EMerging Anticoagulation Reversal Issues in Emergency Medicine

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Pharmacy Grand Rounds
August 14th, 2018
Objectives

• Review the mechanism of action and dosing of prothrombin complex concentrate and andexanet alfa

• Discuss literature evaluating the safety and efficacy of fixed dose prothrombin complex concentrate and andexanet alfa for the reversal of oral anticoagulants

• Outline general recommendations for the use of prothrombin complex concentrate and andexanet alfa
Why Reverse?

- Most significant complication of oral anticoagulation is intracranial hemorrhage
  - Hematoma expansion = poor outcomes and higher mortality
    - Reduced when INR <1.3 and systolic BP <160 mm Hg
- Current anticoagulation reversal guidelines
  - 3F-PCC → 4F-PCC
  - Warfarin: Fixed dose 4F-PCC

<table>
<thead>
<tr>
<th>Guideline</th>
<th>Warfarin</th>
<th>Apixaban, Edoxaban, Rivaroxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurocritical Care Society (2016)</td>
<td>4F-PCC</td>
<td>4F-PCC</td>
</tr>
<tr>
<td>American College of Cardiology (2017)</td>
<td>4F-PCC Variable or Fixed</td>
<td>4F-PCC</td>
</tr>
</tbody>
</table>

INR = International Normalized Ratio  
BP = blood pressure  
3F-PCC = three-factor prothrombin complex concentrate  
4F-PCC = four-factor prothrombin complex concentrate  
Kuramatsu et al. JAMA. 2015;313:824-36  
Frontera et al. Neurocrit Care. 2016;24:6-46  
Tomaselli et al. J Am Coll Cardiol. 2017;70:3042-67
4F-PCC

- Kcentra®
  - Approved in 2013
  - Only 4F-PCC approved for rapid warfarin reversal
  - Coagulation Factors II, VII, IX, X
  - Antithrombotic Proteins C and S

- Indications:
  - Acute major hemorrhage
  - Reversal for urgent surgery/invasive procedure

- Kcentra® dosing*
  - Warfarin:

<table>
<thead>
<tr>
<th>INR</th>
<th>Dose (IU/kg)</th>
<th>Max dose (IU)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 to &lt;4</td>
<td>25</td>
<td>2500</td>
</tr>
<tr>
<td>4 to 6</td>
<td>35</td>
<td>3500</td>
</tr>
<tr>
<td>&gt;6</td>
<td>50</td>
<td>5000</td>
</tr>
</tbody>
</table>

- FXa inhibitors:
  - 50 IU/kg

*Dosing based on Factor IX activity
IU = international unit
FXa = factor Xa

Kcentra® [package insert]. 2017
Goldstein et al. Lancet. 2015;385:2077-87
Tomaselli et al. J Am Coll Cardiol. 2017;70:3042-67
Andexanet Alfa

- Approved in 2018
- Recombinant modified human FXa protein
- Indicated for reversal of apixaban and rivaroxaban in life-threatening or uncontrolled bleeding
## Andexanet Alfa Dosing

<table>
<thead>
<tr>
<th>FXa inhibitor</th>
<th>Last dose</th>
<th>&lt;8 hours or unknown</th>
<th>≥8 hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apixaban</td>
<td>≤5 mg</td>
<td>Low dose</td>
<td></td>
</tr>
<tr>
<td>Apixaban</td>
<td>&gt;5 mg or unknown</td>
<td>High dose</td>
<td>Low dose</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>≤10 mg</td>
<td>Low dose</td>
<td></td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>&gt;10 mg or unknown</td>
<td>High dose</td>
<td></td>
</tr>
</tbody>
</table>

### Dose

<table>
<thead>
<tr>
<th>Dose</th>
<th>Initial IV bolus</th>
<th>IV infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low dose</td>
<td>400 mg at a rate of 30 mg/min</td>
<td>4 mg/min for up to 120 minutes</td>
</tr>
<tr>
<td>High dose</td>
<td>800 mg at a rate of 30 mg/min</td>
<td>8 mg/min for up to 120 minutes</td>
</tr>
</tbody>
</table>

Andexxa® [package insert]. 2018
Assessment Question #1

• For which of the following patients would administration of andexanet alfa be appropriate?
  • On dabigatran, last dose 8 hours ago
  • On apixaban, last dose 6 hours ago
  • On warfarin, last dose 10 hours ago
  • On rivaroxaban, last dose 24 hours ago
Fixed Dose PCC

- Poor evidence to support current dosing practices
  - Highly variable dosing
  - Systematic review included 15 different dosing strategies
- Incidence of thromboembolic events in relation to dose unknown
  - Real world toxicity >> approval trials
  - Are we using too much?

Kcentra® dosing for warfarin reversal

<table>
<thead>
<tr>
<th>INR</th>
<th>Dose (IU/kg)</th>
<th>Max dose (IU)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 to &lt;4</td>
<td>25</td>
<td>2500</td>
</tr>
<tr>
<td>4 to 6</td>
<td>35</td>
<td>3500</td>
</tr>
<tr>
<td>&gt;6</td>
<td>50</td>
<td>5000</td>
</tr>
</tbody>
</table>

Khorsand et al. Thromb Res. 2015;135:9-19
<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Patients</th>
<th>PCC</th>
<th>Fixed dose*</th>
<th>Outcomes</th>
</tr>
</thead>
</table>
| Khorsand et al. (2011)| Observational cohort pilot | Fixed, n = 35 Variable, n = 32 Major/non-ICH bleeding Emergency procedure | Cofact® | 1040 IU or 520 IU | Target INR: 70% vs 81%   
Successful clinical outcome: 91% vs 94%   
Thrombosis rate: 2.9% vs 6.25% |
| Khorsand et al. (2012)| Prospective observational cohort | Fixed, n = 101 Variable, n = 139 Major/non-ICH bleeding | Cofact® | 1040 IU | Target INR: 91.7% vs 94.7%   
Successful clinical outcome: 96% vs 88%   
Thrombosis rate: 1% vs 1.4% |
| Wozniak et al. (2012) | Retrospective cohort | n = 150 Major bleeding Emergency procedure | Octaplex® | 1000 IU | INR ≤1.5: 114 (76%)   
Thrombosis rate: 2% |
| Varga et al. (2013)   | Retrospective cohort | n = 103 Major bleeding Emergency procedure | Octaplex® | 1000 IU | Excellent clinical response: 86 (83.5%)   
Thrombosis rate: 4.9% |
| Klein et al. (2015)   | Retrospective cohort | n = 39 Need for emergent reversal | Kcentra® | 1500 IU | Target INR <2.0: 36 (92.3%)   
Target INR ≤1.5: 28 (71.8%)   
Thrombosis rate: 0% |
| Abdoellakhan et al. (2017)| Retrospective cohort | Fixed, n = 28 Variable, n = 25 ICH | Cofact® | 1000 IU (+ 500 IU) | INR ≤1.5: 68% vs 96%   
Thrombosis rate: 0% vs 8.3% |
| Scott et al. (2018)   | Retrospective cohort | Fixed, n = 30 Variable, n = 31 ICH | Kcentra® | 1000 IU | INR <1.5: 71% vs 53%   
Thrombosis rate: N/A |

*All dosing based on Factor IX
Khorsand et al. 2012

- Prospective observational two-cohort study
- PCC used: Cofact®
- Primary outcome: target INR <2.0 at 15 minutes after PCC infusion

- All patients received 10 mg IV vitamin K

<table>
<thead>
<tr>
<th>Fixed dose</th>
<th>Variable dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>• 1040 IU</td>
<td>• Dose based on initial and target INR and body weight</td>
</tr>
<tr>
<td>Patient characteristic</td>
<td>Fixed dose (n = 101)</td>
</tr>
<tr>
<td>---------------------------------------------</td>
<td>----------------------</td>
</tr>
<tr>
<td>Median age, years (range)</td>
<td>77 (37-95)</td>
</tr>
<tr>
<td>Mean Charlson Comorbidity Index</td>
<td>2.93</td>
</tr>
<tr>
<td>Median baseline INR (range)</td>
<td>5.1 (1.54 to &gt;7.6)</td>
</tr>
<tr>
<td>Baseline INR &gt;7.6, n (%)</td>
<td>35 (35%)</td>
</tr>
<tr>
<td>ICU admissions, n (%)</td>
<td>12 (12%)</td>
</tr>
<tr>
<td>Indication for PCC, n (%)</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal bleed</td>
<td>58 (57%)</td>
</tr>
<tr>
<td>Muscle bleed</td>
<td>9 (9%)</td>
</tr>
<tr>
<td>Intraperitoneal or abdominal wall bleed</td>
<td>10 (10%)</td>
</tr>
<tr>
<td>Hemoptysis</td>
<td>4 (4%)</td>
</tr>
<tr>
<td>Other</td>
<td>20 (20%)</td>
</tr>
<tr>
<td>Transfusion of FFP, n (%)</td>
<td>15 (15%)</td>
</tr>
</tbody>
</table>

FFP = fresh frozen plasma

### Khorsand et al. 2012

<table>
<thead>
<tr>
<th>Measure</th>
<th>Fixed dose (n = 101)</th>
<th>Variable dose (n = 139)</th>
<th>Proportion difference or p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PCC dose, IU (range)</td>
<td>1040 (260-1560)</td>
<td>1560 (520-3120)</td>
<td>p &lt;0.001</td>
</tr>
<tr>
<td>Target INR reached, n (%)</td>
<td>88 (91.7%)</td>
<td>124 (94.7%)</td>
<td>-2.99% (90% CI: -8.6-2.7)</td>
</tr>
<tr>
<td>Successful clinical outcome, n (%)</td>
<td>97 (96%)</td>
<td>122 (88%)</td>
<td>8.27% (90% CI: 2.7-13.9)</td>
</tr>
<tr>
<td>Mortality, n (%)</td>
<td>14 (14%)</td>
<td>36 (26%)</td>
<td>p = 0.025</td>
</tr>
<tr>
<td>Median time to infusion, minutes</td>
<td>130</td>
<td>160</td>
<td>p = 0.015</td>
</tr>
<tr>
<td>Thromboembolic events, n (%)</td>
<td>1 (1%)</td>
<td>2 (1.4%)</td>
<td>N/A</td>
</tr>
</tbody>
</table>
Khorsand et al. 2012

- Fixed dose “non-inferior” to variable dose:
  - Clinical outcome (what matters)
  - Not if considering INR only (what is measured)

- Limitations:
  - Exclusion criteria
    - Intracranial hemorrhage
    - Urgent invasive procedure
  - 32% nonadherence rate in fixed dose cohort
    - Majority received less (~500 IU vs 1040 IU)
    - Works even if a “low” fixed dose
Klein et al. 2015

- Retrospective cohort study
- PCC used: Kcentra®
- Primary outcome: successful INR reversal to <2.0 or ≤1.5

Fixed dose

- 1500 IU
- Dose differed slightly based on vial size

n = 39
### Klein et al. 2015

<table>
<thead>
<tr>
<th>Patient characteristic</th>
<th>Fixed dose (n = 39)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, years (IQR)</td>
<td>70 (60-78)</td>
</tr>
<tr>
<td>Median weight, kg (IQR)</td>
<td>79.5 (72.1-95.3)</td>
</tr>
<tr>
<td>Chronic anticoagulant, n (%)</td>
<td></td>
</tr>
<tr>
<td>Warfarin</td>
<td>38 (97.4%)</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>1 (2.6%)</td>
</tr>
<tr>
<td>Indication for treatment, n (%)</td>
<td></td>
</tr>
<tr>
<td>Intracranial hemorrhage</td>
<td>28 (71.8%)</td>
</tr>
<tr>
<td>Gastrointestinal hemorrhage</td>
<td>4 (10.3%)</td>
</tr>
<tr>
<td>Ruptured abdominal aortic aneurysm</td>
<td>1 (2.6%)</td>
</tr>
<tr>
<td>Intrathoracic hemorrhage</td>
<td>2 (5.1%)</td>
</tr>
<tr>
<td>Spinal cord hemorrhage</td>
<td>1 (2.6%)</td>
</tr>
<tr>
<td>Neck hematoma</td>
<td>1 (2.6%)</td>
</tr>
<tr>
<td>Other emergent surgical indication</td>
<td>2 (5.1%)</td>
</tr>
</tbody>
</table>
Measure | Fixed dose (n = 39)
--- | ---
Median PCC dose, IU (IQR) | 1659 (1569-1710)
Median IU/kg (IQR) | 20.4 (17.3-22.6)
Other reversal agents, n (%) | 36 (92.3%), 11 (28.2%)
  Vitamin K
  FFP
Median INR value (IQR) | 3.3 (2.5-4.0), 1.4 (1.2-1.6)
  Presenting INR
  After single dose 1500 IU
Median percent decrease in INR (IQR) | 56.7 (41.7-70)
Successful reversal with single dose, n (%) | 36 (92.3%), 28 (71.8%)
  Target INR <2.0
  Target INR ≤1.5
Klein et al. 2015

- High rates of successful INR reversal seen with use of fixed dose of 1500 IU
  - No thrombotic adverse events within 7 days
  - Cost savings $\sim$40,000

- Limitations:
  - Small sample size
  - No control group (vs variable dose)
  - Monitoring duration (Is 7 days ideal?)

Andexanet Alfa

- Due to increasing use of FXa inhibitors, number of patients requiring reversal also expected to increase
- No specific antidote available for FXa inhibitors prior to andexanet alfa approval
  - Some studies suggest reversal may be achieved with PCC
- Phase II study (ANNEXA-A and ANNEXA-R) conducted in healthy patients

Zahir et al. Circulation. 2015;131:82-90
### Phase III Study

**ANNEXA-4**

Multicenter, prospective, open-label, single-group

Evaluate the efficacy and safety of andexanet alfa in patients with acute major bleeding

**Outcomes**

- Percent change in anti-FXa activity
- Rate of excellent or good hemostatic efficacy 12 hours after infusion

**67 patients**

- Rivaroxaban, n = 32 (median daily dose = 20 mg)
- Apixaban, n = 31 (median daily dose = 5 mg)
- Enoxaparin, n = 4

## Patient characteristic

<table>
<thead>
<tr>
<th>Patient characteristic</th>
<th>Safety population (n = 67)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, years</td>
<td>77.1</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>35 (52%)</td>
</tr>
<tr>
<td>Mean body-mass index</td>
<td>28.1</td>
</tr>
<tr>
<td>Medical history, n (%)</td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>13 (19%)</td>
</tr>
<tr>
<td>Stroke</td>
<td>17 (25%)</td>
</tr>
<tr>
<td>Deep-vein thrombosis</td>
<td>20 (30%)</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>6 (9%)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>49 (73%)</td>
</tr>
<tr>
<td>Heart failure</td>
<td>23 (34%)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>23 (34%)</td>
</tr>
<tr>
<td>Site of bleeding, n (%)</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>33 (49%)</td>
</tr>
<tr>
<td>Intracranial</td>
<td>28 (42%)</td>
</tr>
<tr>
<td>Other</td>
<td>6 (9%)</td>
</tr>
</tbody>
</table>

## Anti-FXa Activity

<table>
<thead>
<tr>
<th></th>
<th>End of bolus</th>
<th>End of infusion</th>
<th>4 hours</th>
<th>8 hours</th>
<th>12 hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rivaroxaban</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Percent change</td>
<td>-89</td>
<td>-86</td>
<td>-39</td>
<td>-49</td>
<td>-64</td>
</tr>
<tr>
<td>Apixaban</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Percent change</td>
<td>-93</td>
<td>-92</td>
<td>-30</td>
<td>-28</td>
<td>-31</td>
</tr>
</tbody>
</table>

### Excellent or Good Hemostatic Efficacy

<table>
<thead>
<tr>
<th>Subgroup</th>
<th># of patients</th>
<th>Percent adjudicated as excellent or good hemostasis (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients with efficacy analyses</td>
<td>47</td>
<td>79% (64-89)</td>
</tr>
<tr>
<td>Drug</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>26</td>
<td>81% (61-93)</td>
</tr>
<tr>
<td>Apixaban</td>
<td>20</td>
<td>75% (51-91)</td>
</tr>
<tr>
<td>Enoxaparin</td>
<td>1</td>
<td>100%</td>
</tr>
<tr>
<td>Site of bleeding</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>25</td>
<td>84% (64-96)</td>
</tr>
<tr>
<td>Intracranial</td>
<td>20</td>
<td>80% (56-94)</td>
</tr>
<tr>
<td>Other</td>
<td>2</td>
<td>0%</td>
</tr>
<tr>
<td>Andexanet dose</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>42</td>
<td>76% (61-88)</td>
</tr>
<tr>
<td>High</td>
<td>5</td>
<td>100% (48-100)</td>
</tr>
</tbody>
</table>

No infusion reactions

No development of antibodies to FX or FXa

No neutralizing antibodies against andexanet alfa

12 thrombotic events (18%) and 10 deaths (15%) at 30 days

• Effective hemostasis in 79% of patients with major bleeding
  • Substantial reduction in anti-FXa activity
• Limitations:
  • Exclusion criteria
    • Urgent surgery
    • Severe intracranial hemorrhage
  • No control group (vs PCC)
  • ~5 hours from presentation to bolus
Boxed Warnings

**WARNING: ARTERIAL AND VENOUS THROMBOEMBOLIC COMPLICATIONS**
Patients being treated with Vitamin K antagonists (VKA) therapy have underlying disease states that predispose them to thromboembolic events. Potential benefits of reversing VKA should be weighed against the potential risks of thromboembolic events, especially in patients with the history of a thromboembolic event. Resumption of anticoagulation should be carefully considered as soon as the risk of thromboembolic events outweighs the risk of acute bleeding.

- Both fatal and non-fatal arterial and venous thromboembolic complications have been reported with Kcentra in clinical trials and post marketing surveillance. Monitor patients receiving Kcentra for signs and symptoms of thromboembolic events.
- Kcentra was not studied in subjects who had a thromboembolic event, myocardial infarction, disseminated intravascular coagulation, cerebral vascular accident, transient ischemic attack, unstable angina pectoris, or severe peripheral vascular disease within the prior 3 months. Kcentra may not be suitable in patients with thromboembolic events in the prior 3 months. (5.2)

**WARNING: THROMBOEMBOLIC RISKS, ISCHEMIC RISKS, CARDIAC ARREST, AND SUDDEN DEATHS**
See full prescribing information for complete boxed warning

Treatment with ANDEXXA has been associated with serious and life-threatening adverse events, including: (5.1)
- Arterial and venous thromboembolic events
- Ischemic events, including myocardial infarction and ischemic stroke
- Cardiac arrest
- Sudden deaths

Monitor for thromboembolic events and initiate anticoagulation when medically appropriate. Monitor for symptoms and signs that precede cardiac arrest and provide treatment as needed.
Assessment Question #2

• True or False: Fixed dose PCC is non-inferior to variable dose for both INR reduction and clinical outcome in major hemorrhage.
Assessment Question #3

• True or False: Andexanet alfa provides a sustained reduction in anti-FXa activity level 4 hours post-infusion.
Cost of Fixed vs Variable Dose PCC

- 80 kg patient on chronic warfarin therapy presenting with intracranial hemorrhage; INR 5.1
- Kcentra® pricing: $1.54/IU
  - Fixed dose (1500 IU)
    - $1.54/IU x 1500 IU = $2,310
  - Variable dose (35 IU/kg)
    - $1.54/IU x [(35 IU/kg) x 80 kg] = $4,312
- Fixed dose cost savings = $2,002
Cost of Andexanet Alfa vs PCC

• 95 kg patient on apixaban 5 mg BID presenting with intracranial hemorrhage; last dose 6 hours ago

• Andexanet alfa pricing: $2,750/100 mg vial
  • Low dose (400 mg IV bolus + 4 mg/min IV infusion x 120 min) = 880 mg = 9 vials = $2,750/100 mg vial x 9 vials = $24,750

• Kcentra® pricing: $1.54/IU
  • Dose (50 IU/kg)
    • $1.54/IU x [(50 IU/kg) x 95 kg] = $7,315

• Cost difference = $17,435
Fixed Dose PCC Recommendations

Chronic warfarin therapy

Non-life-threatening bleeding
- 10-15 mL/kg FFP + vitamin K

Acute, severe, life-threatening bleeding or need for emergency procedure
- 1500 IU Kcentra® + 10 mg IV vitamin K

Consider increased or additional dose if:
- INR >7.5
- Obese patient (>100 kg)
- Inadequate response with initial dose
Andexanet Alfa Recommendations

Chronic FXa inhibitor therapy

Non-life-threatening bleeding
- 50 IU/kg Kcentra®?

Acute, severe, life-threatening bleeding or need for emergency procedure
- Andexanet alfa
Assessment Question #4

• AB is a 65-year-old female on chronic rivaroxaban therapy for AF presenting with probable upper gastrointestinal bleeding. Patient requires endoscopy.

• Vitals: BP 115/70, HR 99

• Labs: Hgb 9.1 g/dL, CrCl 75 mL/min

• Last dose of rivaroxaban 24 hours ago

AF = atrial fibrillation
Assessment Question #4

• Which anticoagulation reversal agent would you recommend for this patient?
  • PCC
  • Andexanet alfa
  • No reversal agent
Unanswered Questions

Fixed dose PCC:

- Is less more?
- Dose in obese patients?

Andexanet alfa:

- Is it worth the cost?
- FDA dosing appropriate?
Summary

• Ideal PCC dosing for reversal of oral anticoagulation unknown
  • Fixed dosing may provide equivalent efficacy with reduced thrombotic complications and costs

• Andexanet alfa is the only specific reversal agent available for FXa inhibitors but has numerous drawbacks
  • Short half-life
  • Expensive
  • Cumbersome preparation
  • Limited supply
Questions & Discussion
Khorsand et al. Cofact® Dosing

<table>
<thead>
<tr>
<th>Initial INR</th>
<th>7.5</th>
<th>5.9</th>
<th>4.8</th>
<th>4.2</th>
<th>3.6</th>
<th>3.3</th>
<th>3.0</th>
<th>2.8</th>
<th>2.6</th>
<th>2.5</th>
<th>2.3</th>
<th>2.2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight (kg)</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Target</td>
<td>50</td>
<td>1040</td>
<td>1040</td>
<td>1040</td>
<td>780</td>
<td>780</td>
<td>780</td>
<td>520</td>
<td>520</td>
<td>X</td>
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*The dosage is shown as International Units of Factor IX based on a Cofact® batch with 26 IU of F IX per mL as used for this study. This table is based on the manufacturer's algorithm (Sanquin, Amsterdam, The Netherlands).*

PROthrombin complex concentrate: Prospective Evaluation and Rationalisation, number 3 (PROPER3)

- Randomized controlled non-inferiority trial
  - 8 Dutch emergency departments of large academic or teaching hospitals
- Status: ongoing
  - Enrollment expected to end in 2019
  - Goal of 310 patients (282 required)
- 1000 IU fixed PCC dose vs variable dose PCC in vitamin K antagonist-related extracranial bleeding emergencies
- Primary outcome: successful clinical outcome over 24 hours from the end of infusion

Abdoellakhan et al. BMJ Open. 2018;8:e020764