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DIRECT ORAL ANTICOAGULANT TREATMENT AND MILD TRAUMATIC BRAIN INJURY: RISK OF EARLY AND DELAYED BLEEDING AND THE SEVERITY OF INJURIES COMPARED WITH VITAMIN K ANTAGONISTS

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☐ **Abstract—Background: The risk of intracranial hemorrhage (ICH) in patients taking direct oral anticoagulants (DOACs) after mild traumatic brain injury (MTBI) is unclear. Objectives: To assess the differences in the risk of developing early, delayed, and comprehensive bleeding after MTBI among patients treated with DOACs as compared with those treated with vitamin K antagonists (VKAs). Methods: All MTBI patients taking oral anticoagulants in our emergency department between June 2017 and August 2018 were included. All patients on oral anticoagulants underwent immediate cerebral computed tomography (CT) and a second CT scan after 24 h of clinical observation. Results: There were 451 patients enrolled: 268 were on VKAs and 183 on DOACs. Of the DOAC-treated patients, 7.7% (14/183) presented overall intracranial bleeding, compared with 14.9% (40/268) of VKA-treated patients ($p = 0.026$). Early bleeding was present in 5.5% (10/183) of DOAC-treated patients and in 11.6% (31/268) of VKA-treated patients ($p = 0.030$). Multivariable analysis showed that VKA therapy (odds ratio [OR] 2.327), high-energy impact (OR 11.229), amnesia (OR 2.814), loss of consciousness (OR 5.286), Glasgow Coma Scale score < 15 (OR 4.719), and the presence of lesion above the clavicles (OR 2.742) were associated with significantly higher risk of global ICH. A nomogram was constructed to predict ICH using these six variables. Discrimination of the nomogram revealed good predictive abilities (area under the receiver operating characteristic curve: 0.817). Conclusions: DOAC-treated patients seem to have lower risk of posttraumatic intracranial bleeding compared with VKA-treated patients.**

☐ **Keywords—mild traumatic brain injury; anticoagulation; direct oral anticoagulants; intracranial hemorrhage; warfarin**

INTRODUCTION

Direct oral anticoagulants (DOACs) are one of the most recent treatments in clinical practice in decades (1). DOACs have analogue efficacy in thromboembolic prevention compared with vitamin K antagonists (VKAs), and have predetermined dosage and do not require regular international normalized ratio blood test monitoring. These characteristics contribute to the rapid spread of DOACs in clinical practice and are considered a valid alternative to VKAs in patients requiring anticoagulation (2,3).

Oral anticoagulation therapy (OAT) is currently considered the gold standard worldwide for clinical diseases with thromboembolic risk, and despite the

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inaccurate figures on real diffusion, 2% of the U.K. adult population and more than 10% in the U.S. population aged >80 years are treated with oral anticoagulants (4,5).

Nevertheless, OAT exposes patients to a well-known increase in bleeding risk (6). In the case of mild traumatic brain injury (MTBI), OAT becomes a significant risk factor for the development of posttraumatic intracranial hemorrhage (ICH), mostly in aged patients or those with comorbidities (7,8). MTBI is defined as a trauma to the skull or facial region with a Glasgow Coma Scale (GCS) score of 13–15, and the management of anticoagulant-treated patients remains a great and widely discussed challenge for physicians (9). A small proportion (5–15%) of VKA-treated patients develops ICH subsequent to MTBI; overall, <1% needs urgent neurosurgical treatment (10). Despite these data, missing the diagnosis of a posttraumatic hemorrhage can lead to disabilities or death (11). Unlike VKA-treated patients, few data are available on the risk of ICH consequent to MTBI in DOAC-treated patients (12). Although DOAC-treated patients have globally demonstrated lower bleeding risk compared with VKA-treated patients, managing MTBI in DOAC-treated patients is the same as that for VKA-treated patients. Specific management indications for DOAC-treated MTBI are not available, and it is not clear whether the recommendations for oral anticoagulant–treated patients should be applied to them as well (13,14). A recent meta-analysis by Fuller and colleagues reiterated how the data on the risk of adverse events in patients treated with DOACs after MTBI remain limited (15). The aim of the present study is to evaluate the differences in the risk of developing early, delayed, and global bleeding after a minor head injury in patients treated with DOACs, as compared with those treated with VKAs.

METHODS

A retrospective observational study of patients admitted to the Emergency Department (ED) of the University Hospital of Verona, Verona, Italy from June 1, 2017 to August 31, 2018, due to MTBI, was performed. All patients treated with anticoagulants admitted to the ED due to MTBI were considered. All patients with a GCS score of 13–15, regardless of the presence of loss of consciousness (LOC) or amnesia immediately after the injury were included in the study (9). All patients underwent brain computed tomography (CT) scanning. Patients were divided into two groups based on the type of anticoagulant treatment: VKAs vs. DOACs.

The patients were managed according to our internal clinical protocol for mild brain trauma, which is based on the 2002 European Federation of Neurological Societies and 2007 Italian guideline recommendations (9,16). All patients on oral anticoagulant therapy admitted to the ED underwent an immediate CT brain scan (T0) and a second CT scan after 24 h (T1), with a clinical observation period between the two examinations prior to discharge from the ED. All patients were then followed for the next 30 days for late ICH (T2) after discharge.

The exclusion criteria were: MTBI occurred >24 h prior to the trauma; not undergoing CT scan for 24 h; ineffective anticoagulation VKA treatment (defined as prothrombin time international normalized ratio < 1.5); no regular assumption of DOAC therapy (last dose of DOAC taken more than 24 h before); transfer by other EDs or hospitals; not completing the study.

The principal endpoint of this study was the presence of ICH such as subdural, epidural, or parenchymal hematoma; subarachnoid hemorrhage; or cerebral contusion (17).

The presence of bleeding at the T0 CT brain scan was classified as ‘early ICH’; whereas ‘delayed ICH’ indicated the presence of bleeding at the T1 CT scan with a negative previous scan. Global ICH, the major endpoint of the study, is the sum of early and delayed ICH. Figures on neurosurgical treatment, intensive care treatment, or death after hospital admission due to the brain trauma were reported.

The present study was conducted according to our local Ethics Committee rules, the Helsinki declaration and Oviedo Convention statements.

Statistical Analysis

Early, delayed, and global ICH, and all categorial variables considered as risk factors for bleeding, were expressed as percentage and number of events. The rate of ICH in the two treatment groups (DOACs vs. VKAs) was compared with the Fisher’s exact test.

All risk factors associated with a global ICH with $p < 0.05$ in univariate analysis were subsequently entered in a multivariate analysis. A nomogram was created using binary logistic regression coefficients to predict the likelihood of global ICH risk. Discrimination of nomogram, that is, the ability to identify posttraumatic ICH, was verified through the area under the receiver operating characteristic curve: a 0.5 value points out a poor diagnostic capacity (such as a coin toss) and a 1.0 value indicates a complete discrimination.

Because predictive models when validated on an original sample can be overfitted, nomogram discrimination was evaluated also through a bias-corrected area under the curve (AUC) on a bootstrap 5000-replicated sample as an internal validation.

Statistical analyses were performed with Stata version 14.0 (StataCorp, College Station, TX). All tests were two-sided, and $p < 0.05$ was considered statistically significant.

RESULTS

There were 556 patients on anticoagulant therapy admitted to the ED for MTBI during the study period. Patients excluded were: 23 for inadequate anticoagulant treatment at ED arrival, 66 for missing T1 CT brain scan, 9 for inadequate clinical information, and 7 were lost at follow-up. Of the remaining 451 patients, 268 were on VKAs and 183 were on DOACs. Table 1 lists the patients' sex, age, and clinical features.

No significant differences in basal characteristics between the two groups of patients (DOACs vs. VKAs) were observed.

Regarding the studied outcomes, DOAC-treated patients had a lower overall ICH rate compared with the VKA-treated patients. In fact, only 7.7% (14/183) of DOAC-treated patients presented overall bleeding compared with the 14.9% (40/268) of VKA-treated patients (p = 0.026), whereas early bleeding was present in 5.5% (10/183) of DOAC-treated patients compared with the 11.6% (31/268) of VKA-treated patients (p = 0.030). No difference was found for delayed bleeding (3.8 vs. 2.3, p = 0.570).

Globally, 1.6% of patients (7/451) required neurosurgical treatment; 0.7% of the patients (3/451) died as a result of ICH. There was no difference between the DOAC and VKA treatment groups.

Lastly, none of the patients discharged with negative CT scan after 24-h ED observation presented ICH during the following 30 days.

Univariate analysis showed that the following factors were associated with risk of global ICH: VKA treatment (74.1% vs. 57.4%, p = 0.026), high-energy impact (14.8% vs. 1.5%, p < 0.001), posttraumatic amnesia (33.3% vs. 8.1%, p < 0.001), LOC (14.8% vs. 0.8%, p < 0001), GCS score < 15 (29.6% vs. 6.5%, p < 0.001), presence of cranial fracture (9.3% vs. 0.8%, p = 0.001), and trauma beyond the clavicles (77.8% vs. 53.9%, p = 0.001) (Table 2) (18). In the subsequent multivariate analysis, the risk factors confirmed as independent predictors for global ICH in patients on anticoagulant therapy were: VKA therapy (odds ratio [OR] 2.327, 95% confidence interval [CI] 1.117–4.847, p = 0.024), high-energy impact (OR 11.229, 95% CI 3.265–38.617, p < 0.001), amnesia (OR 2.814, 95% CI 1.102–6.556, p = 0.017), LOC (OR 5.286, 95% CI 1.102–25.348, p = 0.037), GCS score < 15 (OR 4.719, 95% CI 1.938–11.492, p = 0.001), and the presence of an objective lesion above the clavicles (OR 2.742, 95% CI 1.297–5.797, p = 0.008). Figure 1 shows the nomogram of the risk model for global posttraumatic ICH in patients on oral anticoagulants. The discriminative ability of the final model was assessed using the AUC (estimated to be 0.806) and the bias-

Table 1. Baseline Characteristics of Patients Evaluated in the ED for Mild Traumatic Brain Stratified by Two Therapy Groups (VKA vs. DOAC)

Variable	Total	VKA	DOAC	*p*-Value
Patients, n (%)	451 (100.0)	268 (59.4)	183 (40.6)	
Gender, n (%)				0.016
Female	238 (52.9)	129 (48.1)	109 (59.9)	
Male	212 (47.1)	139 (51.9)	73 (40.1)	
Age, years, median (IQR)	83 (78–88)	83 (78–88)	82 (78–87)	0.815
>75 years	380 (84.3)	224 (83.6)	156 (85.2)	0.694
>80 years	306 (67.8)	180 (67.2)	126 (68.9)	0.758
Indication to anticoagulation, n (%)				
Atrial fibrillation	403 (89.4)	232 (86.6)	171 (93.4)	0.020
Mechanical valve	19 (4.2)	19 (7.1)	0 (0.0)	< 0.001
Venous thromboembolism	28 (6.2)	17 (6.3)	11 (6.0)	1.000
Neurological issues, n (%)				
Sequelae of stroke	57 (12.6)	24 (9.0)	33 (18.0)	0.006
Decay	84 (18.6)	50 (18.7)	34 (18.6)	1.000
History of epilepsy	10 (2.2)	8 (3.0)	2 (1.1)	0.212
Bedding	17 (3.8)	12 (4.5)	5 (2.7)	0.453
Mechanism of trauma, n (%)				
Accidental fall	320 (71.0)	186 (69.4)	134 (73.2)	0.400
Car accident	17 (3.8)	9 (3.4)	8 (4.4)	0.620
Fall due to syncope	99 (22.0)	64 (23.9)	35 (19.1)	0.248
Other causes	16 (3.5)	10 (3.7)	6 (3.3)	1.000
High-energy impact, n (%)	14 (3.1)	10 (3.7)	4 (2.2)	0.418
Intracranial bleeding, n (%)				
Global	54 (12.0)	40 (14.9)	14 (7.7)	0.026
Immediate	41 (9.1)	31 (11.6)	10 (5.5)	0.030
Delayed	13 (3.2)	9 (3.8)	4 (2.3)	0.570

VKA = vitamin K antagonists; DOAC = direct oral anticoagulant; IQR = interquartile range.

Table 2. Univariable of Pre- and Posttraumatic Risk Factors With Risk of General Intracranial Bleeding after a Mild Traumatic Brain Injury

Variables	Absence of ICH	Presence of ICH	*p*-Value
Total of patients, n (%)	397 (88.0)	54 (12.0)	
VKA treatment	228 (57.4)	40 (74.1)	0.026
Pretrauma conditions			
Previous neurosurgery	8 (2.0)	3 (5.6)	0.134
High-energy impact	6 (1.5)	8 (14.8)	< 0.001
Alcohol abuse	10 (2.5)	0 (0.0)	0.613
Antiplatelet treatment	17 (4.3)	3 (5.6)	0.721
Posttrauma symptoms			
Amnesia	32 (8.1)	18 (33.3)	< 0.001
Loss of consciousness	3 (0.8)	8 (14.8)	< 0.001
Posttrauma seizures	0 (0.0)	0 (0.0)	1.000
Vomiting	9 (2.3)	3 (5.6)	0.167
GCS < 15	26 (6.5)	16 (29.6)	< 0.001
Worsening headache	5 (1.3)	2 (3.7)	0.200
Trauma beyond clavicles	214 (53.9)	42 (77.8)	0.001
Presence of cranial fracture	3 (0.8)	5 (9.3)	0.001
At least one risk factor			< 0.001
At least one risk factor beyond the visible injury			< 0.001

ICH = intracranial hemorrhage; VKA = vitamin K antagonists; GCS = Glasgow Coma Scale.

corrected AUC, which was estimated using 5000-iteration bootstrap and was 0.817, indicating good discriminatory power of the prediction model.

In the univariate analysis, only a previous neurosurgery (15.4% vs. 2.0%, $p = 0.036$), amnesia (23.1% vs. 8.1%, $p = 0.090$), and GCS score <15 (6.5% vs. 23.1%, $p = 0.056$) were associated with delayed hemorrhage (Table 3). No factors were found in the subsequent multivariate analysis.

DISCUSSION

This retrospective study comprises 451 patients: 268 treated with VKAs and 183 treated with DOACs. Lower overall posttraumatic ICH risk in DOAC-treated patients compared with VKA-treated patients ($p = 0.026$) was observed. No differences were noted for either the risk of delayed bleeding (3.8 vs. 2.3, $p = 0.570$) or the need for neurosurgical treatment. These data seem to indicate that evaluation of clinical presentation as well as pre- and posttraumatic risk factors presented by patients upon arrival at the ED can lead to good ICH risk stratification. However, the absence of any risk factors does not seem to exclude the risk of delayed bleeding in either the general anticoagulated group (VKAs + DOACs) or the DOAC-only group.

These results are in line with that previously presented in the literature. The posttraumatic ICH rate observed in the present cohort (12%) is similar to the bleeding rates reported in many recent clinical studies (5–15%) (19).

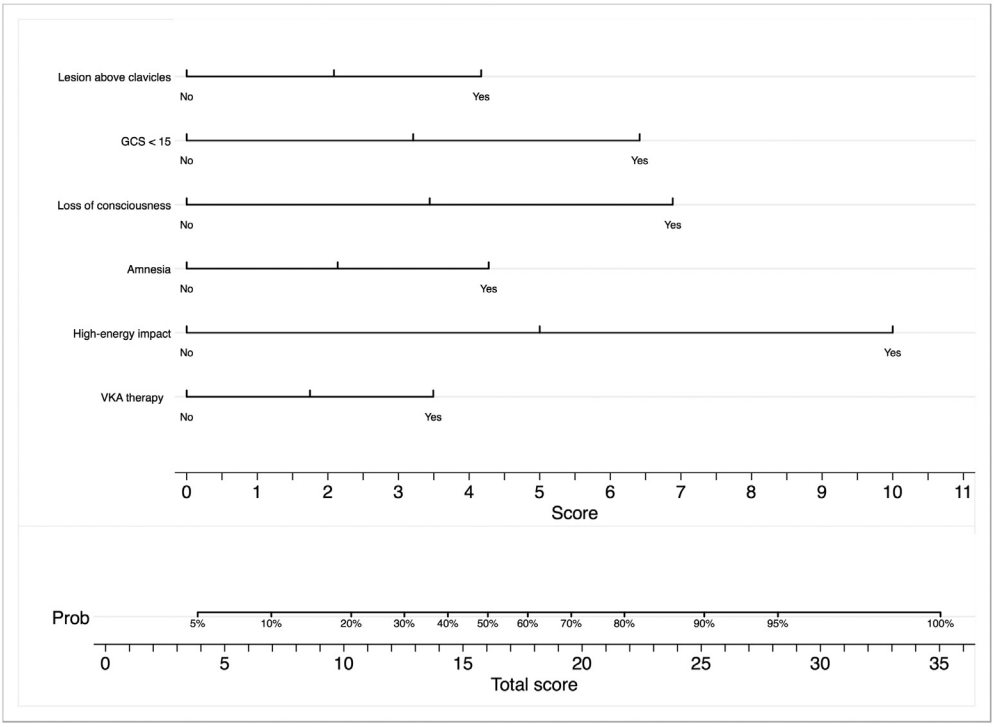

Figure 1. Nomogram predicting the probability of global intracranial bleeding after a minor head injury. For an individual patient, scores for each of the seven variables are summed to give a total score. The horizontal axis representing the total points is then used to calculate the corresponding probability of intracranial hemorrhage (ICH). GCS = Glasgow Coma Scale; VKA = vitamin K antagonists.

Table 3. Univariable of Pre- and Posttraumatic Risk Factors With Risk of Early and Delayed Intracranial Bleeding after Mild Traumatic Brain Injury

Variables	Absence of Immediate ICH	Presence of Immediate ICH	*p*-Value	Absence of Delayed ICH	Delayed ICH	*p*-Value
Total of patients, n (%)	410 (90.9)	41 (9.1)		397 (96.8)	13 (3.2)	
VKA treatment	237 (57.8)	31 (75.6)	0.030	228 (57.4)	9 (69.2)	0.570
Pretrauma conditions						
Previous neurosurgery	10 (2.4)	1 (2.4)	1.000	8 (2.0)	2 (15.4)	0.036
High-energy impact	6 (1.5)	8 (19.5)	<0.001	6 (1.5)	0 (0.0)	1.000
Alcohol abuse	10 (2.4)	0 (0.0)	0.610	10 (2.5)	0 (0.0)	1.000
Antiplatelet treatment	18 (4.4)	2 (4.9)	0.702	17 (4.3)	1 (7.7)	0.447
Posttrauma symptoms						
Amnesia	35 (8.5)	15 (36.6)	<0.001	32 (8.1)	3 (23.1)	0.090
Loss of consciousness	4 (1.0)	7 (17.1)	<0.001	3 (0.8)	1 (7.7)	0.121
Posttrauma seizures	0 (0.0)	0 (0.0)	1.000	0 (0.0)	0 (0.0)	1.000
Vomiting	9 (2.2)	3 (7.3)	0.086	9 (2.3)	0 (0.0)	1.000
GCS < 15	29 (7.1)	13 (31.7)	<0.001	26 (6.5)	3 (23.1)	0.056
Worsening headache	5 (1.2)	2 (4.9)	0.126	5 (1.3)	0 (0.0)	1.000
Trauma beyond clavicles	223 (54.4)	33 (80.5)	0.001	214 (53.9)	9 (69.2)	0.398
Presence of cranial fracture	3 (0.7)	5 (12.2)	0.001	3 (0.8)	0 (0.0)	1.000

ICH = intracranial hemorrhage; VKA = vitamin K antagonists; GCS = Glasgow Coma Scale.

The lower rate of posttraumatic ICH presented by DOAC-treated patients compared with VKAs-treated patients contributes to confirming data previously published about the greater safety of DOACs, compared with VKAs, in posttraumatic bleeding risk (12,14,19).

In an observational study of 225 patients with accidental fall (ground-level) and oral anticoagulant therapy (118 VKAs vs. 107 DOAC), Riccardi et al. observed that the rate of ICH was significantly lower in the DOAC-treated patients ($p < 0.05$) (19). None of the DOAC-treated patients died or required urgent neurosurgical intervention. More recently, a prospective study on a cohort of 206 patients (121 VKAs vs. 85 DOACs) confirmed that the risk of posttraumatic bleeding is greater in VKA-treated patients than in DOAC-treated patients (15.7% vs. 4.7%, relative risk 3.34, 95% CI 1.18–9.46, $p < 0.05$) (12).

In a study published in 2017, Spinola et al. (n = 402 patients) confirmed that DOAC-treated patients show lower bleeding risk when compared with VKA-treated patients (2.6% vs. 10.2%, $p < 0.001$), reporting two deaths in the latter group (20).

A study comparing the risk of increased bleeding in a cohort of 1846 patients with different types of medical treatment showed no differences in the ICH rate after MTBI in patients who received antiplatelet therapy, VKAs, DOACs, dual antithrombotic therapy, or no therapy (chi-squared p-value = 0.86) (21). Other similar works seem to suggest that oral anticoagulant therapy (VKAs + DOACs) does not seem to be a risk factor for the development of posttraumatic ICH when compared with the general population or patients on antiplatelet therapy (14,22). However, it should be noted that anticoagulant-treated patients appeared to be less severely injured than patients without anticoagulant treatment, and this, in turn, could balance the two groups, explaining the lack of difference in the risk for traumatic ICH (22).

The present study confirms, as suggested by Cipriano et al., the pivotal role of careful clinical evaluation of a patient with MTBI and anticoagulation therapy. Analysis of the pre- and posttraumatic risk factors presented by the patient plays a fundamental role in the overall clinical management as well (12). Posttraumatic bleeding seems to be almost always associated with precise anamnestic conditions or with specific presentation symptoms that can be exploited to determine the risk pretest a priori (23). In this context, the example of this nomogram confirms the possibility of constructing instruments with good predictive ability (AUC estimated to be 0.817).

Delayed posttraumatic hemorrhage in patients with OAT after MTBI remains under discussion. Although the published data seem to indicate that delayed posttraumatic ICH is not very frequent and has a minor clinical impact so far, in clinical practice the use of a second CT scan in anticoagulated patients is frequently practiced (14,23). In this current study, only 3.2% of patients with a first negative CT scan developed delayed ICH, with a positive CT scan performed 24 h after. None of these patients died or required urgent neurosurgical intervention, confirming the substantially favorable prognosis associated with delayed posttraumatic ICH (24).

However, if the relative rate of ICH is considered, one of four ICHs (25% of ICH) occurs after a first negative CT scan. There seems to be no difference in this aspect between DOAC- and VKA-treated patients. In their recent meta-analysis, Chauny et al. suggest that repeat CT after a first negative CT scan is not routinely necessary in all

patients on oral anticoagulation treatment, but may be limited to some patients demonstrating particular conditions (25). Verschoof et al. have also recently confirmed that evaluation of the patient could aid avoiding repetitions of unnecessary diagnostic examinations, and that even if present, the delayed ICH seems to have a favorable prognosis (10).

Pharmacokinetically, this aspect seems to be even more probable in DOAC-treated patients, leading to the scheduling of time-delayed CT scan controls, depending on the last drug dose. Further studies are therefore needed to focus on this important aspect.

Limitations

The current study has some limitations. Its retrospective nature exposes it to the bias appropriate to the design of this type of study, and although we performed manual revision of the individual folders, some information may be missing. However, the clinical protocol used in the ED requires the clinician to carefully evaluate the pre- and posttraumatic risk factors presented by the patient, and therefore we believe that the information is accurate. Furthermore, the 24-h observation from admission to ED obliges the opening of a specific observation section in the patient's file in which clinical, anamnestic, and laboratory data are recorded in more detail.

Second, the present protocol (24-h observation and repetition of the CT scan at 24 h from admission) at our department is certainly extensive, aiming to limit as much as possible the underestimation of posttraumatic bleeding.

Third, it was not analyzed whether any treatment was administered to counteract the anticoagulating effect of the drugs in case of posttraumatic ICH. However, the current guidelines state that those treatments are based on supplementation with coagulation factors.

Finally, clear data on the treatment when the patient is discharged home are not available. In the case of a repeated negative CT scan, typical anticoagulation therapy is generally recommended, but those data had not been clearly reconstructed. Therefore, it is not possible to be certain whether the continuation of the therapy after MTBI is safe. The data from this case series indicate that there were no ED readmissions for ICH within 30 days after MTBI.

CONCLUSIONS

Oral anticoagulant therapy is a risk factor for ICH after minor traumatic brain injury. Patients treated with DOACs seem to have lower risk of posttraumatic bleeding compared with patients treated with VKAs, reinforcing the initial indications on the greater safety of DOACs compared with VKAs. The results show that delayed bleeding, although not negligible, seems not to be associated with neurosurgical intervention or death. Finally, even in anticoagulated patients, studying the pre- and posttrauma risk factors can help the clinician stratify and individualize the ICH risk of each patient quickly and safely.

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ARTICLE SUMMARY

1. Why is this topic important?

Oral anticoagulant therapy is currently considered the gold standard for thromboembolic risk, and direct oral anticoagulants are becoming widely used in clinical practice in recent years. Minor head trauma is a major cause of emergency department evaluation. The risk of intracranial hemorrhage in patients taking direct oral anticoagulant after mild traumatic brain injury is unclear.

2. What does this study attempt to show?

The present study attempts to show any possible difference between warfarin and direct oral anticoagulants (DOACs) in early, delayed, and global bleeding risk after mild traumatic brain injury. Moreover, it is aimed to verify which patients' characteristics are associated with higher bleeding risk.

3. What are the key findings?

1 - DOAC-treated patients have lower risk of posttraumatic intracranial bleeding compared with vitamin K antagonists (VKA)-treated patients.

2 - Assessment of pre- and posttraumatic risk factors can predict the likelihood of intracranial bleeding after mild traumatic brain injury.

3 - Delayed bleeding that seems not life-threatening is not a negligible occurrence during oral anticoagulant therapy.

4. How is patient care impacted?

DOACs are safe drugs. The risk of posttraumatic bleeding after minor head injury is reduced compared with patients treated with VKA. This evidence may allow a greater spread of DOACs in clinical practice.