

# Optimal Dosage and Administration Practices for Vitamin K Antagonist Reversal With 4-Factor Prothrombin Complex Concentrate

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## Abstract

Expert consensus and international guidelines recommend urgent co-administration of vitamin K and 4-factor prothrombin complex concentrates (4F-PCCs) to rapidly reverse VKA-related bleeding. This narrative review examined real-world evidence and strategies to optimize international normalized ratio (INR) reversal, hemostasis, and outcomes in patients receiving 4F-PCC in this setting. Key determinants for success include the appropriate use of alternative dosing and administration strategies, such as fixed dosing and increased infusion speed, adherence to institutional guidelines, and removing significant institutional barriers to reduce time to treatment. In the opinion of authors, minimizing the time to treatment with 4F-PCCs is of paramount importance when treating patients with VKA-related bleeding. Practices that safely and feasibly shorten the time to administration should be included in guidelines for institutions responsible for anticoagulant care, and adhered to in centers that perform invasive procedures on patients receiving VKA therapy. Further studies are required to optimize use of 4F-PCC, particularly in relation to the ideal dosing strategy and the role of INR.

## Keywords

hemorrhage, warfarin, anticoagulants, prothrombin complex concentrates

## Introduction

Vitamin K antagonists (VKAs), such as warfarin, are prescribed for prevention and treatment of thromboembolic events (TEEs) in many clinical situations; however, VKA treatment is associated with increased bleeding risk.<sup>1</sup> The goal of urgent reversal of VKA-related bleeding is to rapidly increase the concentration of vitamin K-dependent clotting factors (VKDFs) to reverse international normalized ratio (INR).<sup>2</sup> This may be achieved by co-administration of vitamin K with fresh-frozen plasma (FFP) or prothrombin complex concentrates (PCCs) (plasma-derived purified products containing coagulation factors [Factors II, VII, IX, and X], plus anticoagulant proteins C and S, and antithrombin, depending on the product). Clinical differentiators of 4-factor PCCs (4F-PCCs) versus FFP include faster infusion time, less potential for fluid overload, shorter time to administration (no requirement for thawing/blood-type matching),<sup>3</sup> and reduced risks of pathogen transmission and allergic reactions.<sup>2,4,5</sup> In addition, FFP is associated with transfusion-related acute lung injury (TRALI).<sup>1</sup> TRALI is triggered by the presence of anti-leukocyte antibodies and so is

unlikely to occur with 4F-PCCs, as antibodies are removed during the manufacturing process.<sup>6,7</sup> Current European and US guidelines recommend 4F-PCCs over FFP for rapid reversal of VKA-related bleeding,<sup>5,8-13</sup> and advocate that centers responsible for anticoagulant care and performing invasive procedures on VKA-treated patients maintain inventory of a licensed 4F-PCC.<sup>5</sup> Kcentra<sup>®</sup> (CSL Behring GmbH, Marburg, Germany) is currently the only 4F-PCC approved in the US for urgent VKA reversal in patients with major bleeding or who require urgent surgical/invasive procedures.<sup>14</sup>

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**Table 1.** Dosing of Prothrombin Complex Concentrate (Kcentra®)<sup>14</sup>.

Baseline INR	IU of coagulation factor IX (per kg body weight)	Approximate dose (mL per kg body weight)	Maximum recommended dose (IU)
2 to <4	25	1	2500
4 to ≤6	35	1.4	3500
>6	50	2	5000

INR, international normalized ratio; IU, international unit.

Although the efficacy and safety of 4F-PCCs are well established for VKA reversal,<sup>15-19</sup> there is lack of consensus regarding optimal dosing strategies.<sup>20</sup> On-label dosing of Kcentra is a variable-dose regimen based on bodyweight and pre-treatment INR. It is indicated only for baseline INR >2 (Table 1), with pharmacokinetic analysis showing that a 50 IU/kg dose rapidly increases VKDF concentrations from baseline levels.<sup>14</sup> A drawback of variable dosing is potential administration delays while awaiting pre-treatment INR and bodyweight values.<sup>21</sup> Indeed, complete reversal of major bleeding should be achieved within 6–8 hours.<sup>5</sup> Thus, there is a need to investigate alternative dosing strategies for emergency situations. Several studies have investigated fixed dosing<sup>22</sup> and an American College of Cardiology (ACC) Expert Consensus paper supported use of 2 fixed 4F-PCC doses (1000 IU for reversal of major bleeding; 1500 IU for intracranial hemorrhage [ICH]), in addition to supporting standard-of-care variable dosing.<sup>12</sup> However, there are concerns that these protocols may lead to under-dosing, which could result in suboptimal responses.

The methods of assessing the effectiveness and clinical utility of a dosing regimen can vary. Assessment of clinical hemostasis attainment and clinical outcomes is most commonly employed, although coagulation testing (particularly the proportion of patients achieving a target INR in a given time) may also be used, together with occurrence of adverse events (thromboembolic or otherwise) and cost.

This narrative review examined real-world strategies to optimize INR reversal, hemostasis, and outcomes in patients receiving 4F-PCC for reversal of VKA-related bleeding, focusing on alternative dosing strategies, infusion speed and overcoming institutional barriers to effective, timely reversal of VKA-related bleeding in clinical practice.

## Methods

This publication is not intended as a systematic review. A PubMed search was conducted to identify publications on PCC administration practices and reversal of VKA-related bleeding, published between January 1, 2013 and December 31, 2019. Search terms are provided in Table 2. The results were filtered for English language papers, and screened for relevance to the administration of 4F-PCC in emergency VKA reversal settings (excluding those that use only on-label variable dosing strategies, where dosing strategy is not specified, or involve direct

**Table 2.** Search Parameters for Literature Review.

Search parameters
Date - Publication: 2013/01/01 and 2019/12/31
Kcentra (OR Beriplex OR Confidex) AND administration; Kcentra (OR Beriplex OR Confidex) AND dose; prothrombin complex concentrate* AND dosing; prothrombin complex concentrate* AND dose; prothrombin complex concentrate* AND administration; prothrombin complex concentrate* AND rural OR remote

oral anticoagulation therapy rather than VKAs). Preclinical studies and reviews were excluded. Abstracts from congresses meeting relevance criteria were also included. In total, 54 relevant publications were included.

## Results

### Alternative Dosing Strategies

Studies providing information on all alternative dosing strategies (including fixed dosing, use of low variable doses [ $\leq 25$  IU/kg], repeat dosing and non-INR-based approaches) are described in Table 3.

**Fixed dosing.** Although the approved on-label dosing of 4F-PCCs is a variable regimen dependent on baseline INR and bodyweight, a number of studies have investigated fixed doses for urgent reversal of VKA-related bleeding. The minimum effective and maximum tolerable doses have also been considered. A retrospective study of 103 patients requiring anticoagulation reversal (VKA-related bleeding or prior to an invasive procedure) assessed efficacy of fixed-dosing of 1000 IU 4F-PCC by clinical hemostasis, as well as INR reversal. Excellent clinical response (control of bleeding without requiring additional measures) was seen in 84% of patients. The authors concluded that 1000 IU fixed-dosing appeared effective and well tolerated.<sup>25</sup> Results from another retrospective review of 39 patients<sup>23</sup> concluded that a single, fixed dose of 1500 IU 4F-PCC effectively reduced median INR in 92% of patients with VKA-related bleeding, with no associated TEEs within 7 days. A single, fixed dose of 1500 IU 4F-PCC was also shown to reduce median INR in 100% of patients with VKA-related bleeding or undergoing urgent surgery (n = 37) in another retrospective chart review.<sup>24</sup> In addition, there were no early or late thrombotic complications, or immediate redosing requirements, though 1 patient required a repeat 4F-PCC dose 2 days after the initial dose.<sup>24</sup> While the latter 2 studies support fixed dosing, neither included endpoints for clinical outcomes (e.g. bleeding cessation).

A recent study evaluated the frequency with which an initial fixed 4F-PCC dose of 1500 IU was insufficient to achieve an indication-specific INR ( $\leq 1.4$  for central nervous system [CNS] bleeds and  $< 2$  for all other indications) in patients requiring warfarin reversal.<sup>26</sup> Overall, only 11/63 patients (17%; including 8 patients with CNS bleeds) were eligible to receive a supplemental dose based on failure to achieve their

**Table 3.** Literature Review: Alternative Dosing Strategy Study Information.

Author and year	Study design	N <sup>a</sup>	Reason for reversal	4F-PCC dose	Baseline INR	INR outcomes	Other outcomes
<b>Fixed dosing</b>							
Klein L, et al. 2015 <sup>23</sup>	Retrospective review; single center; March 2014–January 2015	39	Acute bleeding, n = 37 (ICH, 71.8%); surgery, n = 2	1500 IU fixed (median dose 1659 IU; range 1569–1710)	Median 3.3 (range 2.5–4.0)	Median INR after a single dose: 1.4 (range 1.2–1.6). INR reversal to <2 in 92% of patients (median time to post-administration INR measurement: 51 min [range 27–75])	No related thromboembolic adverse events within 7 days
Astrup G, et al. 2018 <sup>24</sup>	Retrospective chart review; single center; 8-month period	37	Acute bleeding, n = 29 (ICH, 45.9%); surgery, n = 7	1500 IU fixed (Average dose 1601 IU; range 1491–1691)	Median 3.1 (range 1.2–>16)	Median INR post 4F-PCC: 1.3 (range 1.2–1.5). INR reversal to <2 in 100% of patients, and <1.5 in 74% of patients (median time to post-administration INR measurement: 65 min [range 50–88])	No early or late thrombotic complications
Varga C, et al. 2013 <sup>25</sup>	Retrospective chart review; single center 1 January 2009–31 October 2009	103	Acute bleeding, n = 76; surgery, n = 27	1000 IU fixed (low dose)	Median 2.8 (range 1.4–24)	The post treatment median INR was 1.4 (IQR, 1.2–1.6). INR <2 reached in 92% of patients; INR ≤1.5 reached in 49% of patients (average time to post-administration INR measurement: 110 min)	84% of patients were deemed to have an “excellent clinical response” (bleeding controlled without additional measures). 4F-PCC was well tolerated; however, 5 (5%) thrombotic events were reported
Fuh L, et al. 2019 <sup>26</sup>	Retrospective study; single center; 1 March 2018–28 February 2019	63	CNS bleed, n = 48; other bleed, n = 9; urgent procedure, n = 6.	1500 IU fixed (low dose)	Median 2.6	Median INR post-treatment: 1.4	No TEE data reported; mortality rate 30%
Abdoellakhan RA, et al. 2017 <sup>27</sup>	Retrospective study; single center; 1 January 2013–1 August 2014 (excluding November 2013)	53 (28 fixed; 25 variable)	ICH	1000 IU fixed; or variable based on body weight, initial INR and target INR (median 1750 IU; range 1000–2500)	Median 3.3 (range 1.7–9), fixed dose group; median 3.1 (range 1.8–9), variable dose group	INR reversal to ≤1.5 in 68% of fixed-dose group, and in 96% of variable-dose group after the initial dose (p = 0.013)	32% of fixed-dose patients, and 8% of variable-dose patients, required re-dosing (p = 0.043). No difference in mortality rate or duration of hospital stage between groups. TEEs reported in 8.3% of variable dose patients vs 0% of fixed dose patients. No difference between groups in door-to-order or door-to-needle time (fixed dose, 60 minutes; variable dose, 81 minutes; p = 0.420)

(continued)

Table 3. (continued)

Author and year	Study design	N <sup>o</sup>	Reason for reversal	4F-PCC dose	Baseline INR	INR outcomes	Other outcomes
Khorsand N, et al. 2012 <sup>28</sup>	Observational prospective study; 2 centers November 2007–July 2010	240 (101 fixed; 139 variable)	Major or clinically relevant, non-intracranial bleeding	1040 IU fixed (low dose); or variable based on body weight, baseline INR and target INR (median 1560 IU; range 520–3120)	Median 5.1 (range 1.5–<7.6), fixed-dose group; median 5.9 (range 1.8–>7.6), variable-dose group	Median post-dose INR 1.5 (range 1–2.9) in the fixed-dose group, and 1.4 (range 0.9–3.4) in the variable-dose group (p = 0.018). INR <2 reached in 92% of fixed-dose patients, and in 95% of variable-dose patients (post-administration INR measurement: 15 min)	3% of patients in each group required a second dose; fixed dose was non-inferior to variable dose for attaining successful clinical outcomes (fixed, 96% of patients; variable, 88%; p < 0.001). Overall occurrence of thrombotic complications 1.3%. Door-to-needle time was shortened by a median of 30 minutes in the fixed dose group
Scott R, et al. 2018 <sup>29</sup>	Retrospective cohort study; single center; January 2014–January 2017	61 (31 weight-based; 30 fixed)	ICH	1000 IU fixed (mean 1045 IU); or weight-based (mean 2120 IU)	Weight-based, mean 3.0; fixed, mean 2.8	INR <1.5 reached in 76% and 53% of patients in the weight-based and fixed groups (p = 0.15)	No difference in need for repeat doses or mortality rates between the 2 groups; TEEs not reported
Bitonti MT, et al. 2019 <sup>30</sup>	Multicenter noninferiority interventional cohort study	54 (30 retrospective [variable], 24 prospective [fixed])	Severe bleeding or need for invasive surgery/procedure	Variable dose (weight and INR-based; according to manufacturer) Fixed dose: 1500 IU in general, or 2000 IU for patients weighing > 100 kg or with INR >7.5 (if weight/INR information already available)	Variable dose: mean 3.8 Fixed dose: mean 4.6	Mean post-infusion INR: Variable dose: 1.3 Fixed dose: 1.4	No TEEs by 7 days in either cohort
Gilbert BW, et al. 2019 <sup>31</sup>	Retrospective cohort study	60 (30 per variable dose cohort and 30 per fixed dose cohort)	Acute major bleeding reversal	Variable dose: weight and INR-based; according to manufacturer Fixed dose: 1500 IU for ICH and 1000 IU for other bleed types; option to add 500 IU for patients with INR > 10 or body weight > 100 kg	Variable dose: median 3.3 Fixed dose: median 3.0	Median post-infusion INR: Variable dose: 1.3 Fixed dose: 1.4	No significant difference between cohorts in terms of incidence of thrombotic events by 7 days
Use of doses ≤50 IU/kg							
Butler JJ, 2015 <sup>32</sup>	Single-case study	1	Lumbar puncture	1020 IU	1.7	INR reversal to 1.3, 30 minutes after 4F-PCC administration	TEEs not reported
Zemrak WR, et al. 2017 <sup>33</sup>	Retrospective review; single center	21	ICH	15 IU/kg (median 1064 IU; range 1000–1114)	Median 1.8 (range 1.7–1.9)	Median post-dose INR: 1.3 (range 1.2–1.3). INR ≤1.5 achieved in 95% of patients at 1-hour post-dose	No patients experienced hematoma expansion within 48 h of 4F-PCC administration. No early (<72 hours) thrombotic events reported
Rivosecchi RM, et al. 2016 <sup>34</sup>	Retrospective observational study; single center; September 2013–July 2015	131 (INR <2, 30; INR 2–3.9, 101)	ICH	25 IU/kg	Range 1.4–1.9; Mean 1.8	INR reversal to ≤1.5 in 87% and to ≤1.3 in 79% of patients in INR <2 group (average time to post-administration INR measurement: 162 min [range 91–408])	Thrombotic complications were similar between patients in the INR <2 and INR 2–3.9 groups

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**Table 3. (continued)**

Author and year	Study design	N <sup>a</sup>	Reason for reversal	4F-PCC dose	Baseline INR	INR outcomes	Other outcomes
Zemrak W, et al. 2019 <sup>35</sup>	Retrospective cohort study; November 2013–January 2017	205 (122 manufacturer-recommended dose group; 83 in the low-dose group)	CNS bleed, n = 121; non-CNS bleed, n = 49; surgery, n = 35	Low-dose: 15 IU/kg (mean 1530 IU); standard dose: 25 IU/kg (mean 2132 U)	Standard dose group median INR 2.8 (IQR 2.3–4); low-dose group median INR 2.6 (IQR 2.2–4.1)	Median post-dose INR 1.3 (IQR 1.2–1.4) in standard dose; median post-dose INR 1.4 (IQR 1.3–1.6) in low-dose group (post-administration INR measurement: approx. 1 hour).	Effective clinical response achieved in 80% of patients in the standard group and 75% in the low-dose group (p = 0.418). Significantly more patients received transfusions of platelets (12.3% vs. 1.2%, p = 0.003) and cryoprecipitate (8.2% vs. 1.2%, p = 0.03) in the standard dose group. No significant difference in incidence of TEEs. More patients in the standard dose group died or were transferred to hospice care (21.3% vs. 9.6%, p = 0.027). TEEs not reported
Wexler AH, et al. 2017 <sup>36, b</sup>	Single-case study	1	GI bleed	3506 IU	16	INR 1.5 within 30 minutes of administration	
Brown CS, et al. 2018 <sup>37</sup>	Case report	2	ICH (patients had left-ventricular assist devices fitted)	~ 15 IU/kg	Case 1, 4.7; Case 2, 3.7	Case 1, INR 2.3 after 42 mins; case 2, INR 1.6 after 60 mins	No thrombotic complications were observed
<b>Repeat dosing</b>							
Gibson G, et al. 2016 <sup>38</sup>	Retrospective review; 2-year period	382 doses, of which 51 were cases of re-dosing (84% received weight-based dosing and 16% received fixed dosing)	Cerebral bleeding	500 IU fixed dose; variable re-dose median 26 IU/kg (IQR 22.6–27.5) Type of PCC not given	Not reported	No difference in INR (absolute or percentage change) between fixed- and variable-dose patients	No difference in hematoma expansion between fixed- and variable-dose patients; TEEs not reported
Malaiyandi DP, et al. 2015 <sup>39</sup>	Retrospective review; single center; November 2013–October 2014	171 overall; 4 received re-dosing	Neurocritically ill	Not given	Not reported	Not reported	No thromboembolic complications within 7 days of the full second dose
<b>Non-INR-based dosing algorithms</b>							
Yohe AS & Livings SE. 2019 <sup>40</sup>	Retrospective single-center review; May 2014–August 2017	114 records	ICH, n = 48; trauma, n = 25; procedure, n = 19; GI bleed, n = 12; genitourinary bleed, n = 2; other, n = 8	Range from <20 IU/kg to ≥40 IU/kg	Median 2.7 (2.3–3.4)	Every 500 IU fIX increase in 4F-PCC dose was associated with a minimal (0.02) increase in INR	0% TEEs at <20 and 30–39.9 IU/kg 8.2% TEEs at 20–29.9 IU/kg 4.3% TEEs at ≥40 IU/kg

(continued)

Table 3. (continued)

Author and year	Study design	N <sup>a</sup>	Reason for reversal	4F-PCC dose	Baseline INR	INR outcomes	Other outcomes
Hirri HM & Green PJ, 2014 <sup>41</sup>	Prospective audit; February–June 2013	67	Acute bleeding or surgery	Cerebral bleeding: 2000 IU; other bleeding: 1500 IU; surgery: 1000 IU (protocol was only followed exactly in 27 [40%] patients)	Not provided	INR corrected to $\leq 1.5$ in 84% of patients	TEEs not reported
Herperts R, et al., 2015 <sup>42</sup>	Observational study	106, with plasma samples from 25 VKA-treated individuals	Surgery, n = 36; Bleeding, n = 70	Variable, INR-based dosing in vivo; TGA ETP-based dosing in vitro		Significant reduction in INR with first bolus of PCC in patients.	In a subgroup requiring a second dose of PCC, TGA-based dosing may be useful
Miller A, et al., 2015 <sup>43</sup>	Retrospective cohort study, January 2010–September 2016	76 (4F-PCC group, n = 38; standard of care group, n = 38)	Acute major bleeding	Dosing based on percentage of available clotting factors at specific INR values (mean 2116 IU)	Not provided	A significantly higher proportion of patients achieved INR $\leq 1.5$ within 6 hours in the 4F-PCC group vs the standard of care group (90% vs 16%, p < 0.001)	Alternative dosing algorithm resulted in use of significantly fewer mean units per patient vs package insert recommendations (2116.1 IU vs 2803.3 IU; p < 0.001). No difference in effective hemostasis, patients requiring >1 dose, length of hospital stay, thrombotic events, or mortality between groups
Smetana KS, et al., 2019 <sup>44</sup>	Retrospective study; January 2012–March 2018	78 (obese patients: BMI $\geq 30$ kg/m <sup>2</sup> )	Warfarin-related major bleeding	Dose according to actual bodyweight (median 2500 IU; IQR 2162.5–3000); adjusted bodyweight (median 2119.5 IU; IQR 1689.8–2730.3)	Adjusted weight group: median INR 3.1 (IQR 2.7–5.1); Actual weight group: median INR 2.8 (IQR 2.2–3.5)	Median post-dose INR was 1.5 (IQR 1.3–1.8) in the adjusted weight group and 1.3 (IQR 1.2–1.5) in the actual weight group (p = 0.005). Achievement of the target INR (<1.4 for ICH; <1.5 for other bleeding) was lower in the adjusted weight group versus actual weight group (36% vs. 68%; p = 0.006)	No differences in mortality or hospital stay between groups; 1 thrombotic event reported in actual group
Infusion speed							
Pabinger I, et al., 2010 <sup>45</sup>	Prospective multinational clinical trial in 15 centers	43	Acute bleeding (n = 23); surgery (n = 26)	25, 35 or 50 IU/kg, depending on baseline INR	Range 1.9–17.4 (<4 in 64% of patients 4–6 in 18% of patients; >6 in 18% of patients)	No difference between infusion speeds ( $\leq 5$ , 5–<10; $\geq 10$ mL/min) in INR attained 30 minutes after PCC infusion	None of the evaluated thrombogenicity markers or pharmacokinetic parameters were affected by infusion speed
Chester K, et al., 2017 <sup>46</sup>	Retrospective review	52 PCC administrations (29 pre- and 23 post-rapid 4F-PCC administration protocol)	Not provided; most were ICH	Not given	Not reported	82% of patients achieved INR <1.4 in the post-cohort (rapid PCC administration) versus 72% of patients in the pre-cohort	No infusion-related adverse events; TEEs not reported
Peyko V, et al., 2019 <sup>47</sup>	Case study	1	Head injury	25 IU/kg (2000 IU), given IO	3.9	Post-dose INR was 1.1 at 90 minutes	TEEs not reported

<sup>a</sup>Number of patients in study, unless stated otherwise.

<sup>b</sup>Case study was not described in the main manuscript as the low dose was administered based on the patient's medical history rather than for correcting a subtherapeutic INR.

<sup>c</sup>Study was not described in the main manuscript due to lack of information on background INR severity.

4F-PCC, 4-factor prothrombin complex concentrate; GI, gastrointestinal; ICH, intracranial hemorrhage; INR, international normalized ratio; IU, international unit; PCC, prothrombin complex concentrate.

INR goal (i.e. 4F-PCC 1500 IU was inadequate). However, the supplemental dose was actually administered in only 2/11 patients, calculated as the remainder of the standard weight- and INR-based dosing (both of these patients had an initial INR >3.5). The authors concluded that a low fixed dose of 1500 IU 4F-PCC was sufficient for achievement of INR goals in the majority of patients.<sup>26</sup>

Additionally, studies have been conducted to compare the use of fixed and variable 4F-PCC dosing. Abdoellakhan et al. conducted a retrospective study comparing 28 patients with VKA-related ICH receiving a fixed dose of 1000 IU 4F-PCC with 25 patients receiving the on-label variable dose based on body weight, initial INR and target INR.<sup>27</sup> In the fixed-dose group, median INR decreased in 68% of patients, versus 96% of patients in the variable-dose group after the initial dose ( $p = 0.013$ ). There was no significant difference in median “door-to-needle” administration interval between dosing groups. It was concluded that 1000 IU was insufficient for reversal of VKA-related ICH.

An observational prospective study over nearly 3 years in 240 patients requiring 4F-PCC for major non-intracranial bleeding demonstrated INR <2 achievement in 92% of patients receiving fixed-dose 1040 IU 4F-PCC versus 95% of patients in the variable-dose group, based on weight and INR.<sup>28</sup> This study failed to demonstrate non-inferiority by the INR outcome. However, a successful clinical outcome (cessation of visual bleeding, no further decrease in hemoglobin, normalized blood pressure, and no further need for PCC or blood transfusion) was judged by the attending physicians in 96% and 88% of the fixed- and variable-dose groups, respectively. The fixed-dose strategy was non-inferior to the variable regimen, in terms of clinical outcome. Notably, the administration interval was shortened in the fixed cohort by a median of 30 minutes.

Another retrospective study, which included 61 patients with VKA-related ICH, found no significant difference in INR reduction or INR target achievement between fixed-dose 1000 IU PCC and on-label 4F-PCC dosing based on bodyweight. INR <1.5 was achieved in 53% (16/30) who received fixed dosing and 71% (22/31) of patients receiving a weight-based 4F-PCC dose ( $p = 0.15$ ).<sup>29</sup> It should be noted that this study had low patient numbers and was underpowered to show a difference between strategies, and also did not investigate hemostatic efficacy. The authors concluded that an optimal dosing strategy for 4F-PCC may involve accounting for both weight and initial INR.

A recent study compared variable-dose 4F-PCC treatment (based on weight and INR) and fixed-dose 4F-PCC treatment (1500 IU, or 2000 IU in specific populations [i.e. patients weighing >100 kg or with a baseline INR >7.5]) respectively. A total of 30 patients were included in the retrospective cohort (variable dose) and 24 in the prospective cohort (fixed dose).<sup>30</sup> Overall, achievement rates for post-infusion INR <2 (primary endpoint) were similar for both cohorts (96.7% for variable dose vs 95.8% for fixed dose;  $p = 0.0035$  for non-inferiority). A greater proportion of patients in the variable dose cohort achieved a post-infusion INR <1.5 compared with the fixed-

dose cohort (90% vs 75%;  $p > 0.45$  for non-inferiority). This observation may be linked to the lower mean baseline INR observed in the variable-dose cohort compared with the fixed-dose cohort (3.8 vs 4.6).<sup>30</sup> Another recent study compared on-label variable-dose 4F-PCC and low fixed-dose approaches (1500 IU for ICH; 1000 IU for other bleed types) in 60 patients requiring acute warfarin reversal (30 per dosing strategy). Target post-infusion INR in this study was <1.6 (primary endpoint). There was no significant difference between treatment groups in number of patients achieving INR <1.6 or <1.4 following 4F-PCC infusion.<sup>31</sup>

**Use of doses  $\leq 50$  IU/kg.** While results from these studies generally support fixed dosing with  $\geq 1000$  IU 4F-PCC if the baseline INR for reversal is >2, few data have been published on 4F-PCC for reversal in patients with baseline INRs <2; there is currently no indicated dose of Kcentra for this particular population.<sup>14</sup> A case study reported that administration of lower than approved weight-based variable-dose 4F-PCC (10 IU/kg; total, 1020 IU) reduced INR to  $\leq 1.5$  within 30 minutes in a patient requiring VKA reversal for a lumbar puncture (although multiple FFP units were initially used to reverse INR from >3 to 1.7).<sup>32</sup> Supporting low variable-dose regimens for patients with low INRs, 15 IU/kg 4F-PCC given to 21 patients with warfarin-associated ICH and baseline INRs ranging from 1.6 to 1.9, reversed INR to  $\leq 1.5$  in 95% of patients, with no hematoma expansion within 48 hours of dosing and no TEEs within 72 hours.<sup>33</sup> In another study in ICH, of 30 patients with low baseline INRs receiving 25 IU/kg 4F-PCC, 87% achieved INR  $\leq 1.5$ .<sup>34</sup> Finally, a retrospective observational study in 205 patients with warfarin-related bleeding found fewer patients met the primary outcome of INR reversal plus effective clinical response in the low variable-dose 4F-PCC group (15 IU/kg; 61.4%) versus the on-label variable-dose 4F-PCC group (25 IU/kg; 75.4%,  $p = 0.033$ ).<sup>35</sup> Baseline INR values were 2.6 in the low variable-dose group and 2.8 in the on-label variable-dose group. This result was primarily driven by the lower number reaching the target INR; there was no difference in rates of effective clinical response and patients in the low variable-dose group had lower mortality. Overall, these studies suggest that low variable-dose 4F-PCC may suffice for urgent reversal of modest INR elevation and management of bleeding.

Additionally, low variable doses of 4F-PCC may be considered in patients at high risk of thrombosis to minimize the risk of TEEs. For example, a case report of a patient at high risk of TEEs who presented with a life-threatening gastrointestinal bleed found that a 35 IU/kg dose of 4F-PCC successfully lowered INR from 16 to 1.5 at 30 minutes post administration.<sup>36</sup> A case report of 2 patients with left-ventricular assist devices who developed warfarin-related ICH reported that  $\sim 15$  IU/kg 4F-PCC successfully reversed INR with no thrombotic complications.<sup>37</sup> Furthermore, in the retrospective observational study described above, no significant difference in TEEs were observed between 25 IU/kg and low variable-dose 4F-PCC (15 IU/kg) with 72 hours (4.1% vs 1.2%;  $p = 0.404$ ).<sup>35</sup> Overall,

given the lack of data, further examination of low variable-dose 4F-PCC strategies is warranted.

**Repeat dosing.** A lack of clinical data on the safety and efficacy of repeat dosing with 4F-PCCs means that labeling advises against re-dosing.<sup>14</sup> However, an international survey of emergent warfarin reversal strategies that included members of the Biomedical Excellence for Safer Transfusion Collaborative, found that most surveyed clinical sites use post-PCC INR values as guidance for 4F-PCC repeat dosing, indicating the real-world practice of re-dosing.<sup>48</sup> In the aforementioned Abdoellakhan et al. study comparing 4F-PCC fixed- versus variable-dosing in patients with VKA-related ICH, repeat dosing was needed in 32% and 8% of fixed- and variable-dose patients, respectively, to achieve  $\text{INR} \leq 1.5$ .<sup>27</sup> In 51 recorded cases of repeat dosing, no difference was observed in INR (absolute or percentage change) or hematoma expansion in patients with cerebral bleeding receiving variable weight-based PCC re-dosing (median 26 IU/kg), or fixed 500 IU re-dosing (type of PCC not reported).<sup>38</sup> Furthermore, TEEs, the main risk associated with re-dosing, were not observed in the 7 days following a full second 4F-PCC dose in 4 neurocritically ill patients identified from a retrospective review of 171 patients receiving 4F-PCC. The authors concluded that 4F-PCC re-dosing might be well tolerated in such patients, although larger prospective studies are needed to support these findings.<sup>39</sup>

**Non-INR-based dosing algorithms.** Pre-treatment INR is widely used to estimate the 4F-PCC dose needed to achieve target INR, either alone or in consideration with bodyweight (Table 1). Apart from fixed dosing, few alternatives to the standard-of-care algorithms for dosing and monitoring anticoagulant therapy have been investigated, despite a 2-year multicenter study in 256 patients concluding that adequate reversal of VKA-related bleeding does not depend on pre-treatment INR.<sup>49</sup> A retrospective review of 114 medical records for patients receiving variable-dose 4F-PCC (dosed based on bodyweight and baseline INR) for reversal of warfarin is also of relevance. A significant linear relationship was observed between 4F-PCC dose and post-dose INR, but bodyweight and baseline INR were not correlated with post-dose INR. These results support alternative 4F-PCC dosing strategies, independent of bodyweight and baseline INR.<sup>40</sup>

Alternative dosing algorithms have been proposed, including regimens based on bodyweight alone, or the indication for administration.<sup>41</sup> Indeed, an audit of warfarin reversal assessing a 3-level dosing protocol (2000 IU for CNS bleeds, 1500 IU for other bleeds and 1000 IU prior to invasive procedures) found the INR was reversed to  $\leq 1.5$  in 84% (56/67) of patients, suggesting a simple protocol can be effective. However, adherence to the protocol was poor, as the medical team did not regularly consult it in emergency situations (the protocol was followed exactly in only 40.2% of patients).<sup>41</sup>

A thrombin generation assay (TGA)-based calculation is an experimental approach to monitoring VKA treatment, bleeding risk, and 4F-PCC reversal of VKA-related bleeding. TGA-

based calculations may be superior to INR-based calculations (based on the linear relationship between hemorrhage-predictive TGA parameters and 4F-PCC dose for the whole therapeutic range versus the exponential relationship demonstrated for INR and dose).<sup>42</sup> TGA-based algorithms cannot, however, replace INR-guided dosing in practice, because calculations based on assays are unsuitable when urgent INR reversal is needed. Although this approach is promising, due to various challenges (including its time-consuming nature and the lack of official standardization or reference values), it requires further study before it can enter routine clinical use.<sup>50</sup>

A hematologist-derived strategy is another algorithm for guiding 4F-PCC dosing, which is based on the percentage of available clotting factors at specific INR values. This strategy was examined in a retrospective cohort study of 76 patients and showed that a higher proportion of patients achieved  $\text{INR} \leq 1.5$  within 6 hours of infusion versus patients treated with an older standard-of-care protocol including products such as FFP, vitamin K and 3F-PCC (90% versus 16%;  $p < 0.001$ ).<sup>43</sup> Patients dosed according to this alternative algorithm also required significantly fewer units of 4F-PCC compared with on-label variable dosing (2116 IU versus 2803 IU;  $p < 0.001$ ). These results suggest this alternative 4F-PCC dosing may be effective for VKA reversal; however, there was no difference between groups in hemostasis restoration, re-dosing, hospital stay duration, or adverse events.

The appropriate dosing strategy for 4F-PCC in obesity has also been questioned. A retrospective study investigated the rate of successful INR reversal in 78 obese patients ( $\text{BMI} \geq 30 \text{ kg/m}^2$ ) experiencing warfarin-related major bleeding when dosed based on adjusted bodyweight compared with actual bodyweight as a cost-saving initiative. Achievement of the target INR was lower in the adjusted weight group versus actual weight group (36% vs 68%;  $p = 0.006$ ), with no differences in mortality or hospital stay, indicating 4F-PCC should be dosed according to the manufacturer's guidelines in obese patients until further data are available.<sup>44</sup>

### Increasing Infusion Speed

Faster infusion speeds are a key advantage of PCCs over FFP for VKA-related bleeding reversal.<sup>3</sup> The maximum recommended 4F-PCC infusion speed is 8.4 mL/min (Kcentra);<sup>14</sup> this cap reflects concerns that more rapid infusion of coagulation factors could trigger TEEs or infusion-related reactions. However, a clinical trial in 43 patients with acute bleeding, or requiring INR reversal for emergency surgical or invasive diagnostic interventions, showed neither an increase in peak levels of thrombogenicity markers, nor greater cumulative elevation, when a median volume of 90 mL 4F-PCC was administered at up to 40 mL/min, versus as low as 2 mL/min.<sup>45</sup> Patients in this study had diverse INRs, age, indications, and BMI, so were representative of patients undergoing reversal of VKA-related bleeding in clinical practice. Infusion speed was not determined by baseline variables, but determined at the investigator's discretion. Ultimately, increasing infusion speed did not affect the INR achieved 30 minutes postinfusion, and the



authors concluded that 4F-PCC could be rapidly infused for effective emergency reversal of VKA-related bleeding.<sup>45</sup> This conclusion is supported by a retrospective study in which rapid intravenous push administration of 4F-PCC (mostly for ICH, maximum infusion speed of approximately 750 IU/15 mL per minute) was well tolerated and effective, although time to administration was longer after implementation of the rapid 4F-PCC administration protocol, possibly due to operational limitations such as additional clarification and approval of orders resulting from the use of 4F-PCC in non-standard locations and off-label indications.<sup>46</sup>

### Alternative Administration Routes

A case study reported successful intraosseous (IO) administration of 4F-PCC when several attempts for IV access failed in a warfarin patient reporting to the emergency department (ED) with a head injury. INR was reduced from 3.9 to 1.1 at 90 mins after 4F-PCC dosing (25 IU/kg). These results suggest that IO 4F-PCC may be a viable alternative route in an emergency situation to avoid delay in treatment when IV access has not been established.<sup>47</sup>

### Removing Institutional Barriers to Urgent 4F-PCC Administration

While several guidelines recommend the use of 4F-PCC for the urgent reversal of VKAs,<sup>5,8-13</sup> significant logistic-, therapy-, or clinician-related barriers and lack of institution-specific treatment protocols represent potential impediments to effective, timely reversal of VKA-related bleeding.<sup>51</sup> In turn, this impedes the attainment of optimal patient outcomes.

**Reducing treatment delays.** Early intervention underlies effective VKA reversal; thus, time to 4F-PCC administration, also known as “door-to-needle time”, is an important determinant of patient outcomes. The time-critical nature of INR reversal was demonstrated in a retrospective cohort study of 853 patients with VKA-related ICH, of whom 307 experienced hematoma enlargement (median baseline INR 2.80 [IQR 2.30–3.41]) and 546 did not (median baseline INR 2.68 [IQR 2.23–3.38]). Achievement of INR <1.3 within 4 hours of admission was associated with lower hematoma enlargement rates than when not achieved (43/217 [20%] vs 264/636 [42%];  $p < 0.001$ ).<sup>52</sup> In addition, a prospective study of 822 patients with VKA-related severe hemorrhage showed that 4F-PCC administration concordant with international guidelines (dose  $\geq 20$  IU/kg, together with vitamin K) within 8 hours of patient admission was associated with a greater proportion of patients achieving post-reversal INR  $\leq 1.5$  (mean baseline INR 4.7) than the non-concordant group.<sup>53</sup> Strategies to reduce the 4F-PCC administration interval include fixed dosing,<sup>22</sup> and, potentially, increasing 4F-PCC infusion speed.<sup>45,46</sup> Stocking 4F-PCC in high-use areas, such as EDs, has also been considered, as this could increase access to 4F-PCC and allow pharmacist preparation by the bedside compared with the central

pharmacy. However, it remains to be seen whether this approach would be effective in reducing administration interval.<sup>54,55</sup>

Targeting institutional delays is another key way in which door-to-needle time can be reduced. In a retrospective study of patients with ICH undergoing VKA-related bleeding reversal, delays to rapid administration of 4F-PCC included hematology consultation, collection of 4F-PCC from the pharmacy or blood transfusion service, and obtaining patients' INR results.<sup>56</sup> Potential solutions to these barriers include point-of-care INR testing,<sup>48</sup> allowing ED doctors to request and prescribe 4F-PCCs without the hematologist's prior approval, expediting delivery of 4F-PCC from the blood transfusion service or pharmacy, and adopting pharmacy verification and dispensing of 4F-PCCs.<sup>3,57-60</sup> Indeed, it was shown that a pharmacist-driven protocol (in which the pharmacist calculated the dose, prepared 4F-PCC and delivered it to the bedside) reduced the administration interval to 35 minutes versus 70 minutes for the blood transfusion service-driven protocol. However, the impact of this reduction on, INR correction/ICH progression was not reported.<sup>54</sup>

Similarly, a retrospective cohort study including 252 patients receiving 4F-PCC for life-threatening bleeding or urgent surgery in the ED found the median time to 4F-PCC administration was significantly shorter when a pharmacist was present at the bedside compared with physician-only teams (66.5 vs 206.5 min;  $p < 0.001$ ). Although no difference in hemostasis or mortality was observed, patients with a pharmacist at the bedside had a shorter hospital stay. However, it should be noted that patients on various forms of oral anticoagulation were included in this study.<sup>61</sup> In support of these findings, another retrospective study of patients with bleeding (the majority of whom received warfarin) found that the time from order to start of administration of PCC (3F- or 4F-PCC) was significantly reduced when an ED pharmacist was involved (median 24 min [IQR 15–35] vs 42 min [IQR 32–59];  $p < 0.001$ ).<sup>3</sup> Furthermore, the implementation of an electronic order set for 4F-PCC for reversing VKA-related ICH demonstrated a significant reduction in the door-to-needle time from 83 to 45 minutes ( $p = 0.02$ ) and a significant improvement in patients receiving the target dose (pre-order set, 29.4% vs post-order set, 92.9% [ $p = 0.001$ ]).<sup>62</sup>

Further consideration could be given to early, pre-hospital, administration of 4F-PCCs. This practice is currently quite rare, but could have a substantial impact.<sup>63</sup> Pre-hospital administration of 4F-PCCs by a mobile stroke unit,<sup>64</sup> air ambulance<sup>63</sup> or emergency retrieval service,<sup>65</sup> particularly in remote settings where access to definitive care may otherwise be unavailable or limited,<sup>66</sup> should also reduce door-to-needle time versus waiting until hospital presentation.<sup>67</sup> Such early intervention has been shown to significantly increase the proportion of patients achieving a target INR of  $\leq 1.5$  from 3.7 upon ED arrival (proportion difference 0.8;  $p < 0.0001$ ), and faster overall time to normalization (181 versus 541 minutes with no early intervention;  $p < 0.001$ ).<sup>63</sup> Similarly, a retrospective cohort study comparing patients with warfarin-associated ICH who had transferred from a local community hospital ( $N = 177$ ) or

presented directly to the ED ( $N = 26$ ), found the time to administration of 4F-PCC was longer in transferred patients (median difference  $-176$  min;  $p \leq 0.001$ ). However, the delay was not associated with worse patient outcomes, with no difference in hematoma expansion, hospital stay, or mortality.<sup>68</sup>

Administration of 4F-PCC may also be delayed as a result of dispensing practices at each institution.<sup>69</sup> 4F-PCC is supplied in vials (500/1000 IU) and requires reconstitution with sterile water. The required dose can be dispensed as described in each package insert, or it can be administered per vial (the amount rounded to allow for use of an exact number of vials). The former option requires an extra step to check the exact contents of each box, reducing waste but potentially resulting in delays in administration.<sup>69</sup>

**Adherence to institutional guidelines.** VKA-related bleeding should be managed according to institutional protocols based on international and expert guidelines that consider the urgency of the clinical situation, assessment of coagulation (location, extent, and severity of bleeding), laboratory testing, reversal agent selection, and dosing strategy.<sup>5,8-13</sup> Despite the life-threatening consequences of acute bleeding, not all EDs have internal protocols guiding anticoagulant reversal,<sup>70</sup> potentially resulting in poor attainment of target INRs and hemostasis. Implementation of an institutional protocol involving 4F-PCC, accompanied by an education program for the clinical team to align reversal strategies,<sup>70</sup> has the potential to reduce door-to-needle times.<sup>71,72</sup> This should translate to improved INR reversal and decreased mortality,<sup>53</sup> as well as potentially reduced use of FFP.<sup>73</sup>

## Discussion

Life-threatening VKA-related bleeding or VKA reversal prior to urgent surgery requires emergency treatment, which can be treated via withholding VKAs, and administering 4F-PCC with vitamin K. Controlled clinical trials of 4F-PCC dosing and administration practices in patients with life-threatening VKA-related bleeding are challenging because of difficulties obtaining patient consent in emergency situations where delays cost lives. A consensus on optimal practices is therefore informed by real-world 4F-PCC use, ranging from expert opinions to anecdotal case studies and retrospective reviews. Indeed, most of the studies identified in our literature search are retrospective and observational in nature. While limited, current literature generally supports fixed dosing,<sup>12,22,28,74</sup> with rationale centered on the critical time saved by eliminating weight- and INR-based calculations, and the potential cost-effectiveness of a fixed-dosing approach.<sup>41,74</sup> A comprehensive review of fixed dosing studies published from the earliest available date in PubMed through 2018, with doses ranging from 200 to 2000 IU, supported a fixed-dose strategy of 1000–1500 IU. However, higher doses may be needed to treat ICH or a higher baseline INR.<sup>75</sup> Nevertheless, in the absence of an ideal dose suitable for all, variable dosing per label instructions is preferred by many institutions.

An important limitation of many studies to date is the use of INR as a surrogate marker of VKA reversal as a key efficacy endpoint. A direct measure of clinical hemostasis/bleeding cessation may be a more clinically relevant outcome. Furthermore, with inconsistent definitions of successful clinical outcomes and safety endpoints, questions remain regarding the minimum effective and maximum tolerable 4F-PCC doses, which respectively carry risks of under- and over-dosing. The ongoing PROPER3 study, a randomized controlled trial comparing fixed vs variable doses of 4F-PCC using hemostatic efficacy as the primary endpoint and INR reversal as the secondary, will hopefully provide further information on the efficacy and safety of these dosing regimens.<sup>76</sup>

In addition, further studies are needed to adequately assess the importance of pre-treatment INR for determining 4F-PCC dose, complemented by studies into alternative algorithms and means of individualized dosing. Furthermore, outcomes of large safety and efficacy re-dosing studies are needed to validate a repeat-dose approach, given the narrow margin between the therapeutic and adverse effects of 4F-PCCs.

Time to treatment is also a key determinant of successful INR reversal and patient outcomes, and can be expedited by pre-hospital administration by mobile units or emergency services, and improvements in hospital logistics.<sup>56,63,64</sup> Logistical improvements could include point-of-care INR testing,<sup>48</sup> clinically appropriate administration of 4F-PCCs by ED doctors or pharmacists,<sup>3,57-59,61</sup> and adopting strategies to improve 4F-PCC access.<sup>55</sup> Implementation of institutional guidelines endorsing autonomous verification and dispensing of 4F-PCCs are associated with better patient outcomes, including INR reversal and hemostasis control,<sup>3,57-59</sup> as are guidelines providing clear recommendations on 4F-PCC dosing and administration practices, even if guidance contravenes label recommendations.<sup>53</sup>

In the opinion of authors, minimizing the time to treatment with 4F-PCCs is of paramount importance when treating patients with VKA-related bleeding. Practices that safely and feasibly shorten the time to administration should be included in guidelines for institutions responsible for anticoagulant care, and in centers that perform invasive procedures on patients receiving VKA therapy.

In summary, there are various key determinants contributing to successful INR reversal, hemostasis, and outcomes in patients receiving 4F-PCC to rapidly reverse VKA-related bleeding. These include appropriate use of alternative dosing and administration strategies (such as fixed dosing and increased infusion speed), adherence to institutional guidelines, and removing significant institutional barriers impacting time to treatment. Clinicians wishing to optimize utilization of 4F-PCC for VKA reversal via any of these strategies will hopefully find the results presented here to be of interest.

## Authors' Note

Details of the literature search methodology employed for this review are provided. Publicly available scientific literature was surveyed for this review; therefore, no ethical permissions were required.

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