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Association of mortality among trauma patients taking preinjury direct oral anticoagulants versus vitamin K antagonists

Zachary J. LaDuke, PharmD[a], Jason P. Hecht, PharmD[a], Anne H. Cain-Nielsen, MS[b], Mark R. Hemmila, MD[b], Wendy L. Wahl, MD[c,*]

[a] Inpatient Pharmacy, Saint Joseph Mercy Ann Arbor, MI
[b] Department of Surgery, University of Michigan Ann Arbor
[c] Department of Surgery, Saint Joseph Mercy Ann Arbor, MI

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ABSTRACT

Background: The population of patients on anticoagulant or antiplatelet therapy for medical conditions is increasing. The objective of this study was to investigate the effects of preinjury anticoagulation or antiplatelet therapy on outcomes after trauma.

Methods: This cohort study analyzed data from the Michigan Trauma Quality Improvement Program from 2012 to 2017 and included trauma patients age ≥16 years with an Injury Severity Score ≥5 treated at 29 hospitals. The primary outcome was in-hospital mortality.

Results: Of 115,042 trauma patients, 44.2% were women and 78.2% were white with a mean age (standard deviation) of 59.1 (23.2) years. A total of 23,196 patients were on antiplatelet therapy, 3,855 on warfarin, 1,893 on warfarin + antiplatelet agent, 1,306 on a direct oral anticoagulant, and 717 patients on direct oral anticoagulant + antiplatelet therapy. We observed an increased risk of mortality in patients on preinjury antiplatelet (odds ratio [OR] 1.17; 95% confidence interval [CI] 1.02–1.33), warfarin (OR 1.32; 95% CI 1.05–1.65), or warfarin + antiplatelet therapy (OR 1.59; 95% CI 1.18–2.14). Patients on a direct oral anticoagulant only were not at statistically increased risk for mortality.

Conclusion: Preinjury antiplatelet and/or warfarin use was associated with an increased risk of mortality after traumatic injury. Preinjury direct oral anticoagulant use was not associated with a statistically increased risk of adverse outcomes.

Introduction

Systemic anticoagulation is the mainstay of treatment for prevention of thromboembolism events attributable to atrial fibrillation or venous thrombotic disease. Conventionally, oral vitamin K antagonists like warfarin have been utilized for these indications despite the presence of drug and food interactions necessitating the need for frequent laboratory monitoring and dosage adjustment. Preinjury warfarin use before traumatic injury has been shown to increase morbidity and mortality even with the existence of effective anticoagulant reversal methods.[1–3]

Direct oral anticoagulants (DOACs) employ one of two mechanisms of action to accomplish systemic anticoagulation—direct thrombin inhibition or inhibition of factor Xa. The rate of DOAC prescribing has accelerated since becoming available in the United States in 2010. DOAC medications offer the advantage of increased patient compliance with therapy and the absence of required laboratory monitoring.[4] In addition, DOACs are associated with a favorable safety profile resulting in significantly less spontaneous major bleeding and in-hospital mortality compared with warfarin.[5–9]

Studies of outcomes after traumatic injury in patients taking preinjury DOAC medication are limited and have typically been small single-center studies or case reports.[10–12] One large multi-institutional observational study focused on the risk of intracranial hemorrhage (ICH) after trauma in patients taking preinjury anticoagulant and/or antiplatelet medications. In a subgroup analysis, aspirin, but not warfarin or DOACs, were associated with

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* Reprint requests: Wendy L. Wahl, MD, FACS, FCCM, Saint Joseph Mercy Ann Arbor, Department of Surgery, 5301 E. Huron River Dr., Ann Arbor, MI 48106-0995.
E-mail address: wendy.wahl@stjoeshealth.org (W.L. Wahl).

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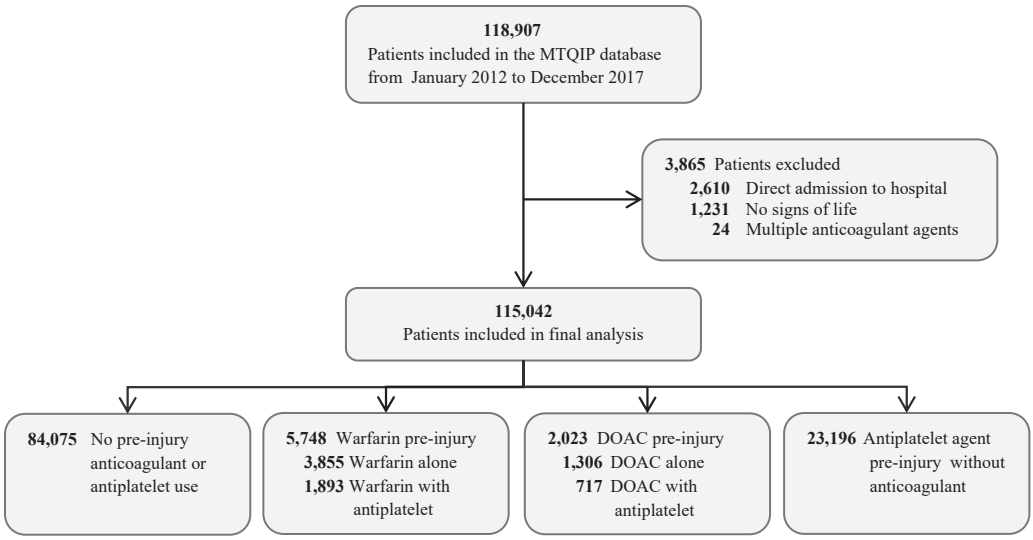


Figure. Study population. *MTQIP*, Michigan Trauma Quality Improvement Program; *DOAC*, direct oral anticoagulant.

an increased risk of ICH.[13] However, in patients with ICH after trauma, preinjury warfarin, aspirin, or clopidogrel use were each significant independent predictors of death; whereas DOAC usage was not.

In this study, we utilize data from the Michigan Trauma Quality Improvement Program (MTQIP), a collaborative quality initiative,[14] to investigate the effects of preinjury anticoagulation and/or antiplatelet therapy on outcomes after trauma.

Methods

Data collection

MTQIP consists of 29 level 1 and 2 trauma centers in the state of Michigan as verified by the American College of Surgeons Committee on Trauma. Data collection uses the existing trauma registry at participating hospitals.[15] MTQIP utilizes a data definitions dictionary, based on the National Trauma Data Standard, with data being transmitted to the coordinating center at 4-month intervals. In addition to standard data elements, supplementary data on preinjury anticoagulant and antiplatelet medication has been collected since January 2012.

The inclusion criteria for MTQIP are as follows: age $\geq$16 years; at least 1 valid trauma code on admission (additional information in supplement); calculated Injury Severity Score (ISS) $\geq$5; and known emergency department (ED) and hospital discharge disposition. Excluded patients, for this study, are those with no signs of life at initial evaluation (ED systolic blood pressure = 0, pulse = 0, Glasgow coma scale = 3), transfers into a hospital after admission to another hospital, or patients taking multiple anticoagulant medications (Figure).[16] All ISS values were derived from registrar-abstracted abbreviated injury scale 2005 codes with 2008 updates.

This study was submitted to the St. Joseph Mercy Ann Arbor Institutional Review Board (Ann Arbor, MI) and given a determination of "not regulated" because the patients had de-identified status in the database.

Analysis

Data were abstracted from the MTQIP database, and the study cohort consists of patients admitted between January 1, 2012, and December 31, 2017. For all outcomes, comparisons were made between patient groupings based on preinjury anticoagulant and/or antiplatelet. Groups were identified as follows: none, warfarin, DOACs, antiplatelets, warfarin + antiplatelets, and DOAC + antiplatelets.

Univariate differences in patient characteristics were evaluated using χ^2 tests for categorical variables and analysis of variance F-tests for continuous variables. Outcomes of interest included mortality, mortality or hospice, serious complications, and need for operations. Serious complications is a composite outcome that includes grade 2 and 3 morbidity events associated with increased mortality or utilization of resources.[14,15] Resource utilization measures investigated were need for any surgical intervention during admission, transfusion with packed red blood cells (PRBC) and/or fresh frozen plasma (FFP) in the first 4 hours after arrival. For calculating the mean number of transfused PRBC or FFP units, patients who did not receive these treatments were excluded.

Statistical comparisons were made using multivariable analyses for the outcome of interest with anticoagulant/antiplatelet use as the independent variable, using none as the reference. Multivariable logistic regression modeling was used to account for differences in patient characteristics, thereby allowing for risk adjustment at the patient level for the different anticoagulation and antiplatelet cohorts. Patient characteristics that were not constantly related to the outcome throughout all values of the variable were entered into models as categories rather than as continuous covariates. To account for the effect of injury severity by injury region, abbreviated injury severity score >2 in the face, head/neck, extremity, chest, and abdominal regions were included in models. In some instances there were missing values for potentially important covariates. To minimize bias, these values were accounted for by using a category for missingness. Additionally, to account for within-hospital clustering, we used cluster-robust standard errors. Odds ratios were reported for logistic regression models.

Statistical methods

Statistical analyses were performed using Stata 15.0 (StataCorp, College Station, TX). Statistical significance was defined as a *P* value <.05. Average values are expressed as the mean ± standard deviation.

Table I
Baseline characteristics

	None (N = 84,075)	Warfarin (N = 3,855)	DOAC (N = 1,306)	*P* value
Age, y ± SD	52.7 ± 22.8	77.7 ± 13.2	77.1 ± 13.1	<.001
Female, number (%)	34,129 (40.6)	2,104 (54.6)	761 (58.3)	<.001
Race, number (%)				<.001
White	62,109 (73.9)	3,535 (91.7)	1,222 (93.6)	
Black	18,346 (21.8)	267 (6.9)	66 (5.1)	
Other	3,620 (4.3)	53 (1.4)	18 (1.4)	
Uninsured, number (%)	9,421 (11.2)	65 (1.7)	15 (1.1)	<.001
Penetrating trauma, number (%)	7,046 (8.4)	24 (0.6)	4 (0.3)	<.001
Injury Severity Score, number (%)				<.001
5–15	6,6742 (79.4)	3,179 (82.5)	1,134 (86.8)	
16–24	10,650 (12.7)	379 (9.8)	106 (8.1)	
25–35	5,204 (6.2)	283 (7.3)	59 (4.5)	
>35	1,479 (1.8)	14 (0.4)	7 (0.5)	
AIS > 2, number (%)				<.001
Head/neck	16,681 (19.8)	929 (24.1)	248 (19.0)	
Face	393 (0.5)	3 (0.1)	0 (0.0)	
Chest	14,922 (17.7)	448 (11.6)	173 (13.2)	
Abdomen	4,839 (5.8)	67 (1.7)	31 (2.4)	
Extremity	24,117 (28.7)	1,416 (36.7)	456 (34.9)	
GCS–Motor, number (%)				<.001
6	71,289 (84.8)	3,267 (84.7)	1,111 (85.1)	
5–2	4,101 (4.9)	122 (3.2)	28 (2.1)	
1	3,382 (4.0)	75 (1.9)	13 (1.0)	
Missing	5,303 (6.3)	391 (10.1)	154 (11.8)	
ED heart rate (bpm)				<.001
51–20	4,764 (5.7)	104 (2.7)	41 (3.1)	
>120	76,799 (91.3)	3,609 (93.6)	1,202 (92.0)	
0–50	773 (0.9)	39 (1.0)	15 (1.1)	
Missing	1,739 (2.1)	103 (2.7)	48 (3.7)	
ED systolic BP (mmHg)				
>90	79,706 (94.8)	3,657 (94.9)	1,238 (94.8)	
61–90	2,058 (2.4)	82 (2.1)	19 (1.5)	
<60	434 (0.5)	11 (0.3)	2 (0.2)	
Missing	1,877 (2.2)	105 (2.7)	47 (3.6)	
Transfer from OSH, number (%)	1,4201 (16.9)	701 (18.2)	204 (15.6)	<.001
Ventilator support, number (%)	34,825 (41.4)	1467 (38.1)	522 (40.0)	<.001
Comorbid diseases, number (%)				<.001
Alcohol use disorder	8,252 (9.8)	141 (3.7)	60 (4.6)	
Cerebrovascular accident	1,004 (1.2)	220 (5.7)	110 (8.4)	
COPD	6,463 (7.7)	611 (15.8)	211 (16.2)	
Chronic renal failure	711 (0.8)	131 (3.4)	20 (1.5)	
Congestive heart failure	1,521 (1.8)	477 (12.4)	131 (10.0)	
Current smoker	23,703 (28.2)	325 (8.4)	121 (9.3)	
Dementia	5,419 (6.4)	469 (12.2)	195 (14.9)	
Diabetes	8,094 (9.6)	845 (21.9)	271 (20.8)	
Disseminated cancer	304 (0.4)	35 (0.9)	15 (1.1)	
Drug use disorder	11,350 (13.5)	73 (1.9)	32 (2.5)	
FDHS	5,916 (7.0)	833 (21.6)	439 (33.6)	
History of MI	322 (0.4)	32 (0.8)	3 (0.2)	
Hypertension	24,055 (28.6)	2,658 (68.9)	930 (71.2)	
Liver disease	658 (0.8)	22 (0.6)	11 (0.8)	
Major psychiatric illness	12,366 (14.7)	551 (14.3)	317 (24.3)	
Steroid use	968 (1.2)	111 (2.9)	66 (5.1)	

SD, standard deviation; *AIS*, abbreviated injury scale; *GCS*, Glasgow coma score; *ED*, emergency department; *BP*, blood pressure; *COPD*, chronic obstructive pulmonary disease; *FDHS*, functionally dependent health status; *MI*, myocardial infarction.

Results

Study population

A total of 118,907 traumatically injured patients with an ISS $\geq$ 5 presented to MTQIP-participating hospitals between January 2012 and December 2017. Of these, 3,865 patients were excluded (Figure). The final study population consisted of 115,042 patients treated at 29 American College of Surgeons verified level 1 or 2 trauma centers.

Of the 115,042 trauma patients, 44.2% were women and 78.2% were white, with a mean age (standard deviation) of 59.1 (23.2) years. A total of 84,075 (73.1%) patients were taking no preinjury anticoagulant or antiplatelet medications, a total of 5,748 (5.0%) were using warfarin before injury, and a total of 2,023 (1.8%) were prescribed a DOAC (Figure). We observed 23,196 patients on antiplatelet agents with an additional 893 patients taking warfarin with an antiplatelet and 717 patients on DOACs and antiplatelet therapy. Of the DOAC patients, 197 were on a direct thrombin inhibitor, 137 were taking a direct thrombin inhibitor and platelet inhibitor, 1109 presented on a factor Xa inhibitor, and 580 patients were taking a factor Xa inhibitor and antiplatelet agent. Baseline characteristics were significantly different across the 3 main anticoagulant cohorts for each category (Table I). Patients who were anticoagulated tended to be older, female, white, and insured. The vast majority of patients presented with a blunt mechanism of traumatic injury with most injuries involving the head and neck region.

Outcome measures

The unadjusted rates of death or discharge to hospice care were 8.8% for warfarin, 6.7% for DOACs, and 4.8% for no anticoagulation. Risk-adjustment model characteristics for the outcome mortality or discharge to hospice are presented in Table II. After adjusting for the differences in baseline characteristics, the likelihood of death or discharge to hospice was increased for warfarin but was not significantly different for DOACs (Table III). A similar finding was present for the outcome of mortality. Patients on warfarin also had a higher incidence of serious complications but those on DOACs did not.

Patients using anticoagulants before injury were less likely to receive a surgical intervention on presentation to a trauma center compared with patients on no anticoagulants (Table III). Anticoagulated patients had a statistically equivalent likelihood of receiving a transfusion of PRBCs within the first 4 hours after arrival as a patient not on anticoagulant or antiplatelet therapy. However, the adjusted odds of a patient taking warfarin receiving at least 1 unit of FFP within the first 4 hours after arrival was significantly higher than for patients in the none group. Conversely, the average unadjusted number of FFP units administered within 4 hours after arrival to the trauma center was higher for the none group.

Concomitant anticoagulant and antiplatelet therapy

We included 4 initial cohorts in the subanalysis for antiplatelet agents: warfarin + antiplatelet agent (n = 1,893), DOAC + antiplatelet agent (n = 717), antiplatelet agent only (n = 23,196), and no anticoagulant or antiplatelet agent (n = 84,075). Findings for each outcome were similar when analyzing patients on both anticoagulant and antiplatelet agents before a traumatic injury as compared with patients using only anticoagulant agents (Table IV).

After risk adjustment, the concomitant use of warfarin + antiplatelet agents led to an increased likelihood of mortality or hospice, mortality alone, and serious complications (Table III). The use of an antiplatelet agent alone was also associated with a significantly increased risk of mortality or hospice, mortality alone, and serious complications. We observed no significant difference in mortality alone, mortality or hospice and serious complications between the none group and the entire DOAC + antiplatelet group (Table IV). When the DOAC results were stratified by class of DOAC agent, the risk of mortality or hospice was higher for patients on direct thrombin inhibitors with an antiplatelet agent (P < .007, odds ratio [OR] 2.27 [1.25–4.11]) compared with those taking a factor Xa inhibitor and antiplatelet agent (P = .92, OR 0.983 [0.709–1.36]). This pattern held when examining those with only a high abbreviated injury scale of 3 or more, where the risk of mortality or hospice was elevated for those receiving antiplatelet agents (P = .011, OR 1.15 [1.03–1.28]), warfarin only (P = .001, OR 1.35 [1.14–1.6]), warfarin and an antiplatelet agent (P = .012, OR 1.39 [1.08–1.8]) compared with those on DOACs alone (P = .275, OR 1.09 [0.86–1.68]) or a DOAC and antiplatelet medication (P = .053, OR 1.32 [0.99–1.75]).

Patients taking warfarin + antiplatelet medication were less likely to receive an operative intervention compared with patients on no anticoagulant or an antiplatelet agent prior to before traumatic injury (Table IV). The likelihood of a PRBC transfusion within 4 h of arrival was higher for those on warfarin + antiplatelet agent compared with the none group. We observed no significant difference in the rate of PRBC transfusion for antiplatelet agents alone or DOAC + antiplatelet medication when compared with the none group. The need for a FFP transfusion within 4 hours of arrival was higher for both warfarin + antiplatelet agent and DOAC +

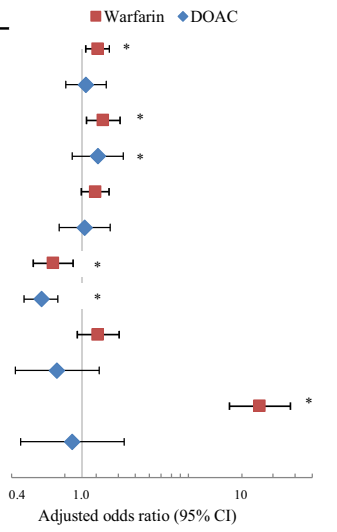
Table II
Multivariable logistic regression model with mortality or hospice as dependent variable

Factor	OR (95% CI)*	*P* value†
Antiplatelet and/or anticoagulant use		
None	(Reference)	
Warfarin only	1.23 (1.04–1.44)	.01
DOAC only	1.05 (0.81–1.37)	.69
Antiplatelet agents only	1.12 (1.01–1.24)	.03
Warfarin + antiplatelet agents	1.44 (1.10–1.88)	<.01
DOAC + antiplatelet agents	1.21 (0.90–1.63)	.22
Age, y		
16–25	(Reference)	
26–45	1.17 (1.04–1.32)	<.01
46–65	2.45 (2.11–2.84)	<.001
66–75	4.73 (3.81–5.88)	<.001
>75	12.44 (9.68–15.97)	<.001
Female	0.78 (0.74–0.82)	<.001
Race		
White	(Reference)	
Black	0.83 (0.71–0.96)	.01
Other	0.8 (0.65–0.99)	.04
Uninsured	1.56 (1.34–1.81)	<.001
Mechanism		
Blunt	(Reference)	
Penetrating	3.0 (2.39–3.76)	<.001
Injury Severity Score		
5–15	(Reference)	
16–24	2.05 (1.83–2.31)	<.001
25–35	6.86 (5.62–8.36)	<.001
>35	11.48 (8.75–15.07)	<.001
AIS > 2		
Head/neck	1.52 (1.33–1.74)	<.001
Face	0.53 (0.38–0.73)	<.001
Chest	1.05 (0.93–1.20)	.42
Abdomen	1.05 (0.88–1.26)	.60
Extremity	0.81 (0.71–0.92)	.001
GCS–motor		
6	(Reference)	
5–2	4.01 (3.53–4.56)	<.001
1	17.82 (14.73–21.55)	<.001
Missing	1.32 (1.08–1.62)	.01
ED heart rate, bpm		
51–120	(Reference)	
>120	1.84 (1.64–2.06)	<.001
0–50	1.98 (1.69–2.32)	<.001
Missing	1.13 (0.81–1.59)	.46
ED Systolic BP, mmHg		
>90	(Reference)	
61–90	2.16 (1.89–2.47)	<.001
≤60	2.76 (1.94–3.92)	<.001
Missing	2.38 (1.61–3.51)	<.001
Transfer from OSH	0.67 (0.60–0.75)	<.001
Ventilator support	2.21 (1.84–2.64)	<.001
Calendar year	1.0 (0.98–1.03)	.87
Comorbid diseases		
Alcohol use disorder	0.8 (0.68–0.95)	<.01
Cerebrovascular accident	1.11 (0.93–1.32)	.24
Chronic obstructive pulmonary disease	1.52 (1.36–1.69)	<.001
Chronic renal failure	1.8 (1.39–2.33)	<.001
Congestive heart failure	1.79 (1.51–2.13)	<.001
Current smoker	0.66 (0.57–0.76)	<.001
Dementia	1.78 (1.53–2.08)	<.001
Diabetes mellitus	1 (0.90–1.12)	.96
Disseminated cancer	6.36 (4.45–9.08)	<.001
Drug use disorder	0.58 (0.48–0.69)	<.001
Functionally dependent health status	1.72 (1.38–2.16)	<.001
History of myocardial infarction	1.34 (0.83–2.18)	.23
Liver disease	5.3 (4.39–6.41)	<.001
Hypertension requiring medication	0.92 (0.80–1.06)	.23
Major psychiatric illness	0.88 (0.80–0.96)	<.01
Steroid use	1.41 (1.14–1.74)	<.01
History of angina within 30 days	1.34 (1.11–1.62)	<.01
History of peripheral vascular disease	1.16 (0.89–1.53)	.28
Currently receiving chemotherapy	1.36 (0.89–2.07)	.15

AIS, Abbreviated Injury Scale; *BP*, blood pressure; *GCS*, Glasgow coma score.
* N = 115,042.
† Reported confidence intervals and *P* values account for clustering of patients within hospitals.

Table III
In-hospital outcomes for pre-injury anticoagulants as compared with no anticoagulants

Outcome measure	None (N=84,075)	Warfarin only (N=3,855)	DOAC only (N=1,306)
Mortality or hospice[†]			
Number (%)	3,996 (4.8)	338 (8.8)	88 (6.7)
AOR (95% CI)	(Reference)	1.23 (1.04–1.44)	1.05 (0.81–1.37)
Mortality			
Number (%)	3,226 (3.8)	240 (6.2)	60 (4.6)
AOR (95% CI)	(Reference)	1.32 (1.05–1.65)	1.23 (0.88–1.71)
Serious complications			
Number (%)	5,251 (6.2)	276 (7.2)	73 (5.6)
AOR (95% CI)	(Reference)	1.19 (1.00–1.42)	1.03 (0.74–1.44)
Surgical intervention			
Number (%)	36,104 (44.2)	1528 (40.9)	526 (40.5)
AOR (95% CI)	(Reference)	0.69 (0.56–0.85)	0.59 (0.47–0.73)
pRBC within 4 hours			
Number (%)[‡]	3,427 (4.1)	72 (1.9)	18 (1.4)
Mean units[§] ± SD	5.03 ± 6.04	2.71 ± 2.52	3.17 ± 2.87
AOR (95% CI)	(Reference)	1.23 (0.93–1.64)	0.72 (0.42–1.25)
FFP within 4 hours			
Number (%) [‡]	2,125 (2.5)	295 (7.7)	15 (1.1)
Mean units[§] ± SD	4.84 ± 5.13	2.40 ± 1.48	2.20 ± 1.61
AOR (95% CI)	(Reference)	10.11 (6.74–15.18)	0.88 (0.45–1.73)



DOAC, direct oral anticoagulant; *AOR*, adjusted odds ratio; *pRBC*, packed red blood cells; *SD*, standard deviation; *FFP*, fresh frozen plasma.
*Denotes $P < .05$.
† Primary outcome.
‡ Percent of patients receiving transfusion.
§ Mean number transfused units for patients receiving transfusion.

antiplatelet agent when compared with patients on no anticoagulant or antiplatelet medication (Table IV).

Discussion

This is the largest study to examine outcomes for preinjury anticoagulation and antiplatelet medication use in a trauma population. When compared with no anticoagulation, warfarin was associated with an increased risk of mortality or discharge to hospice, mortality alone, and serious complications, but DOACs were not. Additionally, antiplatelet agents alone or warfarin plus an antiplatelet agent exhibited increases in mortality, discharge to hospice and serious complications compared with the addition of an antiplatelet agent to the DOAC group of factor Xa inhibitors.

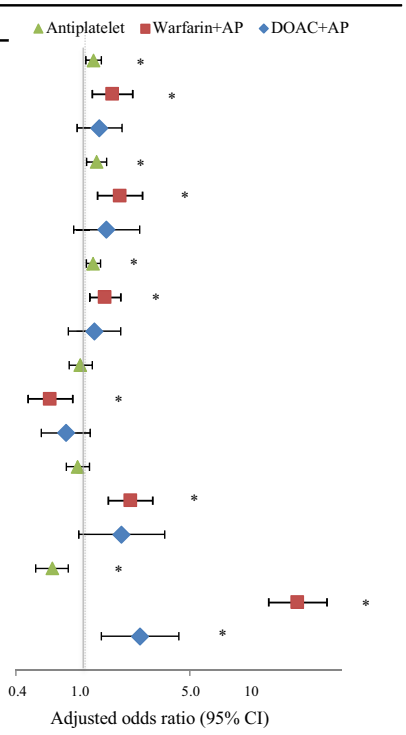
Our study confirms the results of earlier smaller studies analyzing warfarin and DOAC medications in trauma patients for the outcome of mortality. A single-center, retrospective study in 2016 from a level 1 trauma center with 373 warfarin and 112 DOAC patients reported higher mortality for the warfarin group compared with no anticoagulation or DOACs.[12] A study from a single, level 2 trauma center, analyzed patients on anticoagulants presenting with severe blunt trauma but excluded patients with severe traumatic brain injury (TBI). The study concluded that there was a decrease in mortality associated with patients taking DOACs as opposed to warfarin, but those with the worst head injuries were not included, potentially biasing any conclusions about mortality.[10] Finally, a prospective, observational study from the American Association for the Surgery of Trauma Multicenter Trials Group, using data from 16 trauma centers, evaluated outcomes for trauma patients taking DOACs compared with a combination of either warfarin, aspirin, or clopidogrel. The study concluded that DOACs were not associated with a higher rate of traumatic ICH, progression of ICH, or death.[13] A limitation of the study was the low number of DOAC patients (182) compared with a combined group of 1,662 patients using either antiplatelet agents or warfarin. The study did support that patient outcomes for TBI were not worse for those on DOACs compared with warfarin.[13]

There have also been studies in medical patients demonstrating reduced mortality associated with DOACs for patients requiring anticoagulation. A large, multicenter, retrospective cohort study from the American Heart Association/American Stroke Association Get with The Guidelines-Stroke registry assessed the association of anticoagulant type and in-hospital mortality for patients presenting with spontaneous ICH.[5] A total of 141,311 patients were included in the final study population of which 15,036 were warfarin users and 4,918 were on DOACs, the authors found that DOAC use before hemorrhage was associated with a lower risk of in-hospital mortality compared with anticoagulation with warfarin.[5] This study and our study exhibited similar results for patient outcomes. However, our study differed in that it evaluated patients after traumatic injury rather than those with a spontaneous ICH. The use of reversal agents or FFP was also not captured in the spontaneous ICH study.

In addition, we found that antiplatelet agents alone lead to worse outcomes; however, the results of earlier studies investigating the effect of antiplatelet agents on trauma mortality have been mixed. A retrospective analysis of 1,552 TBI patients aged 65 years or older who were taking either warfarin or antiplatelet agents before injury concluded that warfarin, but not antiplatelet agents, was associated with an increased risk of in-hospital mortality.[2] This outcome was consistent across the subgroups of aspirin alone, clopidogrel alone, or the combination of aspirin and clopidogrel.[2] A subsequent meta-analysis evaluated the effect of antiplatelet agents on mortality in patients presenting with a head injury.[1] The authors concluded that there appeared to be a slight increased risk of mortality in patients using preinjury antiplatelet agents; however the results were not statistically different.[1] Contrary to other studies, following risk adjustment, our analysis

Table IV
In-hospital outcomes for pre-injury anticoagulants and antiplatelet agents as compared with no anticoagulants

Outcome Measure	None (N=84,075)	Antiplatelet (N=23,196)	Warfarin + AP (N=1,893)	DOAC + AP (N=717)
Mortality or hospice[†]				
Number (%)	3,996 (4.8)	1,528 (6.6)	221 (11.7)	64 (8.9)
AOR (95% CI)	(Reference)	1.12 (1.01–1.24)	1.44 (1.10–1.88)	1.21 (0.90–1.63)
Mortality				
Number (%)	3,226 (3.8)	985 (4.2)	165 (8.7)	44 (6.1)
AOR (95% CI)	(Reference)	1.17 (1.02–1.33)	1.59 (1.18–2.14)	1.33 (0.86–2.06)
Serious complications				
Number (%)	5,251 (6.2)	1,405 (6.1)	166 (8.8)	50 (7.0)
AOR (95% CI)	(Reference)	1.12 (1.02–1.23)	1.31 (1.07–1.61)	1.13 (0.80–1.60)
Surgical intervention				
Number (%)	36,104 (44.2)	10,279 (44.9)	719 (38.4)	308 (43.2)
AOR (95% CI)	(Reference)	0.94 (0.81–1.10)	0.63 (0.47–0.85)	0.78 (0.56–1.07)
pRBC within 4 hours				
Number (%)[‡]	3,427 (4.1)	320 (1.4)	50 (2.6)	18 (2.5)
Mean units[§] ± SD	5.03 ± 6.04	3.43 ± 4.64	2.90 ± 2.87	2.78 ± 2.13
AOR (95% CI)	(Reference)	0.91 (0.78–1.06)	1.83 (1.36–2.45)	1.62 (0.92–2.87)
FFP within 4 hours				
Number (%)[‡]	2,125 (2.5)	167 (0.7)	231 (12.2)	16 (2.2)
Mean units[§] ± SD	4.84 ± 5.13	3.56 ± 4.23	2.45 ± 1.71	2.56 ± 1.63
AOR (95% CI)	(Reference)	0.65 (0.52–0.80)	16.73 (11.38–24.59)	2.07 (1.24–3.46)



AP, antiplatelet; *DOAC*, direct oral anticoagulant; *AOR*, adjusted odds ratio; *pRBC*, packed red blood cells; *SD*, standard deviation; *FFP*, fresh frozen plasma.
*Denotes $P < .05$.
[†] Primary outcome.
[‡] Percent of patients receiving transfusion.
[§] Mean number transfused units for patients receiving transfusion.

supports antiplatelet agents alone are associated with an adjusted 10% increased odds of mortality or hospice, a 14% increased odds of mortality alone, and a 13% increased odds of developing a serious complication. Of note, although the combination of warfarin and antiplatelet agents was also associated with worse outcomes, the combination of the Factor Xa inhibitor DOACs with an antiplatelet agent was not. However, the combination of direct thrombin inhibitor DOAC and antiplatelet agent had similar mortality rates to those on antiplatelet agents. This finding and the differences in outcomes between the classes of DOACs deserves more study.

Although DOACs continue to be recommended for their ease of use compared with warfarin, there is still hesitation when prescribing DOAC agents attributable to the previous lack of a commercially available reversal agent.[17] Until recently, dabigatran, the least-prescribed DOAC medication, was the only DOAC with a commercially available reversal agent in the United States. The reversal agent for the newer factor-Xa inhibitors, andexanet alfa, has only recently been approved for use in the United States and was not commercially available at the time of this study. The results of this study challenge the previous hesitation in prescribing an agent with no available reversal agent because DOAC medications were associated with lower mortality compared with warfarin.

This comparative effectiveness study has several limitations. First, despite the concurrent collection and submission of the data to MTQIP, it was not feasible to randomize patients before their traumatic injury. Therefore a goal of this study is to provide high-quality pragmatic evidence for prescribers deciding between warfarin or DOACs. Second, all data came from participating Michigan level 1 and 2 trauma centers, therefore the findings may not be applicable to trauma populations treated in other regions, at lower level trauma centers, or at non-trauma facilities. Additionally, patients with minor injuries (ISS <5) were excluded. Although the amount and timing of FFP transfusions were collected, the administration of other reversal agents, such as prothrombin complex concentrates was not collected during most of the study period. Therefore, measurement of the effect of all attempted anticoagulation reversal methods is incomplete. Another weakness is the lack of a specific measure for patient frailty within the data, although the data elements of dementia or functionally dependent health status may act as surrogates. There may have been a bias toward prescribing warfarin to patients who appear frail or have impaired renal function given the renal metabolism of DOACs, contributing to worse outcomes in the warfarin group. However, renal disease and functional health status were included in our logistic regression analysis, but other unmeasured frailty factors could still be present. Last, we performed a limited examination of the effects of the specific class of DOAC agents used by patients because of low numbers and the potential for a type 2 error, although for those taking an antiplatelet agent and a direct thrombin inhibitor, there was a measurable increase in mortality and disposition to hospice, but no difference for those on a direct thrombin inhibitor without an antiplatelet drug.

Compared with no anticoagulation, patients taking warfarin before a traumatic injury have a higher incidence of in-hospital

mortality or hospice care at discharge, in-hospital before injury, DOAC patients had similar mortality and serious complication outcomes compared with patients on no anticoagulant medication. In addition, preinjury antiplatelet therapy alone or with warfarin was also associated with worse outcomes, and antiplatelet therapy with a direct thrombin inhibitor DOAC also had higher overall mortality, antiplatelet therapy with a Xa inhibitor DOAC did not exhibit the same deleterious effects. The potential differences in mortality for patients on antiplatelet therapy and a factor-Xa inhibitor compared with a direct thrombin inhibitor deserve more intense scrutiny.

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Conflict of interest/Disclosure

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References

1. Batchelor JS, Grayson A. A meta-analysis to determine the effect of anticoagulation on mortality in patients with blunt head trauma. *Br J Neurosurg*. 2012;26:525–530.
2. Grandhi R, Harrison G, Voronovich Z, et al. Preinjury warfarin, but not antiplatelet medications, increases mortality in elderly traumatic brain injury patients. *J Trauma*. 2015;78:614–621.
3. Ivascu FA, Howells GA, Junn FS, Bair HA, Bendick PJ, Janczyk RJ. Rapid warfarin reversal in anticoagulated patients with traumatic intracranial hemorrhage reduces hemorrhage progression and mortality. *J Trauma*. 2005;59:1131–1139.
4. Marzec LN, Wang J, Shah ND, et al. Influence of direct oral anticoagulants on rates of oral anticoagulation for atrial fibrillation. *J Am Coll Cardiol*. 2017;69:2475–2484.
5. Inohara T, Xian Y, Liang L, et al. Association of intracerebral hemorrhage among patients taking non–vitamin K antagonist vs vitamin K antagonist oral anticoagulants with in-hospital mortality. *JAMA*. 2018;319:463–473.
6. Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2009;361:1139–1151.
7. Granger CB, Alexander JH, McMurray JJ, et al. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2011;365:981–992.
8. Giugliano RP, Ruff CT, Braunwald E, et al. Edoxaban versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2013;369:2093–2104.
9. Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med*. 2011;365:883–891.
10. Feeney JM, Neulander M, DiFiori M, et al. Direct oral anticoagulants compared with warfarin in patients with severe blunt trauma. *Injury*. 2017;48:47–50.
11. Riccardi A, Spinola B, Minuto P, et al. Intracranial complications after minor head injury in patients taking vitamin K antagonists or direct oral anticoagulants. *Am J Emerg Med*. 2017;35:1317–1319.
12. Maung AA, Bhattacharya B, Schuster KM, Davis KA. Trauma patients on new oral anticoagulation agents have lower mortality than those on warfarin. *J Trauma*. 2016;81:652–657.
13. Kobayashi L, Barmparas G, Bosarge P, et al. Novel oral anticoagulants and trauma: the results of a prospective American Association for the Surgery of Trauma Multi-Institutional Trial. *J Trauma*. 2017;83:827–835.
14. Hemmila MR, Jakubus JL. Trauma quality improvement. *Crit Care Clinics*. 2017;33:193–212.
15. Hemmila MR, Jakubus JL, Cain-Nielsen AH, et al. The Michigan trauma quality improvement program: results from a collaborative quality initiative. *J Trauma*. 2017;82:867–876.
16. Calland JF, Nathens AB, Young JS, et al. The effect of dead-on-arrival and emergency department death classification on risk-adjusted performance in the American College of Surgeons Trauma Quality Improvement Program. *J Trauma*. 2012;73:1086–1092.
17. Barnes GD, Lucas E, Alexander GC, Goldberger ZD. National trends in ambulatory oral anticoagulant use. *Am J Med*. 2015;128:1300–1305.e2.

Discussion

Dr Daniel Eiferman (Columbus, OH): Always good to have an Ohio State guy commenting on the Michigan paper. We'll see how this goes down.

Thanks for inviting me to come and talk. Congratulations for doing this. This, as you pointed out, is probably the best use of retrospective database reviews in all of surgical research because, as you pointed out, you can't prospectively assign people to take their anticoagulation and then go get into a car accident. It's wonderful that you did this. This is extremely relevant and germane to clinical practice. I'm glad that you brought this to our attention.

Given the increasing number of patients that are taking anticoagulation right now and your findings that shows that DOACs may have a better safety profile, my first question to you is, any idea of the mechanism of why DOACs potentially are safer than warfarin or antiplatelets?

My second question for you, I think you answered in your limitations. As you pointed out, not all DOACs have the same mechanism of action. Some are anti-X. Others are direct. How small were your numbers, or were you able to even look at it all to see if there was a difference in outcome by mechanism of action?

The third question that I hope you'll spend the most time on is relating to cost. Reversing warfarin with FFP is several hundred dollars per unit. The same is true of platelets. One dose of reversal agent of a DOAC on the low end is about $7,000. So a very common scenario for us in acute care surgery is the traumatic brain injury patient, where the neurosurgeons will come by and say, "Keep the INR less than 1.5. Keep the platelets above 100."

Now, with DOACs, we have no labs to follow to guide this. So when am I supposed to pull the trigger as the practicing surgeon to give the anticoagulation antidote and spend that great amount of money, because that's really the clinical relevance for those of us.

Thank you for bringing this. Honored to be the discussant. Hopefully that wasn't too painful for a Michigan guy.

Dr Jason Hecht: Thank you very much. I appreciate it. First, talking about the hypothesis for the protective effects of the direct oral anticoagulant, I think that is the million-dollar question here. It was relatively surprising to us when we came across the data and found that.

Really, I think to answer that, you have to look at the differences between the two drugs and what might potentially be different when assessing them. I think first, like you mentioned, warfarin patients likely are being reversed with FFP in a large majority of cases, as opposed to the direct oral anticoagulants, likely getting a PCC product. It's possible that all the additional fluid load from FFP could be leading to some of the worse outcomes down the road in the patient's hospital stay.

I think you also have to probably take a look at the direct activity of these where there's less clotting factors that are going to be

involved and perhaps more wiggle room for alternative clotting pathways to take over. Trauma-induced coagulopathy is obviously a very complex disease state with a lot that's still unknown currently. I think, too, looking at these agents, the fact that there is no full reversal agent available, and at best we're probably getting a partial reversal with our PCC products, there's potential that some of the anticoagulant is still left onboard during the patient's hospital stay. Because of that, patients might be essentially getting early DVT prophylaxis that could be preventing some negative in-hospital outcomes or there could be protective effects from microemboli that could form from the coagulopathy and trauma induced coagulopathy.

The second question, outcomes by the distinct mechanism of action of these. Very similar to what we see in clinical practice, dabigatran is by far the least prescribed of these direct oral anticoagulants. Because of that, we have very few patients in the study on that specific agent, in the number of a couple of hundred as opposed to the 2,000 that we have for the total number. Really, we weren't going to get any high-quality analysis done by comparing those two, but certainly what you would postulate based on the phase 3 data that we have, knowing that dabigatran patients do tend to fare worse. I think we could postulate the same would probably been seen in the trauma population as well.

Lastly, talking about your reversal question and specifically the costs that are involved. PCC products, like you mentioned, are being used off-label for the reversal of these direct oral anticoagulants. Recently, within the last couple of months, we actually did get a dedicated reversal agent that was FDA approved—Andexanet alfa. Unfortunately, that comes with a price tag of about $50,000 for a single dose as compared what we see with Kcentra, being about $5,000 to $7,000, like you mentioned. The cost is only going to increase with these agents.

We do see PCCs being given for warfarin patients as well as specifically with intracranial hemorrhage population. I think in many cases you would be hard-pressed to find hospital administrators or P&T committees that are going to have a problem with giving a PCC for the reversal of a patient that's actively hemorrhaging in front of you. I know specifically at our institution, we haven't run into any roadblocks with that, and I anticipate a lot of other centers around the country are seeing that as well. Certainly, these reversal agents are going to be significantly more expensive than simply using vitamin K or FFP.

Lastly, I want to address detecting when these agents are onboard and when you do need to reverse them. Although we might not be able to know the degree of anticoagulation based on routine coagulation testing we have, we do know that some of our basic coagulation tests like the PT/INR and PTT actually can detect the presence of these anticoagulants. They can tell you—yes or no—is the patient taking the medication and is it in their system? But they might not be able to tell you how anticoagulated the patient actually is. Being able to use those smartly, based on the specific agent that you are dealing with, and also using thromboelastography to detect coagulopathy could be very useful as well.

Dr Jason Smith (Louisville, KY): Looking at the two groups, you kind of touched on it. It would be very interesting to get down to those two groups to see if there is a difference, at least in our own institution, and I think many others across the country. You're seeing a predominance of warfarin being used in a little more elderly patient, have been on it for a longer period of time, maybe older, suffering these injuries. Looking at those different factors that may have caused some of these differences would be important.

One of the things leading into it, and we kind of touched on it, is the amount of reversal that we are doing for these patients. I think what we see—and again what's been reported in a lot of bigger studies—without a massive amount of bleeding, a lot of people are more willing to let the Coumadin ride, for lack of a better term, have a little elevated INR, we'll watch that, we'll be less aggressive in fixing that, because we know a pattern or pathway for us to do that; whereas, if you're on the direct Xa inhibitors, for example, we predominantly just start reversing them as soon as they are through the door whether we know if they are going to need it or not. Did you have a chance to look at that in this data set and say, wait a second, more people got reversed here versus less here. And was that something that came into mind? I thought it was a great paper.

Dr Jason Hecht: One of the big limitations of our study is we were unable to assess the reversal agents that were given. We only started collecting that data in 2018, so we didn't have any of that available during the study period. I think that would be a great question to look at is when are these patients getting reversed? How soon from the time they hit the door and looking at that to see what effect that might be having on hospital outcomes?

Dr Shawn Safford (Roanoke, VA): You admittedly said these are very different populations that you're trying to compare. Had you looked at propensity score matching to help mitigate some of those impacts?

Dr Jason Hecht: We didn't look at propensity scoring specifically. It was an idea we threw around, but we decided to opt for the logistic regression to help account for the different characteristics, like you said, that play a big part in how these patients fare. Overall, we did have 65 different characteristics that we were powered to match for and, once accounting for all of those, is how we came across the adjusted outcomes that we have.

We certainly looked at all of the baseline characteristics that patients might be coming in on, where they were injured, how severely they were injured, and all of that was factored for when looking at this. I agree, it's always going to be a challenge to assess a nonanticoagulated patient population to somebody who is anticoagulated. They're always going to be totally different.

Dr Fred Luchette (Maywood, IL): In Michigan, one of the hospitals published a study 10 or 12 years ago, that patients on Coumadin, if you recognize them at the front door quickly, screen them, and reverse them, mortality goes down. Maybe you can comment in your retrospective study compliance with that protocol or if you have any information at all.

Great presentation. Thank you. And great discussion.

Dr Jason Hecht: Thank you. Again, the trouble when doing a large database study like this is you lose some of the granularity at the site level. Unfortunately, that's one of the things that are lost. When using a big data set, we are able to get nice adjusted results like this to answer a larger clinical question. But some of those fine details like how they are being reversed and how quickly the timing of it is, is unfortunately lost.