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Original Article

Outcomes of Elderly Patients on Direct Oral Anticoagulants (DOACs) Versus Warfarin After Traumatic Brain Injury

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ABSTRACT: ***Background:*** Although evidence supports the improved safety profile of direct oral anticoagulants (DOACs) over warfarin (WF), outcomes among elderly traumatic brain injury (TBI) patients on this regimen remain unclear. This study describes the association between anticoagulation status (DOAC vs. WF use) and the rates of occurrence of intracranial hemorrhage (ICH), hematoma progression, need for surgical intervention and mortality in elderly TBI cases. ***Methods:*** This retrospective cohort study from 2014 to 2019 included all trauma patients > 65 years on either WF or DOACs at the time of injury. The primary outcome was the rate of ICH after TBI. Multivariable regression analysis identified independent predictors of functional dependency and mortality. ***Results:*** A total of 501 elderly TBI patients (mean age = 82 years old) were included. WF users had higher CT Marshall scores *($p = 0.007$)*, more severe TBI (GCS < 8) *($p = 0.003$)* and higher rates of subdural hematomas compared to the DOAC group *($p = 0.003$)*. Patients on DOACs had lower rates of ICH *(42% vs. 57%, $p = 0.001$)* and hospitalization *(30% vs. 41%, $p = 0.013$)* and better Glasgow outcome scale-extended scores at hospital discharge *(mean 6.98 vs. 6.41, $p = 0.005$)*. Multicompartment ICH *(OR 2.30, $p = 0.027$)* and longer hospitalization *(OR 0.04, $p < 0.001$)* were associated with higher functional dependency rates, while higher CT Marshall scores *(OR 1.09, $p < 0.001$)* and poorer baseline frailty status *(OR 0.62, $p = 0.026$)* predicted increased mortality risk. ***Conclusion:*** Elderly TBI patients on DOACs have lower rates of ICH, lower need for hospitalization and better functional outcomes at discharge compared to those taking WF. These findings need further confirmation using prospective multicenter studies.

RÉSUMÉ : Anticoagulants oraux directs (AOD) ou warfarine : résultats après un trauma crânien chez les personnes âgées. ***Contexte :*** Certes, des données probantes étayent la supériorité de l'innocuité des anticoagulants oraux directs (AOD) sur celle de la warfarine, mais les résultats de ces types de traitement anticoagulant chez les personnes âgées ayant subi un trauma crânien (TC) restent obscurs. L'étude visait donc à établir des associations entre le type de traitement anticoagulant (AOD contre warfarine) et les taux d'hémorragie intracrânienne (HIC), d'évolution de l'hématome, de chirurgie et de mortalité dans les cas TC chez les personnes âgées. ***Méthode :*** Il s'agit d'une étude rétrospective de cohorte, couvrant la période de 2014 à 2019 et comprenant tous les patients âgés de plus 65 ans traités par la warfarine ou par les AOD au moment du trauma. Le principal critère d'évaluation était le taux d'HIC après le TC. Une analyse de régression multivariée a permis de dégager des facteurs prévisionnels indépendants de dépendance fonctionnelle et de mortalité. ***Résultats :*** Ont été retenus au total les dossiers de 501 personnes âgées ayant subi un TC (âge moyen : 82 ans). Les patients traités par la warfarine avaient des résultats plus élevés selon la classification TDM de Marshall *($p = 0{,}007$)*, avaient subi un TC plus grave (échelle de Glasgow : < 8) *($p = 0{,}003$)* et connaissaient des taux plus élevés d'hématome sous-dural que les patients traités par les AOD *($p = 0{,}003$)*. Au contraire, ces derniers avaient des taux moins élevés d'HIC *(42 % contre [c.] 57 %; $p = 0{,}001$)* et d'hospitalisation *(30 % c. 41 %; $p = 0{,}013$)* ainsi que de meilleurs résultats sur l'échelle de devenir de Glasgow étendue (GOS-E) au moment du congé de l'hôpital *(moyenne : 6,98 c. 6,41; $p = 0{,}005$)* que les patients de l'autre groupe. Des HIC traversant différentes couches cérébrales *(risque relatif approché [RRA] : 2,30; $p = 0{,}027$)* et des durées d'hospitalisation prolongées *(RRA : 0,04; $p < 0{,}001$)* ont été associées à des taux supérieurs de dépendance fonctionnelle, tandis que des résultats plus élevés selon la classification TDM de Marshall *(RRA : 1,09; $p < 0{,}001$)* et un état aggravé de fragilité au départ *(RRA : 0,62; $p = 0{,}026$)* se sont révélés des facteurs prévisionnels de risque accru de mortalité. ***Conclusion :*** Les personnes âgées traitées par les AOD au moment du trauma ont connu des taux moins élevés d'HIC et des durées d'hospitalisation plus courtes, et obtenu de meilleurs résultats fonctionnels au moment du congé que celles traitées par la warfarine. Ces résultats restent à confirmer par des études prospectives multicentriques.

Keywords: Aging; brain injury – traumatic; critical care; cerebral trauma; neurotrauma

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Highlights

- Direct oral anticoagulant (DOAC) versus warfarin in the elderly population with traumatic brain injury. DOAC led to:
  - Lower rate of intracranial hemorrhage
  - reduced hospitalization needs
  - higher Glasgow outcome scale-extended score at discharge

Introduction

A significant portion of the population, especially older adults, is on anticoagulation or antiplatelet agents for various medical indications. In 2013 alone, US Medicare claims estimated that approximately two-thirds of patients with atrial fibrillation (AF) were on oral anticoagulation primarily in the form of warfarin (WF).[1] The prevalent use of these drugs has consequently led to an increase in the incidence of traumas involving the chronically anticoagulated patient.[2] As a result, numerous neurotrauma centers around the world are now facing the ramifications of this epidemiologic shift and are increasingly burdened with the care of elderly patients on anticoagulation.

Age-related changes in the brain (e.g., cerebral atrophy, dural adherence to the skull, cerebrovascular atherosclerosis and bridging vein fragility) in combination with anticoagulant therapy not only put older adults at high risk of developing intracranial bleeding but also predispose them to poorer outcomes after traumatic brain injury (TBI).[3,4] The management of geriatric TBI therefore requires a nuanced approach and must be guided by meticulous consideration of their complex comorbidities, higher frailty status and increased use of multiple medications, including anticoagulant use, in order to optimize post-injury neurological and functional outcomes. As emerging studies reveal a trend toward more widespread use of anticoagulation in TBI patients with radiological evidence of traumatic intracranial lesions than the general population, new evidence to support improved management and clinical prediction in the high-risk, anticoagulated elderly TBI patients is highly necessary.[5]

The most recent CHEST (American College of Chest Physicians) guidelines recommend the use of direct oral anticoagulants (DOACs) over WF in patients with AF, including those with advanced age.[6] DOACs like dabigatran, rivaroxaban and apixaban are increasingly preferred over WF, as they do not require monthly monitoring, have shorter half-lives, lower risks of fatal bleeding and fewer drug and food interactions.[7] Its use has been associated with decreased mortality compared with WF in the context of spontaneous intracranial hemorrhage (ICH);[8] however, the benefit of DOACs in the setting of traumatic ICH remains unknown.[9,10] Although large-scale randomized controlled trials (RCTs) demonstrate superior pharmacokinetic and pharmacodynamic profile of DOACs over WF, these studies tend to focus largely on younger patients with fewer comorbidities and medications.[11–13] Hence, the true risk of major life-threatening bleeding in elderly users, including those resulting from head trauma, remains underestimated. To address these issues, a retrospective review was performed to describe the pragmatic, real-world outcomes of geriatric trauma patients taking WF or DOAC using data from a large supraregional trauma center.

Methods

Study design, setting and ethics

This is a retrospective observational study of elderly patients who presented to the ED (emergency department) of a supraregional tertiary (level 1) trauma center between April 1, 2014, and March 31, 2019. The study was approved by the Research Ethics Board of the McGill University Health Centre and conducted in accordance with the standard operation procedure of the McGill University Health Centre Research Institute. Patient informed consent was waived for this retrospective epidemiologic study, but confidentiality of patient data was ensured throughout the process of data collection and analysis.

Data source

Information regarding ED visits was obtained using MedUrge, an ED information and database system of the Montreal General Hospital and the DSQ (Dossier Sante Quebec), a provincial database containing up-to-date information on the medication taken by patients. To ensure comprehensive data collection, an additional query was made from the TBI Program database, a local data bank for all admitted TBI patients and the Trauma Registry of the hospital, a prospectively maintained provincial-wide mandated injury surveillance system that contains information about all patients sustaining traumatic injuries. These registries are internally validated and checked by a trauma administrative technician.

Study population/data collection

To find all potential patients, we first used TBI-related search terms to generate a list of patients with at least one of these terms in their presenting story or diagnosis. From the generated list, we kept all those aged 65 years and above and then looked at their home medication at the time of presentation as listed in the ED documentation, medical chart and DSQ-listed medication. All those on oral anticoagulants at the time of trauma were included. Only the first ED visit during the study period was included for data analysis. Urgent visits due to medical emergencies or other nontraumatic ICH were not included. Trauma patients who were on heparin or antiplatelet therapy alone and those without any cranial imaging during admission were additionally excluded.

A standard set of data was obtained from an electronic database search including the medical identification number, age, gender, mechanism of injury, post-resuscitation Glasgow Coma Scale (GCS) score and comorbidities. All imaging details from cranial CT scan performed during admission were evaluated, and findings were cross-checked with official radiology reports. Morphological brain changes were assessed using the Marshall CT scoring, while overall injury severity was graded using the ISS (injury severity score) system. The modified frailty index-5 (mFI-5) score was used to quantify the frailty status of the study population.[14] This index is based on assessment of five domains (i.e., the presence of diabetes mellitus, hypertension, congestive heart failure, COPD/pneumonia and functional dependency), and patients were given 1 point for each factor. The total cumulative score serves as the mFI index with a score of 0 signifying a non-frail state and 5 as a severely frail status.

Exposure

The exposure variable of interest was anticoagulation status. The two levels of this dichotomous variable were either WF or DOACs (i.e., apixaban, dabigatran, rivaroxaban, etc.). To be classified as active users, patients must have these medications included in their current prescription covering the period before the index ED consultation. This information was ascertained from history taking, medication list entered in the triage and DSQ. The international normalized ratio (INR) values upon ED admission were also noted when available. Data on any concurrent antiplatelet and/or use of a reversal agent (i.e., prothrombin complex concentrate [PCCs], vitamin K) in the ED were extracted from in-patient medication and resuscitation records.

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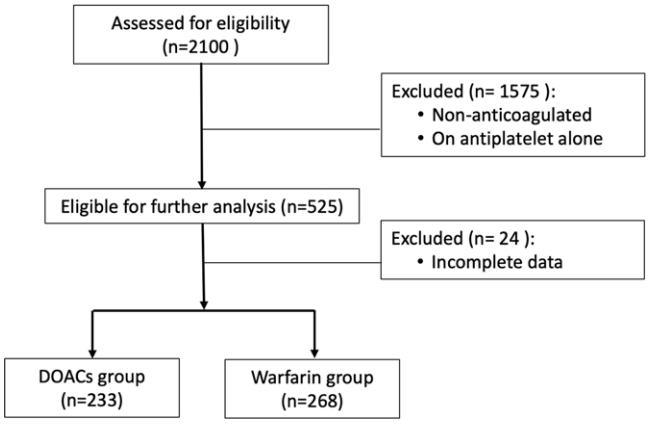

Figure 1. Study flowchart. DOACs = direct oral anticoagulants.

Outcomes

The primary outcome of interest was ICH developing during the index admission for trauma. Any pattern of traumatic intracranial bleed (i.e., subdural, subarachnoid, epidural, intraparenchymal or intraventricular hematoma) identified from the CT scan was considered a positive event. Secondary outcomes included in-hospital mortality, need for operative intervention (craniotomy or craniectomy) for a growing hematoma, need for hospitalization, hematoma progression (all patients had at least one follow-up CT done, and more were done until stability of the hemorrhagic lesions) and hospital length of stay. Finally, to assess functional outcomes, we compared the GOS-E score (Glasgow outcome scale-extended) between DOAC and WF groups with particular attention to the rates of functional dependency defined as GOS-E 4 at discharge.

Statistical analysis

Baseline patient characteristics, grouped according to anticoagulation status, were compared using a chi-square test of independence for categorical variables and a two-sample Student's *t*-test for continuous data. A multivariable logistic regression was performed to investigate the association between anticoagulation status and ICH development, functional dependency (GOS-E 4) and death (GOS-E = 1) while controlling for multiple covariates. A two-sided *p*-value < 0.05 was considered significant. All statistical analyses were carried out using R Statistical Software (version 4.2.1; R Foundation for Statistical Computing, Vienna, Austria).

Results

Clinical characteristics

From April 1, 2014, to March 31, 2019, 2,100 trauma patients aged over 65 years were treated at our level 1 trauma center. After excluding 1,575 patients who were either non-anticoagulated or on antiplatelet monotherapy only, we identified 525 patients who were on either WF or DOACs for anticoagulation. Twenty-four patients were additionally excluded from the final analysis due to incomplete data and imaging information (Figure 1). From the final study population of 501 subjects, 268 (53%) were documented to be taking *WF*, while 233 (47%) were on DOAC prior to the index injury. AF was the most common indication for anticoagulant therapy. Among patients using DOAC, apixaban was the most frequently used drug, and none were taking the newer DOAC agents such as edoxaban or betrixaban.

Table 1. Comparison of patient characteristics between direct oral anticoagulant (DOAC) and warfarin (WF) group

	DOAC (*n* = 233)	WF (*n* = 268)	*p-value*
Age in years, mean (SD)	82.1 (7.64)	82.4 (7.95)	0.746
Male gender, n (%)	114 (49%)	142 (53%)	0.414
History of falls, n (%)	217 (93%)	251 (94%)	0.956
GCS score, mean (SD)	14.3 (1.71)	13.6 (2.85)	0.001
TBI severity n (%)			
Mild TBI (13–15)	220 (94%)	228 (85%)	0.001
Moderate TBI (9–12)	8 (3%)	17 (6%)	0.198
Severe (3–8)	5 (2%)	23 (9%)	0.003
Hypertension, n (%)	170 (73%)	176 (66%)	0.096
Congestive heart failure, n (%)	32 (14%)	46 (17%)	0.351
Modified frailty score, mean (SD)	1.51 (0.906)	1.48 (0.973)	0.732
Severely frail, n (%)	25 (11%)	29 (11%)	1.000
CT Marshall score, mean (SD)	2.00 (1.54)	2.40 (1.74)	0.007
Subdural hemorrhage, n (%)	53 (23%)	95 (35%)	0.003
Subarachnoid hemorrhage, n (%)	45 (19%)	55 (21%)	0.822
Multicompartment hemorrhage, n (%)	38 (16%)	58 (22%)	0.162
INR, mean (SD)[a]	1.22 (0.326)	2.36 (1.01)	<0.001
Aspirin use, n (%)	28 (12%)	39 (15%)	0.484
Use of reversal agent, n (%)	13 (6%)	113 (42%)	<0.001
ISS, mean (SD)[b]	24.9 (8.39)	22.1 (9.36)	0.054

TBI = traumatic brain injury.
[a]INR = international normalized ratio. [b]ISS = injury severity score.

Table 2. Primary and secondary outcome comparison between direct oral anticoagulant (DOAC) and warfarin (WF) group

	DOAC (*n* = 233)	WF (*n* = 268)	*p-value*
Intracranial hemorrhage, n (%)	99 (42%)	154 (57%)	0.001
Hematoma progression, n (%)	46 (20%)	59 (22%)	0.608
Mortality, n (%)	18 (8%)	35 (13%)	0.073
Need for surgical intervention, n (%)	29 (12%)	40 (15%)	0.501
Need for hospitalization, n (%)	69 (30%)	109 (41%)	0.013
Hospital length of stay, mean (SD)	5.83 (15.2)	6.21 (14.8)	0.779
GOS-E, mean (SD)[a]	6.98 (2.00)	6.41 (2.48)	0.005

[a]GOS-E = Glasgow outcome scale-extended.

The mean age of the study cohort was 82.27 years, and 51% *(256/501)* were males. The vast majority of traumas were due to falls as the primary mechanism of injury *(93% [468/501])*, followed by motor vehicular collisions *(5% [25/501])*. Hypertension was the most common comorbidity reported in the study population (Table 1).

Overall, the WF group suffered more severe head injury than the DOAC group as demonstrated by a lower mean GCS score (*WF 13.6 2.85 vs. DOAC 14.3 1.72, p = 0.001*) and a higher proportion of

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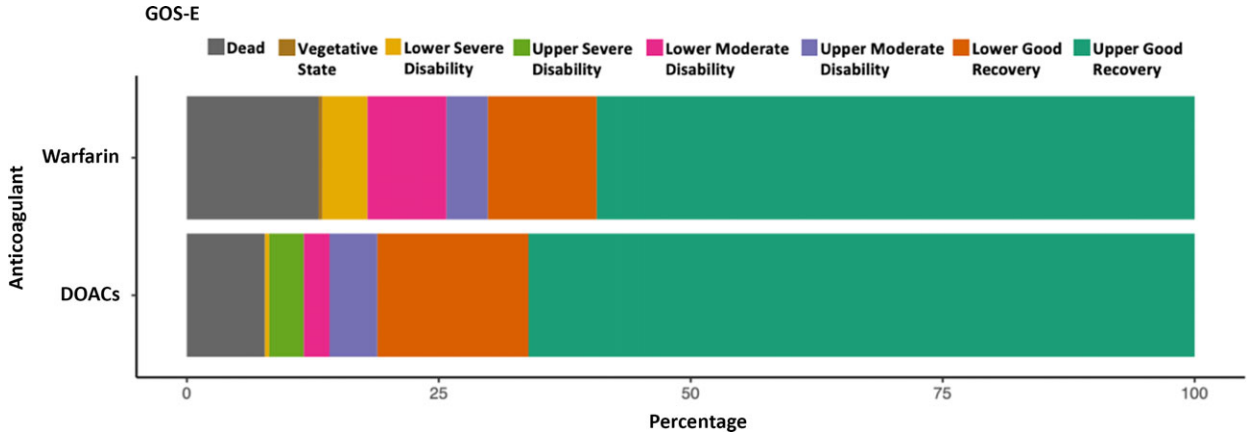

Figure 2. Comparison of percentage of patients between warfarin and DOAC group achieving outcomes based on GOS-E class at hospital discharge. DOACs = direct oral anticoagulants; GOS-E = Glasgow outcome scale-extended.

severe TBI cases (GCS 3–8) (*WF 9% [23/268] vs. DOAC 2% [5/233], p = 0.003*). The two groups were similar in terms of age, sex, comorbidities and frailty status. The extent of both intracranial and extracranial injuries sustained from trauma, as reflected in the overall ISS score, was not significantly different between the two groups (*WF 22.1 9.36 vs.* DOAC *24.9 8.39, p = 0.054*). As expected, the admission INR was higher (mean INR 2.36) among WF users and consequently received reversal agents more frequently than DOAC patients (*WF 42% [113/268] vs. DOAC 6% [13/233], p < 0.001*). There was no significant difference in aspirin intake between the two groups (*WF 15% [39/268] vs. DOAC 12% [28/233], p = 0.484*).

Injury patterns

Although the total rates of multicompartment ICH between WF and DOAC group did not differ significantly, a higher CT Marshall score was observed in those taking WF (*WF 2.40 1.74 vs. DOAC 2.0 1.54, p = 0.007*) (Table 1). Additionally, subdural hematomas (both focal and holohemispheric) occurred more frequently in the WF group, seen in as many as 1/3 of all newcomers with a history of WF intake (*WF 35% [95/268] vs. DOAC 23% [53/233], p = 0.003*). The same pattern is seen for intraparenchymal and subarachnoid hemorrhage with higher rates seen in WF users, albeit not statistically significant on univariate analysis.

Primary and secondary outcomes

The overall crude ICH rate in our study population composed of anticoagulated elderly TBI patients was 50.50% (253/501). Compared to the DOAC group, patients taking warfarin during the period of index trauma had a higher predisposition to develop ICH (*WF 57% [154/26]) vs. DOAC 42% [99/233], p = 0.001*) (Table 2). Despite this, however, the two groups did not differ significantly in the rates of hematoma progression on repeat cranial imaging.

For those requiring hospitalization, the crude in-hospital mortality rate for the entire cohort was 11% (53/501). Although there was no statistically significant difference in mortality rates observed between the two groups (*WF 13% [35/268] vs. DOAC 8% [18/233], p = 0.073*), patients taking DOAC had higher mean GOS-E score, indicating better functional outcomes at the time of discharge compared to WF users (*WF 6.41 2.48 vs. DOAC 6.98 2.00, p = 0.005)* (Figure 2).

The need for hospitalization was significantly higher when a trauma patient was on WF at the time of ED consultation (*WF 41% [109/268] vs. DOAC 30% [69/233], p = 0.013*). The overall mean length of stay in the hospital was 6 days. Fourteen percent (69/501) of the entire combined cohort required surgical intervention in the form of craniotomy or craniectomy for evacuation of hematoma and/or decompressive hemicraniectomy. When comparing the two groups, patients on WF did not have a longer duration of hospital stay nor required more surgical intervention than those using DOAC for anticoagulation.

Predictors of outcomes

Based on our multivariable regression model, we found no significant association of anticoagulation status with rates of ICH development when the estimated effect of other covariates is considered (*OR 0.27, CI: −2.92–0.25, p = 0.113*) (Table 3). The factors demonstrated by logistic regression to have an association with ICH rates were fall history (*OR 1.58, CI: 0.29–3.20, p = 0.031),* use of a reversal agent (*OR 3.05, CI: 2.25–3.96, p < 0.001),* moderate-severe TBI scores (*OR 1.44, CI: 0.47–2.53, p = 0.005)* and length of stay (*OR 0.07, CI: 0.04–0.12, p < 0.001).*

Additional associations of multiple covariates to functional dependency (GOS-E 4) and mortality (GOS-E = 1) were investigated. We found that multicompartment hemorrhage (*OR 2.30, CI: 0.24–4.34, p = 0.027*) and length of stay (*OR 0.04, CI: 0.02–0.06, p < 0.001*) were significant predictors of functional dependency after trauma. The presence of moderate-severe TBI scores was a consistent predictor of higher odds of both functional dependency and mortality. Interestingly, the Marshall scores (*OR 1.09, CI: 0.78–1.44, p < 0.001*) and modified frailty index (*OR 0.62, CI: 0.08–1.17, p = 0.026*) were strong predictors of death even after adjusting for other covariates.

Discussion

Our study reveals significant differences in clinical outcomes among elderly TBI patients (> 65 years old) based on their pre-injury anticoagulation status. Elderly patients taking WF before injury showed a higher incidence of ICH and required hospitalization, despite receiving a reversal agent at nearly seven times the rate compared to patients on DOACs. Conversely, those on DOAC demonstrated greater functional independence at discharge, as evidenced by higher GOS-E scores. Interestingly,

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Table 3. Multivariable logistic regression analysis of independent predictors of intracranial hemorrhage, functional dependency and mortality

Independent predictors	OR	95% confidence interval	*p*-value
Intracranial hemorrhage			
History of fall	1.58	0.29, 3.20	0.031
Use of reversal agent	3.05	2.25, 3.96	<0.001
Moderate-severe TBI	1.44	0.47, 2.53	0.005
Length of stay	0.07	0.04, 0.12	<0.001
Anticoagulation	0.27	−2.92, 0.25	0.113
Functional dependency			
Multicompartment	2.30	0.24, 4.34	0.027
hemorrhage	1.51	0.12, 2.89	0.031
Moderate-severe TBI	0.04	0.02, 0.06	<0.001
Length of stay	−1.27	−2.92, 0.25	0.113
Anticoagulation			
Mortality			
Moderate-severe TBI	0.031	0.38, 2.37	0.007
Marshall score	1.09	0.78, 1.44	<0.001
Frailty score	0.62	0.08, 1.17	0.026
Anticoagulation	0.03	−1.15, 1.16	0.963

TBI = traumatic brain injury.

among anticoagulated elderly TBI patients, factors such as Marshall score, GCS and frailty status, but not the type of anticoagulation used, emerged as robust independent predictors of mortality.

Our findings are consistent with a recently reported population-based survey, which showed an overall increased rate of ICH among WF users compared to those taking DOAC.[15] Grewal et al. reported a 1.43-fold higher risk of ICH among elderly TBI patients on WF compared to matched patients on DOAC. Similar findings are supported by various investigations in general trauma and TBI populations.[16–18] In contrast, Zeeshan et al., in their three-year analysis of a local TBI database from 2014 to 2016, found a higher risk of bleeding associated with the use of DOAC compared to WF using a propensity-score matched analysis.[19] Several striking differences however must be noted between the two studies. Patients enrolled in the latter study comprised younger patients (mean age of 59 and 60 years old) with relatively milder forms of injury (median ISS of 15). Falls contributed only to 42% of TBI in the study of Zeeshan et al., which is generally lower compared to estimates from large-scale epidemiologic research identifying falls as the predominant mechanism of injury in at least half of the TBI patients > 65 years old.[20] Nevertheless, a recent synthesis of evidence by Wu et al. supports an overwhelmingly higher rate of spontaneous ICH associated with WF intake compared to DOAC.[8] In our cohort, we observed a 1.36-fold increased risk of traumatic ICH in elderly TBI patients using WF, further supporting the hemorrhagic risk profile differences between anticoagulant types.

The in-hospital mortality rate for DOAC patients found in our study (8%) falls within the previously reported ranges (6%–40%) comparing TBI outcomes between DOAC and WF.[21–25] Although our findings suggest a higher mortality trend in the WF group, it did not reach statistical significance. Our results suggest that other significant factors, aside from anticoagulation, are more important determinants of death in this population. Indeed, as shown by our multivariable model, the traditional early indicators of poor prognosis in severe TBI based on the Brain Trauma Foundation guideline such as CT findings (as reflected in Marshall score) and TBI severity (as measured by GCS) are more reliable predictors than the type of oral anticoagulant used.[26] Currently, the evidence on the mortality risk associated with DOACs after trauma remains varied. The Trauma Quality Improvement Program analysis by Feeney et al. indicates lower mortality rates and fewer neurosurgical interventions among DOAC patients compared to WF users.[27] In contrast, other studies report higher rates of adverse outcomes, including mortality and need for surgery, among DOAC users during the acute phase of injury.[28,29] On the other hand, a recent meta-analysis of 11 studies found no significant difference in morbidity and mortality outcomes between DOAC and vitamin K antagonist (VKA) users post-TBI.[30] We hypothesize that the variable study population, uncontrolled confounders and differences in anticoagulation management practices contribute to these inconsistent findings. The routine use of reversal agents, for example, varies widely among neurotrauma centers with no standardized guidelines currently in place. FDA-approved reversal agents like idarucizumab and Andexanet alfa for DOACs are costly and not universally available, leading to the use of alternative agents such as PCCs in some settings.[31–33] Our institution did not have access to idarucizumab or andexanet. Ongoing drug development initiatives and increasing demand for specific reversal agents are expected to clarify the survival advantages and mortality benefits of DOAC compared to WF in future studies.

While numerous studies have compared hemorrhage and mortality risks between DOAC and WF users, few have described the functional outcomes of these patients following TBI. Our results indicate that at discharge, patients on DOACs exhibit higher GOS-E scores, with a greater proportion achieving good recovery compared to those on chronic WF therapy. This finding aligns with earlier studies by Scotti et al., who assessed 724 patients on antithrombotic agents, including a subset of patients on DOAC and WF, and Shin et al., who compared smaller cohorts on DOACs and VKA. Both studies demonstrated that DOAC users achieved greater functional independence post-TBI.[22,34] These collective findings highlight an additional benefit of DOACs over WF, translating clinically into reduced impairment and enhanced independent functioning in the elderly population. The exact mechanism underlying this benefit remains unclear; however, the association of DOACs with lower ICH risk suggests potential mitigation of secondary brain injury. Furthermore, emerging evidence hints at a neuroprotective effect of DOAC, indicated by lower rates of dementia and cognitive impairment among elderly AF patients compared to those on WF.[35,36] Whether this nascent property contributed to our findings warrants prospective investigation. If validated, this could significantly influence clinical decision-making, aiding physicians in better patient and family counseling, managing expectations and directing appropriate treatment strategies, particularly in selecting oral anticoagulant agents.

The major strength of this study is the large sample size of uniformly elderly (> 65 years old) anticoagulated TBI patients ($n = 501$). Moreover, we were able to perform risk adjustments by incorporating measures of trauma severity (i.e., ISS) and frailty status (i.e., mFI-5) in our multivariable model to assess the possible contribution of these factors. Frailty, which is defined as a decline in functioning across multiple physiologic systems accompanied by increased vulnerability to stressors, is becoming increasingly advocated in TBI research and is a more reliable indicator of poor outcome.[37] In a recent systematic review by Zhao and colleagues, frailty, rather than age, has significantly predicted both in-hospital and 30-day mortality, adverse discharge and readmission in elderly trauma patients.[38] The result of our study showing the frailty index as a significant predictor of mortality gives further credence to this

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claim. Additionally, the higher subdural rates in the WF group compared to DOAC warrant further investigation. The challenge of maintaining WF within its therapeutic range, in contrast to DOACs, likely contributes to this difference. Furthermore, emerging molecular insights suggest that variations in tissue factor levels between brain and extracerebral tissue may also play a role.[39]

This current study must be interpreted in the context of its limitations. Due to the retrospective nature of this research, ascertainment of accuracy and completeness of record as well as determination of long-term outcomes beyond the hospitalization period was not possible. There may be selection bias in our sample given the highly specialized nature of our institution providing advanced and comprehensive trauma intensive care in the province. It is likely that the TBI population referred to our center represents the more severe polytrauma cases and hence might not adequately reflect the entire spectrum of TBI cases. While examining the prevalence of renal insufficiency in the DOAC and WF groups would be valuable, limitations in data availability and completeness prevented its inclusion in this study. As we intended primarily to compare the outcomes of DOAC and WF, we did not include a control group of non-anticoagulated patients in our sample. Lastly, stratification based on specific DOAC agents was not performed and may potentially be an avenue of improvement in future research. A more comprehensive assessment of anticoagulation status based on the determination of the time of last intake along with agent-specific testing (e.g., thrombin time for direct thrombin inhibitors for dabigatran or anti-factor Xa activity for apixaban and rivaroxaban) will all be helpful additions for future studies to fully elucidate the systemic effect of these drugs.

Conclusions

In an elderly population of TBI patients with predominantly fall-related traumas, DOACs were associated with lower ICH rates, reduced hospitalization needs and higher GOS-E scores at discharge compared to WF. Mortality was significantly associated with established prognostic factors such as Marshall grade, GCS score and frailty status. Given the decreased risk of bleeding and improved outcomes associated with DOACs, their routine use over WF would be favored in high-risk elderly patients. Further validation through longer-term follow-up and multicenter studies is essential to confirm these findings and guide clinical practice.

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