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BRIEF REPORT

Trauma

Management of factor Xa inhibitor–related traumatic non-intracranial bleeding events with andexanet alfa or four-factor prothrombin complex concentrate in a US multicenter observational study

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Abstract

Objectives: This study describes clinical characteristics and management strategies for patients with factor Xa (FXa) inhibitor–related traumatic non-intracranial bleeds who were treated with andexanet alfa or four-factor prothrombin complex concentrate (4F-PCC).

Methods: An observational cohort study (ClinicalTrials.gov Identifier: NCT05548777) was conducted using electronic health records from 354 US hospitals. Included patients were hospitalized with rivaroxaban- or apixaban-related bleeding, had received andexanet alfa or 4F-PCC treatment during their hospitalization, and were discharged between May 2018 and September 2022. This analysis was performed in the subgroup of patients with traumatic non-intracranial critical compartment/non-compressible bleeds or other traumatic bleeds.

Results: The study population included 250 patients (andexanet alfa, $n = 116$; 4F-PCC, $n = 134$). Critical compartment bleeds were the most common (86.8%), with retroperitoneal bleeds the most common subtype (30.9%). Most patients were admitted via the emergency department (82.0%). The median time from presentation to reversal/replacement treatment was 2.7 (interquartile range, 1.2, 6.6) h. For patients treated with andexanet alfa, 63.8% were administered the low-dose regimen. For 4F-PCC, a median of 2000 total units was administered per patient. Other treatment strategies used included intravenous fluids (26.0%), fresh frozen plasma (16.0%), and packed red blood cells (13.2%). Prior to hospital discharge, oral anticoagulants were restarted in 20.4% of patients. Overall, 25 (10.0%) patients died in hospital.

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Conclusion: This analysis provides insights into the clinical characteristics and management strategies, including time to treatment, for patients treated with andexanet alfa or 4F-PCC while hospitalized for FXa inhibitor–related traumatic bleeds.

KEYWORDS
andexanet alfa, blood coagulation factor, factor Xa inhibitors, hemorrhage, injury

1 | INTRODUCTION

1.1 | Background

Trauma is estimated to account for 8% of deaths per year worldwide.[1] Bleeding accounts for approximately 40% of the potentially preventable deaths associated with trauma, with most deaths occurring within 24 h.[2,3] The risk of major bleeding is further exacerbated by the use of anticoagulants, such as oral factor Xa (FXa) inhibitors (FXai), resulting in increased morbidity and mortality.[2,4] A recent meta-analysis of 19 studies found that preinjury anticoagulation in trauma patients was associated with an approximately two-fold higher risk of in-hospital mortality compared with no preinjury anticoagulation.[5]

1.2 | Importance

Inactive four-factor prothrombin complex concentrate (4F-PCC) is approved for the management of bleeding associated with vitamin K–dependent coagulation factors and is also used off-label for the management of FXai-related major bleeding, despite limited clinical trial evidence and lack of a rational pharmacologic mechanism of action.[4,6–8] Andexanet alfa, a recombinant protein specifically designed to reverse the anticoagulant effects of oral FXai, received accelerated approval in the United States and conditional approval in Europe for use as a specific reversal agent for rivaroxaban- or apixaban-related, life-threatening or uncontrolled bleeding. In patients with major bleeding associated with use of FXai who were enrolled in the Andexanet Alfa, a Novel Antidote to the Anticoagulation Effects of Factor Xa Inhibitors (ANNEXA-4) study, treatment with andexanet alfa reduced anti-FXa activity by >90% among patients treated with rivaroxaban or apixaban and was associated with good or excellent hemostatic efficacy at 12 h in 80% of patients.[9,10] In the ANNEXA-I study of andexanet alfa versus usual care (PCC for 86%) in patients with intracranial hemorrhage (ICH) while taking FXai, the proportion of patients achieving hemostatic efficacy was significantly higher with andexanet alfa (67.0%) versus usual care (53.1%; $p = 0.003$), as was reduction in median anti-FXa activity (94.5% vs. 26.9%; $p < 0.001$).[11]

Guidelines issued in 2023 by the European Task Force for Advanced Bleeding Care in Trauma suggest reversal with andexanet alfa in cases of life-threatening bleeding in the presence of an apixaban or rivaroxaban effect, with administration of PCC suggested if andexanet alfa is not available.[12] Similarly, the Western Trauma Association Algorithms Committee guidelines issued in 2021 suggest that in the management of life-threatening bleeding or injury with FXai use, either andexanet alfa or 4F-PCC should be used, with the acknowledgment that andexanet alfa is the only US Food and Drug Administration–approved reversal agent for FXai.[13]

The clinical guidelines further emphasize the need for timely and appropriate management of traumatic bleeds[12,13]; however, data from routine clinical practice on the current management of patients with FXai-related traumatic bleeds are limited.

1.3 | Goals of this investigation

The present analysis describes the clinical characteristics and management strategies used for patients treated with either andexanet alfa or 4F-PCC while hospitalized for a FXai-related traumatic non-intracranial bleed.

2 | METHODS

2.1 | Study design and setting

This is a subgroup analysis of a multicenter observational cohort study (ClinicalTrials.gov Identifier: NCT05548777) that included 4395 adults hospitalized with rivaroxaban- or apixaban-related acute major bleeding at 354 US hospitals who received treatment with andexanet alfa or 4F-PCC; the methods for this study have been detailed previously.[14] Via a study-specific survey, patient data were retrospectively extracted from electronic health record data deidentified in compliance with the Health Insurance Portability and Accountability Act. Institutional review board exemption was obtained by Advarra Institutional Review Board Services, Inc. per Department of Health and Human Services regulations found at 45 Code of Federal Regulations 46.104(d)(4).

2.2 | Selection of participants

In brief, the study included adult patients with a diagnosis of hemorrhagic disorder due to extrinsic circulating anticoagulants (*International Classification of Diseases, 10th Revision* diagnosis code: D68.32) as part of an inpatient admission who were taking rivaroxaban or apixaban at the time of the bleeding event, who received treat-

ment with andexanet alfa or 4F-PCC during hospitalization, and who were discharged between May 2018 and September 2022. The current analysis included patients with traumatic non-intracranial critical compartment/non-compressible bleeds (including retroperitoneal, intramuscular with compartment syndrome, intraarticular, intraocular, pericardial, and intraspinal bleeds) or other traumatic bleeds, hereafter referred to as traumatic bleeds. Patients with ICH in this observational study were evaluated in a separate subgroup, as presented previously[14]; thus, patients with traumatic ICH were excluded from this analysis.

2.3 | Measurements and outcomes

Evaluated patient and clinical characteristics included age, sex, bleed type, impaired mental status on admission, do-not-resuscitate order, comorbidities, systolic blood pressure, prothrombin time, international normalized ratio, oral FXai used, time since last anticoagulant dose, and location of presentation. Time from presentation to treatment ("door-to-treatment time") and dose of andexanet alfa or 4F-PCC treatment were recorded, as were other management strategies used, including intravenous fluids, blood products, and the restart of anticoagulation. Hospital length of stay and in-hospital mortality were also recorded.

2.4 | Data analyses

Continuous variables were summarized as medians with interquartile ranges (IQRs); categorical variables were summarized as counts and percentages. The low number of patients precluded adequate statistical comparisons between groups; thus, these analyses are descriptive only.

3 | RESULTS

3.1 | Patient and clinical characteristics

This analysis included 250 patients hospitalized for traumatic bleeds, 116 of whom were treated with andexanet alfa and 134 with 4F-PCC. Demographic and clinical characteristics at admission are shown in Table 1. Most patients (82.0%) presented directly to the emergency department, while 12.8% were transferred from another hospital and 4.8% were directly admitted. The median (IQR) age was 62.0 (53.0, 74.0) years, and 64.0% of patients were men. The most common comorbidities were hypertension (51.6%), diabetes (40.8%), chronic kidney disease (20.0%), heart failure (18.0%), and history of stroke (17.8%). Overall, 52.4% of patients had received apixaban, and 47.6% had received rivaroxaban; the majority of patients (82.0%) had taken their last anticoagulant dose ≤18 h prior to presentation. Bleeding in a critical compartment represented 86.8% of events. Among patients with critical compartment bleeds, the most common locations were retroperitoneal (30.9%), intramuscular with compartment syndrome (23.5%), and intraarticular (17.1%).

The Bottom Line

The current study evaluated the clinical characteristics and management strategies used for patients who received a commonly used off-label replacement agent, 4-factor prothrombin complex concentrate, or a specific reversal agent, andexanet alfa, for factor Xa inhibitor–associated traumatic non-intracranial bleeds. In this study, 82% of patients presented directly to the emergency department, suggesting the urgency of treatment; however, time from presentation to treatment was approximately 3 hours. Patients most commonly received intravenous fluids as additional treatment, and 10% of patients died in hospital. This study provides valuable insights into an undercharacterized and critically ill patient population.

3.2 | Andexanet alfa and 4F-PCC treatment

Characteristics of the reversal/replacement treatments are shown in Table 2. The median (IQR) door-to-treatment time was 2.7 (1.2, 6.6) h overall. Most patients treated with andexanet alfa received low-dose treatment (63.8%). The median (IQR) dose of 4F-PCC was 2000.0 (1500.0, 3362.5) total units, and most (84.3%) patients received a single dose of 4F-PCC treatment.

3.3 | Other management strategies

Other management strategies used for traumatic bleeds were intravenous fluids (26.0%), fresh frozen plasma (16.0%), packed red blood cells (13.2%), and vitamin K (10.4%; Table 2), with numerically lower use in those treated with andexanet alfa than in those treated with 4F-PCC. Oral anticoagulants were restarted prior to discharge in 20.4% of patients.

3.4 | Length of stay, discharge status, and mortality

In patients discharged alive, the median (IQR) length of hospital stay was 6.0 (4.0, 9.0) days overall (Table 2). A total of 52.8% of patients were discharged home, and 37.2% were discharged to another or to an unknown discharge destination. Overall, 25 (10.0%) patients died in hospital.

4 | LIMITATIONS

Key limitations of this study include the non-randomized study design, as well as limitations inherent to the extraction of data from electronic health care records, including dependency on the availability and granularity of the recorded data.[15] In this study, certain key covariates

TABLE 1 Patient and anticoagulant dosing characteristics for traumatic non-intracranial bleeds.

	All patients ($N = 250$)	Andexanet alfa ($n = 116$)	4F-PCC ($n = 134$)
Age (years), median (IQR)	62.0 (53.0, 74.0)	62.0 (55.0, 72.2)	63.5 (51.0, 75.0)
Sex, *n* (%)			
Male	160 (64.0)	78 (67.2)	82 (61.2)
Bleed types, *n* (%)			
Critical compartment	217 (86.8)	102 (87.9)	115 (85.8)
Other bleed	33 (13.2)	14 (12.1)	19 (14.2)
Critical compartment subtype, *n* (%)	**$N = 217$[a]**	**$n = 102$[a]**	**$n = 115$[a]**
Retroperitoneal	67 (30.9)	23 (22.5)	44 (38.3)
Intramuscular with compartment syndrome	51 (23.5)	23 (22.5)	28 (24.3)
Intraarticular	37 (17.1)	20 (19.6)	17 (14.8)
Intraocular	24 (11.1)	18 (17.6)	6 (5.2)
Pericardial	21 (9.7)	15 (14.7)	6 (5.2)
Intraspinal	16 (7.4)	7 (6.9)	9 (7.8)
Other	10 (4.6)	1 (1.0)	9 (7.8)
Impaired mental status (yes), *n* (%)	**$N = 235$[b]**	**$n = 108$[b]**	**$n = 127$[b]**
	66 (28.1)	31 (28.7)	35 (27.6)
DNR order, *n* (%)	45 (18.0)	26 (22.4)	19 (14.2)
First SBP measurement (mmHg), median (IQR)	120.0 (100.0, 142.8)	120.0 (100.0, 145.0)	120.0 (100.0, 140.0)
INR, median (IQR)	**$N = 191$[b]**	**$n = 84$[b]**	**$n = 107$[b]**
	1.7 (1.2, 3.0)	1.7 (1.2, 3.0)	1.7 (1.2, 3.2)
PT (s), median (IQR)	**$N = 129$[b]**	**$n = 57$[b]**	**$n = 72$[b]**
	15.0 (12.0, 30.0)	14.0 (11.0, 20.0)	16.2 (12.0, 32.2)
Comorbidities, *n* (%)			
Hypertension	129 (51.6)	59 (50.9)	70 (52.2)
Diabetes	102 (40.8)	44 (37.9)	58 (43.3)
CKD	50 (20.0)	23 (19.8)	27 (20.1)
Heart failure	45 (18.0)	21 (18.1)	24 (17.9)
Stroke history[c]	44 (17.8)	22 (19.1)	22 (16.7)
Liver disease	28 (11.2)	11 (9.5)	17 (12.7)
Peptic ulcer disease	15 (6.0)	6 (5.2)	9 (6.7)
Oral FXai, *n* (%)			
Apixaban	131 (52.4)	55 (47.4)	76 (56.7)
Rivaroxaban	119 (47.6)	61 (52.6)	58 (43.3)
Time since last anticoagulant dose, *n* (%)			
<8 h	93 (37.2)	43 (37.1)	50 (37.3)
8–18 h	112 (44.8)	57 (49.1)	55 (41.0)
>18 h	45 (18.0)	16 (13.8)	29 (21.6)
Location of presentation, *n* (%)			
Emergency department	205 (82.0)	98 (84.5)	107 (79.9)
Hospital transfer	32 (12.8)	9 (7.8)	23 (17.2)
Directly admitted	12 (4.8)	8 (6.9)	4 (3.0)
Other/unknown	1 (0.4)	1 (0.9)	0

Abbreviations: 4F-PCC, four-factor prothrombin complex concentrate; CKD, chronic kidney disease; DNR, do-not-resuscitate; FXai, factor Xa inhibitor; INR, international normalized ratio; IQR, interquartile range; PT, prothrombin time; SBP, systolic blood pressure.

[a]Patients with critical compartment bleeds.

[b]Patients with available data.

[c]All patients, $N = 247$; andexanet alfa, $n = 115$; 4F-PCC, $n = 132$.

TABLE 2 Management and outcomes of traumatic non-intracranial bleeds.

	All patients ($N = 250$)	Andexanet alfa ($n = 116$)	4F-PCC ($n = 134$)
Door-to-treatment time (h), median (IQR)	2.7 (1.2, 6.6)	2.9 (1.4, 6.1)	2.5 (1.0, 8.1)
Andexanet alfa initial dose, *n* (%)			
Low dose[a]	–	74 (63.8)	–
High dose[b]	–	42 (36.2)	–
4F-PCC total dose (IU), median (IQR)	–	–	2000.0 (1500.0, 3362.5)
4F-PCC dosing, *n* (%)			
Single	–	–	113 (84.3)
Multiple	–	–	11 (8.2)
Missing	–	–	10 (7.5)
Other treatment strategies, *n* (%)			
IV fluids	65 (26.0)	23 (19.8)	42 (31.3)
Fresh frozen plasma	40 (16.0)	12 (10.3)	28 (20.9)
Packed red blood cells	33 (13.2)	11 (9.5)	22 (16.4)
Vitamin K	26 (10.4)	6 (5.2)	20 (14.9)
Tranexamic acid	7 (2.8)	3 (2.6)	4 (3.0)
Protamine sulfate	6 (2.4)	3 (2.6)	3 (2.2)
Desmopressin	4 (1.6)	1 (0.9)	3 (2.2)
Factor VIIa	2 (0.8)	2 (1.7)	0
Feiba NF	2 (0.8)	2 (1.7)	0
3F-PCC	0	0	0
Restart of anticoagulation, *n* (%)			
Oral anticoagulation	51 (20.4)	27 (23.3)	24 (17.9)
Unfractionated or low molecular weight heparin	35 (14.0)	17 (14.7)	18 (13.4)
Anticoagulation not restarted	164 (65.6)	72 (62.1)	92 (68.7)
LOS (days), median (IQR)	6.0 (4.0, 9.0)	6.0 (4.0, 9.0)	6.0 (4.0, 9.8)
LOS excluding death (days), median (IQR)[c]	6.0 (4.0, 9.0)	6.0 (4.0, 9.0)	7.0 (5.0, 10.0)
Discharge status, *n* (%)			
Discharged home	132 (52.8)	65 (56.0)	67 (50.0)
Death	25 (10.0)	10 (8.6)	15 (11.2)
Other/unknown destination	93 (37.2)	41 (35.3)	52 (38.8)

Abbreviations: 3F-PCC, three-factor prothrombin complex concentrate; 4F-PCC, four-factor prothrombin complex concentrate; IQR, interquartile range; IV, intravenous; LOS, length of stay.

[a]400 mg bolus (delivered at a target rate of 30 mg/min, followed by a 4 mg/min infusion over 120 min).

[b]800 mg bolus (delivered at a target rate of 30 mg/min, followed by an 8 mg/min infusion over 120 min).

[c]All patients, $N = 225$; andexanet alfa, $n = 106$; 4F-PCC, $n = 119$.

(e.g., some laboratory parameters such as anti-FXa levels, indication for and dose of anticoagulation) were underreported. The current study population may not be representative of all patients with FXai-related traumatic bleeds, since it included only those who received andexanet alfa or 4F-PCC.[14] Furthermore, while this study represents a large cohort of patients with traumatic bleeds, the majority (87%) of patients in this analysis had critical compartment hemorrhages, primarily retroperitoneal. The subset of patients with blunt abdominal solid organ injury is of special interest due to the common use, but lower success rate, of non-operative treatment for these types of injuries, as well as the increased risk of mortality associated with preinjury chronic anticoagulation,[16] but this population was not specifically investigated in the current study.

Statistical comparisons between the two treatment groups were not deemed appropriate given the small sample size and low statistical power, as well as our limited ability to rigorously adjust for baseline confounders that may affect outcomes in a trauma population.

Finally, certain outcomes of interest, such as thrombotic events or functional outcomes, were beyond the scope of the current study due to limited reporting, need for endpoint adjudication, and as patient follow-up ended at hospital discharge.[14]

5 | DISCUSSION

This study provides insights into clinical characteristics and management strategies, including time to treatment, among patients treated with andexanet alfa or 4F-PCC while hospitalized with rivaroxaban- or apixaban-related traumatic bleeding events. A literature search for studies of reversal or replacement agent use in patients with traumatic bleeds while taking direct oral anticoagulants (DOACs) found limited evidence on the management of these type of bleeds. In a study that included 75 trauma patients taking DOACs who received reversal treatment, 60 received 4F-PCC and only one received andexanet alfa.[17] This multicenter study, including 250 patients with traumatic bleeds treated with andexanet alfa or 4F-PCC, may help fill this evidence gap.

In the current study, patients with rivaroxaban- or apixaban-related traumatic bleeds most commonly presented directly to the emergency department, suggesting the urgency of treatment for their traumatic bleeds. Prompt use of a reversal agent is a crucial part of the recommended treatment strategy for trauma patients with severe bleeding while on FXai.[12,13] Data on how timing of reversal treatment impacts outcomes in patients with anticoagulant-related traumatic bleeding are lacking; however, earlier anticoagulant reversal has been associated with improved outcomes in patients with ICH.[14,18] In a recent study in patients with anticoagulant-related ICH, door-to-treatment times of ≤1 h were associated with a reduced mortality risk.[18] In the current analysis, the median time from presentation to treatment was approximately 2.7 h in patients with traumatic non-intracranial bleeds, suggesting more rapid treatment as a potential area for improvement.

The most commonly used treatment strategies other than andexanet alfa or 4F-PCC were intravenous fluids, packed red blood cells, fresh frozen plasma, and vitamin K, with consistent and numerically lower use in those treated with andexanet alfa than with 4F-PCC. This pattern was also observed in the overall study population that included all bleed types,[14] and may suggest lower resource utilization with andexanet alfa compared with 4F-PCC for anticoagulant reversal in FXai-related bleeds.

Overall, 10.0% of patients died in hospital: 8.6% of patients in the andexanet alfa group and 11.2% in the 4F-PCC group. This was consistent with the in-hospital mortality reported previously in patients who experienced traumatic injuries while taking DOACs, which ranged from 3% to 19%, although those studies included patients with intracranial bleeding.[19–24] In-hospital mortality in the current population with traumatic bleeds was numerically higher than in the overall study population across both the andexanet alfa (6.0%) and 4F-PCC (10.6%) groups.[14] While mortality differed by bleed location and was highest for ICH and lowest for gastrointestinal bleeds,[14] in-hospital mortality was consistently lower among patients treated with andexanet alfa than with 4F-PCC, regardless of bleed type, including after adjustment for baseline confounders.[14] These findings are consistent with those of other recent indirect comparative studies of patients with FXai-related acute major bleeding treated with andexanet alfa or 4F-PCC, which showed significantly lower mortality with andexanet alfa compared with PCC, although those populations also included patients with intracranial bleeding.[25,26]

In conclusion, this analysis provides insights into the clinical characteristics and current management strategies, including time to treatment, for patients treated with andexanet alfa or 4F-PCC while hospitalized for rivaroxaban- or apixaban-related traumatic bleeds.

AUTHOR CONTRIBUTIONS

Conceptualization: Paul P. Dobesh, Craig I. Coleman, Mark Danese, and Gregory J. Fermann. *Data collection and analysis*: Mark Danese. *Critical review and evaluation of the results and critical review and editing of the paper*: Paul P. Dobesh, Craig I. Coleman, Mark Danese, Eva Lesén, Raymond C. Chang, Onivefu Odelade, and Gregory J. Fermann. *Study supervision*: Paul P. Dobesh, Craig I. Coleman, Eva Lesén, and Gregory J. Fermann.

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CONFLICT OF INTEREST STATEMENT

Paul P. Dobesh served as a consultant for the Pfizer/Bristol Myers Squibb Alliance, AstraZeneca, and Janssen Pharmaceuticals. Craig I. Coleman received research funding and/or consulting honoraria from Janssen Pharmaceuticals, Bayer AG, and AstraZeneca. Mark Danese is an employee of Outcomes Insights, which received research funding related to cardiovascular disease from Amgen and Boston Scientific. Eva Lesén, Raymond C. Chang, and Onivefu Odelade are employees of AstraZeneca. Gregory J. Fermann served on a speakers bureau for Janssen Pharmaceuticals and AstraZeneca, served as a consultant for Milestone Pharmaceuticals, and received research funding from Siemens PCORI and the National Institutes of Health.

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REFERENCES

1. GBD 2017 Causes of Death Collaborators. Global, regional, and national age-sex-specific mortality for 282 causes of death in 195 countries and territories, 1980-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet*. 2018;392(10159):1736-1788. doi:10.1016/S0140-6736(18)32203-7
2. Hunt BJ, Neal MD, Stensballe J. Reversing anti–factor Xa agents and the unmet needs in trauma patients. *Blood*. 2018;132(23):2441-2445. doi:10.1182/blood-2018-06-850396
3. Tisherman SA, Schmicker RH, Brasel KJ, et al. Detailed description of all deaths in both the shock and traumatic brain injury hypertonic saline trials of the Resuscitation Outcomes Consortium. *Ann Surg*. 2015;261(3):586-590. doi:10.1097/SLA.0000000000000837
4. Tomaselli GF, Mahaffey KW, Cuker A, et al. 2020 ACC expert consensus decision pathway on management of bleeding in patients on oral anticoagulants: a report of the American College of Cardiology Solu-

tion Set Oversight Committee. *J Am Coll Cardiol*. 2020;76(5):594-622. doi:10.1016/j.jacc.2020.04.053
5. Lee ZX, Lim XT, Ang E, Hajibandeh S, Hajibandeh S. The effect of preinjury anticoagulation on mortality in trauma patients: a systematic review and meta-analysis. *Injury*. 2020;51(8):1705-1713. doi:10.1016/j.injury.2020.06.010
6. Milling TJ Jr, Frontera J. Exploring indications for the use of direct oral anticoagulants and the associated risks of major bleeding. *Am J Manag Care*. 2017;23(4 suppl):S67-S80.
7. Lu G, Lin J, Bui K, Curnutte JT, Conley PB. Andexanet versus prothrombin complex concentrates: differences in reversal of factor Xa inhibitors in in vitro thrombin generation. *Res Pract Thromb Haemost*. 2020;4(8):1282-1294. doi:10.1002/rth2.12418
8. Ip B, Pan S, Yuan Z, et al. Prothrombin complex concentrate vs conservative management in ICH associated with direct oral anticoagulants. *JAMA Netw Open*. 2024;7(2):e2354916. doi:10.1001/jamanetworkopen.2023.54916
9. Connolly SJ, Crowther M, Eikelboom JW, et al. Full study report of andexanet alfa for bleeding associated with factor Xa inhibitors. *N Engl J Med*. 2019;380(14):1326-1335. doi:10.1056/NEJMoa1814051
10. Milling TJ Jr, Middeldorp S, Xu L, et al. Final study report of andexanet alfa for major bleeding with factor Xa inhibitors. *Circulation*. 2023;147(13):1026-1038. doi:10.1161/CIRCULATIONAHA.121.057844
11. Connolly SJ, Sharma MA, Cohen AT, et al. Andexanet for factor Xa inhibitor-related acute intracerebral hemorrhage. *N Engl J Med*. 2024;390(19):1745-1755. doi:10.1056/NEJMoa2313040
12. Rossaint R, Afshari A, Bouillon B, et al. The European guideline on management of major bleeding and coagulopathy following trauma: sixth edition. *Crit Care*. 2023;27(1):80. doi:10.1186/s13054-023-04327-7
13. Peck KA, Ley EJ, Brown CV, et al. Early anticoagulant reversal after trauma: a Western Trauma Association critical decisions algorithm. *J Trauma Acute Care Surg*. 2021;90(2):331-336. doi:10.1097/TA.0000000000002979
14. Dobesh PP, Fermann GJ, Christoph MJ, et al. Lower mortality with andexanet alfa vs 4-factor prothrombin complex concentrate for factor Xa inhibitor-related major bleeding in a U.S. hospital-based observational study. *Res Pract Thromb Haemost*. 2023;7(6):102192. doi:10.1016/j.rpth.2023.102192
15. Kaji AH, Schriger D, Green S. Looking through the retrospectoscope: reducing bias in emergency medicine chart review studies. *Ann Emerg Med*. 2014;64(3):292-298. doi:10.1016/j.annemergmed.2014.03.025
16. Reina R, Anand T, Bhogadi SK, et al. Nonoperative management of blunt abdominal solid organ injury: are we paying enough attention to patients on preinjury anticoagulation? *Am J Surg*. 2022;224(5):1308-1313. doi:10.1016/j.amjsurg.2022.06.019
17. Emigh B, Kobayashi L, Kopp M, et al. The AAST prospective observational multicenter study of the initial experience with reversal of direct oral anticoagulants in trauma patients. *Am J Surg*. 2021;222(2):264-269. doi:10.1016/j.amjsurg.2020.12.034
18. Sheth KN, Solomon N, Alhanti B, et al. Time to anticoagulation reversal and outcomes after intracerebral hemorrhage. *JAMA Neurol*. 2024;81(4):363-372. doi:10.1001/jamaneurol.2024.0221
19. Kobayashi L, Barmparas G, Bosarge P, et al. Novel oral anticoagulants and trauma: the results of a prospective American Association for the Surgery of Trauma Multi-Institutional Trial. *J Trauma Acute Care Surg*. 2017;82(5):827-835. doi:10.1097/TA.0000000000001414
20. Feeney JM, Neulander M, DiFiori M, et al. Direct oral anticoagulants compared with warfarin in patients with severe blunt trauma. *Injury*. 2017;48(1):47-50. doi:10.1016/j.injury.2016.08.016
21. Yuval JB, Felix KJ, Demma J, et al. Mortality in relation to presence and type of oral antithrombotic agent among adult trauma patients: a single-center retrospective cohort study. *Eur J Trauma Emerg Surg*. 2022;48(1):497-505. doi:10.1007/s00068-020-01429-7
22. LaDuke ZJ, Hecht JP, Cain-Nielsen AH, Hemmila MR, Wahl WL. Association of mortality among trauma patients taking preinjury direct oral anticoagulants versus vitamin K antagonists. *Surgery*. 2019;166(4):564-571. doi:10.1016/j.surg.2019.04.039
23. Blasius FM, Laubach M, Andruszkow H, et al. Impact of anticoagulation and antiplatelet drugs on surgery rates and mortality in trauma patients. *Sci Rep*. 2021;11(1):15172. doi:10.1038/s41598-021-94675-7
24. Dezman ZD, Comer AC, Smith GS, Narayan M, Hess JR, Hirshon JM. The severity of bleeding and mortality in trauma patients taking dabigatran. *J Emerg Med*. 2016;51(3):238-245. doi:10.1016/j.jemermed.2016.05.005
25. Cohen AT, Lewis M, Connor A, et al. Thirty-day mortality with andexanet alfa compared with prothrombin complex concentrate therapy for life-threatening direct oral anticoagulant-related bleeding. *J Am Coll Emerg Physicians Open*. 2022;3(2):e12655. doi:10.1002/emp2.12655
26. Costa OS, Connolly SJ, Sharma M, et al. Andexanet alfa versus four-factor prothrombin complex concentrate for the reversal of apixaban- or rivaroxaban-associated intracranial hemorrhage: a propensity score-overlap weighted analysis. *Crit Care*. 2022;26(1):180. doi:10.1186/s13054-022-04043-8

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