

To reverse or not to reverse: Direct oral anticoagulants in mild traumatic brain injury

Louisa B. Chen, MD MBA, Mikhail Stiffler, BS, Omkar S. Pawar, MSCE, BDS, James T. Ross, MD MS, and Amy P. Rushing, MD, Cleveland, OH

BACKGROUND:	The growing usage of direct oral anticoagulants (DOACs) has brought into question the need for pharmacologic reversal in patients who develop traumatic brain injuries (TBIs). While there are specific benefits in reversal for TBI patients on warfarin, the impact has not been clearly shown in DOAC populations. This study evaluated radiographic and clinical outcomes among patients with isolated mild TBIs to determine whether DOAC usage or its reversal confers measurable differences in early outcomes.
METHODS:	We conducted a retrospective review of adults (18 to 99 y) with isolated mild TBI (Glasgow Coma Scale: 13 to 15) after ground-level falls at a Level I trauma center from 2016 to 2024. The primary outcome was radiographic hemorrhage progression, defined as >2-mm increase in hemorrhage or need for >2 head computed tomographies within 24 hours. Secondary outcomes included Glasgow Coma Scale decline, intensive care unit length of stay, neurosurgical intervention, thromboembolic events, disposition, and inpatient mortality. Multivariable logistic regression and propensity score matching were used to evaluate associations between DOAC usage, reversal therapy, and outcomes.
RESULTS:	Among 273 patients, 96 (35%) were taking a DOAC, and of these, 41 received four-factor prothrombin complex concentrate and 18 received andexanet alfa. DOAC patients demonstrated similar rates of radiographic progression, intensive care unit length of stay, and discharge disposition compared with non-DOAC patients. In multivariate analysis, DOAC usage was not associated with increased radiographic progression, measured by subdural hemorrhage growth (47.5% vs. 44.8%; $p = 0.70$) or increased need for >2 computed tomography scans (49.1% vs. 48.9%, $p = 1.00$). Among DOAC users, reversal was also not associated with improved radiographic progression or secondary outcomes. No significant outcome differences were observed between reversal with four-factor prothrombin complex concentrate and andexanet alfa.
CONCLUSIONS:	In isolated mild TBI after ground-level falls, DOAC usage was not associated with worsened clinical outcomes or increased radiographic progression. Pharmacologic reversal offered no measurable benefit. These findings support selective reversal in stable mild TBI. (<i>J Trauma Acute Care Surg.</i> 2026;00: 000–000 Copyright © 2026 Wolters Kluwer Health, LLC. All rights reserved.)
LEVEL OF EVIDENCE:	Therapeutic/Care Management; Level III.
KEY WORDS:	Traumatic brain injury (TBI), intracranial hemorrhage (ICH), anticoagulation, DOAC reversal, andexanet alpha

BACKGROUND

The widespread adoption of direct oral anticoagulants (DOACs) has created a significant clinical challenge in how to care for patients taking DOACs who develop a traumatic brain injury (TBI).^{1–3} This question is particularly important for older adults in whom falls are

the leading cause of TBI, and of whom ~36% were taking an antiplatelet or anticoagulant in a recent large US study.⁴

Since the first DOAC was approved in 2010, their usage has expanded rapidly for stroke prevention in atrial fibrillation and treatment of venous thromboembolism, surpassing warfarin prescriptions nationwide.^{5,6} DOACs offer predictable pharmacokinetics, fewer food and drug interactions, and eliminate the need for routine International Normalized Ratio (INR) monitoring.⁵ However, while the negative impact of warfarin in TBI and the reversal strategy using intravenous vitamin K and four-factor prothrombin complex concentrate (4F-PCC) is well established in formal guidelines by multiple critical care societies, the clinical impact of DOACs in TBI and its optimal reversal strategy remains uncertain.^{1–3,7–10} Andexanet alfa (Andexxa; AstraZeneca) was approved by the FDA in 2018 for life-threatening bleeding related to factor Xa inhibitors (Apixaban and Xarelto), yet its use has been limited by high cost (approximately \$27,000 to \$49,000 per treatment) and restricted availability, with

Submitted: December 1, 2025; Revised: June 13, 2026; Accepted: June 16, 2026, Published online: Month DD, YYYY.

From the Department of Surgery, University Hospitals Cleveland Medical Center, Cleveland, OH (L.B.C., O.S.P., J.T.R., A.P.R.); Department of Surgery, Case Western Reserve University School of Medicine, Cleveland, OH (J.T.R., A.P.R.).

This study was presented at the 39th Eastern Association for the Surgery of Trauma Annual Scientific Assembly, January 20–23, 2026, Atlanta, Georgia.

Address for correspondence: Louisa B. Chen, MD, MBA, University Hospitals Cleveland Medical Center, 11100 Euclid Avenue, Cleveland, OH 44106; email: louisa.chen@uhhospitals.org.

Supplemental Digital Content is available for this article. Direct URL citations are provided in the HTML and PDF versions of this article on the journal's website, www.jtrauma.com.

DOI: 10.1097/TA.00000000000005133

J Trauma Acute Care Surg
Volume 00, Issue 00

fewer than 15% of US hospitals maintaining supply.^{1,11} Consequently, 4F-PCC continues to be the preferred reversal agent, with surveys indicating that more than two-thirds of trauma surgeons still prefer it to Andexanet alfa—even in cases of life-threatening hemorrhage.¹¹

Given the rising prevalence of DOAC use and the lack of consensus on reversal in mild TBI, we evaluated outcomes among anticoagulated patients with isolated mild TBI after ground-level falls. We compared clinical and radiographic outcomes between patients managed with and without pharmacologic reversal (4F-PCC or Andexanet alfa) to determine whether reversal, and the choice of reversal agent, offers measurable benefit in this population.

METHODS

Population

We conducted a retrospective review of adults (ages 18 to 99) admitted to a Level I trauma center between July 2016 and August 2024, with isolated mild TBI following a ground-level fall. Mild TBI was defined as a Glasgow Coma Scale (GCS) score of 13 to 15 on presentation. Demographic data, including age, sex, admission laboratory values, and comorbidities, were abstracted from an institutional trauma registry. Data on prehospital anticoagulant and antiplatelet use (including timing of last dose) and radiographic findings were abstracted from the electronic medical record. Among patients taking DOACs, outcomes were compared between those reversed with 4F-PCC (Kcentra) and those reversed with Andexanet alfa. Data were stored in REDCap. This study was approved by our institutional IRB. The STROBE guideline was used to ensure proper reporting of methods, results, and discussion (Supplemental Digital Content 1, <http://links.lww.com/TA/F624>).

Outcomes

The primary outcome was radiographic progression of intracranial hemorrhage (ICH), defined as (1) >2 mm increase in hemorrhage thickness from initial computed tomography (CT) or (2) need for >2 head CT scans during the first 24 hours of admission. At our institution, patients with ICHs routinely undergo repeat CT imaging at ~6-hour intervals until stability is confirmed, with a minimum of two scans obtained in all cases. Additional imaging beyond the standard protocol is performed selectively based on clinical concern (change in GCS) or radiographic concern for progression. Radiographic concern is specifically better encapsulated by the existence of a third scan, as it can capture clinically meaningful changes that may not be fully reflected by size-based measurements alone, including evolution of a subarachnoid hemorrhage, progression of a multicompartiment hemorrhage, or the development of new hemorrhagic foci. During the study period, all patients with ICH received neurosurgical consultations. The

radiologists' interpretations were corroborated with measurements by the data entrants due to variations in documentation (ie, labeling as increased/decreased without numerical labeling). Secondary outcomes included decline in GCS score by ≥ 1 point at discharge, intensive care unit (ICU) length of stay (LOS), neurosurgical intervention (craniotomy, craniectomy, fracture repair, invasive monitor, shunt/drain placement), thromboembolic events, discharge disposition (home vs. nonhome facility), and inpatient mortality.

Statistical Analysis

Two analytic comparisons were performed. First, outcomes were compared between patients taking DOACs and patients not taking anticoagulants or antiplatelet agents at presentation. Second, within the DOAC cohort, outcomes were compared between those reversed with 4F-PCC (Kcentra) and those reversed with Andexanet alfa. For this study, patients taking any dose of an antiplatelet agent (including aspirin and Plavix) were excluded from the analysis. Continuous variables were summarized as medians with interquartile ranges and compared using the Wilcoxon rank-sum test. Categorical variables were summarized as counts and percentages and compared using the χ^2 or Fisher exact test, as appropriate.

Multivariable logistic regression was used to identify factors associated with the outcomes, adjusting for clinically relevant covariates. Within the DOAC cohort, propensity score (PS) analysis was performed to reduce confounding by indication. PS were estimated using a probit model adjusting for age, sex, race, preinjury domicile, admission GCS score, presence of skull fracture, hemorrhage burden, platelet count, INR, creatinine, and hemoglobin. Patients were matched using a 1:1 nearest-neighbor matching algorithm within a caliper of 0.5 of the PS with no common support. Covariate balance before and after matching was assessed using standardized mean differences (Supplemental Digital Content 2, <http://links.lww.com/TA/F625>). A subgroup analysis was further performed among patients aged older than 65 years to evaluate outcomes related to DOAC use and reversal in this age group. In this analysis, neither DOAC use nor reversal was associated with differences in radiographic progression or short-term clinical outcomes, consistent with the primary analysis. All statistical analyses were performed using Stata (version 17; StataCorp). Statistical significance was defined as a two-sided p -value <0.05.

RESULTS

Of the 1,862 patients who presented with an isolated ICH between July 2016 and August 2024, 1,589 patients were excluded based on the following: 855 patients were not on any anticoagulation at the time of presentation, 45 patients presented after a non-fall mechanism, 19 patients were taking only antiplatelet medications at the time of presentation, and 670 patients

met two or more of these listed criteria. As a result, our study included 273 patients, with 96 on a DOAC medication and 177 not on a DOAC medication. 37 (14%) were taking a DOAC without reversal, 41 (15%) were reversed with 4F-PCC (Kcentra), and 18 (7%) were reversed with Andexanet alfa. The decision to give a reversal agent was at the discretion of the clinical team, including the treating emergency medicine, trauma surgery, or neurosurgery physicians. The choice of reversal agent depended not only on clinician preference but also on the availability of Andexanet alfa (which was not available at any of the referring centers; Fig. 1).

Impact of Direct Oral Anticoagulants in Patients With Mild Traumatic Brain Injury

Patients taking DOACs were older (median age: 81 vs. 75 y; $P < 0.001$), more likely to have a history of arrhythmia (78% vs. 33%; $p < 0.001$), and had higher admission INR values (1.2 vs. 1.1; $p < 0.001$) than non-DOAC patients. Patients taking DOACs were less likely to present with multiple hemorrhages (32% vs. 49%; $p = 0.026$). In the univariate analysis, no significant differences were observed between the DOAC and non-DOAC groups in rates of radiographic hemorrhage progression, decline in GCS, ICU or hospital LOS, or discharge disposition (Table 1).

In multivariable analysis, DOAC use was not associated with radiographic progression, indicated by > 2 CT scans [odds ratio (OR): 1.17, CI: 0.64 to 2.15; $p = 0.59$] or increased subdural hemorrhage (SDH) growth ≥ 2 mm (OR: 0.81, CI: 0.46 to 1.45; $p = 0.49$). No significant differences were observed in midline shift increase, GCS decline, ICU or hospital LOS, or discharge disposition between DOAC and non-DOAC groups (Table 2).

After PS matching within patients taking DOACs, rates of > 2 CT scans (41% vs. 45%; $p = 1.00$) and SDH

growth ≥ 2 mm (48% vs. 34%; $p = 0.42$) remained comparable between patients on DOACs who did and did not undergo reversal. Reversal was not associated with GCS decline or improved discharge outcomes (Table 3). Post-matching, the covariate balance was achieved across the adjusted baseline variables, with all standardized mean differences $< 10\%$ (Supplemental Digital Content 3, <http://links.lww.com/TA/F626>).

In the age older than 65 years subgroup analysis, reversal use was not independently associated with radiographic progression outcomes, including > 2 CT scans (OR: 1.28; 95% CI: 0.44 to 3.72; $p = 0.64$) or SDH growth ≥ 2 mm (OR: 1.03; 95% CI: 0.36 to 2.91; $p = 0.94$). Similarly, reversal was not associated with midline shift increase or other secondary outcomes (Table 4).

Comparison of Reversal with Andexanet Alfa and Four-factor Prothrombin Complex Concentrate

Comparisons between 4F-PCC and Andexanet alfa revealed no significant differences across outcomes, although a trend toward decline in GCS was noted in the Andexanet alfa group ($p = 0.062$; Table 5; Supplemental Digital Content 4, <http://links.lww.com/TA/F627>).

DISCUSSION

For patients admitted with mild TBI after ground-level falls, we observed the following: (1) the use of DOACs was not associated with worse short-term radiographic or clinical outcomes, (2) DOAC reversal was not associated with significant differences in short-term radiographic or clinical outcomes, and (3) the choice of reversal agent was not associated with differences in outcome. Our findings add to a growing body of evidence

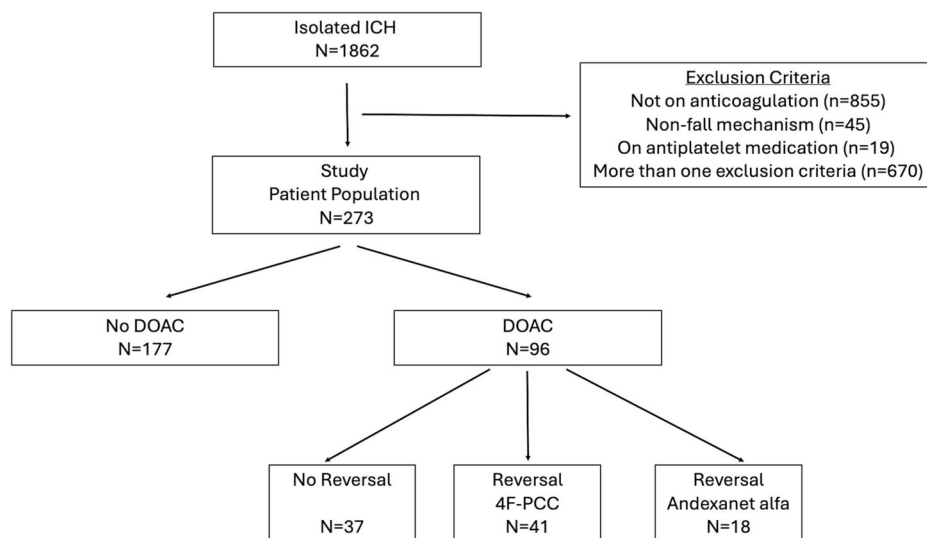


Figure 1. Consort diagram for patient population.

TABLE 1. Comparison of Patient Demographics, Injury Characteristics, and Outcomes of Patients With Mild TBI on DOAC and Not on DOAC

	No-DOAC (n = 177)	DOAC (n = 96)	p
Age, median (IQR)	75 (66 to 83)	81 (75 to 87)	<0.001
Sex (F), n (%)	76 (43.9)	43 (44.8)	0.90
Race (white), n (%)	144 (82.3)	85 (88.5)	0.22
Preinjury domicile (non-home), n (%)	20 (11.5)	12 (12.6)	0.84
Hemoglobin, median (IQR)	12.4 (11.2 to 13.7)	12.2 (10.8 to 13.9)	0.44
Platelets, median (IQR)	203 (164 to 265)	199.5 (147 to 249.5)	0.48
Creatinine, median (IQR)	0.97 (0.76 to 1.24)	0.995 (0.82 to 1.31)	0.40
INR, median (IQR)	1.1 (1.0 to 1.3)	1.3 (1.1 to 1.6)	<0.001
Comorbidities, n (%)			
Arrhythmia	58 (33.0)	75 (78.1)	<0.001
Dementia	22 (12.5)	18 (18.8)	0.21
CVA	28 (15.9)	17 (17.7)	0.73
Substance use history	32 (18.2)	7 (7.3)	0.018
DVT	16 (9.1)	16 (16.7)	0.077
PE	8 (4.5)	11 (11.5)	0.045
CHF	28 (15.9)	30 (31.3)	0.005
Admission GCS, median (IQR)	15 (14 to 15)	15 (14 to 15)	0.74
Skull fracture, n (%)	30 (17.6)	11 (11.5)	0.22
No. hemorrhages, n (%)			0.026
1	88 (50.6)	65 (67.7)	
2	50 (28.7)	19 (19.8)	
3 to 4	36 (20.7)	12 (12.5)	
Primary hemorrhage, n (%)			0.82
Epidural	3 (1.7)	1 (1.0)	
Subdural	105 (60.3)	63 (65.6)	
Subarachnoid/intraventricular	54 (31.0)	25 (26.0)	
Intracerebral	12 (6.9)	7 (7.3)	
Total CT-scan count, n (%)			1.00
2	83 (50.9)	45 (51.1)	
3	53 (32.5)	28 (31.8)	
≥4	27 (16.6)	15 (17.0)	
> 2CT scans, n (%)	80 (49.1)	43 (48.9)	1.00
SDH growth ≥2 mm, n (%)	84 (47.5)	43 (44.8)	0.70
MLS change (≥2 mm), n (%)	41 (23.2)	27 (28.1)	0.38
Inpatient mortality, n (%)	16 (9.0)	12 (12.5)	0.41
Neurosurgical intervention, n (%)	16 (9.1)	11 (11.5)	0.53
ICU admission, n (%)	107 (60.5)	47 (49.0)	0.074
Decline in GCS, n (%)	18 (11.9)	8 (9.8)	0.67
Thromboembolic event, n (%)	6 (3.4)	7 (7.3)	0.23
Change in domicile at discharge, n (%)	73 (45.9)	33 (39.3)	0.34
LOS (d), median (IQR)	5 (3 to 10)	4 (2 to 10)	0.27
ICU LOS (d), median (IQR)	3 (2 to 6)	4 (2 to 10)	0.30

CHF, congestive heart failure; CVA, cerebrovascular accident; DVT, deep venous thrombosis; IQR, interquartile range; MLS, midline shift; PE, pulmonary embolism.

that challenges the assumption that DOACs worsen patient outcomes in TBI and must be reversed.¹⁻³

Our study addresses a common clinical dilemma: how to treat patients taking DOACs who present with mild TBI after ground-level falls. Our finding that DOAC use was not associated with radiographic progression or adverse short-term outcomes is consistent with studies such as a meta-analysis by Chai-Adisaksopha et al¹² which showed that DOAC therapy carries a lower risk of

bleeding progression compared with warfarin therapy. Furthermore, the same meta-analysis found that DOAC therapy is associated with lower odds of mortality compared with warfarin, which reinforces the notion that DOACs confer a safer anticoagulation risk profile than vitamin K antagonists.

Our results are similar to previously published literature describing injuries among patients taking DOACs. The proportion of DOAC-treated patients in

TABLE 2. Multivariate Analysis of Primary and Secondary Outcomes of Patients With Mild TBI on DOAC and Not on DOAC (Subgroup Analysis > 65)

Outcomes	OR (95% CI)	p
Total CT-scan count	1.17 (0.64 to 2.15)	0.59
SDH growth ≥ 2 mm	0.81 (0.46 to 1.45)	0.49
MLS change (≥ 2 mm)	1.56 (0.81 to 2.99)	0.17
Death during hospitalization	1.51 (0.61 to 3.75)	0.36
Neurosurgical intervention	1.43 (0.55 to 3.69)	0.45
ICU admission	0.81 (0.45 to 1.44)	0.47
GCS worsening	0.99 (0.37 to 2.62)	0.98
Thromboembolic event	1.42 (0.40 to 5.08)	0.58
Change in domicile	0.79 (0.42 to 1.48)	0.46
LOS (d), median (IQR)	2.66 (-6.59 to 11.92)	0.57
ICU LOS (d), median (IQR)	0.30 (-1.71 to 2.32)	0.76

IQR, interquartile range; MLS, midline shift.

this series (approximately one-third of all mild TBI admissions) is consistent with national data demonstrating the steady rise of DOAC use among older adults.⁴ Prior multicenter and registry studies have reported DOAC exposure rates of 25% to 40% among anticoagulated trauma patients, consistent with our findings.^{2,3} This supports the generalizability of our cohort and underscores the growing relevance of this population for trauma systems nationwide. Furthermore, in the subgroup analysis of patients older than 65 years, neither DOAC use nor reversal was associated with differences in radiographic progression or short-term clinical outcomes, consistent with the primary analysis. These findings suggest that age alone should not prompt routine reversal in otherwise stable mild TBI.

Our observation that DOAC use was not associated with increased hemorrhage progression or adverse outcomes corroborates several prior investigations reporting similar safety profiles. Large observational studies and meta-analyses have demonstrated that patients with DOAC-associated TBI experience similar or lower rates of hemorrhage progression, neurosurgical intervention, and mortality compared with warfarin users.^{2,3,13} The present analysis extends those findings by focusing specifically on mild TBIs, where the clinical decision to reverse anticoagulation is particularly uncertain. Within this subset, our data suggest that DOAC therapy does not independently predict radiographic progression or neurologic deterioration, supporting conservative management and close monitoring rather than routine reversal.

Evaluating reversal practices provides additional insight into current variability in trauma care. Our findings mirror existing literature with multiple retrospective reviews and meta-analyses demonstrating persistent uncertainty regarding the benefit of reversal for ICHs in patients on factor Xa inhibitors.^{14–17} Moreover, the economic and logistical barriers to Andexanet alfa use remain substantial, with limited hospital access and high per-treatment cost.^{1,11} Together, these findings reinforce the need for judicious selection of reversal candidates and

TABLE 3. Comparison of Patient Demographics, Injury Characteristics, and Outcomes of Patients With Mild TBI on DOAC Who Received Reversal and Patients Without Reversal

Variable	No Reversal (n = 37)	Reversal (n = 59)	p
Age, median (IQR)	81 (76 to 86)	81.5 (73 to 88)	0.75
Sex (F), n (%)	18 (48.6)	25 (42.4)	0.67
Race (white), n (%)	31 (83.8)	54 (91.5)	0.33
Preinjury domicile (non-home), n (%)	4 (10.8)	8 (15.3)	0.76
Hemoglobin, median (IQR)	12.2 (10.8 to 14.0)	12.1 (10.7 to 13.8)	0.98
Platelets, median (IQR)	211 (149 to 283)	195 (147 to 238)	0.50
Creatinine, median (IQR)	0.99 (0.75 to 1.20)	1.03 (0.83 to 1.47)	0.31
INR, median (IQR)	1.45 (1.15 to 1.70)	1.30 (1.10 to 1.60)	0.42
Comorbidities, n (%)			
Arrhythmia	27 (73.0)	48 (81.4)	0.45
Dementia	9 (24.3)	9 (15.3)	0.29
CVA	6 (16.2)	11 (18.6)	1.00
Substance use history	3 (8.1)	4 (6.8)	1.00
DVT	8 (21.6)	8 (13.6)	0.40
PE	4 (10.8)	7 (11.9)	1.00
CHF	10 (27.0)	20 (33.9)	0.51
Admission GCS, median (IQR)	15 (14 to 15)	15 (14 to 15)	0.45
Skull fracture, n (%)	8 (22)	3 (5)	0.02
No. hemorrhages, n (%)			0.27
1	27 (73)	38 (64)	
2	8 (22)	11 (19)	
3 to 4	2 (5)	10 (17)	
Primary hemorrhage, n (%)			0.32
Epidural	1 (3)	0	
Subdural	21 (57)	42 (71)	
Subarachnoid/ intraventricular	12 (32)	13 (22)	
Intracerebral	3 (8)	4 (7)	
Total CT-scan count, n (%)			0.14
2	12 (41)	13 (45)	
3	14 (48)	8 (28)	
≥ 4	3 (10)	8 (28)	
> 2 CT scans, n (%)	12 (41)	13 (45)	1.00
SDH growth ≥ 2 mm, n (%)	14 (48)	10 (34)	0.42
MLS change (≥ 2 mm), n (%)	7 (24)	8 (28)	1.00
Inpatient mortality, n (%)	3 (10)	3 (17)	0.71
Neurosurgical intervention, n (%)	4 (14)	7 (24)	0.50
ICU admission, n (%)	15 (52)	20 (69)	0.28
Decline in GCS, n (%)	2 (8)	4 (17)	0.41
Thromboembolic event, n (%)	3 (10)	4 (14)	1.00
Change in domicile, n (%)	11 (42)	12 (50)	0.78
LOS (d), median (IQR)	3 (2 to 10)	5 (3 to 10)	0.18
ICU LOS (d), median (IQR)	3 (2 to 4)	6 (2 to 10)	0.12

CHF, congestive heart failure; CVA, cerebrovascular accident; DVT, deep venous thrombosis; IQR, interquartile range; MLS, midline shift; PE, pulmonary embolism.

highlight the absence of evidence supporting empiric reversal in stable, mild injuries. These results are especially timely as andexanet alfa was removed from the US market in Dec 2025 during the preparation of this manuscript. A randomized controlled trial (ANNEXA-I) examining andexanet alfa compared with usual care in

TABLE 4. Multivariate Analysis of Primary and Secondary Outcomes of Patients With Mild TBI on DOAC Who Underwent Reversal (Subgroup Analysis >65)

Outcomes	OR (95% CI)	<i>p</i>
Total CT-scan count	1.28 (0.44 to 3.72)	0.64
SDH growth ≥ 2 mm	1.03 (0.36 to 2.91)	0.94
MLS change (≥ 2 mm)	1.45 (0.46 to 4.57)	0.51
Death during hospitalization	2.90 (0.57 to 14.6)	0.19
Neurosurgical intervention	1.29 (0.27 to 6.10)	0.74
ICU admission	1.58 (0.56 to 4.44)	0.38
GCS worsening	3.42 (0.42 to 27.6)	0.24
Thromboembolic event	1.90 (0.25 to 14.26)	0.532
Change in domicile	1.18 (0.36 to 3.77)	0.77
LOS (d), median (IQR)	2.06 (-1.33 to 5.46)	0.22
ICU LOS (d), median (IQR)	2.88 (-1.46 to 7.23)	0.18

IQR, interquartile range; MLS, midline shift.

patients on rivaroxaban/apixaban with ICH showed a doubling of thrombosis (14.6% vs. 6.9%) and thrombosis-related deaths (2.5% vs. 0.9%) at 30 days.¹⁷

The findings in this study add to the growing body of evidence that DOACs appear to have a limited impact in mild TBI and that routine reversal of DOACs may not be necessary. In addition, large-scale multicenter investigations demonstrate that TBIs associated with DOACs carry a risk profile that is on par with, or in some cases more favorable than, those associated with warfarin.¹⁸

Several limitations are noted. This is a single-center, retrospective study and therefore subject to potential selection bias and unmeasured confounding. Management decisions, such as choice of reversal agent, were dependent on individual clinician judgment. Andexanet alfa availability also affected decision-making, as it was only

available at the tertiary center. The interval of 6 hours between CT scans had minor variations in timing due to hospital logistics and the availability of radiology resources. The exclusion of patients on aspirin, although designed to isolate the effects of DOACs, limits applicability to mixed antithrombotic populations frequently encountered in clinical practice. The relatively small number of patients receiving Andexanet alfa limits direct comparison between reversal agents. In addition, radiographic progression was defined using clinically meaningful thresholds (> 2 mm increase or > 2 follow-up CTs in 24 h), but subtle or non-measurable changes could have been missed. These factors may attenuate the power to detect small but clinically relevant differences. In addition, this study did not address the question of whether patients taking DOACs have increased rates of delayed hemorrhage, as has been observed in patients on warfarin.^{7,18}

Taken together, these limitations suggest that while the current findings support the safety of withholding reversal in mild TBI, they should not alone prompt a change in practice guidelines. Instead, they provide essential evidence that can support prospective, multicenter investigations designed to establish standardized criteria for DOAC reversal in TBI. Future studies should incorporate cost-effectiveness analyses, assess functional and long-term outcomes, and explore biomarker-based measures of anticoagulant effect to define patient subgroups that may benefit from reversal.

In conclusion, this study suggests that DOAC use does not worsen outcomes in mild TBI and that routine reversal with 4F-PCC or Andexanet alfa offers no demonstrable advantage. These findings support a selective, rather than reflexive, approach to reversal and highlight the need for larger prospective trials to refine guidelines for anticoagulated trauma patients.

TABLE 5. Comparison of Outcomes of Patients With Mild TBI on DOAC Who Underwent Reversal With 4F-PCC or Andexanet Alfa Compared With Patients Without Reversal

	No Reversal (n = 34)	Reversal With 4F-PCC (n = 35)	Reversal With Andexanet Alfa (n = 17)	<i>p</i>
Total CT-scan count, n (%)				0.19
2	17 (53)	19 (59)	6 (40)	
3	12 (38)	6 (19)	4 (27)	
≥ 4	3 (9)	7 (22)	5 (33)	
> 2CT scans, n (%)	15 (47)	13 (41)	9 (60)	0.51
SDH growth ≥ 2 mm, n (%)	15 (44)	15 (43)	8 (47)	1.00
MLS change (≥ 2 mm), n (%)	8 (24)	9 (26)	7 (41)	0.40
Inpatient mortality, n (%)	3 (9)	6 (17)	2 (12)	0.71
Neurosurgical intervention, n (%)	4 (12)	4 (11)	2 (12)	1.00
ICU admission, n (%)	14 (41)	17 (49)	10 (59)	0.48
Decline in GCS, n (%)	2 (7)	2 (7)	4 (29)	0.06
Thromboembolic event, n (%)	3 (9)	2 (6)	2 (12)	0.69
Change in domicile at discharge, n (%)	12 (39)	10 (36)	8 (50)	0.65
LOS (d), median (IQR)	3 (2 to 6)	5 (3 to 10)	6 (3 to 9)	0.17
ICU LOS (d), median (IQR)	3 (2 to 4)	4 (2 to 7)	3 (2 to 7)	0.64

IQR, interquartile range; MLS, midline shift.

AUTHORSHIP

L.B.C., O.S.P., J.T.R., and A.P.R. participated in conception and study design. L.B.C., M.S., O.S.P., J.T.R., and A.P.R. participated in data analysis and interpretation. M.S. and L.B.C. participated in drafting the manuscript. J.T.R. and A.P.R. participated in critical revision.

ACKNOWLEDGMENT

The authors thank Daniel Forman for his work in helping collect data.

DISCLOSURE

The authors declare no conflicts of interest. JTACS COI Disclosure forms for all authors have been supplied and are provided as Supplemental Digital Content (<http://links.lww.com/TA/F628>).

This work was supported in part by the National Center for Advancing Translational Sciences NIH 1K12TR005469-01 (JTR), and by NIH NCATS UM1TR004528 (JTR).

REFERENCES

- Popma E, Davis N, West MA. Reversal of antithrombotic medications in patients with traumatic brain injury: what you need to know. *J Trauma Acute Care Surg*. 2025;99(6):828–835.
- Nederpelt CJ, Van Der Aalst SJM, Rosenthal MG, Krijnen P, Huisman MV, Peul WC, et al. Consequences of pre-injury utilization of direct oral anticoagulants in patients with traumatic brain injury: a systematic review and meta-analysis. *J Trauma Acute Care Surg*. 2020;88:186–194.
- Kobayashi L, Barmparas G, Bosarge P, Brown CV, Bukur M, Carrick MM, et al. Novel oral anticoagulants and trauma: results of a prospective AAST multicenter trial. *J Trauma Acute Care Surg*. 2017;85(5):825–832.
- Chen LB, Stiffler M, Pawar O, Rushing AP, Ross JT. 10-year trend in anticoagulant and antiplatelet use in patients with traumatic brain injury. Orlando FL: Presented at: Academic Surgical Congress; 2026.
- Chen A, Stecker E, Warden BA. Direct oral anticoagulant use: a practical guide to common clinical challenges. *J Am Heart Assoc*. 2020;9(13):e017559.
- Joglar JA, Chung MK, Armbruster AL, Benjamin EJ, Chyou JY, Cronin EM, et al. 2023 ACC/AHA/ACCP/HRS guideline for the diagnosis and management of atrial fibrillation: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation*. 2024;149(1):e1–e156.
- Puzio TJ, Murphy PB, Kregel HR, Ellis RC, Holder T, Wandling MW, et al. Delayed intracranial hemorrhage after blunt head trauma while on direct oral anticoagulant therapy: systematic review and meta-analysis. *J Am Coll Surg*. 2021;232:1007–1016.
- Iaccarino C, Carretta A, Demetriades AK, Di Minno G, Giussani C, Marcucci R, et al. Management of antithrombotic drugs in patients with isolated traumatic brain injury: an intersociety consensus document. *Neurocrit Care*. 2024;40(1):314–327.
- Wiegele M, Schöchl H, Haushofer A, Ortler M, Leitgeb J, Kwasny O, et al. Diagnostic and therapeutic approach in adult patients with traumatic brain injury receiving oral anticoagulant therapy: an Austrian interdisciplinary consensus statement. *Crit Care*. 2019;23:62.
- Frontera JA, Lewin JJ, Rabinstein AA, Aisiku 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(1):6–46.
- Fasanya C, Arrillaga A, Caronia C, Rothburt L, Japhe T, Hahn Y, et al. Use of andexanet alfa for factor Xa inhibitor reversal in US verified trauma centers: a national survey. *Clin Appl Thromb Hemost*. 2024;30:10760296241238013.
- Chai-Adisaksopha C, Hillis C, Isayama T, Lim W, Iorio A, Crowther M. Mortality outcomes in patients receiving direct oral anticoagulants: a systematic review and meta-analysis of randomized controlled trials. *J Thromb Haemost*. 2015;13(11):2012–2020.
- Scotti P, Séguin C, Lo BWY, de Guise E, Troquet JM, Marcoux J. Antithrombotic agents and traumatic brain injury in the elderly population: hemorrhage patterns and outcomes. *J Neurosurg*. 2019;133(2):486–495.
- Xiang AJ, Sadafi SL, Principato R, Shaikh A, Nowrouzi M, Eshaghpour A, et al. Andexanet alfa vs standard of care for factor Xa inhibitor-induced intracranial hemorrhage: a systematic review and meta-analysis. *Res Pract Thromb Haemost*. 2025;9(7):103201.
- 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(1):255–261.
- Irizarry-Gatell VM, Bacchus MW, De Leo EK, Zhang Y, Lagasse CA, Khanna AY, et al. The use of andexanet alfa vs 4-factor prothrombin complex concentrates in the setting of life-threatening intracranial hemorrhage. *Blood Coagul Fibrinolysis*. 2024;35(3):94–100.
- Connolly SJ, Sharma M, Cohen AT, Demchuk AM, Czlonskowska A, Lindgren AG, et al. Andexanet for factor Xa inhibitor-associated acute intracerebral hemorrhage. *N Engl J Med*. 2024;390(19):1745–1755.
- Nishijima DK, Offerman SR, Ballard DW, Vinson DR, Chettipally UK, Rauchwerger AS, et al. Immediate and delayed traumatic intracranial hemorrhage in patients with head trauma and preinjury warfarin or clopidogrel use. *Ann Emerg Med*. 2012;59(6):460–468; e1–7.