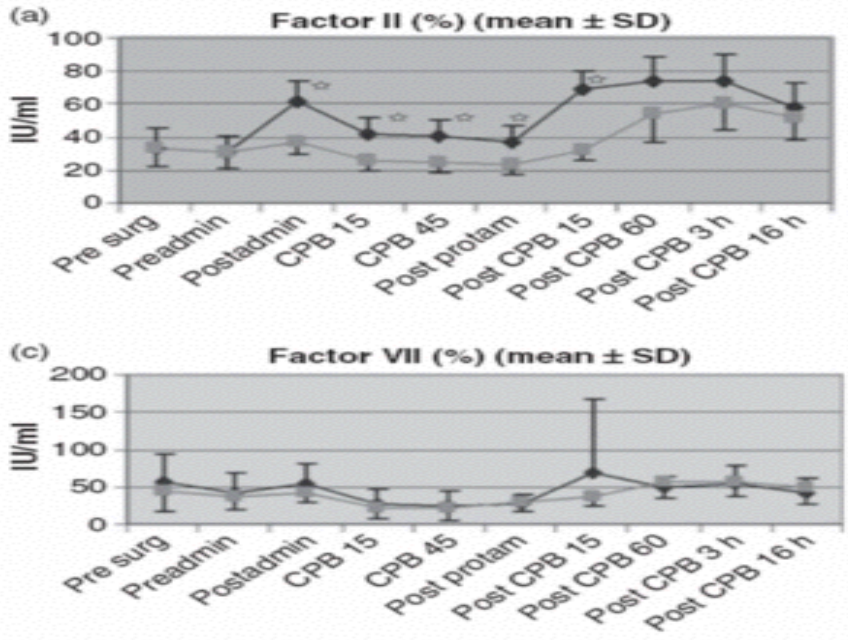
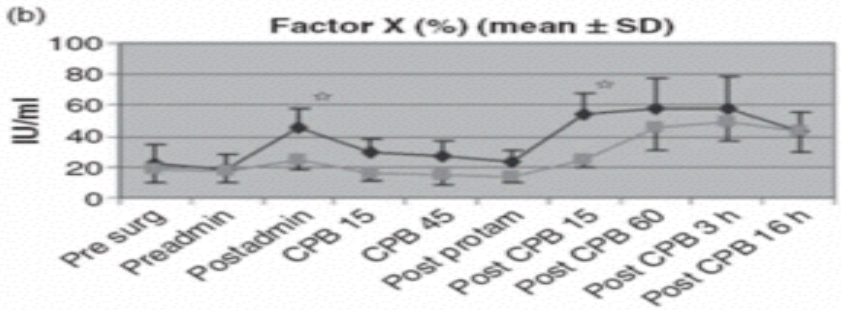
Vox Sanguinis (2010) **99**, 251–260

DOI: 10.1111/j.1423-0410.2010.01339.x

ORIGINAL PAPER

Comparison of fresh frozen plasma and prothrombin complex concentrate for the reversal of oral anticoagulants in patients undergoing cardiopulmonary bypass surgery: a randomized study





FFP 800 ml
PCC ?

FFP: 50 Units RBC in 19 pts.
PCC: 33Units of RBC in 16 pts.

CONCLUSION:
PCC reverses anticoagulation safely, faster and with less bleeding AND LESS Requirement of Blood

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PCC use in VKA- Associated ICH

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PCC use in VKA- Associated ICH

- Rapid correction of INR needed.
- Role of Vit K -

  Vit K along with FFP was the main stay of treatment till PCC was available.

  Vit K - Onset action after 2 hrs

  Peak at 24 hrs
- Role of FFP
- Large volume of FFP required.
- INR correction by FFP within 30 min only in less than 10 % of patient
- INR correction by FFP takes place usually after 24 hours.

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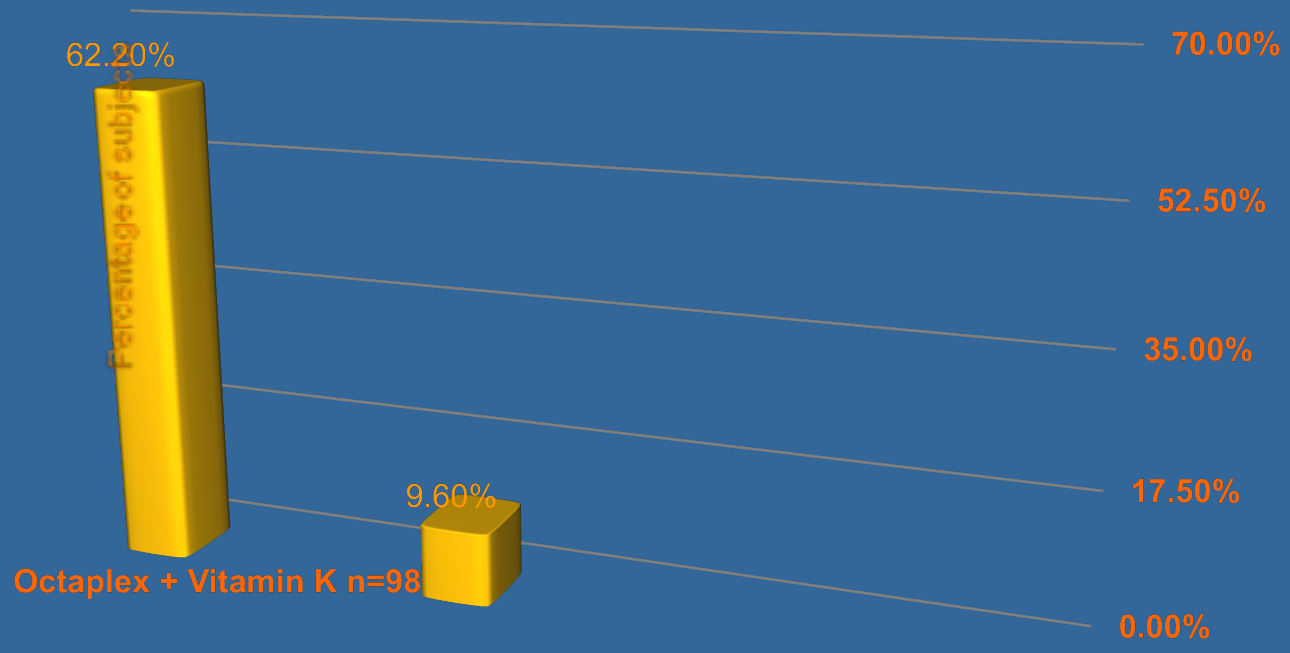
Proportion of subjects experiencing a reduction of INR (<1.3 at 30 minutes after end of infusion)



Octaplex – Plasma (%) [95% CI] = 52.6 [39.4, 65.9]
(prespecified superiority margin >0)

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Guidelines for the Management of Spontaneous Intracerebral Hemorrhage

A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association

The American Academy of Neurology affirms the value of this guideline as an educational tool for neurologists.

Endorsed by the American Association of Neurological Surgeons, the Congress of Neurological Surgeons, and the Neurocritical Care Society

J. Claude Hemphill III, MD, MAS, FAHA, Chair; Steven M. Greenberg, MD, PhD, Vice-Chair; Craig S. Anderson, MD, PhD; Kyra Becker, MD, FAHA; Bernard R. Bendok, MD, MS, FAHA; Mary Cushman, MD, MSc, FAHA; Gordon L. Fung, MD, MPH, PhD, FAHA; Joshua N. Goldstein, MD, PhD, FAHA; R. Loch Macdonald, MD, PhD, FRCS; Pamela H. Mitchell, RN, PhD, FAHA; Phillip A. Scott, MD, FAHA; Magdy H. Selim, MD, PhD; Daniel Woo, MD, MS; on behalf of the American Heart Association Stroke Council, Council on Cardiovascular and Stroke Nursing, and Council on Clinical Cardiology

Purpose—The aim of this guideline is to present current and comprehensive recommendations for the diagnosis and treatment of spontaneous intracerebral hemorrhage.

Methods—A formal literature search of PubMed was performed through the end of August 2013. The writing committee met by teleconference to discuss narrative text and recommendations. Recommendations follow the American Heart Association/American Stroke Association methods of classifying the level of certainty of the treatment effect and the class of evidence. Prerelease review of the draft guideline was performed by 6 expert peer reviewers and by the members of the Stroke Council Scientific Oversight Committee and Stroke Council Leadership Committee.

Results—Evidence-based guidelines are presented for the care of patients with acute intracerebral hemorrhage. Topics focused on diagnosis, management of coagulopathy and blood pressure, prevention and control of secondary brain injury and intracranial pressure, the role of surgery, outcome prediction, rehabilitation, secondary prevention, and future considerations. Results of new phase 3 trials were incorporated.

Conclusions—Intracerebral hemorrhage remains a serious condition for which early aggressive care is warranted. These guidelines provide a framework for goal-directed treatment of the patient with intracerebral hemorrhage. **(*Stroke*. 2015;46:000-000. DOI: 10.1161/STR.0000000000000069.)**

Key Words: AHA Scientific Statements ■ blood pressure ■ coagulopathy ■ diagnosis ■ intracerebral hemorrhage ■ intraventricular hemorrhage ■ surgery ■ treatment

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ing low-molecular-weight heparin; however, reversal may be incomplete.[39]

American Heart Association | American Stroke Association

VKA-Related ICH

Guidelines exist for reversal of OACs.[76] For ICH patients taking VKA, rapid correction of the international normalized ratio (INR) is recommended.[76,77] Fresh frozen plasma (FFP), along with vitamin K, has been the mainstay of treatment in the United States for years, but more recently, prothrombin complex concentrates (PCCs), the activated PCC FEIBA (factor VIII inhibitor bypassing activity), and recombinant activated factor VIIa (rFVIIa) have emerged as potential therapies. Administration of intravenous vitamin K alone is insufficient for reversal in the first hours but should be part of all acute VKA reversal strategies in a dose of 5 to 10 mg, usually given slowly via the intravenous route. Onset of action begins by 2 hours and is maximal at ≈24 hours if liver function is normal.[78] FFP administration requires thawing and cross matching, carries a risk of allergic and infectious transfusion reactions, and often requires large volumes for full INR correction. Likelihood of INR correction at 24 hours was linked to time to FFP administration in 1 study, although 17% of patients still did not have an INR <1.4 by this time, which suggests that FFP administered in this manner may be insufficient for rapid correction of coagulopathy.[79] Shortcomings of FFP have led to interest in alternative agents for VKA reversal.

MANAGEMENT OF ICH AHA/ASA 2015

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New Anticoagulation Mediated ICH

1. Minor bleed – lasting less than 1 hour, small amount of blood in stool, urine or oral cavity
2. Major, non-life threatening bleed – is considered a significant amount of blood loss accompanied by a drop in Hgb >2 mg/dL .
3. Life-threatening bleed – intracerebral, uncontrol bleeding into any extremity with risk of compartment syndrome
4. Massive trauma bleeding – loss of complete blood volume (approximately 0.7 L/kg lean body weight) within 24 hours or half of blood volume within three hour.

Life-threatening bleeding in patients on warfarin

Life-threatening bleed – intracerebral, uncontrol bleeding into any extremity with risk of blood loss.

Prothrombin Complex Concentrate (PCC)

INR	Dose of PCC	Maximum Dose
2.0 – 3.9	25 units/kg	2500 units
4.0- 6.0	35 units/kg	3500 units
≥ 6.1	50 units/kg	5000 units

- Repeat dosing is not recommended.
- *Round doses to the nearest vial size.

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STS/SCA BLOOD CONSERVATION CLINICAL PRACTICE GUIDELINES

Warfarin reversal with Prothrombin complex concentrate (PCC):

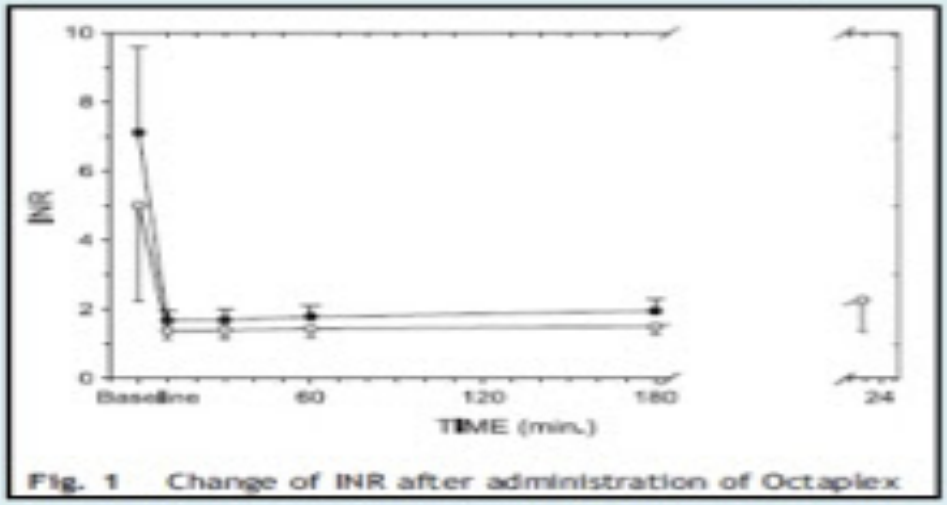

Fig. 1 Change of INR after administration of Octaplex

Lubetsky A, et al: Efficacy and safety of a prothrombin complex concentrate (OctaplexR) for rapid reversal of oral anticoagulation. *Thromb Res* 2004;113:371-378.

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TRANSFUSION PRACTICE

TRANSFUSION 2006;46:1279-1285.

Effect of fresh-frozen plasma transfusion on prothrombin time and bleeding in patients with mild coagulation abnormalities

Omar I. Abdel-Wahab, Brian Healy, and Walter H. Dzik

CONCLUSION :

It is concluded that transfusion of FFP for mild abnormalities of coagulation values results in partial normalization f PT in a minority of patients and fails to correct the PT in 99 percent of patients.

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Adverse effect / complication

PCCs are known to carry a risk of thromboembolic complications and disseminated intravascular coagulation (DIC).

It is generally accepted that a suitable PCC preparation should contain all of the 4 coagulation factors in a well-balanced proportion and that it also should contain protein C (PC) and protein S (PS). Additionally, the concentration of activated coagulation factors should be kept at a minimum. Some preparations also contain small amounts of antithrombin (AT) and heparin in order to reduce the thrombotic risk after treatment with PCC.

Other adverse drug reactions of these preparations are related to acute tolerability. Rarely, antibodies (inhibitors) against the proteins administered are seen with PCCs.

Only very few clinical ADRs have been seen with octaplex® to date.

Immune system disorders: Replacement therapy may rarely lead to the formation of circulating antibodies inhibiting one or more of the human prothrombin complex factors. If such inhibitors occur, the condition will manifest itself as a poor clinical response.

Allergic or anaphylactic-type reactions and an increase in body temperature have not been observed in clinical studies with octaplex® but may rarely occur.

Nervous system disorders: Headache may rarely occur.

Vascular disorders: There is a risk of thromboembolic episodes following the administration of human prothrombin complex.

General disorders and administration site conditions: Increase in body temperature has not been observed but may rarely occur.

Investigations: A transient increase in liver transaminases has been rarely observed.

While the development of antibodies (inhibitors) against coagulation factors is a common feature in haemophilia treatment, it seems to be a very rare event after the administration of the less purified PCCs. A final statement on the development of inhibitors in previously treated patients cannot be made. Data on the occurrence of inhibitors in previously untreated patients are not available.

4 Factor PCC for Warfarin Related Bleeding

Question: Is 4-factor PCC as effective as FFP for hemostasis and INR correction in patients with warfarin-related bleeding?

Design: open-label, non-inferiority RCT

Patients: INR ≥2.0 with major bleeding

Intervention: 4-factor non-activated PCC (Octaplex)

Comparison: FFP

Outcome:

- Hemostasis at 24 hours
- INR correction ½ hour after infusion finished

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Sarode R. Circulation. 2013 Sep 10;128(11): 1234-43. PMID: 2393511

4 Factor PCC for Warfarin Related Bleeding

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Table 7. Rapid INR Reduction (Intention-to-Treat Efficacy Population)

	No. (%) of Patients [95% CI]		
	4F-PCC (n=98)	Plasma (n=104)	Difference 4F-PCC Minus Plasma, % (95% CI)
Rapid INR reduction*	61 (62.2) [52.6 to 71.8]	10 (9.6) [3.9 to 15.3]	52.6† (39.4 to 65.9)

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Sarode R. Circulation. 2013 Sep 10;128(11): 1234-43. PMID: 2393511

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Regular Article Thrombosis Research (2004) 113, 371–378

Efficacy and safety of a prothrombin complex concentrate (Octaplex®) for rapid reversal of oral anticoagulation

Aaron Lubetsky[a,*], Ron Hoffman[b], Reuven Zimlichman[d], Amiram Eldor[c,1], Joseph Zvi[d], Viktor Kostenko[e], Benjamin Brenner[b]

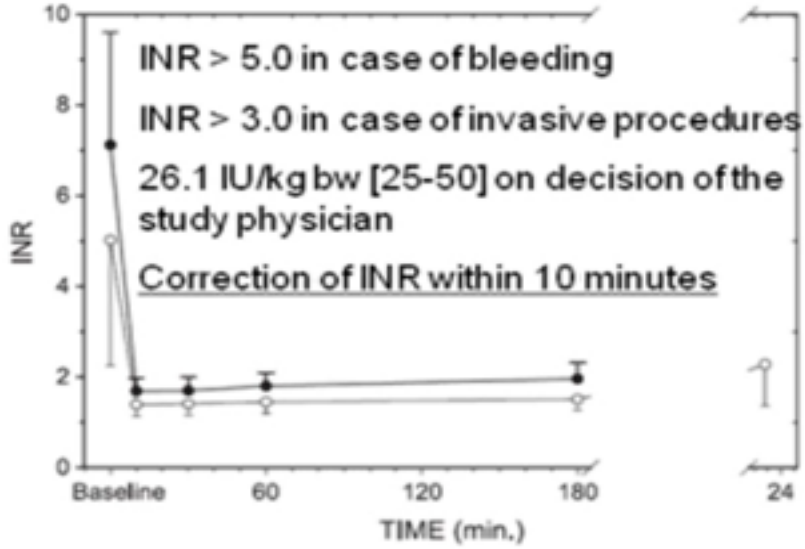

Fig. 1 Change of INR after administration of Octaplex during 24 h follow-up in bleeding (full symbols) and surgical patients (open symbols). Except for baseline, all INR values were significantly higher in bleeding patients. Values represent mean ± S.D.

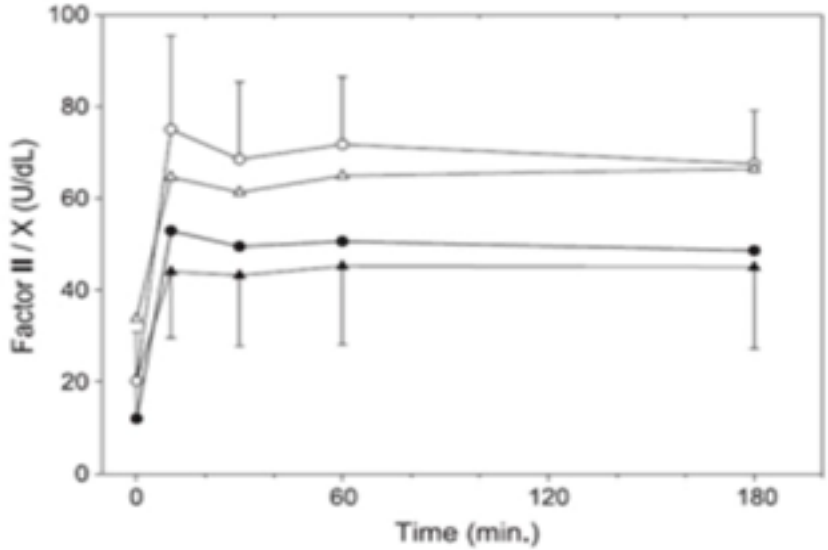

Fig. 2 Levels of coagulation factors II (circles) and X (triangles) before and after administration of Octaplex® to bleeding (full symbols) and surgical (open symbols) patients. Values represent mean ± S.D.

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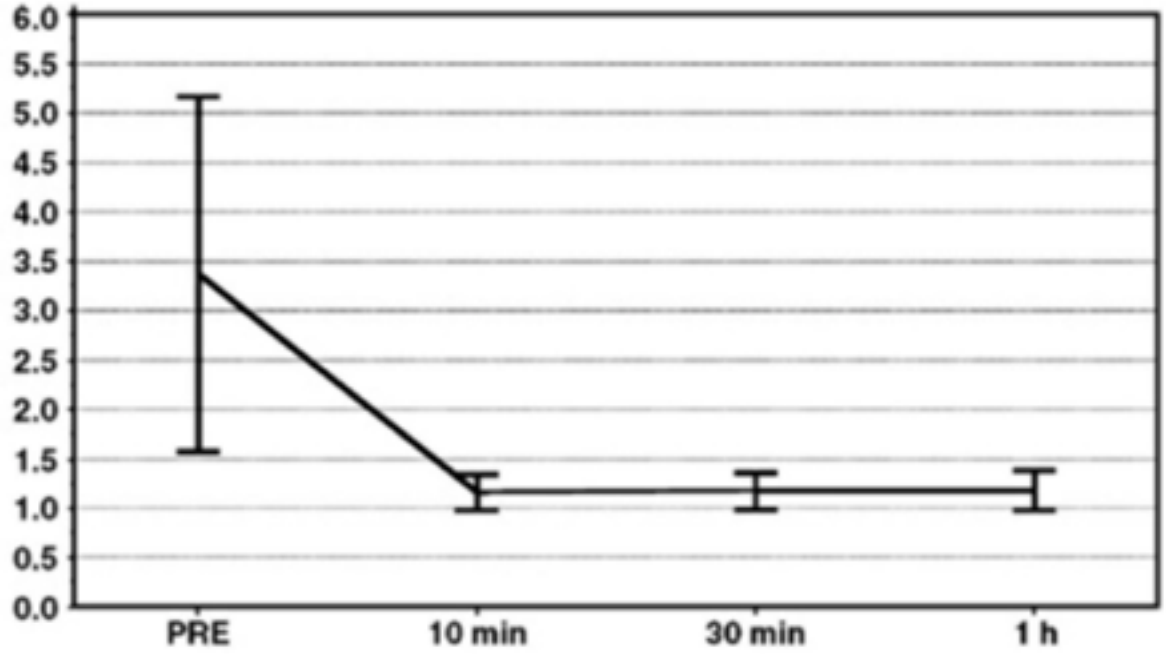
REGULAR ARTICLE Thrombosis Research (2007) xx, xxx–xxx

Prothrombin complex concentrate (Octaplex®) in patients requiring immediate reversal of oral anticoagulation

Hanno B. Riess [a], Andreas Meier-Hellmann [b], Johann Motsch [c], Mazen Elias [d], Friedrich W. Kursten [e,*], Carl-Erik Dempfle [f]



Median dose: 41.1 (15.3-83.3) IU/kg bw

Median INR declined from 2.8 (1.5-9.5) to 1.1 (1.0-1.9) within 10 min

In 93% of all patients INR decrease < 1.4 within one hour

Figure 1 INR development (mean ± SD) from baseline before infusion to 1 h post-infusion of the per protocol population, $n = 56$.