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

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ABSTRACT

Background: Warfarin has been the oral anticoagulant of choice for the treatment of thromboembolic disease. However, upwards of 50% of all new anticoagulant prescriptions are now for direct oral anticoagulants (DOAC). Despite this, outcome data evaluating preinjury anticoagulants remains 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 was obtained from 29 level 1 and 2 trauma centers from 2012 to June 30, 2018. Overall, 8312 patients who were aged65 years or older, suffering a ground level fall, and with an Abbreviated Injury Scale score (AIS)-head 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.

Keywords: Traumatic brain injury, Anticoagulants, Antiplatelet agents, Factor Xa Inhibitors, Warfarin

INTRODUCTION

Older adults account for upwards 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

MTQIP 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 four-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 was extracted from the MTQIP database and the study cohort consists 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 is a composite outcome which 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 need 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 (**Supplement**). Odds ratios (OR) as well as confidence intervals (CI) 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 was performed by a biostatistician using Stata 15.0 (StataCorp, College Station, TX). Statistical significance was defined as a p-value < 0.05. Average values are expressed as the mean ± 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 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 preadmission 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 alonewere 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 to 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 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 multi-center study of 8312 older adults from the MTQIP database evaluated outcomes following TBI in older adults with preinjury use of anticoagulant and/or antiplatelet 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]

DOAC 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] Similiarly, 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.

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 was 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.

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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, No (%)	1919 (52.8)	314 (46.9)	143 (34.5)	99 (52.7)	49 (42.2)	<0.001
Race, No (%)						
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, No (%)	80 (2.2)	9 (1.3)	4 (1.0)	2 (1.1)	0 (0.0)	<0.001
OSH, No (%)	1093 (30.1)	223 (33.3)	128 (30.9)	39 (20.7)	32 (27.6)	0.027
ISS, No (%)						
5-15	1549 (42.6)	222 (33.2)	132 (31.9)	85 (45.2)	44 (37.9)	
16-24	1229 (33.8)	226 (33.8)	137 (33.1)	55 (29.3)	35 (30.2)	<0.001
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, No (%)						
3	1740 (47.9)	249 (37.2)	141 (34.1)	91 (48.4)	48 (41.4)	
4	1140 (31.4)	215 (32.1)	134 (32.4)	52 (27.7)	36 (31.0)	<0.001
5	752 (20.7)	205 (30.6)	139 (33.6)	45 (23.9)	32 (27.6)	
AIS >2, No (%)						

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, No (%)						
6	2705 (74.5)	490 (73.8)	309 (74.6)	144 (76.6)	83 (71.6)	
5-2	372 (10.2)	70 (10.5)	35 (8.5)	17 (9.0)	12 (10.3)	0.087
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)	
51-120	3402 (93.7)	620 (92.7)	384 (92.8)	170 (90.4)	175 (90.5)	0.048
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	51 (1.4)	11 (1.6)	7 (1.7)	2 (1.1)	0 (0.0)	
Ventilator, No (%)	871 (24.0)	245 (36.6)	128 (30.9)	43 (22.9)	36 (31.0)	<0.001
Comorbidities,No (%)						
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

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

Table 2. Mortality or Hospice Stratified by Head AIS

AIS Head – 3		
Cohort	Mortality/Hospice	p-value*
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		
Cohort	Mortality/Hospice	p-value*
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		
Cohort	Mortality/Hospice	p-value*
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%)	

* Calculated using Pearsons Chi-Squared test

Abbreviations: AIS, abbreviated injury score; DOAC, direct oral anticoagulant

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

Abbreviations: DOAC, direct oral anticoagulant; LOS, length of stay; ICU, intensive care unit

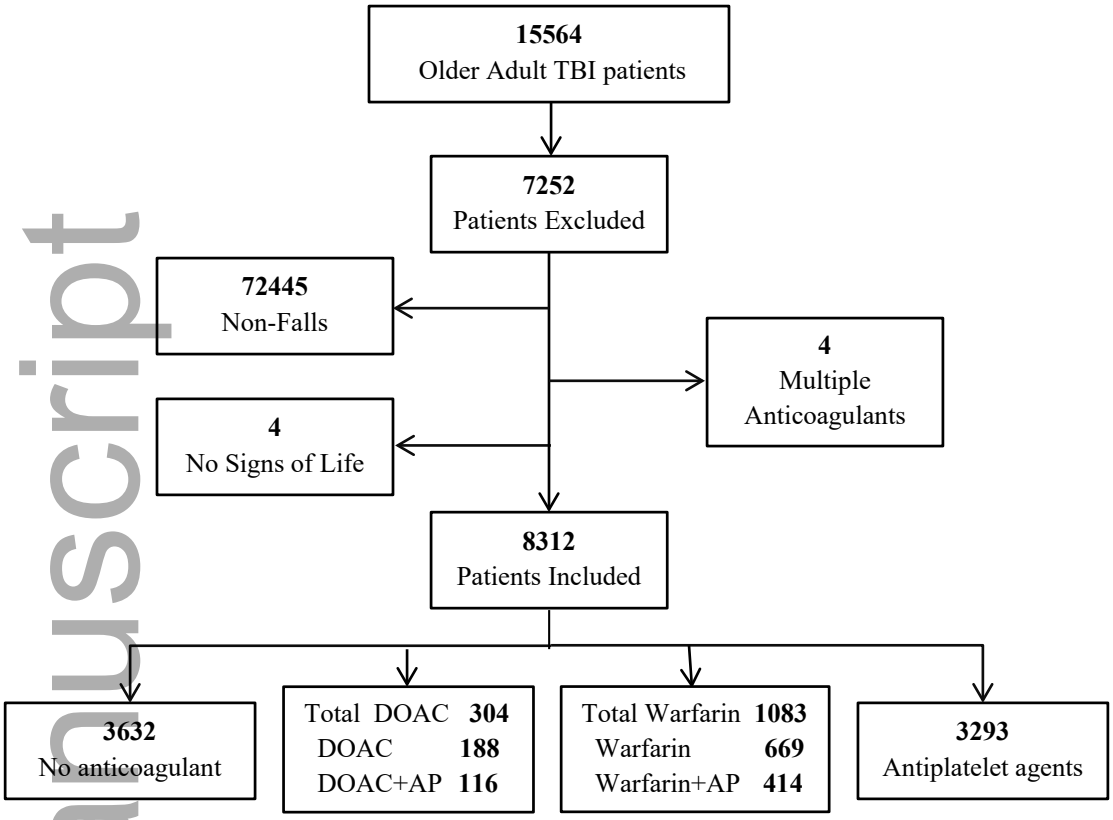
Figure 1 Legend:

Abbreviations: TBI, traumatic brain injury; DOAC, direct oral anticoagulant.

Figure 2 Legend:

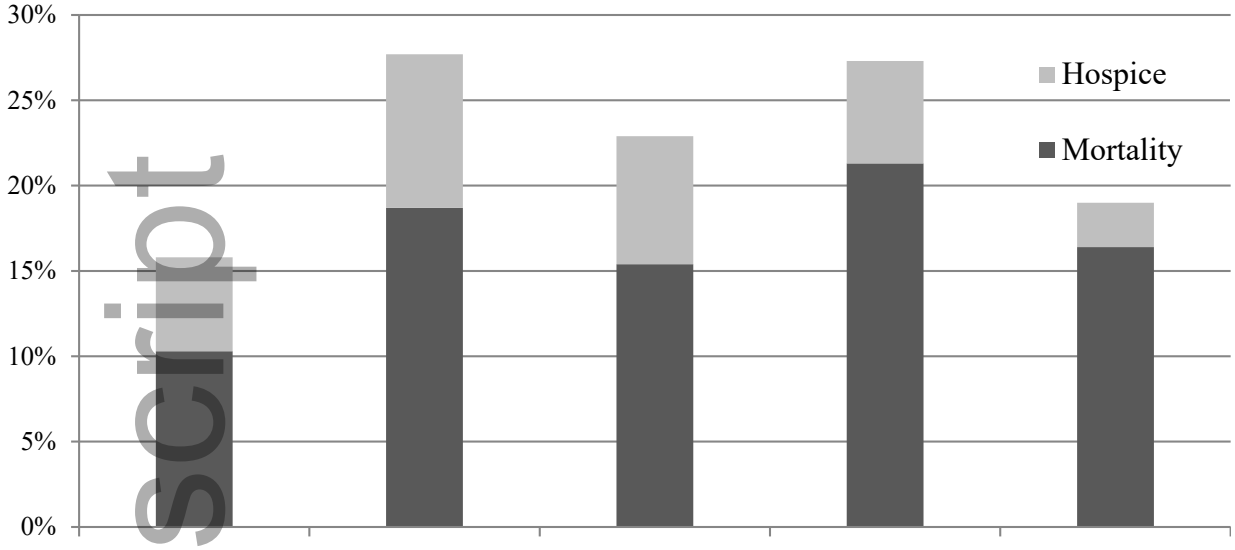
Abbreviations: AOR, adjusted odds ratio

Figure 1. Study Population



Abbreviations: TBI, traumatic brain injury; DOAC, direct oral anticoagulant; AP, antiplatelet agent

Figure 2. Mortality or Hospice



	No Anticoagulant	Warfarin	DOAC	Warfarin + AP	DOAC + AP
AOR (95% CI)	Reference	1.60 (1.27 – 2.01)	1.67 (1.07 – 2.59)	1.61 (1.18 – 2.21)	0.93 (0.46 – 1.87)

Abbreviations: AOR, adjusted odds ratio; DOAC, direct oral anticoagulant; AP, antiplatelet agent