

# Fixed Versus Variable Dosing of Prothrombin Complex Concentrate for Bleeding Complications of Vitamin K Antagonists—The PROPER3 Randomized Clinical Trial

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**Study objective:** To determine if a fixed dose of 1000 IU of 4-factor prothrombin complex concentrate (4F-PCC) is as effective as traditional variable dosing based on body weight and international normalized ratio (INR) for reversal of vitamin K antagonist (VKA) anticoagulation.

**Methods:** In this open-label, multicenter, randomized clinical trial, patients with nonintracranial bleeds requiring VKA reversal with 4F-PCC were allocated to either a 1,000-IU fixed dose of 4F-PCC or the variable dose. The primary outcome was the proportion of patients with effective hemostasis according to the International Society of Thrombosis and Haemostasis definition. The design was noninferiority with a lower 95% confidence interval of no more than –6%. When estimating sample size, we assumed that fixed dosing would be 4% superior.

**Results:** From October 2015 until January 2020, 199 of 310 intended patients were included before study termination due to decreasing enrollment rates. Of the 199 patients, 159 were allowed in the per-protocol analysis. Effective hemostasis was achieved in 87.3% (n=69 of 79) in fixed compared to 89.9% (n=71 of 79) in the variable dosing cohort (risk difference 2.5%, 95% confidence interval –13.3 to 7.9%,  $P=.27$ ). Median door-to-needle times were 109 minutes (range 16 to 796) in fixed and 142 (17 to 1076) for the variable dose ( $P=.027$ ). INR less than 2.0 at 60 minutes after 4F-PCC infusion was reached in 91.2% versus 91.7% ( $P=1.0$ ).

**Conclusion:** The large majority of patients had good clinical outcome after 4F-PCC use; however, noninferiority of the fixed dose could not be demonstrated because the design assumed the fixed dose would be 4% superior. Door-to-needle time was shortened with the fixed dose, and INR reduction was similar in both dosing regimens. [Ann Emerg Med. 2021;■:1-11.]

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### INTRODUCTION

The optimal dosing strategy for 4-factor prothrombin complex concentrates (4F-PCCs) in vitamin K antagonist (VKA)-related bleeding is unknown. Prominent guidelines, such as those from the American Society of Hematology and the American College of Cardiology (ACC), acknowledge the use of 4F-PCC as the agent of choice over plasma, leaving the optimal dosing strategy either undiscussed or ambiguous.<sup>1,2</sup>

Traditionally, a variable dosing strategy—which uses patient-specific characteristics, such as body weight and

international normalized ratio (INR), to achieve a certain target INR—is used as recommended by the manufacturer.<sup>3,4</sup> In this way, a dose is calculated to achieve a specific target INR. Previous studies that tested 4F-PCC used achievement of that target INR as a primary or coprimary outcome.

ACC and Dutch Society for Internal Medicine (NIV) guidelines recommend a fixed dose of 1000 IU of 4F-PCC as an alternative to variable dosing.<sup>2,5</sup> This dosing offers advantages of being simpler, faster, and less expensive than variable dosing while potentially preserving effectiveness of bleeding cessation. Fixed-dosing effectiveness has been suggested in (retrospective) nonrandomized studies and is

**Editor's Capsule Summary***What is already known on this topic*

Dosing of 4-factor prothrombin complex concentrate (4F-PCC) is generally based on a patient's international normalized ratio and body weight. Fixed-dose 4F-PCC has been recommended as equally effective yet simpler and faster to administer.

*What question this study addressed*

Is a fixed dose of 1000 IU 4F-PCC noninferior to variable dosing in hemostatic effectiveness for patients with Vitamin K antagonist-related extracranial bleeding?

*What this study adds to our knowledge*

In this randomized but underpowered trial, effective hemostasis was comparable with fixed and variable dosing, but noninferiority was not demonstrated. Door-to-needle time was shorter with fixed dosing, and correction of international normalized ratio was comparable.

*How this is relevant to clinical practice*

Fixed-dose 4F-PCC may be an option in reversing vitamin K antagonist-related bleeding; however, further investigation is needed.

thought to result from faster treatment initiation.<sup>6-8</sup> Its effectiveness, however, has yet to be confirmed in a randomized prospective study.

Therefore, the PROPER-3 (Prothrombin complex concentrate Prospective Evaluation and Rationalization, study number 3) study was initiated as a multicenter, randomized controlled trial to test the fixed dose of 4F-PCC for noninferiority in clinical outcome versus the variable dose in VKA-related extracranial bleeding emergencies.

**METHODS****Study Design and Setting**

PROPER-3 was an investigator-initiated, randomized, multicenter, pragmatic open-label, blinded endpoint trial. The study mainly took place in the emergency departments of 6 large Dutch academic or teaching hospitals (Table E1, available at <http://www.annemergmed.com>). The study was reviewed and approved by the University Medical Center Groningen medical ethics committee and the institutional review boards at each site prior to patient enrollment. The trial

was preregistered in the EU clinical trials register (EU-CTR Identifier: 2014-000392-33).

**Selection of Patients**

We randomized patients presenting with bleeding emergencies on VKA requiring 4F-PCC if they were 18 years of age or older and suffered from an extracranial bleed. The decision to use 4F-PCC was not a part of the study; patients could be randomized in the study when the indication for 4F-PCC was set according to local protocol and national guidelines. In Dutch clinical practice, 4F-PCC is the agent of choice for direct VKA reversal, with national guidelines advising against the use of plasma, 3-factor PCC, or activated PCC for this indication.<sup>5</sup> Intracranial hemorrhage was not included, as pilot data for these bleeds were not supporting a fixed dose.<sup>9</sup> Availability of the baseline INR was not required for randomization.

In order to minimize study-related delays in the emergency setting, randomization by phone call was used to randomly assign patients in a 1:1 ratio to receive either a fixed (intervention group) or variable (control group) dose of 4F-PCC. Allocation was concealed by using randomization software, allocating with permuted block sizes of 4 and 6.<sup>6</sup> Randomization outcome masking was not attempted, as it would imply 4F-PCC preparation by a third party available 24/7, thus introducing serious treatment delay. A deferred informed consent procedure was approved by the ethics board to prevent treatment delay, taking place after the emergency setting was stabilized.<sup>10</sup> If the subject died before regaining ability to give consent, analysis of the data was allowed.

**Intervention**

The intervention group was assigned to receive 4F-PCC in a fixed dose of 1000 IU factor IX, independent of body weight and INR. The control group received a variable dose of 4F-PCC as calculated per manufacturer's instructions, determined either by body weight, baseline INR, and target INR (Cofact, Sanquin), or body weight and baseline INR (Beriplex/Kcentra, CSL Behring).<sup>3,4</sup>

Both Cofact and Beriplex products were considered equivalent, resembling Dutch clinical practice. 4F-PCC products are being dosed to factor IX amount; therefore, the hemostatic potency is considered equipotent when the same amount of factor IX is administered. This is further advocated by guidelines not limiting given dosing advice to specific 4F-PCC brands.<sup>2,5</sup> Although this manner of dosing does not account for the hemostatic potency of the other

clotting factors and anticoagulants contained in the products that actually do differ between brands, randomization is expected to even out bias by product formulations. 4F-PCC was not supplied by the study, and brands were according to hospital formulary (Table E2, available at <http://www.annemergmed.com>).

The study only intervened in initial 4F-PCC dose. All other treatment aspects, such as the use of vitamin K or packed RBCs, were in accordance with the hospital treatment protocol. Patients were followed up for assessment of hemostatic effect in the first 48 hours, clinical development in the remainder of hospital stay, and mortality up to 30 days after intervention.

### Methods of Measures

The primary outcome was the proportion of good hemostatic effectiveness, assessed according to the International Society on Thrombosis and Haemostasis definition for effective hemostasis in major bleeding management (Figure E1, available at <http://www.annemergmed.com>).<sup>11</sup> In short, hemostasis was considered effective when visible bleeding was stopped within 4 hours. For musculoskeletal bleeds, it was considered effective when pain was reduced and swelling was improved within 24 hours. For nonvisible bleeds, it was considered effective if the hemoglobin level did not decrease more than 10% at 48 hours compared to baseline at presentation. Additionally, invasive interventions (eg, fasciotomy, endoscopy) were either not necessary or performed without bleeding complications. Outcome was effective hemostasis, noneffective hemostasis, or not assessable. Treating physicians were explicitly instructed to observe hemostatic effectiveness instead of achievement of target INR. Additional 4F-PCC in the follow-up was allowed if required for bleeding management, but for study purposes, the subject would be judged to have failed the primary outcome. If additional 4F-PCC was given regardless of hemostatic effect—for example, to achieve a specific target INR, irrespective of hemostatic effectiveness—this was considered a violation of protocol. These cases were excluded from per-protocol analysis. A blinded independent adjudication committee assessed the primary endpoint. The safety outcomes were thromboembolic events during hospital stay (defined as any newly diagnosed ischemic or thromboembolic complication, such as deep venous thrombosis, pulmonary embolism, ischemic stroke, or coronary occlusion after initial 4F-PCC administration) and all-cause mortality up to 30 days after intervention.

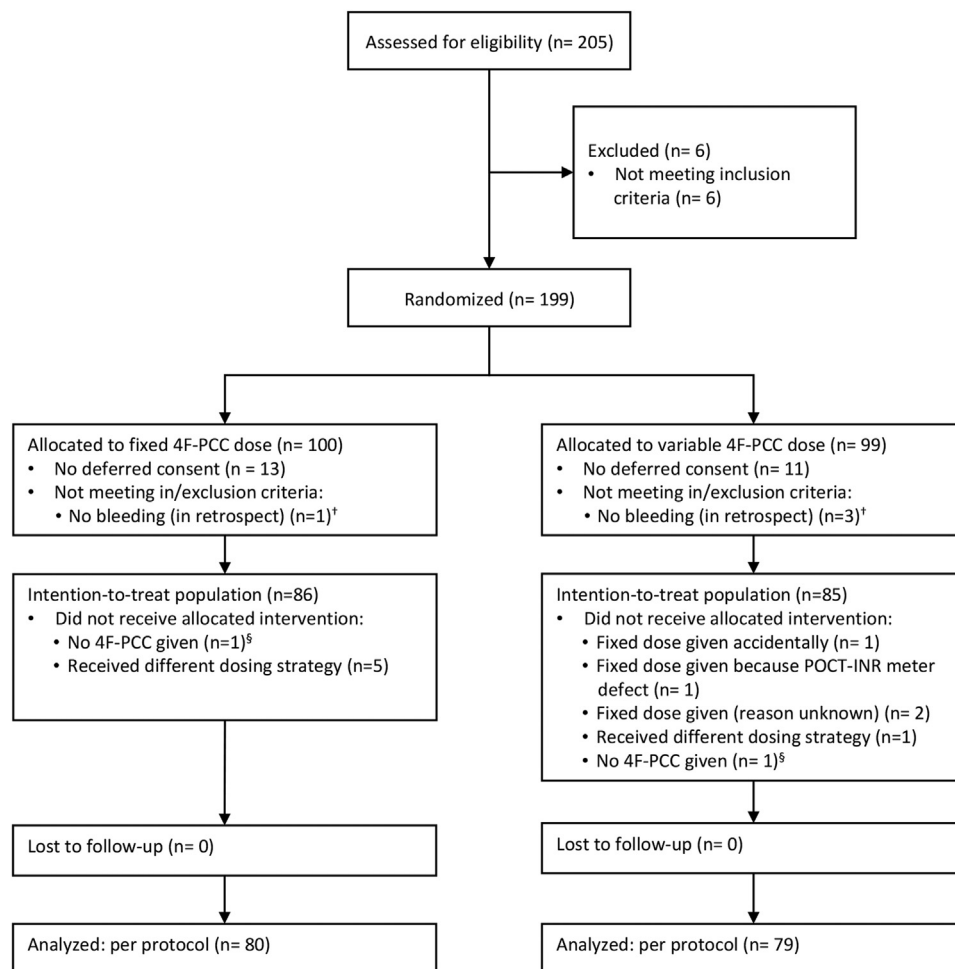
INR outcomes and door-to-needle time were secondary end points. INR measurements were requested at baseline

and 1 and 24 hours after infusion of 4F-PCC. Use of other hemostatic agents (eg, vitamin K, plasma), transfusion of RBCs, and invasive interventions were also recorded. The door-to-needle time was defined as the time between presentation in the ED and start of initial 4F-PCC infusion. For patients who presented elsewhere (eg, an inpatient ward) with their bleeding complications, door-to-needle times were not assessed.

### Primary Data Analysis

The primary hypothesis was noninferiority of the fixed dose to the variable dose in terms of good hemostatic effectiveness. Based on prior work, in which the fixed dose was seen to be superior by a risk difference of 8%, we conservatively assumed an expected risk difference of 4% superiority of the fixed dose in our study setting.<sup>7</sup> A noninferiority margin (for the lower bound of the 95% confidence interval [CI] of the between-group difference) of  $-6\%$  was chosen based on historical performance of the active comparator and prior discussion with experts in the field, deeming up to  $-10\%$  clinically acceptable, accounting besides hemostatic effectiveness for other factors of acceptability (ie, cost savings, treatment failure detection, and rescue options).<sup>6,7,12</sup> With a 1-sided alpha of 0.025 and 80% power, this resulted in a sample size of 282 patients. With the deferred consent procedure in mind, planning 310 patients compensated for an anticipated 10% dropout rate by patients not providing consent.

For the primary outcome including preplanned subgroup analyses, the per-protocol population was used (Figure 1). Absolute risk difference was estimated and 95% confidence limits were calculated using the Farrington–Manning method. The per-protocol population was defined as patients complying with all inclusion and exclusion criteria and receiving the allocated intervention. The per-protocol population was primarily used given the noninferiority design. While analysis of the intention-to-treat population in superiority trials seeks better treatment, even in the presence of noncompliant subjects, for noninferiority trials, noncompliant subjects dilute the true effect of treatments toward equivalence.<sup>13</sup> Depending on the presence of noninferiority, a sensitivity analysis was planned using the intention-to-treat population. Secondary and safety outcomes were tested for superiority, using the per-protocol population for effectiveness outcomes and the safety population for safety outcomes. The safety population was defined as all patients who received study treatment, irrespective of protocol violations, corresponding to the intention-to-treat



**Figure 1.** Patient flow chart. *POCT-INR*, point-of-care test for international normalized ratio. † = included in safety population (ie, intention-to-treat-S), as these patients did receive 4F-PCC. § = excluded from intention-to-treat-S.

population, excluding patients who did not receive 4F-PCC (intention-to-treat-S).

Interim analyses for efficacy or futility were not planned. However, because of a strongly decreasing accrual rate, a sample size reestimation was conducted using the observed between-group difference instead of the expected +4% difference. Reestimation with the observed between-group difference led to an unexpected increase in sample size, to 656 required patients. When corrected for the 10% anticipated dropout, this meant a total of 722 patients. Additional participating centers were sought but not found. Thus, accounting for the decreased inclusion rates, this would imply to continue inclusion for at least 5 additional years, essentially doubling the current duration of the study. This was considered unfeasible and unacceptable for the relevance of the results. Recruitment was therefore suspended, and the study was terminated on January 1, 2020.

## RESULTS

### Characteristics of Study Subjects

From October 2015 through December 2019, a total of 199 patients were randomized to receive either the fixed (n=100) or the variable (n=99) 4F-PCC dose (Figure 1). After randomization, 24 patients (13 versus 11 patients in fixed and variable groups, respectively) did not provide consent. In addition, 4 patients (1 versus 3 in the fixed and variable groups, respectively) proved to have no bleeding in retrospect. These 4 patients were excluded from per-protocol and intention-to-treat analyses but included in the safety analysis. Twelve patients were excluded from the per-protocol analysis (Figure 1). In both groups, 4F-PCC treatment was not initiated in 1 patient. In the variable dose group, 4 patients received a fixed dose for various reasons (Figure 1). Furthermore, allocated treatment was compromised in 5 patients in the fixed-dose group and 1 in

the variable-dose group by administration of additional 4F-PCC doses with the sole purpose of achieving doctor-specified target INRs (ie, received a different dosing strategy). After excluding these, 80 versus 79 patients in the fixed and variable groups, respectively, were available for per-protocol analysis.

The baseline characteristics are shown in Table 1. As shown, the fixed and variable groups were largely comparable at baseline. The median INR at study entry was 4.6 (range 1.5 to 16.8) for the fixed dose versus 4.2 (1.8 to 18) for the variable dose. Distribution of indications for VKA use differed, with fewer patients with atrial fibrillation (67.5% versus 81.0%) and more patients with venous thrombosis (21.3% versus 13.9%) and mechanical valves (11.3% versus 3.8%) in the fixed versus variable group. Use of concomitant antithrombotic medication (Table 1) besides VKA at presentation was seen less

frequently in the fixed-dose group (11.3%, versus 22.1% in variable-dose group). With regard to the bleeding type, fewer musculoskeletal bleeds were seen in the fixed-dose group (11.3%) as compared to the variable-dose group (24.1%).

### Main Results

The primary outcome was not assessable in 1 patient in the fixed-dose group. The primary event of effective hemostasis was seen in 69 of 79 (87.3%) assessable patients receiving a fixed dose and 71 of 79 (89.9%) assessable patients receiving a variable dose. This resulted in a risk difference of  $-2.5\%$  favoring the variable dose, with a 2-sided 95% CI of  $-13.3\%$  to  $7.9\%$  (Figure 2).

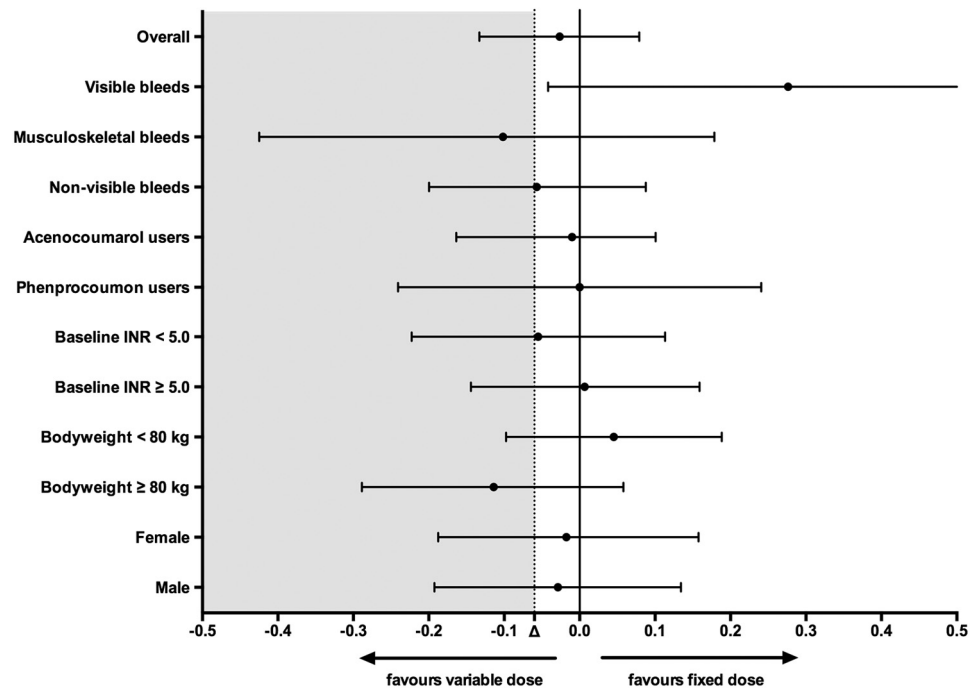
Considering the observed risk difference and 95% CI, noninferiority at the noninferiority margin of  $-6\%$  was not demonstrated ( $P=.27$ ). Prespecified subgroup

**Table 1.** Demographics and baseline characteristics (per-protocol population).

Baseline Characteristic		Fixed Dose n=80		Variable Dose n=79	
Sex, female, n (%)		36	45.0%	34	43.0%
Age, y, median (min-max)		79.5	(33-95)	78	(40-115)
Body weight, kg, mean (SD)		76.3	(±16)	77.6	(±18)
Baseline INR, median (min-max)		4.55	(1.5-16.8)	4.2	(1.8-18)
Hemoglobin, mean (SD)		6.2	(±1.5)	6.2	(±1.7)
Thrombocyte count, median (min-max)		216	(124-1400)	218	(71-702)
Serum creatinine, median (min-max)		96.5	(43-652)	104	(51-607)
Indication for VKA use*	Atrial fibrillation, n (%)	54	67.5%	64	81.0%
	Venous thrombosis, n (%)	17	21.3%	11	13.9%
	Mechanical valve, n (%)	9	11.3%	3	3.8%
	Other, n (%)	2	2.5%	3	3.8%
Duration of VKA use	<2 weeks, n (%)	1	1.3%	3	3.8%
	2 weeks-3 months, n (%)	3	3.8%	5	6.3%
	>3 months, n (%)	75	93.8%	65	82.3%
	Unknown, n (%)	1	1.3%	6	7.6%
Concomitant antithrombotics*		9	11.3%	17	22.1% <sup>†</sup>
	Acetylsalicylic acid, n (%)	4	5.0%	7	9.1%
	Carbasalate calcium, n (%)	2	2.5%	5	6.5%
	Clopidogrel, n (%)	3	3.8%	4	5.2%
	Dipyridamol, n (%)	1	1.3%	0	
	Nadroparin, n (%)	1	1.3%	2	2.6%
Type of VKA	Acenocoumarol, n (%)	63	78.8%	62	78.5%
	Phenprocoumon, n (%)	17	21.3%	17	21.5%
Type of bleeding	Visible, n (%)	12	15.0%	8	10.1%
	Musculoskeletal, n (%)	9	11.3%	19	24.1%
	Nonvisible, n (%)	59	73.8%	52	65.8%

\*Multiple options per subject possible.

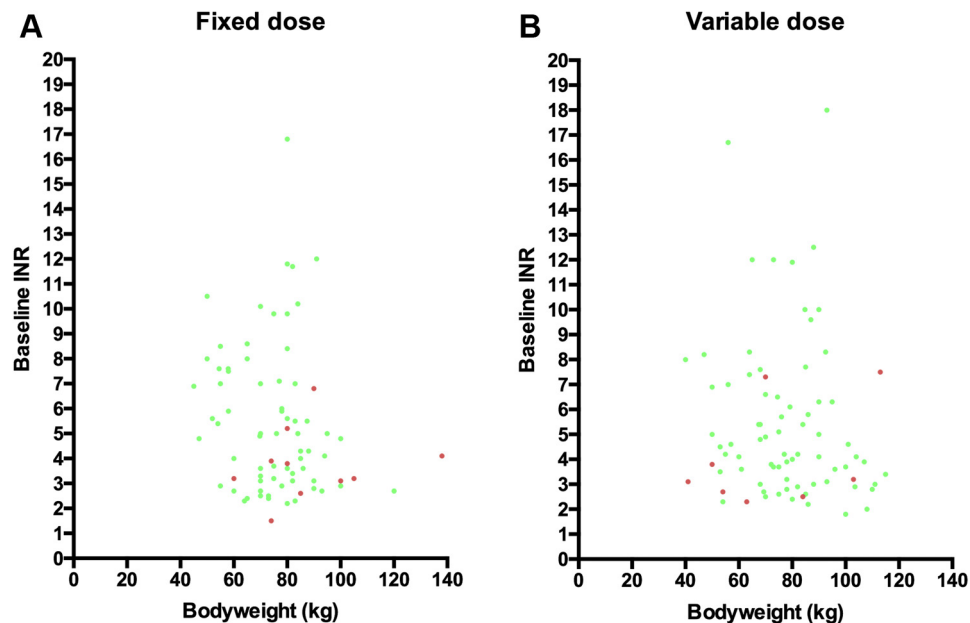
<sup>†</sup>Status unknown for 2 subjects.



**Figure 2.** Primary outcome defined as hemostatic effectiveness visual display. Dots represent the proportion difference of good hemostatic effectiveness found between groups. Bars represent the 95% CI for the proportion difference. Overall depicts the primary outcome result in the per-protocol population. The noninferiority margin ( $\Delta$ ) set at -0.06 is displayed by the dotted vertical line, while the gray zone represents a clinically relevant difference (ie, zone of inferiority).

analyses (Figure 2) of the primary outcome demonstrated a rather homogenous effect when differentiated by sex, body weight more than or less than 80 kg, baseline INR more than or less than 5.0,

and type of VKA. Visual analysis of hemostatic effectiveness distribution among subjects in relation to baseline INR and body weight did not reveal specific subgroup differences (Figure 3).



**Figure 3.** Hemostatic effectiveness in relation to the baseline INR and body weight of subjects. A, fixed-dose arm. B, variable-dose arm. Green dots represent subjects with effective hemostasis. Red dots represent subjects with noneffective hemostasis.

For the intention-to-treat population, effective hemostasis was seen in 74 of 84 (88.1%) assessable patients in the fixed group and 76 of 85 (89.4%) assessable patients in the variable group. This resulted in a risk difference of  $-1.3\%$  favoring the variable dose, with a 95% CI of  $-11.5\%$  to  $9.0\%$  (Figure E2, available at <http://www.annemergmed.com>).

Door-to-needle times were significantly shorter for the fixed-dose group, with median times being 109 (16 to 796) minutes in fixed-dose group and 142 (17 to 1,076) minutes in the variable-dose group (difference,  $-33$  minutes; 95% CI  $-56$  to  $-4$  minutes; Table 2; Figure E3, available at <http://www.annemergmed.com>). Door-to-needle times were not available for 5 patients in the fixed-dose group and 6 patients in the variable-dose group. In one patient in the fixed-dose group, this was because the time of admission to the ED was missing, and in all other patients, it was because they presented with active bleeding elsewhere (ie, not in the ED). The median initial 4F-PCC dose was lower for the fixed-dose group (1000 IU, versus 1750 IU in the variable-dose group [difference,  $-750$  IU; 95% CI  $-1000$  to  $-500$  IU]). A comparable proportion of patients in both groups reached an INR of 2.0 or less 60 minutes after

4F-PCC infusion—91.2% when receiving a fixed dose versus 91.7% when receiving a variable dose (odds ratio [OR] 1.07, 95% CI 0.33 to 3.48). The median INR achieved with the fixed dose, 1.6 (1.1 to 2.7), was slightly higher than the INR with the variable dose (1.4 [1 to 6]) (difference, 0.2; 95% CI 0.1 to 0.3; Figure 4).

In the per-protocol analysis, repeated dosing was seen in 4 patients (5.0%) in the fixed-dose group and 1 (1.3%) in the variable-dose group (OR 0.24, 95% CI 0.03 to 2.23). All these patients received additional 4F-PCC due to lack of hemostatic effectiveness except for 2 patients in the fixed dose group, who received additional 4F-PCC when the bleed was already halted but required further INR correction for invasive surgery with high bleeding risk.

In the fixed-dose group, 71.3% of patients received vitamin K in the initial (PCC) management of the bleed, while 79.7% did so in the variable-dose group (OR 1.59, 95% CI 0.76 to 3.30). RBC transfusion was comparable, with 62.5% of patients receiving at least 1 unit in the fixed-dose group compared to 62.0% in the variable-dose group (OR 0.95, 95% CI 0.50 to 1.81). The median number of

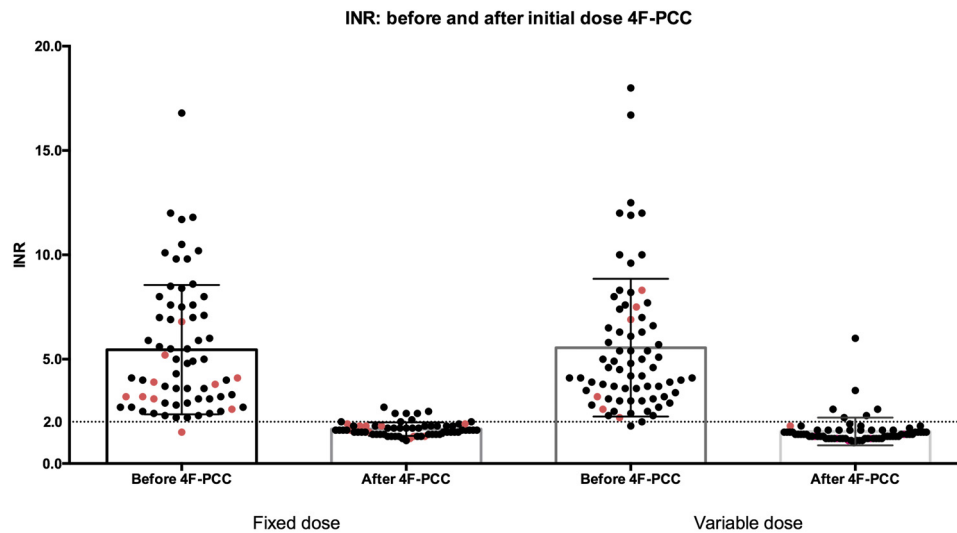
**Table 2.** Secondary outcomes. For categorical variables, ORs with 95% CIs are presented; for continuous variables, the differences of the medians with 95% CIs are presented.

Outcome Parameter	Fixed Dose n=80		Variable Dose n=79		OR or difference 95% CI	
Patients reaching INR $\leq 2.0$ 60 min after 4F-PCC infusion, n (%) <sup>*</sup>	62	91.2%	66	91.7%	1.07	0.33-3.48
INR 60 minutes after 4F-PCC infusion, median (min-max) <sup>*</sup>	1.6	(1.1-2.7)	1.4	(1-6)	0.2	0.1-0.3
Initial 4F-PCC dose (IU), median (min-max)	1000	(1000-1000)	1750	(750-2750)	-750	-1000 to -500
Additional 4F-PCC dose required, n (%)	4	5.0%	1	1.3%	0.24	0.03-2.23
Total administered dose of 4F-PCC (IU), median (min-max)	1000	(1000-3000)	1750	(750-2750)	-750	-750 to -500
Door-to-needle time (minutes), median (min-max) <sup>†</sup>	109	(16-796)	142	(17-1076)	-33	-56 to -4
ICU stay, n (%)	16	20.0%	11	13.9%	0.65	0.28-1.50
Duration of hospital stay (days), median (min-max)	4	(1-24)	5	(0-54)	-1	-1 to 0
Thrombotic complications during hospital stay, n (%) <sup>‡</sup>	1	1.2%	2	2.3%	2.07	0.31-30.1
In-hospital all, n (%)—cause mortality <sup>‡</sup>	4	4.7%	7	8.1%	1.82	0.51-6.45
All-cause mortality at 30 days after initial 4F-PCC administration, n (%) <sup>‡</sup>	8	9.3%	10	11.6%	1.28	0.48-3.43

<sup>\*</sup>INR 60 minutes after 4F-PCC infusion was known for 68 and 72 patients in fixed- and variable-dose groups, respectively.

<sup>†</sup>Door-to-needle times were available for 75 and 73 patients, respectively.

<sup>‡</sup>Safety outcomes measured over safety population with 86 patients in each group.



**Figure 4.** INR correction after initial PCC dose one hour after administration. Box represents values below median, while whiskers represent the interquartile range. Red dots are patients with noneffective hemostasis.

RBC units administered was 2.0 for both groups within the first 48 hours and during hospital stay (Table E3, available at <http://www.annemergmed.com>). Invasive interventions were distributed equally among groups (Table E4, available at <http://www.annemergmed.com>).

Plasma (Omniplasma, Sanquin NV/ one unit=200 mL solvent detergent plasma) was administered more frequently in the fixed-dose group, with 7 patients (8.8%) receiving 1 or more units versus 1 patient (1.3%) in the variable-dose group (OR 0.13, 95% CI 0.02 to 1.11). In post hoc analysis comparing frequency distributions of various baseline and treatment parameters in subjects who received plasma to those who did not, no discriminating factors could be identified. INR reversal was complete (ie, INR was less than 2.0) for most patients within 60 minutes of initial PCC dose, and sustained (Figure E4, available at <http://www.annemergmed.com>). Furthermore, post hoc subgroup analysis of the primary outcome demonstrated similar hemostatic effectiveness profiles when excluding patients who received plasma (total n=72 versus n=78, effective: 88.9% versus 89.7%) (Figure E2, available at <http://www.annemergmed.com>).

One thrombotic complication during hospital stay was seen with the fixed dose (1.2%), and 2 events with the variable dose (2.3%, OR 2.07, 95% CI 0.31 to 30.1). Overall occurrence of thrombotic complications was 1.7% in the safety population. Details of thrombotic complications are provided in Table E5 (available at <http://www.annemergmed.com>). For in-hospital mortality, 4 events (4.7%) and 7 events (8.1%, OR 1.82, 95% CI 0.51 to 6.45), respectively, were seen; 8 (9.3%) versus 10 (11.6%) patients died all-cause at 30 days after

initial 4F-PCC administration (OR 1.28, 95% CI 0.48 to 3.42).

## LIMITATIONS

A limitation was the open-label design probably increasing awareness of the practical aspects of 4F-PCC for VKA reversal. Another limitation is the robustness of the comparator: while the variable dose is considered standard of care, this status is based on history rather than efficacy determined in clinical trials.

Although we could only include patients using the short-acting VKA acenocoumarol (half-life approximately 8 to 11 hours) or the long-acting VKA phenprocoumon (half-life approximately 160 hours), results are expected to be extrapolatable to patients using the intermediate-acting VKA warfarin (half-life approximately 40 to 50 hours). This is based on the good direct INR reversal seen at 60 minutes for both short- and long-acting VKA regardless of dosing strategy (Table 2) and no substantially different hemostatic effectiveness between acenocoumarol and phenprocoumon subgroups (Figure 2).

The most important limitation is that the study was stopped prematurely, for reasons previously mentioned. While designing the study, and as of today, only one source of data was available to inform our trial assumptions. Although our assumptions were conservatively chosen, being restricted to one data source still carried an inevitable risk of misclassification of trial assumptions. In the event of equivalent treatments, to declare noninferiority, our trial design would have been underpowered, with only approximately 37% power.



Prematurely stopping underpowered the study and compromised the ability to assess the primary outcome variable for noninferiority with respect to control of bleeding. However, all endpoint data for all included patients were still obtained and reported, observing a minimal nonsignificant difference in hemostatic effectiveness of the fixed dose as compared to the variable dose. Moreover, this is currently the largest randomized, multicenter trial reporting effectiveness of fixed dosing of 4F-PCC.

## DISCUSSION

The results of the PROPER-3 study show that, among 199 randomized patients requiring 4F-PCC for nonintracranial bleeding emergencies, both fixed and variable dosing regimens lead to very good hemostatic effectiveness. Effective hemostasis was observed in 87.3% when using a 1000-IU fixed dose and 89.9% when using the variable dose. CI for the risk difference of  $-2.5\%$  was  $-13.3$  to  $7.9\%$ , so noninferiority was not demonstrated at the preplanned margin. The fixed dose was administered more quickly, reducing door-to-needle time by a median of 33 minutes while maintaining a similar proportion between groups of patients achieving postinfusion INR of 2.0 or less.

Of the 310 planned patients in the calculated sample size, only 199 were included until early termination of the study. After inclusion rates decreased, in part due to increasing use of nonVKA anticoagulants, we recalculated the required sample size with the actual, observed difference in outcome. A negative actual risk difference of  $-2.5\%$  was found, as opposed to the anticipated positive difference of at least  $+4\%$  based on previous work. The found risk difference led to a recalculated sample size much larger than planned for a definitive study, incongruous with the strongly decreased inclusion rate. This made continuation of the study unfeasible.

A nonpreplanned Bayesian analysis of the observed data on primary outcome was carried out to identify the likelihood of the true value for the proportion difference being  $-6\%$  or more. Assuming noninformative Beta(1,1) priors, there is a 76% posterior probability that fixed dosing is noninferior to variable dosing at the noninferiority margin of  $-6\%$ . For a noninferiority margin of  $-10\%$ , the posterior probability of the fixed dose being noninferior would be 93%.

The fixed-dose cohort had a median door-to-needle time 33 of minutes less than the variable-dose group, a finding similar to that in a previous nonrandomized study in 2 Dutch hospitals.<sup>7</sup> The fixed dose is therefore, importantly,

more compliant with the first recommendation in major bleeding guidelines, instructing to minimize time to intervention in preventing further complications.<sup>14</sup> Given the randomized design, this difference is likely attributed to the dosing regimen, as logistical issues were identical in both arms. Although not specifically collected, it was found that in some bleeding situations, the baseline INR was not required to set the indication for 4F-PCC, favoring the fixed dose. Moreover, some patients could be randomized before arrival at the ED. Other factors associated with the variable dose that might have contributed are baseline INRs determined by laboratory assay instead of point-of-care test; dose calculation and, if required, decisionmaking on target INR; and delay in reconstitution given the larger median dose.

Another important finding is that median postinfusion INRs of 1.6 and 1.4 both produced very good clinical response in the fixed and variable groups, respectively. INR was 2.0 or less in 91.2% of fixed-dosed patients and 91.7% of patients receiving a variable dose. In view of the lack of data defining the optimal target INR in VKA-related bleeding, this finding puts into question local postinfusion INR policies of 1.5 and lower to obtain effective hemostasis and raises the question of whether 4F-PCC should be dosed to a specific target INR at all for extracranial bleeding.<sup>15,16</sup> The patients with noneffective hemostasis all demonstrated postinfusion INRs of less than 2.0—more specifically, with a median INR of 1.6 (1.2 to 1.9) for those who received a fixed dose and 1.5 (1.1 to 1.5) for those with a variable dose (Figure 3).

Interestingly, a tendency toward more plasma usage was seen in the fixed-dose group—evidently not as alternative to correct INR, as most of these patients already achieved INR of less than 2.0 within 60 minutes postinfusion of 4F-PCC (and half of these patients even 1.5 or less), and the mean dose was only 1.5 plasma units. Additional 4F-PCC after the initial randomized dose was seen in 4 patients in the fixed-dose group, of whom only 2 patients received additional doses for a lack of hemostatic effectiveness of the initial dose. If additional dosing would be allowed for primary outcome assessment, hemostasis would have been assessed as being effective in these 2 patients.

Thromboembolic events were similar in the fixed- and variable-dosing groups; however, the study was not sufficiently powered to reveal a difference. In-hospital mortality appeared numerically lower for the fixed dose, while mortality rates at 30 days after initial PCC administration approximated 10% in both groups (8 events in the fixed-dose group and 10 events in the variable-dose group). These numbers correspond with earlier reports.<sup>17,18</sup>

A confounding factor could be the larger number of patients with mechanical valves in the fixed-dose group (11.3%, versus 3.8% in the variable group). These patients often have a higher therapeutic target INR, which could have contributed to the higher median baseline INR seen in the fixed-dose group (4.55, versus 4.2 in the variable group).<sup>19</sup> Furthermore, vitamin K is not always coadministered with 4F-PCC in patients with mechanical valves, which could have contributed to the lower number of vitamin K coadministrations in the fixed-dose group (71.3%, versus 79.7% in the variable-dose group).<sup>19</sup> Both the higher median baseline INR and the lower number of vitamin K coadministrations could have negatively affected the proportion of successful outcome of the fixed dose (ie, have led to an underestimation of the effect size of the fixed dose).

While conducting the study, several reports were published investigating a fixed dose of 1500 IU.<sup>8,20</sup> Given the results on hemostatic effectiveness of the fixed dose as compared to the variable dose, we do not see any indication for the use of 1500 IU. The majority of patients responded well in terms of hemostatic effectiveness of the 1000 IU fixed dose, while 4 patients (5%) lacked effectiveness, requiring additional 4F-PCC. Based on this, we would support the use of a 1000 IU fixed dose with the option of additional dosing if clinically indicated, as opposed to the use of a fixed dose of 1500 IU for all.

We observed a minimal nonsignificant difference in performance of the fixed dose as compared to the variable dose in terms of hemostatic effectiveness, with a larger-than-expected CI for the risk difference. This, together with the expected decreasing size of the population treated with VKA, makes future studies comparing fixed and variable dosing challenging. Thus, until noninferiority is demonstrated or refuted, the practical implications for patient care should be carefully considered.

In conclusion, while we were unable to demonstrate noninferiority of the fixed dose of 1000 IU of 4F-PCC in terms of hemostatic effectiveness in the management of VKA bleeding, the reduced door-to-needle time and ease of administration, coupled with a comparable effect on INR and good clinical effectiveness, suggest that fixed dosing is a viable alternative to variable dosing.

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