PHARMACOTHERAPY

ORIGINAL RESEARCH ARTICLES

Effect of Preinjury Oral Anticoagulants on Outcomes Following Traumatic Brain Injury from Falls in Older Adults

Jason P. Hecht[1]* Zachary J. LaDuke,[1] Anne H. Cain-Nielsen,[2] Mark R. Hemmila,[2] and Wendy L. Wahl[3]

[1]Inpatient Pharmacy, Saint Joseph Mercy, Ann Arbor, Michigan, USA; [2]Department of Surgery, University of Michigan, Ann Arbor, Michigan, USA; [3]Department of Surgery, The Ohio State University Wexner Medical Center, Columbus, Ohio, USA

Background Warfarin has been the oral anticoagulant of choice for the treatment of thromboembolic disease. However, upward of 50% of all new anticoagulant prescriptions are now for direct oral anticoagulants (DOAC). Despite this, outcome data evaluating preinjury anticoagulants remain scarce following traumatic brain injury (TBI). Our study objective is to determine the effects of preinjury anticoagulation on outcomes in older adults with TBI.

Methods Patient data were obtained from 29 level 1 and 2 trauma centers from 2012 to June 30, 2018. Overall, 8312 patients who were aged 65 years or older, suffering a ground level fall, and with an Abbreviated Injury Scale (AIS) head score of ≥ 3 were identified. Patients were excluded if they presented with no signs of life or a traumatic mechanism besides ground level fall. Statistical comparisons were made using multivariable analyses with anticoagulant/antiplatelet use as the independent variable.

Results Of the total patients with TBI, 3293 were on antiplatelet agents (AP), 669 on warfarin, 414 on warfarin + AP, 188 on DOACs, 116 on DOAC + AP, and 3632 on no anticoagulant. There were 185 (27.7%) patients on warfarin and 43 (22.9%) on a DOAC with a combined outcome of mortality or hospice as compared to 575 (15.8%) in the no anticoagulant group ($p<0.001$). After adjusting for patient factors, there was an increased risk of mortality or hospice in the warfarin (OR 1.60; 95% CI 1.27–2.01) and DOAC group (OR 1.67; 95% CI 1.07–2.59) as compared to no anticoagulant. Warfarin + AP was associated with an increased risk of mortality or hospice (OR 1.61; 95% CI 1.18–2.21) that was not seen with DOAC + AP (OR 0.93; 95% CI 0.46–1.87) as compared to no anticoagulant.

Conclusions In older adults with TBI, preinjury treatment with warfarin or DOACs resulted in an increased risk of mortality or hospice whereas preinjury AP therapy did not increase risk. Future studies are needed with larger sample sizes to directly compare TBI outcomes associated with preinjury warfarin versus DOAC use.

Key Words traumatic brain injury, anticoagulants, antiplatelet agents, factor Xa inhibitors, warfarin.
(Pharmacotherapy 2020;40(7):604–613) doi: 10.1002/phar.2435

Conflicts of interest: M.R.H. and A.H.C. receive salary support from Blue Cross Blue Shield of Michigan and Blue Care Network (a nonprofit mutual company) through their grant support of the Michigan Trauma Quality Improvement Program. The company had no role in the study. Z.J.L., W.L.W., and J.P.H. have no conflicts to disclose.

*Address for correspondence: Jason P. Hecht, Inpatient Pharmacy, Saint Joseph Mercy Ann Arbor, 5301 Mcauley Drive, Ypsilanti, MI 48197; e-mail: jason.hecht@stjoeshealth.org.

Older adults account for upward of 30% of all trauma admissions and 50% of all trauma-related deaths in the United States.[1] Traumatic brain injury (TBI) is one of the most common injuries occurring in older adults as well as one of the most fatal.[1,2] Although 75% of TBIs are classified as mild, more severe TBIs can be devastating injuries when they occur and contribute to long-term sequela that affect all aspects of a patient's life.[3] Patients with advanced age also frequently present with significant preinjury comorbidities and prescription medication treatments that often exacerbate their traumatic injuries and impact subsequent recovery. As the population has continued to age and life expectancy is increasing, the median age of traumatic admissions has increased from 56 to 65 years old since the year 2000.[4] Increasing life expectancy is also leading to a rise in the indications for anticoagulation therapy, such as atrial fibrillation (AF) and venous thromboembolism (VTE), which can greatly complicate the care of the older adult trauma patient.[5,6]

Anticoagulant medications are used for the prevention of stroke in AF as well as the treatment and prevention of VTE. Historically, the vitamin K antagonist warfarin has been the anticoagulant of choice due to its established efficacy, ease of laboratory monitoring, and availability of reversal agents. Despite the availability of effective reversal agents like vitamin K, fresh frozen plasma (FFP), and prothrombin complex concentrate (PCC), it is well established that preinjury warfarin usage leads to increased morbidity and mortality following TBI.[7–9] In a prior study involving all types of traumatic injury, we found that preinjury antiplatelet and/or warfarin use was associated with an increased risk of mortality.[10] However, preinjury direct oral anticoagulant (DOAC) use was not associated with a statistically increased risk of adverse outcomes.

The DOACs apixaban, rivaroxaban, dabigatran, and edoxaban work by inhibiting specific clotting factors and are noted to have increased patient compliance and satisfaction as compared to warfarin.[11,12] The DOACs have also been shown to have superior safety profiles for spontaneous bleeding as compared to warfarin. These facts have led to a dramatic increase in prescribing of these agents in recent years.[13–18] Despite the clear advantages of DOACs, there are also drawbacks such as no commercially available laboratory assays for monitoring drug levels, costly reversal agents, and conflicting results on outcomes following traumatic injury, all of which have limited even more widespread use of these agents.[19–22]

This study was performed using data from a collaborative quality initiative, the Michigan Trauma Quality Improvement Program (MTQIP). Our objective was to determine the effects on mortality and hospital complications of preinjury anticoagulation in older adult patients aged 65 years or older with TBI on warfarin or DOAC therapy. We hypothesized that older adults with TBI on preinjury DOAC agents would have increased rates of mortality, resource utilization, and serious complications when compared to warfarin or antiplatelet therapy.

Methods

Data Collection

Michigan Trauma Quality Improvement Program consists of 29 American College of Surgeons Committee on Trauma verified level 1 and 2 trauma centers in Michigan. Data collection uses the existing trauma registry with standardized addition of MTQIP specific data elements at all participating hospitals.[23] MTQIP utilizes a data definitions dictionary, based upon the National Trauma Data Standard with data being transmitted to the coordinating center at 4-month intervals. Data extractors from all participating trauma centers are graded annually on data accuracy and inter-rater reliability. Supplementary data on preinjury anticoagulant and antiplatelet medication usage has been collected since January 2012.

The inclusion criteria for MTQIP are as follows: at least one valid trauma code on admission; calculated Injury Severity Score (ISS) ≥ 5; and emergency department (ED) and hospital discharge disposition must be known. Additionally, patients were included in this study if they suffered a ground level fall, were ≥ 65 years old, and had TBI as defined by an Abbreviated Injury Scale (AIS) head score of ≥ 3. Excluded patients are those with no signs of life at initial evaluation (ED systolic blood pressure = 0, Pulse = 0, Glasgow Coma Scale = 3) or a traumatic mechanism other than ground level fall.[24] Patients were also excluded for potential coding errors where more than one anticoagulant was present upon admission. All ISS values were derived from registrar abstracted AIS 2005 codes with 2008 updates.

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

Analysis

Data were extracted from the MTQIP database and the study cohort consist of patients admitted between January 1, 2012, and June 30, 2018. For all outcomes, comparisons were made between patient groupings based upon preinjury medications. Patients in the antiplatelet group were taking an antiplatelet agent alone with no anticoagulant medication prescribed. Antiplatelet agents included aspirin and P2Y12 inhibitors such as clopidogrel, ticagrelor, and prasugrel.

Univariate differences in patient characteristics were evaluated using chi-squared tests for categorical variables and analysis of variance F-tests for continuous variables. Outcomes of interest included a combined end point of mortality or hospice, serious complications, and resource utilization. Serious complications are a composite outcome that includes grade 2 and 3 morbidity events associated with increased mortality or utilization of resources: decubitus ulcer, deep vein thrombosis (DVT), enterocutaneous fistula, extremity compartment syndrome, pneumonia, PE, unplanned intubation, unplanned return to the operation room, adult respiratory distress syndrome, acute kidney injury requiring dialysis, cardiac arrest, myocardial infarction, severe sepsis, or stroke.[23,25] Resource utilization measures investigated were needed for surgery during admission, transfusion with fresh frozen plasma (FFP) in the first 4 hours after arrival, transfusion with platelets in the first 4 hours after arrival, hospital length of stay (LOS), or intensive care unit (ICU) LOS. When calculating the mean number of transfusions, patients who did not receive transfusions were excluded.

Statistical comparisons were made using multivariable analyses for the outcome of interest with anticoagulant/antiplatelet use as the independent variable and using no anticoagulant/antiplatelet as the reference category. Two-stage multivariable logistic regression modeling was used to account for differences in patient characteristics to allow for risk adjustment for the various anticoagulation and antiplatelet cohorts (Tables S1A and S1B). Odds ratios (ORs) as well as confidence intervals (CIs) were reported for all outcomes of interest based on adjustment for patient-specific factors.

To account for patient differences, a two-stage modeling approach was used. In the first stage, patient "risk scores" were created by using regression (logistic regression for binary outcomes, linear regression for continuous outcomes) to model the outcome of interest, including patient case-mix factors, injury severity, time trend (year), and trauma center level as covariates. Characteristics that were not constantly related to the outcome throughout all values of the variable were entered into models as categories instead of continuous covariates. To account for the effect of injury severity by injury region, AIS score> 2 in the extremity, chest, and abdominal regions were included in models. In a few instances there were missing values for covariates. To minimize bias, these values were accounted for using a category for missingness. From the first-stage models, patient-level linear predictions ("risk scores") were obtained. In second-stage logistic regression models, each outcome of interest was modeled using patient-level risk scores as a covariate and including anticoagulant/antiplatelet use as our independent variable. Additionally, to account for within-hospital clustering, cluster-robust standard errors were used.

Statistical Methods

Statistical analyses were performed by a biostatistician using Stata 15.0 (StataCorp, College Station, TX, USA). Statistical significance was defined as a p-value < 0.05. Average values are expressed as the mean $\pm$ standard deviation (SD).

Results

Study Population

Overall, 8312 older adults aged 65 years or older were admitted to participating MTQIP hospitals with a TBI after a ground level fall during the study (Figure 1). There were 1387 (16.7%) patients on a preinjury anticoagulant, of which 304 (3.7%) were on a DOAC and 1083 (13.0%) on warfarin. 3293 (39.6%) patients were on an antiplatelet agent alone, and 3632 (43.7%) patients were on no preinjury anticoagulation or antiplatelet medication (no anticoagulant). Of the 304 patients in the DOAC group, 116 (38.2%) were taking a concomitant antiplatelet agent; 414 (38.2%) patients in the warfarin group were taking a concomitant antiplatelet

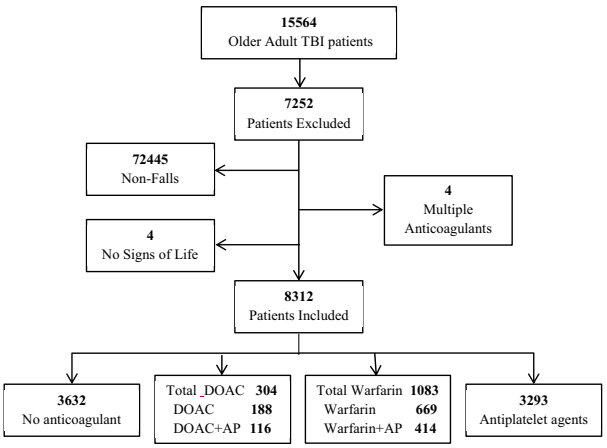

Figure 1. Study population. AP = antiplatelet agent; DOAC = direct oral anticoagulant; TBI = traumatic brain injury.

agent. The majority of patients taking DOACs were receiving factor Xa inhibitors (n=259, 85.2%) as opposed to direct thrombin inhibitors (n=45, 14.8%).

Anticoagulated patients tended to be male, insured, and had more preinjury congestive heart failure, diabetes, and hypertension (Table 1). Patients taking preinjury warfarin, as compared to DOAC, were more likely to have an ISS ≥ 25 (33.0% vs. 25.5%; $p<0.001$) as well an AIS head score ≥ 4 (62.7% vs. 51.6%; $p<0.001$), respectively. Patients in the preinjury DOAC group were more likely to present with an order for "do not resuscitate" (DNR) as compared to patients in the warfarin group (15.5% vs. 10.6%; $p<0.05$). Overall, there were 944 (11.4%) patients in the study with a pre-admission DNR and among this group 591 (62.6%) survived to hospital discharge.

Anticoagulant Outcomes

Patients in the no anticoagulant group had a rate of combined mortality or hospice of 15.8% (n=575). The DOAC alone group had 43 patients (22.9%) with a combined outcome of mortality or hospice, as compared to the warfarin alone group with 185 patients (27.7%); $p<0.001$ (Figure 2). After adjusting for patient factors, preinjury warfarin (OR 1.60; 95% CI 1.27–2.01) and DOACs (OR 1.67; 95% CI 1.07–2.59) were significantly associated with combined mortality or hospice when compared to the no anticoagulant group. Mortality or hospice was also stratified by preinjury agents and head AIS score, as seen in Table 2. Within the DOAC alone group, there was no significant difference between direct thrombin inhibitors (OR 1.16; 95% CI 0.37–3.64) or factor Xa inhibitors (OR 1.38; 95% CI 0.94–2.01) with regard to combined mortality or hospice when compared to patients on no anticoagulant.

Serious complications occurred in 11.8% of patients taking warfarin alone (OR 1.32; 95% CI 0.94–1.85) and to 6.9% of patients taking DOACs alone (OR 1.15; 95% CI 0.69–1.92) as compared to no anticoagulant (Table 3). There was no difference in the need for surgery between the warfarin and DOAC alone groups (warfarin OR 0.79; 95% CI 0.60–1.04; DOAC OR 1.31; 95% CI 0.73–2.36). However, patients on warfarin alone were significantly more likely to receive FFP infusions (OR 9.48; 95% CI 5.37–16.70) compared to patients on no anticoagulant, whereas patients taking DOACs alone (OR 1.06; 95% CI 0.30–3.77) were not. Warfarin alone patients received an average of 2.3 units of FFP transfusions for anticoagulation reversal. Preinjury warfarin therapy was also associated with a longer hospital LOS as compared to DOACs (6.7 days vs. 5.2 days, $p<0.001$, respectively). After risk adjustment, patients taking warfarin alone as compared to no anticoagulant were expected to have a significantly longer LOS (+0.43 days, 95% CI 0.09–0.78 days); although the expected difference in LOS for patients taking DOACs compared to no anticoagulant was longer, the results were not significantly different (+0.29 days, 95% CI −0.31 to 0.89 days).

Antiplatelet Outcomes

The antiplatelet group had 564 (17.1%) patients with an outcome of combined mortality or hospice as compared to 15.8% in the no anticoagulation group. After adjusting, there was no significant increased risk of combined mortality or hospice in the antiplatelet group as compared to patients on no anticoagulant (OR 1.13; 95% CI 0.94–1.36). There were 113 (27.3%) patients taking preinjury warfarin with an antiplatelet agent with the outcome of mortality or hospice and after adjustment this remained significantly increased as compared to no anticoagulation (OR 1.61; 95% CI 1.18–2.21). Patients taking a DOAC with an antiplatelet agent had a 19.0% rate of combined mortality or hospice, which was not significantly higher than no anticoagulation (OR 0.93; 95% CI 0.46–1.87).

Preinjury antiplatelet agents alone were associated with an increased risk of serious complications (OR 1.30; 95% CI 1.07–1.58), but

Table 1. Baseline Characteristics

	None (N=3632)	Warfarin (N=669)	Warfarin + AP (N=414)	DOAC (N=188)	DOAC + AP (N=116)	p
Age, years ± SD	80.3 ± 8.7	81.1 ± 7.8	81.2 ± 7.4	81.2 ± 7.7	80.8 ± 6.9	< 0.001
Female, n (%)	1919 (52.8)	314 (46.9)	143 (34.5)	99 (52.7)	49 (42.2)	< 0.001
Race, n (%)						
White	3156 (86.9)	616 (92.1)	379 (91.5)	179 (95.2)	107 (92.2)	< 0.001
Black	348 (9.6)	37 (5.5)	29 (7.0)	8 (4.3)	6 (5.2)	
Other	128 (3.5)	16 (2.4)	6 (1.4)	1 (0.5)	3 (2.6)	
Uninsured, n (%)	80 (2.2)	9 (1.3)	4 (1.0)	2 (1.1)	0 (0.0)	< 0.001
OSH, n (%)	1093 (30.1)	223 (33.3)	128 (30.9)	39 (20.7)	32 (27.6)	0.027
ISS, n (%)						
5–15	1549 (42.6)	222 (33.2)	132 (31.9)	85 (45.2)	44 (37.9)	< 0.001
16–24	1229 (33.8)	226 (33.8)	137 (33.1)	55 (29.3)	35 (30.2)	
25–35	835 (23.0)	217 (32.4)	143 (34.5)	47 (25.0)	37 (31.9)	
> 35	19 (0.5)	4 (0.6)	2 (0.5)	1 (0.5)	0 (0.0)	
AIS head, n (%)						
3	1740 (47.9)	249 (37.2)	141 (34.1)	91 (48.4)	48 (41.4)	< 0.001
4	1140 (31.4)	215 (32.1)	134 (32.4)	52 (27.7)	36 (31.0)	
5	752 (20.7)	205 (30.6)	139 (33.6)	45 (23.9)	32 (27.6)	
AIS > 2, n (%)						
Chest	156 (4.3)	24 (3.6)	10 (2.4)	8 (4.3)	3 (2.6)	0.41
Abdomen	11 (0.3)	2 (0.3)	0 (0.0)	1 (0.5)	1 (0.9)	0.69
Extremity	97 (2.7)	14 (2.1)	4 (1.0)	2 (1.1)	4 (3.4)	0.22
GCS motor, n (%)						
6	2705 (74.5)	490 (73.8)	309 (74.6)	144 (76.6)	83 (71.6)	0.087
5–2	372 (10.2)	70 (10.5)	35 (8.5)	17 (9.0)	12 (10.3)	
1	173 (4.8)	39 (5.8)	29 (7.0)	7 (3.7)	5 (4.3)	
Missing	382 (10.5)	70 (10.5)	41 (9.9)	20 (10.6)	16 (13.8)	
ED HR (bpm)						
> 120	93 (2.6)	22 (3.3)	14 (3.4)	6 (3.2)	2 (1.7)	0.048
51–120	3402 (93.7)	620 (92.7)	384 (92.8)	170 (90.4)	175 (90.5)	
0–50	54 (1.5)	6 (0.9)	5 (1.2)	5 (2.7)	1 (0.9)	
ED SBP (mmHg)						
> 90	3495 (96.2)	635 (94.9)	399 (96.4)	178 (94.7)	106 (91.4)	0.003
≤ 90	1 (1.4)	11 (1.6)	7 (1.7)	2 (1.1)	0 (0.0)	
Ventilator, n (%)	871 (24.0)	245 (36.6)	128 (30.9)	43 (22.9)	36 (31.0)	< 0.001
Comorbidities, n (%)						
CVA	147 (4.0)	48 (7.2)	24 (5.8)	19 (10.1)	13 (11.2)	< 0.001
COPD	348 (9.6)	102 (15.2)	60 (14.5)	21 (11.2)	15 (12.9)	< 0.001
Renal failure	77 (2.1)	22 (3.3)	15 (3.6)	2 (1.1)	4 (3.4)	0.140
CHF	183 (5.0)	100 (14.9)	81 (19.6)	21 (11.2)	17 (14.7)	< 0.001
Current smoker	258 (7.1)	27 (4.0)	18 (4.3)	9 (4.8)	4 (3.4)	0.006
Dementia	843 (23.2)	99 (14.8)	67 (16.2)	47 (25.0)	18 (15.5)	< 0.001
Diabetes	742 (20.4)	163 (24.4)	161 (38.9)	43 (22.9)	33 (28.4)	< 0.001
Disseminated cancer	49 (1.3)	14 (2.1)	5 (1.2)	2 (1.1)	1 (0.9)	0.018
FDHS	683 (18.8)	150 (22.4)	80 (19.3)	52 (27.7)	39 (33.6)	< 0.001
History of MI	39 (1.1)	5 (0.7)	21 (5.1)	0 (0.0)	1 (0.9)	< 0.001
Hypertension	2178 (60.0)	488 (72.9)	329 (79.5)	135 (71.8)	94 (81.0)	< 0.001
Liver disease	37 (1.0)	3 (0.4)	4 (1.0)	1 (0.5)	0 (0.0)	0.003

AIS = abbreviated injury scale; BP = blood pressure; BPM = beats per minute; CHF = congestive heart failure; COPD = chronic obstructive pulmonary disorder; CVA = cerebrovascular accident; DOAC = direct oral anticoagulant; ED = emergency department; FDHS = functionally dependent health status; GCS = Glasgow coma score; HR = heart rate; ISS = injury severity score; MI = myocardial infarction; No AC = no anticoagulant; OSH = outside hospital; SBP = systolic blood pressure; SD = standard deviation.

were not associated with an increased need for a surgery (OR 0.89; 95% CI 0.71–1.12). Platelet transfusions for reversal were common in the antiplatelet alone group (OR 4.11; 95% CI 2.45–6.88) compared to the no anticoagulant group.

Discussion

This large multicenter study of 8312 older adults from the MTQIP database evaluated outcomes following TBI in older adults with preinjury use of anticoagulant and/or antiplatelet

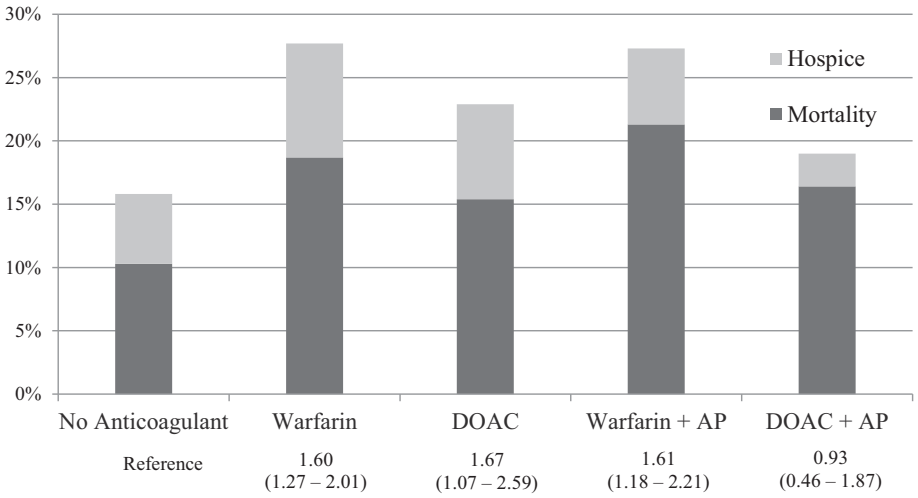

Figure 2. Mortality or hospice. AOR = adjusted odds ratio; AP = antiplatelet agent; DOAC = direct oral anticoagulant.

Table 2. Mortality or Hospice Stratified by Head AIS

Cohort	Mortality/ Hospice (%)	p-Value[a]
AIS head – 3		
No anticoagulant, n (%)	64 (3.7)	< 0.001
Antiplatelet, n (%)	67 (4.5)	
DOAC alone, n (%)	12 (8.6)	
Warfarin alone, n (%)	29 (7.4)	
AIS head – 4		
No anticoagulant, n (%)	81 (7.1)	< 0.001
Antiplatelet, n (%)	58 (5.4)	
DOAC alone, n (%)	8 (9.1)	
Warfarin alone, n (%)	30 (11.5)	
AIS head – 5		
No anticoagulant, n (%)	229 (30.5)	< 0.001
Antiplatelet, n (%)	221 (30.5)	
DOAC alone, n (%)	28 (36.4)	
Warfarin alone, n (%)	144 (41.9)	

AIS = abbreviated injury score; DOAC = direct oral anticoagulant.
[a]Calculated using Pearson's chi-squared test.

agents. Preinjury warfarin use, as compared to no anticoagulant, was associated with a significant increase in mortality or discharge to hospice, serious in-hospital complications, and longer hospital LOS. Despite having the same mechanism of injury and age profile as the no anticoagulant patients, the preinjury warfarin cohort had significantly worse head injuries as evidenced by higher AIS head scores, lower admission GCS score, and more patients requiring ventilator support. This result is similar to and confirms the results found in previous evaluations of preinjury warfarin use.[22,26]

Direct oral anticoagulant use was also found to increase mortality or hospice in the adjusted analysis as compared to the no anticoagulation group. When compared directly to warfarin in the unadjusted analysis there was a statistically lower rate of mortality or hospice in the DOAC group. Unfortunately, sample sizes in our analysis were too small for an appropriately robust adjusted analysis comparing the two groups. However, many previous studies of trauma patients have yielded similar results. A study of 162 patients on preinjury anticoagulant therapy with blunt traumatic injuries and an AIS head score of < 4 found a significantly lower mortality in patients taking DOACs (4.9%) as compared to warfarin (20.8%).[27] Similarly, a study looking at 186 older adults with TBI on preinjury anticoagulants and found an increased in-hospital mortality with warfarin as compared to DOACs despite adequate reversal agent administration in the warfarin group.[28] Our study, as well as those previously reported, should serve as hypothesis generating for a larger analysis directly comparing preinjury warfarin to DOAC.

Table 3. Unadjusted Study Outcomes

	No Anticoagulant	Antiplatelet	DOAC Alone	Warfarin Alone	p-Value
Serious complications, n (%)	243 (6.7)	270 (8.2)	13 (6.9)	79 (11.8)	< 0.001
Surgery, n (%)	579 (16.6)	498 (15.3)	34 (18.1)	141 (21.6)	0.002
Hospital LOS, days ± SD	5.6 ± 5.7	5.6 ± 5.9	5.2 ± 4.6	6.7 ± 7.4	< 0.001
ICU LOS, days ± SD	4.2 ± 4.6	4.2 ± 8.0	3.5 ± 3.4	4.4 ± 4.8	0.48

DOAC = direct oral anticoagulant; ICU = intensive care unit; LOS = length of stay.

The finding that preinjury warfarin and DOAC use yielded similar hospital outcomes following TBI when compared to patients taking no anticoagulation or antiplatelet agents, is especially interesting given the lack of dedicated reversal agent for DOACs during our study period. Both idarucizumab and andexanet alfa were not available during the entirety of our study period so this data was unable to be included. PCC products have been recommended in national guidelines as a potential hemostatic agent for DOACs with small human studies showing variable efficacy.[29–32]

This study of preinjury DOACs represents data from before commercially available reversal agents such as andexanet alfa.[33] One hypothesis for preinjury DOAC outcomes not appearing worse than warfarin despite the lack of specific reversal agents could be that patients were receiving only a partial or minimal reversal with PCC agents. Studies of severe TBI have found that the coagulation cascade is dramatically altered due to large release of tissue factor and other micro particles.[34] It is possible that residual DOAC inhibition of the clotting cascade after partial reversal may help reverse early hypercoagulability in TBI. Future studies are needed to determine the clinical outcomes of patients with TBI taking preinjury DOAC reversed with idarucizumab and andexanet alfa. Previous studies have also suggested that preinjury warfarin use is a significant risk factor for delayed new or worsening hemorrhage which could also be responsible for the results found in this study.[35] It is unknown based on the current literature whether this same risk applies to preinjury DOACs.

Due to the lack of an available DOAC reversal agent until recently, it is possible that there could be a prescribing bias in outpatients to use warfarin in individuals deemed to be frail or at high risk for falls. Although it is impossible to account for this completely in an observational study, we attempted to control for baseline comorbidities. Functionally dependent health status upon admission was also used a surrogate for frailty and was more prevalent in the DOAC population than warfarin. Pre-admission DNR was also recorded, with the DOAC population having a higher prevalence than warfarin. Patients who were anticoagulated were much more likely to have a history of stroke, COPD, and hypertension than patients not on a preinjury anticoagulant. This difference is unavoidable in an observational study, which emphasized the need for our use of a robust multivariate regression analysis.

Patients presenting with a TBI on antiplatelet agents were also found to have similar outcomes to patients taking no anticoagulants prior to injury. To our knowledge, this study of 3293 TBI patients taking preinjury antiplatelet agents is the largest analysis of its kind in TBI patients and expands upon the results of previous literature. A retrospective study of 364 patients with TBI on antiplatelet agents by Sumiyoshi and colleagues found on univariate analysis a significant association with in-hospital mortality. However, once entered into multivariate analysis this effect was not present.[36] Another large retrospective analysis at a single center of 1051 patients on antiplatelet agents found no difference in hospital outcomes whether single or dual antiplatelet therapy was used preinjury in elderly TBI patients.[8] Although a significant limitation is that information is not available on outcomes for specific antiplatelet agents, the results of our study appear to confirm that preinjury antiplatelet agents as a whole do not worsen outcomes following TBI.

To help isolate the effects of head injuries and minimize mortality associated with injuries to other organ systems, patients were included in this analysis if their mechanism of injury was a low-level fall. Very few patients presented with an AIS score> 2 in any organ system besides head, so all morbidity and mortality seen can likely be attributed to the TBI. We also aimed to consider pre-admission DNR as a contributing factor, especially since this study was evaluating mortality in a geriatric population. DNR status was not included in the risk adjustment, despite it being an important consideration, because extensive data validation performed within MTQIP has discovered that there is poor adherence to the DNR status definition making it an unreliable variable.

The primary limitation of this study is its observational design. However, the nature of the study question is not conducive to a prospective study where patients are randomized prior to a traumatic injury. MTQIP is a large multicenter registry with prospectively collected data that is submitted with frequent audits making it a high quality of evidence. Although the statistical analysis was designed with small sample sizes in mind, it remains a limitation that there may not have been enough patients in the anticoagulant groups to answer the study question definitively. There was also a disparity in the number of

patients who presented on preinjury warfarin as compared to DOACs. It is likely that there are important factors at play that influenced prescribing patterns that are unable to be discerned by this analysis. For example, more patients in the preinjury DOAC group presented with a DNR order, which could be a surrogate for greater health literacy. It is possible that there are differences between these two groups in access to care, high risk clinical features, or other important variables that favor one type of anticoagulant over the other.

Another significant limitation of this study is the absence of coagulation laboratory tests upon admission and reversal agents administered. MTQIP began mandatory reporting of this data in January 2018 which made it unavailable for a significant time period within our study. Degree of anticoagulation as well as reversal has been shown previously to predict adverse outcomes with preinjury warfarin.[37,38] A study by Pieracci and colleagues looking at 40 patients on preinjury warfarin, including 22 within the therapeutic range, found that overall mortality was increased in the therapeutic warfarin group as compared to patients taking warfarin with subtherapeutic International Normalized Ratio (INR) levels.[39] There have also been previous studies that have found conflicting results of preinjury warfarin not having any significant effects on outcomes following head injuries.[40,41] The availability of INR values for our present study would have helped to shed light on these conflicting results.

Patient data were collected from level 1 and 2 trauma centers from across the state of Michigan. Despite the heterogeneity of this design the results may not be applicable to other regions of the country or non-designated trauma centers. Another significant limitation is that cause of death during the hospitalization was not able to be discerned in the database.

Conclusion

Older adult patients aged 65 years or greater presenting with a TBI on preinjury warfarin were found to have an increase in mortality or hospice, serious complications, and use of hospital resources as compared to no anticoagulation. Preinjury DOAC agents, including factor Xa and direct thrombin inhibitors, also showed a higher rate of mortality or hospice and serious complications as compared to no anticoagulation. Future studies are needed with larger sample sizes to directly compare outcomes with preinjury warfarin directly to DOACs.

Acknowledgments

The authors would like to acknowledge the following MTQIP Members for their commitment to improving patient care through participation in MTIQP and collection of the data utilized in this study: John Fath, James Wagner, Cara Seguin, Tracey Stockinger, Sharon Morgan, and Gail Colton, of Beaumont Hospital – Dearborn; Allan Lamb, Kathy Franzen, Ramona Dinu, and Heather Payton, of Beaumont Hospital – Trenton; Michael Rebock, Barb Smith, Catherine Levinson, Corinna Azar, and Robin Lebeis, of Beaumont Hospital – Farmington Hills; Randy Janczyk, Michelle Schnedler, Holly Bair, and Shannon Zientek, of Beaumont Hospital – Royal Oak; Tom Rohs, Sally Ossewaarde, Sabrina Luke, and Jodie Vining, of Ascension Borgess Hospital; Scott Davidson, Rita Cox, Patricia Benoit, Krisann Woodley, Tonya King-Stratton, Loretta Farrell, Mary Loney, and Dominique Termaat, of Bronson Methodist Hospital; Sujal Patel, Debbie Falkenberg, Kenda Parker, Kristin Wolfgang, Julie Macdougall, and Deanne Krajkowski, of Covenant HealthCare; Anna Ledgerwood, Maidei Munemo, Lisa Salerno, La Toya Kimbrough, Greta Eagger, and Katherine Dhue, of Detroit Receiving Hospital; Brian Shapiro, Zachary Landers, Jennifer Sunderman, and Raquel Yapchai, of Genesys Regional Medical Center; Jeffrey Johnson, Andrea Nelson, Cheryl Church, and Velma Cuevas, of Henry Ford Hospital; Scott Barnes, Chris McEachin, Michelle Schwarb, and Rose Morrison, of Henry Ford Macomb Hospital; Leo Mercer, Mike McCann, Michelle Maxson, Gloria Lahoud, Shirley Ulmer, and Amber Dombrowski, of Hurley Medical Center; Nicholas Nunnally, Ashley Brown, Alisha Sholtis, and Erin Veit, of McLaren Lapeer Region; Mandip Atwal, Susan Schafer, Marita Vandenberg, Leslie Frezza, and April Pizzo, of McLaren Macomb; John Ketner, Courtney Berry, Megan Wright, and Carolyn Ivan, of McLaren Oakland; Thomas Veverka, Shari Meredith, Tom Wood, Michelle Abedrabo, Teresa Rollin, and Lori Coppola, of MidMichigan Health; Steven Slikkers, Shamarie Regenold, Tanya Jenkins, Allen Stout, and Jill Jean, of Munson Healthcare; Peter Lopez, Joann Burrington, Rebecca Steele, and Carly Callahan, of Providence Hospital; Marco Hoesel, Gwyneth Navas, Melissa Keller, Lisa Zanardelli, TiJuan Davis, Danielle Finn, and Patricia Danhoff, of Sinai-Grace Hospital; John Kepros, Penny Stevens, Kristen Jorae, Paige Harakas, Christopher Stimson, and Maria Maier, of Sparrow Health System; Gaby Iskander, Amy Koestner, Jennifer Haverkamp, Kathy Crystal, Elizabeth Delrue, Gayle Mack, Kristen Thornton, and Kelly Burns, of Spectrum Health; Wayne Vanderkolk, Sherri Veurink-Balicki, Kristi Diephouse, and Coleen Kelly, of Mercy Health Saint Mary's; Joseph Buck, Karrie Brown, Melissa Cunningham, Melissa Jeffrey,

Marie Westfall, and Kathleen Waderlow, of St. John Hospital; Wendy Wahl, Mary-Margaret Brandt, Kathy Kemph, Donna Tommelein, Nancy Hofman, and Rebecca Peterson, of St. Joseph Mercy Ann Arbor; Alicia Kieninger, Carol Spinweber, Michele Hunt, and Ellen Noone-Eustice, of St. Joseph Mercy Oakland; Thomas Oweis, Rick Ricardi, Mikki Favor, Jessica Landry, and Ruth Vernacchia, of St. Mary Mercy Livonia Hospital; Samer Kais, Kerri Chernauckas, Kelly Bourdow, Erin Perdue, and Nancy Walter, of St. Mary's of Michigan; Cindy Wegryn, Chris Wagner, Sara Samborn, and Diane Tuttle-Smith, of Michigan Medicine; Larry Lewis, Tammy Luoma, Jodi McCollum, Sarah Sutter, and Lisa Taylor, of UP Health System Marquette.

References

1. Table 10, Committee on Trauma, American College of Surgeons. NTDB Annual/Pediatric Report 2016. Chicago, IL.
2. **Taylor CA, Bell JM, Breiding MJ, Xu L.** Traumatic brain injury–related emergency department visits, hospitalizations, and deaths – United States, 2007 and 2013. MMWR Surveill Summ 2017;66(9):1–16.
3. **CDC.** Injury and traumatic brain injury (TBI)-related death rates, by age group – United States, 2006. MMWR 2010;59:303.
4. **Dimaggio C, Ayoung-Chee P, Shinseki M, et al.** Traumatic injuries in the United States: in-patient epidemiology 2000–2011. Injury 2016;47(7):1393–403.
5. **Lane DA, Skjoth F, Lip GYH, Larsen TB, Kotecha D.** Temporal trends in incidence, prevalence, and mortality of atrial fibrillation in primary care. J Am Hearst Assoc 2017;6(5): e005155.
6. **Heit JA, Spencer FA, White RH.** The epidemiology of venous thromboembolism. J Thromb Thrombolysis 2016;41:3–14.
7. **Tollefsen MH, Vik A, Skandsen T, et al.** Patients with moderate and severe traumatic brain injury: impact of preinjury platelet inhibitor or warfarin treatment. World Neurosurg 2018;114:e209–17.
8. **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 (3):614–21.
9. **Franko J, Kish K, O'Connell BG, Subramanian S, Yuschak JV.** Advanced age and preinjury warfarin anticoagulation increase the risk of mortality after head trauma. J Trauma Acute Care Surg 2006;61:107–10.
10. **LaDuke ZL, Hecht JP, Cain-Nielsen AH, Hemmila MR, Wahl WL.** Association of mortality among trauma patients taking preinjury direct oral anticoagulants versus vitamin K antagonists. Surgery 2019;166(4):564–71.
11. **Lakkireddy DR, Karst E, Mahapatra S, Winterfield JR, Mansour M.** *Heart Rhythm* 2018, Abstract B-LBCT02-03.
12. **Benzimra M, Bonnamour B, Duracinsky M, et al.** Real-life experience of quality of life, treatment satisfaction, and adherence in patients receiving oral anticoagulants for atrial fibrillation. Patient Prefer Adher 2018;12:79–87.
13. **Barnes GD, Lucas E, Alexander GC, Goldberger ZD.** National trends in ambulatory oral anticoagulant use. Am J Med 2015;128(12):1300–5.e2.
14. **Connolly SJ, Ezekowitz MD, Yusuf S, et al.** Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med 2009;361(12):1139–51.
15. **Granger CB, Alexander JH, McMurray JJ, et al.** Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med 2011;365(11):981–92.
16. **Patel MR, Mahaffey KW, Garg J, et al.** Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med 2011;365(10):883–91.
17. **Dentali F, Riva N, Crowther M, Turpie AGG, Lip GYH, Ageno W.** Efficacy and safety of the novel oral anticoagulants in atrial fibrillation: a systemic review and meta-analysis of the literature. Circulation 2012;126:2381–91.
18. **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(5):463–73.
19. **Batey M, Hecht J, Callahan C, Wahl W.** Direct oral anticoagulants do not worsen traumatic brain injury after low-level falls in the elderly. Surgery 2018;164(4):814–9.
20. **Wood B, Nascimento B, Rizoli S, et al.** Anticoagulated trauma patient in the age of the direct oral anticoagulants: a Canadian perspective. Scand J Trauma Resusc Emerg Med 2017;25 (1):76.
21. **Zeeshan M, Jehan F, O'Keeffe T, et al.** The novel oral anticoagulants have worse outcomes compared with warfarin in patients with intracranial hemorrhage after TBI. J Trauma Acute Care Surg 2018;85(5):915–20.
22. **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 Acute Care Surg 2017;83:827–35.
23. **Hemmila MR, Jakubus JL.** Trauma quality improvement. Crit Care Clin 2017;33:193–212.
24. **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 Acute Care Surg 2012;73:1086–92.
25. **Hemmila MR, Jakubus JL, Cain-Nielsen AH, et al.** The Michigan trauma quality improvement program: results from a collaborative quality initiative. J Trauma 2017;82:867–76.
26. **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(4):652–7.
27. **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.
28. **Prexl O, Bruckbauer M, Voelckel W, et al.** The impact of direct oral anticoagulants in traumatic brain injury patients greater than 60-years-old. Scand J Trauma Resusc Emerg Med 2018;26:20.
29. **Tomaselli GF, Mahaffey KW, Cuker A, et al.** 2017 ACC expert consensus decision pathway on management of bleeding in patients on oral anticoagulants: a report of the American College of Cardiology Task Force on Expert Consensus Decision Pathways. J Am Coll Cardiol 2017;70:1–26.
30. **Grandhi R, Newman WC, Zhang X, et al.** Administration of 4-factor prothrombin complex concentrate as an antidote for intracranial bleeding in patients taking direct factor Xa inhibitors. World Neurosurg 2015;84:1956–61.
31. **Zheng Y, Tormey C.** The use of 4F-PCC to correct direct oral anticoagulant-induced coagulopathy: an observational analysis. Blood 130(Suppl 1), 4912.
32. **Majeed A, Agren A, Holmstrom M, et al.** Management of rivaroxaban or apixaban associated major bleeding with prothrombin complex concentrates: a cohort study. Blood 2017;130:1706–12.
33. **Siegal DM, Curnutte JT, Connolly SJ, et al.** Andexanet alfa for the reversal of factor Xa inhibitor activity. NEJM 2015;373:2413–24.
34. **Huang M, Hu Y, Dong X.** High concentrations of procoagulant microparticles in the cerebrospinal fluid and peripheral blood of patients with acute basal ganglia hemorrhage are associated with poor outcome. Surg Neurol 2009;72(5):481–9.
35. **Menditto VG, Lucci M, Polonara S, Pomponio G, Gabrielli A.** Management of minor head injury in patients receiving oral anticoagulant therapy: a prospective study of a 24-hour observation protocol. Ann Emerg Med 2012;59(6):451–5.
36. **Sumiyoshi K, Hayakawa T, Yatsushige H.** Outcome of traumatic brain injury in patients on antiplatelet agents: a

retrospective 20-year observational study in a single neurosurgery unit. Brain Inj 2017;31(11):1445–54.
37. **Falzon CM, Celenza A, Chen W, Lee G.** Comparison of outcomes in patients with head trauma, taking preinjury antithrombotic agents. Emerg Med J 2013;30(10):809–14.
38. **Herou E, Romner B, Tomasevic G.** Acute traumatic brain injury: mortality in the elderly. World Neurosurg 2015;83 (6):996–1001.
39. **Pieracci FM, Eachempati SR, Shou J, Hydo LJ, Barie PS.** Degree of anticoagulation, but not warfarin use itself, predicts adverse outcomes after traumatic brain injury in elderly trauma patients. J Trauma 2007;63(3):525–30.
40. **Ahmed N, Bialowas C, Kuo YH, Zawodniak L.** Impact of preinjury anticoagulation in patients with traumatic brain injury. South Med J 2009;102(5):476–80.
41. **Fortuna GR, Mueller EW, James LE, Shutter LA, Butler KL.** The impact of preinjury antiplatelet and anticoagulant pharmacotherapy on outcomes in elderly patients with hemorrhagic brain injury. Surgery 2008;144(4):598–605.

Supporting Information

The following supporting information is available in the online version of this paper:

Table S1A. Example of first-stage multivariable logistic regression model used to create risk score, with mortality or hospice as the dependent variable.

Table S1B. Example of second-stage multivariable logistic regression model to assess the effect of anticoagulant/antiplatelet use, with mortality or hospice as the dependent variable.