Anticoagulation Reversal in Intracranial Hemorrhage

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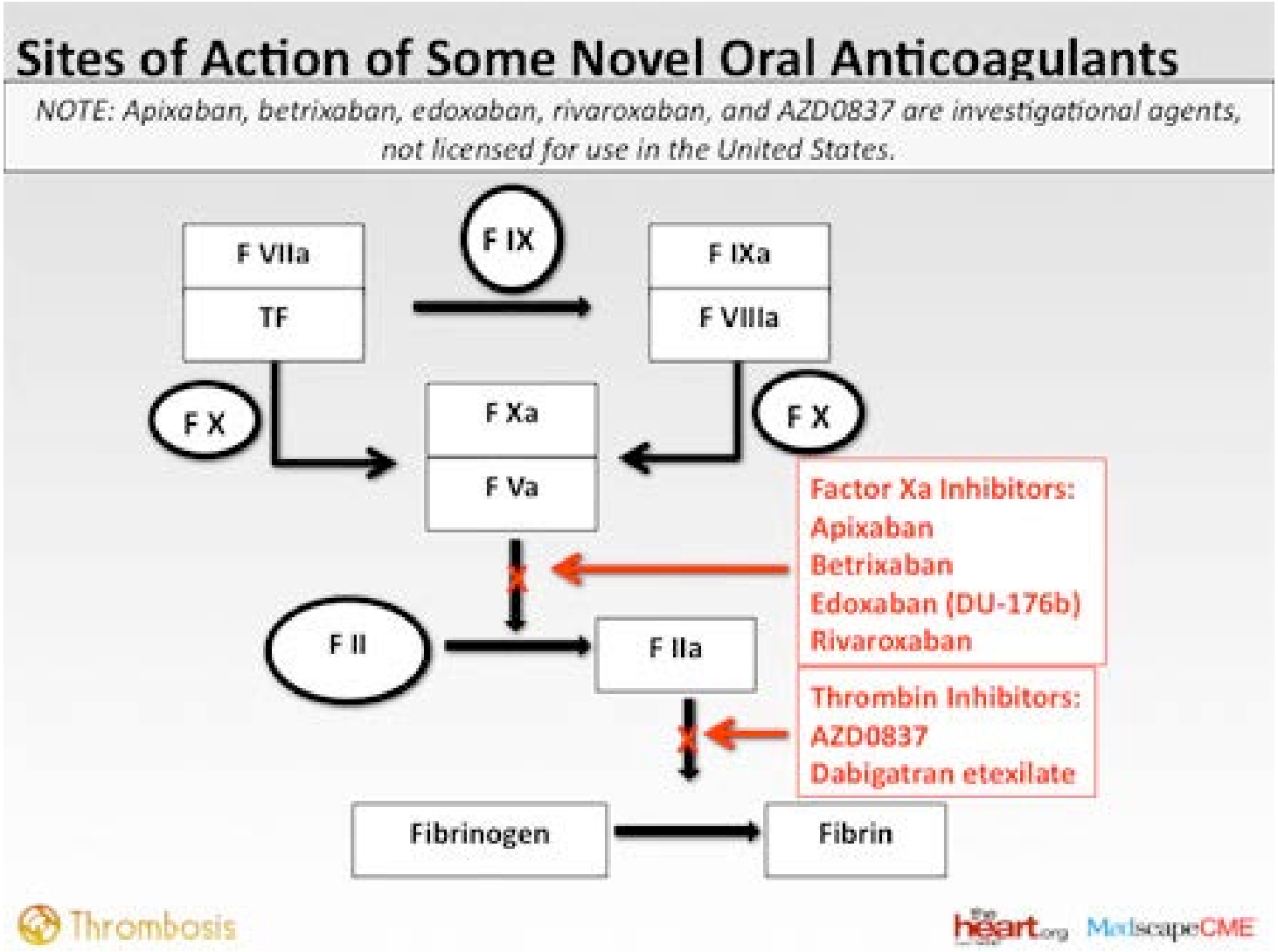
Background

Note: Warfarin inhibits the production of Factors II, VII, IX, and X.



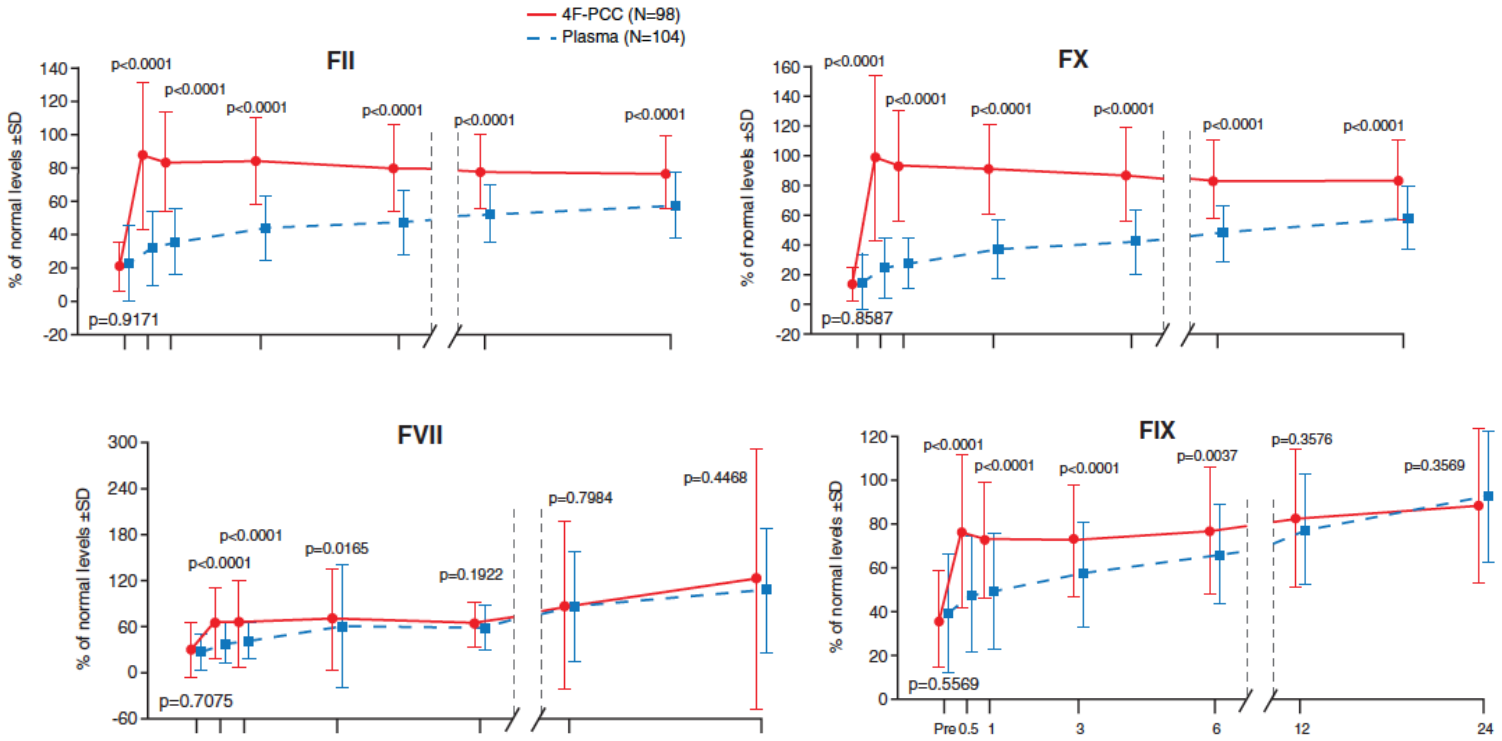
Background – NOACs

	Dabigatran	Rivaroxaban	Apixaban
Target	Factor II (Thrombin)	Factor Xa	Factor Xa
Half-life	12-14hrs	7-12hrs	8-14hrs
Lab marker?	PT, INR, PTT, TT, ECT. Hemoclot thrombin inhibitor assay?	PT, INR, anti-Xa	PT, INR, anti-Xa
Risk of relevant bleeding	3% per yr	3.6% per yr	1.4-2% per yr
Risk of ICH	0.3%/yr	0.8%/yr	0.3%/yr

PCCs increase Factor II and X levels

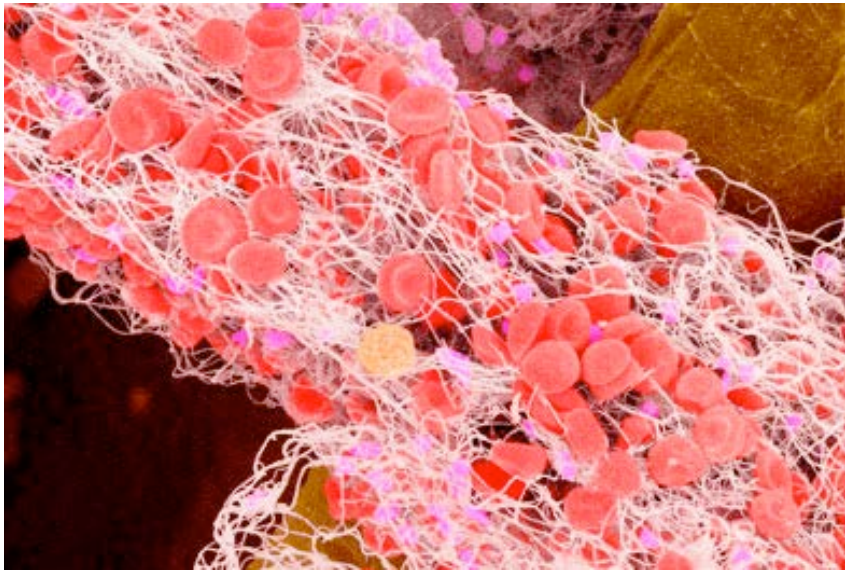
Efficacy and Safety of a Four-Factor Prothrombin Complex Concentrate (4F-PCC) in Patients on Vitamin K Antagonists Presenting with Major Bleeding: A Randomized, Plasma-Controlled, Phase IIIb Study

Ravi Sarode, Truman J. Milling, Jr., Majed A. Refaai, Antoinette Mangione, Astrid Schneider, Billie L. Durn and Joshua N. Goldstein



What can we use to reverse NOACs?

Agent	Factor II	Factor VII	Factor IX	Factor X
Profilnine	+	Minimal	+	+
FEIBA	+	+	+	+
Kcentra	+	+	+	+
Novo7	-	+	-	-



Animal studies

- Mouse ICH model (Zhou 2013; Zhou 2011):
  - FFP, PCC, and Novo7 prevent RIV-induced hematoma expansion.
  - PCC and FFP prevent DAB-induced hematoma expansion (Novo7 did not).
- Rabbit ear bleeding time (Martin 2013; Godier 2013):
  - Novo7 reversed RIV and AP-induced bleeding time, but neither it nor PCC reversed actual bleeding.
- Rabbit kidney incision (Pragst 2012):
  - PCC reversed DAB-induced blood loss after kidney incision.
- Rat hemostasis (Fukuda 2012):
  - Novo7 and PCC reversed edoxaban-related PT.

Human studies

- Eerenberg 2011:
  - PCC reversed rivaroxaban-induced PT.
  - PCC did not reverse dabigatran-induced PTT.
- Marlu et al 2012:
  - PCC corrected some RIV-induced TEG changes.
  - Novo7 corrected some RIV-induced TEG changes
  - FEIBA corrected all RIV-induced TEG changes.
  - Novo7 and FEIBA corrected some DAB-induced
- Dinkelaar et al 2013:
  - Effect of agents on reversal is assay dependent.

What are people doing?

- Kreuziger et al 2013: Survey of hematology directors, 48 responders. Of their algorithms:
  - All but one included factor concentrate:
    - 50% activated PCC
    - 66% nonactivated PCC
    - 83% activated Factor VIIa
- Rybinnik et al 2013: Survey of 221 vascular neurologists.
  - 53% FFP, 24% Novo7, 61% PCC
- German Society of Neurology:
  - Recommends PCC (Steiner et al2013)

Proposed trial

- Traumatic intracranial hemorrhage
  - High risk of morbidity/mortality
  - Usually with a known/more recent time of onset than spontaneous ICH
- Alternative – enroll all ICH?
  - Both spontaneous and traumatic
  - Presumed mechanism of action (ongoing bleeding) is similar.

Inclusion

- Inclusion:
  - Age>18
  - Any intracranial blood on CT
  - Exclusion:
  - GCS<5
  - Use of NOACs (?just include Xa inhibitors?)
  - Underlying coagulopathy other than NOAC use
  - Acute thromboembolic process

Study design

- Enrollment: Written Informed consent
- Intervention:
  - Single intravenous weight based dose of PCC vs. placebo.
- Coagulation studies:
  - Pretreatment
  - Postinfusion
  - 24 hours
  - 72 hours

Study design

- Outcomes:
  - 24 hour followup head CT
  - 24 hour neurologic exam
  - 30 day outcome, 90 day outcome
- Endpoint:
  - Phase II portion: Change in hematoma volume
    - Futility analysis examining change in neurologic outcome.
  - Phase III portion: 90 day mRS

Other agents?

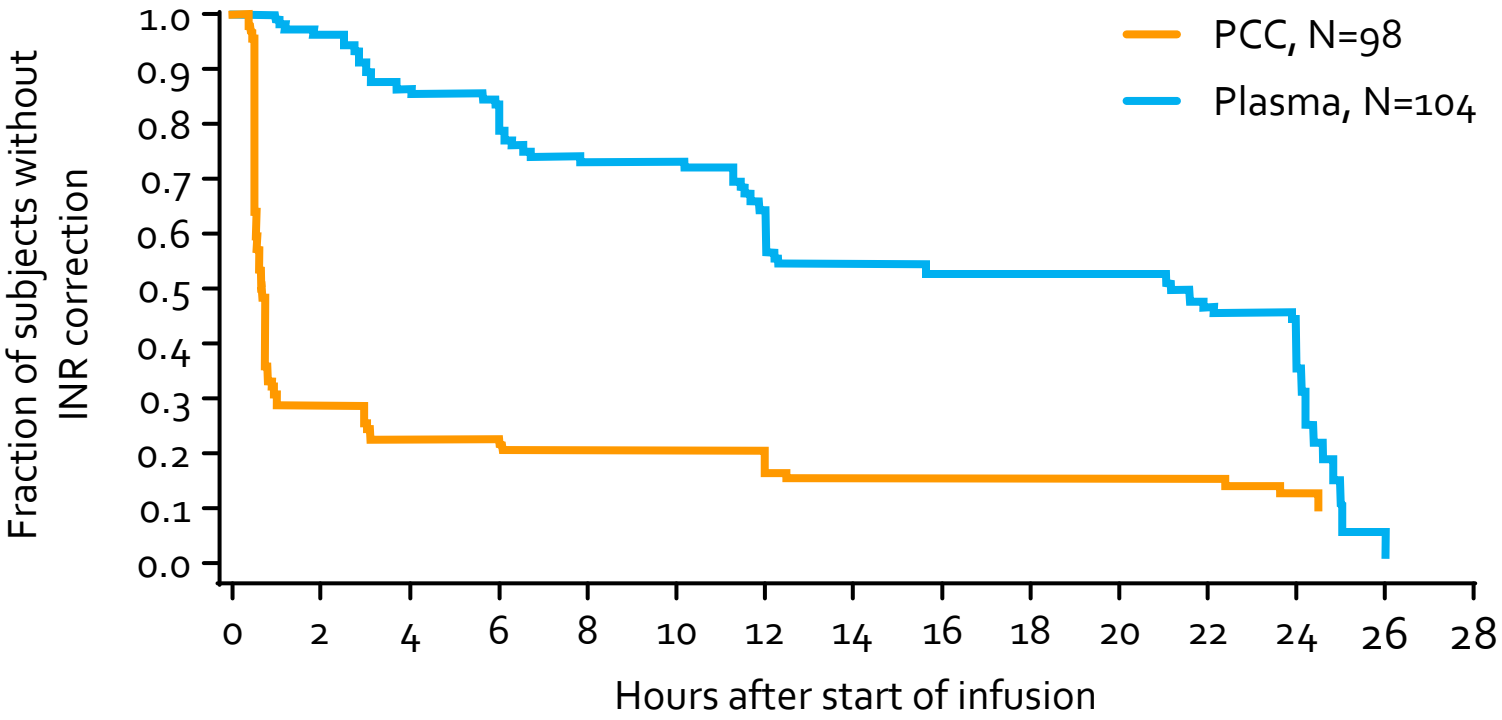
- **PRT064445- Portola pharmaceuticals – Xa inhibitor antidote**
- aDabi-Fab – dabigatran inhibitor?

Questions

Kcentra results

Time To INR Correction

- **Subjects receiving PCC-4 achieved INR correction (≤1.3) more rapidly than those receiving plasma**



KCentra: Rapid INR Reduction

Rating	No. (%) subjects [95% CI]		Difference PCC – plasma (%) [95% CI]
	PCC-4 (N=98)	Plasma (N=104)	
Rapid INR reduction	61 (62.2) [52.6, 71.8]	10 (9.6) [3.9, 15.3]	52.6 [39.4, 65.9]

- Rapid decrease in INR defined as INR ≤1.3 at 30 min after the end of infusion

PCC-4 was superior to plasma for rapid decrease in INR.

KCentra: Hemostatic Efficacy

Rating	No. (%) subjects [95% CI]		Difference PCC – plasma (%) [95% CI]
	PCC-4 (N=98)	Plasma (N=104)	
"Effective" hemostasis	71 (72.4) [63.6, 81.3]	68 (65.4) [56.2, 74.5]	7.1 [–5.8, 19.9]

- "Effective" hemostasis defined as a rating of excellent or good (on a 3-point scale of excellent, good, poor/none) by the blinded EAB

PCC-4 was non-inferior to plasma for hemostatic efficacy in the first 24 hours.