Prothrombin Complex Concentrate- Indications and Applications

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Prothrombinex®-VF Composition

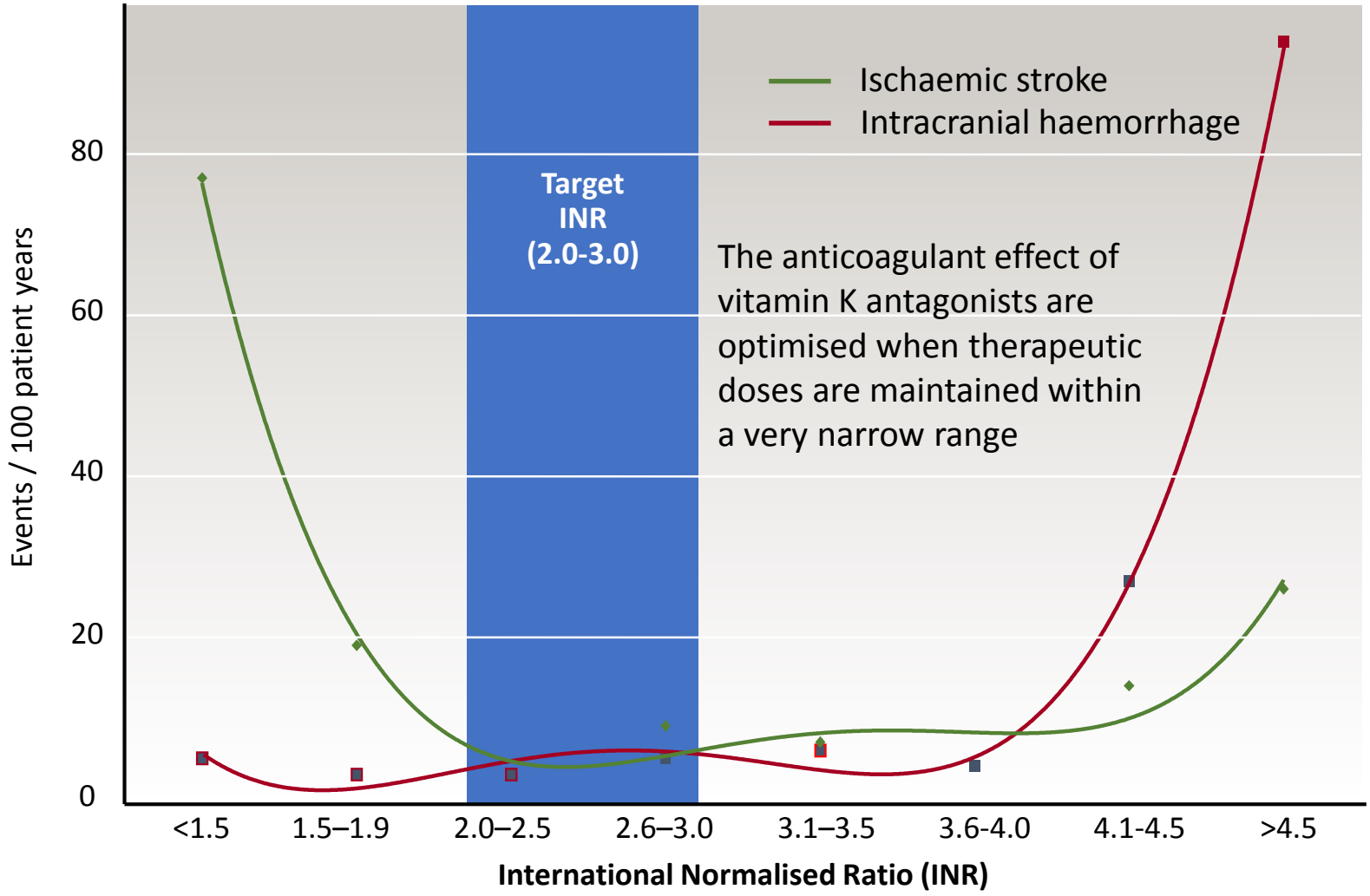
Active ingredients	**500 IU Vial**
Factor IX	500 IU
Factor II	approx. 500 IU
Factor X	approx. 500 IU
Excipients	
Human plasma proteins (including low levels of factors V and VII)	≤500 mg
Antithrombin III	25 IU
Heparin sodium	192 IU
Sodium+	112 mg
Phosphate+	65 mg
Citrate+	180 mg
Chloride+	27 mg

Coagulation Factor Elimination Half-Lives

Factor Elimination Half-Lives F	Factor II	Factor VII	Factor IX	Factor X
Elimination t1/2 (h)	60 (46–66)	4.2 (3.9–6.6)	17 (14–68)	31 (24–41)

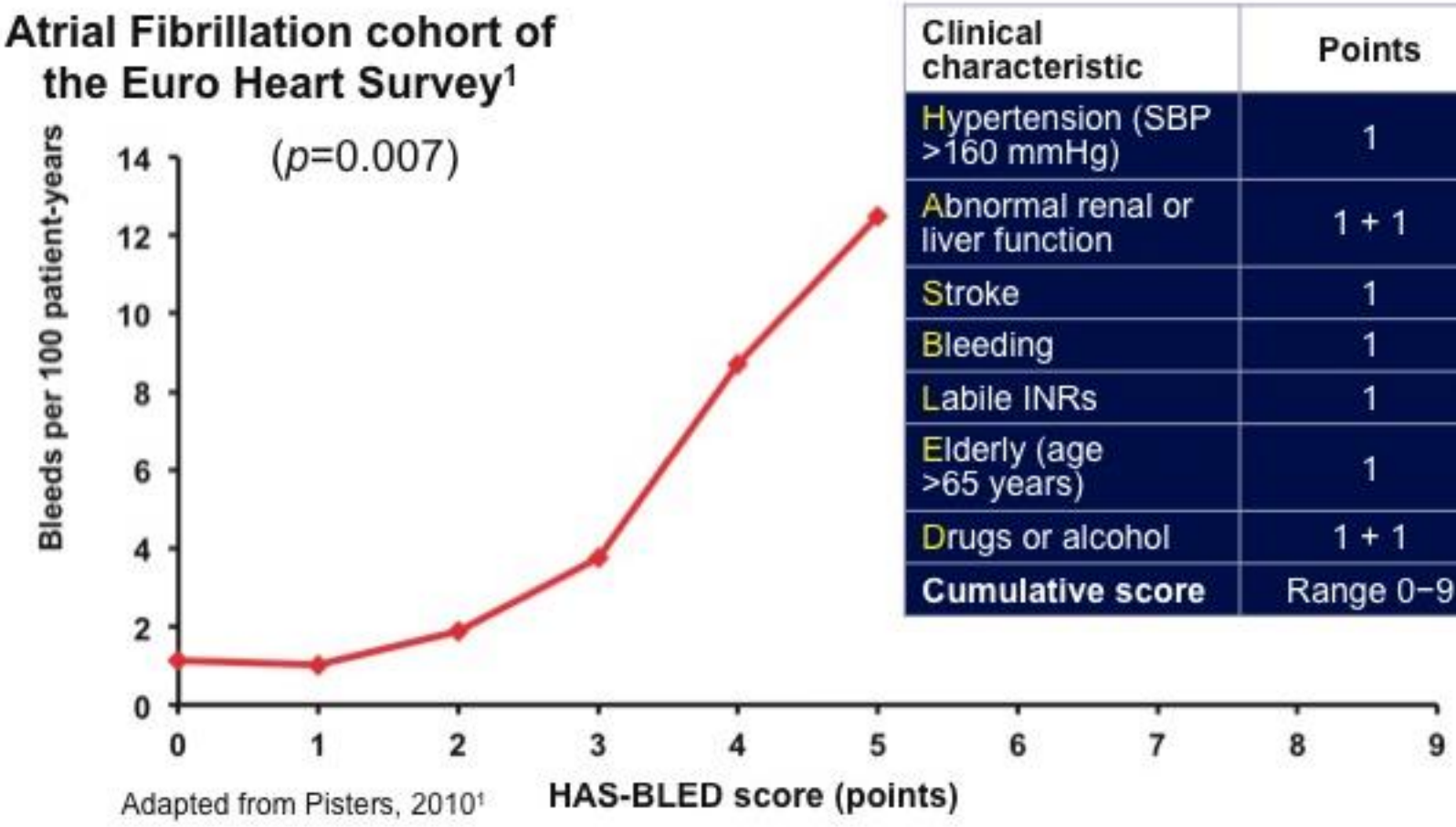
Prothrombin Complex Concentrate for Warfarin Reversal

Therapeutic Range of VKA for AF



Hylek EM, et al. *N Eng J Med.* 2003;349:1019-1026.

Risk of Major Bleeding and HAS-BLED Score



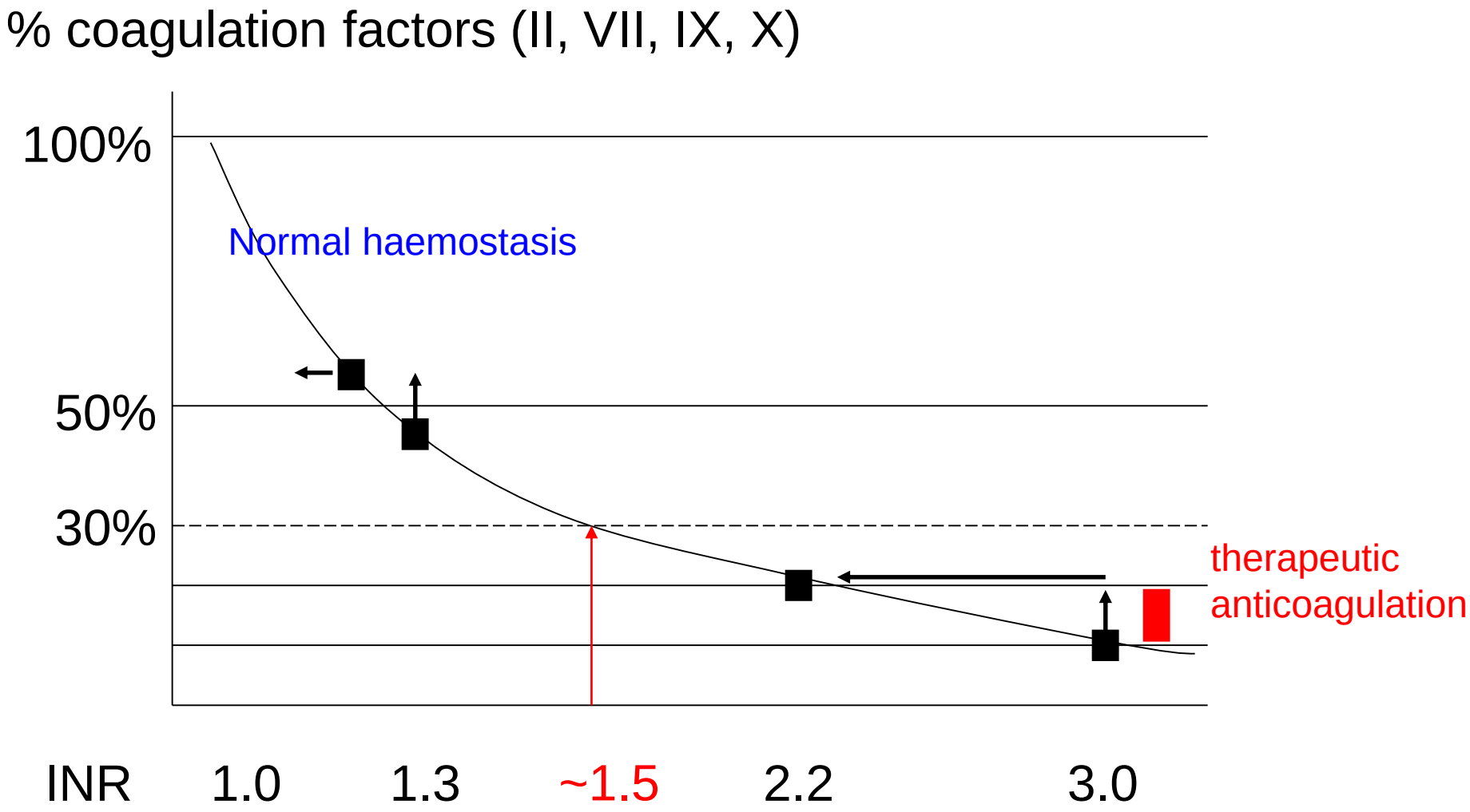
Adapted from Pisters, 2010[1]

Clinical characteristic	Points
Hypertension (SBP >160 mmHg)	1
Abnormal renal or liver function	1 + 1
Stroke	1
Bleeding	1
Labile INRs	1
Elderly (age >65 years)	1
Drugs or alcohol	1 + 1
Cumulative score	Range 0–9

Number of patients	798	1,286	744	187	46	8	2	0	0	0
Number of major bleeding events	9	13	14	7	4	1	0	0	0	0

1. Pisters R *et al. Chest* 2010;138:1093–1100.

Relationship of INR to factor level is **non-linear**



Bleeding risk on warfarin in VTE patients

	Major bleed	Intracranial haemorrhage	Case-fatality
Overall, per 100 per year	**7.22 (7.19-7.24)**	**1.15 (1.14-1.16)**	**13.4 (9.4-17.4)**
Initial 3m warfarin, Per 100 per year	2.06 (2.04-2.08)	1.48 (1.4-1.56)	9.3 (3.1-20.3)
Beyond 3m warfarin, per 100 per year	**2.74 (2.71-2.77)**	**0.65 (0.63-0.68)***	**9.1 (2.5-21.7)**

Linkins et al., Ann Intern Med 2003;139:893-900

Linkins et al., J Thromb Haemost 2010;8(10):2201-11

33 studies involving 10,757 patients with 4374 patient-years
*44% fatality (vs. 4% EC major bleeds)

Intracranial bleeding on warfarin therapy

- 877 major bleeds among 23,518 (pooled analysis of 15 studies)
- The proportion intracranial bleeds significantly higher in patients with ischemic stroke (36%; P=0.02) compared with patients with VTE (10%).
- Fatal ICH did not differ significantly according to indication (8% to 20%)
- ICH more likely to be fatal than extra cranial major bleeds
  - 44% vs. 4% overall –all indications

Linkins et al., J Thromb Haemost 2010;8(10):2201-11

When is it necessary to reverse warfarin?

- Major bleeding
- Urgent surgery
- High INR

How should we reverse warfarin?

- Vitamin K
- Prothrombin Complex Concentrate
- Fresh Frozen Plasma

Prothrombinex-VF use in warfarin reversal and other indications

- **Audit of PTX-VF use aimed to assess:**
  - The effect of lower (< 25 IU/kg) versus higher doses (25–50 IU/kg) for warfarin reversal
  - The effect when combined with FFP for warfarin reversal
- Royal Perth Hospital (855 beds) all patients prescribed PTX-VF at from 1 November 2009 to 1 May 2010
- 334 vials of PTX-VF were prescribed to 84 patients
- 69 patients had a single prescription
- 12 patients had 2 prescriptions
- 3 patients had three, four seven prescriptions respectively,
- Totalling 107 prescriptions.

Kruger et al, MJA 2012; 196: 462–465

3 Prescriptions of PTX-VF, with and without fresh frozen plasma, for warfarin reversal

	PTX-VF with FFP (*n* = 36)	PTX-VF alone (*n* = 30)	*P*
Mean PTX-VF dose, IU/kg* (95% CI)	20.4 (18.3–22.9)	15.7 (13.2–18.7)	0.007
Mean INR before treatment† (95% CI)	2.7 (2.4–3.2)	2.5 (2.2–2.9)	—
Mean INR after treatment† (95% CI)	1.4 (1.3–1.5)	1.6 (1.5–1.8)	—
Median number of fresh frozen plasma units	2	—	—
Number of prescriptions given with vitamin K	22	13	0.15
Median vitamin K dose, mg (intravenous)	10	5	—

PTX-VF = Prothrombinex-VF. INR = international normalised ratio. * Geometric mean. † Back-transformed mean. ◆

PTX-VF was prescribed 66 times for warfarin reversal:
Imminent surgery (33 prescriptions)
Clinically significant bleeding (33 prescriptions)
The INR decreased to 1.5 or less in 40 of 66 prescriptions

In 16 of 33 bleeding patients, haemostasis was achieved with PTX-VF and other blood products

Patients prescribed vitamin K was not significantly different between groups
Significant difference in the rate of change in INR between groups (P =0.008), with the PTX-VF alone group decreasing by a smaller amount, although this group also had a smaller mean dose of PTX-VF (P= 0.007).

4 Lower-dose versus higher-dose PTX-VF prescriptions for warfarin reversal

	Lower dose (< 25 IU/kg) (*n* = 52)	Higher dose (25–50 IU/kg) (*n* = 14)	*P*
Mean PTX-VF dose, IU/kg* (95% CI)	16.1 (14.4–17.7)	29.1 (26.1–32.5)	< 0.001
Mean INR before treatment† (95% CI)	2.5 (2.3–2.9)	2.9 (2.3–3.8)	—
Mean INR after treatment† (95% CI)	1.5 (1.4–1.6)	1.5 (1.3–1.8)	—
Median number of fresh frozen plasma units	2	2	0.80
Number of prescriptions given with vitamin K	26	9	0.31
Median vitamin K dose, mg (intravenous)	10	10	—

PTX-VF = Prothrombinex-VF. INR = international normalised ratio. * Geometric mean. † Back-transformed mean. ◆

No significant difference was found between groups for the number of FFP units or the number of vitamin K prescriptions
No difference in the rate of change in INR between groups (P = 0.56)

Twenty-one prescriptions of PTX-VF for coagulopathy primarily due liver synthetic dysfunction, shock or multiorgan failure
13 prescriptions for active bleeding; 8 for impending procedures

The mean INR decreased from 2.2 to 1.7
Haemostasis was achieved with haemostatic agents in 9 of the 13 patients with active bleeding; the others required surgical intervention.

Prothrombinex use for the reversal of warfarin: is fresh frozen plasma needed?

- 105 patients who had received warfarin were reviewed (Royal Perth & Charles Gairdner Hosp)
- 74 patients administered PTX without FFP
- 31 patients administered PTX and FFP
- PTX was administered for bleeding in 51 patients:

Crawford et al, Med J Aust 2006; 184 (7): 365-366.

Prothrombinex use for the reversal of warfarin: is fresh frozen plasma needed?

- 71% receiving PTX and 67.7% PTX + FFP were given Vit K
- PTX Doses:
  - PTX alone group (913 IU or 13.1 IU/kg)
  - PTX + FFP (742 IU or 12.3 IU/kg)
- 7 of 89 patients (7.9%) received the ASTH 2004 Guideline recommended PTX dose
- The remaining patients received < 25 IU/kg
- All patients with bleeding achieved haemostasis after PTX
- Achievement of haemostasis did not require normalisation of INR
- No correlation with FFP and low dose PTX worked!

Outcomes of warfarin reversal with FFP *versus* 4F-PCC in ED

- Octaplex – 4f-PCC: 1500 IU for ICH and 1000 IU for other major bleeds ***vs*** FFP
- Retrospective before and after introduction of PCC in Canada
- 4F-PCC fewer adverse events compared with FFP
  - No VTE/ATE
  - (more CHF with FFP)
  - Faster reversal
  - Less RBC transfusion

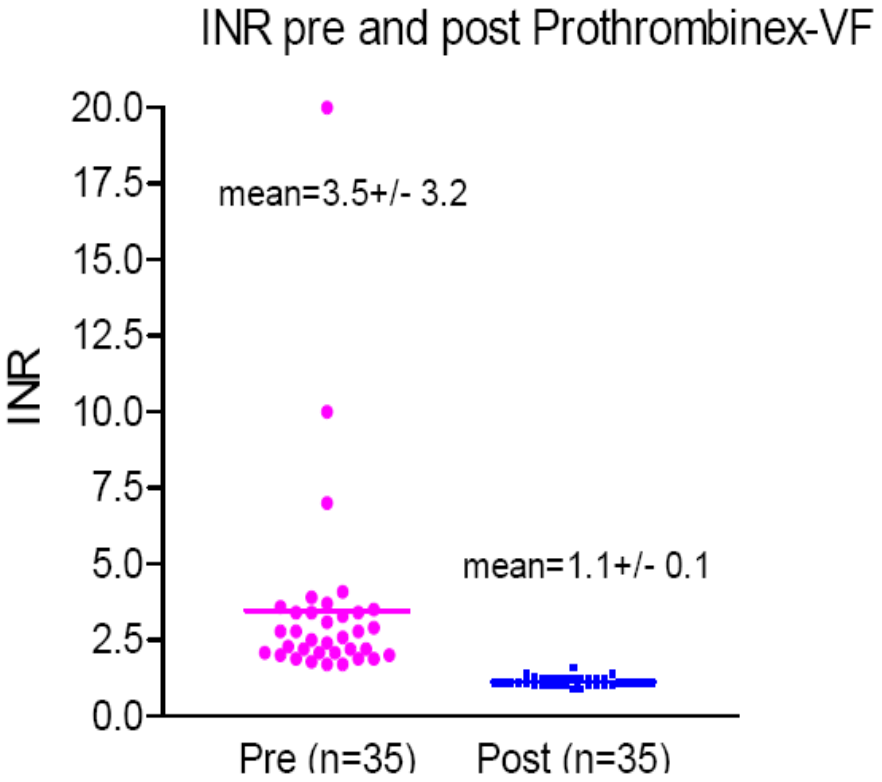
Hickey Circulation. 2013;128:360-364

Efficacy of Prothrombinex-VF and complete reversal

Indications for warfarin
- AF
- MVR
- VTE

Reason for Complete Reversal (urgent)
- Serious active bleeding
- Surgery/procedure, low risk thrombosis
- High risk of bleeding

91% achieves the target INR



Tran et al., Intern Med J. 2011 41(4):337-343

*Mean Prothrombinex-VF dose 34.7 IU/kg (25-50 IU/kg)
No Vitamin K or FFP

Poor outcome despite INR reversal with Prothrombin Complex Concentrate

Intracranial haemorrhage type	No.	In-hospital mortality
Intraparenchymal	71	30 (42.3%)
Subdural	61	21 (34.4%)
Epidural	1	0
Subarachnoid	8	1 (12.5%)

Median presentation to PCC treatment time	**213 minutes**
Median dose PCC	1000 units
% INR < 1.5 at 1 hr	72%

Dowlatshahi et al Stroke. 2012;43:1812-1817

Regular Article

Thromb Res. 2012;129(2):146-151

Thromboembolic safety and efficacy of prothrombin complex concentrates in the emergency reversal of warfarin coagulopathy

Ammar Majeed [a,b,*], Anna Eelde [a], Anna Ågren [a], Sam Schulman [a,c,1], Margareta Holmström [a,1]

During 2002 to 2010 **prospectively included 160 patients treated with PCC** for emergency reversal of warfarin either for bleeding or because of the need of emergency surgery

The median INR before and after treatment with PCC was 3.5 and 1.4
The mean dose of PCC was 1800 IU.
In addition to PCC, 74% of the patients received vitamin K and 34% received plasma
The clinical efficacy was good in 146 (91%), moderate in 6 (4%), poor in 4 (2.5%) and non-evaluable in 4 patients.
4 patients with **"poor"** efficacy had VKA-associated ICH as indication for reversal with PCC
Four of the 6 patients with moderate effect had also ICH

A possible relationship to PCC was considered if objectively verified thromboembolism occurred within 7 days of PCC administration
Six patients (3.8%) developed thromboembolic events (3 strokes, 1 myocardial infarction, 1 deep vein thrombosis, 1 splenic infarction)

ASTH Guidelines

POSITION STATEMENT

MJA 2004; 181: 492–497

Warfarin reversal: consensus guidelines, on behalf of the Australasian Society of Thrombosis and Haemostasis

Ross I Baker, Paul B Coughlin, Alex S Gallus, Paul L Harper, Hatem H Salem and Erica M Wood; the Warfarin Reversal Consensus Group

Clinical focus

MJA 198 (4) · 4 March 2013

Guidelines

An update of consensus guidelines for warfarin reversal

Dose of Prothrombinex-VF to reverse the anticoagulant effect of warfarin according to initial and target INR

		Initial INR			
		1.5-2.5	**2.6-3.5**	**3.6-10.0**	**>10.0**
Target INR	**0.9-1.3**	30 IU/kg	35 IU/kg	50 IU/kg	50 IU/kg
	1.4-2.0	15 IU/kg	25 IU/kg	30 IU/kg	40 IU/kg

Tran et al., Intern Med J. 2011 41(4):337-343

Management of warfarin therapy with bleeding§

Clinical Situation	Recommendation
INR ≥1.5 with life-threatening* (critical organ) bleeding	Cease warfarin therapy and administer • Vitamin K_1 5.0-10.0 mg intravenously (2C), • ***and*** Prothrombinex-VF **50.0** IU/kg intravenously (GPP) • ***and*** Fresh Frozen Plasma 150-300mL (GPP). If Prothrombinex-VF is unavailable, administer FFP 15mL/kg
INR ≥2.0 with clinically significant bleeding (not life-threatening)	Cease warfarin therapy and administer • Vitamin K_1 5.0-10.0 mg intravenously (2C) • ***And*** Prothrombinex-VF **35.0-50.0** IU/kg intravenously (GPP) If Prothrombinex-VF is unavailable, administer fresh frozen plasma 15mL/kg (ASTH, 2004 - PCC-HT (25–50 IU/kg) AND FFP (150–300mL)
Any INR with minor bleeding	Omit warfarin, repeat INR the following day and adjust warfarin dose to maintain INR the target therapeutic range (2C) If bleeding risk is high # or INR >4.5 consider vitamin K1, 1.0–2.0mg orally or 0.5–1.0mg intravenously (GPP)

#Recent major bleeding <4wk, major surgery <2 wk, platelet count <50x10/9/L, known liver disease, concurrent antiplatelet therapy

Tran MJA 2013;198(4):1-7

Management of patients on warfarin with high INR without bleeding

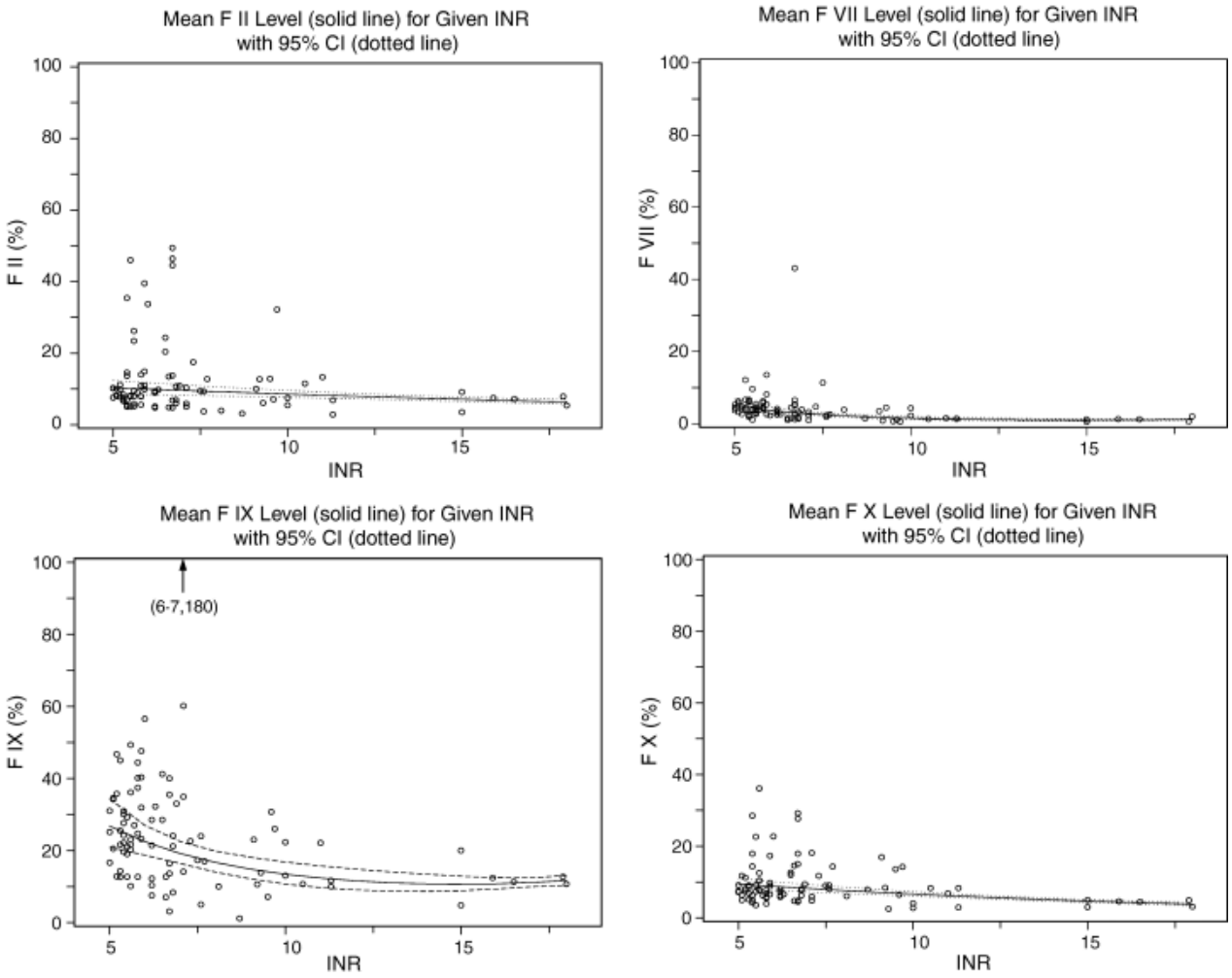
Clinical Setting	Action
INR higher than the therapeutic range but < 4.5 and absent bleeding	• Lower or omit the next dose of warfarin. Resume therapy at a lower warfarin dose when the INR approaches therapeutic range. • If the INR is only minimally above therapeutic range (up to 10%), dose reduction is generally not necessary (2C)
INR 4.5–10.0 and absent bleeding	• Cease warfarin therapy; consider reasons for elevated INR and patient-specific factors. Vitamin K1 is usually unnecessary (2C) • BUT If bleeding risk is high#: consider vitamin K1 1.0–2.0mg orally or 0.5–1.0mg IV **(GPP)** • measure INR within 24 h & resume warfarin at a reduced dose once INR approaches therapeutic range
INR > 10.0 and absent bleeding	• Cease warfarin therapy, administer 3.0–5.0 mg vitamin K1 orally or intravenously **(2C)*** • If bleeding risk is high#, consider prothrombinex –VF, 15-30 IU/kg • Measure INR in 12-24hours. Close monitoring over the following week **(GPP)**. Resume warfarin therapy at a reduced dose once INR approaches therapeutic range #Recent major bleeding <4wk, major surgery <2 wk, platelet count <50x10/9/L, known liver disease, concurrent antiplatelet therapy

Tran MJA 2013;198(4):1-7

*extrapolated from oral Vitamin K1 in absence of iv data

Poor correlation of supratherapeutic INR and vitamin K-dependent procoagulant factor levels during warfarin therapy

the vitamin K-dependent coagulation factor levels decreased minimally from an INR of 5·0 to >15·0.
There is also increased individual variation in the observed factor levels when INR >5·0.



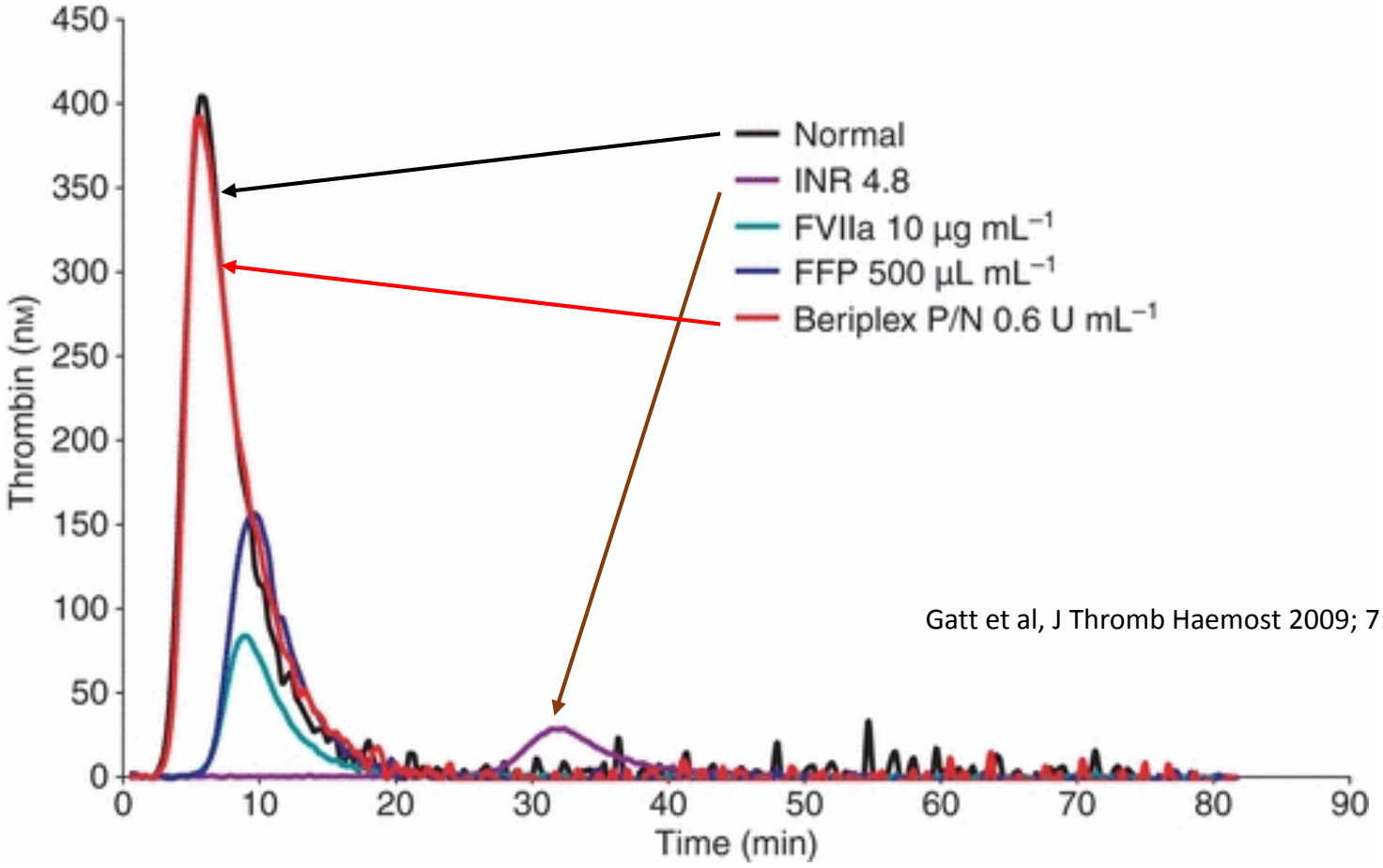
Sarode et al, Br J Haematol 2006; 132: 604-607

PCC and effect on thrombin generation (TG)

- Studied the effects of FFP, rFVIIa and Beriplex P/N on the INR and TG, using the calibrated automated thrombography assay in *ex vivo* warfarinized plasma
- Beriplex P/N was the only agent that completely normalized TG and the INR
- Endogenous thrombin potential (ETP) and the peak thrombin showed a significant negative correlation with all INRs
- The ETP and velocity of TG reached a plateau at an INR of ~ 4.0.

Gatt et al, J Thromb Haemost 2009; 7: 1123-1127.

Optimizing warfarin reversal – an *ex vivo* study



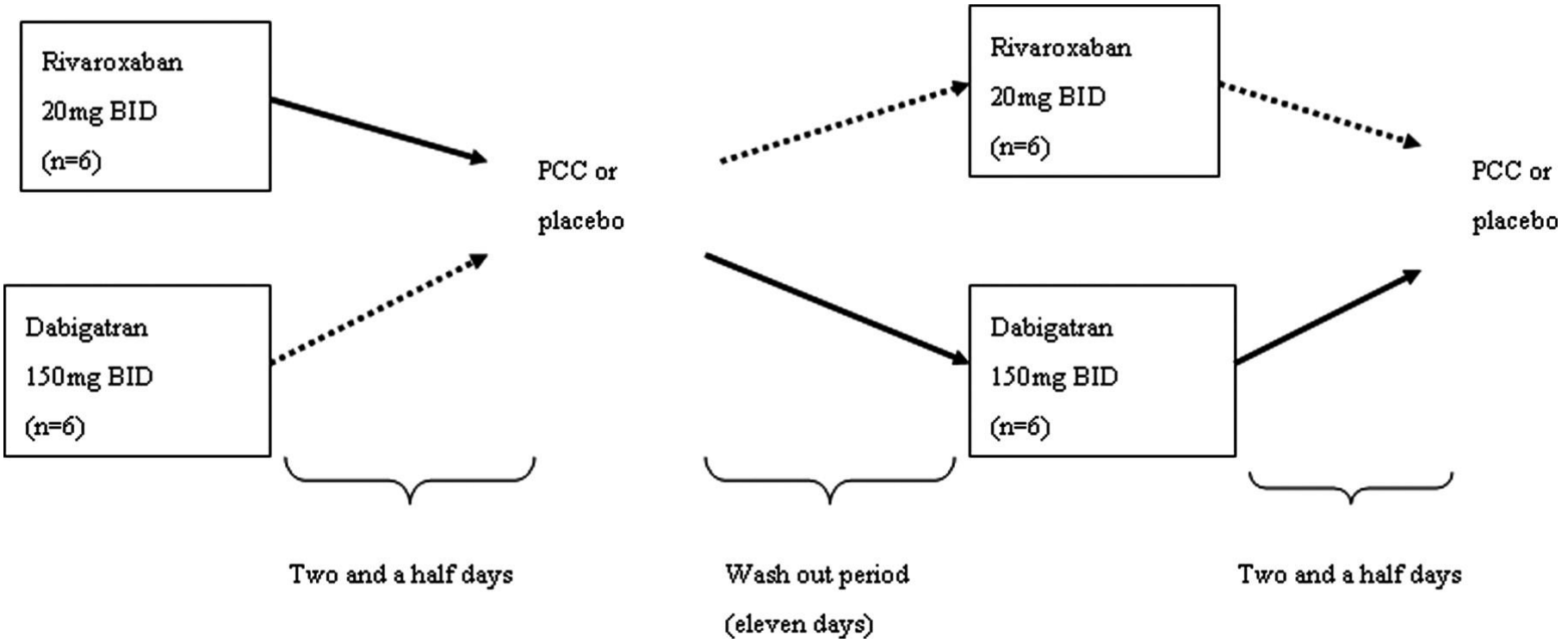
Gatt et al, J Thromb Haemost 2009; 7: 1123-1127.

Reversibility profiles obtained using different agents to reverse an INR of 4.8

This shows that Beriplex P/N can completely normalize the thrombogram, whereas other agents have only a partial effect

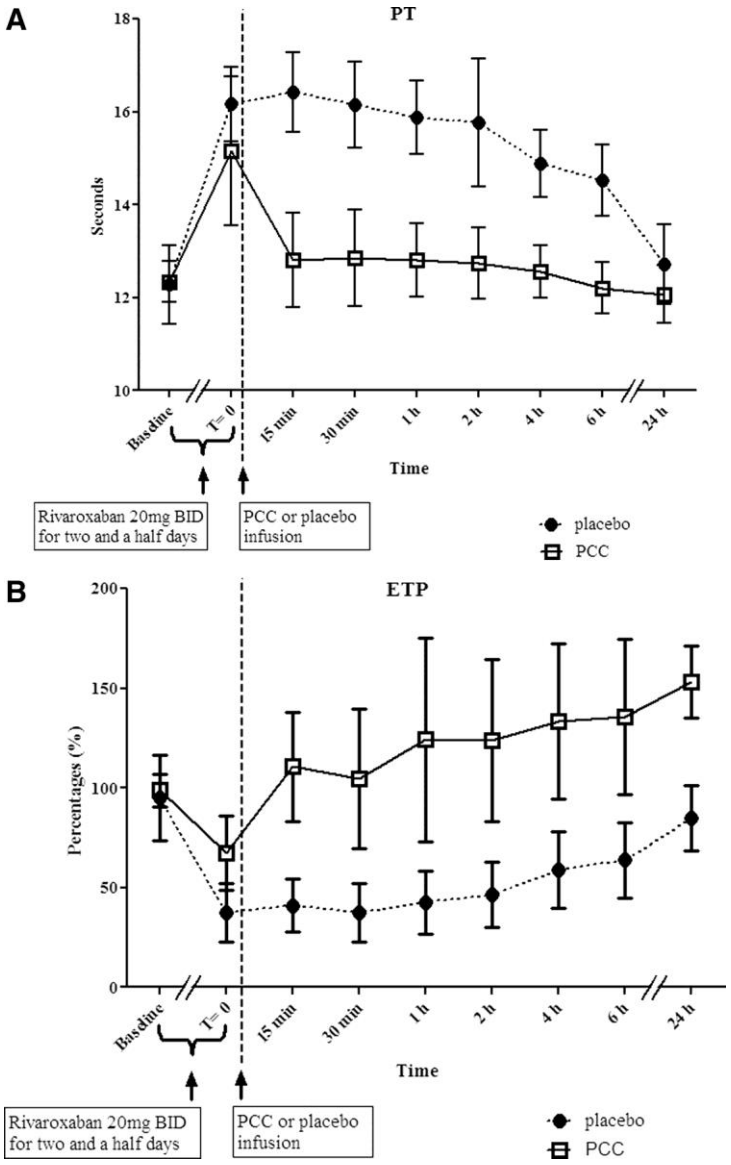
Prothrombin Complex Concentrate for DOAC Reversal

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



Elise S. Eerenberg et al. Circulation. 2011;124:1573-1579

Effect of rivaroxaban followed by PCC or placebo on coagulation tests



PT

Placebo

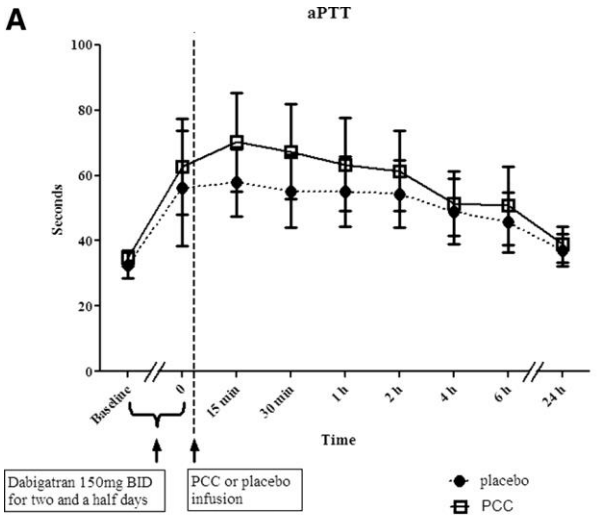
PCC

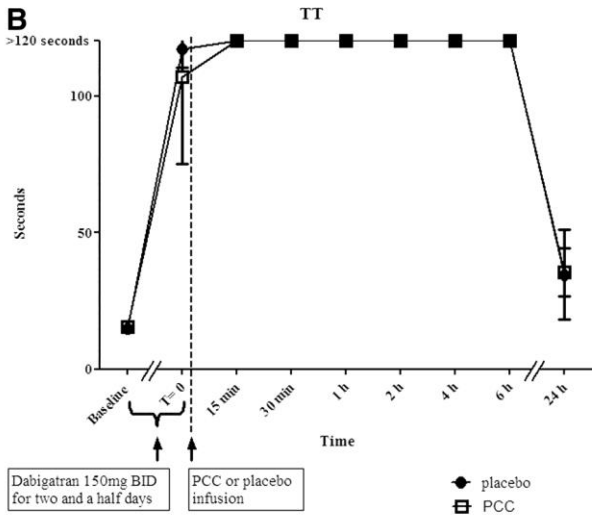
ETP

Elise S. Eerenberg et al. Circulation. 2011;124:1573-1579

Effect of dabigatran followed by PCC or placebo on coagulation tests

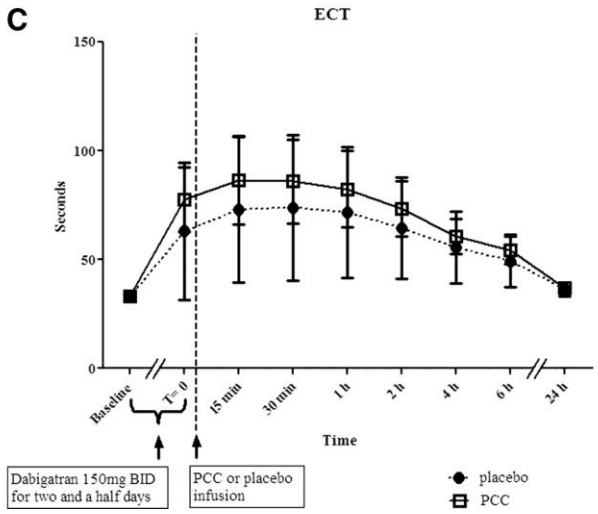
aPTT





TT

ECT

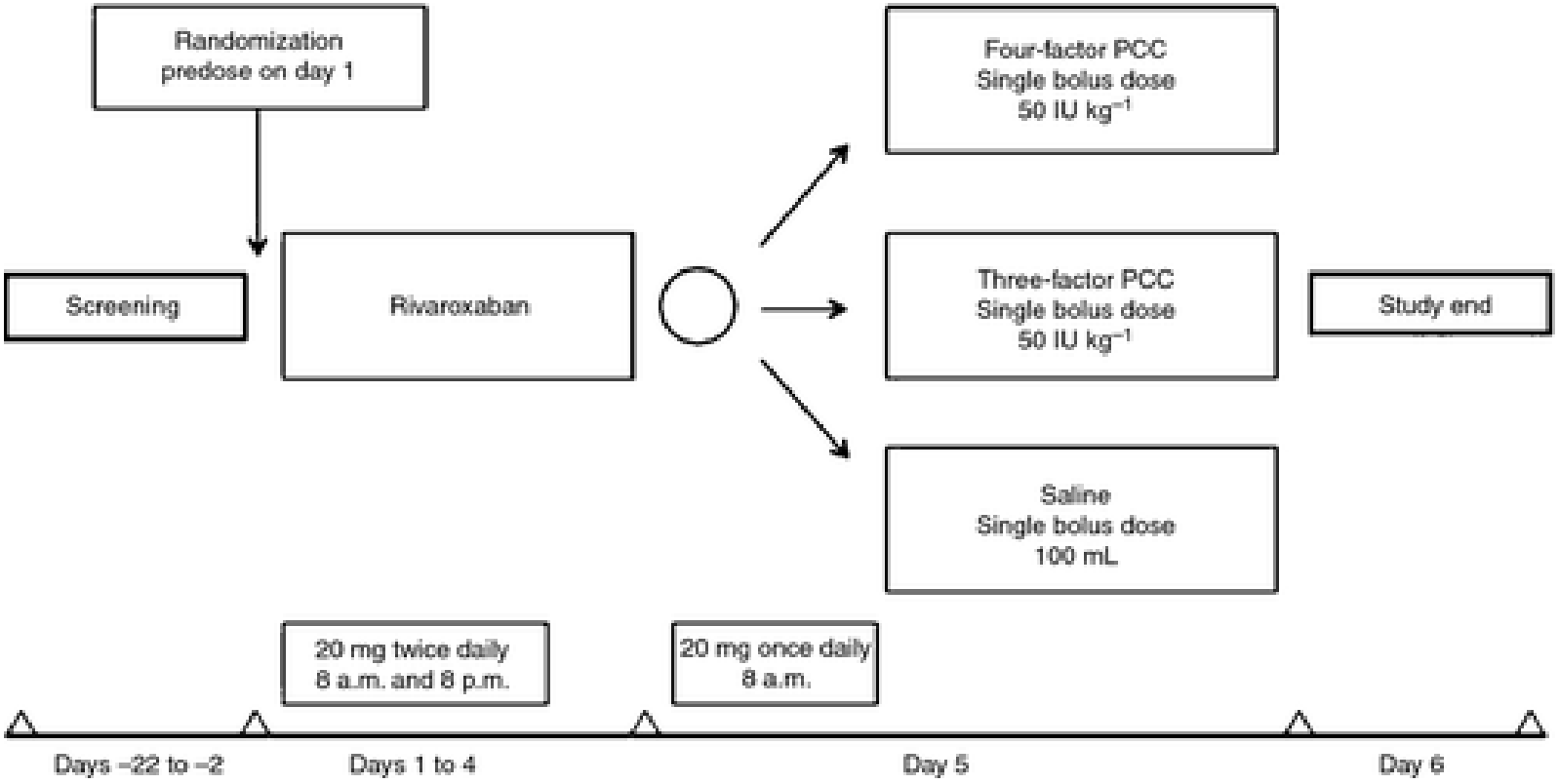


Placebo

PCC

Elise S. Eerenberg et al. Circulation. 2011;124:1573-1579

Comparison of three-factor and four-factor PCC regarding reversal of the anticoagulant effects of rivaroxaban in healthy volunteers (M. LEVI et al JTH 2014)



J Thromb Haemost 2014; 12: 1428–36

Table 1 Contents of the prothrombin complex concentrates

	Beriplex	Profilnine
Factor II	270 IU	288 IU
Factor VII	150 IU	Not detected
Factor X	340 IU	166 IU
Protein S	210 IU	Not detected
Protein C	270 IU	Not detected

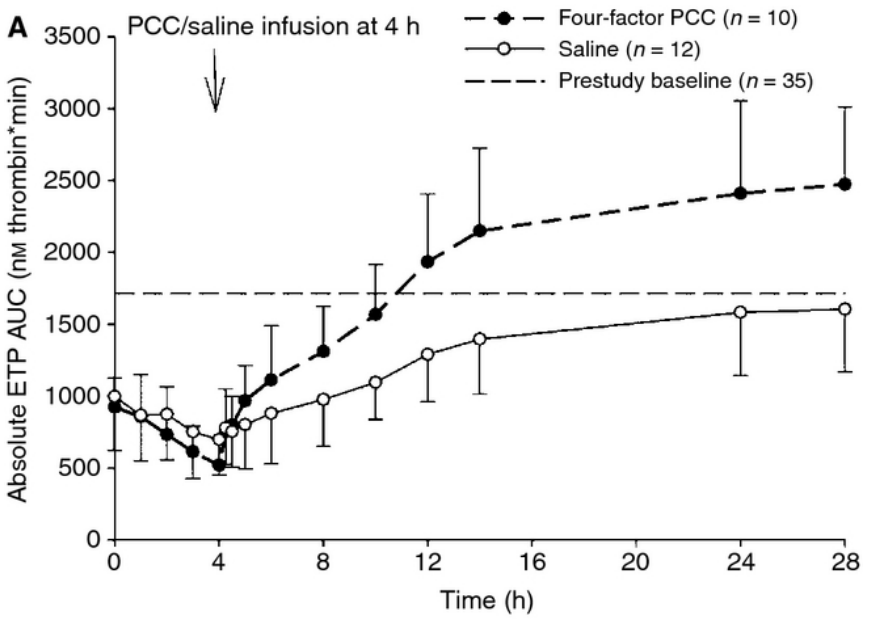
Concentration of coagulation factors in the two prothrombin complex concentrates per 250 IU of FIX according to the certificate of analysis of both products.

J Thromb Haemost 2014; 12: 1428–36

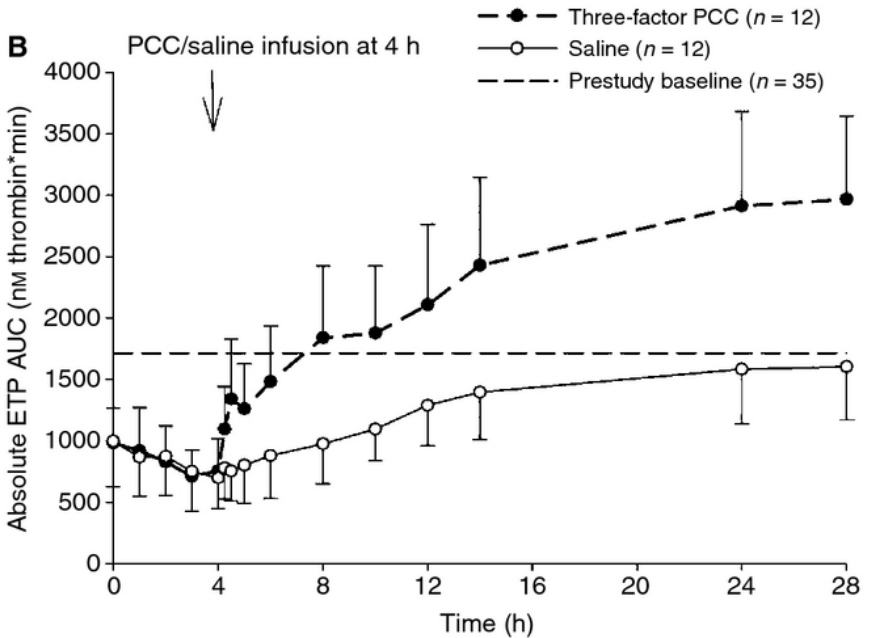
Effects of Beriplex P/N and Profilnine SD on **endogenous thrombin potential (ETP)**

three-factor PCC produced a faster reversal of ETP than that observed with four-factor PCC.

J Thromb Haemost 2014; 12: 1428–36



4F

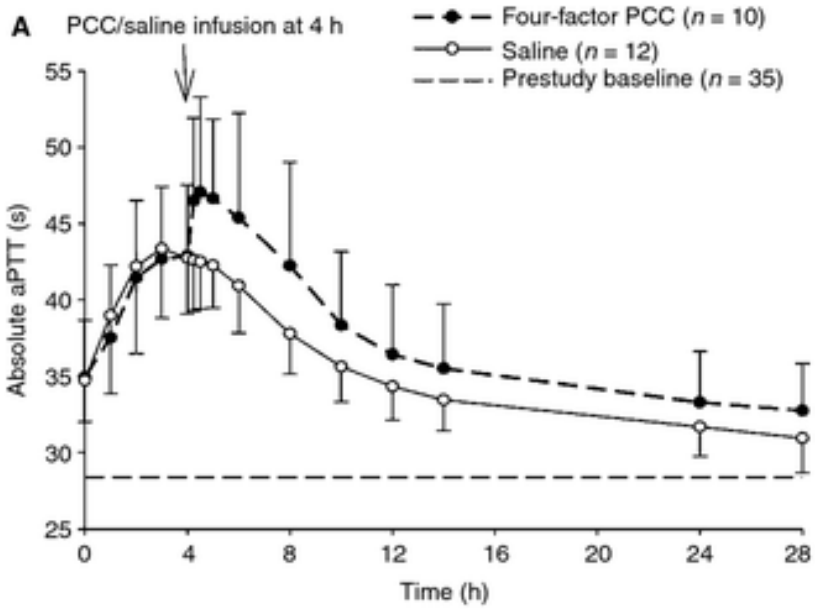


3F

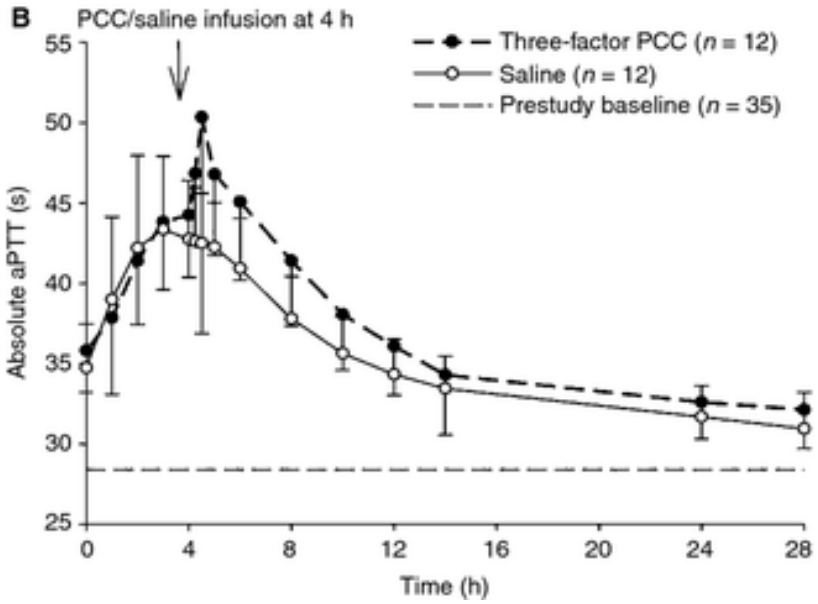
Effects of Beriplex P/N and Profilnine SD **on APTT**: Initial prolongation--?trace heparin effect

Also NO change in lag time and Xa by Beriplex P/N and Profilnine SD

No thromboembolism by Beriplex P/N and Profilnine SD



4F



3F

J Thromb Haemost 2014; 12: 1428–36

CLINICAL TRIALS AND OBSERVATIONS

Management of rivaroxaban- or apixaban-associated major bleeding with prothrombin complex concentrates: a cohort study

Ammar Majeed,[1-4] Anna Ågren,[1,3] Margareta Holmström,[1,3] Maria Bruzelius,[1,3] Roza Chaireti,[3,5,6] Jacob Odeberg,[1,3,7] Eva-Lotta Hempel,[1,3] Maria Magnusson,[6,8,9] Tony Frisk,[10] and Sam Schulman[11,12]

Blood. 2017;130(15):1706-1712

Prospective multicentre study
Conducted in Sweden January 2014 and October 2016

Apixaban (n=39); Rivaroxaban (n=45)

The Question

- Is 4-factor PCC effective in the management of major bleeding on rivaroxaban or apixaban?
- What PCC dose to use?

Unactivated **P**rothrombin complex concentrates for the **R**eversal of **A**nti-factor **TE**n inhibitors (**UPRATE**)

4-factor PCC given as a fixed dose of 1500-2000

Slide courtesy Ammar Majeed

Study population

Inclusion criteria

- Adult patients
- On rivaroxaban or apixaban
  - last dose taken within 24 hours
- Active Major bleeding according to ISTH definition
  - Bleeding in critical organ
  - Fall Hb >20g/L OR transfusion of ≥ 2 units RBC
  - Fatal bleeding
- Supportive therapy failed / inappropriate

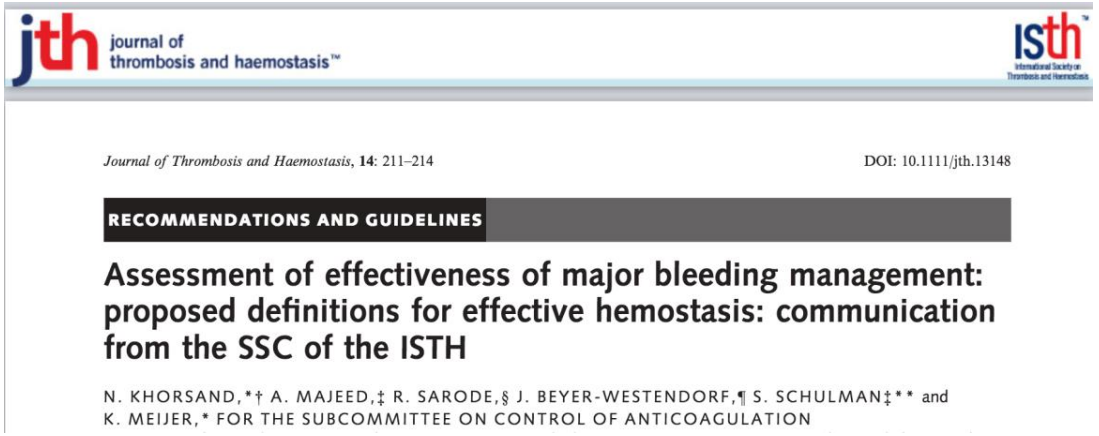
The treatment (intervention)

- 4-Factor PCC
  - 2000 IU for body weight > 65kg
  - 1500 IU for body weight less than 65kg
  - PCC dose may be repeated if inadequate effect of first dose
    - max total dose 50 IU/kg
  - Emphasise on short door to needle time

Primary Outcome

- Assessment of PCC effectiveness in bleeding management
  - Combination of clinical, radiological and laboratory findings

ISTH criteria



jth journal of thrombosis and haemostasis™

ISTH International Society on Thrombosis and Haemostasis

Journal of Thrombosis and Haemostasis, **14**: 211–214 DOI: 10.1111/jth.13148

RECOMMENDATIONS AND GUIDELINES

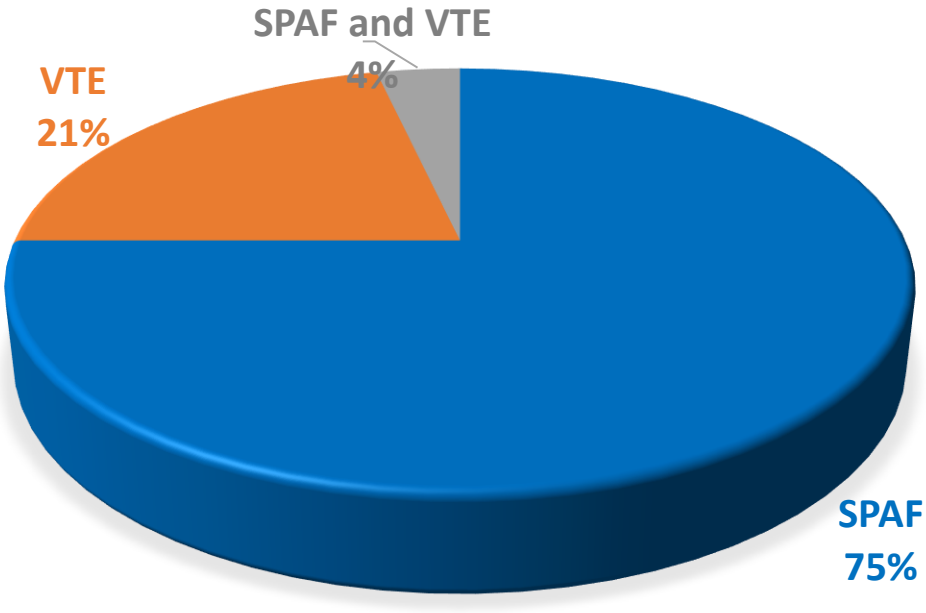
Assessment of effectiveness of major bleeding management: proposed definitions for effective hemostasis: communication from the SSC of the ISTH

N. KHORSAND,*† A. MAJEED,‡ R. SARODE,§ J. BEYER-WESTENDORF,¶ S. SCHULMAN‡** and K. MEIJER,* FOR THE SUBCOMMITTEE ON CONTROL OF ANTICOAGULATION

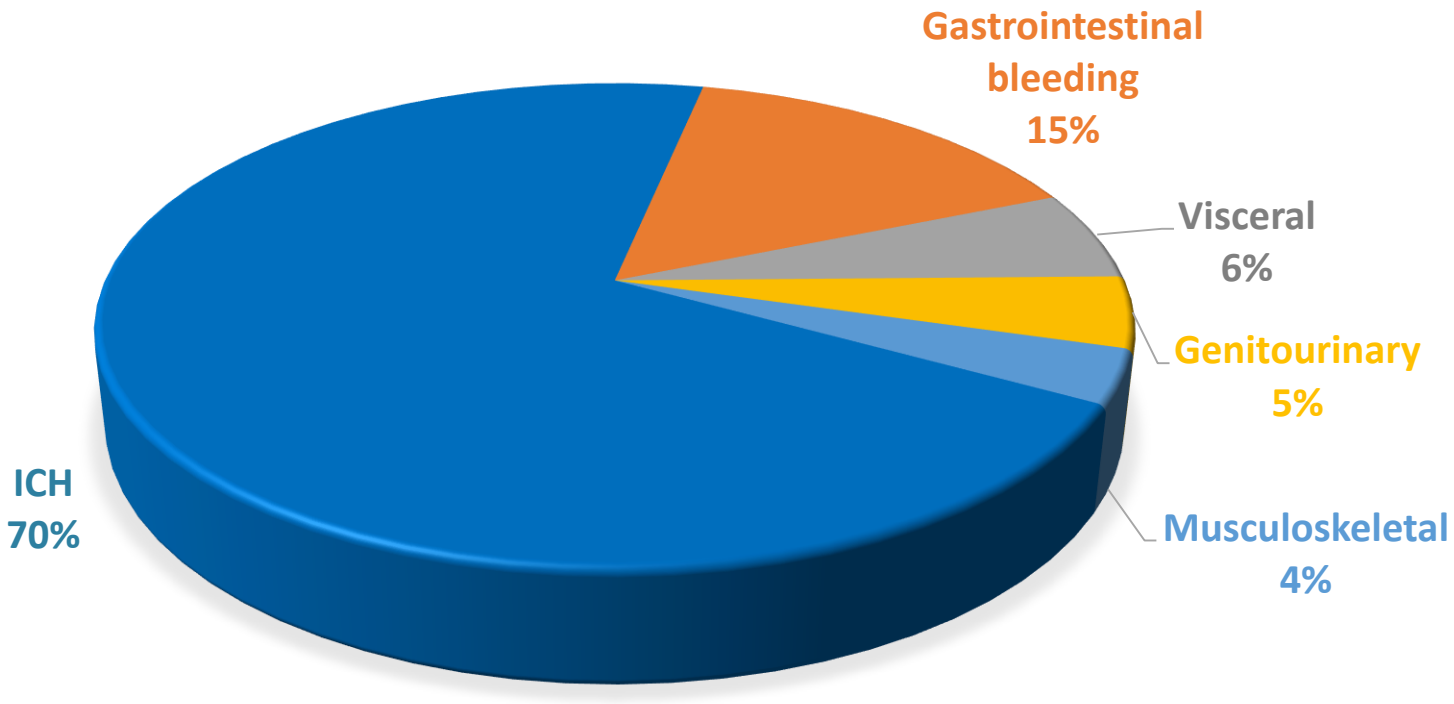
Safety Outcomes

- Arterial or venous thromboembolic events
- 30 day mortality
  - Cause of death

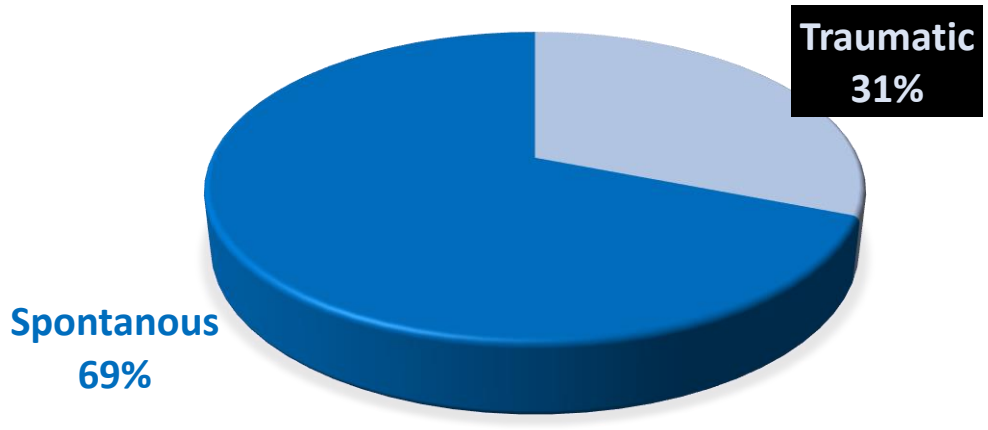
Indication for NOAC



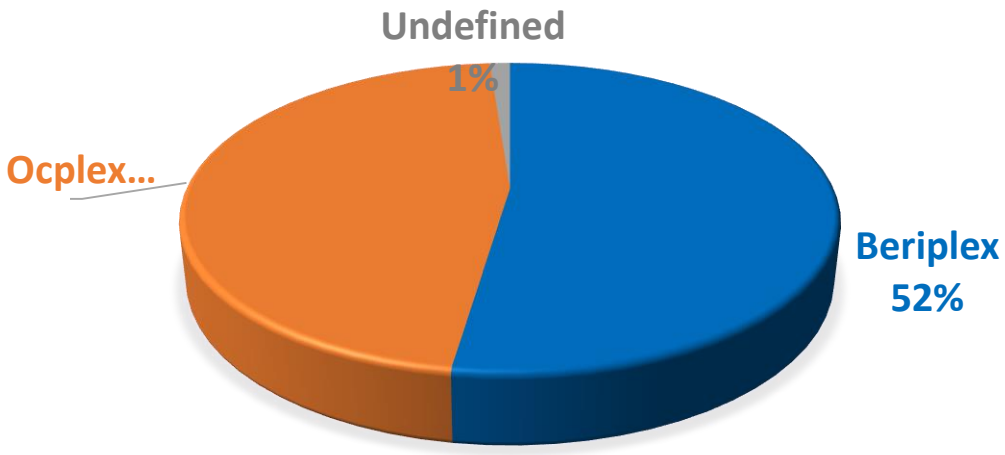
Bleeding Location



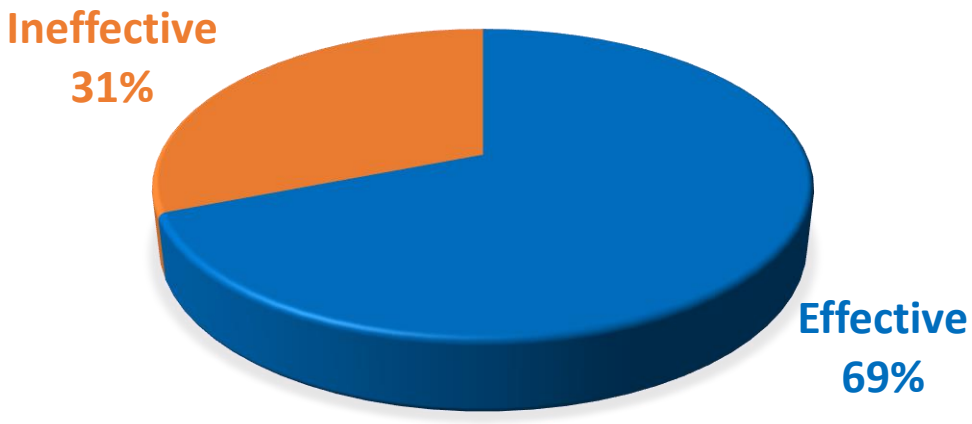
Cause of bleeding



Type of PCC given



Effectiveness according to ISTH criteria



Effectiveness assessment by bleeding location (ISTH criteria)

Location	Effective: N (%)	Ineffective: N (%)
ICH	43 (72%)	16 (27%)
GI	8 (62%)	5 (38%)
Genitourinary	3 (75%)	1 (25%)
Musculoskeletal	3 (100%)	0 (0%)
Visceral	1 (20%)	4 (80%)

Thromboembolic events

Age	Sex	Anticoagulant	Dose	Indication	Bleeding	PCC Dose, IU (IU/kg)	Thrombo-embolism	Timing from PCC (d)	Outcome
80	Female	Riva	20mgx1	SPAF	ICH	1500 (29)	Stroke	10	Discharged. Died after 112 days of new stroke
71	Female	Apixaban	5mgx2	SPAF	ICH	2000 (27)	Stroke	5	Died after 18 days from ICH
73	Male	Rivar	20mgx1	SPAF	ICH	2000 (27)	Suspected PE	15	Died after 16 days from ICH.

Death

- 15 patients died within 7 days
  - 87% had ICH
- 27 patients died within 30 days
  - 74% with ICH
- Cause of death at 1 month:
  - Bleeding 67%
  - Sepsis and MOF 26%
  - Cardiac arrhythmia 4% (1 patient)
  - Stroke 4% (1 patient)

Summary

- Prothrombin Complex Concentrate is the recommended measure for warfarin reversal
- Also shows effectiveness for NOAC reversal in the absence of specific ‘antidotes’