The use of andexanet alfa vs. 4-factor prothrombin complex concentrates in the setting of life-threatening intracranial hemorrhage

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Objective Andexanet alfa is a targeted reversal agent for life threatening hemorrhage associated with direct acting oral anticoagulants (DOACs), but there is uncertainty regarding the benefit when compared to 4-factor prothrombin complex concentrate (4F-PCC) for this indication. We investigated the clinical outcomes and cost associated with reversal of DOACs in the setting of life-threatening intracranial hemorrhage (ICH).

Methods A retrospective evaluation was conducted to evaluate patients with ICH in the setting of anticoagulation with DOAC from 9/1/2013 to 4/30/2020. Patients were included in the study if they received reversal with either andexanet alfa or 4F-PCC.

Results Eighty-nine patients were included in the study. There was no statistically significant difference in 30-day mortality between patients who received andexanet alfa or 4F-PCC (52% vs. 35%, $P = 0.14$). Radiographic stability of bleed was identified in 57% of patients receiving andexanet alfa vs. 58% of patients receiving 4F-PCC ($P = 0.93$). Median length of stay was not different between the andexanet alfa and 4F-PCC populations (7 days [IQR 6 – 12] vs. 6 days [IQR 3–12], $P = 0.66$). Median cost of reversal agent was higher in patients receiving andexanet alfa compared to 4F-PCC ($15 000 [IQR 15 000–$27 000] vs. $11 650 [IQR $8567–$14 149]).

Conclusion Among patients with life-threatening intracranial hemorrhage in the setting of DOAC therapy, no clinical differences were observed with respect to selection of reversal agent. Prothrombin complex concentrates remain a viable alternative to reversal of DOAC therapy though multicenter, randomized, prospective studies are needed to further evaluate the role of 4F-PCC in the reversal of DOAC therapy. *Blood Coagul Fibrinolysis* 35:94–100 Copyright © 2024 Wolters Kluwer Health, Inc. All rights reserved.

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Introduction

In 2010, dabigatran was the first direct oral anticoagulant (DOAC) approved by the FDA for patients with stroke or nonvalvular atrial fibrillation. Subsequently, apixaban, rivaroxaban, and edoxaban, all direct oral anticoagulants, were FDA approved over the next decade. DOAC therapy is prescribed for many indications including treatment and prevention of deep vein thrombosis (DVT) and pulmonary embolism (PE), as well as prevention of major cardiovascular events in patients with atrial fibrillation and coronary or peripheral artery disease. DOAC therapy may offer many advantages over vitamin K antagonists, namely warfarin, including lack of dietary restrictions, lack of routine therapeutic monitoring, rapid onset of action, and minimal drug-drug interactions. Disadvantages may include uncertain dosing in obese or underweight patients or those with renal dysfunction, and until recently, lack of a specific reversal agent.

Initial randomized studies demonstrated lower rates of bleeding, including intracranial hemorrhage (ICH), and similar rates of clinical efficacy in patients prescribed DOAC therapy as compared to vitamin K antagonists [1,2]. Despite this, some clinicians were cautious in the use of DOAC therapy due to the lack of a specific reversal agent. At the time, reversal of DOAC therapy was limited to off-label utilization of 4-factor prothrombin complex concentrates [4F-PCC]. As opposed to direct reversal of the DOAC therapy, 4F-PCC augments factors II, VII, IX, and X to assist in clot formation and ultimately promote hemostasis. Clinical data have shown 4F-PCC had approximately 65–85% efficacy in the off-label treatment of DOAC related bleeding, including ICH [3–5].

In response to this unmet need of a targeted reversal agent, idarucizumab, a dabigatran-specific reversal agent, was introduced in 2015. Andexanet alfa was subsequently

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introduced in 2018 for the reversal of life-threatening hemorrhage in patients receiving rivaroxaban or apixaban. In the ANNEXA-4 open label study, a 92% decrease in Anti-Xa levels was noted in patients treated with andexanet alfa for rivaroxaban- or apixaban-related bleeding [6]. Excellent hemostasis was obtained with andexanet alfa in reversing both agents. These results led to the inclusion of both 4F-PCC and andexanet alfa as potential reversal agents in anticoagulation reversal consensus guidelines developed by many subspecialty societies over the last few years [7–10]. However, it should be noted that guideline development was based on studies that excluded patients with Glasgow Coma Score (GCS) of 7 or less, intracranial hemorrhage volume >60 ml, or expected survival less than 1 month. Thus, the efficacy of andexanet alfa in clinical practice, without these exclusions, is unknown.

A recent retrospective, single institution study comparing andexanet alfa and 4F-PCC in 44 patients showed no statistically significant difference in clot stability on brain imaging, functional outcome, or thromboembolic complications between these two agents [11]. Another single center retrospective study with 29 total patients showed higher rates of excellent hemostasis, but more thromboembolic events and higher costs in those treated with andexanet alfa [12]. However, it should be noted that the 4F-PCC group in this study had lower GCS and larger ICH volume compared to the andexanet alfa cohort, therefore possibly representing a more severe group of patients in the 4F-PCC arm. A cost-comparative study of 4F-PCC vs. andexanet alfa in ICH showed 4F-PCC was more cost effective compared to andexanet alfa which had six times greater cost, though this cost discrepancy has lessened in 2022 due to manufacturing acquisition changes and resultant price decline of andexanet alfa [13].

At our academic medical center, providers may utilize either andexanet alfa or 4F-PCC for the reversal of DOAC therapy. 4F-PCC may be used in patients receiving apixaban or rivaroxaban with life threatening hemorrhage or need for emergent surgery. Andexanet alfa on the other hand, is restricted to life threatening hemorrhage in patients with confirmed therapeutic anticoagulation with apixaban or rivaroxaban. This is assessed through measurement of unfractionated heparin (UFH) anti-Xa levels which have been correlated to apixaban or rivaroxaban concentrations on a standard curve. Real-time discussions are had with providers who wish to utilize reversal agents in patients who have UFH levels below the threshold for therapeutic anticoagulation. After risk-benefit discussion, the provider ultimately is able to decide whether or not to proceed with anticoagulation reversal. A pharmacist retroactively reviews all 4F-PCC and andexanet alfa orders the following business day to provide timely written feedback through the office of the Chief Medical Officer regarding use of reversal agents that fell outside of institutional protocols. These nonpunitive letters provide timely education to providers and allow increased dialogue on emerging evidence in this setting.

Because of the uncertainty in benefit, thromboembolic complications, and differences in economic landscape between these two agents in DOAC-related ICH, we aimed to retrospectively evaluate the use of these agents in our most critical and vulnerable patients, namely intracranial hemorrhage.

Methods

Study design

We conducted a retrospective cohort study at a Level 1 trauma center and Comprehensive Stroke Center accredited by The Joint Commission and American Stroke Association/American Heart Association. The analysis was limited to patients who received DOAC reversal with either 4F-PCC or andexanet alfa in the setting of ICH from 9/1/2013 through 4/30/2020. Dosing of andexanet alfa was based on product labeling and 4F-PCC was dosed by provider with a recommendation for 50 units/kg body weight rounded to nearest vial size. No hard limit was placed on dosing cap for 4F-PCC. Patients included in the cohort were greater than 18 years of age, had life-threatening ICH that required ICU level care, received at least one dose of apixaban or rivaroxaban prior to presentation and received a dose of 4F-PCC or andexanat alfa.

Anti-Xa levels were ordered at the discretion of the treating teams prior to the administration of 4F-PCC, but were not used to guide administration or dose. When andexanet alfa first became available, our institution's protocol which was designed to avoid overuse, stated that if an anti-Xa was <0.3 units/ml, which correlated to the low therapeutic end of our institution's unfractionated heparin protocol, then use of andexanet alfa was not recommended, but could be given at the discretion of the treating attending. In May of 2018 we were able to correlate our anti-Xa assay to rivaxaroban and apixaban specific concentrations. A therapeutic anti-Xa level greater than 0.6 units/ml on the institution-specific UFH apixaban or rivaroxaban curve was chosen and dosing of andexanet alfa was not recommended at levels below this cut-off, but again could be given at the discretion of the attending physician. An anti-Xa cutoff of >0.6 units/ml was chosen to correlate with a rivaroxaban or apixaban concentration of 75 ng/ml, based on the Annexa-4 study. The list of patients meeting criteria was obtained retrospectively from the Integrated Data Repository of our institution. All information was gathered using the electronic medical record software (EPIC) available at the institution. All patients were included in the final analysis, irrespective of whether an anti-Xa levels was available prior to 4F-PCC or andexanet alfa administration and irrespective of the anti-Xa level when available. The study was approved by the Institutional Review Board.

The authors have declared that there are no conflicts of interest.

Outcomes and measurements

The primary outcome was 30-day all-cause mortality after administration of either 4F-PCC or andexanet alfa for DOAC-related ICH. Secondary outcomes included progression of ICH based on imaging, ICU length of stay (days), hospital length of stay (days), documented thrombosis post reversal, and pharmacy acquisition cost of pharmacotherapeutic reversal. Thrombosis postreversal agent administration was defined as any arterial or venous thrombosis noted on imaging from time of reversal agent to hospital discharge. To determine ICH progression, when available, imaging obtained within 24 h after anticoagulation reversal was compared to baseline imaging obtained on admission. All imaging was retrospectively reviewed by a single vascular neurologist who assessed for (i) radiographic stability of bleed, defined as stable from reversal agent to follow up imaging, (ii) objective changes in the volume of the intracranial hemorrhage, (iii) evidence of progression of bleed. Each of these were evaluated using a nominal scale. Patients who expired within 24 h of reversal who did not have repeat imaging were classified as not achieving radiographic stability of bleed. The method for measuring an intracerebral hematoma was performed via the calculation of A*B*C/2 where A is equal to the maximum length of the hematoma, B is equal to the width perpendicular to A, and C is the number of slices on CT that the hematoma is visible. Intracranial hemorrhages were measured in this method if localized to only one territory. Intracranial hemorrhages that involved multiple territories or patients with multiple hemorrhages were not measured. Additionally, subdural hematomas, subarachnoid hemorrhages, and hemorrhagic tumors were unable to be measured. Discharge disposition was also measured and compared between those receiving 4F-PCC and andexanet alfa. Cost analysis was determined by using average wholesale price (AWP) at the time of publication. Cost of 4F-PCC was calculated using $3.14/unit and andexanet alfa was $3000 per 200 mg vial. Cost for andexanet alfa was calculated as high dose and low dose, $15 000 and $27 000, respectively.

Laboratory analysis

All coagulation analyses were performed on an ACL Top 750 analyzer (Instrumentation Laboratory Bedford, MA, USA). The HemosIL Liquid Anti-Xa reagent was obtained from Instrumentation Laboratory. DOAC calibrators (Technoview Apixaban and Rivaroxaban Calibrator Sets) were procured from Diapharma (Diapharma Group, Inc., West Chester, OH, USA). Heparin activity (units/ml) was derived from a hybrid calibration line using unfractionated and low molecular weight heparin calibrators (Instrumentation Laboratory).

For initial measurements, DOAC concentrations were derived in real time from a standard calibration line by measuring the anti-Xa activity of the commercial DOAC calibrators.

Subsequently, additional measurements used a DOAC concentration derived from a heparin anti-Xa calibration curve. This approach was employed because not all medical technologists on all shifts were able to set up the DOAC calibrators, whereas heparin calibration is available around the clock every day. The rivaroxaban and apixaban calibrators were used to develop a calibrator line where anti-Xa heparin activity (units/ml) = **m** × DOAC ng/ml + **c.** Such a relationship will hold if, and only if, all assays are performed on the same analyzer with the same lot number of reagents and if the calibration line is shown to be stable. Using this information, one can derive the DOAC concentration by rearranging the equation thus: DOAC concentration ng/ml = (anti-Xa heparin activity − **c**)/**m**. The relationships between anti-Xa activity in heparin IU/ml and DOACs were as follows: anti-Xa heparin activity = 0.009 × rivaroxaban ng/ml − 0.0081, $R^2 = 0.997$. Anti-Xa heparin activity = 0.0068 × apixaban ng/ml + 0.0472, $R^2 = 0.997$.

Statistical analysis

All statistical analysis were generated using Microsoft Excel (version 16.16.27) and SAS software (Cary, NC). Continuous variables in demographics and baseline characteristics were analyzed via a Mann–Whitney *U*-test. Nominal variables including primary outcome of 30-day mortality, differences in discharge disposition, thrombosis after ICH reversal, radiographic stability of ICH, progression of ICH, and objective change in ICH were analyzed via chi-square test. A *P*-value of 0.05 was used to determine significance.

Results

Baseline demographics

Eighty-nine patients received anticoagulation reversal after diagnosis of life-threatening intracranial hemorrhage at our institution (n-23 andexanet alfa and n-66 4F-PCC). The decision of which reversal agent to administer was determined by the primary team (neurology, neurosurgery, emergency medicine or intensive care) or, in some cases, a hematologist if hematology consult was obtained. No patients received multiple doses of either agent. Table 1 details baseline characteristics which were well balanced between the two groups with the exception of gender with the andexanet alfa group having a higher proportion of males when compared to the 4F-PCC group (78% vs. 48%, $P = 0.01$). The median age at admission was 77 years [IQR 69–85] vs. 77.5 years [IQR 70–83] in the andexanet alfa group vs. 4F-PCC group respectively. The majority of patients were receiving apixaban at the time of reversal, with 60% and 87% in the 4F-PCC and andexanet alfa groups respectively. At the time of

Table 1 Demographics and baseline characteristics

Demographics	Andexanet alfa $N=23$ *n* (%)	4F-PCC $N=66$ *n* (%)
Sex		
Male	18 (78)	32 (48)
Female	5 (22)	34 (52)
Age, years (median, [IQR])	77 [69–85]	77.5 [70–83]
Weight (kg, median, [IQR])	83.9 [73.6–101.8]	79.3 [65–93]
Admission GCS (median, [IQR])	13 [11–14]	13 [9–14]
Home anticoagulation		
Apixaban	20 (87)	40 (61)
Rivaroxaban	3 (13)	25 (38)
Edoxaban	0 (0)	1 (1)
Indication for anticoagulation		
Atrial fibrillation	18 (78)	54 (82)
DVT/PE	2 (9)	11 (17)
CVA	0 (0)	1 (1)
Multiple	2 (9)	0 (0)
Unknown	1 (4)	0 (0)
Use of antiplatelets		
Any antiplatelet	20 (87)	40 (61)
Aspirin	6 (26)	26 (39)
Clopidogrel	1 (4)	6 (9)
Dual antiplatelet	0 (0)	4 (6)
UFH antifactor Xa level >0.6 prior to reversal	15 (65)	24 (36)

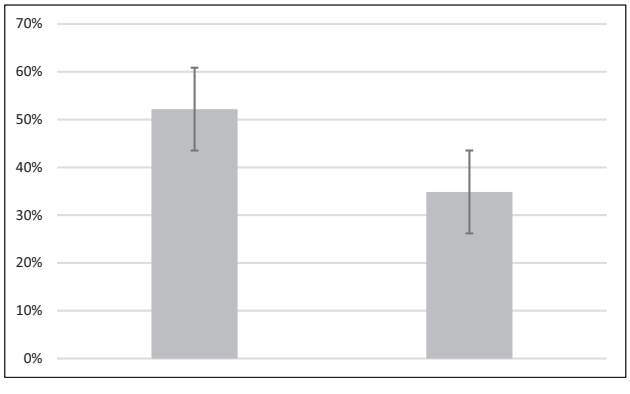
∗GCS – Glasgow Coma Scale. ∗DVT – deep venous thromboembolism. ∗PE – pulmonary embolism. ∗CVA – cerebrovascular accident. ∗UFH – unfractionated heparin.

reversal, a baseline UFH antifactor Xa level was available in 51 patients. Of these patients, 15 (65%) of andexanet alfa patients and 24 (36%) of 4F-PCC patients had a level <0.6. The median baseline GCS on admission was not statistically different between the two groups. Six patients received high-dose andexanet alfa whereas 17 received low-dose. Doses of 4F-PCC ranged from 1048 units to 9448 units with a median dose of 49 units/kg [IQR 45–51].

Outcomes

Figure 1 details all-cause mortality at 30 days was not statistically different between the andexanet alfa and 4F-PCC groups (52% vs. 35%, $P=0.14$). In-hospital mortality was observed in 22% and 26% of andexanet alfa and 4F-PCC groups respectively. As seen in Table 2, discharge disposition (expired, discharged home, hospice, skilled nursing facility [SNF], or transfer) was not statistically significant between the 2 groups, $P=0.4$.

Fig. 1



Mortality 30 days after reversal with andexanet alfa or 4F-PCC. (a) Andexanet alfa ($n=12/23$). (b) Four-factor prothrombin complex concentrate ($n=23/66$), $P=0.14$.

Table 2 Discharge disposition

	PCC ($n=66$)	(%)	Andexanet alfa ($N=23$)	(%)	*P* value
Home	12	(18)	1	(4)	0.4
Expired	17	(26)	5	(22)	
Hospice	4	(6)	3	(13)	
Subacute Nursing Facility	30	(45)	11	(48)	
Transfer	3	(5)	3	(13)	

Hemostatic efficacy was assessed by radiographic evidence of stability of ICH and objective improvement in intracranial hemorrhage volume. In those with repeat imaging available (n-23 andexanet alfa and n-54 4F-PCC), radiographic stability was similar between those receiving andexanet alfa and those receiving 4F-PCC (57% vs. 58%, $P=0.93$). Similarly, there was no statistically significant difference in the objective improvement of intracranial hemorrhage volume after administration of either reversal agent (10% vs. 8%, $P=0.18$). Progression of life-threatening intracranial hemorrhage was observed in 24% of andexanet alfa patients and 23% of 4F-PCC patients, $P=0.74$. Repeat imagining was not available in 12 patients, all in the 4F-PCC group. Of these, 9 patients expired prior to 24 h and were classified as not achieving radiographic stability. Three patients had limited bleeding on first image without clinical indication for repeat imaging due to symptomatic resolution within 24 h. These patients were classified as achieving radiographic stability.

Hospital length of stay (LOS) and intensive care unit length of stay (ICU LOS) were not significantly different. Median hospital LOS was 7 days [IQR 6–12] vs. 6 days [IQR 3–12] ($P=0.66$) and median ICU LOS 4 days [IQR 2–7] vs. 3 days [IQR 0–7] ($P=0.5$) in the andexanet alfa and 4F-PCC groups, respectively. While clinical outcomes did not differ, the median cost of therapy was numerically higher at $15 000 [IQR $15 000–$27 000] vs. $11 650.90 [IQR $8567–$14 149] in the andexanet alfa vs. the 4F-PCC groups, respectively.

The major safety outcome of interest was the incidence of thrombosis in patients receiving reversal with andexanet alfa or 4F-PCC. There was no statistically significant difference between the two groups, though numerically thrombosis occurred in a lower proportion of patients receiving andexanet alfa compared to 4F-PCC (13% vs. 26%, $P=0.17$).

Discussion

Direct oral anticoagulants have revolutionized how providers anticoagulate patients since their approval in 2010

however, their initial use was hampered by the lack of specific reversal agents. In May 2018, andexanet alfa was approved for the reversal of anticoagulation in patients treated with rivaroxaban and apixaban for life-threatening hemorrhages. The widespread acceptance of andexanet alfa has since been limited due the availability of alternative reversal agents such as inactivated 4F-PCC, which have historically been a fraction of the cost of andexanet alfa. Our retrospective review highlights our clinical experience of using andexanet alfa compared to inactivated 4F-PCC at a single institution for the reversal of DOAC therapy in the setting of life-threatening intracranial hemorrhage.

Although data is emerging in the area of DOAC reversal, focused data in intracranial hemorrhage is limited [11–15]. Parsels and colleagues recently published on a matched cohort of patients with ICH who received either andexanet alfa or 4F-PCC [14]. Patients were matched according to chronological admission date and similar baseline ICH volume. As noted, our patients were not matched, though there was not a statistically significant difference in median GCS at presentation. Similar to our study, they reported good to excellent hemostasis within 24 h of reversal with andexanet alfa or 4F-PCC (92.3% vs. 88.5%, $P = 1$). The small sample size ($n = 26$ in each group) limits the power to identify a significant difference in therapy, though numerically, the outcomes appear similar.

Pham and colleagues conducted a multicenter study to evaluate the achievement of International Society on Thrombosis and Haemostasis (ISTH) defined 'excellent hemostasis' in the setting of DOAC reversal for ICH with either andexanet alfa or 4F-PCC [15]. This study included a larger population with 47 patients receiving andexanet alfa and 62 receiving 4F-PCC. Hemostasis was not statistically significant between the andexanet alfa and 4F-PCC groups respectively (71.1% vs. 70.7%, $P = 1$). After adjusting for multiple factors (age, ICH score, regional mass effect, and midline shift), nonsignificance was retained (adjusted $P = 0.654$). While these numbers appear lower than previously reported in other studies, when you combine 'good to excellent' hemostasis, the numbers more closely resemble that of other reports (81.6% vs. 79.3%). Cost differences observed were similar to what was seen in our study with median andexanet alfa treatment $23 602 vs. 4F-PCC treatment at $6692.

Conversely to these reports, there have also been retrospective studies that have demonstrated andexanet alfa to be superior when compared to 4F-PCC in elements such as the rate of thrombotic events and 30-day mortality [16]. The variations seen within these studies and our current study may be attributed to differences in the anti-Xa reversal recommendations used at various institutions as well as societal guidelines. Meta-analyses have been performed to better account for these variations with a stronger sample size, but have also demonstrated equivocal results without a clear, superior reversal agent emerging [17].

A significant number of patients in our study were receiving anticoagulation for atrial fibrillation as compared to other indications. This is similar to the ANNEXA-4 trial for andexanet alfa where 68% of the patients in the efficacy population had the indication of atrial fibrillation for anticoagulation [3]. In our study, more patients were anticoagulated with apixaban (87%) compared to rivaroxaban (13%). We similarly had more males (78%) than females (22%). An interesting finding was that our cohort also had a high number of patients treated concomitantly with antiplatelet agents such as aspirin (26%) or clopidogrel (4%). The presence of these antiplatelet agents may contribute to persistence of intracranial hemorrhage. Antiplatelet agents are not inhibited by andexanet alfa whereas 4F-PCC contains Factors II, VII, IX and X which may contribute to thrombin generation in the setting of antiplatelet use allowing for clot stabilization in this setting. It is important to note that there is little evidence on the efficacy of andexanet alfa or 4F-PCCs against antiplatelet agents.

Our primary outcome demonstrated a numerically different though non-statistically significant difference in all-cause mortality 30 days after administration of reversal agent for DOAC therapy. As patients in both cohorts were similar in terms of GCS scores, we do not believe this to be due to an inherent difference in clinical presentation. Hemostatic efficacy was assessed radiographically by determining clinical resolution of bleed from admission to discharge in addition to measurements of intracranial volume and the presence of persistent intracranial hemorrhage after reversal agent administration. No statistically significant differences were found between the andexanet alfa group and the 4F-PCC group regarding these outcomes of hemostatic efficacy. There were also no significant differences between hospital LOS or ICU LOS between these two cohorts. However, there was a numerical difference in overall cost of therapy.

Due to cost, the pervasive use of andexanet alfa has been limited and may not be available for anticoagulation reversal at many institutions. Our institution was an early adopter of andexanet alfa. In order to utilize in the most effective manner, criteria were based on anti-Xa levels demonstrating therapeutic anticoagulation as well as timing of last DOAC dose. In our guidelines, an anti-Xa level greater than 0.6 units/ml is an indication for reversal with the dose of andexanet alfa (low vs. high) determined by the timing of last DOAC administration. Anti-Xa levels are ordered STAT and are usually available for clinical interpretation within 15–30 min which was deemed to not delay reversal when indicated. Nederpelt and colleagues at Massachusesetts General Hospital describe their use of anti-Xa levels to decide upon

andexanet alfa dosing, but the corresponding apixaban or rivaroxaban level was not reported [18]. In their study, levels <0.1 did not require reversal, levels between 0.2 and 1 were discussed with the hematology attending, and levels greater than 1 received andexanet alfa for reversal. To our knowledge, this is the first study to report on utilization of anti-Xa levels that were correlated to apixaban and rivaroxaban concentrations to guide reversal of DOAC therapy.

In addition to proactive criteria validation at the time of order verification, our facility has retroactive pharmacist review of all andexanet alfa, 4F-PCC, coagulation Factor VIIa, and idarucizumab use which occurs on the next business day. If use occurs outside of approved criteria, the case is presented to a hematologist for review. If it is agreed that use was not in-line with institutional criteria, the case is sent to the Chief Medical Officer to disseminate a letter to ordering provider and attending provider. This letter is nonpunitive and serves to educate providers on institutional guidelines for use. It is meant to provide the opportunity for additional dialogue surrounding use of these agents. If providers feel there is evidence to support the use of andexanet alfa or 4F-PCC, they are encouraged to utilize the Pharmacy and Therapeutics Committee approved pathway for requesting changes to criteria. This retrospective feedback was implemented in 2013 has allowed our institution to provide focused and timely feedback regarding utilization of reversal agents at our facility.

Our study is limited by its retrospective nature and single-center evaluation. Volume of ICH was not calculated in all patients due to the mixed nature of patient presentation including multitrauma and multifocal bleeds. Radiographic stability was subjectively reviewed by a single-reviewer to eliminate bias, though future studies may be required to objectively assess true volume of hemorrhage changes between groups. Because our study has a limited sample size and included outcomes of patients prior to FDA approval of andexanet alfa, our statistics are performed with the assumption of unequal variances. A greater number of patients receiving 4F PCC (64%) had anti-Xa level below 0.6 units/ml as compared to the those receiving andexanet alfa (35%). Thus, more patients receiving andexanet alfa would be expected to have DOAC levels of >75 ng/ml compared to the 4F PCC arm. It remains unknown whether differences in outcomes would have been seen if levels of anticoagulation were equivalent between the andexanet alfa and 4F-PCC group. Currently, our guidelines include initial evaluation and administration of andexanet alfa based on an anti-Xa level, but still allow provider choice to utilize an alternative agent (i.e. 4F-PCC). Serum anti-Xa levels are not readily available at many institutions and indeed, were not part of the criteria for the initial andexanet alfa efficacy trials and therefore, may have led to an overall lower use of andexanet alfa at our facility compared to other centers.

Conclusions

Our study did not find statistically significant differences in clinical outcomes when comparing reversal of life-threatening intracranial hemorrhage with andexanet alfa vs. 4F-PCC. To our knowledge, this is the first report of anti-Xa level guided reversal with pharmacist review of all reversal agents the following business day. Given the higher cost of andexanet alfa, reversal with alternative agents will likely continue at many institutions. It is prudent to note that recent manufacturing changes with andexanet alfa have resulted in a 55% price reduction for andexanet alfa effective April 1, 2022. This decreased the gap in cost associated with utilization when compared with that of 4F-PCC which may allow for expanded use where it has not otherwise been seen. Our study adds to the literature to validate the use of 4F-PCC in areas that may not have access to andexanet alfa. High-quality, prospective randomized trials are needed to better elucidate the differences between these agents and will provide vital information to create more effective use guidelines.

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Conflicts of interest

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References

1 Granger CB, Alexander JH, McMurray JJ, Lopes RD, Hylek EM, *et al.* Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2011; **365**:981–992.
2 Agnelli G, Buller HR, Cohen A, Curto M, Gallus AS, Johnson M, *et al.* Oral apixaban for the treatment of acute venous thromboembolism. *N Engl J Med* 2013; **369**:799–808.
3 Zada I, Wang S, Akerman M, Hanna A. Four-factor prothrombin complex concentrate for the reversal of direct oral anticoagulants. *J Intensive Care Med* 2021; **36**:58–62.
4 Koyama H, Yagi K, Hara K, Matsubara S, Tao Y, Uno M. Combination therapy using prothrombin complex concentrate and vitamin K in anticoagulated patients with traumatic intracranial hemorrhage prevents progressive hemorrhagic injury: a historically controlled study. *Neurol Med Chir (Tokyo)* 2021; **61**:47–54.
5 Costa OS, Baker WL, Roman-Morillo Y, McNeil-Posey K, Lovelace B, White CM, *et al.* Quality evaluation of case series describing four-factor prothrombin complex concentrate in oral factor Xa inhibitor-associated bleeding: a systematic review. *BMJ Open* 2020; **10**:e040499.
6 Connolly SJ, Crowther M, Eikelboom JW, Gibson CM, Curnette JT, Lawrence JH, *et al.* Full study report of andexanet alfa for bleeding associated with factor Xa inhibitors. *N Engl J Med* 2019; **380**:1326–1335.

7 Tomaselli GF, Mahaffey KW, Cuker A, Dobesh PP, Doherty JU, Eikelboom JW, *et al.* 2020 ACC expert consensus decision pathway on management of bleeding in patients on oral anticoagulants. *J Am Coll Cardiol* 2020; **76**:594–622.

8 Witt DM, Nieuwlaat R, Clark NP, Ansell J, Holbrook A, Skov J, *et al.* American Society of Hematology 2018 guidelines for management of venous thromboembolism: optimal management of anticoagulation therapy. *Blood Adv* 2018; **2**:3257–3291.

9 Christensen H, Cordonnier C, Kõrv J, Lal A, Ovesen C, Parrucker JC, *et al.* European stroke organisation guideline on reversal of oral anticoagulants in acute intracerebral haemorrhage. *Eur Stroke J* 2019; **4**:294–306.

10 Frontera JA, Lewin JJ 3rd, Rabinstein AA, Aisku IP, Alexandrov AW, Cook AM, *et al.* Guideline for reversal of antithrombotics in intracranial hemorrhage: a statement for healthcare professionals from the neurocritical care society and society of critical care medicine. *Neurocrit Care* 2016; **24**:6–46.

11 Ammar AA, Ammar MA, Owusu KA, Brown SC, Kaddouh F, Elsamadicy AA, *et al.* Andexanet alfa versus 4-factor prothrombin complex concentrate for reversal of factor Xa inhibitors in intracranial hemorrhage. *Neurocrit Care* 2021; **35**:255–261.

12 Barra ME, Das AS, Hayes BD, Rosenthal ES, Rosovsky RP, Fuh L, *et al.* Evaluation of andexanet alfa and four-factor prothrombin complex concentrate (4F-PCC) for reversal of rivaroxaban- and apixaban-associated intracranial hemorrhages. *J Thromb Haemost* 2020; **18**:1637–1647.

13 Frontera JA, Bhatt P, Lalchan R, Yaghi S, Ahuja T, Papadopoulos J, *et al.* Cost comparison of andexanet versus prothrombin complex concentrates for direct factor Xa inhibitor reversal after hemorrhage. *J Thromb Thrombolysis* 2020; **49**:121–131.

14 Parsels KA, Seabury RW, Zyck S, Miller CD, Krishnamurth S, Darko W, *et al.* Andexanet alfa effectiveness and safety versus four-factor prothrombin complex concentrate (4F-PCC) in intracranial hemorrhage while on apixaban or rivaroxaban: a single-center, retrospective, matched cohort analysis. *Am J Emerg Med* 2022; **55**:16–19.

15 Pham H, Medford WG, Horst S, Levesque M, Ragoonanan D, Price C, *et al.* Andexanet alfa versus four-factor prothrombin complex concentrate for the reversal of apixaban- or rivaroxaban-associated intracranial hemorrhages. *Am J Emerg Med* 2022; **55**:38–44.

16 Vestal ML, Hodulik K, Mando-Vandrick J, James ML, Ortel TL, Fuller M, *et al.* Andexanet alfa and four-factor prothrombin complex concentrate for reversal of apixaban and rivaroxaban in patients diagnosed with intracranial hemorrhage. *J Thromb Thrombolysis* 2021; **8**:1–9.

17 Nederpelt CJ, Naar L, Krijnen P, le Cessie S, Kaafarani HMA, Huisma MV, *et al.* Andexanet alfa or prothrombin complex concentrate for factor Xa inhibitor reversal in acute major bleeding: a systematic review and meta-analysis. *Crit Care Med* 2021; **49**:e1025–e1036.

18 Nederpelt CJ, Naar L, Sylvester KW, Barra ME, Roberts RJ, Velmahos GC, *et al.* Evaluation of oral factor Xa inhibitor-associated extracranial bleeding reversal with andexanet alfa. *J Thromb Haemost* 2020; **18**:2532–2541.