Novel oral anticoagulants and trauma: The results of a prospective American Association for the Surgery of Trauma Multi-Institutional Trial

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Marko Bukur: grant, Bio2 Medical, Inc. Jacob Quick: grant, Atox Bio, Inc. Martin Schreiber: grants, Arsenal Medical and Velico Medical, Inc. The remaining authors have nothing to disclose.

Reviewer Disclosures

The reviewers have nothing to disclose.

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BACKGROUND: The number of anticoagulated trauma patients is increasing. Trauma patients on warfarin have been found to have poor outcomes, particularly after intracranial hemorrhage (ICH). However, the effect of novel oral anticoagulants (NOAs) on trauma outcomes is unknown. We hypothesized that patients on NOAs would have higher rates of ICH, ICH progression, and death compared with patients on traditional anticoagulant and antiplatelet agents.

METHODS: This was a prospective observational trial across 16 trauma centers. Inclusion criteria was any trauma patient admitted on aspirin, clopidogrel, warfarin, dabigatran, rivaroxaban, or apixaban. Demographic data, admission vital signs, mechanism of injury, injury severity scores, laboratory values, and interventions were collected. Outcomes included ICH, progression of ICH, and death.

RESULTS: A total of 1,847 patients were enrolled between July 2013 and June 2015. Mean age was 74.9 years (SD ± 13.8), 46% were female, 77% were non-Hispanic white. At least one comorbidity was reported in 94% of patients. Blunt trauma accounted for 99% of patients, and the median Injury Severity Score was 9 (interquartile range, 4–14). 50% of patients were on antiplatelet agents, 33% on warfarin, 10% on NOAs, and 7% on combination therapy or subcutaneous agents.Patients taking NOAs were not at higher risk for ICH on univariate (24% vs. 31%) or multivariate analysis (incidence rate ratio, 0.78; confidence interval 0.61–1.01, $p = 0.05$). Compared with all other agents, patients on aspirin (90%, 81 mg; 10%, 325 mg) had the highest rate (35%) and risk (incidence rate ratio, 1.27; confidence interval, 1.13–1.43; $p < 0.001$) of ICH. Progression of ICH occurred in 17% of patients and was not different between medication groups. Study mortality was 7% and was not significantly different between groups on univariate or multivariate analysis.

CONCLUSION: Patients on NOAs were not at higher risk for ICH, ICH progression, or death. (*J Trauma Acute Care Surg.* 2017;82: 827–835. Copyright © 2017 American Association for the Surgery of Trauma. All rights reserved.)

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

KEY WORDS: Anticoagulation; oral anticoagulants; trauma; injury.

Trauma remains the fifth leading cause of death in the United States and the ninth leading cause of death among persons older than 65 years.[1] The number of elderly trauma patients taking anticoagulants and antiplatelet agents has been steadily increasing.[2–5] Patients on oral antithrombotics (OATs), both warfarin and antiplatelet agents, are at increased risk of intracranial hemorrhage (ICH) after trauma.[2,4,6] Patients on warfarin have also been found to have increased mortality after injury, particularly among those with ICH.[2,4,7–10] Similar increases in mortality have been seen in trauma patients on antiplatelet agents, although the data are less robust, with some studies demonstrating increased mortality and others failing to do so.[8,11–14] There is evidence to suggest that rapid recognition and reversal of anticoagulation in patients with ICH can decrease progression of hemorrhage and improve outcomes.[2,4,15–17] The evidence supporting platelet transfusion in patients on antiplatelet agents is less robust, but transfusion may reduce mortality in patients with ICH.[14,18]

The past 6 years have seen the release of several novel oral anticoagulants (NOAs). There is a paucity of data on the impact of NOAs on patient outcomes after traumatic injury. Several case reports have emerged describing significant bleeding complications and ICH associated with the use of these novel agents.[19–21] Additionally, unlike warfarin, with the exception of dabigatran whose antibody idarucizumab was approved in 2015, there is no standardized protocol for reversal of NOAs. Though there is some suggestion that administration of prothrombin complex (PCC) and hemodialysis may be useful.[22–25]

The objective of this study was to identify the injury patterns and outcomes among trauma patients taking NOAs. We hypothesized that patients taking NOAs would have higher rates of ICH, ICH progression, and death after trauma compared with patients on traditional OATs.

PATIENTS AND METHODS

A prospective, multicenter, observational study was conducted through the American Association for the Surgery of Trauma Multi-Institutional Trials Committee. The study was

Submitted: July 29, 2016, Revised: January 24, 2017, Accepted: February 8, 2017, Published online: March 15, 2017.

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Presentations: This study was presented as a podium presentation at the 75th Annual Meeting of the American Association for the Surgery of Trauma and Clinical Congress of Acute Care Surgery in Waikoloa, Hawaii September 14, 2016.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text, and links to the digital files are provided in the HTML text of this article on the journal's Web site (www.jtrauma.com).

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DOI: 10.1097/TA.0000000000001414

observational and did not alter patient care; all clinical management decisions were dictated by individual attendings and enrolling center protocols. After institutional review board approval, 16 Level 1 trauma centers participated in data collection over a 2-year period ending in July of 2015. All trauma patients admitted to the hospital and confirmed to be taking dabigatran, rivaroxaban, apixaban, warfarin, aspirin, or clopidogrel were eligible for enrollment in the study. Interfacility transfers confirmed to be on the preceding medications were eligible for inclusion. Patients were excluded if they were prisoners, minors (age <18 years), or pregnant.

Mandatory data collected included demographics, comorbidities (definitions based on National Trauma Databank Appendix 3),[26] type of anticoagulant, mechanism of injury, and admission vital signs. Race was included due to the known variations in clotting and bleeding risk among different racial groups,[27] as well as the increased sensitivity to warfarin among Asians.[28] Optional data collected included injuries, Injury Severity Score (ISS), body region Abbreviated Injury Scale (AIS), laboratory values of coagulation including thromboelastography, interventions, and reversal agents including vitamin K, PCC, and hemodialysis, transfusion of fresh-frozen plasma, cryoprecipitate, and platelets. Severe injury was defined as ISS of 10 or higher, body region AIS of 3 or higher, and Glasgow Coma Scale (GCS) of 8 or lower. Shock was defined as systolic blood pressure lower than 90 on admission. Outcomes collected included ICH, progression of ICH, bleeding, angiographic and surgical interventions, complications (see Supplemental Digital Content 1, http://links.lww.com/TA/A893), and death. All data collected were submitted through the American Association for the Surgery of Trauma Multi-Institutional Trials Committee online data entry system.

Based on data collected for 2 years before study initiation at the primary center, the overall mortality for all trauma admissions was 3.6%. To have 80% power to detect a twofold increase in mortality with 95% confidence, we estimated that 600 patients were required per study arm. The rate of ICH among this same population was 16.5%. To detect a twofold increase in the rate of ICH with 80% power and 95% confidence, we estimated that 107 patients were required per study arm. Due to a significant imbalance in the number of patients between study arms, a post hoc power analysis was performed to compensate for the unbalanced enrollment. Correcting for the 9:1 ratio of OAT: NOA patient, and assuming similar mortality and ICH rates, 2,727 OAT and 303 NOA patients were required to detect a twofold increase in mortality, and 486 OAT and 54 NOA patients to detect a similar increase in ICH with 80% power and alpha = 0.05.

The primary outcome of the study was mortality, this was a mandatory reporting outcome, and no patients missing this variable were included in the analysis. Secondary outcomes included ICH and ICH progression, these were also mandatory data fields. Data analysis was performed using STATA/MP Version 14.1 (StataCorp, College Station, TX). Continuous variables were described using mean and SD if normally distributed, and median and interquartile range (IQR) if not normally distributed. Univariate analysis used the Pearson χ^2 for categorical variables. Continuous variables were tested using the nonparametric Kruskal–Wallis test; those that followed a normal distribution were analyzed using one-way analysis of variance. All independent variables were checked in STATA for collinearity with variance inflation factors, all variance inflation factors used for multivariate analyses were close to 1. Multivariate analysis was performed to analyze risk of death, ICH, and ICH progression between the patient groups. Odds ratios (OR) were used to report outcomes less frequent than 20%, and incidence rate ratios (IRR) for those more frequent than 20%. Selection of variables for multivariate analysis was based on variables with significant differences in univariate analysis (p values <0.05 when comparing NOAs to OAT and p values <0.001 for subgroup analysis). Multivariate logistic regression models were tested for goodness of fit using the Hosmer–Lemeshow χ^2. Because significant variability existed in trauma protocols between centers and enrollment was significantly different between centers, generalized estimating equations with robust variance using Poisson regression with log link were used to account for the cluster effect when estimating relative risk. All variables were checked for missing data, any variable with significant missing data points was analyzed for distribution of missing data if used for multivariate analysis.

RESULTS

NOA Versus OAT

During the study period, a total of 1,847 patients were enrolled from 16 Level 1 trauma centers.

The majority of patients in the study were on antiplatelet agents (50%) or warfarin (33%), NOAs comprised 10%. Seven percent of patients were on multiple agents, subcutaneous, or intravenous heparins and were felt to not be representative of the study group and were eliminated from further analysis. Demographics, mechanism of injury, presenting physiology, injury severity scores, and outcomes for patients on NOAs and those on OATs are presented in Table 1. Univariate analysis of patients on NOAs compared with those on OATs demonstrated no significant difference in age, sex, mechanism of injury, ISS, AIS, or percent of patients with GCS of 8 or lower (Table 1). Patients on NOAs were more likely to be non-Hispanic white, less likely to be Hispanic, and more likely to have a history of cardiac arrhythmia. Shock upon presentation was more frequent among patients on NOAs compared with OATs; however, there was no difference in percent of patients needing transfusion (13% vs. 15%, $p = 0.71$), surgical/angiographic procedures (19% vs. 22%, $p = 0.48$), or bleeding requiring intervention (3% vs. 4%, $p = 0.57$).

Attempted reversal of anticoagulation was significantly less likely among patients on NOAs compared with OATs on univariate (19% vs. 31%, $p = 0.001$) and multivariate analyses (OR, 0.48; confidence interval [CI], 0.31–0.75; $p = 0.001$) correcting for age, race, ISS of 10 or higher, shock, ICH, bleeding, and need for surgical procedure (Table 2).

Patients on NOAs had a significantly lower rate of ICH compared with OATs on univariate analysis (24% vs. 31%, $p = 0.04$). Of those with ICH, the distribution of hemorrhage and hemorrhage severity by head AIS were similar between patients on NOAs and traditional OATs (Table 1). There was a trend toward reduced risk (IRR, 0.78; CI, 0.61–1.01, $p = 0.05$) of ICH among patients on NOAs on multivariate analysis

TABLE 1. Demographics, Injury Patterns, Admission Physiology, and Injury Severity of Patients on OATs Versus NOAs

	All	OAT	NOA	*p* value
N	1,847	1,665	182	
Age (SD)	75 (14)	75 (14)	77 (14)	0.069
Female	46%	46%	52%	0.131
Cardiac arrhythmia	38%	**32%**	**57%**	**<0.001**
Race*				**0.018**
Black	3%	3%	1%	
Asian	3%	9%	1%	
Hispanic	11%	**12%**	**7%**	
Non-Hispanic white	77%	**76%**	**87%**	
Mechanism				0.492
Fall	71%	71%	76%	
Motor vehicle accident	15%	15%	14%	
Found down	3%	4%	3%	
ICH	30%	**31%**	**24%**	**0.037**
EDH	1%	1%	2%	0.606
SDH	19%	19%	17%	0.432
SAH	16%	16%	12%	0.107
IPH	7%	7%	7%	0.716
GCS ≤8	5%	5%	4%	0.478
Shock (SBP <90)	3%	**2%**	**6%**	**0.006**
ISS median (IQR)	9 (4, 14)	9 (4, 14)	9 (4, 11)	0.196
ISS ≥10	43%	44%	39%	0.208
Head AIS ≥3 **	80%	80%	82%	0.760
Transfusion PRBC	15%	15%	13%	0.709
Reversed	30%	**31%**	**19%**	**0.001**
Progression of ICH	17%	17%	19%	0.813
Any complication	23%	23%	21%	0.588
H-LOS, median (IQR)	3 (2, 6)	3 (2, 6)	3 (2, 6)	0.508
Death	7%	7%	7%	0.758
Death among ICH	14%	15%	12%	0.607

*Race: Missing/Other 110 (6%).

**Among patients with ICH (n = 540, 21 (4%) missing Head AIS).

Missing data <1% unless specifically noted in table and statistically significant values denoted in bold.

SBP, systolic blood pressure; EDH, epidural hemorrhage; SDH, subdural hemorrhage; SAH, subarachnoid hemorrhage; IPH, intraparenchymal hemorrhage.

adjusting for age, race, mechanism of injury, ISS, and GCS, although this did not achieve statistical significance (Table 2). Rates of progression for patients on NOAs were no different from OATs on univariate (19% vs. 17%, $p = 0.81$) or multivariate analysis (OR, 1.17; CI, 0.43–3.22; $p = 0.76$) correcting for enrollment site, age, shock, GCS of 8 or lower, location of ICH, neurosurgical procedures, reversal, and transfusion (Table 2).

Death was not different on univariate analysis (7% vs. 7%, $p = 0.75$) or multivariate analysis (OR, 1.49; CI, 0.71–3.12; $p = 0.29$) correcting for age, mechanism of injury, GCS of 8 or lower, ISS of 10 or higher, shock, ICH, progression, reversal, transfusion, bleeding, surgical procedures or complications (Table 2). Similarly, death among patients with ICH was not different between NOAs and OATs on univariate analysis (12% vs. 15%, $p = 0.61$) or multivariate analysis (OR, 0.69; CI, 0.18–2.60; $p = 0.58$) after correcting for mechanism of injury, shock, GCS of 8 or lower, neurosurgical procedures, reversal, progression, and complications (Table 2).

Subgroup Analysis of Medication Groups

To further determine if there were any differences in outcomes between patients on the different anticoagulants, a subgroup analysis of each individual OAT compared to the NOAs was performed. Demographics, mechanism of injury, and injury severity are presented in Table 3. Sex distribution was similar between groups. The difference in age distribution was statistically significant, with patients on aspirin being significantly younger than all other groups. Patients on both warfarin and NOAs were more likely to be non-Hispanic white and less likely to be Hispanic compared with patients on aspirin or clopidogrel. Patients on clopidogrel were significantly more likely to have coronary artery disease (CAD) and cerebrovascular accidents (CVA), whereas congestive heart failure and arrhythmias were more common among patients on warfarin and NOAs. Falls were significantly less likely in patients on aspirin alone compared to all other medication groups. ISS was significantly lower among patients on warfarin alone, and the percent of patients with ISS of 10 or higher was highest among patients on aspirin alone. Distribution of AIS across medication groups was similar; however, the percentage of patients with missing data was large (Table 3). On univariate analysis, bleeding requiring intervention, surgical interventions, complications, hospital length of stay (H-LOS), and mortality were similar between medication groups (Table 4) Reversal attempts were significantly more likely among patients on warfarin (Table 4). On multivariate analysis adjusting for age, race, ISS of 10 or higher, shock, bleeding, ICH, and surgical intervention, reversal was significantly more likely in patients on warfarin (OR, 8.50; CI, 5.77–12.54; $p < 0.001$), and clopidogrel (OR, 1.94; CI, 1.37–2.74; $p < 0.001$) (see Supplemental Digital Content 1, http://links.lww.com/TA/A893).

On univariate analysis, ICH was significantly more frequent among patients on aspirin compared with all other medication groups (Table 4). Aspirin was also associated with increased risk of ICH (IRR, 1.27; CI 1.13–1.43; $p < 0.001$) on multivariate analysis adjusting for age, race, mechanism of injury, ISS, and GCS (Table 5). Progression of injury was similar between medication groups on both univariate (Table 4) and multivariate analyses (see Supplemental Digital Content 1, http://links.lww.com/TA/A893).

Study mortality was not significantly different between medication groups on univariate analysis (Table 4) or on multivariate analysis, after correcting for age, mechanism of injury, ISS, GCS, shock, ICH, progression of ICH, reversal, bleeding, transfusion, complications, and surgical interventions (see Supplemental Digital Content 1, http://links.lww.com/TA/A893). Among patients with ICH, mortality was significantly higher in patients on warfarin on univariate analysis (Table 4). On multivariate analysis, after controlling for age, mechanism of injury, GCS, ISS, shock, location of ICH, progression of ICH, reversal, complications, and neurosurgical procedures; aspirin (OR, 8.14; CI, 1.57–42.32; $p = 0.01$), clopidogrel (OR, 5.54; CI, 1.06–28.84; $p = 0.04$) and warfarin (OR, 8.44; CI, 1.72–41.36; $p = 0.01$) were all associated with increased OR

TABLE 2. Multivariate Analysis of Outcomes for Patients on NOAs Versus OATs

Outcome	NOA	AUROC	Hosmer-Lemeshow χ^2
ICH	IRR, 0.78 (CI, 0.61–1.01, $p = 0.050$)		
Progression of ICH	OR, 1.17 (CI, 0.43–3.22, $p = 0.761$)	0.83 (CI 0.79–0.88)	0.69
Death	OR, 1.49 (CI 0.71–3.12, $p = 0.287$)	0.89 (CI 0.87–0.92)	0.14
Death among ICH	OR, 0.69 (CI 0.18–2.60, $p = 0.584$)	0.88 (CI 0.83–0.93)	0.54
Reversed	OR, 0.48 (CI 0.31–0.75, $p < 0.001$)	0.78 (CI 0.76–0.81)	0.39

See supplemental digital content for remainder of multivariate analyses.
AUROC, area under the roc curve.

for death, whereas NOAs were not (OR, 5.25; CI, 0.69–40.23; $p = 0.11$; Table 6).

DISCUSSION

NOA Versus OAT

Multiple studies have confirmed the efficacy of NOAs for stroke prevention in patients with atrial fibrillation and for treatment of VTE, as well as a favorable bleeding risk profile compared with warfarin.[29] The 2016 American College of Chest Physicians recommendations on antithrombotic therapy reflect this evidence and recommend NOAs as the first-line therapy for VTE.[30] Despite the data to support these agents, we found the overall use of NOAs to be low (10%). With the oldest drug, dabigatran, having only been released 6 years ago, it is possible that the novelty of these drugs negatively impacted the prescribing habits of physicians. Cost may also contribute to the low number of patients on NOAs as the approximate cost for dabigatran is US $246/month; rivaroxaban, US $255/month; and apixaban, US $287/month compared with approximately US $15/month for generic warfarin.[31–33] However, given the new American College of Chest Physicians recommendations, convenience of dosing, and absence of monitoring requirements, the number of patients on NOAs presenting to trauma centers may increase in the future.

The study population consisted primarily of elderly (age ≥65 years) patients with the most common mechanisms of injury being falls, which is consistent with the majority of geriatric trauma studies.[2,4,6,8,11] Comorbidities were common, but varied between drug groups (Table 3). Distribution of comorbidities likely reflects the clinical indications for each medication with CVA and CAD associated with antiplatelet agents and arrhythmias more common among patients on warfarin and NOAs. Because of this collinearity, comorbidities were eliminated from multivariate analysis of outcomes.

TABLE 3. Subgroup Analysis: Demographics, Mechanism of Injury, Admission Physiology, and Injury Severity by Anticoagulant Agent

	ASA*	Clopidogrel	Warfarin	NOA	*p* value
N	478	443	605	182	
Age (SD)	**73 (14)**	75 (13)	76 (14)	77 (14)	**0.005**
Female	42%	49%	47%	52%	0.119
Blunt	98%	98%	99%	98%	0.438
Race**					**0.001**
Black	2%	5%	3%	1%	
Asian	5%	3%	2%	1%	
Hispanic	14%	12%	**9%**	**7%**	
Non-Hispanic white	74%	73%	**81%**	**87%**	
Comorbidities					
CVA	11%	**33%**	15%	20%	**<0.001**
CAD	31%	**58%**	29%	32%	**<0.001**
Congestive heart failure	11%	15%	**24%**	**23%**	**<0.001**
Arrhythmia	19%	17%	**51%**	**57%**	**<0.001**
Mechanism					
Fall	**64%**	74%	75%	76%	**0.001**
Motor vehicle accident	17%	13%	14%	14%	0.418
Found down	3%	4%	4%	3%	0.815
GCS ≤8	5%	5%	5%	4%	0.823
Shock (SBP <90)	1%	3%	2%	**5%**	0.042
ISS Median (IQR)	10 (5, 16)	9 (4, 14)	**6 (3, 12)**	9 (4, 11)	**<0.001**
ISS ≥10	**50%**	42%	38%	39%	**0.001**
Head AIS ≥3†	45%	40%	36%	35%	0.124
Chest AIS ≥3†	21%	**15%**	20%	26%	**0.045**
Abdomen AIS ≥3†	8%	6%	6%	4%	0.527
Extremity AIS ≥3†	18%	11%	17%	12%	0.137

*ASA: 325 mg n = 54 (11%), 81 mg n = 423 (89%), 1 missing.
**Race: Missing/Other 110 (6%).
†Missing data: Head AIS 21 (4%), Chest AIS 830 (45%), Abdomen AIS 915 (50%), Extremity AIS 701 (38%).
Missing data <1% unless specifically noted in table and statistically significant values denoted in bold.
ASA, aspirin.

TABLE 4. Subgroup Analysis: Outcomes by Anticoagulant Agent

	ASA	Clopidogrel	Warfarin	NOA	*p* value
N	478	443	605	182	
Bleeding	4%	3%	4%	3%	0.289
Any surgery	25%	19%	20%	19%	0.138
Reversed	16%	25%	**47%**	19%	**<0.001**
ICH	**35%**	33%	27%	24%	**0.009**
Progression*	14%	16%	19%	19%	0.661
Craniotomy/craniectomy	5%	4%	4%	2%	0.569
Any complication	24%	23%	20%	21%	0.433
H-LOS median (IQR)	3 (2, 6)	3 (2, 6)	3 (2, 7)	3 (2, 6)	0.832
Death	5%	7%	7%	7%	0.091
Death among ICH	13%	13%	**19%**	12%	**0.006**

*Among those with ICH (n = 561).
Missing data <1% unless specifically noted in table and statistically significant values denoted in bold.

TABLE 5. Subgroup analysis: Risk Factors for ICH: Multivariate Analysis Adjusted for Age, Race, Mechanism of Injury, ISS, GCS, and Anticoagulant ($p < 0.001$ on Univariate Analysis)

	IRR	CI	*p* value
Age	**1.01**	**1.00–1.01**	**<0.001**
Black*	1.20	0.83–1.7	0.326
Asian*	**1.91**	**1.61–2.26**	**<0.001**
Hispanic*	1.28	0.97–1.67	0.087
Assault**	1.06	0.67–1.66	0.808
Struck by vehicle**	1.02	0.80–1.32	0.825
Found down**	**1.40**	**1.16–1.68**	**<0.001**
Motorcycle accident**	1.02	0.72–1.44	0.914
Motor vehicle accident**	**0.52**	**0.31–0.88**	**0.014**
ISS ≥10	**1.18**	**1.02–1.36**	**0.030**
GCS ≤8	**1.93**	**1.58–2.35**	**<0.001**
Aspirin	**1.27**	**1.13–1.43**	**<0.001**
Plavix	1.01	0.85–1.20	0.934
Warfarin	0.99	0.87–1.14	0.951
NOA	0.82	0.64–1.04	0.111

*Compared with non-Hispanic white.
**Compared with falls.

The results of this study conform to published data demonstrating a high rate of ICH among anticoagulated patients with an overall rate of 30%.[34–38] There was a lower rate (Tables 1 and 4) and a trend toward reduced risk of ICH among patients on NOAs (Table 2). Our power calculations anticipated a more even distribution of patients between our study arms; however, after correcting for the uneven distribution of patients between OATs and NOAs, we still had an adequate enrollment to detect a twofold increase in ICH rates. Contrary to our hypothesis, it does not appear that NOAs increase the risk of ICH compared with OATs. It is possible that there is a modest reduction in risk of ICH associated with NOAs, but a larger study is needed to confirm this possibility. Expected risk factors associated with ICH included advanced age, ISS of 10 or higher, and GCS of 8 or lower which have all been associated with ICH in prior studies.[6,9,35,38–40] The other independent predictor of ICH found on multivariate analysis was Asian race. An association between hypocoagulability as well as hypersensitivity to warfarin among those of Asian descent has been documented and may account for this finding.[28,41] Asian race has also been associated with increased risk of ICH among patients with atrial fibrillation.[42]

The rate of ICH progression was high at 17%, but similar to prior studies.[8,43,44] In this population, we were unable to detect a significant increase in ICH progression among patients on NOAs compared to OATs on univariate analysis or multivariate logistic regression (Tables 1 and 2). However, given the low number of patients on NOAs and comparatively low rate of ICH among patients on NOAs, the current study is underpowered to detect a modest increase in rates of progression.

Mortality of our population was lower compared with prior studies of patients on OAT.[8,11] It is possible that progress in geriatric trauma care since the publication of prior studies have reduced mortality rates for patients on OAT as the mortality seen in the current study is near that of control groups in prior publications. Patients on NOAs had no difference in unadjusted or adjusted mortality rates when compared with patients on OAT. Nor was there any difference in death among patients with head injury when comparing patients on NOAs with those on OAT on univariate analysis or multivariate analysis (Tables 1 and 2). However, post hoc analysis correcting for the 9:1 ratio of enrollment revealed we would need over 2,000 patients in the OAT group and 303 patients in the NOA group to detect a significant difference in mortality. As such, we are underpowered to definitively eliminate an increased mortality risk associated with NOAs, and a larger study containing more NOA patients is required to eliminate this possibility. Mortality was associated with age, low GCS, progression of ICH, and complications which is similar to previous studies.[8,11,35]

Subgroup Analysis of Medication Groups

Subgroup analysis was performed to further determine if there were any differences in outcome between patients on NOAs and those on the different categories of OAT. We were again unable to detect any significant increase in ICH, progression, death, or death among head injuries in patients on NOAs compared with those on aspirin, clopidogrel, or warfarin. Surprisingly, the subgroup analysis demonstrated the highest rate (35%) and risk (IRR, 1.27; CI, 1.13–1.43; $p < 0.001$) of ICH to be in patients using aspirin alone, with the majority of those patients (90%) documented to be on the lower 81 mg daily dose. There are several possible explanations for this finding. First, among all studied agents aspirin may carry the highest risk of ICH. Several past studies have documented an increased risk of ICH, ICH progression, and mortality associated with aspirin use.[4,12,43] It is possible that the lack of consistency in the literature is due to the retrospective nature and small sample size in the majority of published studies. To our knowledge, the current study has the largest prospectively gathered sample of patients on OAT with 478 patients on aspirin alone. Alternatively, patients on aspirin may have been frailer or more prone to hemorrhage compared with the other groups. However, demographics appear similar between drug groups (Table 3), with the exception of aspirin patients being significantly younger than all other medication groups. Patients on aspirin were significantly less likely to fall and trended toward more MVAs.

TABLE 6. Subgroup Analysis: Independent Predictors of Death Among Patients With ICH by Medication Group

	OR	CI	*p* value
Found down*	3.99	1.28–12.45	0.017
Motor vehicle accident*	5.43	1.83–16.14	<0.001
GCS ≤8	19.48	8.56–44.33	<0.001
Progression of ICH	14.12	7.03–28.35	<0.001
Reversed	2.17	0.99–4.76	0.054
Aspirin	8.14	1.57–42.32	0.013
Clopidogrel	5.54	1.06–28.84	0.042
Warfarin	8.44	1.72–41.36	0.009
NOA	5.25	0.69–40.23	0.111

*Compared with falls.
AUROC, 0.89; CI, 0.85–0.94.
Hosmer-Lemeshow χ^2, 0.135.
See supplemental digital content for remainder of multivariate analysis.

This was associated with slightly higher median ISS and percent of patients with ISS of 10 or higher among aspirin patients (Table 3). Given these differences, it is possible that aspirin patients sustained on average a greater impact of injury. However, the highest rates of ICH were found with low-energy mechanisms, such as falls, whereas MVA was inversely related to ICH (Table 5). The percent of Asian patients was higher among the aspirin group, though this did not reach statistical significance on univariate analysis (Table 3), this may, in part, explain the increased rates of ICH. Lastly, it is possible that there is an underlying condition associated with aspirin use that predisposes patients to ICH. One such condition is brain atrophy. A study by Dunham et al.[45] found a significantly increased rate of brain atrophy in patients on platelet inhibitors compared with similar patients not on OAT. They also found a higher rate of ICH associated with preexisting brain atrophy but not with OAT use. However, we found no increase in ICH among patients on clopidogrel compared with other drug groups. Further analysis of rates of brain atrophy within the current study population will be needed to determine if this accounts for the increased rates of ICH among patients on aspirin.

In contrast to previously published data,[15] we were unable to detect a protective effect associated with reversal of anticoagulation. In fact, reversal was associated with increased Odds Ratio for death (OR, 1.9; CI, 1.1–2.3; $p = 0.02$). The majority of patients (82%) with ICH in this study presented with a GCS of 15. It is possible that physicians were disinclined to attempt reversal and expose patients to risks of transfusion related complications in the absence of radiographic progression or neurologic deterioration. This may be particularly true in patients receiving antiplatelet agents and NOAs, in whom transfusion, PCC, hemodialysis, and other reversal methods have not been well documented to improve outcomes.[8,24,46,47] This is supported by the fact that only 548 patients (30%) in the study population as a whole and 311 (55%) in the ICH group underwent an attempt at reversal. Reversal was also not uniformly applied and was significantly less likely among patients on aspirin (the group with the highest rate of ICH) and NOAs. The current study is underpowered to detect a modest benefit associated with reversal, particularly in groups who infrequently underwent attempts at reversal.

The study had several limitations. It was observational by design, so no causal relationships can be determined. Although we have attempted to correct for bias, the study population consisted primarily of patients on warfarin and antiplatelet agents, whereas the percentage of patients on NOAs was low. Additionally, only patients on some type of oral anticoagulant were collected without a true control group of patients not receiving anticoagulation available for comparison. Patient enrollment was voluntary at each center, creating the possibility for sampling bias as not every patient at each center who met inclusion criteria was required to be enrolled. It is possible that reporting bias led to patients requiring admission or those with severe injuries being overrepresented in this population. Lastly, all study sites were Level 1 trauma centers and may serve as referral centers for nontrauma hospitals which allows for significant sampling bias as most hospitals are comfortable with the workup and treatment of minor injuries in patients on aspirin or clopidogrel, but may transfer patients on newer agents, such as the NOAs, or patients with supratherapeutic INR levels to trauma centers even in the absence of injuries.

In conclusion, among this group of anticoagulated trauma patients, we were unable to detect a higher rate of head injury, progression of ICH, or death in patients on NOAs compared with those on traditional OATs. Surprisingly, patients on aspirin had the highest rate and risk of ICH.

DISCLOSURE

The authors declare no conflicts of interest.
This study was not funded or supported financially by any private, governmental or educational institution.

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DISCUSSION

Dr. Charles Wade (Houston, Texas): This is a prospective, multi-center, observational study conducted in 16 sites to identify injury patterns and outcomes among trauma patients taking novel anticoagulants compared to those taking traditional oral anticoagulants.

Stated in the methods the primary outcome of this study was mortality. The comparison of the mortality between the novel and the traditional anticoagulants does not appear to be directly addressed in the results of the paper.

However, they have now looked at that group and shown that the mortality rate was the same, at about 7%. Additionally, endpoints of interest included incidence of intracerebral hemorrhage and progression. I have a few comments and questions.

The strength of this effort is that it has 16 diverse Level I trauma centers allowing broad application of the findings. However, in the analysis and in the paper they did not address the site differences or the possible influence of site. This appears now to have been done in the presentation.

In the paper ICH, ICH progression and complications are not defined specifically. The diversity of the centers is, again, a question here. There are centers that advocate secondary CT at a set time after admission, and there are others that only conduct an assessment if clinical signs are present.

Was a common definition for the evaluation of progression used? In the definition of progression were patients who presented with a negative CT and subsequently diagnosed with intracranial hemorrhage included in the progression population? Finally, as patients with ICH may die prior to a secondary evaluation for progression, how were these patients accounted for?

The authors have added to the complexity of their analysis by subdividing the study population in the paper into seven

groups. This includes classification of warfarin by effectiveness based on INR.

They have demonstrated a clear, threefold increase in intracranial hemorrhage progression and in death with increasing INR in this population. In other treatment groups were there any indications of dose adequacy or effectiveness?

Finally, the authors in their title focus on baby aspirin as the effector; however, they have not specifically addressed this in their analysis. While 90% of the patients were on aspirin, on low dose, was this considered?

Again, I would like to thank the Association for the privilege of discussing this paper.

Dr. Garth Utter (Sacramento, California): I'm concerned that there may be some differences among the centers and among the patients on these different types of anticoagulation in terms of the decision to admit the patient or not.

If a lot of these patients in some of the categories are not admitted, that could have substantially affected your results. Do you have any information on the proportions of patients in each of these categories that were admitted?

Dr. Leslie M. Kobayashi (San Diego, California): Thank you for the thoughtful comments and questions.

Thank you.

Dr. Wade, first to address the question of whether or not progression had a standard definition. We did provide each of the centers with an appendix describing and defining each of the complications and outcomes. This definition was also available on the AAST's multi-institutional trial data collection system online.

We defined progression of head injury to include radiographic progression with increase in size of an existing hemorrhage, presence of a new hemorrhage not previously seen on a prior head CT, and progression was also defined as patients who had a negative head CT on admission and then a new head bleed at subsequent head CT.

Additionally, we also had clinical progression of head injury defined as a decrease in functional neurologic status on observation and repeat clinical exams.

We did consider that many centers have different protocols in terms of routine, repeat CT scans of the head. So center was also added to the logistic regression for progression of head injury, mortality, and mortality among head-injured patients. It did not significantly change the impact of medication groups, although we did note significant differences between the centers.

Dr. Coimbra, I'm sure, will like to know that while U.C.S.D. had the highest rate of intracranial hemorrhage progression, it had the lowest rate of mortality as well as mortality among head-injured patients.

We did think about mortality in terms of patients dying, not being able to have progression of head injury, or having a complication because they were dead. On analysis of patients who died early, which we defined as death within the first 24 hours, there were no significant differences on univariate analysis during the, between each of the medication groups.

Surprisingly, aspirin patients, again, did the worst with 42% of aspirin deaths occurring within the first 24 hours compared to 19 percent of Plavix patients, 36% of warfarin patients, and only 8% of patients on NOAs dying within the first 24 hours.

We did do several subgroup analyses and, as Dr. Wade pointed out, while we can measure efficacy of warfarin with INR, there is really no good way that most of us are routinely checking the efficacy of antiplatelet function for Plavix or aspirin.

And there is really no agreed-upon way to measure the therapeutic effect of the novel oral agents. Because of this we performed three separate logistic analyses for each of the medication groups.

First was to compare the groups grossly to each other. Second was to compare NOAs to oral antithrombotics as a bivariate analysis. And then third was to add in the effect of INR on patients on warfarin.

We did collect TEG data on some of our patients. We are hoping to present the effect of lab results on outcomes as a second follow-up study to this first study.

We did note that the majority of patients in the aspirin-only group were on the lower-dose baby aspirin. We did not perform a secondary analysis for these patients specifically as it only consisted of 54 patients, total, among 1,800 in the study group.

Dr. Utter, I agree 100%. There is a significant possibility for bias, both in admission protocols per center for patients on anticoagulants as well as the possibility for bias in terms of inter-facility transfers as I think most community hospitals would be comfortable discharging patients on aspirin where initial evaluation at that center showed no injuries but they may be less comfortable sending home patients on the NOAs even in the presence of a negative workup. So that's certainly a potential for bias in this study.

We did not specifically query any of our centers regarding routine admission in patients on aspirin, Plavix, warfarin or NOAs when they have a negative initial workup.

Thank you.