Fixed Dose 4FPCC for Urgent Warfarin Reversal:

Does one dose fit all?

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Learning Objectives:

1. Summarize current guideline recommendations for emergent vitamin-K antagonist (VKA) reversal
2. Describe the different prothrombin complex concentrate (PCC) dosing regimens evaluated in the literature
3. Evaluate the safety, efficacy, and cost impact of a fixed dose PCC dosing regimen

I. Vitamin K antagonists (VKA)

A. Warfarin[1]
   i. Most commonly prescribed VKA world wide[2]
      a. Approximately 2.5 million adults and children in the US[3]
   ii. Indication
      a. Treatment and prophylaxis of venous thromboembolism (VTE), pulmonary embolism (PE)
      b. Prophylaxis of thromboembolic complications of atrial fibrillation (Afib) and cardiac valve replacement
      c. Reduction of mortality risk associated with recurrent myocardial infarction (MI) and embolization after MI and cerebral vascular accidents
   iii. Pharmacology
      a. Inhibits formation of vitamin K-dependent clotting factors II, VII, IX, X, and proteins C and S
      b. Drug and food interactions
         1. CYP1A2, 3A4, 2C9, and 2C19
         2. Vitamin K-containing food
      c. Full therapeutic effect usually seen within 5 to 7 days
      d. Half-life is ~40 hours
   iv. Monitoring
      a. Prothrombin time (PT)
      b. International normalize ratio (INR)
      c. INR goals
         1. 2 – 3
         2. 2.5 – 3.5
   v. Elevated (international normalized ratio) INR and risk of hemorrhage
      a. Relative risk of thromboembolic events increases significantly at INR > 5
   vi. Risk factors for supratherapeutic INR[4]
      a. Patient comorbidities
         1. Heart failure
      b. Acute illnesses
         1. Infections
         2. Gastrointestinal illnesses
      c. Medication interactions
         1. Antibiotics
         2. Amiodarone
         3. Nonsteroidal anti-inflammatory drugs (NSAIDs)
      d. Large day-to-day variations in vitamin K intake
B. Other common VKAs
   i. Acenocoumarol
   ii. Phenprocoumon
   iii. Dicoumarol

II. VKA associated hemorrhage

A. Incidence and epidemiology
   i. In the US, major hemorrhage occurs at an annual rate of 1.7 – 3.4% in patients on warfarin therapy[5]
      a. Intraparenchymal hemorrhage (IPH) accounts for 90% of all VKA associated deaths[6]
         1. VKA use more than doubles the risk of spontaneous IPH
         2. IPH occurs in 0.3 – 1.1% of patients on VKA therapy
            a) Accounts for 3500 IPH per year in the US

      b. Intracerebral hemorrhage (ICH) expansion
         1. The hazard ratio of mortality increases by 5% with every 10% increase in ICH volume[7]
         2. Each milliliter absolute increase in ICH volume shifts patient outcomes from independence to dependence by 7% ICH expansion has been shown to occur at INR as low as 1.4[8]

      c. Gastrointestinal bleed (GIB)[9]
         1. Warfarin associated with up to 12% of GIB cases
         2. GIB occurs at an average rate of 3% of patients treated with warfarin
         3. Incidence
            a) Life-threatening hemorrhage: 5%
            b) Fatal hemorrhage: 1%

B. Major hemorrhage[5]
   i. Lack of consistent definitions of bleeding in the literature
   ii. Historically classified as fatal, major, life-threatening, excessive, clinically significant
      a. Fatal and intracranial hemorrhages not always considered among major bleeds in clinical trials and studies
      b. Federal Drug Administration (FDA) encourages continued use of definitions utilized in previous studies
   iii. Major bleeding in non-surgical patients
      a. Criteria for major bleeding according to the European Agency for the Evaluation of Medicinal Products (EMEA) Control of Anticoagulation Subcommittee
         1. Symptomatic bleeding in critical area or organ and/or
            a) Intracranial, intraspinal, intraocular, retroperitoneal, intraarticular, or pericardial, or intramuscular with compartment syndrome, and/or
            b) Bleeding causing a fall in hemoglobin (Hgb) level of 2 mg/dL or leading to transfusion of $\geq$ 2 units of whole blood

III. Treatment principles

A. Hold VKA therapy[9]
B. Assess the bleed[10]
    i. Vital signs
    ii. Physical exam to assess for external evidence of hemorrhage
        a. e.g., epistaxis, scalp laceration, open fracture
    iii. Diagnosis of internal hemorrhage
        a. e.g., endoscopy, computed tomography (CT) scan, ultrasound
    iv. Bleeding site accessibility and intervention feasibility
    v. Severity
    vi. Laboratory tests
        a. Levels of anticoagulation
            1. Complete blood count (CBC) with platelets, INR, PT time, activated partial thromboplastin time (aPTT)
        b. Markers of blood loss
            1. Hgb, hematocrit, serum lactate, arterial blood gas pH, and basic metabolic panel
        c. Organ function
            1. Liver function tests, SCr
    vii. Clinical presentation
        a. Hemodynamic instability
        b. Tachycardia
        c. Shortness of breath
        d. Palor
    viii. Need for emergent procedures
C. Treatment overview[9]
    i. Hold VKA therapy
    ii. Check INR
    iii. Consider administration of oral or IV vitamin K
    iv. Administer clotting factor supplement if indicated

Table 1. General treatment of VKA reversal based on urgency[9]

No rush (reversal needed >24 hr)	Expedited (reversal needed in 1-24 hr)	Emergent (reversal needed in < 1 hr)
• INR 4.5 – 10 without bleeding	• INR > 10 without bleeding • INR 4.5 – 10 with minor bleeding	• INR > 1.4 with VKA-associated major bleeding
Hold warfarin	• Hold warfarin • Give oral or low-dose IV vitamin K	• Hold warfarin • High dose IV vitamin K • Clotting factor supplement

Table 2. Characteristics of therapies for warfarin reversal[11]

Product	Time to Affect (after administration)	Duration of Effect	Risk of Thrombosis
Oral Vitamin K	24 h	Days	Not significant
Intravenous Vitamin K	8 – 12 h	Days	Not significant
Fresh Frozen Plasma	Immediate	12 -24 h	Not significant
PCC	Immediate	12 – 24 h	+

D. Review of guideline recommendations for VKA reversal

i. American College of Chest Physicians (ACCP)[12]
   a. For major bleeding
      1. Vitamin K 5 – 10 mg IV
      2. Rapid reversal with 4FPCC rather than FFP
ii. American Heart Association and American Stroke Association (AHA/ASA)[13]
   a. Elevated INR and spontaneous intracranial hemorrhage (ICH)
      1. Vitamin K 5 – 10 mg IV
      2. 3FPCC or 4FPCC might be considered over FFP
iii. Neurocritical Care Society (NCS) and Society of Critical Care Medicine (SCCM)[6]
   a. INR > 1.4 and ICH
      1. Vitamin K 10 mg IV
      2. 4FPCC preferred over 3FPCC and FFP
         a) Dose based on weight and INR
iv. British Committee for Standards in Haematology (BCSH)[14]
   a. Major bleeding
      1. Vitamin K 5 mg IV
      2. 4FPCC
         a) 25 – 50 IU/kg

E. Time to INR reversal[15]
   i. A retrospective study demonstrated that time to initiation of VKA reversal was the most important determinant for INR normalization
      a. No difference in morbidity or mortality
      b. Every 30-minute delay in plasma infusion reduces the probability of successful INR correction within 24 hours by 20%

IV. Kcentra® review[16]

A. FDA approved in 2013 for urgent reversal of VKA-associated acute major bleeding or need for urgent surgery or invasive procedure
   i. First 4FPCC approved in the US
B. Considered therapeutically equivalent to European 4FPCC product, Beriplex®
C. Non-activated 4FPCC that is prepared from US sourced plasma
   i. Plasma is purified, heat-treated, nanofiltered, and lyophilized
D. Components
   i. FII, FVII, FIX, FX, and antithrombotic proteins C and S
   ii. Heparin, antithrombin III, albumin

E. Pharmacokinetics

TABLE 3. 4FPCC component half-lives[17]

Factor	Factor II	Factor VII	Factor IX	Factor X	Protein C	Protein S
Terminal half-life (mean, hours)	60.4	5.0	41.2	31.8	49.6	59.4

F. Mechanism of action
   i. Reverses the effects of VKA by increasing plasma levels of vitamin-K dependent coagulation factors
G. Adverse effects

Table 4. Cardiovascular and central nervous system adverse effect of Kcentra®[16, 17]

System	Adverse Effect	
Cardiovascular	Hypotension (5% to 7%) Tachycardia (3% to 5%) Atrial fibrillation (4%) Hypertension (1% to 3%) Pulmonary embolism (≤2%) Pulmonary edema (2%) Cerebrovascular accident (1% to 2%)	Arteriovenous fistula site complication (clot, ≤1%) Chest pain (1%) Deep vein thrombosis (1%) Venous thrombosis (calf, 1%; radial vein: ≤1%) Thrombosis (microthrombosis of toes, ≤1%)
Central nervous system	Headache (1% to 8%) Insomnia (1% to 5%) Intracranial hemorrhage (3%) Mental status changes (3%)	

H. Contraindications

   i. Known anaphylactic or severe systemic reactions to 4FPCC or any component in 4FPCC
   ii. Patients with disseminated intravascular coagulation (DIC)
   iii. Patients with known heparin-induced thrombocytopenia

I. Warning and precautions
   i. Boxed Warning (Appendix A)
      a. Arterial and venous thromboembolic complications
         1. Fatal and non-fatal arterial and venous thromboembolic events reported in clinical trials
   ii. Hypersensitivity reactions
   iii. Thromboembolic risk/complications
      a. Patient becomes exposed to risk of thrombosis associated with indication for anticoagulation
      b. European pharmacovigilance study reported a <1% risk (21/647,250) of thromboembolic events possibly related to 4FPCC administration over 15 years[18]

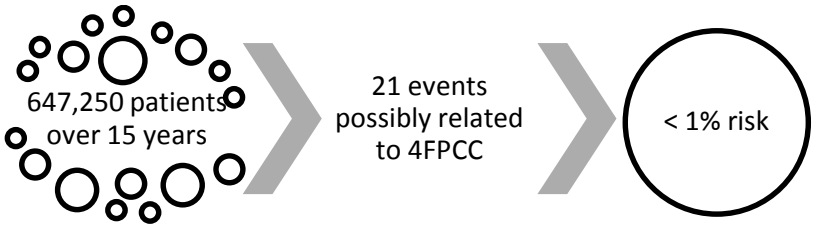

Figure 1. Thromboembolic risk of 4FPCC[18]

iv. Transmissible infectious agents
    a. No causal relationship since introduction of a virus filtration step in 1996

J. Supplied
    i. Single use vial
        a. 500 IU FIX/20 mL sterile water for injection diluent
        b. 1000 IU FIX/40 mL sterile water for injection diluent
    ii. Actual potency of coagulation factors are stated on each carton

K. Administration
    i. 0.12 mL/kg/min (~3 units/kg/min) up to 70 kg
    ii. Maximum rate of 8.4 mL/min (~210 units/min)

L. Dosing strategies – dosed based on FIX content of vial; each lot may be different
    i. Discretion of treating physician[19]
        a. Conflicting outcomes
    ii. Bodyweight and presenting INR
        a. Kcentra® FDA approved dosing[16]

Table 5. Package insert recommended dosing [17]

Pre-treatment INR	2 to 3.9	4 to 6	> 6
Dose of Kcentra® (IU of FIX/kg of body weight)	25	35	50
Maximum dose (units of FIX)	Not to exceed 2500	Not to exceed 3500	Not to exceed 5000

iii. Bodyweight, presenting INR, and INR target[20]
    a. Standardized dosing nomogram
    b. Studied with Cofact®, a European 4FPCC product unavailable in US

Table 6. 4FPCC dosing nomogram[20]

BW	Initial INR											
	Dose (Total mL of Cofact®)											
	7.5	5.9	4.8	4.2	3.6	3.3	3.0	2.8	2.6	2.5	2.3	2.3
50 kg	60	60	60	50	50	50	40	40	30	30	30	30
60 kg	80	70	70	60	60	60	50	50	40	40	40	30
70 kg	90	80	80	70	70	70	60	50	40	40	40	40
80 kg	100	100	90	90	90	80	80	70	60	50	50	40
90 kg	100	100	100	90	90	90	80	80	70	60	50	40
100 kg	100	100	100	100	100	90	90	80	70	70	60	50

V. Fixed dose 4FPCC

A. Used in hospitals in the Netherlands as early as 1995[21]
B. Reports of doses as low as 200 IU FIX[22]
C. Systematic review of dosing strategies[19]
    i. Systematic review to analyze INR reversal and efficacy of different PCC dosing strategies currently in practice
        a. Variability in outcome definitions within the included studies
    ii. Identified 15 different PCC dosing strategies used in 28 studies, including four randomized trials
        a. Strategies based on those listed above
    iii. PCC doses ranged from 8 to 50 IU unit per kg of FIX
    iv. Included both 3FPCC and 4FPCC
    v. 4FPCC studies
        a. Positive INR reversal ranged from 43 to 92%
        b. Positive clinical responses ranged from 57 to 96%
        c. van Aart et al. reported low INR target attainment and proportion of clinical response with a low fixed dose of 500 IU[20]

Table 7. Outcomes of fixed dose 4FPCC studies[19]

Author	PCC Brand	Protocol Dose	Reached Target INR n/total (%)	Positive Clinical Response n/total (%)
Dowlatshahi[23]	Octaplex®	1000 IU	57/78 (72)	NR
Khorsand[20]	Cofact®	1040 IU	21/30 (70)	32/35 (91)
Khorsand –Cohort 1[24]	Cofact®	1040 IU	88/96 (92)	97/101 (96)
van Aart – Cohort 1[25]	Cofact®	500 IU	20/47 (43)	27/47 (57)
Yasaka – PCC cohort	PPSB-HT Nichitaku®	500 or 1000 IU	NR	9/11 (82)
Yasaka	PPSB-HT Nichitaku®	200, 500, 1000, or, 1500 IU	33/42 (79)	NR

VI. Literature review: fixed dose PCC

<table>
<tr><td colspan="2">Sarode R, Milling TJ, Refaai MA, et al. 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. Circulation. 2013;128(11):1234-43.[23]</td></tr>
<tr><td>Objective</td><td>Safety and efficacy evaluation of 4FPCC when compared to plasma for urgent VKA reversal</td></tr>
<tr><td>Intervention</td><td>• 4FPCC group (median 510 units of FIX per vial of Kcentra®)
• INR 2 - <4; 25 IU of FIX/kg
• INR 4 – 6; 35 IU of FIX/kg
• INR > 6; 50 IU of FIX/kg</td></tr>
<tr><td>Inclusion Criteria</td><td>• ≥ 18 years old
• INR ≥ 2 within 3 hours prior to study treatment
• Presenting with an active major bleed
• Life-threatening or potentially life-threatening
• Acute bleed associated with a fall in Hgb > 2 g/dL
• Bleeding requiring transfusion of blood product</td></tr>
<tr><td>Exclusion Criteria</td><td>See Appendix C</td></tr>
<tr><td>Outcomes</td><td>Co-Primary Outcomes
• Hemostatic efficacy over 24 hours
• Effective (excellent or good), or poor
• Rapid INR reduction (INR ≤ 1.3) at 30 minutes after infusion</td></tr>
<tr><td>Hemostatic Efficacy (4FPCC group)</td><td><table><tr><th>Primary rating</th><th>4FPCC (overall)*</th><th>25 IU FIX/kg</th><th>35 IU FIX/kg</th><th>50 IU FIX/kg</th></tr><tr><td>Excellent, n (%)</td><td>44 (44.9)</td><td>NR</td><td>NR</td><td>NR</td></tr><tr><td>Good, n (%)</td><td>27 (27.6)</td><td>NR</td><td>NR</td><td>NR</td></tr><tr><td>Effective, n (%)</td><td>71 (72.45)</td><td>36 (74.5)</td><td>16 (72.75)</td><td>18 (69.2)</td></tr></table>*Median FIX dose of 2475 IU; NR = not reported</td></tr>
<tr><td>Rapid INR Reduction</td><td>• 61/98 (62.2%) of patients overall reached an INR ≤ 1.3 at 30 minutes post infusion*
*Median FIX dose of 2475 IU</td></tr>
<tr><td>Thromboembolic Events</td><td>• 8 thromboembolic events were reported
• 4/8 (50%) thromboembolic events determined to be related to 4FPCC</td></tr>
</table>

Junagade P, Grace R, Gover P. Fixed dose prothrombin complex concentrate for the reversal of oral anticoagulation therapy. Hematology. 2007;12(5):439-40.[24]	
Overview	
Objective	Safety and efficacy assessment of a variable-fixed dose 4FPCC strategy
Trial design	Single arm, retrospective audit
Type of PCC used	4FPCC (Beriplex®)
Patients	21 patients receiving treatment identified during hospital audit
Outcomes	Clinical response and post-treatment INR < 2.0
Interventions	500, 1000, or 1500 IU FIX of Beriplex®
Statistics	Not provided

Results	

Baseline Characteristics	• INR > 2.0 for all patients (range 2.0 – 20)
	• 10/21 with life-threatening bleed (ICH, hematemesis, melena, hemoptysis, or rectal bleeding)
	  • 4/10 (40%) received 500 IU of FIX
	  • 6/10 (60%) received 1000 IU of FIX
	• Four patients presented with INR > 20
	• Overall, 18/21 (86%) received 500 – 1000 IU of FIX; 3/21 (14%) received 1500 IU of FIX

Primary Outcomes	• INR < 2.0 in 88% of cases at median of 2.5 hours post-infusion (range 1 – 17 hr) • All patients with life-threatening bleed (n = 10) had a clinical response and INR < 2.0 • None of the patients experienced a thromboembolic event
Conclusions	
Author's Conclusion	Due to the relatively small number of patients included in the analysis, no firm recommendations can be made about fixed dosing without further randomized clinical trials
Strengths	• Used Beriplex® as study medication; considered therapeutically equivalent to Kcentra® • Included patients with life-threatening hemorrhage, including ICH
Limitations	• Small sample size (n=21) • No comparator group • Patients with life-threatening hemorrhage not stratified by hemorrhage type • Use of vitamin K, FFP, or other blood products not reported • Statistical analysis information not provided
Take Home Points	• Small, retrospective audit with many limitations • Hypothesis generating

Khorsand N, Veeger NJ, Muller M, et al. Fixed versus variable dose of prothrombin complex concentrate for counteracting vitamin K antagonist therapy. Transfus Med. 2011;21(2):116-23[21]	
Overview	
Objective	Investigation of efficacy and feasibility of a fixed dosed strategy compared to a variable dosing regimen
Trial design	Observational cohort pilot study
Type of PCC used	4FPCC (Cofact®)
Patients	<u>Inclusion Criteria</u> • Reversal of VKA treatment indicated for major or clinically relevant non-cranial bleeding or for an emergency invasive procedure • Any obvious bleed accompanied by a systolic blood pressure <90 mm Hg, or Hgb <65 g/L or a Hgb decrease of >20 g/L in 24 h, or transfusion requirements ≥2 units of red blood cells, or retro-peritoneal bleeding, or intra-ocular bleeding, or/and bleeding that requires an invasive procedure to stop the bleeding • Indication for PCC and target INR was left to the discretion of the physician

<table>
<tr><td>Outcomes</td><td><u>Primary outcome</u>
Proportion of patients that achieved target INR within 20 minutes after PCC infusion
Major bleeds: target INR <1.5
Invasive procedures using epidural anesthesia: target INR <1.8
All other bleeds and invasive procedures: target INR < 2.0</td><td><u>Secondary Outcome</u>
Proportion of patients who reached their target INR in each target INR category
Number of patients in cohort 1 needing an extra PCC infusion after the initial fixed dose
Proportion of patients with successful clinical outcome as judged by the attending physician
Visual bleeding had stopped, and/or Hgb decrease stopped, and/or blood pressure normalized and/or there was no need for further transfusion.</td></tr>
<tr><td>Interventions</td><td colspan="2">Fixed dose patients were compared to a historical, variable dose patient cohort after their institution adopted a fixed dose regimen
All patients received 10 mg IV vitamin K
<u>Cohort 1-Fixed Dose</u>
1040 IU of FIX for major bleeding
530 IU FIX for an emergency invasive procedure
<u>Cohort 2-Variable Dose</u>
Dose based on presenting INR, target INR and body weight
Refer to Appendix D</td></tr>
<tr><td>Statistics</td><td colspan="2">Differences between cohorts were evaluated using the Student t -test or Mann–Whitney U-test for continuous data
Fisher’s exact test for categorical data
P value <0.05 (two sided) was used to indicate statistical significance</td></tr>
<tr><td colspan="3">Results</td></tr>
<tr><td>Baseline Characteristics</td><td colspan="2">No statistically significant differences in baseline characteristics between cohorts
<table>
<tr><th></th><th>Fixed Dose (n = 35)</th><th>Variable Dose (n = 32)</th></tr>
<tr><td>Age in years, median (range)</td><td>76 (28 – 93)</td><td>74 (43 – 93)</td></tr>
<tr><td>Male n (%)</td><td>16 (46)</td><td>18 (56)</td></tr>
<tr><td>Indication for PCC, n (%)
Major non-cranial bleeding
Invasive procedure</td><td>
18 (51)
7 (49)</td><td>
19 (59)
13 (18.8)</td></tr>
<tr><td>Baseline INR, median (range)
Baseline INR > 5, n (%)</td><td>4.7 (2.0 to > 9.0)
17 (49)</td><td>4.7 (1.8 to > 9.0)
15 (4)</td></tr>
<tr><td>ICU admissions, n (%)</td><td>4 (11.4)</td><td>7 (21.9)</td></tr>
</table></td></tr>
</table>

<table>
<tr><td>Outcomes</td><td>
<table>
<tr><th></th><th>Fixed Dose (n = 35)</th><th>Variable Dose (n = 32)</th><th>p value</th></tr>
<tr><td>PCC dose, median IU FIX (range)</td><td>1040 (260 – 1820)</td><td>1560 (260 – 5200)</td><td>< 0.0001</td></tr>
<tr><td>Target INR reached, n/total (%)
INR target < 1.5
INR target < 1.8
INR target < 2</td><td>21/30 (70)
5/7 (71)
3/3 (100)
13/20 (65)</td><td>22/27 (81)
4/5 (80)
3/4 (75)
15/18 (83)</td><td>0.37</td></tr>
<tr><td>Successful clinical outcome, n/total (%)</td><td>32/35 (91)</td><td>30/32 (94)</td><td>1.0</td></tr>
<tr><td>Mortality rate, n (%)</td><td>6 (17)</td><td>10 (31)</td><td>0.25</td></tr>
</table>
<u>PCC dose in Cohort 1</u>
• 10/35 (28.8%) received a fixed dose of 520 IU FIX
• 22/35 (62.8%) received a fixed dose of 1040 IU FIX; one patient received and additional dose of 520 IU FIX
• Two patients were unexpectedly treated with 260 IU and 1820 IU FIX

<u>Thromboembolic events</u>
• Fixed Dose: one patient developed a MI 10 days after PCC infusion
• Variable Dose: two patients developed a fatal pulmonary embolism at one and five days after PCC infusion, respectively
</td></tr>
<tr><td colspan="2">Conclusions</td></tr>
<tr><td>Author’s Conclusion</td><td>The relatively low fixed dose regimen demonstrated promising results in regards to successful clinical outcome. However, there was a trend for low INR target attainment in the fixed dose group.</td></tr>
<tr><td>Strengths</td><td>• Used a 4FPCC (Cofact®)
• Assessed clinical outcome as an endpoint
• Observational study design; good representation of clinical practice</td></tr>
<tr><td>Limitations</td><td>• Relatively small sample size
• Patients with intracranial hemorrhage excluded
• Potential for collection bias in the retrospective Cohort 2
• Did not use Beriplex®/KCentra®
• Clinical outcome was assessed by various providers
• Use of FFP or other blood products not reported</td></tr>
<tr><td>Take Home Points</td><td>• Comparable efficacy between fixed and variable dosing
• Median dose in the variable dose cohort was 1560 IU FIX</td></tr>
</table>

Khorsand N, Veeger NJ, van Hest RM, et al. An observational, prospective, two-cohort comparison of a fixed versus variable dosing strategy of prothrombin complex concentrate to counteract vitamin K antagonists in 240 bleeding emergencies. Haematologica 2012; 97:1501-1506.[25]

Overview

Objective	Assessment of non-inferiority of low fixed dose PCC compared to a variable PCC dosing regimen	
Trial Design	Observational, prospective, two-cohort comparison study	
Type of PCC used	Cofact®	
Patients	Inclusion Criteria • Major or clinically relevant, non-intracranial hemorrhage	Exclusion Criteria • ICH • Urgent invasive procedure • Patients not taking VKA
Outcomes	Primary • Proportion of patients that achieved an INR of < 2.0 at 15 minutes after PCC infusion	Secondary • Successful clinical outcome as determined by attending physician (cessation of visual bleeding, no further decrease in Hgb, normalized blood pressure, and no further PCC or blood products given)
Interventions	• Fixed dose: 1040 IU • Variable dose: based on body weight, presenting INR, and target INR • Both groups received 10 mg of intravenous vitamin K	
Statistics	• Non-inferiority of fixed dose regimen hypothesized with a margin of 4% for primary outcome • Student's t-test or Mann-Whitney test for continuous data • Fischer's exact test for categorical data	

Results

Baseline Characteristics

	Fixed dose (n=101)	Variable dose (n=139)	*P* value
Male, N (%)	50 (50%)	71 (51%)	0.90
Age (yr), median (range)	77 (37-95)	79 (23-98)	0.18
Weight (kg), median (range)	72 (36-136)	75 (23-98)	0.80
Baseline INR, median (range) - baseline INR > 7.6, N (%)	5.1 (1.54->7.6) 35 (35%)	5.9 (1.8->7.6) 49 (35%)	1
ICU admission at entry, N (%)	12 (12%)	12 (9%)	0.51
Indication for PCC treatment, N (%) GI bleed Muscle bleed Intraperitoneal or abdominal bleed Hemoptysis Other	 58 (57%) 9 (9%) 10 (10%) 4 (4%) 20 (20%)	 79 (57%) 17 (12%) 8 (6%) 5 (4%) 30 (22%)	0.73

Outcomes		**Fixed dose* (n = 101)**	**Variable dose (n = 139)**	
	Target INR reached, %	91.7	94.7	-2.99% (90% CI; -8.6 to 2.7)
	Successful clinical outcome, %	96	86	8.27% (90% CI; 2.7 – 13.9)
	PCC dose in IU FIX/patient, median (range)	1040 (260 – 1560)	1560 (520 – 3120)	$p < 0.001$
	INR after PCC treatment, median	1.48	1.40	$p = 0.018$
	Time to infusion in minutes, median	130	160	$p = 0.015$
Conclusions				
Author's Conclusion	• Fixed dose PCC is non-inferior to a variable dosing strategy with regard to successful clinical outcome • Treat all patents with clinically major or clinically relevant VKA-associated non-intracranial bleeds with low fixed dose PCC • Fixed dose regimen reduces time to treatment			
Strengths	• Prospective study with a comparator group • Utilized a clinical outcome to analyze efficacy			
Limitations	• Observed a 32% non-adherence rate in the fixed dose group • Did not include patients with ICH			
Take Home Points	• Non- inferior in reaching INR target (INR < 2) • Non-inferior in successful clinical outcome • *Post hoc* analysis showed that low fixed dose was non-inferior when presenting INR was < 7.5 • Shorter time to infusion with low fixed dose PCC			

Klein L, et al, Evaluation of fixed dose 4-factor prothrombin complex concentrate for emergent warfarin reversal, Am J Emerg Med (2015), http://dx.doi.org/10.1016/j.ajem.2015.05.017[26]		
Overview		
Objective	Evaluation of efficacy, safety, and cost of fixed dose protocol	
Trial Design	Retrospective cohort study of patients from March 2014 to January 2015	
Type of PCC used	4FPCC (Kcentra®)	
Patients	Inclusion Criteria • All patients that received 1500 IU of 4FPCC per hospital protocol for any clinical indication for emergent VKA reversal • Patients that were on chronic VKA therapy	Exclusion Criteria • No available post-4FPCC value • Acute VKA overdose • Patients younger than 18 years old

<table>
<tr><td>Outcomes</td><td><u>Primary</u>
• Successful INR reversal (post-INR < 2.0 and post-INR < 1.5)</td><td><u>Secondary</u>
• Thrombotic events within 7 days (DVT, PE, ACS, limb ischemia secondary to venous or arterial process, and non-hemorrhagic stroke or TIA)
• Cost data incurred by the hospitalized patient</td></tr>
<tr><td>Interventions</td><td colspan="2">1500 IU of Kcentra® (or closest to 1500 IU based on vial size) administered prior to presenting INR values were available</td></tr>
<tr><td>Statistics</td><td colspan="2">• Descriptive statistics to report demographic data
• Wilcoxon signed rank test for comparison of presenting INR and post-INR median values
• Mann-Whitney U test and Fisher exact test for comparison of post-INR values less than 1.5 or greater than 1.5</td></tr>
<tr><td colspan="3">Results</td></tr>
<tr><td>Baseline Characteristics</td><td colspan="2">• 39 total patients included; 2 patients not included due to missing post-INR data
• Age (yr): 70 (60-78)
• Weight (kg): 79.5 (72.1-95.3)
<table>
<tr><td>Chronic anticoagulant</td><td>• Warfarin: 38 (97.4%, 92.4- 100)
• Rivaroxaban: 1 (2.6%, 0-7.6)</td></tr>
<tr><td>Location of administration</td><td>• Emergency department: 29 (74.4%, 60.7-88.1)
• Intensive care unit: 6 (15.4%, 4.1-26.7)
• General floor: 3 (7.7%, 0-16)
• Operating room: 1 (2.6%, 0-7.6)</td></tr>
<tr><td>Indication for treatment</td><td>• Intracranial hemorrhage: 28 (71.8%, 57.5-85.9)
• Gastrointestinal hemorrhage: 4 (10.3%, 0.8-19.8)
• Ruptured abdominal aortic aneurysm: 1 (2.6%, 0-7.6)
• Intrathoracic hemorrhage: 2 (5.1%, 0-12.0)
• Spinal cord hemorrhage: 1 (2.6%, 0-7.6)
• Neck hematoma: 1 (2.6%, 0-7.6)
• Other emergent surgical indication: 2 (5.1%, 0-12.0)</td></tr>
</table></td></tr>
<tr><td>4FPCC Administration Data

* P < 0.001</td><td colspan="2">• 4FPCC dose administered: 1659 IU FIX (range, 1569 – 1710)
• IU FIX/kg administered: 20.4 (17.3 – 22.6)

<u>Other reversal agents</u>
• Vitamin K: 36 (92.3%, 83.9-100)
• FFP: 11 (28.2%, 14.0-42.3)

<u>INR values</u>
• Presenting INR: 3.3 (2.5-4.0)*
• After single dose 1500 IU: 1.4 (1.2-1.6)*
• Percent decrease in INR: 56.7% (41.7-70)
• Time to post-administration INR (min): 51 (27-75)</td></tr>
</table>

Primary Outcomes	Successful INR reversal with single dose 1500 IU administration • < 2.0 INR target: 36 (92.3%, 83.9-100) • ≤ 1.5 INR target: 28 (71.8%, 57.7-85.9) • One patient required a second dose of 4FPCC for reversal	
Secondary Outcomes	Safety • No thromboembolic events within 7 days • 30 patients (76.9%, 63.7-90.1) alive to hospital discharge	Cost analysis • Fixed dose cost: $2264 per patient (range, $2118-2988), plus $757 a single for additional dose • Total cost: $90,017 over the study period • Difference of $40,273 when compared to package insert dosing
Conclusions		
Author's Conclusion	• 1500 IU of 4FPCC demonstrated good efficacy and safety when used for emergent warfarin reversal	
Strengths	• Provided explanations for treatment failures • Did not exclude patients with intracranial hemorrhage	
Limitations	• Relatively small sample size • Did not use a control arm for comparison • Included patients that also received FFP (n = 11) • Four patients with presenting INR < 2 were included in the analysis	
Take Home Points	• Analysis of hospital P&T-approved protocol • Pre-treatment INR was not needed prior to 4FPCC infusion • Cost avoidance of ~$40,000 over the study period	

VII. Summary of evidence

A. Variety of study methods used to examine the role of fixed dose 4FPCC
   i. Limited number of studies directly comparing efficacy and safety of fixed dose 4FPCC compared to variable dosing
   ii. Few studies specifically evaluating Beriplex®/Kcentra®

B. Patients studied
   i. Clinical trials for approval have extensive exclusion criteria
   ii. A number of fixed dose studies have had limited exclusion criteria and may provide better external validity

C. Efficacy outcomes
   i. Fixed dose studies have demonstrated similar efficacy to variable dosing
   ii. Fixed dose strategies have shown at least as effective reversal and clinical outcome to clinical trials use for FDA approval of Kcentra®

D. Safety outcomes
   i. Clinical trial and meta-analysis data have demonstrated a low but significant risk for thromboembolic events
   ii. Fixed dosing strategies have shown similar or less frequent rates of thromboembolic events

E. Limitations of current data

i. Time from hemorrhage to infusion of 4FPCC
    a. Faster time to 4FPCC infusion may improve clinical outcomes
        1. Further studies needed to adequately assess impact
ii. Thromboembolic events
    a. Difficult to assess relationship due to comorbid conditions that place patients at risk for thromboembolic events
    b. Patients with previous history of thromboembolic events have often been excluded from clinical trials

VIII. Conclusion

A. The use of a fixed dose (~1500 IU FIX) of 4FPCC is a practical option for emergent reversal of VKA
    i. Similar safety and efficacy to higher doses based on package insert recommended dosing
        a. Body weight and INR based
        b. Package insert and guideline recommended dosing regimens
    ii. Reduction in time to infusion and VKA reversal
    iii. Potential for significant cost avoidance

IX. Recommendations

A. 1500 IU FIX of 4FPCC (Kcentra®) should be considered for patients requiring emergent VKA reversal
    i. Criteria for use
        a. Patients presenting with major bleed or need for emergent operative intervention
        b. Recent history of chronic VKA use
    ii. Obtain pre-treatment INR
    iii. Administer ~1500 IU FIX; do not need to wait for pre-treatment INR result
        a. One ~500 IU FIX vial and one ~1000 IU FIX vial
    iv. Administer 10 mg IV vitamin K
    v. Recheck INR 15 to 30 minutes after 4FPCC infusion

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X. Appendices

Appendix A. Kcentra® Boxed Warning[17]

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.**

Appendix B. Studies and Clinical Trials Supporting the Clinical Efficacy of 4FPCC (Kcentra®/Beriplex®)

Study (year)	Trial design and	Patient population	Intervention		Patients receiving 4FPCC (n)	Pretreatment INR, median (range)	INR correction < 1.3 (%)
Evans, et al.	Non-randomized study	INR > 8 and major bleeding	30 IU/kg of 4FPCC and 5 mg IV vitamin K		n = 10	> 20 (15.8 to > 20)	100 30 min after start of infusion
Preston, et al.	Non-randomized study	Bleeding or requiring major surgery	4FPCC and 2 – 5 mg IV vitamin K		n = 42	3.98 (2 -27.6)	70 20 min after start of infusion
Pabinger, et al.	Phase III, single-arm, uncontrolled multicenter study	VKA reversal to control bleeding or prior to emergency surgery	4FPCC and most patients received IV vitamin K		n = 43	3.3 (2 to > 17)	93 30 min after the start of infusion
Sarode, et al.	Phase IIIb RCT comparing 4FPCC versus plasma	VKA reversal to control major bleeding	Presenting INR 2 – 4 4 – 6 > 6	4FPCC dose 10 ml/kg 12 ml/kg 15 ml/kg	n = 98	3.9 (1.8 – 20)	62 30 min after the start of infusion
Refaai, et al.	Phase IIIb RCT comparing 4FPCC versus plasma	VKA reversal for patients requiring emergency surgery of invasive procedure	Presenting INR 2 – 4 4 – 6 > 6	4FPCC dose 10 ml/kg 12 ml/kg 15 ml/kg	n = 87	2.9 (2.0 – 17.0)	55.2 30 min after the start of infusion

Appendix C. Exclusion Criteria from Kcentra® Approval Study[23]

• Expected survival of <3 d or expected surgery in <1 d • Acute trauma for which reversal of vitamin K antagonists alone would not be expected to control or resolve the acute bleeding event • Use of unfractionated or low-molecular-weight heparin <24 h before enrollment or expected need <24 h after start of infusion† • History of thrombotic event, myocardial infarction, disseminated intravascular coagulation, cerebral vascular accident, transient ischemic attack, unstable angina pectoris, severe peripheral vascular disease at ≤3 mo of enrollment • Known history of antiphospholipid antibody syndrome • Suspected/confirmed sepsis at enrollment • Large blood vessel rupture (eg, aortic dissection or ruptured aortic aneurysm) • Preexisting progressive fatal disease with a life expectancy of <2 mo	• Known inhibitors to factors II, VII, IX, or X; or hereditary protein C or S deficiency; or heparin-induced, type II thrombocytopenia • Treatment with any other investigational medicinal product ≤30 d before study • Presence or history of hypersensitivity to components of the study medication • Patients with intracranial hemorrhage: o Glasgow Coma Scale score <7 o Intracerebral hematoma volume >30 cm3 (assessed by ABC/2 formula) o For subdural hematomas: maximum thickness ≥10 mm, midline shift ≥5 mm o For subarachnoid hemorrhage: any evidence of hydrocephalus o Infratentorial intracranial hemorrhage location o Epidural hematomas o Intraventricular extension of hemorrhage o Modified Rankin Scale score >3 before intracranial hemorrhage

Appendix D. PCC Variable Dosing Regimen (Cohort 2) for Khorsand, et al. Pilot Study[21]

Initial INR →		7·5	5·9	4·8	4·2	3·6	3·3	3·0	2·8	2·6	2·5	2·3	2·2
	↓ Body weight (kg)												
Target	50	1040	1040	1040	780	780	780	520	520	X	X	X	X
INR	60	1300	1300	1040	1040	780	780	780	520	X	X	X	X
≤2·1	70	1560	1300	1300	1300	1040	1040	780	780	X	X	X	X
	80	1560	1560	1560	1300	1300	1040	1040	780	X	X	X	X
	90	1560	1560	1560	1560	1300	1300	1040	780	X	X	X	X
	100	1560	1560	1560	1560	1560	1300	1040	1040	X	X	X	X
Target	50	1560	1560	1560	1300	1300	1300	1040	1040	780	780	780	780
INR	60	2080	1820	1820	1560	1560	1560	1300	1300	1040	1040	1040	780
≤1·5	70	2340	2080	2080	1820	1820	1820	1560	1560	1300	1040	1040	1040
	80	2600	2600	2340	2340	2340	2080	2080	1820	1560	1300	1300	1040
	90	2600	2600	2600	2340	2340	2340	2080	2080	1820	1560	1300	1040
	100	2600	2600	2600	2600	2600	2340	2340	2080	1820	1820	1560	1300

The dosage is shown as International Units of Factor IX, based on a Cofact® batch with 26 IU of F IX mL^{-1} as used for this study. This table is based on manufacturer's algorithm (Sanquin, Amsterdam, The Netherlands) (van Aart *et al.*, 2006).