Prothrombin Complex Concentrate - Indications and Applications

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Head of the Australian Centre for Blood Diseases, Monash University
# Prothrombinex®-VF Composition

<table>
<thead>
<tr>
<th>Active ingredients</th>
<th>500 IU Vial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Factor IX</td>
<td>500 IU</td>
</tr>
<tr>
<td>Factor II</td>
<td>approx. 500 IU</td>
</tr>
<tr>
<td>Factor X</td>
<td>approx. 500 IU</td>
</tr>
<tr>
<td><strong>Excipients</strong></td>
<td></td>
</tr>
<tr>
<td>Human plasma proteins</td>
<td>≤500 mg</td>
</tr>
<tr>
<td>(including low levels of factors V and VII)</td>
<td></td>
</tr>
<tr>
<td>Antithrombin III</td>
<td>25 IU</td>
</tr>
<tr>
<td>Heparin sodium</td>
<td>192 IU</td>
</tr>
<tr>
<td>Sodium+</td>
<td>112 mg</td>
</tr>
<tr>
<td>Phosphate+</td>
<td>65 mg</td>
</tr>
<tr>
<td>Citrate+</td>
<td>180 mg</td>
</tr>
<tr>
<td>Chloride+</td>
<td>27 mg</td>
</tr>
</tbody>
</table>
Coagulation Factor Elimination Half-Lives

<table>
<thead>
<tr>
<th>Factor Elimination Half-Lives F</th>
<th>Factor II</th>
<th>Factor VII</th>
<th>Factor IX</th>
<th>Factor X</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elimination t1/2 (h)</td>
<td>60 (46–66)</td>
<td>4.2 (3.9–6.6)</td>
<td>17 (14–68)</td>
<td>31 (24–41)</td>
</tr>
</tbody>
</table>
Prothrombin Complex Concentrate for Warfarin Reversal
Therapeutic Range of VKA for AF

The anticoagulant effect of vitamin K antagonists are optimised when therapeutic doses are maintained within a very narrow range.

Risk of Major Bleeding and HAS-BLED Score

Atrial Fibrillation cohort of the Euro Heart Survey¹

(p=0.007)

Adapted from Pisters, 2010¹

<table>
<thead>
<tr>
<th>Clinical characteristic</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension (SBP &gt;160 mmHg)</td>
<td>1</td>
</tr>
<tr>
<td>Abnormal renal or liver function</td>
<td>1 + 1</td>
</tr>
<tr>
<td>Stroke</td>
<td>1</td>
</tr>
<tr>
<td>Bleeding</td>
<td>1</td>
</tr>
<tr>
<td>Labile INRs</td>
<td>1</td>
</tr>
<tr>
<td>Elderly (age &gt;65 years)</td>
<td>1</td>
</tr>
<tr>
<td>Drugs or alcohol</td>
<td>1 + 1</td>
</tr>
</tbody>
</table>

Cumulative score: Range 0–9

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>798</th>
<th>1,286</th>
<th>744</th>
<th>187</th>
<th>46</th>
<th>8</th>
<th>2</th>
<th>0</th>
<th>0</th>
<th>0</th>
<th>0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of major bleeding events</td>
<td>9</td>
<td>13</td>
<td>14</td>
<td>7</td>
<td>4</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

The relationship of INR to factor level is non-linear.

- Normal haemostasis
- Therapeutic anticoagulation

<table>
<thead>
<tr>
<th>INR</th>
<th>1.0</th>
<th>1.3</th>
<th>~1.5</th>
<th>2.2</th>
<th>3.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>30%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>100%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
# Bleeding risk on warfarin in VTE patients

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

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
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 ($P = 0.007$).
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:

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

INR pre and post Prothrombinex-VF

Pre (n=35)  Post (n=35)

Mean = 3.5 +/- 3.2
Mean = 1.1 +/- 0.1

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

Tran et al., Intern Med J. 2011 41(4):337-343
Poor outcome despite INR reversal with Prothrombin Complex Concentrate

<table>
<thead>
<tr>
<th>Intracranial haemorrhage type</th>
<th>No.</th>
<th>In-hospital mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intraparenchymal</td>
<td>71</td>
<td>30 (42.3%)</td>
</tr>
<tr>
<td>Subdural</td>
<td>61</td>
<td>21 (34.4%)</td>
</tr>
<tr>
<td>Epidural</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Subarachnoid</td>
<td>8</td>
<td>1 (12.5%)</td>
</tr>
</tbody>
</table>

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

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).
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

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

<table>
<thead>
<tr>
<th>Target INR</th>
<th>Initial INR</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>1.5-2.5</td>
</tr>
<tr>
<td>0.9-1.3</td>
<td>30 IU/kg</td>
</tr>
<tr>
<td>1.4-2.0</td>
<td>15 IU/kg</td>
</tr>
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</table>

Tran et al., Intern Med J. 2011 41(4):337-343
<table>
<thead>
<tr>
<th>Clinical Situation</th>
<th>Recommendation</th>
</tr>
</thead>
</table>
| INR ≥1.5 with life-threatening* (critical organ) bleeding | Cease warfarin therapy and administer  
  - **Vitamin K<sub>1</sub> 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<sub>1</sub> 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 <50x10⁹/L, known liver disease, concurrent antiplatelet therapy

Tran MJA 2013;198(4):1-7
# Management of patients on warfarin with high INR without bleeding

<table>
<thead>
<tr>
<th>Clinical Setting</th>
<th>Action</th>
</tr>
</thead>
</table>
| 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 |

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*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.

Optimizing warfarin reversal – an *ex vivo* study

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

Effect of rivaroxaban followed by PCC or placebo on coagulation tests

Effect of dabigatran followed by PCC or placebo on coagulation tests

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)
Table 1 Contents of the prothrombin complex concentrates

<table>
<thead>
<tr>
<th></th>
<th>Beriplex</th>
<th>Profilnine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Factor II</td>
<td>270 IU</td>
<td>288 IU</td>
</tr>
<tr>
<td>Factor VII</td>
<td>150 IU</td>
<td>Not detected</td>
</tr>
<tr>
<td>Factor X</td>
<td>340 IU</td>
<td>166 IU</td>
</tr>
<tr>
<td>Protein S</td>
<td>210 IU</td>
<td>Not detected</td>
</tr>
<tr>
<td>Protein C</td>
<td>270 IU</td>
<td>Not detected</td>
</tr>
</tbody>
</table>

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

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

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

Ammar Majeed, Anna Ågren, Margareta Holmström, Maria Bruzelius, Roza Chaireti, Jacob Odeberg, Eva-Lotta Hempel, Maria Magnusson, Tony Frisk, and Sam Schulman

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 Prothrombin complex concentrates for the Reversal of Anti-factor TEN inhibitors (UPRATE)

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

• Arterial or venous thromboembolic events
• 30 day mortality
  • Cause of death
Indication for NOAC
Bleeding Location

ICH 70%
Gastrointestinal bleeding 15%
Visceral 6%
Genitourinary 5%
Musculoskeletal 4%
Cause of bleeding

- Spontaneous: 69%
- Traumatic: 31%
Type of PCC given

- Beriplex 52%
- Ocplex... 1%
- Undefined 1%
Effectiveness according to ISTH criteria

- Effective: 69%
- Ineffective: 31%
## Effectiveness assessment by bleeding location (ISTH criteria)

<table>
<thead>
<tr>
<th>Location</th>
<th>Effective: N (%)</th>
<th>Ineffective: N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICH</td>
<td>43 (72%)</td>
<td>16 (27%)</td>
</tr>
<tr>
<td>GI</td>
<td>8 (62%)</td>
<td>5 (38%)</td>
</tr>
<tr>
<td>Genitourinary</td>
<td>3 (75%)</td>
<td>1 (25%)</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>3 (100%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Visceral</td>
<td>1 (20%)</td>
<td>4 (80%)</td>
</tr>
</tbody>
</table>
## Thromboembolic events

<table>
<thead>
<tr>
<th>Age</th>
<th>Sex</th>
<th>Anticoagulant</th>
<th>Dose</th>
<th>Indication</th>
<th>Bleeding</th>
<th>PCC Dose, IU (IU/kg)</th>
<th>Thromboemboli sm</th>
<th>Timing from PCC (d)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>80</td>
<td>Female</td>
<td>Riva</td>
<td>20mgx 1</td>
<td>SPAF</td>
<td>ICH</td>
<td>1500 (29)</td>
<td>Stroke</td>
<td>10</td>
<td>Discharged. Died after 112 days of new stroke</td>
</tr>
<tr>
<td>71</td>
<td>Female</td>
<td>Apixaban</td>
<td>5mgx2</td>
<td>SPAF</td>
<td>ICH</td>
<td>2000 (27)</td>
<td>Stroke</td>
<td>5</td>
<td>Died after 18 days from ICH</td>
</tr>
<tr>
<td>73</td>
<td>Male</td>
<td>Rivar</td>
<td>20mgx 1</td>
<td>SPAF</td>
<td>ICH</td>
<td>2000 (27)</td>
<td>Suspected PE</td>
<td>15</td>
<td>Died after 16 days from ICH</td>
</tr>
</tbody>
</table>
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’