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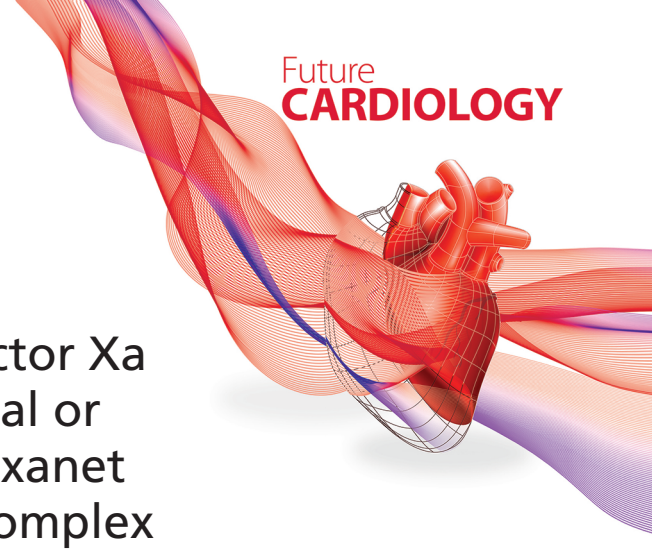

Real-world management of oral factor Xa inhibitor-related bleeds with reversal or replacement agents including andexanet alfa and four-factor prothrombin complex concentrate: a multicenter study

Craig I Coleman*[,1], Paul P Dobesh[2], Sherry Danese[3], Julie Ulloa[3] & Belinda Lovelace[4]

[1]Department of Pharmacy Practice, University of Connecticut School of Pharmacy, 69 North Eagleville Road, Unit 3092, Storrs, CT 06269-3092, USA

[2]Department of Pharmacy Practice & Science, College of Pharmacy, University of Nebraska Medical Center, 986145 Nebraska Medical Center, Omaha, NE 68198-6145, USA

[3]Outcomes Insights, 2801 Townsgate Road, Suite 330, Westlake Village, CA 91361, USA

[4]Portola Pharmaceuticals Inc. 270 E. Grand Avenue South San Francisco, CA 94080, USA

*Author for correspondence: Tel.: (860) 972 2096; Fax: (860) 545 2277; craig.coleman@hhchealth.org

Aim: We describe the real-world utilization and outcomes associated with managing oral factor Xa inhibitor (FXai)-related major bleeds. **Materials & methods:** Electronic records from 45 US hospitals were queried (ICD-10-CM billing codes D68.32, T45.515x or T45.525x) to identify major bleed hospitalizations related to FXai use. Patient demographics, bleed type (intracranial hemorrhage, gastrointestinal, critical compartment, traumatic, other), FXai taken, reversal or replacement agents administered (including andexanet alfa, four-factor prothrombin complex concentrate, fresh frozen plasma, others), in-hospital mortality and length of stay were recorded. **Results:** Of 3030 FXai-related hospitalizations for major bleeds, patients averaged 68 years old and 47% were women. In-hospital mortality was highest for intracranial hemorrhage (23%, n = 507) and lowest for gastrointestinal bleeds (4%, n = 1453). In-hospital mortality was lowest (4%) for bleeds managed with andexanet alfa (n = 342), compared with 10% for four-factor prothrombin complex concentrate (n = 733), 11% for fresh frozen plasma (n = 925) and 8% for both other agents (n = 794) and no agents (n = 438). Median length of stay was 5 days across all agents, while ICU length of stay was shorter andexanet alfa (2 days) compared with other agents (3 days). **Conclusion:** In-hospital mortality differed by bleed type and agents administered. Andexanet alfa was associated with the lowest rate of in-hospital mortality across all bleed types.

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Keywords: anticoagulation • bleeding-related hospitalization • DOAC andexanet alfa • four-factor prothrombin complex concentrate • FXa inhibitor • gastrointestinal bleeds • intracranial hemorrhage • real-world

Direct-acting oral anticoagulants (DOACs) are used for the treatment or prevention of venous thromboembolism (VTE), reducing the risk of stroke and systemic embolism and prevention of major adverse cardiac events. Current DOAC agents include oral Factor-Xa inhibitors (FXai)-apixaban, betrixaban, edoxaban, rivaroxaban-that inhibit the conversion of prothrombin to thrombin and a direct thrombin inhibitor (dabigatran).

FXai use is growing year over year in the USA [1] and at least 6 million US adults are estimated to be treated with FXai therapy [2]. In a MarketScan analysis of 137,203 US patients with VTE, 98.7% of all patients receiving their first anticoagulant were treated with warfarin in early 2012, which dropped to only 17.5% of VTE patients in late 2017; over the same time period, FXai prescriptions rapidly increased, with rivaroxaban and apixaban accounting for over 80% of first-time oral anticoagulant prescriptions in late 2017 [3]. Compared with warfarin, FXai agents are recommended over vitamin K antagonists for stroke prevention in patients with non-valvular atrial fibrillation [4] and treatment of venous thromboembolism [5,6] as they are associated with half the risk of intracranial

hemorrhage (ICH), which carries high risk of mortality or subsequent disability [7,8]. However, FXai agents still hold the inherent risk of serious or even fatal bleeding events, involving the brain, other critical organ bleeds and those requiring hospitalization, transfusion and/or surgery.

In the absence of targeted therapies, nonspecific agents have been used to manage FXai-associated bleeding through replenishing clotting factors, although these agents have not been proven to provide adequate replacement of inhibited factors reverse FXai. These agents include fresh frozen plasma (FFP), three- or four-factor prothrombin complex concentrate (PCC), activated prothrombin complex concentrate, recombinant activated factor VII and tranexamic acid. Although PCCs have some ability to reverse abnormal laboratory parameters (prothrombin time and endogenous thrombin potential) [9,10], they may be associated with a risk of postrepletion thromboembolic complications when used in treatment of FXai-related bleeding [11,12]. Further, PCCs are unable to reverse the pharmacodynamic effect of direct FXai (anti-Xa activity) and have been shown to restore thrombin generation only at low (<75 ng/ml) levels of FXai [13].

More recently, product-specific reversal agents have been developed to directly target and bind to FXai, reversing their anticoagulant activity as demonstrated by an over 90% reduction in anti-Xa activity and return of endogenous thrombin production [14]. In May 2018, coagulation FXa (recombinant), inactivated-zhzo (USAN andexanet alfa) was approved by the US FDA to reverse the FXai agents apixaban and rivaroxaban in life-threatening or uncontrolled bleeding. With the approval of specific reversal agents for DOACs, a number of medical organizations have updated guidelines and best practice documents [4,15, 16, 17]. In general, these organizations recommend the use of specific reversal agents, idarucizumab for dabigatran and andexanet alfa for apixaban and rivaroxaban, for severe bleeding events such as ICH and exsanguinating gastrointestinal (GI) bleeding.

The objective of the current study was to describe patient demographics, utilization of reversal or replacement agents including andexanet alfa and four-factor prothrombin complex concentrate (4F-PCC) and outcomes associated with management of FXai-associated major bleeds in US hospitals.

Materials & methods

Study design

This multicenter, retrospective survey captured electronic medical records (EMR) for adult patients hospitalized for FXai-related bleeding between January 2016 and September 2019. Representative hospitals were identified by study investigators to comprise a variety of settings (academic affiliation, nonacademic, trauma and stroke center status) and hospital sizes. Hospitals were categorized based on their trauma level status (American Trauma Society [ATS] 1 or 2), certified stroke center status (yes or no) and bed size (<500 or ≥500). Hospital pharmacists were then invited to participate and all participation was voluntary.

Study population

Records from the 45 US-based hospitals who agreed to participate were included. To increase the specificity of initial patient screening, only hospitalizations with ICD-10 (International Classification of Diseases-Tenth Revision) billing codes of D68.32x, T45.515x or T45.525x, indicative of bleeding due to extrinsic factors (i.e., anticoagulant and antithrombotic) at the time of inpatient admission or during the hospital stay, were further screened for inclusion. Within these, only hospitalizations in which patients specifically received a FXai prior to admission were included in the study.

Data collection

Data was collected from electronic medical records by pharmacists that had confirmed familiarity and prior experience with data extraction from the electronic medical records at their site. Pharmacists were provided training on data entry into a standardized electronic case report form prior to data collection and study investigators were available to answer questions related to data collection. In order to minimize any bias in data collection, pharmacists were made aware of the general purpose of the study by an independent third-party research organization conducting the data collection, but were not informed of any potential analyses to be performed. Pharmacists were invited to participate each month and contributed EMR data only from the prior month. Cases were reviewed by pharmacists at each site and entered into an electronic case report form which was uploaded to a central database managed by the third party research organization.

Details collected from the medical records included patient age at hospitalization, sex, bleed type (GI bleed, ICH, critical compartment bleed [noncompressible bleeding in the thorax, abdomen, retroperitoneum or pelvis], trau-

Table 1. Baseline characteristics for hospitalizations for direct-acting oral anticoagulant-related bleeds from 2016–2019 in a sample of 45 US hospitals.

	Total sample n = 3030	Andexanet alfa n = 342	4F-PCC n = 733	FFP n = 925	All other† n = 794	No reversal administered n = 438
Age	67.6	69.1	70.1	66.9	66.8	67.3
Gender, n (%)						
– Male	1605 (53%)	188 (55%)	369 (50%)	474 (51%)	452 (57%)	224 (51%)
– Female	1424 (47%)	154 (45%)	364 (50%)	451 (49%)	341 (43%)	214 (49%)
FXa inhibitor						
– Apixaban	45%	47%	51%	42%	46%	39%
– Edoxaban	6%	3%	8%	6%	5%	5%
– Rivaroxaban	49%	50%	41%	52%	49%	56%
– Other	<1%	0%	0%	<1%	0%	0%
Bleed Type						
– GI	48%	40%	41%	50%	53%	52%
– ICH	17%	20%	23%	16%	14%	11%
– Critical compartment	4%	3%	4%	4%	4%	3%
– Traumatic	26%	31%	29%	27%	23%	19%
– Other	6%	6%	3%	3%	6%	15%

†All other: 3-factor PCCs, recombinant Factor VIIa, activated 4F-PCC, tranexamic acid and vitamin K.
4F-PCC: Four-factor prothrombin complex concentrate; FFP: Fresh frozen plasma; GI: Gastrointestinal; ICH: Intracranial hemorrhage.

matic not otherwise specified, or other), length of hospital stay and level of care (inpatient versus ICU), anticoagulant administered prior to the bleed, reversal or replenishing agent and in-hospital mortality status. For each data category, the electronic case report form contained a list of available options. Since this study included contribution of routine data extracted from the EMR and did not contain any patient identifiers, it was accordingly considered minimal risk (45.CFR.46.1029j; common rule).

Statistical analyses

This descriptive analysis detailed the prevalence of each reversal or replacement agent used, overall and stratified bleed type. In-hospital mortality was reported as n (%) and stratified by bleed type and for each reversal or replacement agent. Length of stay (LOS) and ICU LOS were reported as median interquartile range (IQR), stratified by each reversal or replacement agent and for bleed type. LOS was not calculated for the other bleeds category due to the low sample size and the variability across bleed types included in the other bleeds category. Bleed types were mutually exclusive, but reversal or replacement agents could be used concomitantly; thus, the proportion of patients who received a sole reversal or replacement agent (i.e., received only that agent) was also reported. Due to the descriptive nature of this study, no inferential comparisons were made across subgroups. All data were analyzed using R version 3.4.4 (R Core Team 2017).

Results

Among the 45 participating hospitals across the US, 14,418 bleeding-related hospitalizations were identified between January 2016 and September 2019. Of these, 3030 (21%) were associated with the anticoagulant effects of FXa inhibitors, an average of 3.6 bleeds/hospital/month. The incidence of FXai-related bleeds increased over the study period from 18% (2017) to 24% (2019) when novel FXa inhibitors were adopted of the standard of care in atrial fibrillation and treatment of VTE. Of the 45 hospitals included, the mean number of beds was 465; 56% had <500 beds, while 44% had 500 beds or more. Two thirds (67%) of the hospitals were Advanced Primary Stroke Centers, 64% were ATS Level 1 facilities and 36% were ATS Level 2.

The mean age of the patients at the time of hospitalization was 67.6 years and females represented 47% of the population. The FXa inhibitors used prior to admission included rivaroxaban (49%), apixaban (45%), edoxaban (6%) and betrixaban (<1%). Baseline patient demographics at the time of hospitalization are summarized across each reversal or replacement agent used in Table 1. Patient demographics including age, gender and clinical characteristics including FXai use at baseline and bleed type were relatively similar across reversal or replacement agents.

Table 2. Bleed types shown by management including reversal or replacement agents administered.

	Total sample n = 3030	Andexanet alfa n = 342	4F-PCC n = 733	FFP n = 925	All other† n = 794	No reversal administered n = 438
All bleeds	3030	342 (11%)	733 (24%)	925 (31%)	794 (26%)	438 (14%)
GI bleed	1453	137 (9%)	303 (21%)	466 (32%)	423 (29%)	228 (16%)
ICH	507	67 (13%)	170 (34%)	146 (29%)	111 (22%)	47 (9%)
Critical compartment	113	11 (10%)	26 (23%)	36 (32%)	34 (30%)	14 (12%)
Traumatic	781	105 (13%)	214 (27%)	250 (32%)	180 (23%)	82 (10%)
Other Bleed	176	22 (13%)	20 (11%)	27 (15%)	46 (26%)	67 (38%)
Single agent‡	1940	83%	72%	47%	86%	–

†All other: 3-factor PCCs, recombinant Factor VIIa, activated 4F-PCC, tranexamic acid and vitamin K.
‡Used as a single agent, with no other concomitant reversal or replacement agents administered (reversal or replacement agents were not mutually exclusive).
4F-PCC: Four-factor prothrombin complex concentrate; FFP: Fresh frozen plasma; GI: Gastrointestinal; ICH: Intracranial hemorrhage.

Prevalence of bleed types & reversal or replacement agents used

Over half of hospitalizations occurred after presentation to the emergency department (58%), while 24% were direct admissions, 8% were admitted after observation and 5% involved transfer from another hospital facility. Bleed types and reversal or replacement agent used are summarized in Table 2. Almost half of all FXai-related bleeds were GI (48%), followed by traumatic bleeds not otherwise specified (26%), ICH (17%), critical compartment (4%) and other bleeds (6%). Of the 3030 bleeds, 11% were treated with andexanet alfa, 24% with 4F-PCC, 31% with FFP, 26% with other agents (3F-PCCs, activated 4F-PCC, recombinant Factor VIIa, tranexamic acid, vitamin K, protamine sulfate) and in 14% no reversal or replacement agents were administered (percentages add to more than 100% since concomitant use was allowed). Although reversal and replacement agents were not mutually exclusive, bleeds were often managed with only a single agent. Of the 342 bleeds managed with andexanet alfa, it was the sole reversal agent administered in 83% of hospitalizations; of the 733 bleeds managed with 4F-PCC, it was the sole replacement agent used in 72%; of the 925 bleeds managed with FFP, it was the sole replacement agent used in 47%. For agents in the 'other agents' category, the agent used was used as the sole agent in 86% of cases.

In-hospital mortality

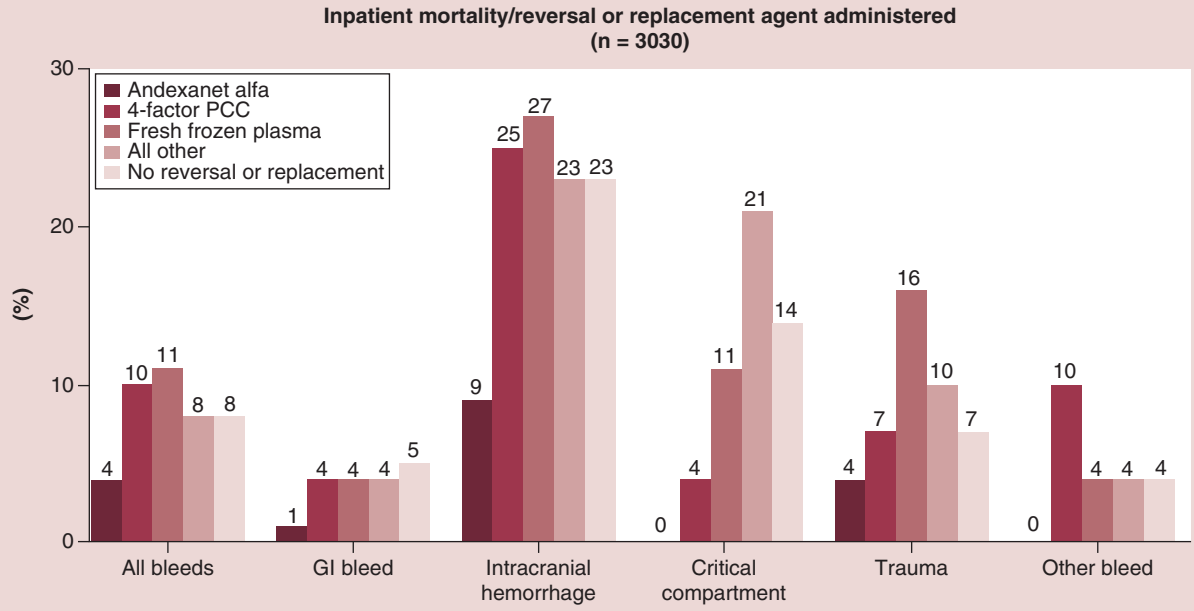
In-hospital mortality occurred in 271 (9%) of all hospitalizations; mortality stratified by bleed type and reversal or replacement agents administered is summarized in Figure 1. In-hospital mortality for those treated with andexanet alfa (n = 342) was 4% overall and 9% for patients with ICH, 4% for traumatic, 1% for GI and 0% for critical compartment and all other bleeds. In-hospital mortality for those treated with 4F-PCC (n = 733) was 10% overall (25% ICH, 7% traumatic, 4% GI, 4% critical compartment and 10% for other bleeds). In-hospital mortality for those treated with FFP was 11% (27% ICH, 16% traumatic, 4% GI, 11% critical compartment and 4% for other bleeds). In-hospital mortality for those treated with all other agents was 8% overall (23% ICH, 10% traumatic, 4% GI, 21% critical compartment and 4% for other bleeds. In-hospital mortality for patients receiving no reversal or replacement agents was 8% overall (23% ICH, 7% traumatic, 5% GI, 14% critical compartments and 4% other bleeds).

Total hospital LOS & ICU LOS

Table 3 summarizes the hospital LOS and time in ICU stratified by bleed type for each reversal or replacement agent. LOS and ICU LOS were longest for patients with ICH and critical compartment bleeds and shortest for patients with GI bleeds. Median (IQR) LOS for patients treated with andexanet alfa was 2 (1–4) ICU days and 5 (3–6) days total. Median LOS for patients treated with 4F-PCC was 3 (2–5) ICU days and 5 (4–7) days total. Median LOS for patients treated with FFP was 3 (2–5) ICU days and 5 (4–8) days total. Median (IQR) for all other agents was 3 (2–5) ICU days and 5 (4–8) days total. Median (IQR) for those receiving no reversal or replacement was 2 (1–3) ICU days and 3 (2–5) days total.

Discussion

While using a specific reversal agent is recommended for life-threatening DOAC-associated bleeding by committees including the Emergency Medicine Cardiac Research and Education Group [17] and the American Heart Association,



	All bleeds	GI bleed	Intracranial hemorrhage	Critical compartment	Traumatic	Other bleed
			Deaths/total hospitalizations			
Total	271 / 3030	57 / 1453	115 / 507	13 / 113	78 / 781	8 / 176
Andexanet alfa	12 / 342	2 / 137	6 / 67	0 / 11	4 / 105	0 / 22
4F-PCC	74 / 733	12 / 303	43 / 170	1 / 26	16 / 214	2 / 20
FFP	105 / 925	20 / 466	40 / 146	4 / 36	40 / 250	1 / 27
All other†	67 / 794	15 / 423	25 / 111	7 / 34	18 / 180	2 / 46
No reversal administered	34 / 438	12 / 228	11 / 47	2 / 14	6 / 82	3 / 67

Figure 1. In-hospital mortality shown by bleed type for each reversal or replacement agent.
†All other: 3-factor PCCs, recombination factor VIIa, activated 4F-PCC, tranexamic acid, and vitamin K.
4F-PCC: Four-factor prothrombin complex concentrate; FFP: Fresh frozen plasma; GI: Gastrointestinal.

American College of Cardiology and Heart Rhythm Society [4], the lack of head to head trials or comparative observational data limits knowledge of outcomes associated with various reversal and replacement agents. Existing data has generally been limited to a prospective clinical trial for andexanet alfa [14] and observational studies for 4F-PCC [11,12,18,19]. This study fills a gap in understanding of real-world management of bleeds by describing in-hospital mortality and hospital LOS among 3030 FXai-related major bleeding hospitalizations in 45 hospitals over 3.5 years. On average, there were 3.6 FXai-related bleeds per hospital per month, most of which (86% overall) were managed with some type of reversal or replacement treatment. In-hospital mortality was lowest for patients treated with andexanet alfa across all bleed types. LOS was highest for the more severe ICH and critical compartment bleeds compared with GI bleeds; but was similar across reversal or replacement agents used. ICU LOS was similarly higher for more severe bleeds and was on average 1 day shorter for andexanet alfa compared with 4F-PCC, FFP

Table 3. Median length of hospital stay shown by bleed type and reversal or replacement agent administered.

Bleed type†	LOS	Median (ICR)					
		Total sample n = 3030	Andexanet alfa n = 342	4F-PCC n = 733	FFP n = 925	All other‡ n = 794	No reversal administered n = 438
All bleeds	ICU	3.0 (2.0–5.0)	2.0 (1.0–4.0)	3.0 (2.0–5.0)	3.0 (2.0–5.0)	3.0 (2.0–5.0)	2.0 (1.0–3.0)
	Total	5.0 (3.0–7.0)	5.0 (3.0–6.0)	5.0 (4.0–7.0)	5.0 (4.0–8.0)	5.0 (4.0–8.0)	3.0 (1.8–5.0)
GI	ICU	2.0 (1.0–4.0)	2.0 (1.0–2.0)	2.0 (1.0–3.0)	3.0 (2.0–4.0)	3.0 (2.0–4.0)	1.0 (1.0–2.0)
	Total	4.0 (3.0–6.0)	4.0 (3.0–5.0)	4.0 (3.0–5.0)	5.0 (3.0–6.0)	5.0 (4.0–7.0)	3.0 (2.0–4.0)
ICH	ICU	4.0 (3.0–6.0)	4.0 (3.0–6.0)	4.0 (3.0–6.0)	6.0 (3.0–7.0)	4.0 (3.0–7.0)	2.0 (1.0–3.0)
	Total	7.0 (4.0–10.0)	7.0 (6.0–8.0)	7.0 (4.0–9.0)	8.0 (6.0–10.0)	8.0 (4.0–10.0)	4.0 (2.0–5.0)
Critical compartment	ICU	4.0 (2.0–6.0)	5.0 (4.0–7.0)	3.0 (2.0–5.0)	5.0 (3.3–7.0)	4.0 (3.0–5.0)	2.0 (1.0–3.0)
	Total	6.5 (4.0–10.0)	7.0 (6.0–9.0)	5.5 (4.0–8.8)	8.5 (5.0–10.0)	6.0 (5.0–9.0)	3.0 (1.0–5.0)
Traumatic	ICU	3.0 (2.0–5.0)	2.0 (1.0–3.5)	3.0 (2.0–5.0)	3.0 (2.0–6.0)	3.0 (2.0–5.0)	2.0 (1.0–4.0)
	Total	5.0 (4.0–8.0)	5.0 (3.0–6.0)	6.0 (4.0–8.0)	5.0 (4.0–9.0)	6.0 (4.0–9.0)	3.0 (1.0–5.0)

†Other bleeds were not included in the length of stay analysis due to the low sample size and variability of types of bleeds.
‡All other: 3 Factor-PCCs, recombinant Factor VIIa, activated 4F-PCC, tranexamic acid and Vitamin K.
4F-PCC: Four-factor prothrombin complex concentrate; FFP: Fresh frozen plasma; GI: Gastrointestinal; ICH: Intracranial hemorrhage; LOS: Length of stay.

and other agents. These results suggest that among a large real-world sample, mortality and LOS may differ by bleed type and reversal or replacement agents.

In alignment with prior research, this study showed in-hospital mortality differences across bleed types, with ICH having the highest rate of mortality compared with other types of bleeds including GI, critical compartment, traumatic bleeds and other types of bleeds. In a MarketScan analysis of 3081 atrial fibrillation (AF) patients hospitalized for a major bleed, overall inpatient mortality was 3.0%, while inpatient mortality for ICH was the highest across bleed types at 14.0% [20]. A German cohort study reported in-hospital mortality rate of 19.9% for DOAC-related ICH bleeds, which rose to a mortality rate of 29.5% within 90 days of discharge [18]. Majeed *et al.* reported an overall 30-day mortality rate of 32% among 84 patients taking DOACs and treated with PCC and 34% mortality within those with ICH bleeds [11]. A multicenter study of ICH bleeds managed with PCC among 663 patients reported that upon discharge, 26.7% either died or were discharged to hospice [19]. In ANNEXA-4, the pivotal study for andexanet alfa, the overall mortality rate was 14% within 30 days of the bleeding event, with a large proportion (64%) of included bleeds being ICH [14]. In the current study, which included 507 ICH hospitalizations, ICH bleeds treated with andexanet alfa (n = 67) had a 9% mortality rate, which was the lowest rate across all agents. Rates were higher for other commonly used agents, including 4F-PCC (n = 170, 25%) and FFP (n = 146, 27%). Andexanet alfa was also associated with the lowest rate of in-hospital mortality across other bleed types, including GI, critical compartment, traumatic bleeds not otherwise specified and other bleed types. Further study is warranted to confirm mortality differences across different agents, particularly with adjustment for baseline stroke severity and ICH volume in relevant patients and other measures to account for bleed size and severity.

LOS is another common measure to assess hospitalization and healthcare resource use outcomes. Major bleeding events often accompanied by long hospital stays, high rates of readmission and risk of mortality [21]. In this study, overall length of stay was relatively similar across all agents, although they were longer for patients with ICH compared with GI bleeds, as would be expected based on the severity of ICH bleeds. ICU length of stay, at 2 days, was on average 1 day shorter for patients treated with andexanet alfa, compared with 3 days for 4F-PCC, FFP and other agents. Hospitalizations where no agent was administered typically were associated with shorter length of stays compared with hospitalizations where any agent was administered, which could have been indicative of no agents being administered for less severe bleeds. Further research is needed to characterize length of stay, ICU length of stay and healthcare resource utilization including readmission rate across different reversal or replacement agents, particularly using real-world data. Additionally, it will be important to determine if the shorter ICU stay for patients that received andexanet alfa may be related to the severity of bleeding for these patients, or as a result of the properties and safety profile of the treatment itself. Andexanet alfa provides a rapid decrease in anti-FXa activity within two minutes and has an elimination half-life between 3 and 4 h and a pharmacodynamic half-life of one hour [22]. Comparatively, in the setting of VKA reversal, 4F-PCC decreases international normalized ratio (INR)

rapidly to ≤1.3 within 30 min of initiation and of the coagulation factors contained within 4F-PCC, their various half-lives range from 4 to 60 h, with factor II having the longest, 60 h, elimination half-life [23].

A key strength of this study is that this cohort reflects real-world management of FXai-related major bleeds across 45 hospitals with varying size, location and level of care for trauma and stroke patients. Few studies have provided large, real-world results concerning management of FXai-related bleeds with reversal or replacement agents. With the passage of the 21st Century Cures Act in 2016, recognition of the value of real-world data in supporting clinical decision making and FDA regulatory submissions has increased [24,25] and future research should further leverage real-world observational databases to better understand actual usage and clinical outcomes associated with reversal or replacement agents. The results must be interpreted in light of limitations related to the observational nature of the study and data collection using electronic medical records and hospitalization events identified by ICD10 coding. As a consequence, we cannot exclude the potential influence of missed, inaccurate or incomplete medical records. Additionally, hospitalization records provide detail limited to the current admission and do not capture previous medical or prescription history, longitudinal outcomes or patient management after discharge. Since andexanet alfa was approved by the FDA in May 2018, data collection was limited to May 2018 onwards rather than the entire study period; however, patients treated with andexanet alfa had overall similar baseline characteristics in terms of age, gender, FXai use and bleed type, except that a higher proportion of patients with traumatic bleeds were treated with andexanet alfa compared with other agents. Given the limited data available concerning patient baseline characteristics since data were captured via pharmacist survey of EMR, direct comparisons are limited due to potential selection bias. It is possible that baseline characteristics, bleed size and severity and other potential confounders could have differed across different reversal or replacement agents and that specific agents may have been selected because patients either had lower or higher risk of death, either due to bleed severity or patient characteristics (e.g., comorbid conditions or concomitant medications). It is also crucial to note that reversal or replacement agents could have been used concomitantly; while andexanet alfa and 4F-PCC were generally used as the sole management agent, FFP was used alone in fewer than half of all FFP-managed bleeds and could have further been paired with transfusion in addition to other agents. Future studies may benefit from further reporting on the concomitant administration of reversal or replacement agents, functional outcomes and mortality after discharge, assessment of hemostatic efficacy after reversal agent use and practice patterns related to FXai restart.

Conclusion

This study provides real-world data on utilization and outcomes associated with reversal or replacement agents used in the management of FXai-related major bleeds. In this sample of 3030 hospitalizations, in-hospital mortality differed by bleed type and the reversal or replacement agent used. Andexanet alfa was associated with the lowest mortality rate across all bleed types and a shorter ICU stay compared with other agents. Further study and replication in large representative samples is warranted.

Summary points

- This real-world study describes the utilization and outcomes associated with 3030 oral factor Xa inhibitor associated bleeding-related hospitalizations in the USA.
- In 342 bleeds treated with andexanet alfa, it was the sole agent in 82.7%. In 733 bleeds treated with four-factor prothrombin complex concentrate, it was the sole agent in 72.4%. Of 3030 fXa inhibitor bleeds, 14% (438) were not administered any bleeding management reversal agent.
- In-hospital mortality differed by bleed type and agents administered. In-hospital mortality was highest for intracranial hemorrhage (22.7%) and lowest for gastrointestinal bleeds (3.9%). Andexanet alfa was associated with the lowest rate of in-hospital mortality across all bleed types.
- Further study is warranted to confirm clinically relevant differences in mortality.

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No writing assistance was utilized in the production of this manuscript.

Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

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