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Incidence of thrombotic complications related to weight-based dosing of activated prothrombin complex concentrate (aPCC) for reversal of apixaban and rivaroxaban in obese patients

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Abstract
Factor eight inhibitor bypassing activity (aPCC) is recommended as a non-specific reversal agent for direct oral anticoagulants (DOACs) according to the 2017 American College of Cardiology (ACC) guidelines for reversal of anticoagulation. Factor eight inhibitor bypassing activity carries a black box warning for thrombotic events such as stroke, pulmonary embolism, deep vein thrombosis, and myocardial infarction, particularly at high doses. This was a retrospective, single-center, cohort investigation that included patients who received a weight-based dose of aPCC for reversal of apixaban and rivaroxaban between January 1, 2015, and December 31, 2020. Patients were grouped by BMI as obese (BMI $\geq$ 30 kg/m^2) or non-obese (BMI $<$ 30 kg/m^2) for analysis. The primary outcome of this investigation was the occurrence of thrombotic complications [venous thromboembolism (VTE), myocardial infarction, stroke] documented in the medical record at any point during hospitalization after administration of aPCC. Secondary outcomes included bleeding complications, in-hospital mortality, ICU and hospital length of stay. Patients in the obese group were younger [76.4 years (SD +/− 11.3 years) vs. 69.6 years (SD +/− 12.4 years); $p < 0.0001$] and a higher proportion had a diagnosis of diabetes mellitus prior to admission [37 (19.2%) vs. 35 (36.8%); $p = 0.0011$]. There was no difference in the primary outcome of thrombotic events between non-obese and obese patients [12 (6.2%) vs. 5 (5.3%); $p = 0.75$], or for any of the secondary outcomes of bleeding, in-hospital mortality or length of stay. This investigation did not reveal a difference in rates of thrombosis or bleeding events between obese and non-obese patients who received aPCC for reversal of apixaban and rivaroxaban.

Keywords Thromboembolism · Blood coagulation factors · Hemorrhage · Factor Xa inhibitors

Highlights

- 4-Factor PCCs (including both PCC and aPCC) are recommended as a first-line non-specific reversal agent for DOACs such as apixaban and rivaroxaban.
- There is a lack of data regarding appropriate dosing strategies, optimal dosing weight and safety outcomes with regard to use of aPCC for DOAC reversal.
- This investigation compared incidence of thrombotic and bleeding complications of aPCC for reversal of apixaban and rivaroxaban in obese and non-obese patient groups.
- Based on our findings, there is no difference in thrombotic or bleeding complications between obese and non-obese patients when aPCC is used for reversal of apixaban and rivaroxaban.

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Introduction

Over the last decade direct oral anticoagulants (DOACs) such as apixaban and rivaroxaban have become an attractive alternative to vitamin K antagonists (VKAs) due to their comparable efficacy and lower risk of bleeding complications. For these reasons, they are now preferred therapy in place of VKAs for the treatment of venous thromboembolism (VTE) and prevention of complications related to atrial fibrillation [1, 2]. However, bleeding complications still occur with DOACs and treatment of clinically significant bleeding may involve administration of a reversal agent. Several therapies have been evaluated for the treatment of life-threatening and clinically significant bleeding in patients receiving DOACS. Andexxa® [coagulation factor Xa (recombinant), inactivated –zhzo] is an approved by the US Food and Drug Administration (FDA) for the treatment for life-threatening or uncontrolled bleeding in patients who are receiving rivaroxaban or apixaban. Despite FDA approval for this indication, many institutions continue to use non-specific reversal agents such as four-factor prothrombin complex concentrates (PCC) and activated prothrombin complex concentrates (aPCC) because of similar efficacy and lower cost relative to Andexxa® [3–6]. The inactivated 4PCC commercially available in the United States is KCentra®, which contains clotting factors II, VII, IX, X, Proteins C and S, Antithrombin III, human albumin and heparin. KCentra® is FDA-approved for the reversal of VKAs [7]. The aPCC available in the United States is factor eight inhibitor bypassing activity (FEIBA®), which contains activated clotting factor VII as well as non-activated factors II, IX, and X. FEIBA® is FDA-approved for control and prevention of bleeding in patients with hemophilia A and B [8].

Despite their use as treatments for life-threatening bleeding associated with DOACs, neither PCC nor aPCC are currently FDA-approved for reversal of bleeding related to DOACs [4, 5]. However, the efficacy of 4PCC for reversal of DOACs has been well established in multiple trials and these agents are recommended as a first-line non-specific reversal agent for DOACs by both the 2017 American College of Cardiology Expert Consensus on Management of Bleeding and the Neurocritical care/Society of Critical Care Medicine Joint Statement on the Reversal of Antithrombotics in Intracranial Hemorrhage at a dose of 50 units/kg [8, 9]. PCC is weakly recommended over aPCC because it has been studied in vivo in humans for bleeding reversal, while aPCC has only been studied for DOAC reversal in animal models and ex-vivo human blood samples spiked with DOACs [9].

While no large-scale studies have been conducted on aPCC dosing in obesity, some case reports have examined different dosing strategies for other non-specific reversal agents such as recombinant factor VIIa (rVIIa). Their findings suggest that calculating a dose of non-specific reversal agents based on total body weight may overestimate the patient's blood volume and the amount of reversal agent required [11, 12]. This could potentially lead to unintended thrombotic events in frequencies disproportionate to the healthy-weight population. The appropriate dosing range as well as the appropriate dosing weight for aPCC when used for DOAC reversal in obese patients have yet to be elucidated. The purpose of the current investigation was to assess the rates of thrombotic complications in non-obese versus obese patients who received weight-based dosing of aPCC for DOAC reversal.

Methods

Study population

This was a retrospective, single-center cohort study conducted to assess the safety of current dosing strategies of aPCC in obese versus non-obese patients for apixaban and rivaroxaban reversal. Activated Prothrombin Complex Concentrate is the only factor Xa inhibitor reversal agent on formulary at the study site. Patients were evaluated for inclusion in the study if they were at least 18 years old and received aPCC for apixaban and rivaroxaban reversal between January 1, 2015, and December 31, 2020. Patients were excluded if their aPCC dose or administration were not properly documented, if they received aPCC for any indication other than DOAC reversal (i.e., hemophilia, warfarin reversal), if they were deemed to have an "unsurvivable" injury per physician documentation, or if they left against medical advice (AMA) after aPCC administration. Additionally, patients taking dabigatran were excluded from this investigation since dabigatran has a drug-specific reversal agent on formulary at the study site.

Study data were collected and managed using REDCap electronic data capture tools hosted at the University of Tennessee Health Science Center [13, 14]. REDCap (Research Electronic Data Capture) is a secure, web-based software

Table 1 BMI categories based on AHA/ACC/TOS (American Heart Association, American College of Cardiology and the Obesity Society)

Classification	BMI
NORMAL	18.5–24.9 kg/m^2
Overweight	25–29.9 kg/m^2
Obesity Class I	30–34.9 kg/m^2
Obesity Class II	35–39.9 kg/m^2
Obesity Class III	> 40 kg/m^2

platform designed to support data capture for research studies.

Patients were classified based on BMI categories per AHA/ACC/TOS (American Heart Association, American College of Cardiology and the Obesity Society) categories shown in Table 1. For comparison of primary and secondary endpoints, patients were separated into non-obese (BMI < 30 kg/m^2) and obese (BMI ≥ 30 kg/m^2) groups.

Patients were dosed with aPCC according to the study site's protocol which allows for dosing of aPCC in the range of 20–50 units/kg of actual body weight for DOAC reversal when the patient or family member reported a dose of factor Xa inhibitor in the past 24 h or if there was an unknown time from last administration of factor Xa inhibitor. The specific dose is chosen at the discretion of the interdisciplinary medical team and is irrespective of the dose of factor Xa inhibitor. In addition, no other pharmacologic reversal agents, such as recombinant factor VIIa, andexanet alfa, 3 factor PCC, or tranexamic acid are included in the institutional protocol for the reversal of life-threatening bleeding due to factor Xa inhibitors. The utilization of blood products for hemorrhagic shock or anemia were at the discretion of the prescribing provider.

The primary outcome was incidence of thrombotic complications documented in the medical record at any point during hospitalization. Thrombotic complications were pre-defined as: VTE including deep vein thrombosis (DVT) and pulmonary embolism (PE), acute ischemic stroke, and myocardial infarction. Secondary outcomes included bleeding complications documented in the medical record at any point during hospitalization, hospital and ICU length of stay, in-hospital mortality. Bleeding complications were defined as continuation ofacute bleeding episode (gastrointestinal bleeding (GIB), surgical site bleeding, hemorrhage evolution or hematoma expansion on CT, etc.) after aPCC was administered.

Statistical analysis

All statistical analyses were conducted with SAS [Version 9.4 (TS1M4); SAS Institute, Inc.; Cary, NC, USA]. Continuous variables were evaluated for normality through a holistic evaluation of Shapiro-Wilk test, Kolmogorov–Smirnov test, and histograms. Variables found to have normal distribution were presented as mean and standard deviation. Between groups comparisons were made with a t test. Those variables found to have a non-normal distribution were presented as median and interquartile range. Between group comparisons were made with Mann–Whitney U. Categorical variables were presented as count and proportion of group. Between group comparisons were made with a chi square or Fisher's Exact test as appropriate. Assuming an 8% rate of VTE in the BMI < 30 group, a total of 274 patients would be needed to achieve 80% power to find an absolute difference of 7% between the groups at an alpha level of 0.05.

Results

A total of 930 patients were assessed for inclusion during the study period. Of these, 288 patients were included in the final analysis. Reasons for exclusion are detailed in Fig. 1, with the most common being that aPCC was used for something other than DOAC reversal. Of patients included in the final analysis, 193 were classified as non-obese (BMI < 30 kg/m^2) and 95 were classified as obese (BMI ≥ 30 kg/m^2).

As compared to the non-obese group, those in the obese group were younger [76.4 years (SD +/− 11.3 years) vs. 69.6 years (SD +/− 12.4 years); $p < 0.0001$] and a higher proportion had a diagnosis of diabetes mellitus prior to admission [37 (19.2%) vs. 35 (36.8%); $p = 0.0011$). The complete baseline demographics are available for review in Table 2.

Reasons for reversal were similar between groups. The most common indications for reversal were intracranial hemorrhage [143 (74.1%) vs. 63 (66.3%); $p = 0.16$] and gastrointestinal bleeding [20 (10.4%) vs. 12 (12.6%); $p = 0.56$]. The most common DOAC was apixaban [124 (64.3%) vs. 65 (68.4%); $p = 0.48$] followed by rivaroxaban [68 (35.2%) vs. 30 (31.6%); $p = 0.54$]. A large portion of hemorrhages requiring reversal in both groups were due to traumatic injury [101 (53.4%) vs. 41 (43.6%); $p = 0.12$].

Total mean doses of aPCC used in non-obese vs. obese patients were 2500 units (SD +/− 1060) and 3500 units (SD +/− 1426) respectively ($p \leq 0.001$). Patients received an average weight-based dose of 34.4 units/kg (SD +/− 13.3units/kg) and 35.4 units/kg (SD +/− 13.1 units/kg) for the non-obese and obese groups respectively (see Table 3).

The results of the primary and secondary outcomes are detailed in Table 4. There was no difference in the primary

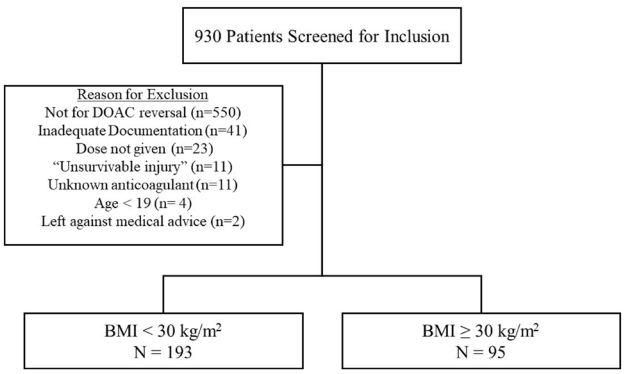

Fig. 1 Study population and exclusion criteria

Table 2 Baseline demographics

Characteristic	BMI < 30 (n=193)	BMI ≥ 30 (n= 95)	p-value
Age (years)	76.4	69.8	< 0.001
Female (n, %)	92 (47.7)	43 (45.3)	0.70
Average actual body weight (kg)	71.9	106	< 0.001
Average BMI (kg/m2)	24.4	35.7	< 0.001
BMI category (n, %)			
Normal	91 (47.1)	–	
Overweight	102 (52.9)	–	
Obesity Class I	–	52 (54.7)	
Obesity Class II	–	28 (29.5)	
Obesity Class III	–	15 (15.8)	
Ethnicity (n, %)			
White	178 (92.2)	95 (100)	
Black	12 (6.2)	–	
Hispanic	1 (0.5)	–	
Other/unknown	2 (1.0)	–	
Comorbid conditions (n, %)			
Diabetes mellitus (DM)	37 (19.2)	35 (36.8)	0.001
Atrial fibrillation (AF)	131 (67.9)	69 (72.6)	0.41
Hypercoagulable condition	14 (7.3)	9 (9.5)	0.51
Coronary artery disease (CAD)	59 (30.6)	21 (22.1)	0.13
Atherosclerotic disease	52 (26.9)	22 (23.2)	0.49
History of venous thromboembolism (VTE)	43 (22.8)	20 (21.1)	0.81
History of myocardial infarction	11 (5.7)	4 (4.2)	0.78
DOAC reported (n, %)			
Apixaban	124 (64.3)	65 (68.4)	0.48
Rivaroxaban	68 (35.2)	30 (31.6)	0.54
Unknown	1 (0.5)	0 (0)	> 0.999
DOAC indication (n, %)			
Multiple indications	9 (4.7)	5 (2.3)	0.78
Atrial fibrillation	125 (64.8)	71 (74.7)	0.09
PE/DVT treatment or secondary prophylaxis	46 (23.8)	19 (20)	0.43
Hypercoagulable state	4 (2.1)	2 (2.1)	1.00
Other/unknown	13 (16.7)	3 (3.2)	0.21
Received vte prophylaxis (n, %)	54 (28)	30 (21.6)	0.5275
Restarted treatment anticoagulation	38 (19.7)	21 (22.1)	0.6329

outcome of thrombotic events between groups [12 (6.2%) vs. 5 (5.3%); p = 0.75]. The distribution of thrombotic events in the defined BMI categories were: Below normal BMI 1 (5.8%), Normal BMI 5 (29.4%), Overweight 6 (35.3%), Obesity Class I 2 (11.8%), Obesity Class II 1 (5.9%), Obesity Class III 2 (11.8%). The most common types of thrombotic events were DVT [4 (33.3%) vs. 2 (40%); p ≥ 0.999] and ischemic stroke [2 (19.7%) vs. 1 (20%); p ≥ 0.999].

There was no difference in the occurrence of bleeding events following aPCC administration [14 (7.3%) vs. 8 (8.4%); p = 0.73]. The distribution of bleeding events in the defined BMI categories were: Below normal BMI 0 (0%), Normal BMI 5 (22.7%), Overweight 9 (40.9%), Obesity Class I 5 (22.7%), Obesity Class II 2 (9.1%), Obesity Class III 1 (4.6%). The most common type of documented bleeding event following aPCC administration was expansion of hemorrhage/hematoma as demonstrated by CT scan [9 (4.6%) vs. 3 (3.2%); p = 0.38].

When compared to the non-obese group, the obese group did not have a higher occurrence of in hospital mortality [41 (21.4%) vs. 14 (14.9%); p = 0.19]. Similarly, the obese group did not have a longer median ICU length of stay [2 days (IQR 1.5) vs. 1.8 days (IQR 2.5); p = 0.19] but did have an overall significantly shorter hospital length of stay [9 days (IQR 5.2) vs. 6.7 (IQR 7.7) days; p = 0.01].

Three patients experienced cardiac arrest after aPCC administration, all of which occurred in patients with a BMI > 30 m^2/kg. Two of the patients were grouped into Obesity

Table 3 Reversal information

Characteristic	BMI < 30 (n = 193)	BMI ≥ 30 (n = 95)	p-value
Indication for reversal (n, %)			
Intracranial hemorrhage	143 (74.1)	63 (66.3)	0.17
GI bleed	20 (10.4)	12 (12.6)	0.56
Emergent surgery	9 (4.7)	9 (9.5)	0.11
Retroperitoneal hemorrhage	5 (2.6)	6 (6.3)	0.11
Other	22 (11.4)	17 (17.9)	0.12
Bleed related to trauma (n, %)	101 (53.4)	41 (43.6)	0.12
Total aPCC dose (units)	2500	3500	< 0.001
Average aPCC dose per kg (units/kg)	34.4	35.4	0.46
Repeat dose required (%)	6 (3.1)	2 (2.1)	1.00
Initial dose < 20 units/kg	2 (1.0)	2 (2.1)	0.60
Hemostasis not achieved	2 (1.0)	–	> 0.999
No reason specified	2 (1.0)	–	> 0.999

Table 4 Primary and secondary outcomes

Characteristic	BMI < 30 (n = 193)	BMI ≥ 30 (n = 95)	p-value
Thrombotic events (n, %)	12 (6.2)	5 (5.3)	0.75
Multiple events	2 (16.7)	–	1.00
Pulmonary embolism	1 (8.3)	–	1.00
DVT	4 (33.3)	2 (40)	1.00
Myocardial infarction	3 (25)	–	0.51
Stroke	2 (19.7)	1 (20)	1.00
Other	4 (30.8)	3 (60)	0.33
Bleeding events (n, %)	14 (7.3)	8 (8.4)	0.73
Multiple events	2 (14.3)	2 (25)	0.6
GI bleed	3 (21.4)	3 (37.5)	0.62
Hematoma/hemorrhage expansion	9 (4.6)	3 (3.2)	0.38
New intracranial hemorrhage	1 (7.1)	–	1.00
Other	4 (28.6)	3 (37.5)	1.00
Median hospital length of stay (days)	9 (5.2)	6.7 (7.7)	0.01
Median ICU length of stay (days)	2 (1.5)	1.8 (2.5)	0.19
In-hospital mortality (n, %)	41 (21.4)	14 (14.9)	0.19
Cardiac arrest following aPCC (n, %)	–	3 (3.2)	0.035

Class III (BMI > 40 m^2/kg). Events occurred relatively close to aPCC administration (0.2 h, 4 and 26 h after administration).

Discussion

This investigation compared rates of thrombotic and bleeding events in non-obese (BMI < 30 kg/m^2) and obese (BMI ≥ 30 kg/m^2) patients receiving aPCC for reversal of apixaban and rivaroxaban and found no difference in occurrence of thrombotic events as they relate to BMI. The study site employs a weight-based dosing protocol (20–50 units/kg of actual body weight) with aPCC for DOAC reversal. This is administered as a one-time infusion at a maximum rate of 2 units/kg/minute. The average dose of aPCC used in this study was 35 units/kg, which represents a lower dose than guideline recommended therapy [9, 10]. Despite this, an overall rate of thrombosis of 6% was seen in our patient population. This is slightly higher than the rate of thrombotic events reported in previous studies with PCC [15–17]. Majeed et al. conducted a prospective cohort study on efficacy of PCC for apixaban and rivaroxaban reversal and reported an overall rate of thrombosis of < 2% [16]. Smith and colleagues conducted a retrospective cohort study on the effectiveness of PCC for apixaban and rivaroxaban reversal and found no incidence of thrombotic events in their patient population [17]. The median doses of PCC used in these studies were 27 units/kg and 36 units/kg respectively. Of note, both investigations used PCC, a pharmacologically distinct product from aPCC

used in the current investigation and differences in study design and patient population may account for the differences observed in rate of thrombotic events.

In our patient population, the low rate of repeat dosing and re-bleeding events suggest that sufficient hemostasis was achieved following a single dose of aPCC. The lower median dose of aPCC utilized in our study supports findings from previous investigations suggesting that a dose of 50 units/kg is not required to sufficiently reverse factor Xa inhibitors such as apixaban and rivaroxaban [16–18]. Dager and colleagues assessed the efficacy and safety of low (< 25 units/kg) versus high (50 units/kg) doses of aPCC in 66 patients on apixaban and rivaroxaban with major bleeding. There was no difference in patient outcomes between doses groups, calling into question the need for larger doses of 50 units/kg recommended by current society guidelines [9, 10, 18]. Utilization of lower doses of aPCC for reversal of these agents may also contribute to overall significant cost savings as demonstrated by Hormese and colleagues. Their investigation compared low (< 25 units/kg) and high (50 units/kg) doses of PCC for reversal of apixaban and rivaroxaban. They found comparable hemostatic effectiveness between the two groups (87.5% vs. 91.3%) with half as many thrombotic events occurring in the low-dose group (8.3% vs. 4.4%) and an estimated cost savings of $3102 per patient [19]. In addition, the rate of thrombotic events was comparable to what was observed in the ANNEXA-4 trail evaluating the use of andexanet alfa for the reversal of major bleeding in patients recently exposed to a factor Xa inhibitor. In the ANNEXA-4 study, investigators found a 10% rate of thrombotic events in patients who received Andexanet alfa [20]. In our study we found a rate of 5.3–6.2% depending on the patient group. Of interest, the rate of VTE prophylaxis in our study was relatively low regardless of the group. In the ANNEXA-4 study, the rate for the use of any anticoagulant was reported as 62% with a VTE rate of 2% following the initiation of any anticoagulation. The differences in the rate of VTE prophylaxis in our study and the ANNEXA-4 study may account for the variability in thrombotic event rates.

We found no difference between BMI groups with regard to secondary endpoints of ICU length of stay or in-hospital mortality. We did, however, find that obese patients had a shorter overall hospital length of stay when compared with non-obese patients [9 days (IQR 5.2) vs. 6.7 (IQR 7.7) days; $p = 0.01$]. One potential reason for this difference could be that despite being heavier, the obese group was significantly younger than the non-obese group.

A total of three patients in our cohort experienced cardiac arrest after aPCC administration, all of which occurred in the obese group [0 (0%) vs. 3 (3.16%); $p = 0.035$]. This was found to be statistically significant, however, a causal relationship between aPCC administration and cardiac arrest cannot be determined from these findings.

This study has several limitations, one being its retrospective nature. Additionally, since all data were extracted from the medical record, the information is limited based on accuracy of documentation. During the inclusion period, the study site underwent conversion from paper-charting to documentation in an electronic medical record. Because of this, documentation of aPCC dosing and administration prior to 2016 were often missing or incomplete. Additionally, because both choice of formulary non-specific reversal agents and dosing practices vary widely by institution, our findings related to rate of overall thrombosis may not be widely generalizable to all patient populations. This investigation does, however, add to the limited body of knowledge regarding safety and efficacy of aPCC for reversal of apixaban and rivaroxaban, since most published works have only examined safety and efficacy of PCC with regard to these agents. The findings of the current investigation support claims of previous studies that 4F-PCCs is a safe and efficacious reversal method for DOACs, though further studies of a prospective nature are needed to confirm these findings.

Conclusions

This investigation did not reveal a difference in rates of thrombosis or bleeding events between obese and non-obese patients who received an average dose of 35 units/kg of actual body weight of aPCC for reversal of apixaban and rivaroxaban. Further prospective investigation is warranted to determine the true rate of thrombotic complications related to aPCC use, as well as the optimal dosing range for DOAC reversal.

Funding No funding was received for conducting this study.

Data availability All data was collected through REDCap (Research Electronic Data Capture). All statistical analyses were conducted with SAS (Version 9.4 [TS1M4]; SAS Institute, Inc.; Cary, NC, USA).

Declarations

Conflict of interest The authors have no relevant financial or non-financial interests to disclose.

Ethical approval Ethical approval was waived by the local Ethics Committee of University of Tennessee Medical Center in view of the retrospective nature of the study and all the procedures being performed were part of the routine care.

Consent to participate Not applicable.

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