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Repeat CT Head Scan is Not Indicated in Trauma Patients Taking Novel Anticoagulation: A Multi-Center Study

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Presentations: This study will be presented as a podium presentation at the 78th Annual Meeting of the American Association for the Surgery of Trauma and Clinical Congress of Acute Care Surgery in Dallas, Texas September 21st, 2019.

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, 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 inclusion criteria (NOAC: n=346; warfarin: n=431), 54% of whom received a repeat CTH. ICH-d 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 $\geq$ 3 was associated with increased odds of developing ICH-d (aOR 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.

Level of Evidence: Prognostic/epidemiologic study, level III

Key Words: Novel anticoagulants, trauma, intracranial hemorrhage

Background:

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 exams in the emergency department, admission for 24-hour observation, and discharge home (8-12).

The incidence of ICH-d in anticoagulated patients ranges from 0.3-6% (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 over 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). NOACs are commonly prescribed for non-valvular 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). Additionally, 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, has been demonstrated in the non-surgical literature (21, 22). Yet, 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 as well as 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, does not result in clinically significant worse outcomes.

Methods:

Trauma patients presenting to five Northern California Level-1 trauma centers between 2016-2018 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 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 non-oral 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 (PCC), 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 4-6 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 ± standard deviation and non-normally distributed data are reported as medians with 25% to 75% interquartile ranges (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 Chi-squared 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. ISS was not included in the model due to co-linearity with AIS head. An alpha 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. Armonk, NY: IBM Corp.

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 ≥3, and presentation GCS. The patients taking NOACs were slightly older (77±13

vs. 75±15, 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 in the NOAC group were anticoagulated for atrial fibrillation 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 non-aspirin 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 to 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) in the warfarin group compared to 6 hours (IQR 6-7) in the NOAC group, p=0.99. There were ten cases of ICH-d in the warfarin group compared to four 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 the lesion was actually a calcification and not an acute traumatic hemorrhage (**Figure 1**).

Out 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). The most common mechanism of injury was a fall (13/14). Median ISS was higher in patients with ICH-d than the rest of the cohort at 13 (IQR 6-21) vs. 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 4-6 hours, and the other has no protocol and the decision is provider dependent. In the NOAC group, the 4 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.

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 non-equivocal read (positive or negative for acute hemorrhage) to create the multivariable model. In this analysis, AIS head ≥ 3 and reversal administration were associate with increased the odds of developing ICH-d (aOR 32.70, $p<0.01$ & aOR 59.83, $p<0.01$, respectively). NOAC 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 cut off values to allow stratification by head injury severity. An AIS head score ≥ 3 increased the odds of ICH-d by nearly four-fold compared to a cut off 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 due to 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 to 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, 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. 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 2 or 3 reversal agents (**Table 6).**

Discussion

The purpose of this study was to determine the incidence of ICH-d in trauma patients taking NOACs as well as 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 the incidence of ICH-d was 2.3%, and there were no cases of neuro-intervention 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 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. Additionally, since there were no cases of ICH-d that led to neuro-intervention 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 neuro-interventions or deaths due to head injury in over 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 over 375. Our study adds to the current body of evidence by including over 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 over 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 ICH-d were taking a concomitant antiplatelet in our study. Lastly, the half-life of NOACs is 5-17 hours (25) whereas that of warfarin is 20-60 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 head AIS ≥ 3 strongly increased the odds of ICH-d. However, a head AIS ≥ 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. Additionally, 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 prior to 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 to 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 to a median ISS of 4 in our study. Additionally, MVCs accounted for a third of the injuries compared to 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 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 to 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 to 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 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, as 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, over half of the patients received a repeat CTH after an initial negative, suggesting 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 due to 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 to 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 that are at higher risk for ICH-d after a negative CTH are those with AIS head ≥ 3 and caution should be taken to apply these findings to this higher risk subset of patients. However, regardless of AIS head, patients on NOACs in our study, did not experience clinically significant worse outcomes after ICH-d.

Author Contribution

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

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Conflicts of Interest

There are no identifiable conflicts of interest to report.

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Figure Legends

Figure 1. Incidence of delayed intracranial hemorrhage (ICH-d) for trauma patients suspected of having traumatic brain injury with a negative initial computed tomography head (CTH).

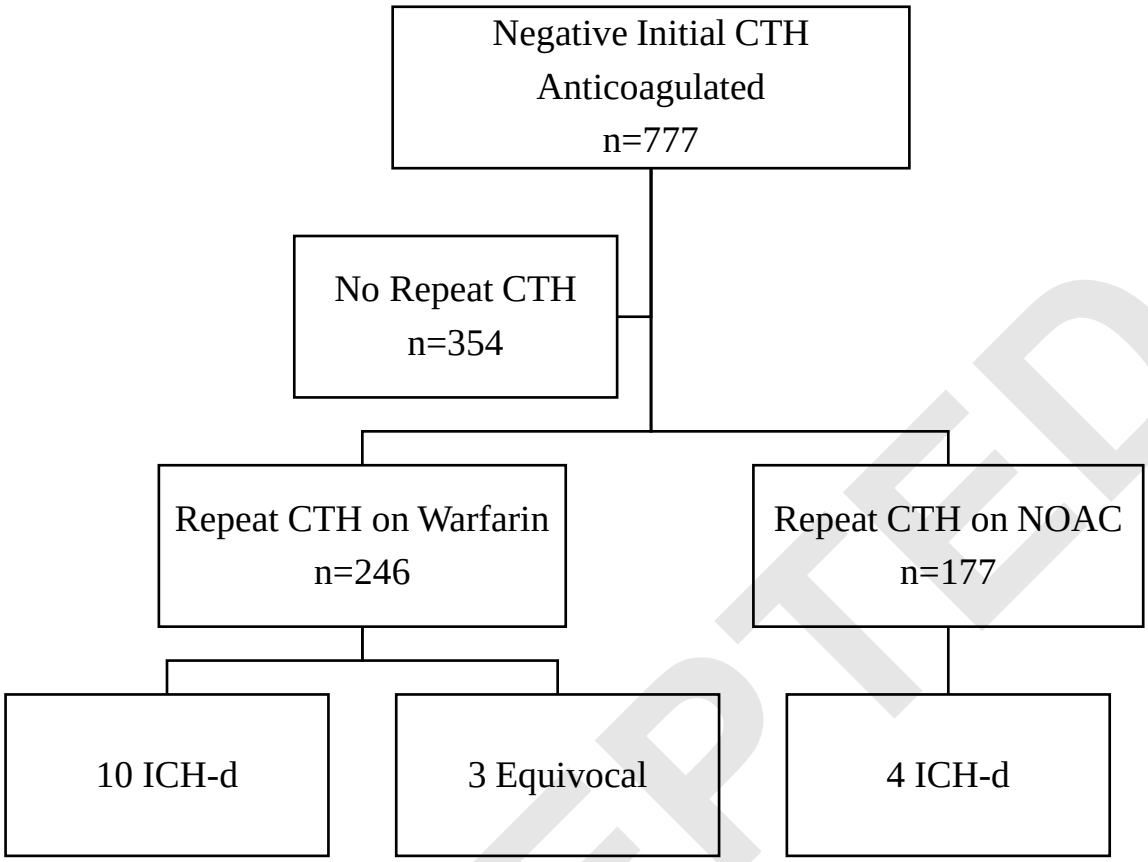

Figure 1. Incidence of delayed intracranial hemorrhage (ICH-d) for trauma patients suspected of having traumatic brain injury with a negative initial computed tomography head (CTH).

Table 1. Demographics and Injury Characteristics: Entire Cohort

Patient factors	**Warfarin**	**NOAC**	***p*-value**
N	431	346	
Age, Mean (SD)	75 (15)	77 (13)	**0.03**
Sex, % Male (n)	49 (211)	51 (176)	0.60
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)	3 (14)	3 (9)	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	62 (266)	70 (241)	**0.02**
PE/DVT	19 (81)	17 (60)	0.60
Heart Valve	6 (25)	<1 (2)	**<0.01**
Malignancy	<1 (1)	<1 (2)	0.59
Other	13 (58)	12 (41)	0.43
Mechanism of Injury, % (n)			
Fall	84 (361)	87 (302)	0.17
MVC	9 (40)	7 (25)	0.30
Assault	3 (12)	2 (7)	0.49
Auto vs Bike	<1 (3)	<1 (1)	0.63
Auto vs Pedestrian	1 (6)	2 (8)	0.34
Other	<1 (9)	<1 (3)	0.24
Concomitant Anti-Platelet, % (n)			
Aspirin	6 (24)	8 (26)	0.27
Plavix or Other	10 (17)	2 (6)	**<0.01**

NOAC: Novel Oral Anticoagulant. SD: Standard Deviation. *****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%). ISS: Injury Severity Score. AIS: Abbreviated Injury Scale. INR: International Normalized Ratio. ED: Emergency Department. GCS: Glasgow Coma Scale. Afib: Atrial Fibrillation. PE: Pulmonary Embolism. DVT: Deep Vein Thrombosis. MVC: Motor Vehicle Collision. Auto: Automobile.

Table 2. Demographics and Injury Characteristics: Only Patients with a Repeat CTH

Patient factors	**Warfarin**	**NOAC**	***p*-value**
N	246	177	0.10
Age, Mean (SD)	77 (14)	79 (13)	0.22
Sex, % Male (n)	50 (122)	51 (90)	0.80
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)	4.5 (11)	3.4 (6)	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	65 (159)	65 (115)	0.94
PE/DVT	15 (37)	21 (37)	0.12
Heart Valve	7 (17)	0 (0)	**0.04**
Malignancy	0.4 (1)	0.6 (1)	1.00
Other/unknown	13 (32)	14 (24)	0.83
Mechanism of Injury, % (n)			
Fall	86 (211)	92 (162)	0.07
MVC	7 (17)	2 (4)	**0.04**
Assault	3 (7)	3 (5)	0.99
Auto vs Bike	<1 (2)	0 (0)	0.51
Auto vs Pedestrian	2 (4)	3 (5)	0.50
Other	2 (5)	<1 (1)	0.41
Concomitant Anti-Platelet, % (n)			
Aspirin	5 (13)	6 (10)	0.87
Plavix or Other	3 (7)	1 (2)	0.31

CTH: Computed Tomography Head. NOAC: Novel Oral Anticoagulant. SD: Standard Deviation.*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. ISS: Injury Severity Score. AIS: Abbreviated Injury Scale. INR: International Normalized Ratio. ED: Emergency Department. GCS: Glasgow Coma Scale. Afib: Atrial Fibrillation. PE: Pulmonary Embolism. DVT: Deep Vein Thrombosis. MVC: Motor Vehicle Collision. Auto: Automobile.

Table 3. Delayed Intracranial Hemorrhage: Entire Cohort

	Age	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. ISS: Injury Severity Score. AIS-H: Abbreviated Injury Scale Head. INR: International Normalized Ratio. NI: Neuro-surgical Intervention. M: Male. F: Female. Vit K: Vitamin K. PCC: Prothrombin Complex Concentrate. FFP: Fresh Frozen Plasma. EVD: External Ventricular Drain. Crani: Craniectomy. MVC: Motor Vehicle Collision. NOAC: Novel Oral Anticoagulant.

Table 4. Univariable & Multivariable Analysis of Patient Factors and Odds of Developing Delayed Intracranial Hemorrhage: Patients with a Repeat CTH

	Univariable OR (95% CI)	***p*-value**	**Multivariable aOR (95% CI)**	***p*-value**
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		
# Comorbidities	1.05 (0.83-1.32)	0.68	1.17 (0.86-1.58)	0.32
AIS Head ≥ 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		

CTH: Computed Tomography of the Head. OR: Odds Ratio. CI: Confidence Interval. aOR: Adjusted Odds Ratio. AIS: Abbreviated Injury Scale. INR: International Normalized Ratio. GCS: Glasgow Coma Scale. NOAC: Novel Oral Anticoagulant. Afib: Atrial Fibrillation. DVT: Deep Vein Thrombosis. PE: Pulmonary Embolism. MVC: Motor Vehicle Collision. Auto: Automobile. Ped: Pedestrian. Note: ISS has been removed from the model due to co-linearity with AIS head. *N/A: Not Applicable used to denote no association with the outcome.

Table 5. Stratification of Head AIS and Odds of Developing Delayed Intracranial Hemorrhage: Patients with a Repeat CTH

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

AIS: Abbreviated Injury Scale. CTH: Computed Tomography of the Head. OR: Odds Ratio. aOR: Adjusted Odds Ratio. CI: Confidence Interval.

Table 6. Demographics, injury characteristics, and outcomes: Repeat CTH vs. No Repeat CTH groups

Patient factors & Outcomes	Repeat CTH (n=423)	No Repeat CTH (n=354)	*p*-value
Age in years, Mean (SD)	78 (14)	74 (14)	**<0.01**
Sex, % Male (n)	50 (212)	49 (175)	0.85
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)	4 (17)	2 (6)	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)	42 (177)	48 (169)	0.10
Indications for Anticoagulation, % (n)			
Afib	65 (274)	66 (233)	0.76
PE/DVT	17 (74)	19 (67)	0.61
Heart Valve	4 (17)	3 (10)	0.37
Malignancy	<1 (2)	<1 (1)	1.00
Other	13 (56)	12 (43)	0.65
Mechanism of Injury, % (n)			
Fall	88 (373)	82 (290)	**0.01**
MVC	5 (21)	12 (44)	**<0.01**
Assault	3 (12)	2 (7)	0.44
Auto vs Bike	<1 (2)	<1 (2)	1.00
Auto vs Pedestrian	2 (9)	1 (5)	0.46
Other	1 (6)	2 (6)	0.76
Concomitant Anti-Platelet, % (n)			
Aspirin	5 (23)	7 (27)	0.22
Plavix or other	2 (9)	4 (14)	0.13
Neuro-intervention, n	2	0	0.50
Reversal Agents, % (n)			
1 agent	6 (26)	11 (39)	0.09
2 agents	2 (10)	6 (22)	**<0.01**
3 agents	<1 (1)	2 (7)	**0.03**
Readmission, % n	3 (13)	3 (9)	0.66
Deaths from head injury, n	3	0	0.26

CTH: Computed Tomography of Head. SD: Standard Deviation.
*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%). NOAC: Novel Oral Anticoagulant. ISS: Injury Severity Score. AIS: Abbreviated Injury Score. INR: International Normalized Ratio. ED: Emergency Department. GCS: Glasgow Coma Scale. Afib: Atrial Fibrillation. PE: Pulmonary Embolism. DVT: Deep Vein Thrombosis. MVC: Motor Vehicle Collision