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ORIGINAL ARTICLE

# Three-Factor Versus Four-Factor Prothrombin Complex Concentrate for the Emergent Management of Warfarin-Associated Intracranial Hemorrhage

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**Abstract**
*Background* Four-factor prothrombin complex concentrates (PCC) produce a more rapid and complete INR correction compared with 3-factor PCC in patients receiving warfarin. It is unknown if this improves clinical outcomes in the setting of intracranial hemorrhage (ICH).
*Methods* This multicenter, retrospective cohort study included patients presenting with warfarin-associated ICH reversed with either 4- or 3-factor PCC. The primary outcome was in-hospital mortality. Secondary outcomes were 30-day mortality, discharge location, intensive care unit (ICU) and hospital-free days, INR reversal, and thromboembolic (TE) events at 90 days. Each was analyzed using regression analysis. Continuous and binary outcomes were analyzed using linear and logistic regression, respectively, while ordinal regression was used for discharge location.
*Results* Of the 103 patients, 63 received 4-factor PCC. Median age was 79 years [interquartile intervals(IQI 73–84)], median presenting INR was 2.7 (2.2–3.3), and presenting ICH was intraparenchymal in 51% of patients. In-hospital and 30-day mortality were 25 and 35%, respectively. In-hospital mortality was greater among those who received 4-factor PCC, yet was not statistically significant (OR 2.2, 95% CI 0.59–9.4, $p = 0.26$), as having Glasgow Coma Scale (GCS) $\leq 8$ explained most of the difference (OR 48, 95% CI 14–219, $p < 0.001$). The effect of 4-factor PCC was not statistically significant in any of the secondary analyses. Crude rates of TE events were higher in the 4-factor PCC group (19 vs. 10%), though not significantly.
*Conclusions* In-hospital mortality was not improved with the use of 4- versus 3-factor PCC in the emergent reversal of warfarin-associated ICH. Secondary clinical outcomes were similarly nonsignificant.

**Keywords** Intracranial hemorrhage · Intraparenchymal hemorrhage · Hemostasis · Prothrombin complex concentrate · Vitamin K antagonist · Warfarin

## Introduction

Intracranial hemorrhage (ICH) is the most life-threatening complication associated with anticoagulation therapy. ICHs, whether spontaneous or traumatic in nature, or subdural or intraparenchymal in location, tend to be more severe in anticoagulated patients, leading to worse functional outcomes and higher mortality [1–3].

Prothrombin complex concentrate (PCC) is plasma-derived, concentrated mixtures of vitamin k-dependent clotting factors, which have been studied for the reversal of coagulopathy in patients receiving warfarin [4–15]. Three-factor PCC contains factors II, IX, X, and non-therapeutic

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amounts of factor VII [16]. Four-factor PCC contains therapeutic amounts of factor VII in addition to factors II, IX, and X [17, 18]. Human prothrombin complex (Kcentra®) is the only 4-factor PCC available in the USA and the only Food and Drug Administration (FDA)-approved medication for INR reversal in the setting of warfarin-associated major hemorrhage [18].

Guidelines for the reversal of antithrombotics in ICH [including intraparenchymal hemorrhage (traumatic or spontaneous), intraventricular hemorrhage, subdural hematoma], published jointly by the Neurocritical Care Society and Society of Critical Care Medicine, recommend reversing anticoagulation in warfarin-associated ICH with 4-factor PCC over either 3-factor PCC or fresh-frozen plasma (FFP) [1, 17, 19]. This recommendation is based on retrospective data suggesting more rapid and reliable INR reversal with 4-factor PCC [1, 17]. However, data correlating these effects to improved clinical outcomes are lacking. Only four retrospective studies comparing 3- and 4-factor PCC have been published, with variable results and not solely evaluating ICH [4–7].

The objective of our study was to evaluate the comparative in-hospital mortality of 3-factor and 4-factor PCC in those presenting with warfarin-associated ICH.

## Methods

### Study Design

This retrospective cohort study was conducted over a 2-year period (October 1, 2013–August 31, 2015) at Intermountain Healthcare (IHC), a 22-hospital health system. All data were retrieved from IHC's Enterprise Data Warehouse, a central data repository of all IHC patient encounter data. No research funding was provided. The protocol included a waiver of informed consent and was approved by the IHC Institutional Review Board.

### Study Population and PCC Dosing

Patients included in this study were $\geq$18 years old and received either 3-factor PCC (Profilnine®, Grifols Biologicals Inc. Los Angeles, CA; 2010) [16] or 4-factor PCC (Kcentra®, CSL Behring GmbH. Marburg, Germany; 2013) [18] for the emergent reversal of warfarin-associated ICH. Patients were excluded if they were pregnant, had an ICH within the previous 6 months, hemorrhage caused by catastrophic or penetrating head trauma (expected survival $<$12 h), hemorrhagic conversion of acute ischemic stroke, isolated subarachnoid hemorrhage, tumor-associated bleeding, INR $<$1.2 on presentation, which we used to account for provider preference in treating INRs outside of guideline recommendations for warfarin reversal, or if there were insufficient data to appropriately assess stated objectives.

Patients with an ICH were identified using *International Classification of Diseases, Ninth Revision* (ICD-9) codes 430, 431, 432.0, 432.1, 432.9, 852.0x, 852.2x, 852.4x, or 853.0, specifying subdural, subarachnoid, intraventricular, intraparenchymal, intracerebral, and epidural hemorrhage, which have been used in previously published studies on warfarin-associated ICH [20, 21]. Both traumatic and non-traumatic hemorrhages were included. Medical charts were reviewed manually to confirm the incident diagnosis, the presence of an active warfarin prescription, and the use of PCC for emergent INR reversal.

Baseline demographics collected were those known or believed to impact outcomes with warfarin-associated ICH (Table 1). These variables included age, presenting systolic blood pressure, GCS at presentation, presenting and post-reversal INR, comorbidities, concomitant anticoagulant and antiplatelet medications, indication for anticoagulation, ICH subtype (intraparenchymal vs. subdural), surgical procedures during hospitalization, and whether or not the ICH was related to trauma.

PCC use during the study period was dependent on time of enrollment rather than on patient-specific factors. Three-factor PCC was used exclusively in 2013 prior to the approval and widespread availability of 4-factor PCC in the USA. Four-factor PCC became more widely used in all IHC facilities in mid-2014 following FDA approval and was used preferentially, barring contraindications, after that time.

At IHC, PCC is dosed using an emergent reversal guideline (Fig. 1), which was approved in the middle of the study period. Dosing recommendations are based on presenting INR and patient weight, similar to the package insert of each product. Patients in this study could also receive vitamin K and/or FFP as part of anticoagulation reversal and were prescribed at the discretion of the attending physician.

### Outcomes

The primary outcome, in-hospital mortality, was defined as all-cause mortality during the patient's index hospitalization. Secondary outcomes included intensive care unit (ICU)- and hospital-free days at day 28, 30-day mortality, post-reversal INR collected as first INR drawn following PCC administration, discharge location (home, acute rehab facility, skilled nursing facility, or hospice/death), and thromboembolic (TE) events within 90 days, defined as venous thromboembolism (pulmonary embolism, deep vein thrombosis) or arterial TE (stroke, systemic embolism) using *ICD-9* codes and Natural Language Processing as previously described and validated [22, 23].

**Table 1** Baseline characteristics

| Baseline characteristics | Total cohort ($n = 103$) | 4-factor PCC ($n = 63$) | 3-factor PCC ($n = 40$) | Unadjusted $p$-value* | Adjusted $p$-value* |
|---|---|---|---|---|---|
| Age | 79 (73–84) | 80 (73–86) | 77 (73–82) | 0.237 | 0.747 |
| Male *n* (%) | 51 (49.5) | 34 (54) | 17 (42.5) | 0.351 | 0.747 |
| GCS | 15 (9–15) | 15 (10–15) | 14.5 (9–15) | 0.565 | 0.854 |
| GCS $\leq$8 *n* (%) | 24 (23.3) | 15 (23.8) | 9 (22.5) | 1 | 1 |
| Systolic blood pressure | 156 (130–174) | 160 (133–176) | 155 (128–170) | 0.581 | 0.854 |
| Anticoagulation indication | | | | | |
| Atrial fibrillation *n* (%) | 65 (63.1) | 43 (68.3) | 22 (55.0) | 0.25 | 0.747 |
| Venous thromboembolism *n* (%) | 29 (28.2) | 15 (23.8) | 14 (35.0) | 0.314 | 0.747 |
| Prosthetic valve *n* (%) | 6 (5.8) | 3 (4.8) | 3 (7.5) | 0.675 | 0.889 |
| Other *n* (%) | 8 (7.8) | 5 (7.9) | 3 (7.5) | 0.296 | 0.747 |
| Comorbidities | | | | | |
| Cancer *n* (%) | 25 (24.3) | 16 (25.4) | 9 (22.5) | 0.922 | 1 |
| Diabetes *n* (%) | 35 (34.0) | 20 (31.7) | 15 (37.5) | 0.698 | 0.875 |
| Hypertension *n* (%) | 80 (77.7) | 47 (74.6) | 33 (82.5) | 0.487 | 0.852 |
| Heart failure *n* (%) | 26 (25.2) | 16 (25.4) | 10 (25.0) | 1 | 1 |
| Peripheral vascular disease *n* (%) | 5 (4.9) | 4 (6.3) | 1 (2.5) | 0.646 | 0.875 |
| Ischemic Stroke/TIA *n* (%) | 22 (21.4) | 15 (23.8) | 7 (17.5) | 0.607 | 0.854 |
| *Concomitant Anticoagulant n (%)* | 2 (1.9) | 0 (0) | 2 (5.0) | 0.148 | 0.747 |
| Enoxaparin *n* (%) | 1 (1.0) | 0 (0) | 1 (2.5) | 0.388 | 0.747 |
| Heparin *n* (%) | 1 (1.0) | 0 (0) | 1 (2.5) | 0.388 | 0.747 |
| *Concomitant Antiplatelet n (%)* | 37 (35.9) | 26 (41.2) | 11 (27.5) | 0.293 | 0.747 |
| Aspirin *n* (%) | 35 (34.0) | 24 (38.1) | 11 (27.5) | 0.372 | 0.747 |
| Clopidogrel *n* (%) | 2 (1.9) | 2 (3.2) | 0 (0) | 0.52 | 0.854 |
| INR admission[a] | 2.7 (2.2–3.3) | 2.6 (2.2–3.1) | 2.8 (2.3–3.7) | 0.411 | 0.747 |
| Presenting hemorrhage | | | | | |
| Subdural *n* (%) | 51 (49.5) | 33 (52.4) | 18 (45.0) | 0.597 | 0.854 |
| Intraparenchymal *n* (%) | 52 (50.5) | 30 (47.6) | 22 (55.0) | 0.597 | 0.854 |
| Surgical procedure *n* (%) | 15 (14.6) | 11 (17.6) | 4 (10.0) | 0.395 | 0.747 |
| ICH associated with trauma *n* (%) | 52 (50.5) | 35 (55.6) | 17 (42.5) | 0.276 | 0.747 |

[a] Signifies initial values upon emergency department admission

* Statistical comparisons are between 3-factor PCC and 4-factor PCC cohorts. Demographics are reported as medians with IQI unless specified otherwise

*GCS* Glasgow Coma Scale, *ICH* intracranial hemorrhage, *INR* international normalized ratio, *IQI* interquartile intervals, *PCC* prothrombin complex concentrate, *TIA* transient ischemic attack

## Statistical Analysis

Descriptive statistics were reported using proportions for binomially distributed variables and medians with interquartile intervals (IQI) for continuous variables. Simple tests of comparison of stratified distributions' central tendencies used Fisher's exact test and Pearson's Chi-square test for comparing pairs of binomially distributed variables with and without sparse cells, respectively. Wilcoxon rank-sum test, a nonparametric analogue of Student's $t$ test, was used to compare unpaired, non-Gaussian, continuous distributions. Bootstrapped Kolmogorov–Smirnov (K–S) test was used to compare ordinal, discrete distributions. The bootstrapped K–S test is able to handle instances in which many ties are present between distributions [24].

Inferential statistics were computed using generalized linear models in which the treatment effect (receipt of 4-factor PCC versus 3-factor PCC) was the main effect of interest, controlling for potential confounders where appropriate. The treatment effect on any continuous outcome was analyzed using linear regression, while the treatment effect on any binary outcome was measured using logistic regression. Finally, the treatment effect on the ordinal outcome (viz., discharge disposition) was measured using ordinal logistic regression. Regression diagnostics were conducted for the primary analysis.

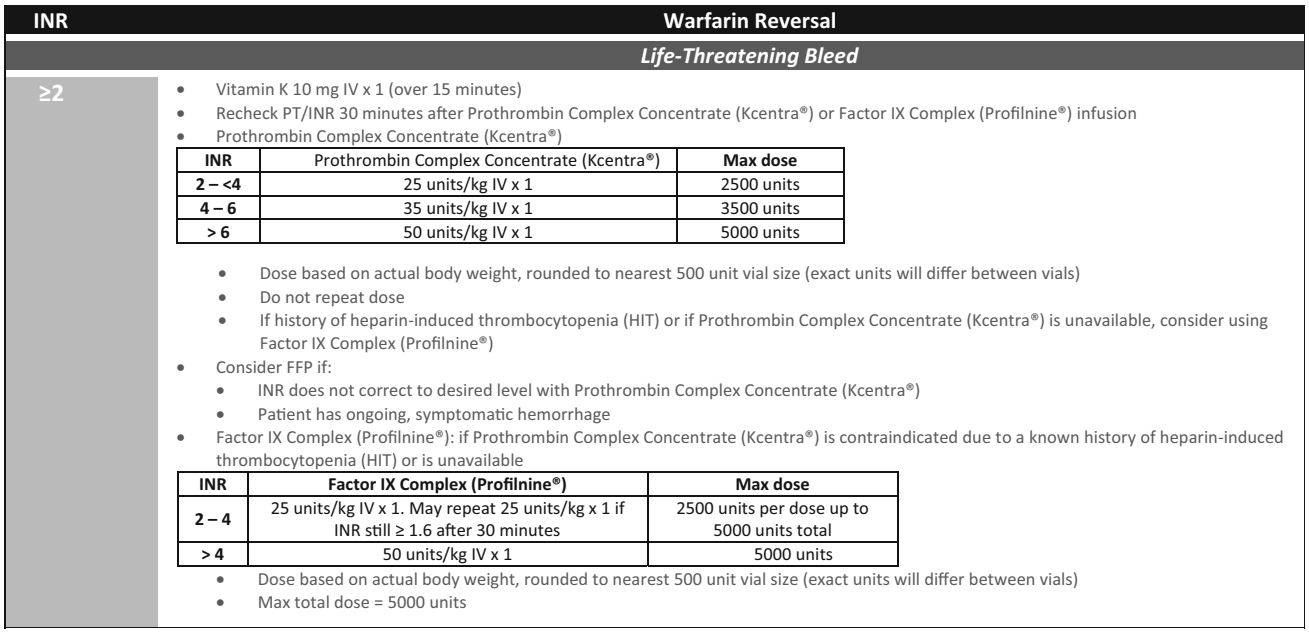


**Fig. 1** Prothrombin complex concentrate recommended dosing strategies for INR reversal in warfarin-associated life-threatening hemorrhages—taken from the "Antithrombotic Bleeding Mitigation Guideline" at Intermountain Healthcare

Specifically, in order to assess model calibration, the Hosmer–Lemeshow (H–L) goodness-of-fit (GOF) test was conducted for 5 through 15 bins [25]; note that the null hypothesis of the H–L GOF test is that the model is sufficiently calibrated. To assess the model's discriminatory ability, the area under the curve (AUC) of the receiver operator characteristic (ROC) was computed [25].

To assess the robustness of the primary analysis, a sensitivity analysis was conducted by use of a propensity score-matching procedure per the recommendation outlined by Hosmer and Lemeshow [25]. Readers interested in the specific approach are encouraged to reference the current article's Electronic supplementary material. Additionally, a subgroup analysis was conducted that mirrored the primary analysis but excluded the eight patients who received multiple doses of 4- or 3-factor PCC.

Finally, the *p*-values associated with hypothesis testing beyond that of the pre-specified primary analysis were adjusted to account for the multiplicity effect of multiple hypothesis testing as specified by Benjamini and Hochberg [26]. Further detail is included in the Electronic supplementary material.

## Results

### Patients and PCC Dosing

There were 146 patients admitted to an IHC facility for ICH and treated with a PCC product during the study period. Upon confirmatory chart review and after applying exclusion criteria, 103 patients were included (63 received 4-factor PCC and 40 received 3-factor PCC) (Fig. 2). Baseline characteristics can be found in Table 1. The median age was 79 years (IQI 73–84) and 49.5% were male. Median GCS upon emergency department admission was 15 (IQI 9–15), and 23.3% of patients presented with GCS $\leq$8. Atrial fibrillation was the indication for anticoagulation in the majority of patients (63.1%), followed by venous thromboembolism (28.2%). At the time of event, 35.9% of patients were taking antiplatelet medications. Subdural and intraparenchymal hemorrhages made up 49.5 and 50.5% of presenting hemorrhages, respectively. Half of all patients developed ICH secondary to trauma. Median INR upon presentation was 2.7 (IQI 2.2–3.3; range 1.4–11) which was reversed to a median INR of 1.3 (IQI 1.2–1.5; range 1–2.3). Groups were similar across baseline characteristics.

Dosing of PCC products and utilization of other reversal agents can be found in Table 2. The median total dose and weight-based dose of PCC were similar in both groups: 4-factor PCC 2000 units and 25 units/kg versus 3-factor PCC 2000 units and 26 units/kg, respectively. Eight patients received a second dose of PCC, 3 patients in the 4-factor PCC group, and 5 in the 3-factor PCC group. Overall, 95.1% of patients received vitamin K as part of the reversal strategy. This was similar between cohorts. FFP was used in combination with PCC in 38.8% of patients but was used less often with 4-factor PCC (26.9 vs. 52.5%; adjusted $p = 0.168$).

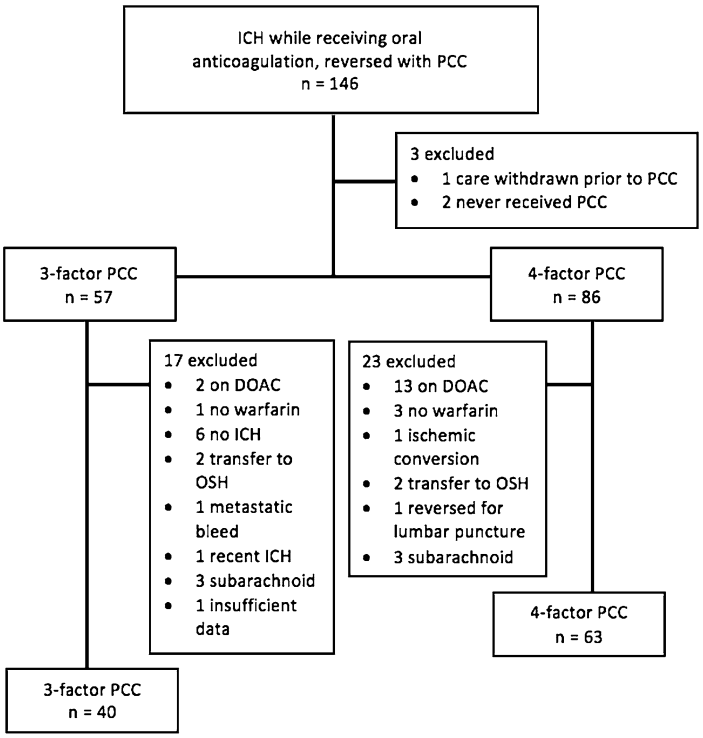


**Fig. 2** Patient inclusion and study flow

Legend: DOAC = direct oral anticoagulant, including dabigatran, rivaroxaban, apixaban; ICH = intracranial hemorrhage; OSH = outside hospital; PCC = prothrombin complex concentrate

**Table 2** PCC product dosing and concomitant medication and blood product use

| Reversal | 4-factor PCC ($n = 63$) | 3-factor PCC ($n = 40$) | Unadjusted $p$-value | Adjusted $p$-value* |
|---|---|---|---|---|
| Median dose, units (IQI) | 2088 (1665–2500) | 2000 (1500–3248) | 0.393 | 0.747 |
| Median dose, units/kg (IQI) | 25 (23–29) | 26 (20–41) | 0.023 | 0.483 |
| Vitamin K, *n* (%) | 62 (98.4) | 36 (90) | 0.163 | 0.746 |
| FFP, *n* (%) | 17 (26.9) | 21 (52.5) | 0.004 | 0.168 |

* Due to the multiplicity effect of testing multiple hypotheses; *adjusted p-values* provide a more appropriate assessment of statistical significance by controlling and limiting the false discovery rate at 5%, per the method of Benjamini and Hochberg (see Electronic supplementary material for additional detail)

*FFP* fresh-frozen plasma, *PCC* prothrombin complex concentrate

## Outcomes

Primary and secondary outcomes data are outlined in Table 3. By multivariable logistic regression, those who received 4-factor PCC trended toward higher rates of in-hospital mortality (28.6 vs. 20.0%), although the effect was not statistically significant (OR 2.2, 95% CI 0.59–9.4, $p = 0.26$), adjusting for an indicator of subdural versus intraparenchymal hemorrhage and whether presenting GCS was $\leq 8$ versus $> 8$. The primary logistic model seemed to be well calibrated (H–L GOF test $p > 0.9$) and featured good discriminatory ability (AUC of ROC:0.867). The results of the sensitivity analysis using propensity matching were consistent with the primary analysis. The subgroup analysis that excluded the eight patients who received multiple doses of 4- or 3-factor PCC featured similar results (OR 2.1, 95% CI 0.52–11.3, $p = 0.32$) to those of the primary analysis.

There was no statistically significant difference in any secondary outcomes between groups, even before adjusting for the false discovery rate. Post-reversal INR was lower with 4-factor PCC, though not significantly (1.2 vs. 1.3; OR −0.078, 95% CI −0.174–0.017; $p = 0.747$). ICU-free days (26.3 vs. 27.1; OR −1.845, 95% CI −5.251–1.561; $p = 0.51$), and hospital-free days (23.8 vs. 24.2; OR −1.322, 95% CI −4.486–1.843; $p = 0.57$) at day 28 were similar. Discharge location was also similar between groups ($p = 0.927$). Mortality did not diverge at day 30, again remaining similar between the 4- and 3-factor PCC groups (36 vs. 35%; OR −0.053, 95% CI −1.058–0.97; $p = 0.92$).

**Table 3** Primary and secondary outcomes

| Outcome variable | 4-factor PCC ($n = 63$) | 3-factor PCC ($n = 40$) | 4-factor PCC coefficient (95% CI) | Unadjusted $p$-value | Adjusted $p$-value[a] |
|---|---|---|---|---|---|
| Primary outcome | | | | | |
| In-hospital mortality, $n$ (%) | 18 (28.6) | 8 (20.0) | 0.776 (−0.523–2.243) | 0.261 | *NA* |
| Secondary outcome | | | | | |
| INR reversal[b] | 1.2 (1.2–1.4) | 1.3 (1.2–1.5) | −0.078 (−0.174–0.017) | 0.107 | 0.747 |
| Hospital-free days[c] | 23.8 (22.0–25.7) | 24.2 (21.7–26.1) | −1.322 (−4.486–1.843) | 0.409 | 0.747 |
| ICU-free days[c] | 26.3 (24.1–27.4) | 27.1 (25.7–28) | −1.845 (−5.251–1.561) | 0.285 | 0.747 |
| 30-day mortality, $n$ (%) | 23 (36.5) | 14 (35.0) | −0.053 (−1.058–0.97) | 0.917 | 1 |
| Discharge disposition, $n$ (%) | | | 0.037 (−0.805–0.883) | 0.927 | 1 |
| Home | 11 (17.5) | 6 (15.0) | | | |
| Rehab | 16 (25.4) | 11 (27.5) | | | |
| Skilled nursing facility | 15 (23.8) | 11 (27.5) | | | |
| Hospice/death | 21 (33.3) | 12 (30.0) | | | |
| Resumption of anticoagulation at discharge, $n$ (%) | 7 (11.1) | 4 (10.0) | 0.118 (−1.151–1.515) | 0.859 | 1 |
| Thromboembolic event, $n$ (%) | 12 (19.0) | 4 (10.0) | −0.745 (−2.199–0.645) | 0.29 | 0.747 |

[a] Due to the multiplicity effect of testing multiple hypotheses; *adjusted p-values* provide a more appropriate assessment of statistical significance by controlling and limiting the false discovery rate at 5%, per the method of Benjamini and Hochberg (see Electronic supplementary material for additional detail)

[b] First INR value drawn after administration of PCC

[c] ICU- and hospital-free days are through day 28

*ICU* intensive care unit, *PCC* prothrombin complex concentrate

TE events occurred in 15.5% of patients including 12 patients (19%) treated with 4-factor PCC and 4 patients (10%) treated with 3-factor PCC (OR 0.745; 95% CI 0.645–2.199, adjusted $p = 0.51$).

## Discussion

We did not find any improvement in in-hospital mortality in patients with warfarin-associated ICH treated with 4- compared with 3-factor PCC. These results remained even after adjusting for hemorrhage type (intraparenchymal vs. subdural) and presenting GCS ($\leq 8$ vs. $> 8$), two factors we felt to be most closely associated with mortality in this population. None of the six secondary analyses measured a statistically significant effect, even prior to adjustment for multiple hypothesis testing.

Overall, INR corrected from 2.7 to 1.3 or less after receipt of either PCC product, which is similar to previously reported data [4, 5, 13]. Reversal was similar in both groups for first post-treatment INR. This differs from some studies, which found greater INR reversal with 4- versus 3-factor PCC (first post-treatment INRs 1.2 vs. 1.4; $p < 0.01$) [4, 5], but is similar to other studies, which found no significant difference in INR reversal (first post-treatment INRs 1.3 in both groups) [7, 13]. FFP was used more frequently in the 3-factor PCC group which could have arguably contributed to the similar INR reversal; however, the difference in FFP use was not significant after adjustment. Additionally, FFP does not reliably and rapidly reduce INR values to $< 1.4$, and unlikely contributed greatly to the further reduction of INR in combination with 3-factor PCC [27, 28].

While studies have shown improved outcomes using either 3-factor PCC [8, 9] or 4-factor PCC [10, 29] in patients with warfarin-associated ICH compared to FFP, studies directly comparing the two products are lacking [1]. Our study is the first of its kind comparing the clinical effectiveness of 4- versus 3-factor PCC solely in patients presenting with ICH. One study of 165 patients presenting with any warfarin-associated major hemorrhage showed reduced mortality in those receiving 4-factor PCC (OR 0.19; 95% CI 0.06–0.54, $p = 0.002$), as well as those with post-reversal INR $\leq 1.5$ regardless of PCC type [4]. However, more patients presenting with ICH were administered 3-factor PCC in this study, potentially contributing to increased mortality in this group.

A retrospective review of stroke registries containing over 1500 patients with warfarin-associated ICH assessed clinical outcomes associated with various reversal strategies [11]. The analysis showed higher 30-day mortality with 4-factor PCC compared to 3-factor PCC; however, the

4-factor PCC group also contained patients treated with the combination of 3-factor PCC and recombinant activated factor VII, which has been associated with increased thrombotic complications [11, 30–33]. Our study showed a nonsignificant increase in in-hospital mortality in those receiving 4-factor PCC and no difference in any secondary outcomes between 4- and 3-factor PCC.

While various bleeding events, including gastrointestinal hemorrhage, can be life threatening, these patients are inherently different to those with ICH. We chose to limit our study to ICH patients to create a more homogeneous population and determine the comparative effectiveness of PCC in patients at highest risk of death. Variability remains in our population due to the different predicted outcomes and clinical trajectories in patients with traumatic versus spontaneous hemorrhages and subdural versus intraparenchymal location. Hemorrhage type was evenly distributed between groups, and this potential variability was addressed by correcting for hemorrhage type in the primary analysis. Also, while previous studies have focused on surrogate outcomes such as INR reversal following PCC administration, we chose to address clinical outcomes. These more clinically relevant outcomes will ultimately be needed to provide answers regarding the true comparative effect of these agents.

Notably, the rate of TE events in our study is higher than in some previous reports [4, 7, 13, 14]. We followed patients for 90-days after PCC administration, which may have contributed to our higher rate of thrombotic events, as many studies have only reported 7-day [13, 14] or in-hospital [4] thrombotic rates. Studies reporting rates of 9–10% followed patients for longer periods of time (30–60 days) [15, 34]. IHC did not have a protocol in place to evaluate for TE events following administration of PCC. This was left up to the discretion of the treating physician. We were unable to assess if these TE events were clinically significant or incidental findings. It is unknown if PCC contributes to late thrombotic events, or if this is a sequelae of not reinitiating anticoagulation, which has shown to worsen outcomes in atrial fibrillation patients presenting with ICH [34, 35].

There are several limitations to this study and inherent to the retrospective study design. Without a protocol in place at IHC to recheck INR values at specified times following PCC administration, we were unable to collect absolute time to INR reversal, a variable previously shown to be achieved faster with 4-factor PCC [4, 36, 37]. Mortality in warfarin-associated ICH is a dynamic process impacted by many factors including time to INR reversal and without these data it is unclear if increased time to reversal in one or both groups may have confounded our results. We were also unable to collect historical prognostic variables including volume of presenting ICH, exact hemorrhage location, intraventricular extension, midline shift, and pupillary function, components included within the ICH Score [38]. These variables were included in some similar studies to better define patients' expected clinical course [11, 29], but left out of other recent studies [4–7, 15]. Unfortunately, documentation at IHC facilities did not uniformly include this information and we did not retrospectively calculate hemorrhage volumes. The lack of information on these factors known to impact mortality in this population represents a limitation to our study, and without these we relied upon presenting GCS as a surrogate for clinical severity.

We attempted to address patient morbidity using the surrogate of disposition following ICH by collecting data on discharge location. This is not a standard measure of functional outcome in this population, however. Using a validated functionality score such as the modified Rankin Score or Glasgow Outcome Scale would have been a better indicator of overall clinical effectiveness; however, our institutions only recently begun collecting these data.

Lastly, although our study is one of the largest to date comparing 4- and 3-factor PCC, the small sample size prevented us from including other variables in our outcome analyses, such as concomitant use of FFP, indication for anticoagulation, re-initiation of anticoagulation, concomitant antiplatelet use, and platelet transfusions.

## Conclusions

In-hospital mortality was not improved with the use of 4-factor PCC compared to 3-factor PCC in the emergent reversal of warfarin-associated ICH. The effect on secondary clinical outcomes was similarly nonsignificant. Given the uncertainty surrounding clinical benefit, relative TE events, and higher acquisition cost of 4-factor PCC, future research should focus on comparative cost-effectiveness, specifically regarding functional outcomes, of 4- and 3-factor PCC in patients presenting with warfarin-associated ICH.

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