

What current treatment approaches are used to manage serious bleeding with NOACs?

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PROHEMOSTATIC AGENTS

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- Prothrombin Complex Concentrates: 3 vs 4 component, activated vs non activated
- Recombinant Factor VIIa (rFVIIa, NovoSeven)
- Antifibrinolytics: Tranexamic acid (TXA)

Procoagulant PCCs and Factor Replacement Products

Vitamin K-dependent coagulation factors	4-Factor PCC*	Plasma	4F-PCC activated (FEIBA))	3-Factor PCC*	rFVIIa
II	✓	✓ †	✓	✓	
VII	✓	✓ †	✓ activated	Low levels ^{2,3}	✓ activated
IX	✓	✓ †	✓	✓	
X	✓	✓ †	✓	✓	
Protein C	✓				
Protein S	✓				

*Factors in PCCs are ~25x more concentrated than the factors in plasma.

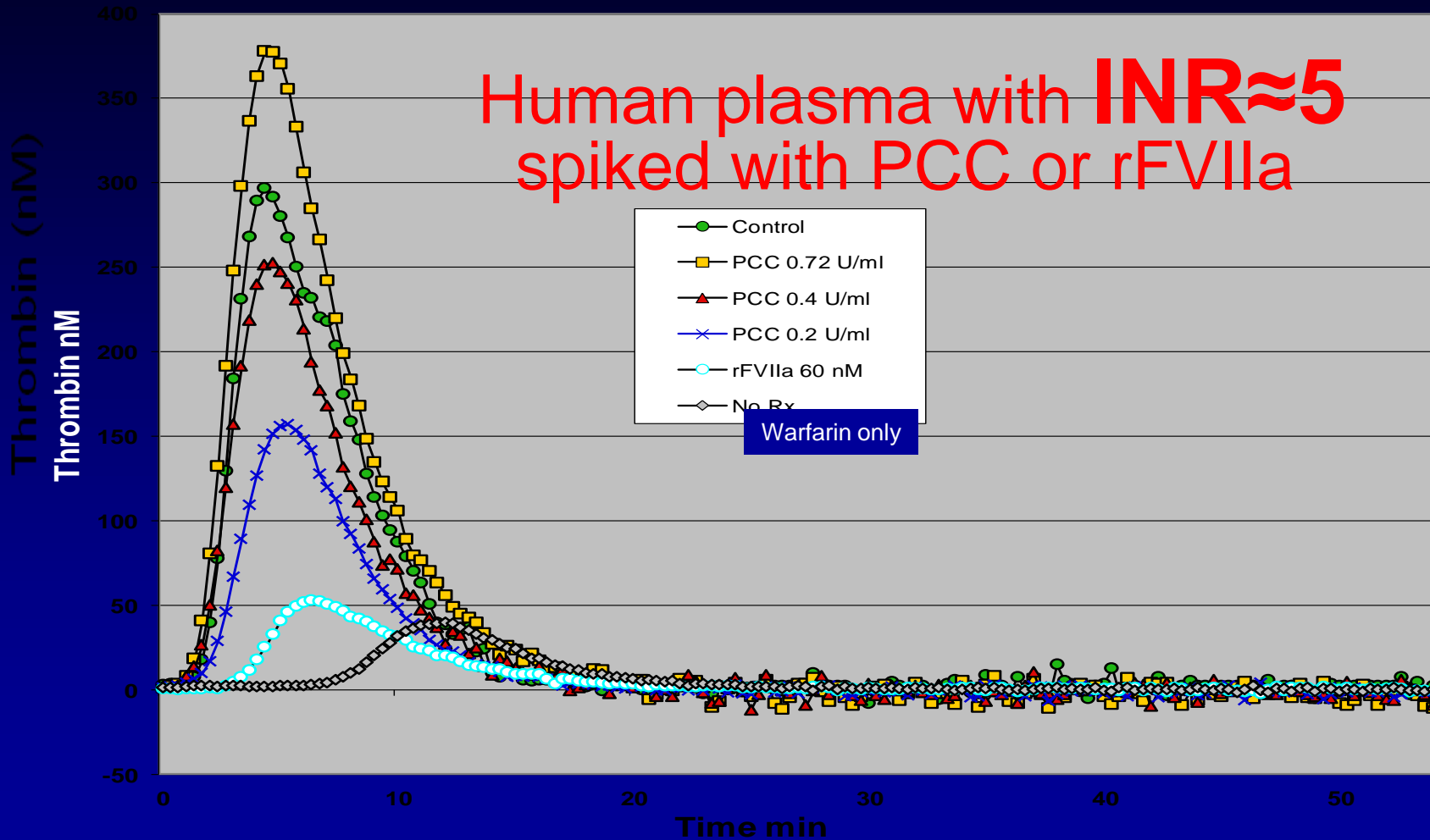
†In plasma, total content of factors relative to volume is low; large volumes are required for reversal.

Adapted with permission from Zareh M et al. *West J Emerg Med.* 2011;12:386-392. 2. Bebulin (Factor IX Complex) Prescribing Information. Baxter Healthcare Corporation. July 2012. 3. Profilnine (Factor IX Complex) Prescribing Information. Grifols Biologicals Inc. August 2011.

Recombinant Factor VIIa (rFVIIa)

Warfarin Reversal by rFVIIa or PCC (KCENTRA)

Thrombin Generation Assay



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.

N Engl J Med
Volume 363(19):1791-1800
November 4, 2010



Study Overview

- We examined the incidence of thromboembolic events associated with off-label use of rFVIIa in patients with bleeding problems.
- Coronary arterial thrombotic events and abnormal clotting among older patients were more common with rFVIIa than with placebo.



Population and Dose-Group Distribution in Placebo-Controlled Trials of rFVIIa

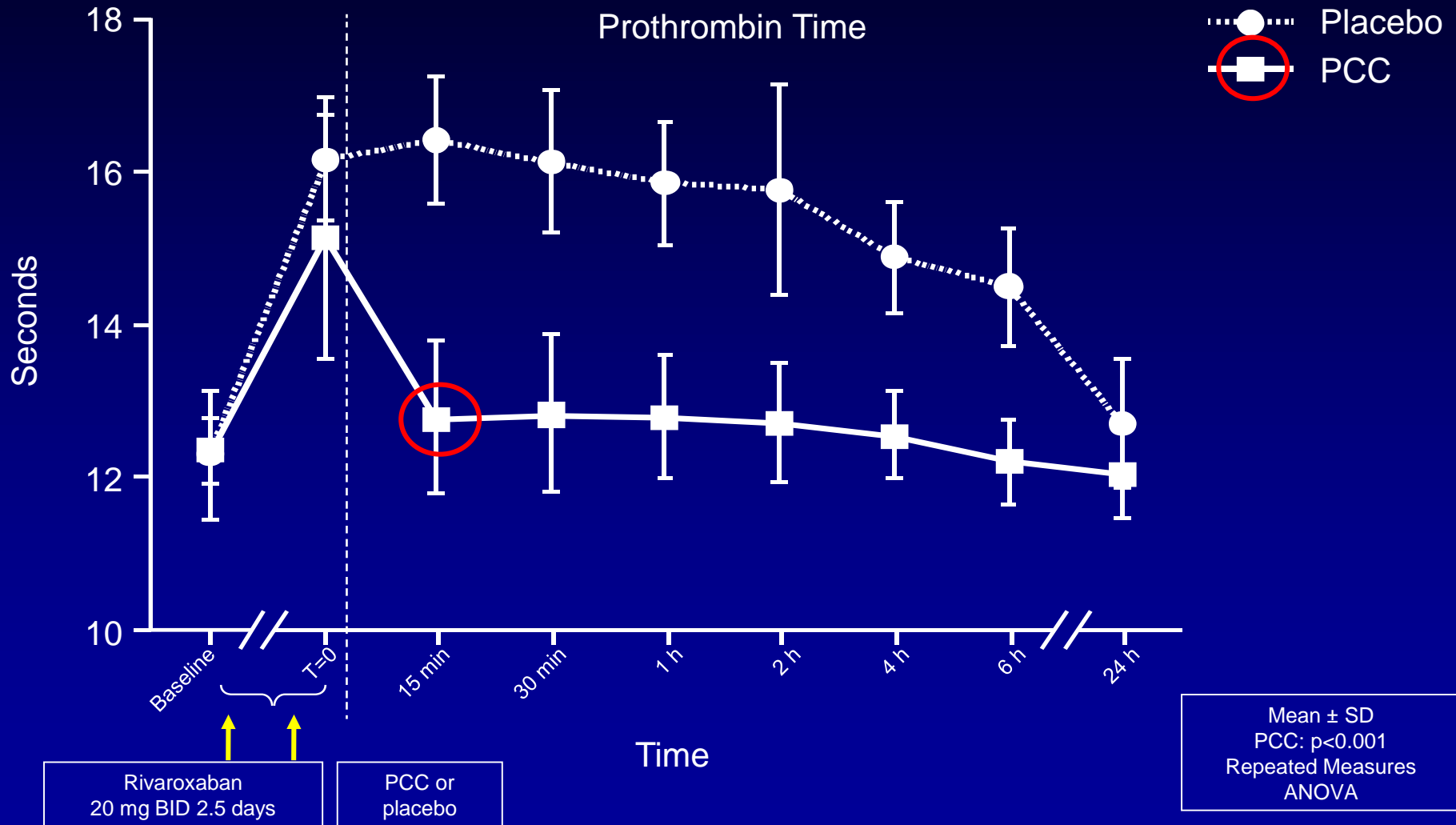
	Age	Placebo	rFVIIa	Total
		n=1653	n=2815	n=4468 (%)
Patient trials		1536	2583	4119 (92.2)
CNS bleeding (5 studies)	65	423	974	1397 (31)
Liver disease (7 studies)	54	449	795	1244 (27.8)
Trauma (3 studies)	36.5	428	409	837 (18.7)
Cardiac surgery (3 studies)	45.4	114	153	267 (6.0)
Traumatic brain injury (1 study)	50.9	36	61	97 (2.2)
Spinal surgery (1 study)	46.6	13	36	49 (1.1)
Others (6 studies)	38.5	73	155	228 (5.1)
Healthy volunteer trials (9 studies)	27.2	117	232	349 (7.8)

**PROTHROMBIN
COMPLEX
CONCENTRATES
(PCCs)**

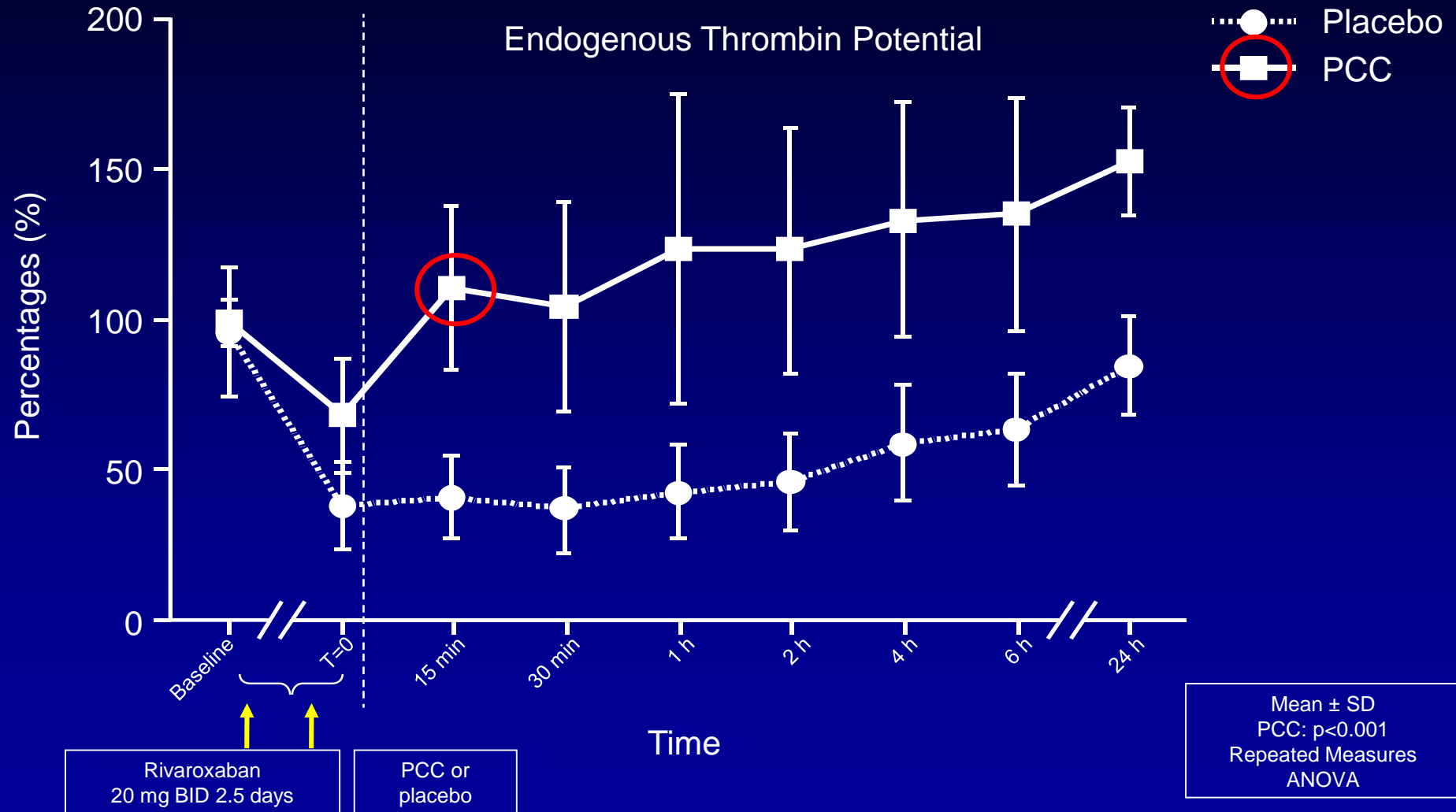
Reversing NOACs with PCCs: what is the evidence?

- PCCs may have potential to reverse bleeding, although available data is from animal studies.
- There is a lack of correlation between reversing laboratory tests and bleeding; extrapolating animal models and human volunteer data to bleeding patients should be cautiously interpreted.
- However, PCCs should be considered as part of a multimodal approach with hemodynamic and hemostatic resuscitation with major bleeding episodes

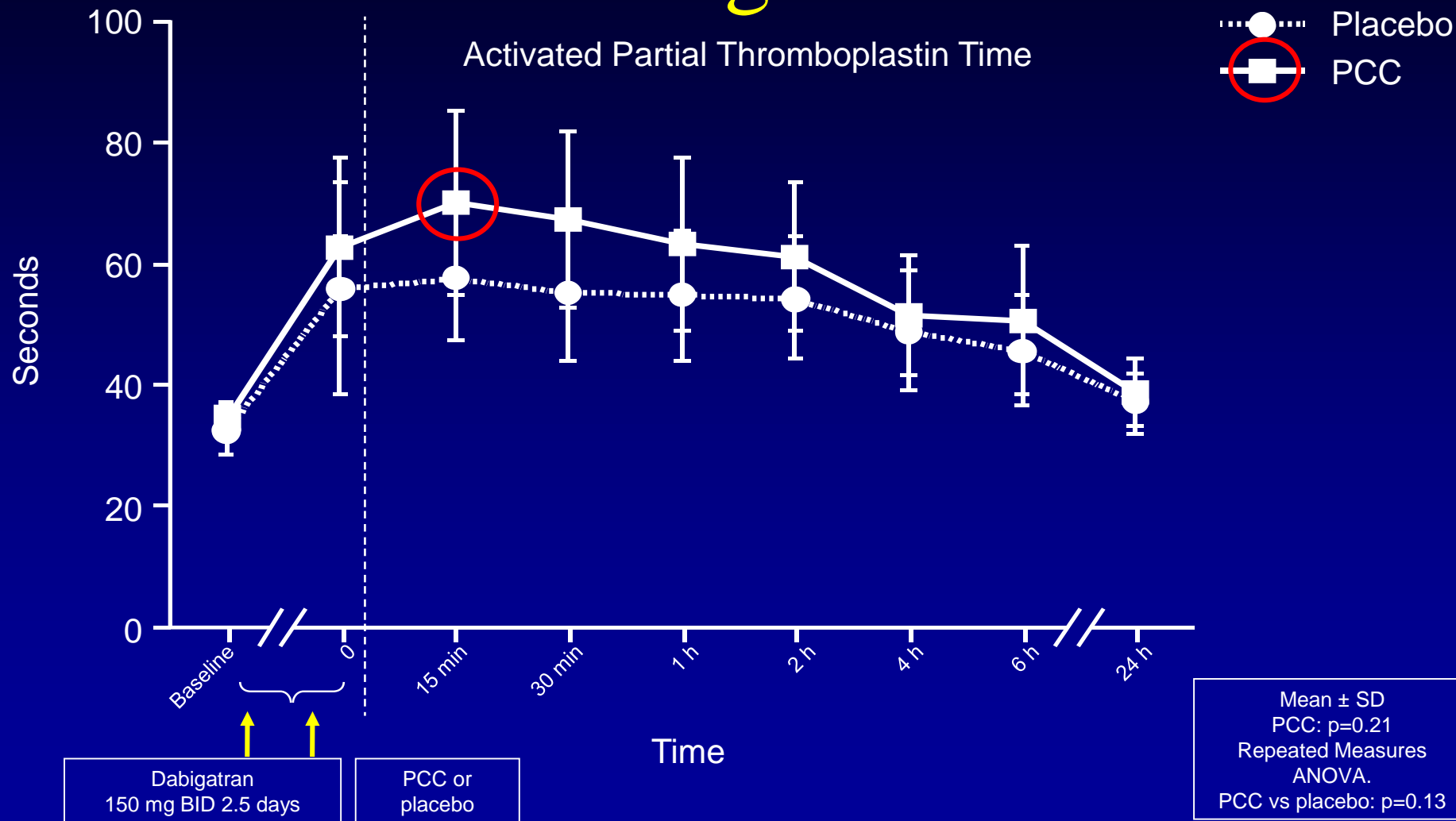
Rivaroxaban



Rivaroxaban



Dabigatran



Effects of three- and four-factor prothrombin complex concentrates in reversing the anticoagulant effect of rivaroxaban

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Marcel Levi, Todd Moore, Carlos Castillejos,
Scott Berkowitz, Dagmar Kubitzka, Sam
Goldhaber, Jeff Weitz, Jerrold Levy

Conclusion

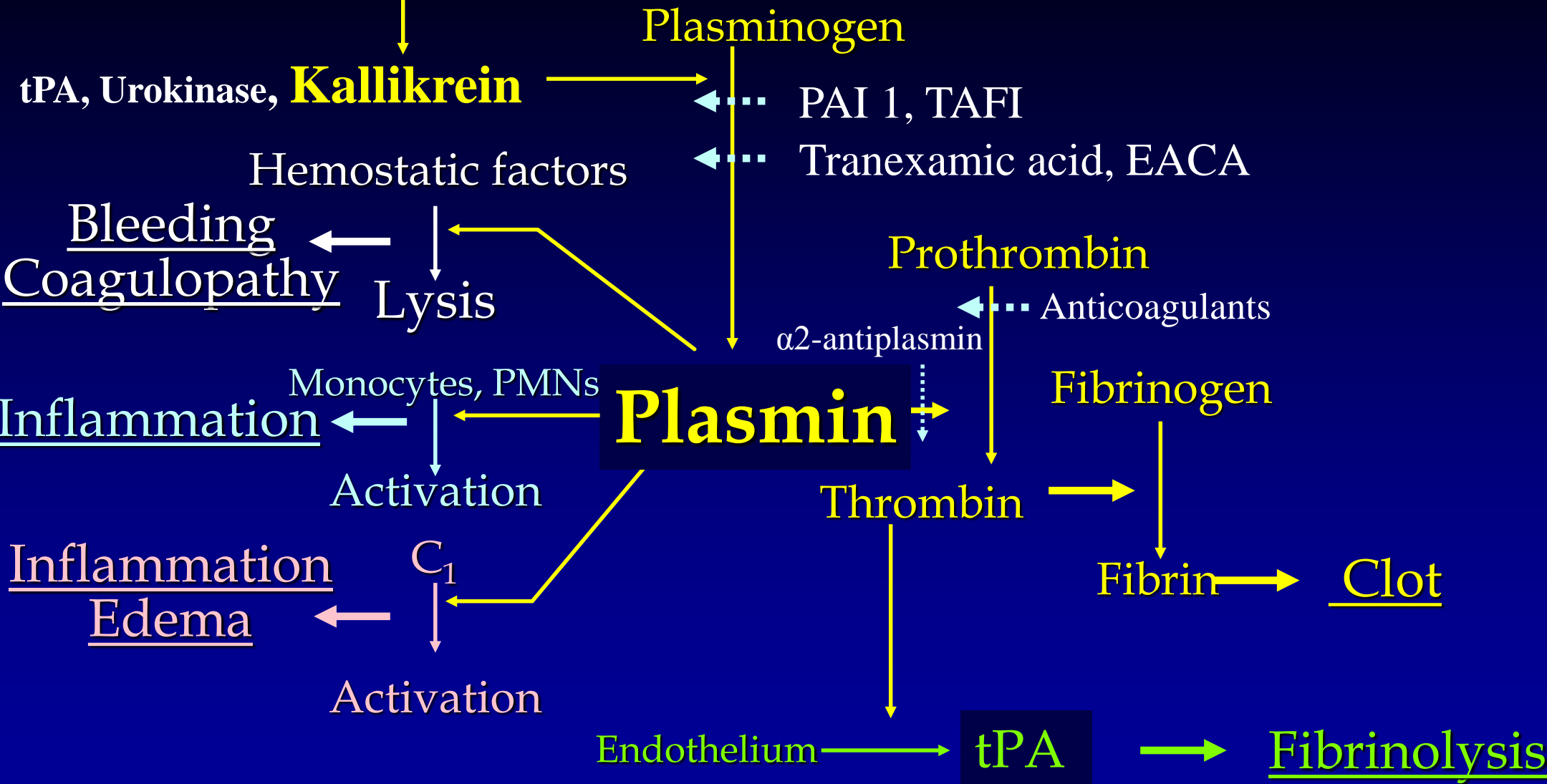
- Both Beriplex and Profilnine can reverse anticoagulant effect of rivaroxaban
- Beriplex had a greater effect on reversing PT
- Profilnine had a greater effect on reversing thrombin generation- perhaps due to increased Protein C/S and heparin in Beriplex
- Both PCCs were well tolerated in volunteers without signs of prothrombotic effects

TRANEXAMIC ACID

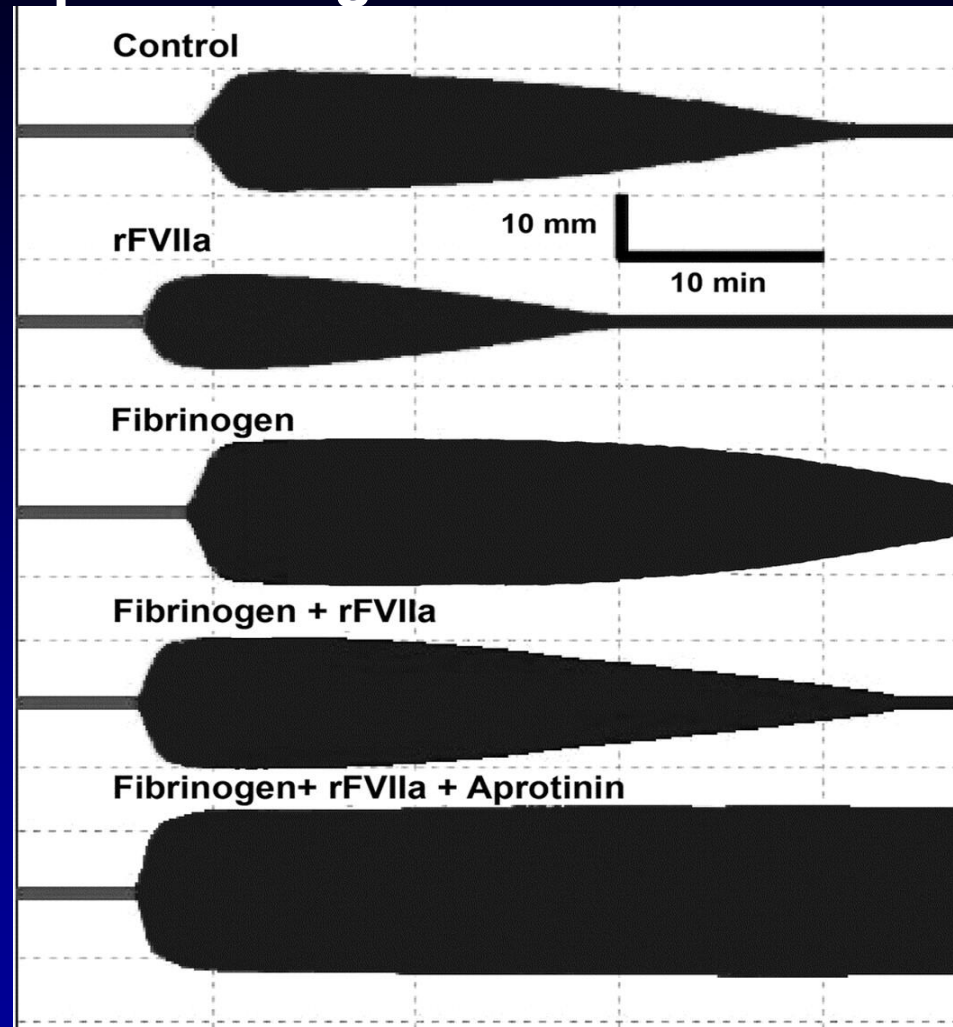
Critical Role of Fibrinolysis in Bleeding and Tranexamic Acid Rx

- Hyperfibrinolysis with extensive tissue injury in trauma- (CRASH2- Lancet 2010)
- Extensive data in cardiac/ortho surgery
- Liver transplantation / diseases
- Postpartum hemorrhage (WOMAN trial- <http://www.thewomantrial.lshtm.ac.uk/>)
- Excessive menstrual bleeding
- No data in NOAC induced bleeding..yet

TISSUE INJURY



Thromboelastography recordings obtained with the ROTEM(R) device after the addition of rFVIIa and/or fibrinogen in the presence of tissue type plasminogen activator in volunteer plasma



Tanaka, K. A. et al. Anesth Analg 2008;106:732-738

Summary

- PCCs reverse Xa inhibitors in vitro and in anticoagulated volunteers; bleeding data is based on animal bleeding models.
- PCCs attenuate bleeding in animal models of NOACs
- rFVIIa is only partially effective in most models
- TXA is widely studied in trauma/surgery where fibrinolysis is a critical component
- Therapy for bleeding should be multimodal