Repeat computed tomography head scan is not indicated in trauma patients taking novel anticoagulation: A multicenter study

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BACKGROUND: The number of trauma patients on prehospital novel oral anticoagulants (NOACs) is increasing. After an initial negative computed tomography of the head (CTH), practice patterns are variable for obtaining repeat CTH to evaluate for delayed intracranial hemorrhage (ICH-d). However, the risks and outcomes of ICH-d for patients on NOACs are unclear. We hypothesized that, for these patients, the incidence of ICH-d is low, similar to that of warfarin, and when it occurs, it does not result in clinically significant worse outcomes.

METHODS: Five level 1 trauma centers in Northern California participated in a retrospective review of anticoagulated trauma patients. Patients were included if their initial CTH was negative. Primary outcomes were incidence of ICH-d, neurosurgical intervention, and death. Patient factors associated with the outcome of ICH-d were determined by multivariable regression.

RESULTS: From 2016 to 2018, 777 patients met the inclusion criteria (NOAC, n = 346; warfarin, n = 431), 54% of whom received a repeat CTH. Delayed intracranial hemorrhage incidence was 2.3% in the NOAC group and 4% in the warfarin group ($p = 0.31$). No NOAC patient with ICH-d required neurosurgical intervention or died because of their head injury. Two warfarin patients received neurosurgical intervention, and three died from their head injury. Head Abbreviated Injury Scale ≥3 was associated with increased odds of developing ICH-d (adjusted odds ratio, 32.70; $p < 0.01$).

CONCLUSION: The incidence of ICH-d in patients taking NOAC is low. In this study, patients on NOACs who developed ICH-d after an initial negative CTH did not need neurosurgical intervention or die from their head injury. Repeat CTH in this patient population does not appear necessary. (*J Trauma Acute Care Surg.* 2020;89: 301–310. Copyright © 2020 American Association for the Surgery of Trauma.)

LEVEL OF EVIDENCE: Prognostic/epidemiologic study, level III.
Therapeutic, level IV.

KEY WORDS: Novel anticoagulants; trauma; intracranial hemorrhage.

Unintentional injuries are the third leading cause of death in the United States after heart disease and cancer.[1] Patients on anticoagulants are at higher risk of mortality after injury and are increasing in number as the North American population ages.[2–5] Evaluation of these patients typically includes a computed tomography of the head (CTH) on arrival to the trauma center to assess for intracranial hemorrhage.[6,7] If this initial CTH is negative, subsequent management specific to repeat CTH imaging varies considerably based on the provider or institutional policy. In anticoagulated patients, there is concern for delayed intracranial hemorrhage (ICH-d), which occurs when acute hemorrhage is not present on the initial CTH but develops later. For patients on anticoagulants, there are no national guidelines for repeat imaging after an initial negative CTH, leading to a variety of practices including routine repeat CTH, serial neurologic examinations in the emergency department, admission for 24-hour observation, and discharge home.[8–12]

The incidence of ICH-d in anticoagulated patients ranges from 0.3% to 6%.[5,8,10,11,13–17] However, this information is derived almost entirely from studies of patients taking warfarin or warfarin combined with antiplatelet agents. Warfarin has been the most commonly prescribed anticoagulant for more than 50 years. In the past decade, there has been a shift to the use of novel oral anticoagulants (NOACs): direct thrombin inhibitors like dabigatran, and factor Xa inhibitors like apixaban and rivaroxaban.[18,19] Novel oral anticoagulants are commonly prescribed for nonvalvular atrial fibrillation and are recommended as first-line treatment for venous thromboembolism by the American College of Chest Physician 2016 Guidelines.[18,20] Some benefits of NOACs over warfarin include faster onset, less food and drug interactions, and reduced spontaneous intracranial bleeding risk.[19,21,22] In addition, the Food and Drug Administration has approved reversal agents for dabigatran and the Xa inhibitors, idarucizumab and andexanet alfa, respectively, allowing for reversal in the event of bleeding or overdose.

The safety profile of NOACs and specifically their reduced risk of spontaneous intracranial hemorrhage have been demonstrated in the nonsurgical literature.[21,22] Nevertheless, the risks associated with prehospital NOAC use in trauma patients remain unclear. Specifically, the risk for developing ICH-d and the associated clinical outcomes of those with ICH-d are largely unknown. Therefore, the purpose of this study was to determine the incidence of ICH-d and the clinical outcomes associated with ICH-d in trauma patients on NOACs with an initial negative CTH. We hypothesized that, for patients on NOACs, the incidence of ICH-d is low, similar to that of warfarin, and when it occurs, it does not result in clinically significant worse outcomes.

PATIENTS AND METHODS

Trauma patients presenting to five Northern California level 1 trauma centers between 2016 and 2018 were reviewed for study inclusion. Inclusion criteria were prehospital oral anticoagulation; clinical concern for possible traumatic brain injury based on head strike, external injury, or mechanism; and an initial CTH scan interpreted as negative for acute hemorrhage by a radiologist. Oral anticoagulation included warfarin or

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any of the NOAC agents (including dabigatran, apixaban, and rivaroxaban). Patients taking anticoagulation with a concomitant antiplatelet agent (including aspirin, clopidogrel, or other) were included. Exclusion criteria were taking nonoral anticoagulation (enoxaparin), dual antiplatelet agents, or dead on arrival. Institutional review board approval was obtained by each participating center.

Data collected included demographics, type of anticoagulant, use of concomitant antiplatelet agent, mechanism of injury, number of medical comorbidities, and indications for anticoagulation. Additional data collected included Injury Severity Score (ISS), head Abbreviated Injury Scale (AIS), presentation Glasgow Coma Scale (GCS), International Normalized Ratio (INR), and results of repeat CTH, if obtained. The number of different reversal agents given was reviewed, as well as the specific types, including vitamin K, prothrombin complex concentrates (PCCs), fresh frozen plasma (FFP), cryoprecipitate, and platelets. Clinical outcomes included neurosurgical intervention, death, and readmission within 30 days.

Consistent with current practice variability, the decision to repeat CTH varied among the different institutions. At some institutions, the decision was provider dependent and no specific policy existed; at others, repeat CTH was routinely performed or patients were routinely observed for 4 to 6 hours in the ED. If a repeat CTH was obtained, the time interval between the initial and repeat CTH scan was recorded, and the results of the CTH were used to determine the incidence of ICH-d.

A power analysis was performed using 80% power and 95% confidence, which estimated that 65 patients taking a NOAC and 65 patients taking warfarin were needed to detect a difference in neurosurgical intervention and 68 patients per group were required to detect a difference in mortality after traumatic intracranial hemorrhage based on previously published data.[23]

Normally distributed continuous data are reported as mean ± SD, and nonnormally distributed data are reported as median with 25% to 75% interquartile range (IQR). Proportions were calculated for categorical variables. Baseline characteristics and outcome differences were analyzed using Student's *t* test and the Mann-Whitney *U* test, as applicable. Similarly, the χ^2 test or Fisher's exact test were used for analyzing differences between categorical variables. Within the subgroup of patients who had a repeat CTH, a univariable analysis was performed to determine which patient factors were associated with increased odds of developing ICH-d. Variables with $p < 0.20$ on univariable analysis and those that were considered to be clinically relevant were subsequently included in a multivariable regression analysis. Injury Severity Score was not included in the model because of colinearity with head AIS. An α value of <0.05 was used to define statistical significance in the multivariable model. Statistical analysis was performed using IBM SPSS Statistics for Windows (version 25.0; IBM Corp., Armonk, NY).

RESULTS

The study cohort consisted of 777 anticoagulated trauma patients with a negative initial CTH. Of these patients, 431 (55%) were taking warfarin and 346 (45%) were taking a NOAC. The patients in these two groups were similar in terms of sex, number of medical comorbidities, ISS, head AIS score of ≥3, and presentation GCS. The patients taking NOACs were slightly older (77 ± 13 vs. 75 ± 15 years, $p = 0.03$) and had a lower INR value on arrival (1.3 ± 0.40 vs. 2.7 ± 1.9, $p < 0.01$). Fall and motor vehicle collision (MVC) were the most common mechanisms of injury in both groups. Atrial fibrillation and deep vein thrombosis/pulmonary embolism were the two most common indications for anticoagulation in both groups. More patients were anticoagulated for atrial fibrillation in the NOAC group than those in the warfarin group. Lastly, the proportion of patients taking concomitant aspirin was similar in the two groups. However, more patients taking warfarin were also taking clopidogrel or a nonaspirin antiplatelet agent (Table 1).

To obtain the incidence of ICH-d in each group, patients who did not have a repeat CTH were then excluded (n = 354), leaving 423 patients, or 54% of the original cohort. Of those with a repeat CTH, 58% (n = 246) were taking warfarin and 42% (n = 177) were taking a NOAC ($p = 0.10$). Within this group of patients with a repeat CTH, there were no major differences in demographics or rate of concomitant antiplatelet use between those arriving on NOACs compared with warfarin. More patients in the warfarin group were taking anticoagulation for presence of a heart valve. Fall remained the most common mechanism of injury for both groups, while patients taking warfarin suffered from MVC more often than those taking NOACs (7% vs. 2%, $p = 0.04$). As expected, patients in the warfarin group had a higher average arrival INR (2.7 ± 1.6 vs. 1.4 ± 0.5, $p < 0.01$) (Table 2). The median time to repeat CTH was 6 hours (IQR, 6–7 hours) in the warfarin group compared with 6 hours (IQR, 6–7 hours) in the NOAC group ($p = 0.99$). There were 10 cases of ICH-d in the warfarin group compared with 4 cases in the NOAC group (4% vs. 2.3%, $p = 0.31$). Three additional patients in the warfarin group had equivocal CTH readings after repeat imaging. Two of these patients received a third CTH scan that was negative for acute hemorrhage in both cases. The third patient with an equivocal repeat CTH did not receive a third CTH and had no negative sequela. A neurosurgeon reviewed the imaging after consultation by the primary team and suspected that the lesion was actually a calcification and not an acute traumatic hemorrhage (Fig. 1).

Of the 14 total patients with ICH-d, 71% (n = 10) were on warfarin and 29% (n = 4) were on a NOAC. None of the patients who developed an ICH-d were taking a concomitant antiplatelet agent. The median time interval from initial CTH to repeat was 6 hours (IQR, 6–7 hours). The most common mechanism of injury was a fall (13 of 14 patients). Median ISS was higher in patients with ICH-d than the rest of the cohort at 13 (IQR, 6–21) versus 4 (IQR, 1–9) ($p < 0.01$; Table 3). The 10 cases of ICH-d in the warfarin group occurred at 3 different centers; one of these centers routinely obtains a repeat CTH, one routinely observes patients for 4 to 6 hours, and the other has no protocol and the decision is provider dependent. In the NOAC group, the four cases of ICH-d occurred across two centers; one of which routinely obtains a repeat CTH, and the other is provider dependent. Two centers had no cases of ICH-d. For patients included in the multivariable regression model, there was no difference in sex, indication for anticoagulation, or mechanism of injury among patients from the different centers.

TABLE 1. Demographics and Injury Characteristics: Entire Cohort

Patient Factors	Warfarin	NOAC	*p*
n	431	346	
Age, mean (SD), y	75 (15)	77 (13)	0.03
Sex, male, n (%)	211 (49)	176 (51)	0.60
No. medical comorbidities, mean (SD)	4.5 (2.6)	4.6 (2.5)	0.82
ISS,* mean (SD)	5.4 (6.6)	4.8 (5.0)	0.16
Head AIS ≥3, n (%)	14 (3)	9 (3)	0.60
INR,† mean (SD)	2.7 (1.9)	1.3 (0.4)	<0.01
ED GCS, mean (SD)	14.6 (1.2)	14.7 (0.9)	0.43
Indications for anticoagulation, n (%)			
Afib	266 (62)	241 (70)	0.02
PE/DVT	81 (19)	60 (17)	0.60
Heart valve	25 (6)	2 (<1)	<0.01
Malignancy	1 (<1)	2 (<1)	0.59
Other	58 (13)	41 (12)	0.43
Mechanism of injury, n (%)			
Fall	361 (84)	302 (87)	0.17
MVC	40 (9)	25 (7)	0.30
Assault	12 (3)	7 (2)	0.49
Auto vs. bike	3 (<1)	1 (<1)	0.63
Auto vs. pedestrian	6 (1)	8 (2)	0.34
Other	9 (<1)	3 (<1)	0.24
Concomitant antiplatelet, n (%)			
Aspirin	24 (6)	26 (8)	0.27
Plavix or other	17 (10)	6 (2)	<0.01

*ISS: among warfarin patients, n = 6 (1%) missing data; among NOAC patients, n = 7 (2%) missing data.

†INR: among warfarin patients, n = 3 (<1%) missing data; among NOAC patients, n = 25 (7%).

ED, emergency department; Afib, atrial fibrillation; PE, pulmonary embolism; DVT, deep vein thrombosis; Auto, automobile.

Univariable analysis of various patient factors and the outcome of ICH-d was performed on the 420 patients who had a repeat CTH with a definitive or nonequivocal read (positive or negative for acute hemorrhage) to create the multivariable model. In this analysis, a head AIS score of ≥3 and reversal administration were associated with increasing the odds of developing ICH-d (adjusted odds ratio, 32.70 [$p < 0.01$] and 59.83 [$p < 0.01$], respectively). Novel oral anticoagulant use was a covariable in the model and was not associated with ICH-d on univariable or multivariable analysis (Table 4). Regression analysis was then performed at different head AIS cutoff values to allow stratification by head injury severity. A head AIS score of ≥3 increased the odds of ICH-d by nearly fourfold compared with a cutoff of head AIS ≥2 (Table 5).

In an analysis of the entire cohort, including those with and without a repeat CTH, two of the 431 patients on warfarin required neurosurgical intervention because of intracranial hemorrhage (one received an external ventricular drain, and the other required a craniectomy). Both patients had received a repeat CTH with findings of ICH-d. None of the 346 patients on NOACs needed neurosurgical intervention. Notably, there were three deaths due to head injury after development of ICH-d in the warfarin group and no deaths from head injury in the NOAC group ($p = 0.26$). Patients in the warfarin group were more likely to receive at least one reversal agent compared with those in the NOAC group (60 patients vs. 5 patients, respectively; $p < 0.01$). They were also more likely to receive two reversal agents (29 patients vs. 3 patients, respectively, $p < 0.01$); however, there was no difference between the warfarin and NOAC groups when comparing the number of patients who received three or more reversal agents (5 patients vs. 3 patients, respectively; $p = 0.74$). In the warfarin group, the specific reversal agents given were vitamin K (n = 46), FFP (n = 27), PCC (n = 17), platelets (n = 2), cryoprecipitate (n = 1), and tranexamic acid (n = 1). In the NOAC group, the reversal agents given were FFP (n = 4), platelets (n = 3), PCC (n = 2), and cryoprecipitate (n = 2). The rate of readmission between the two groups was similar ($p = 0.16$).

Lastly, the entire cohort was then divided into those who received a repeat CTH and those who did not. Patients who received a repeat CTH were more likely to be older (78 ± 14 vs. 74 ± 14 years, $p < 0.01$) and have a slightly lower presentation GCS (14.6 vs. 14.8, $p < 0.01$). However, patients who underwent repeat CTH also had less overall comorbidities (4.0 vs. 5.3, $p < 0.01$), and lower ISS (4.3 vs. 6.2, $p < 0.01$). There was no difference in proportion of patients taking NOACs between the two groups (repeat vs. no repeat CTH) or indications for anticoagulation. The most common mechanism of injury overall was fall.

TABLE 2. Demographics and Injury Characteristics: Only Patients With a Repeat CTH

Patient Factors	Warfarin	NOAC	*p*
n	246	177	0.10
Age, mean (SD), y	77 (14)	79 (13)	0.22
Sex, male, n (%)	122 (50)	90 (51)	0.80
No. medical comorbidities, mean (SD)	4.0 (2.2)	3.9 (2.1)	0.81
ISS,* mean (SD)	4.4 (5.4)	4.0 (4.7)	0.38
Head AIS ≥3, n (%)	11 (4.5)	6 (3.4)	0.58
INR,† mean (SD)	2.7 (1.6)	1.4 (0.5)	<0.01
ED GCS, mean (SD)	14.6 (1.1)	14.6 (1.2)	0.96
Indications for anticoagulation, n (%)			
Afib	159 (65)	115 (65)	0.94
PE/DVT	37 (15)	37 (21)	0.12
Heart valve	17 (7)	0 (0)	0.04
Malignancy	1 (0.4)	1 (0.6)	1.00
Other/unknown	32 (13)	24 (14)	0.83
Mechanism of injury, n (%)			
Fall	211 (86)	162 (92)	0.07
MVC	17 (7)	4 (2)	0.04
Assault	7 (3)	5 (3)	0.99
Auto vs. bike	2 (<1)	0 (0)	0.51
Auto vs. pedestrian	4 (2)	5 (3)	0.50
Other	5 (2)	1 (<1)	0.41
Concomitant antiplatelet, n (%)			
Aspirin	13 (5)	6 (10)	0.87
Plavix or other	7 (3)	1 (2)	0.31

*ISS: among warfarin patients, n = 3 (1%) missing data; among NOAC patients, n = 7 (4%) missing data.

†INR: among NOAC patients, n = 9 (5%) missing data.

ED, emergency department; Afib, atrial fibrillation; PE, pulmonary embolism; DVT, deep vein thrombosis; Auto, automobile.

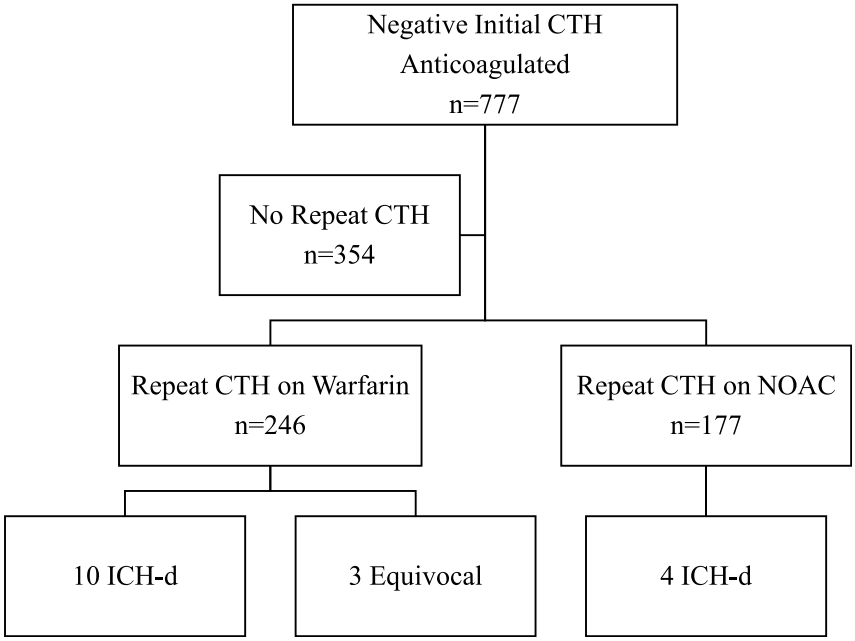

Figure 1. Incidence of ICH-d for trauma patients suspected of having traumatic brain injury with a negative initial CTH.

However, a higher percentage of falls occurred in the repeat CTH group, while MVCs occurred more commonly for those with no repeat CTH. Patients who did not receive a repeat CTH were more likely to receive two or three reversal agents (Table 6).

DISCUSSION

The purpose of this study was to determine the incidence of ICH-d in trauma patients taking NOACs and associated clinical outcomes in cases of ICH-d. We hypothesized that, for patients on NOACs, the incidence of ICH-d is low, similar to that of warfarin, and when it occurs, does not result in clinically significant worse outcomes. Our results support our hypothesis given that the incidence of ICH-d was 2.3% and there were no cases of neurointervention or deaths due to head injury after development of ICH-d. These findings suggest that, after an initially negative CTH, a routine repeat CTH may not be indicated in trauma patients on NOACs. We also evaluated patients taking warfarin and found the incidence of ICH-d to be 4% with two patients needing neurosurgical intervention and three deaths from head injury. Therefore, the same conclusion

TABLE 3. ICH-d: Entire Cohort

	Age, y	Sex	MOI	ISS	AIS-H	INR	NI	Reversal Agent	Death
Warfarin									
	83	M	Fall	1	0	2.9	No	Vit K	No
	87	F	Fall	11	0	1.3	No	None	No
	86	M	Fall	5	0	1.0	No	None	No
	92	F	Fall	9	3	1.7	No	PCC	No
	95	F	Fall	14	0	3.9	No	Vit K, FFP	No
	50	M	Fall	17	4	3.7	No	Vit K, PCC	Yes
	76	M	Fall	17	4	3.2	EVD	Vit K, FFP	Yes
	71	M	Fall	22	3	2.4	No	Vit K, PCC	No
	78	M	Fall	26	5	1.9	Crani	Vit K, PCC	Yes
	79	M	MVC	29	4	1.9	No	Vit K	No
NOAC									
	72	M	Fall	0	0	1.1	No	None	No
	84	M	Fall	1	0	1.2	No	None	No
	81	F	Fall	10	3	1.2	No	None	No
	68	F	Fall	22	3	1.3	No	None	No

MOI, mechanism of injury; AIS-H, Abbreviated Injury Scale for the Head; NI, neurosurgical intervention; M, male; F, female; Vit K, vitamin K; EVD, external ventricular drain; Crani, craniectomy.

TABLE 4. Univariable and Multivariable Analysis of Patient Factors and Odds of Developing ICH-d: Patients With a Repeat CTH

	Univariable, OR (95% CI)	*p*	Multivariable, aOR (95% CI)	*p*
Age	1.01 (0.96–1.05)	0.78	1.02 (0.96–1.09)	0.54
Male sex	1.82 (0.60–5.52)	0.29		
No. comorbidities	1.05 (0.83–1.32)	0.68	1.17 (0.86–1.58)	0.32
Head AIS ≥3	58.82 (16.89–204.83)	<0.01	32.70 (6.90–155.07)	<0.01
INR	0.94 (0.61–1.45)	0.77	0.47 (0.17–1.33)	0.16
GCS	0.85 (0.65–1.11)	0.23	1.02 (0.62–1.67)	0.95
Concomitant antiplatelet	N/A*	N/A		
NOAC	0.54 (0.17–1.75)	0.30	0.68 (0.11–4.12)	0.67
Reversal administered	28.74 (9.02–91.61)	<0.01	59.83 (9.59–373.47)	<0.01
Anticoagulation indication				
Afib	1.99 (0.55–7.26)	0.30		
DVT/PE	0.79 (0.17–3.59)	0.76		
Heart valve	N/A	N/A		
Malignancy	N/A	N/A		
Mechanism				
Fall	1.74 (0.22–13.62)	0.60		
MVC	1.49 (0.19–11.92)	0.71		
Assault	N/A	N/A		
Auto vs. bike/ped	N/A	N/A		

Note: ISS has been removed from the model because of colinearity with head AIS.
*N/A, not applicable used to denote no association with the outcome.
OR, odds ratio; CI, confidence interval; aOR, adjusted odds ratio; Afib, atrial fibrillation; DVT, deep vein thrombosis; PE, pulmonary embolism; Auto, automobile; Ped, pedestrian.

should not necessarily be drawn for patients on prehospital warfarin.

Like other published studies, our findings showed the incidence of ICH-d to be low, within the reported range of 0.3% to 6%.[5,8,10,11,13–17] However, nearly all prior studies focus on patients taking warfarin with or without an antiplatelet agent. Only one prior study focused on ICH-d specifically for trauma patients taking NOACs (n = 249) and concluded that routine repeat CTH was unnecessary since the incidence of ICH-d was 1.2% and no ICH-d patients required neurosurgical intervention or died.[9] Currently, the percentage of ICH-d that is considered clinically important is unclear. In addition, since there were no cases of ICH-d that led to neurointervention or death from head injury in our study, the specific number of patients needed to detect a clinically important percentage of ICH-d for patients taking NOACs is difficult to ascertain. However, when combining the results of our study with another similar study,[9] there were no neurointerventions or deaths due to head injury in more than 375 patients taking NOACs who received a repeat CTH after a negative initial CTH. Therefore, the number of patients needed to detect a clinically important percentage of ICH-d can be estimated to be more than 375. Our study adds to the current body of evidence by including more than 300 patients on NOACs from various institutions with variable repeat head imaging practices and by demonstrating no neurosurgical interventions or increased mortality in the few patients who developed ICH-d.

The three main factors that may have contributed to the low incidence of ICH-d in NOAC patients were frequent low-speed mechanisms of injury, rare use of concomitant antiplatelet agents, and the relatively short half-lives of NOACs. First, the majority of patients presented after a fall, which can be considered a relatively low-speed mechanism of injury. This is further supported by the overall low injury severity and head AIS scores. More severe mechanisms of injury, such as a traffic accidents or assaults, have been shown to increase the risk of ICH-d in anticoagulated patients.[24] Therefore, since more than 80% of patients in this study suffered from a fall, most were at lower risk of ICH-d. Second, only 10% of patients taking NOACs were also taking a concomitant antiplatelet agent. Use of anticoagulation in combination with an antiplatelet agent increased the risk of ICH-d in a meta-analysis of anticoagulated trauma patients.[24] The majority or 90% of patients taking NOACs were not taking a concomitant antiplatelet agent in our study. This likely resulted in lower risk for ICH-d, although none of the 14 patients with

TABLE 5. Stratification of Head AIS and Odds of Developing ICH-d: Patients With a Repeat CTH

	Univariable, OR (95% CI)	*p*	Multivariable, aOR (95% CI)	*p*
Head AIS ≥1	6.40 (2.15–10.02)	<0.01	6.45 (1.60–25.97)	0.01
Head AIS ≥2	9.08 (3.03–27.21)	<0.01	8.50 (2.06–35.09)	<0.01
Head AIS ≥3	58.82 (16.89–204.83)	<0.01	32.70 (6.90–155.07)	<0.01

OR, odds ratio; aOR, adjusted odds ratio; CI, confidence interval.

TABLE 6. Demographics, Injury Characteristics, and Outcomes: Repeat CTH Versus No Repeat CTH Groups

Patient Factors and Outcomes	Repeat CTH (n = 423)	No Repeat CTH (n = 354)	*p*
Age, mean (SD), y	78 (14)	74 (14)	<0.01
Sex, male, n (%)	212 (50)	175 (49)	0.85
No. medical comorbidities, mean (SD)	4.0 (2.2)	5.3 (2.8)	<0.01
ISS,* mean (SD)	4.3 (5.1)	6.2 (6.6)	<0.01
Head AIS ≥3, n (%)	17 (4)	6 (2)	0.06
INR†, mean (SD)	2.2 (1.4)	2.1 (1.8)	0.44
ED GCS, mean (SD)	14.6 (1.2)	14.8 (0.9)	<0.01
Patients taking NOAC, n (%)	177 (42)	169 (48)	0.10
Indications for anticoagulation, n (%)			
Afib	274 (65)	233 (66)	0.76
PE/DVT	74 (17)	67 (19)	0.61
Heart valve	17 (4)	10 (3)	0.37
Malignancy	2 (<1)	1 (<1)	1.00
Other	56 (13)	43 (12)	0.65
Mechanism of injury, n (%)			
Fall	373 (88)	290 (82)	0.01
MVC	21 (5)	44 (12)	<0.01
Assault	12 (3)	7 (2)	0.44
Auto vs. bike	2 (<1)	2 (<1)	1.00
Auto vs. pedestrian	9 (2)	5 (1)	0.46
Other	6 (1)	6 (2)	0.76
Concomitant antiplatelet, n (%)			
Aspirin	23 (5)	27 (7)	0.22
Plavix or other	9 (2)	14 (4)	0.13
Neurointervention, n	2	0	0.50
Reversal agents, n (%)			
1 agent	26 (6)	39 (11)	0.09
2 agents	2 (2)	22 (6)	<0.01
3 agents	1 (<1)	7 (2)	0.03
Readmission, n (%)	13 (3)	9 (3)	0.66
Deaths from head injury, n	3	0	0.26

*ISS: among repeat CTH patients, n = 10 (2%) missing data; among no repeat CTH patients, n = 3 (1%) missing data.
†INR: among repeat CTH patients, n = 9 (2%) missing data; among no repeat CTH patients, n = 19 (5%).
ED, emergency department; Afib, atrial fibrillation; PE, pulmonary embolism; DVT, deep vein thrombosis.

ICH-d were taking a concomitant antiplatelet in our study. Lastly, the half-life of NOACs is 5 to 17 hours,[25] whereas that of warfarin is 20 to 60 hours.[26] Thus, cessation of NOACs after injury could reduce anticoagulation effectiveness within hours, lowering the likelihood of being fully anticoagulated at the time of repeat CTH and reducing the risk of ICH-d.

Although the incidence of ICH-d was similar between patients taking NOACs and those taking warfarin, none of the patients taking a NOAC required neurosurgical intervention or died due to their head injury after development of ICH-d. In contrast, for patients on warfarin, two required neurosurgical intervention and three died from their head injury after developing ICH-d. This occurred even though patients on NOACs were slightly older and were less likely to receive reversal agents. Overall, we found that a head AIS score of ≥3 strongly increased the odds of ICH-d. However, a head AIS score of ≥3 did not translate to worse clinical outcomes for patients taking NOACs.

One explanation for this finding may be related to a difference in functional factor VII (FVII) between patients in the two groups. In the setting of disruption of vascular beds, tissue factor (TF), a transmembrane receptor for FVII, is exposed. Higher TF expression is present in the brain and, when bound with FVIIa, creates a hemostatic complex.[27,28] Although NOACs do not directly affect FVII, warfarin prevents the biologic function of FVII by inhibiting vitamin K, an essential cofactor for FVII activity.[29] Therefore, the potential benefits of the intracranial TF/FVII hemostatic complex are lost for patients taking warfarin, possibly contributing to worse clinical outcomes. In addition, the different half-lives of NOACs and warfarin, as mentioned previously, may further explain the difference in outcomes. For example, if the last dose of a NOAC was taken 8 hours before injury, by the time repeat CTH is performed, about 14 hours after the injury (median, 6 hours after arrival), the effectiveness of the NOAC would likely be reduced. Conversely, if warfarin were stopped at a similar time before injury, its effects would continue for much longer, increasing the risk for a clinically significant ICH-d. The inability for those on warfarin to form the potentially protective TF/FVII hemostatic complex and their higher likelihood of being fully anticoagulated at the time of repeat CTH

may lead to more frequent clinically significant worse outcomes following ICH-d.

Regarding surgical intervention and death in NOAC patients, one single-center study contradicts our findings.[30] Although the focus of that study was on patients presenting with an initial ICH, whereas our focus was on ICH-d, the authors found that 70 trauma patients on prehospital NOAC had higher rates of ICH progression, neurosurgical intervention, and mortality compared with those on warfarin. An explanation for this difference is related to overall injury burden faced by the different patient populations. In their study, the median ISS was 15 compared with a median ISS of 4 in our study. In addition, MVCs accounted for a third of the injuries compared with less than 10% of the injuries in our study. Therefore, the significantly higher injury burden and mechanism of injury likely led to the difference in clinical outcomes after ICH. Furthermore, the authors noted that reversal for patients on NOACs was still evolving at the time of the study and no reversal strategies were readily available for patients on NOACs, suggesting that they would have been less likely to receive reversal after identification of initial ICH.

In our study, we assumed that all repeat imaging was routine because the overall median time to repeat CTH was 6 hours, the typical time interval between initial and routine CTH used at our center. However, at centers that do not obtain routine repeat CTH, providers may have obtained a repeat CTH out of heightened clinical concern or after a change in mental status, and the CTH was, in fact, not routine. We evaluated this potential selection bias by comparing patients who received a repeat CTH with those who did not. Interestingly, we found that those with repeat CTH had a slightly lower ISS, less medical comorbidities, and were more likely to present after a fall compared with an MVC. Those who received a repeat CTH had a slightly lower GCS, although the clinical significance of this difference is unclear. Overall, the comparison between these groups suggests that selection bias did not play a major role in the decision to repeat a CTH in more severely injured patients as one might expect.

This study has several limitations. First, the average injury severity was low across the cohort. However, since most anticoagulated patients are older and often suffer from low energy mechanisms of injury, such as a fall, this group represents the overwhelming majority of anticoagulated patients. Ultimately, clinical judgment outweighs our findings, and our results should not be extrapolated to more severely injured patients. Another limitation of the study is that we were unable to determine the level of anticoagulation in patients on NOACs, because there are currently no readily available point-of-care tests to determine this metric. Therefore, patients in the NOAC group may not have been compliant with their medication and therefore may not have been anticoagulated, resulting in improved clinical outcomes. Next, the practices among the different institutions varied regarding policies for repeat CTH and reversal protocol and agents, with the most common practice being provider-dependent decision. Ultimately, more than half of the patients received a repeat CTH after an initial negative, suggesting that many providers are still electing to obtain a repeat CTH. Although a limitation of the study, this highlights the equipoise of the clinical scenario. Unfortunately, we were unable to account for site variability within our regression model because of the small number of outcomes in our study. However, the focus of this study was to examine the overall occurrence of ICH-d and the cumulative adverse clinical outcomes that can occur after ICH-d in patients taking NOACs compared with those taking warfarin. Lastly, readmission may have occurred at outside hospitals and would therefore not be captured in our study.

In conclusion, we found the incidence of ICH-d in trauma patients taking prehospital NOAC to be low at 2.3%. For the patients who developed ICH-d while on a NOAC, none required neurosurgical intervention or died as result of their head injury. Our findings suggest that routine repeat CTH after an initial negative CTH may not be indicated for trauma patients on NOACs. A subset of patients who are at higher risk for ICH-d after a negative CTH is those with a head AIS score of ≥3, and caution should be taken to apply these findings to this higher risk subset of patients. However, regardless of head AIS score, patients on NOACs in our study did not experience clinically significant worse outcomes after ICH-d.

AUTHORSHIP

C.M.C., G.B., J.A.B., J.M.G., A.M.K., L.Z.K., R.P., T.D.B., and G.P.V. designed this study. C.M.C., G.B., and G.P.V. searched the literature. C.M.C., G.B., J.A.B., R.C.D., A.M.K., L.Z.K., and T.D.B. collected the data. C.M.C., G.B., and G.P.V. analyzed the data. All authors participated in data interpretation, critical revision, and article preparation.

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DISCLOSURE

The authors declare no conflicts of interest.

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DISCUSSION

BELLAL JOSEPH, M.D. (Tucson, Arizona): Good morning. I'd like to thank the AAST and the Program Committee for allowing me to discuss this paper. I commend Dr. Cohan and her colleagues for their work challenging a difficult question we all deal with on a daily basis, the practice of repeat head CT after an initial negative head CT.

This retrospective cohort study of five Level I trauma centers reports an incidence of about 1 in 40 patients with a delayed bleed. No patients required intervention or died from this.

This practice aligns along with our center's practice, as well as my bias, a delayed CT is not needed. However, I do believe we need to be careful interpreting the results and methods of this study.

I have a few questions.

Why did the authors not include physical exam, especially change in neuro exam? We know from previous work that physical exam has a 100 percent negative predictive value for intervention or progress.

There were a large number of patients excluded by lack of CT. Can you tell me anything about these patients? And for those patients who long did you watch these patients before you knew if they had a delayed bleed?

There were different practices across different institutions. How do you feel this impacts the translation of your data?

Is there a way to look back to determine who got the repeat head CTs so there is more homogenous data?

And then how will your study group practice going forward?

You included all patients with antiplatelets and NOACs and analyzed it as such. Could you do a sub-analysis separating out the antiplatelet patients? I believe these are two separate groups.

Finally, as this is reported as an MIT, you report that the reversal protocols differs at each institution and this was not accounted for in the regression. So how do we interpret this data? What will you tell centers on implementing this practice and the reversal protocols?

And, finally, are you ready to define practice based on 173 patients?

Were you able to convince your neurosurgical colleagues and your emergency medicine colleagues on this practice?

Excellent job by the authors. I applaud them for tackling this difficult question. I think they're setting up the stage for a prospective multi-institutional trial.

Thank you.

CAITLIN COHAN, M.D. (Oakland, California): Thank you, Dr. Joseph, for your questions. The first question, why was physical exam not included, especially a change in the neuro exam, I think that's a great point and would have been very interesting to look at.

We did collect the initial GCS at time of arrival for all patients in this study, but we did not document a change. And I think that's something we can do going forward in a prospective, observational fashion.

The next question was about the patients without a repeat head scan, how long were they observed, and did they have any progression. The patients were observed depending on what center they were at for up to six hours.

One center doesn't have a specified time for observation but will admit a patient if they had a loss of consciousness at the time of their injury so they could have a cognitive evaluation.

If they were admitted then progression would have been captured in our data collection and we did not see that in the NOAC group.

How did the different practices amongst the different institutions impact translation? There were different practices amongst the different institutions and also within the institutions so translation is suboptimal. But we did find that the clinical outcomes remained consistent in the NOAC group, despite these differences in practice.

Is there any way to look at data to determine who got a repeat head CT scan so the data is more homogenous? When we calculated the incidence of delayed hemorrhage we excluded those without a repeat and we did that not only to look at confirmed cases of delayed hemorrhage but also an attempt to make the population more homogenous.

We did not do that for other aspects of analysis in our study. And that's something that we can look into moving forward for the manuscript.

How will your study group practice going forward? I think the next step for us will be in creating a risk stratification model. We did identify head AIS greater than or equal to three to be a key patient risk factor.

And I think that may make up a small subset of patients who should get a repeat, potentially. But the majority would likely not need a repeat.

Could you perform a sub-analysis of the patients who were taking the NOACs in addition to antiplatelets separately? This is an interesting point because a recent study came out last year, sponsored by the AAST, from 16 different centers that actually showed patients who were on aspirin when they arrive have a higher likelihood of intracranial hemorrhage compared to those who are on Plavix alone, Warfarin alone, or NOAC alone. So this is definitely a population that's at risk.

But the focus of our study, in particular, was on the anticoagulants. We included patients who were also taking aspirin or Plavix to see if that added an additional risk for delayed hemorrhage. And of all the patients with a delayed hemorrhage none of them were taking an antiplatelet agent in our study.

How can the data be interpreted in light of the different reversal protocols from the different centers? I think this is really hard to say given how new these reversal agents are and with andexanet alpha just being approved earlier this year for commercial production.

So, I think there is going to be a lot of adjustment and flux to the reversal protocols among centers for years to come as we learn more about their risks and become more familiar with them.

Interestingly, in our study none of the patients who actually developed a delayed hemorrhage in the NOAC group received a reversal agent. In the Warfarin group nearly all of them got Vitamin K and PCC or FFP.

Are you ready to define practice on the size of your study? I don't think that we're quite ready to determine practice based on this retrospective study but I do think that it adds to the body of growing evidence that supports potentially a better safety profile of these agents, especially in the setting of trauma.

If you combine our study with a similar one out of Cedars Sinai and U.C. San Diego, almost 400 patients on NOACs were evaluated after trauma with an initial negative head scan and when delayed hemorrhage occurred, there were no neurointerventions or deaths.

And, lastly, were you able to convince your emergency medicine and neurosurgery colleagues of this practice? Our emergency medicine colleagues, yes, they are definitely onboard with this since they face a lot of issues with overcrowding and are the ones who see these patients, sometimes with a GCS of 15 waiting for a repeat scan so they are definitely onboard.

For the neurosurgery attendings, I would have to discuss that with them. Thank you.