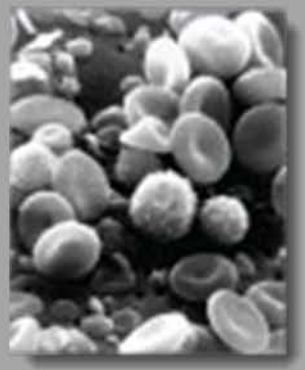


12th Annual Canadian Blood Services International Symposium

Plasma: Transfuse it, Fractionate it or Forget it?

Canadian Blood Services
it's in you to give

Prothrombin Complex Concentrates: Reversal of Warfarin Therapy

Mark Blostein, MD, FRCP
Associate Director, Division of Hematology
Director, Anticoagulant Clinic and Coagulation Laboratories, Jewish General Hospital
Associate Professor of Medicine, McGill University, Montreal, QC

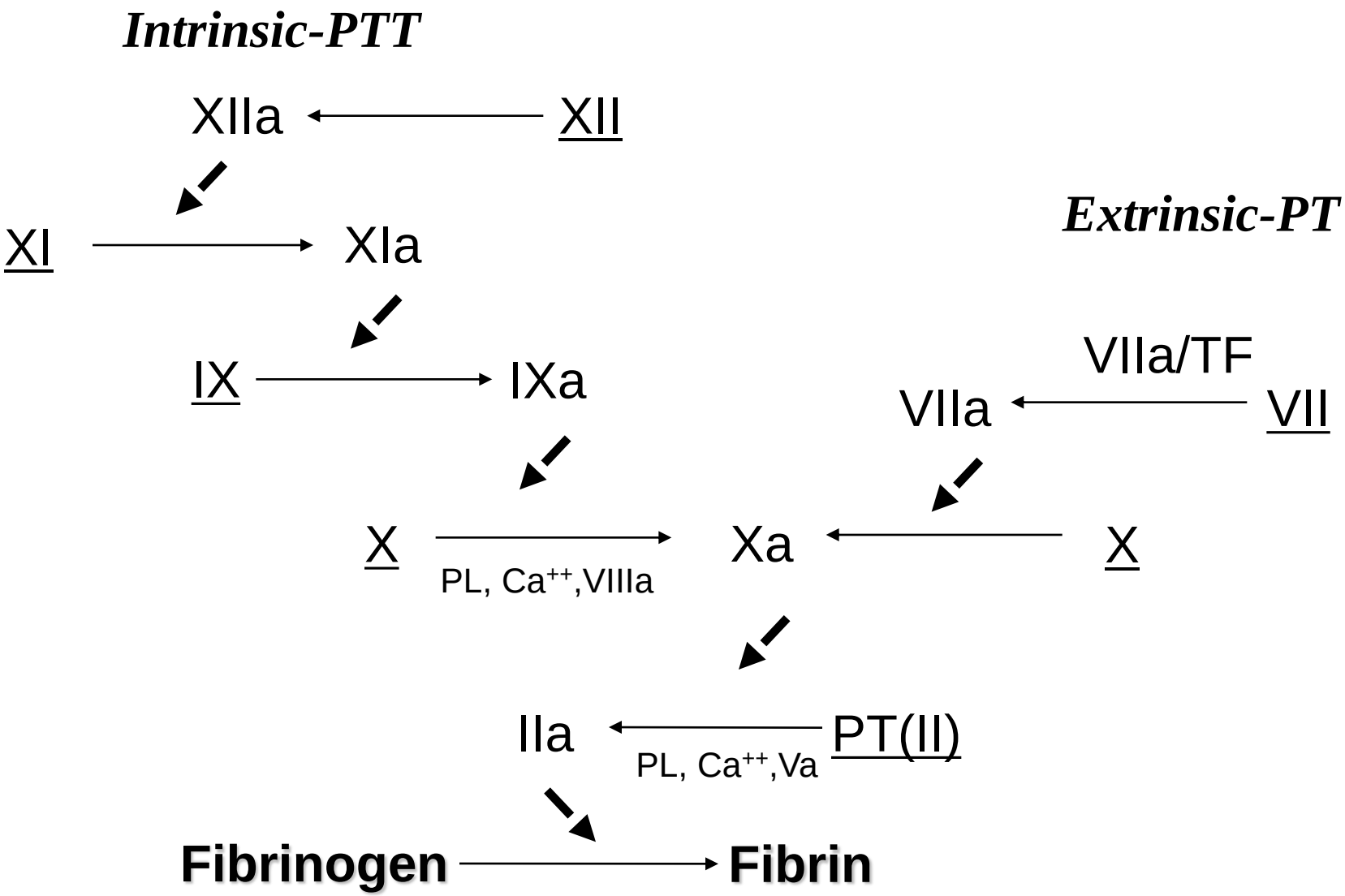
Disclosures

Advisory Boards: Bayer, Boehringer-Ingelheim, Octapharma, CSL-Behring, Alexion

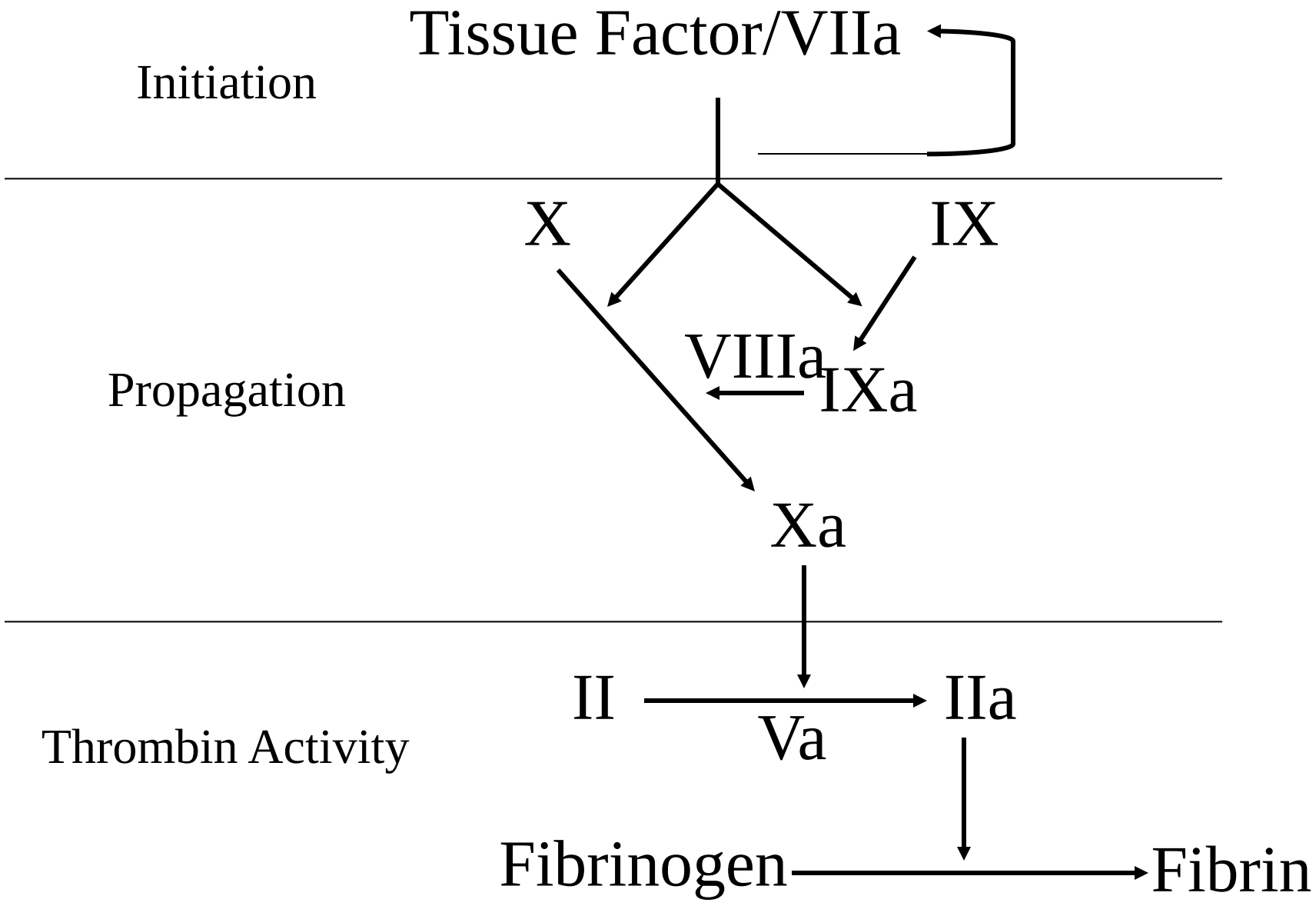
Research funding: Boehringer-Ingelheim, Pfizer-BMS

Speaker’s honoraria: Octapharma, Pfizer, CSL-Behring

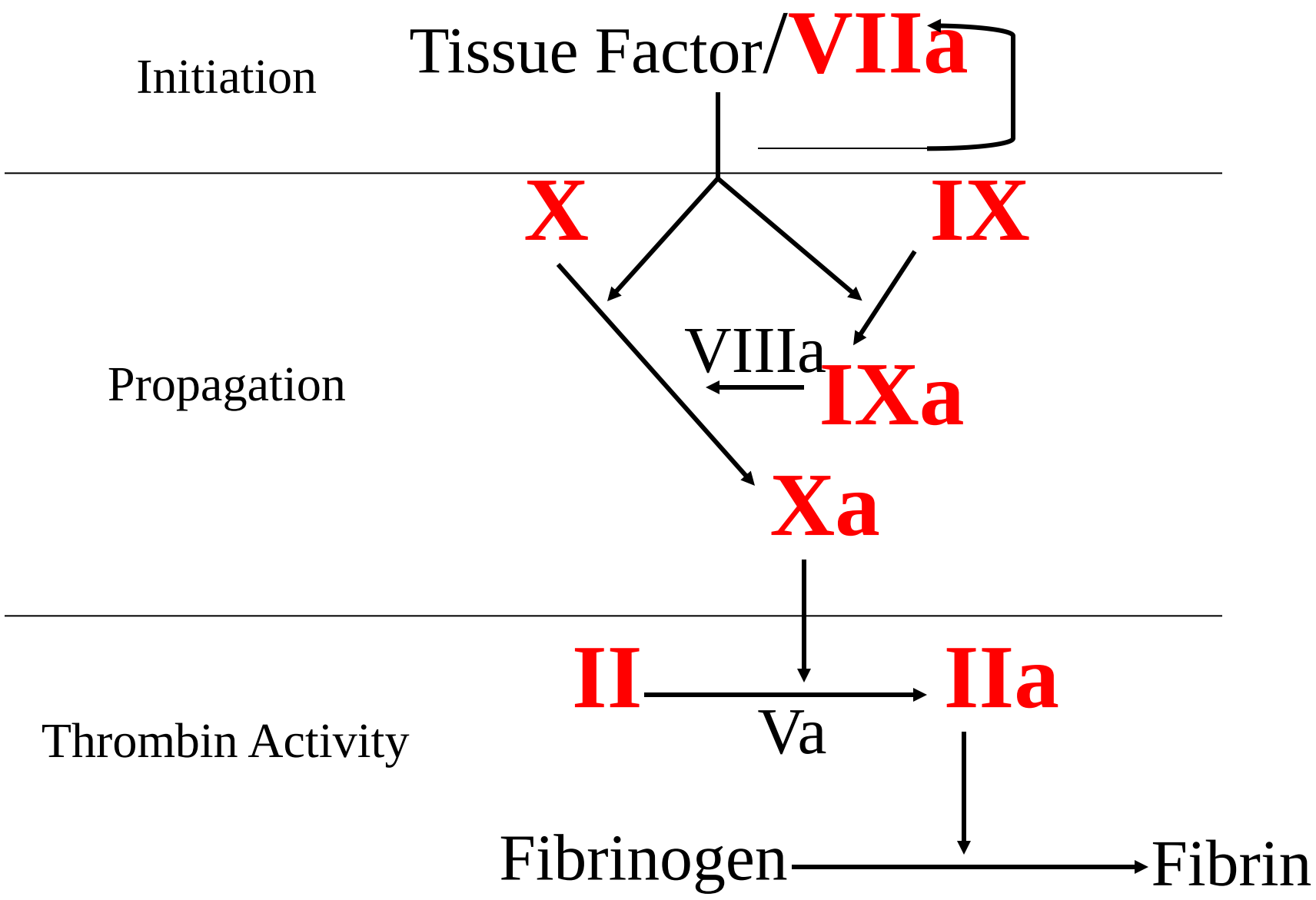
Blood Coagulation Cascade



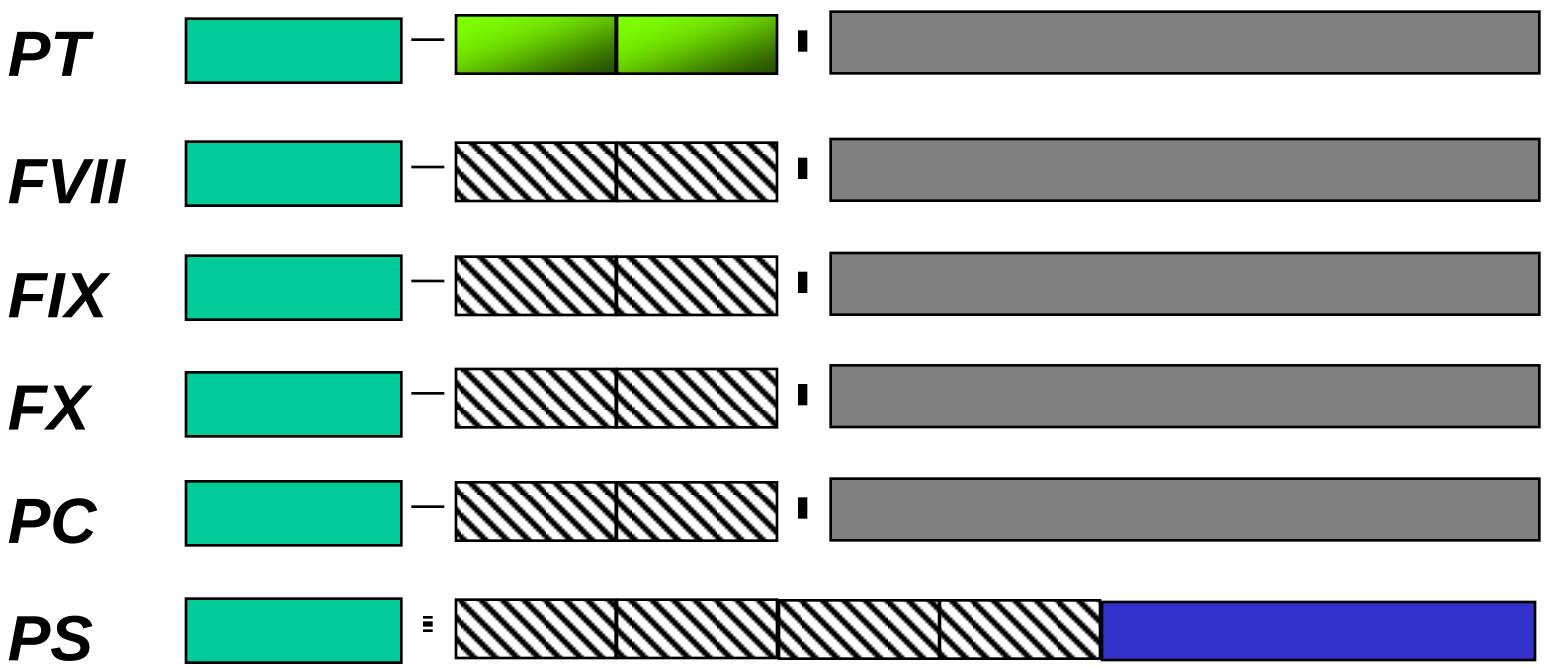
NEW Blood Coagulation Cascade



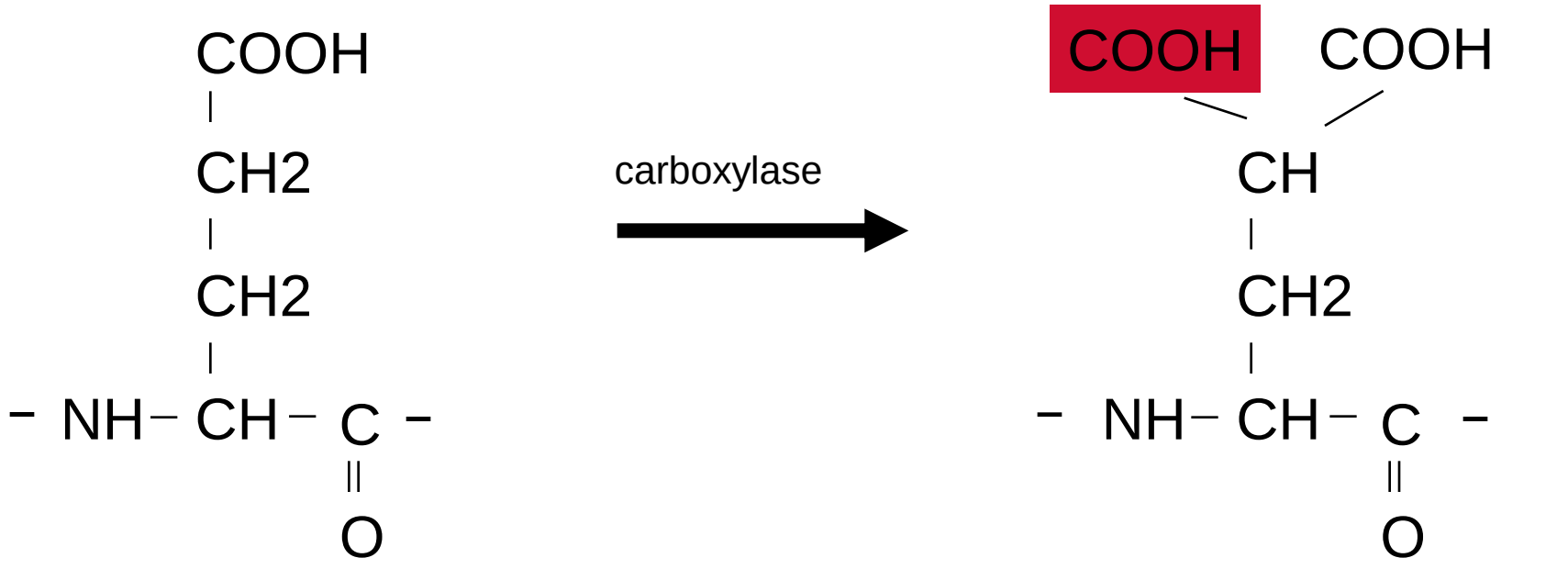
Vitamin K dependent Factors



Each vitamin K dependent protein contains 9-12 Gla residues

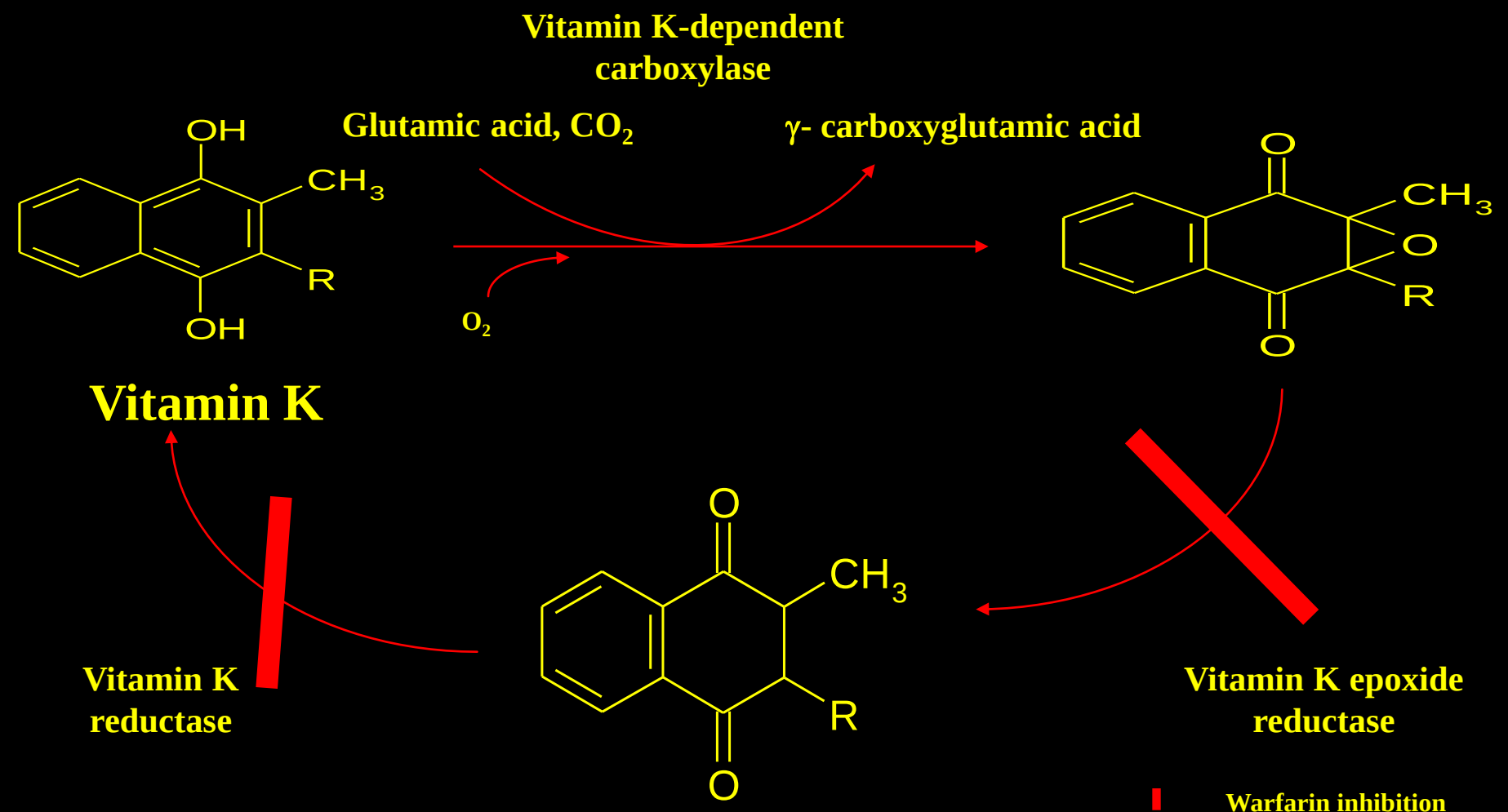


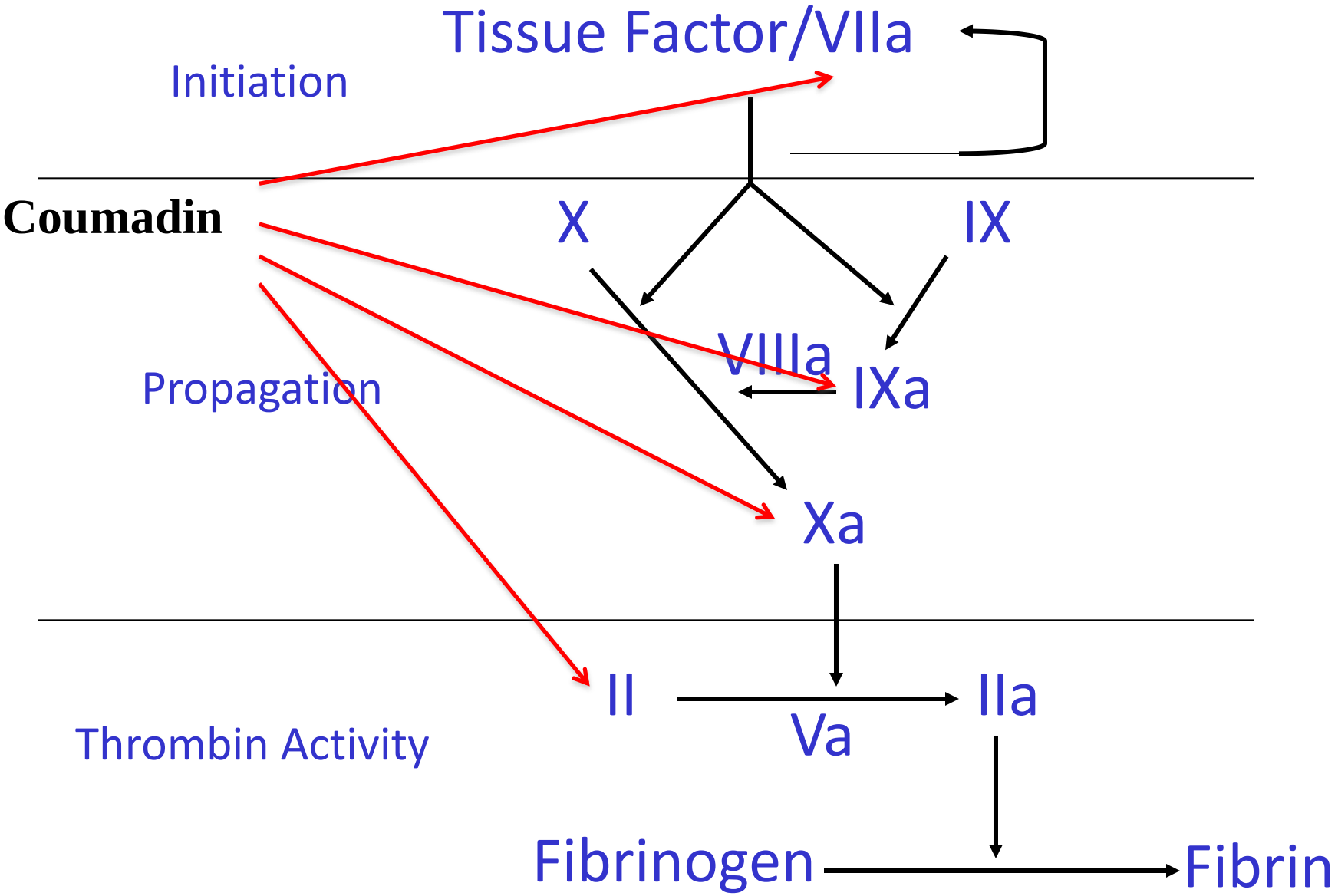
What is γ-carboxylation?



Glutamic acid

γ-carboxyglutamic acid


Vitamin K-dependent carboxylase
Glutamic acid, CO_2
γ- carboxyglutamic acid
O_2
Vitamin K
Vitamin K reductase
Vitamin K epoxide reductase
Warfarin inhibition


Tissue Factor/VIIa
Initiation
Coumadin
X
IX
VIIIa
IXa
Propagation
Xa
II
IIa
Va
Thrombin Activity
Fibrinogen
Fibrin

What do we Anticoagulate?

1. VTE (DVT/PE) Treatment
2. VTE Prevention
    A. Surgery (esp. orthopedics)
    B. Medical patients
3. Stroke prevention i.e. Atrial Fibrillation
4. Prosthetic Heart Valves

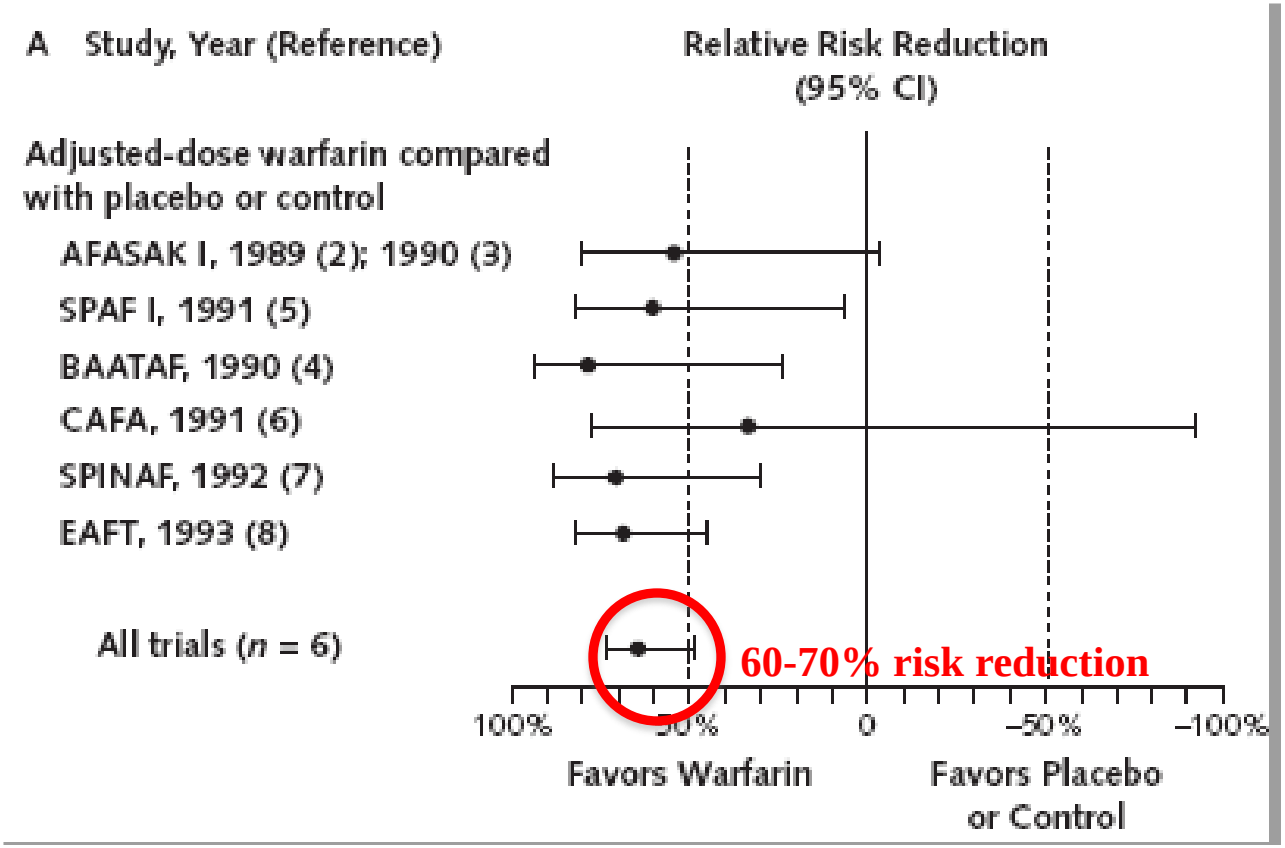
Problems with Coumadin:

1.Requires ~3-4 days for its effect and 3-4 days to wear off making it impractical for patients who require procedures
2.Many drug and food interactions that interfere with its pharmacokinetics
3.Narrow toxic-to-therapeutic window
4.Requires monitoring

Annals of Internal Medicine | REVIEW

Meta-analysis: Antithrombotic Therapy to Prevent Stroke in Patients Who Have Nonvalvular Atrial Fibrillation

Robert G. Hart, MD; Lesly A. Pearce, MS; and Maria I. Aguilar, MD



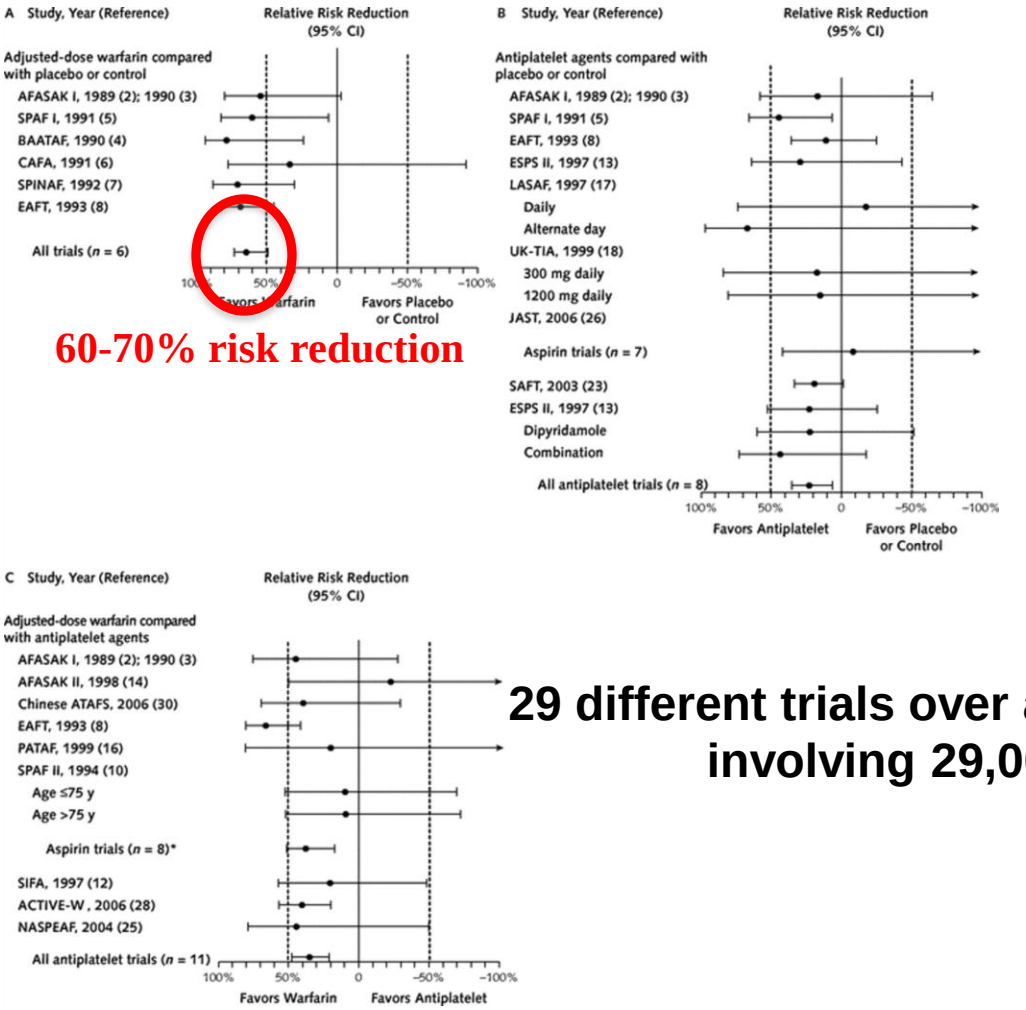
29 different trials over a period of 30 years involving 29,000 patients

Hart *Ann Intern Med* 2007;146:857-867

Annals of Internal Medicine
Established in 1927 by the American College of Physicians

From: Meta-analysis: Antithrombotic Therapy to Prevent Stroke in Patients Who Have Nonvalvular Atrial Fibrillation

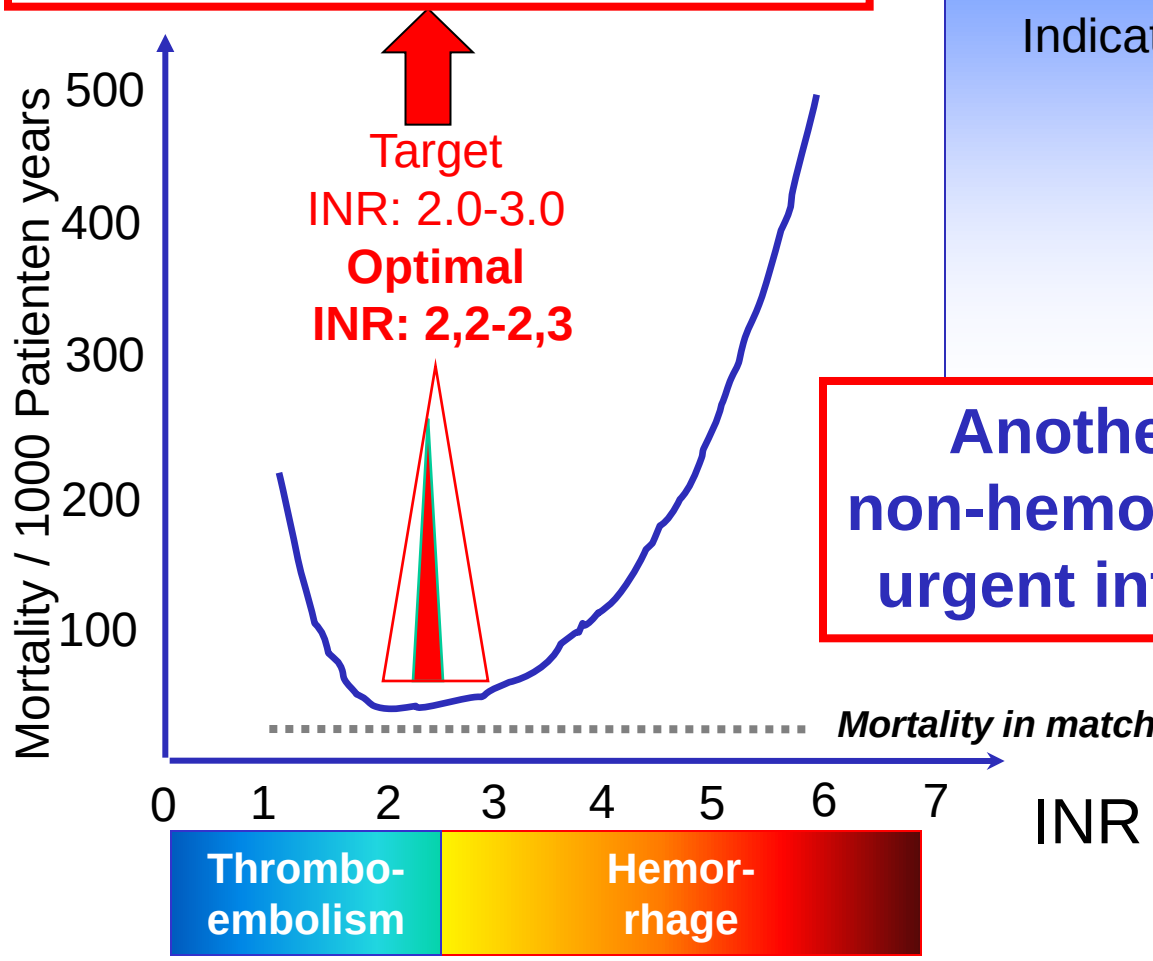
Ann Intern Med. 2007;146(12):857-867.



29 different trials over a period of 30 years involving 29,000 patients

Warfarin, INR and Mortality

1.1-1.5 % major bleeds/pts-y
(30 000 emergencies/y [G])



Analysis of 1 250 000 INR-values
42 451 patients: 3 533 death

Indications:		
	AF	58%
	VTE	25%
	Stroke/TIA	22%
	Heart valves	18%
	Myocardial Infarction	3%

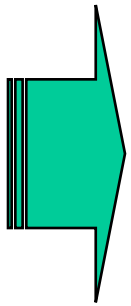
Another > 30 000/y non-hemorrhagic induced urgent interventions [G]

Odén, A, BMJ 2002; 325: 1073-75
Palareti, G, Lancet 1996; 348:423-428
Go, AS, JAMA 2003;290:2685-2692

Treatment option for reversal of OAT

Withhold VKA:

Half lifes:	11 h	Acenocoumarol (Sintrom)
	40 h	Warfarin (Coumadin)
	31 h	Fluindione (Previscan)
	140 h	Phenprocoumon



Will take
>>24 h
to reach
INR < 1.5

Application of vitamin K:

oral: slow decrease of INR, start within 12-24 h

i.v. : slow decrease of INR, start within 6-8 h

s.c.: ???role

Factor replacement:

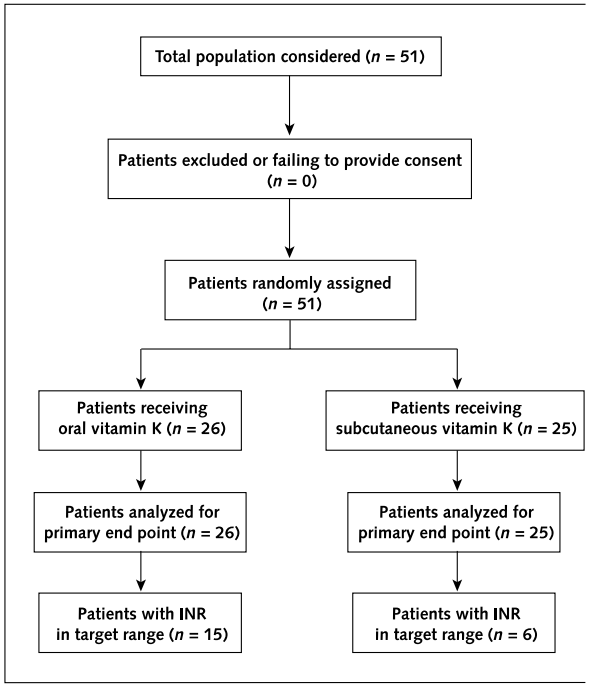
immediate increase in factor activities

Ansell, J, Chest 2004;126:204S-233S
Baglin, TP, Br J Haematoll 2006;132:277-285
Aguilar, MI, Nayo Clin Proc 2007;83:82-92
Schulman,S, Transfus Me Rev 2007; 21:37-48

Oral Vitamin K Lowers the International Normalized Ratio More Rapidly Than Subcutaneous Vitamin K in the Treatment of Warfarin-Associated Coagulopathy

A Randomized, Controlled Trial

Mark A. Crowther, MD, MSc; James D. Douketis, MD; Terri Schnurr, RN; Luigi Steidl, MD; Valentina Mera, MD; Carolina Ultori, MD; Achille Venco, MD; and Walter Ageno, MD



Annals of Internal Medicine | ARTICLE

Oral Vitamin K Versus Placebo to Correct Excessive Anticoagulation in Patients Receiving Warfarin

A Randomized Trial

Mark A. Crowther, MD, MSc; Walter Ageno, MD; David Garcia, MD; Luqi Wang, PhD; Dan M. Witt, PharmD; Nathan P. Clark, PharmD; Mark D. Blostein, MD; Susan R. Kahn, MD, MSc; Sara K. Vesely, PhD; Sam Schulman, MD; Michael J. Kovacs, MD; Marc A. Rodger, MD, MSc; Phillip Wells, MD, MSc; David Anderson, MD, MSc; Jeffery Ginsberg, MD; Rita Selby, MD, MSc; Sergio Siragusa, MD; Mauro Silingardi, MD; Mary Beth Dowd, PharmD; and Clive Kearon, MD, PhD

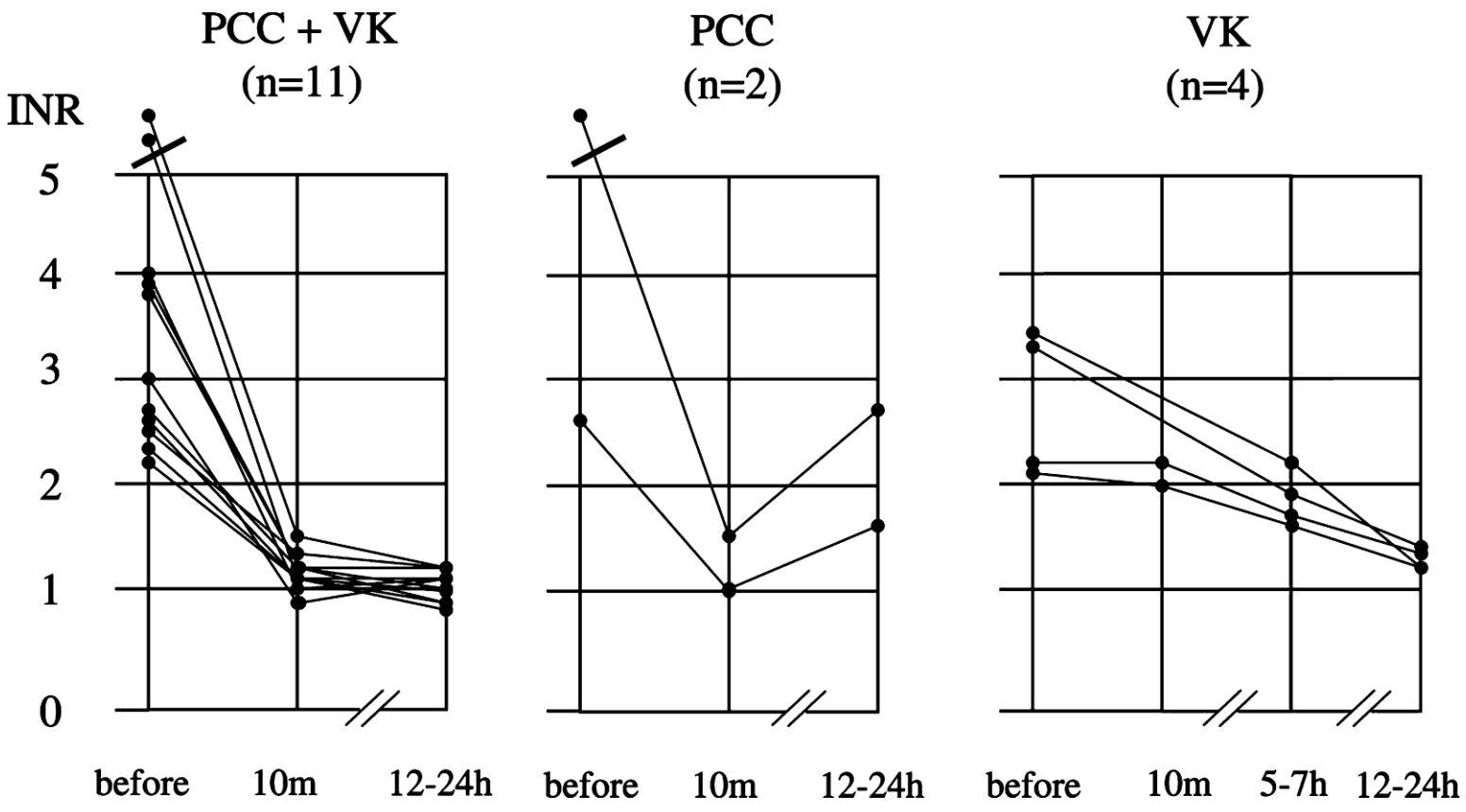
Table 2. Major Clinical Outcomes

Outcome	Day 90				Day 30				Day 7			
	Vitamin K Group [95% CI], *n (%)*	Placebo Group [95% CI], *n (%)*	Risk Difference (95% CI), *percentage points*	*P* Value	Vitamin K Group [95% CI], *n (%)*	Placebo Group [95% CI], *n (%)*	Risk Difference (95% CI), *percentage points*	*P* Value	Vitamin K Group [95% CI], *n (%)*	Placebo Group [95% CI], *n (%)*	Risk Difference (95% CI), *percentage points*	*P* Value
Any bleeding event	56 (15.8 [12.1 to 20.0])	60 (16.3 [12.6 to 20.4])	−0.5 (−6.1 to 5.1)	0.86*	41 (11.5 [8.4 to 15.3])	47 (12.7 [9.5 to 16.6])	−1.2 (−6.2 to 3.8)	0.63†	28 (7.9 [5.3 to 11.2])	34 (9.2 [6.5 to 12.6])	−1.3 (−5.7 to 3.0)	0.52†
Major bleeding event	9 (2.5 [1.2 to 4.8])	4 (1.1 [0.3 to 2.8])	1.5 (−0.8 to 3.7)	0.22‡	–	–	–	–	–	–	–	–
Thromboembolism	4 (1.1 [0.3 to 2.9])	3 (0.8 [0.2 to 2.4])	0.3 (−1.4 to 2.0)	0.72‡	2 (0.6 [0.1 to 2.0])	1 (0.3 [0.0 to 1.5])	0.3 (−0.9 to 1.5)	0.62†	1 (0.3 [0.0 to 1.6])	1 (0.3 [0.0 to 1.5])	0.0 (−1.0 to 1.1)	1.00†
Death	7 (2.0 [0.8 to 4.0])	7 (1.9 [0.8 to 3.9])	0.1 (−2.2 to 2.4)	0.94‡	1 (0.3 [0.0 to 1.6])	5 (1.4 [0.4 to 3.1])	−1.1 (−2.7 to 0.5	0.22†	0 (0.0 [0.0 to 1.0])	1 (0.3 [0.0 to 1.5])	0.3 (−1.1 to 0.5)	1.00†

* Prespecified primary outcome.
† Post hoc exploratory analysis.
‡ Prespecified secondary outcome.

In a double blind randomized trial of 763 non-bleeding patients, oral vitamin K did not reduce bleeding when INRs were between 4 and 10

Treatment, time and INR



Yasaka M et al. Thromb Res. 108:25-30, 2002

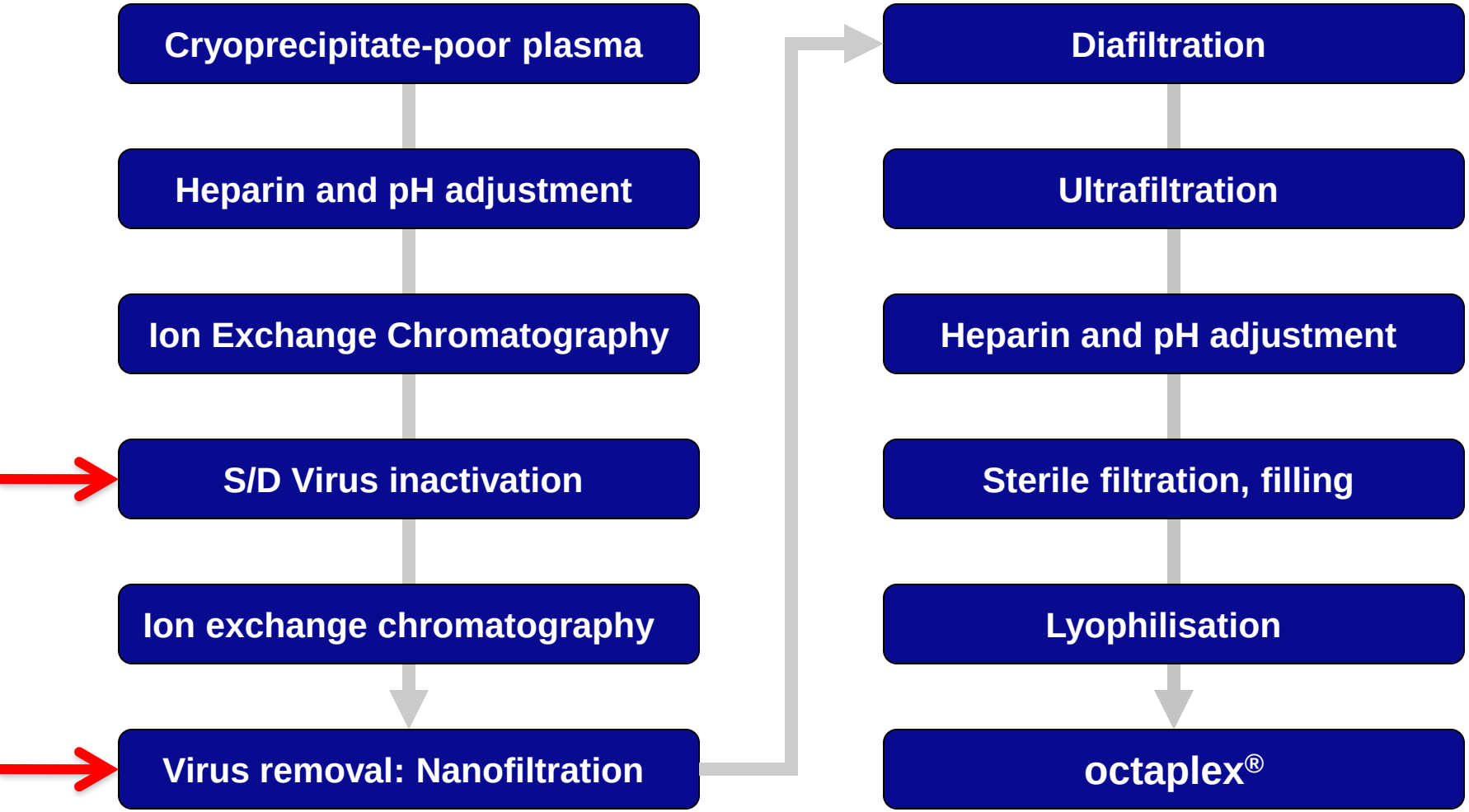
What are prothrombin complex concentrates (PCCs)?

Concentrated product of the vitamin dependent coagulation factors

- Prothrombin
- Factor VII
- Factor IX
- Factor X
- Protein C
- Protein S
- Heparin

Two commercial products in Canada: **Octaplex** (Octapharma) and **Beriplex** (CSL Behring)

octaplex manufacturing process



Benefits of prothrombin complex concetnrate (PCC) over fresh frozen plasma (FFP) for reversal of warfarin

PCC vs Plasma

FFP

- Blood group specific
- Slow process to acheive target INR
- Takes time to thaw
- Large volumes needed
- Varying content of coagulation factors
- Unpredictable effect
- Not virus inactivated
- Risk of TRALI

PCC

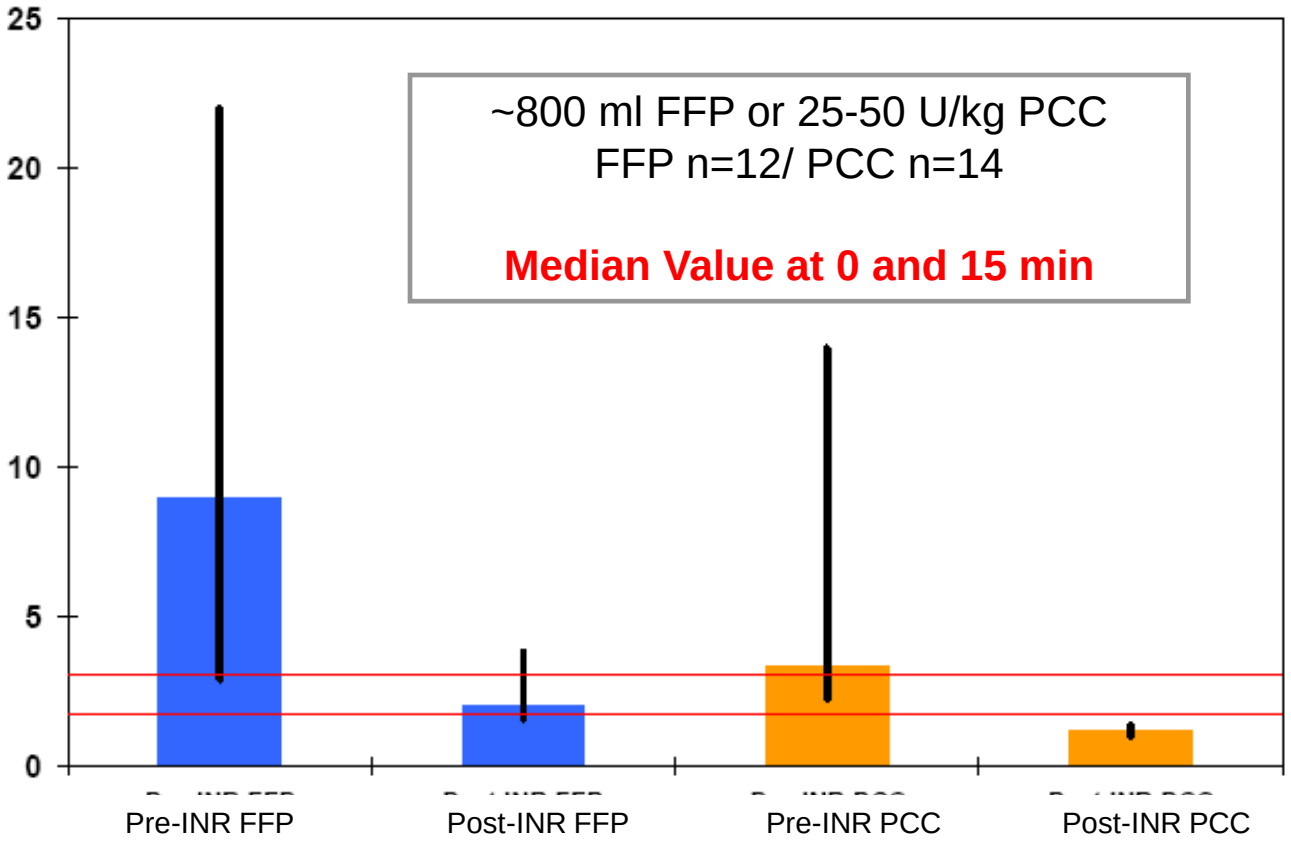
- Not blood group specific
- Fast application: 10 mins
- Room temperated
- Small volume
- Standardised content of coagulation factors (1:1:1:1 ratio of FII, FVII, FIX, FX)
- Predictable effect
- Virus inactivated
- No risk of TRALI

1,5 liter

≈

60 ml

12 patients given FFP and 14 patients given PCC Not a randomized trial…. PCCs resulted in a lower INR



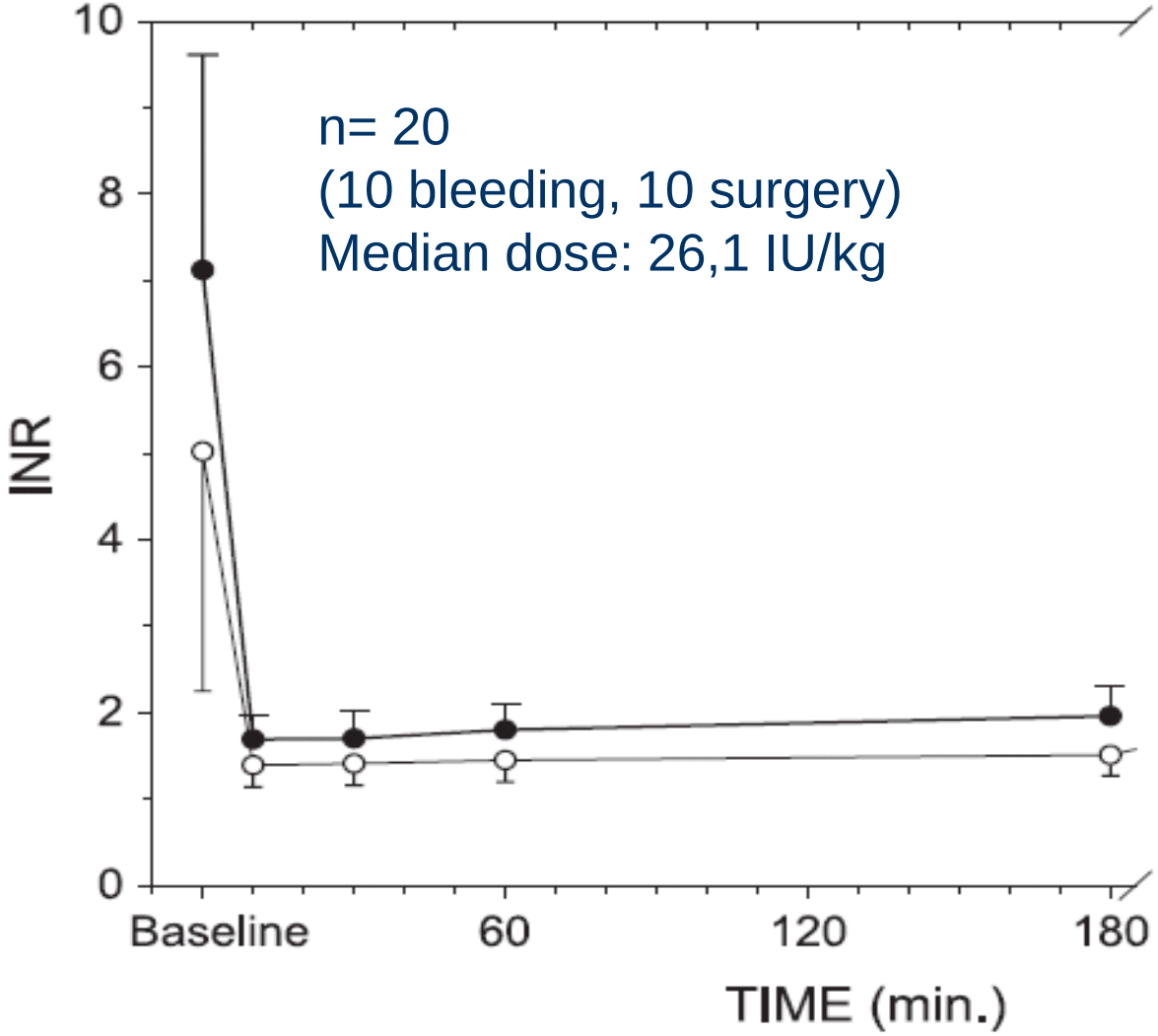
MakrisM et al; Thromb Hamost 1997; 77:477-480

Clinical studies: LEX-202

Study number	LEX-202
Study centres (Number)	Israel and Russia (n=6)
Number of patients	20 patients with major bleedings (INR>5) or surgical/invasive procedures during treatment with oral anticoagulants (INR>3)
Treatment period	Bleeding or procedure related
Study drug (Batches used)	Octaplex (n=3)
Amount of study drug used	37,250 IU

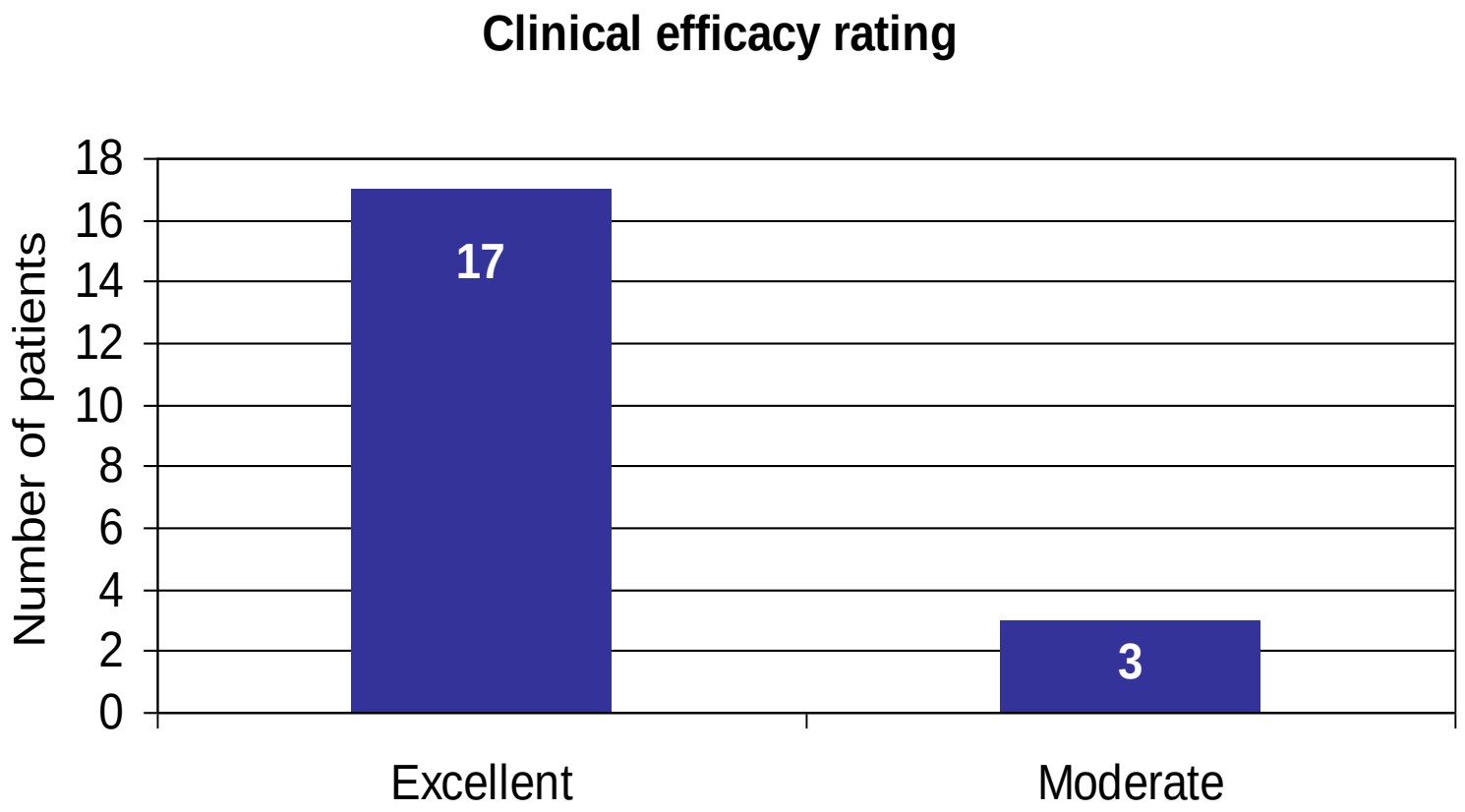
Lubetsky, A, Thromb Res 2004;113:371-378

Clinical studies: LEX-202



Lubetsky, A, Thromb Res 2004;113:371-378

Clinical studies: LEX-202



Mean dosage: 26.1 IU FIX/kg BW
Dosage range: 13.7-43.8 IU FIX/kg BW

Lubetsky, A, Thromb Res 2004;113:371-378

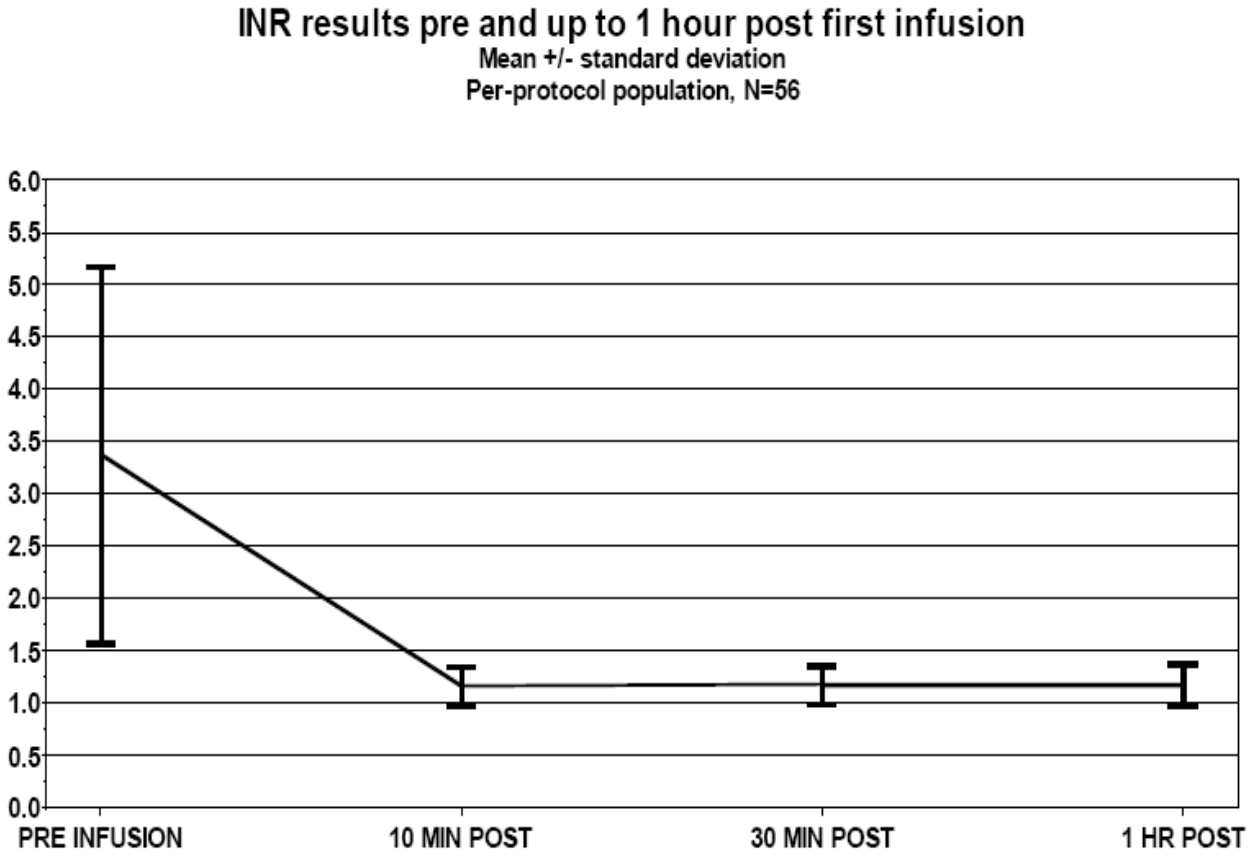
Clinical studies: LEX-203

Efficacy and Safety of OCTAPLEX® in Patients Under Oral Anticoagulant Therapy and Undergoing Surgery or Invasive Procedures

A Prospective, Non-Randomised, Non-Controlled, Open-Label, Multi-Centre Phase III – Study (N = 60)

Clinical studies: LEX-203

Correction of INR.



Dosing recommendations

The dose will depend on the INR before treatment and the targeted INR. In the following table approximate doses (mL / kg body weight of the reconstituted product) required for normalisation of INR (≤1.2 within 1 hour) at different initial INR levels are given.

Initial INR	2.0 - 2.5	2.5 - 3.0	3.0 - 3.5	>3.5
Approximate dose* (mL octaplex® / kg body weight)	0.9 - 1.3	1.3 - 1.6	1.6 - 1.9	>1.9

One vial of octaplex is 20 mL and contains 500 IU FIX

For example:

Recommended dose of octaplex for a 70 kg patient with starting INR of 2.5:

1.3 mL x 70 kg = 91 mL octaplex

91 mL octaplex / 20 mL per vial = 4.55 vials octaplex (2275 IU octaplex)

PRODUCT COMPOSITION:

- One 20 mL vial of octaplex® contains the following:

Human Coagulation Factor II	220-760 IU
Human Coagulation Factor VII	180-480 IU
Human Coagulation Factor IX	400-620 IU
Human Coagulation Factor X	360-600 IU
Protein C	140-620 IU
Protein S	140-640 IU
Heparin	80-310 IU
Sodium citrate	17-27 mmol/L

- Reconstituted solution contains approximately 25 IU of prothrombin complex per mL

INDICATIONS:

Recommended in:

A. Reversal of warfarin therapy or vitamin K deficiency in patients exhibiting major bleeding manifestations.

B. Reversal of warfarin therapy or vitamin K deficiency in patients requiring urgent (<6 hour) surgical procedures.

If a study is available all qualified patients should be encouraged to participate in the study rather than receiving open-label product.

Contraindicated in:

A. Patients with a history of Heparin Induced Thrombocytopenia

Not recommended* for:

A. Elective reversal of oral anticoagulant therapy pre – invasive procedure.
B. Treatment of elevated INRs without bleeding or need for surgical intervention. For management of vitamin K antagonist overdose with elevated INR but without bleeding, please refer to the ACCP 2008 recommendations.
C. Massive transfusion
D. Coagulopathy associated with Liver dysfunction
E. Patients with recent history of thrombosis, myocardial infarction, recent ischemic stroke or Disseminated Intravascular Coagulation (DIC)

B. Pediatric patients – there is insufficient evidence available to allow a recommendation for use of this product in this patient population.
C. Congenital factor II or X deficient patients – use of the product should be at the discretion of the local Hemophilia clinic.

DOSING, ADMINISTRATION & MONITORING:

The following recommendation is based on review of literature and the desire to prevent thrombotic complications. The subcommittee is aware that it may be less than the manufacturer's recommended dose in many individuals.

For adult patients:

40 mL octaplex® (1000 IU Factor IX activity*) **and** 10 mg Vitamin K IV

*A higher or second dose may be needed in extremes of INR or weight, suggest consultation with a specialist in hematology or transfusion medicine in these situations.

Maximum total dose: **120 mL or 3000 IU Factor IX activity.**

Administration: Must be administered intravenously.
The rate of infusion should not exceed 2- 3mL/min.

Post dose monitoring: INR – 10-15 minutes
Clinical outcomes (incl. thrombotic events) – 24 hour and 30 day

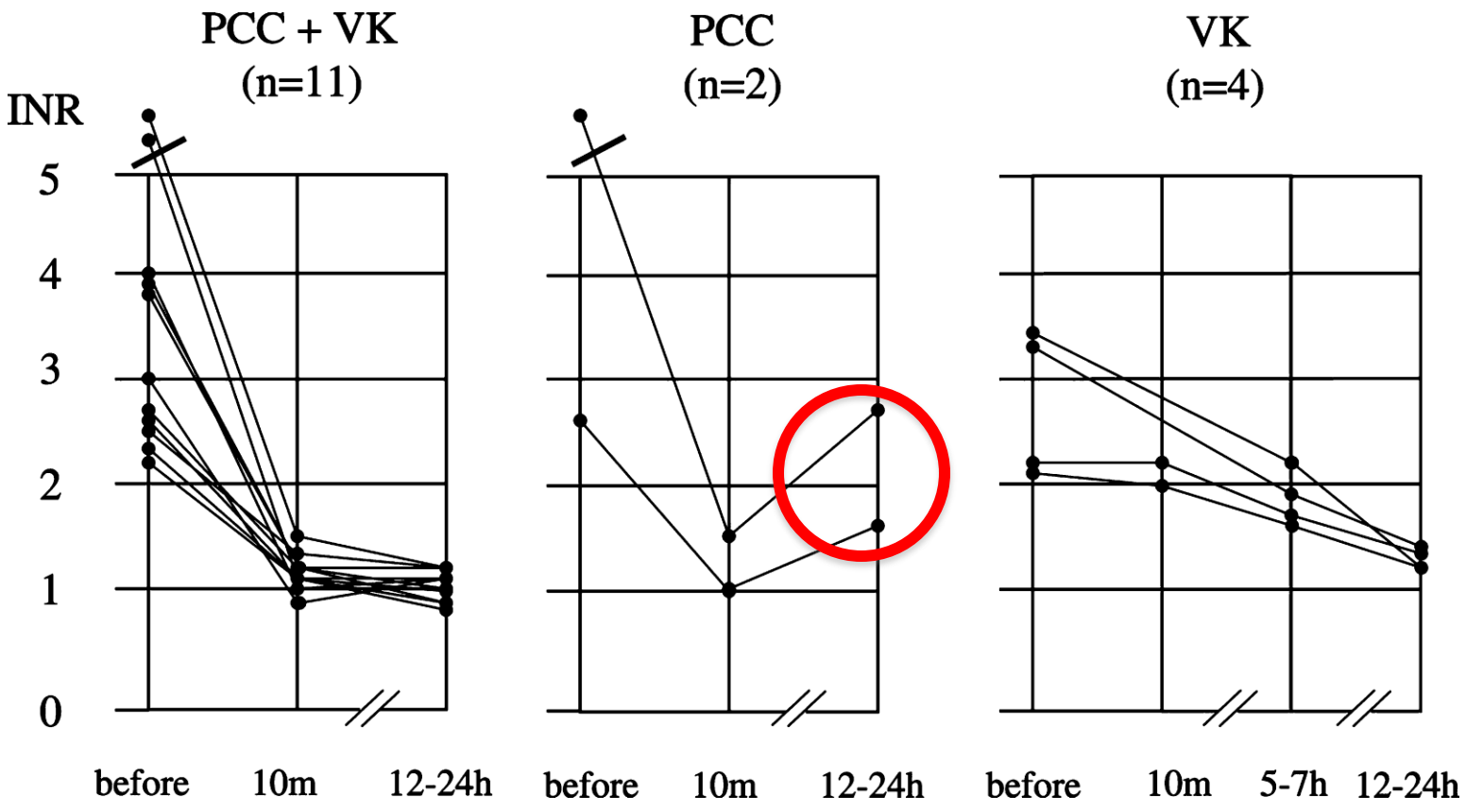
Jewish General Hospital (JGH) Experience

- Approval from Thrombosis and Hematology not needed
- Use reviewed retrospectively
- 1000 FIX units for ‘everyone’
  - Easier to implement
  - Scientific evidence for using BW and INRs not robust
  - Guide dose by INR 15-30 minutes post infusion
- NEED TO BE ON WARFARIN

JGH Experience: Issues

- Use of vitamin K
- Protocol stipulates that 10 mg IV vitamin K be given
- Should be given in most circumstances except when reversal is needed only temporary e.g. surgical procedures such as pacemakers, cardiac cath,
- Preparation of product

Treatment, time and INR



Yasaka M et al. Thromb Res. 108:25-30, 2002

JGH Experience

- Cost:
- $750 per 1000 FIX units vs. $200-250 per unit of FFP
  - i.e. same cost, maybe even cheaper than FFP
  - Definite reduction in costs of administration such as nursing costs

ORIGINAL RESEARCH

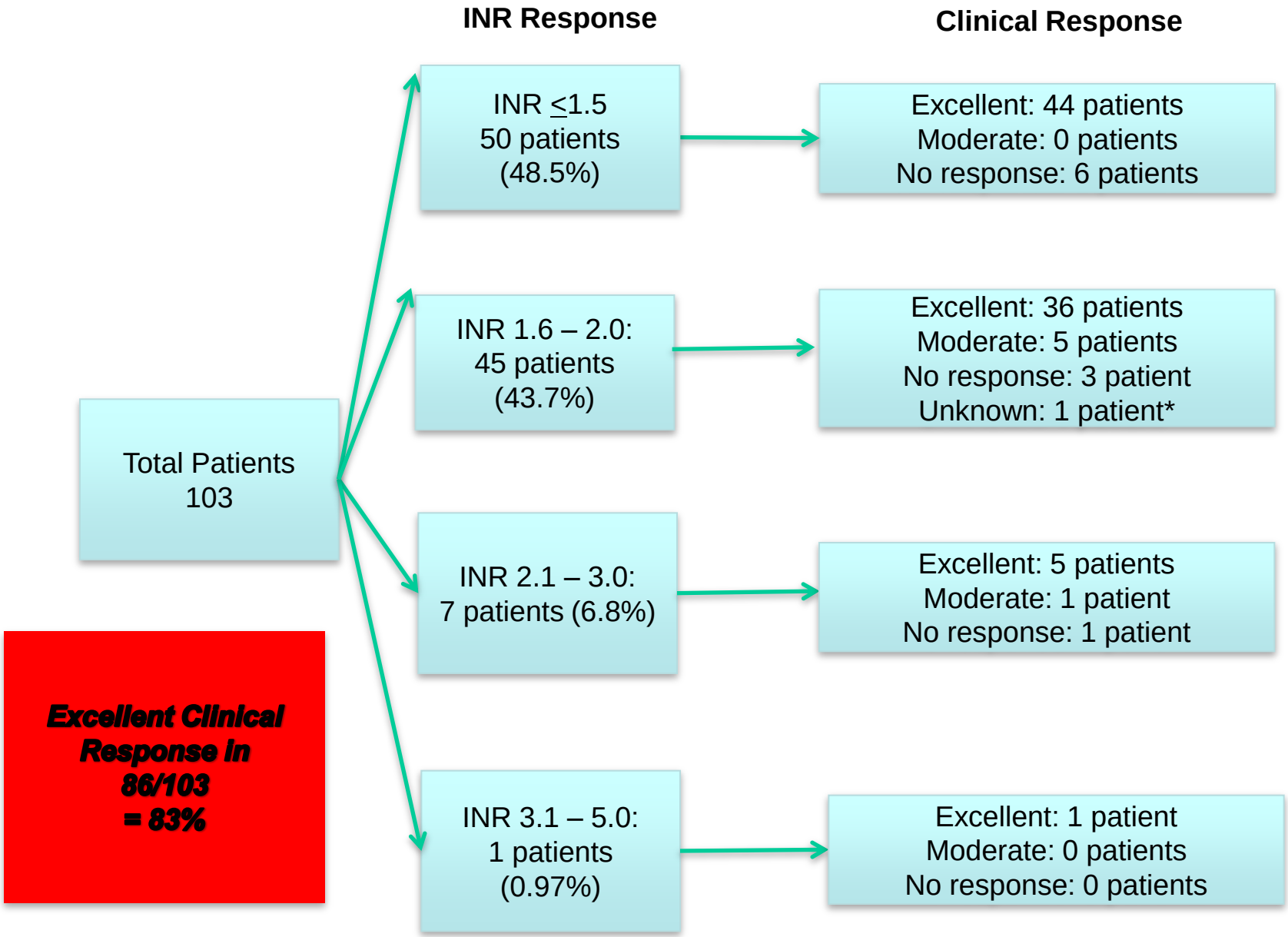
The effectiveness and safety of fixed low-dose prothrombin complex concentrates in patients requiring urgent reversal of warfarin

Cindy Varga, Sultan Al-Touri, Stella Papadoukakis, Stephen Caplan, Susan Kahn, and Mark Blostein

Transfusion, 53:1451, 2013

- Retrospective chart review of 103 patients who received PCCs for bleeding or need for an urgent procedure while patient on coumadin
- Received 1000 U (~16.7 U/kg) regardless of size and INR
- INR checked 30 minutes after infusion with the option of administering more if needed as judged by the treating physician
- Assessed clinical efficacy, INR response and toxicity within 30 days

Message 1: INR response not great (~50%<1.5) to PCC but clinical response excellent



Transfusion, 53:1451, 2013

Message 2: Intracranial Haemorrhage (ICH) do poorly despite PCCs

Clinical Presentation	No. (N = 103)	**Clinical Response No. (%)**			Deaths due to bleeding (no.)	No. pts > 1 dose	Thrombosis
		Excellent	Moderate	None			
ICH	**22**	**14 (63.6)**	**0 (0.0)**	**8 (36.4)**	**7**	**6**	**0**
Extracranial Bleed	**54**	**47 (87.0)**	**5 (9.3)**	**2 (3.7)**	**1**	**8**	**3**
Gastrointestinal	34	28 (82.4)	5 (14.7)	1 (2.9)	1	6	2
Traumatic	8*	6 (75.0)	0 (0.0)	1 (12.5)	0	2	0
Genito-urinary	7	7 (100.0)	0	0	0	0	0
Mucosal bleed	2	2 (100.0)	0	0	0	0	1
Epistaxis	1	1 (100.0)	0	0	0	0	0
Hemothorax	1	1 (100.0)	0	0	0	0	0
Hemoptysis	1	1 (100.0)	0	0	0	0	0
Procedure	**27**	**26 (96.3)**	**1 (3.7)**	**0**	**0**	**3**	**2**

Transfusion, 53:1451, 2013

Message 3: Toxicity low

- Of 103 patients, 5 thrombotic events within 30 days
- All patient had other comordities

Thrombosis	Days post PCC	Dose (IU)	Pre INR	Post INR	Management/ Clinical Outcome
Deep Venous Thrombosis	4	2000IU	3.2	1.9	Bridged to warfarin
Non ST-elevation myocardial infarction	1	1500 IU	8.3	1.9	Treated conservatively. Good cardiac outcome.
Non ST-elevation myocardial infarction	1	1000 IU	4.4	3.2	Treated conservatively. Good cardiac outcome.
Bilateral Deep Venous Thrombosis	30	1000 IU	2.00	1.60	Bridged to warfarin
Non ST-elevation myocardial infarction	1	1000 IU	2.90	1.40	Treated conservatively. Good cardiac outcome.

Transfusion, 53:1451, 2013

New changes in NAC recommendations - 2011

National Advisory Committee on Blood and Blood Products | Comité consultatif national sur le sang et les produits sanguins

DOSING, ADMINISTRATION & MONITORING:
The following recommendation is based on review of literature and the desire to prevent thrombotic complications. The working group is aware that it is less than the manufacturer's recommended dose in many individuals. This is in part due to the fact the package insert recommendations will correct factor levels to normal despite the fact that normal hemostasis does not require 100% factor levels. The working group would also like to highlight that 50% of patients in the audit responded to the previously recommended standardized dose of 1000 IU (40 mL octaplex®).

For adult patients:

Dosing of prothrombin complex concentrate should be based on the INR as per the table below. If the INR is unknown and major bleeding is present, 80 mL should be administered.

	INR <3.0	INR 3.0-5.0	INR >5.0
Dose of Prothrombin Complex	**40 mL (1000 IU)**	**80 mL (2000 IU)**	**120 mL (3000 IU)**

Administration: Must be administered intravenously.
May be administered by direct IV push, syringe pump or minibag.
The manufacturer's recommended maximal rates of infusion are:

- octaplex® = 3mL/min
- Beriplex® P/N = 8 mL/min.

Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Heart Association®

Efficacy and Safety of a 4-Factor Prothrombin Complex Concentrate 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

- Randomized open label- 4 Factor PCC vs FFP
- 200 patients, ~100 per arm
- Non-surgical

Table 2. Dose of Study Treatment per Baseline INR

Baseline INR	4F-PCC Dose, IU of Factor IX per kg Body Weight*	Plasma Dose, mL per kg Body Weight*
2 to <4	25	10
4–6	35	12
>6	50	15

4F-PCC indicates 4-factor prothrombin complex concentrate; and INR, international normalized ratio.

*Dose calculation based on 100 kg body weight for patients weighing >100 kg. Maximum dose ≤5000 IU of factor IX (4F-PCC) or ≤1500 mL (plasma).

Primary endpoint analysis

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)

4F-PCC indicates 4-factor prothrombin complex concentrate; CI, confidence interval; and INR, international normalized ratio.

*INR ≤1.3 at 0.5 h after end of infusion.

†4F-PCC noninferior to plasma: lower limit of 95% CI more than –10% Farrington–Manning *P* value for noninferiority $P<0.0001$ rejecting null hypothesis of inferiority of 4F-PCC; 4F-PCC superior to plasma: lower limit of 95% CI >0.

Table 5. Hemostatic Efficacy (Intention-to-Treat Efficacy Population)

Primary Rating	No. (%) of Patients [95% CI] 4F-PCC (n=98)	Plasma (n=104)	Difference 4F-PCC Minus Plasma, % (95% CI)
Hemostatic efficacy rating by category*			
Excellent	44† (44.9)	45† (43.3)	
Good	27 (27.6)	23 (22.1)	
Poor/none	27 (27.6)	36 (34.6)	
Noneffective	25 (25.5)	33 (31.7)	
Missing primary rating	2 (2.0)	3 (2.9)	
Effective hemostasis	71 (72.4) [to 81.2]	68 (65.4) [56.2 to 74]	7.1‡ (–5.8 to 19.9)

Effective hemostasis indicates hemostatic efficacy rated as excellent or good. 4F-PCC indicates 4-factor prothrombin complex concentrate; and CI, confidence interval.

*Hemostatic efficacy assessed by a blinded independent board.

†*P*=0.50 by Cochran–Mantel–Haenszel test.

‡4F-PCC noninferior to plasma: lower limit of 95% CI more than –10% Farrington–Manning *P* value for noninferiority *P*=0.0045 rejecting null hypothesis of inferiority of 4F-PCC.

- **Toxicity**

Table 8. Summary of AEs (Intention-to-Treat Safety Population)

AE	No. (%) of Patients	
	4F-PCC (n=103)	Plasma (n=109)
Any nonserious AE*	66 (64.1)	71 (65.1)
Related AE†	10 (9.7)	23 (21.1)
AE leading to treatment discontinuation	0	3 (2.8)
Serious AE*	32 (31.1)	26 (23.9)
Related serious AE†	2 (1.9)	4 (3.7)
AEs of interest		
Deaths to day 30	6 (5.8)	5 (4.6)
Deaths to day 45	10 (9.7)	5 (4.6)
Related deaths (to day 45)‡	1 (1.0)	0
Thromboembolic AE	8 (7.8)	7 (6.4)
Related thromboembolic AE†	4 (3.9)	3 (2.8)
Fluid overload or similar cardiac event	5 (4.9)	14 (12.8)
Related fluid overload or similar cardiac event†	0	7 (6.4)

4F-PCC indicates 4-factor prothrombin complex concentrate; and AE, adverse event.

*Defined in Table XIV in the online-only Data Supplement.

†Defined as events for which there was a relationship to study treatment in the opinion of the investigator. AEs with missing relationship were considered treatment related.

‡As assessed by the Safety Adjudication Board; no deaths in either group were classified as related by an investigator.

Vaccines, Blood & Biologics

Blood & Blood Products
- Approved Products
- Licensed Products (BLAs)
- Fractionated Plasma Products

Resources for You
- Fractionated Plasma Products

Kcentra (Prothrombin Complex Concentrate, Human)

STN: BL 125421/0
Proper Name: Prothrombin Complex Concentrate (Human)
Tradename: Kcentra
Indication:

- For urgent reversal of acquired coagulation factor deficiency induced by vitamin K antagonist (VKA, e.g., warfarin) therapy in adult patients with acute major bleeding.

Product Information

- Product Labeling - Prothrombin Complex Concentrate (Human) (PDF - 1.5MB)

Supporting Documents

- April 29, 2013 Approval Letter - Prothrombin Complex Concentrate (Human)
- Summary Basis for Regulatory Action - Kcentra (PDF - 634KB)
- Approval History, Letters, Review, and Related Documents - Kcentra

Related Information

- FDA approves Kcentra for the urgent reversal of anticoagulation in adults with major bleeding

Page Last Updated: 05/21/2013
Note: If you need help accessing information in different file formats, see Instructions for Downloading Viewers and Players.

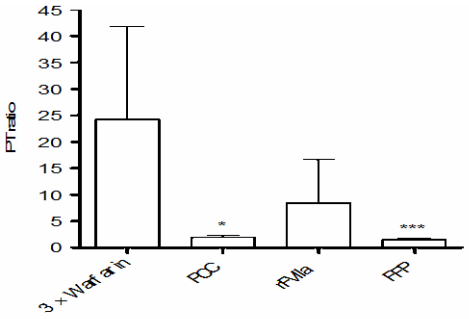
U.S. Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
Ph. 1-888-INFO-FDA (1-888-463-6332)
Email FDA

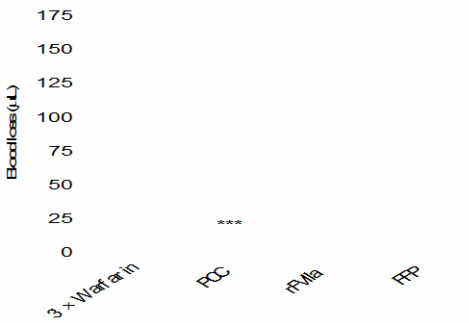
What about the New Oral Anticoagulants Dabigatran (Pradax) Rivaroxaban (Xarelto) Apixaban (Eliquis)?

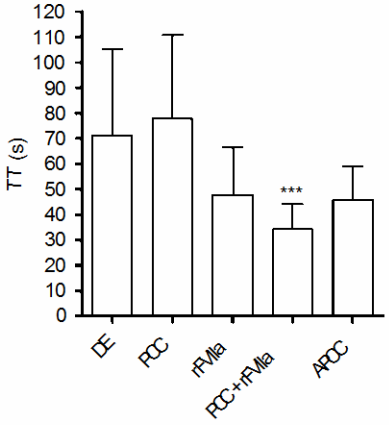
Journal of Thrombosis and Hemostasis, 10:1830, 2012

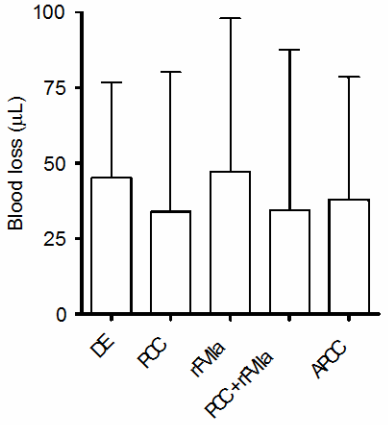
Prothrombin complex concentrates reduce blood loss in murine coagulopathy induced by warfarin, but not in that induced by dabigatran etexilate

M. D. LAMBOURNE,* L. J. ELTRINGHAM-SMITH,† S. GATAIANCE,† D. M. ARNOLD,*‡
M. A. CROWTHER‡ and W. P. SHEFFIELD*†
*Canadian Blood Services, Research and Development; †Department of Pathology and Molecular Medicine; and ‡Department of Medicine, McMaster University, Hamilton, Ontario, Canada









Warfarin x 3

Dabigatran

Journal of Thrombosis and Hemostasis, 10:1841, 2012

Reversal of dabigatran anticoagulation by prothrombin complex concentrate (Beriplex P/N) in a rabbit model

I. PRAGST,* S. H. ZEITLER,* B. DOERR,* F. J. KASPEREIT,* E. HERZOG,* G. DICKNEITE* and J. VAN RYN†
**CSL Behring GmbH, Marburg; and †Boehringer Ingelheim Pharma GmbH & Co KG, Biberach, Germany*

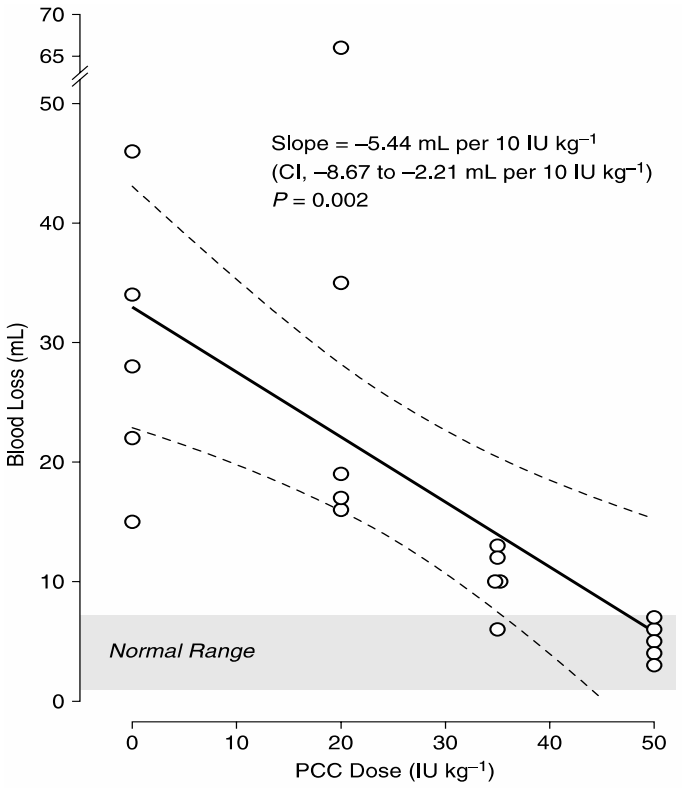


Fig. 4. Blood loss after kidney incision in dabigatran-treated rabbits receiving PCC doses in the range of 0–50 IU kg^{-1}. Graphic conventions as in Fig. 3. CI, 95% confidence interval; PCC, prothrombin complex concentrate.

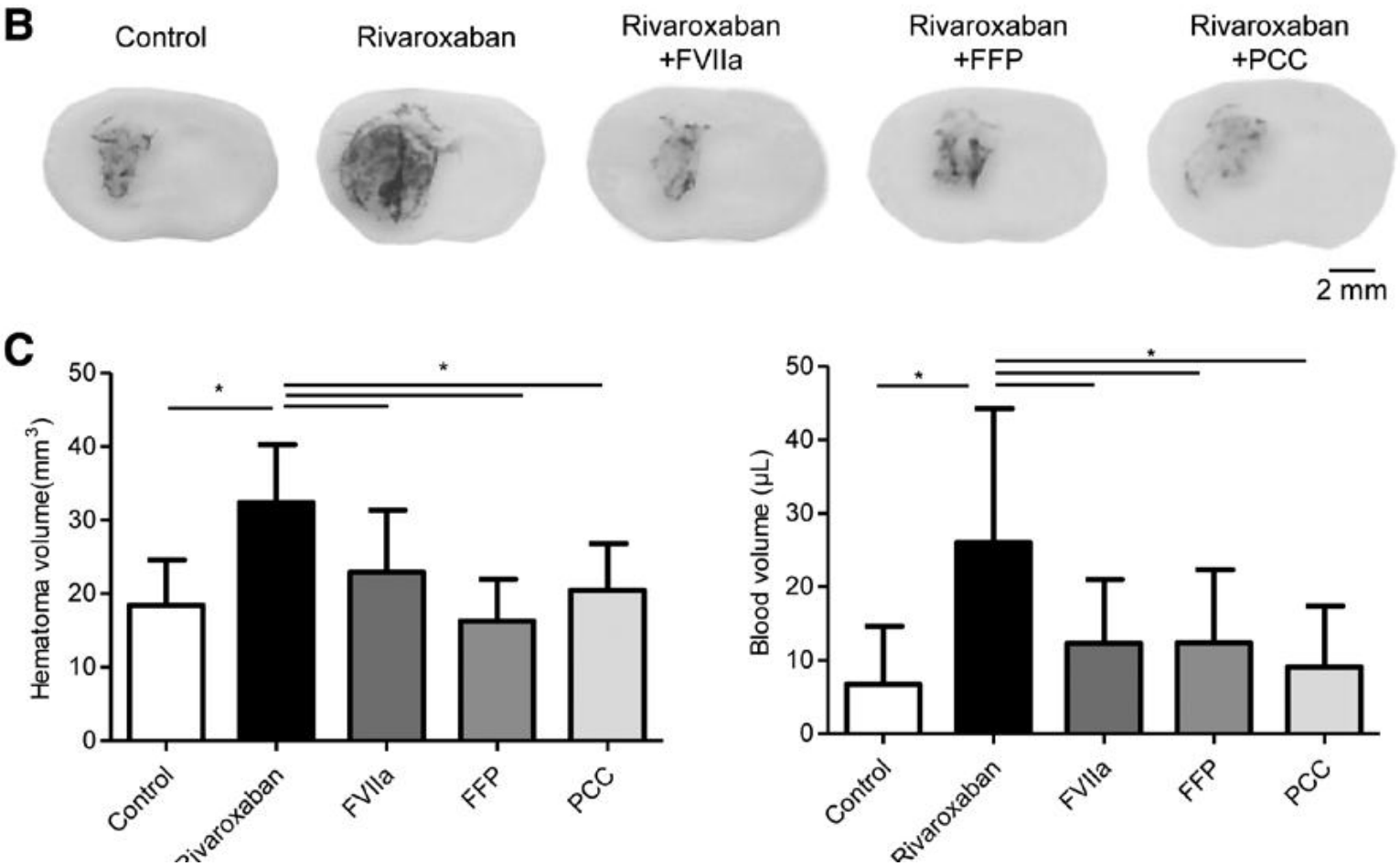
Stroke
JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Heart Association | American Stroke Association

Stroke 2013, online

Hemostatic Therapy in Experimental Intracerebral Hemorrhage Associated With Rivaroxaban

Wei Zhou, Markus Zorn, Peter Nawroth, Ulf Bütehorn, Elisabeth Perzborn, Stefan Heitmeier and Roland Veltkamp

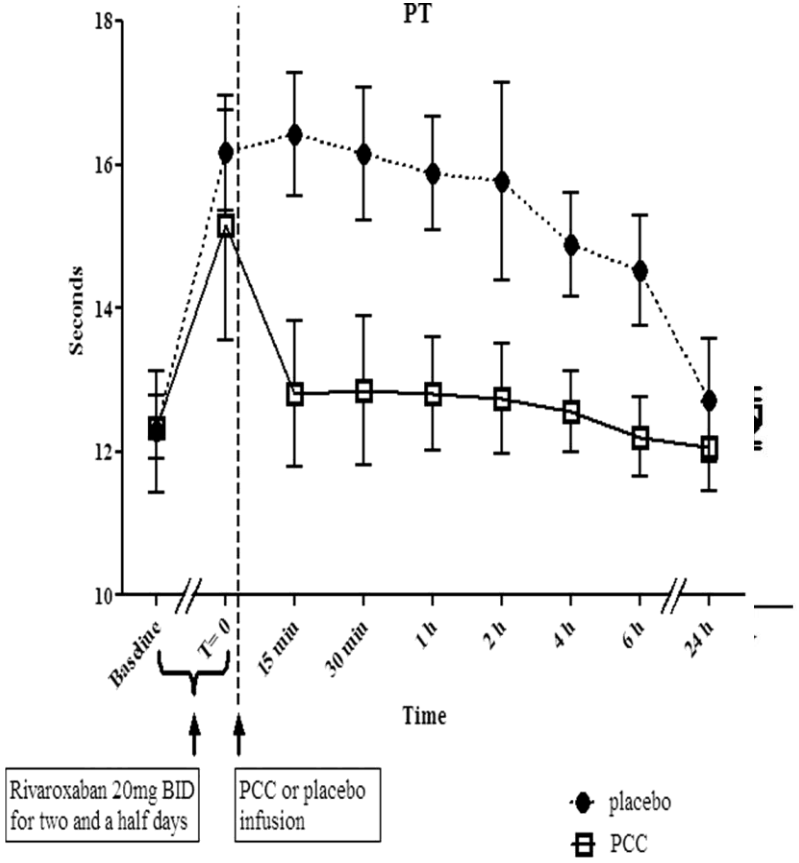


Reversal of Rivaroxaban and Dabigatran by Prothrombin Complex Concentrate : A Randomized, Placebo-Controlled, Crossover Study in Healthy Subjects

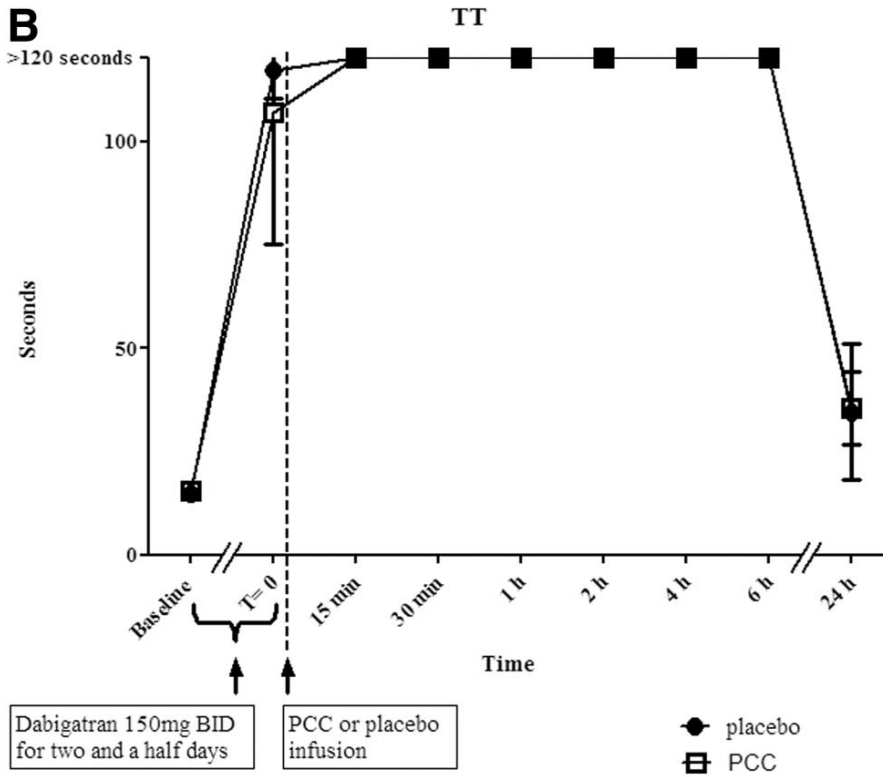
Elise S. Eerenberg, Pieter W. Kamphuisen, Meertien K. Sijpkens, Joost C. Meijers, Harry R. Buller and Marcel Levi

Circulation 124:1573, 2011

Rivaroxaban



Dabigatran



Current Protocols

***Rivaroxaban*:**

- Cohort of patients with bleeding on rivaroxaban
- Multi center registry across Canada
- Funded by Octapharma
- ***Use of Beriplex (PCC)***: 25-50 U/kg

***Dabigatran*:**

- Cohort of patients with bleeding on dabigatran
- Multi center registry across Canada
- Funded by Baxter
- ***Use of FEIBA (activated PCC)***
  - Anecdotal cases