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Delayed intracranial hemorrhage after mild traumatic brain injury in patients on oral anticoagulants: is the juice worth the squeeze?

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Abstract. – OBJECTIVE: Mild Traumatic Brain Injury (MTBI) in anticoagulated patients is a common challenge for Emergency Department (ED) Physicians. Anticoagulation is considered a risk factor for developing delayed intracranial hemorrhage (ICH) after MTBI. The occurrence of this event in patients on Vitamin K Antagonists (VKA) or Direct Oral Anticoagulants (DOACs) remains unclear. Primary endpoint: to analyze the role of anticoagulants as risk factors for developing delayed ICH after MTBI and evaluate the indications to repeat a cranial computed tomography (CT) after a period of observation. Secondary endpoint: to assess the difference in the prevalence rate of delayed ICH in patients on VKA versus those on DOACs.

PATIENTS AND METHODS: We evaluated all consecutive patients admitted to our ED for MTBI, which had a control CT for late ICH after a negative CT at admission. We used a propensity score match (PSM) on factors affecting the need for oral anticoagulation to adjust the comparison between anticoagulated *vs.* non-anticoagulated patients for the baseline clinical characteristics.

RESULTS: Among 685 patients enrolled, 15 (2.2%) developed ICH at control CT. After PSM, the incidence of ICH, although slightly higher, was not statistically different in anticoagulated patients *vs.* non-anticoagulated (2.3% *vs.* 0.6%, *p*=0.371). Among the 111 patients on VKA, 5 (4.5%) had a late ICH, compared to 4 out of 99 (4.0%) on DOACs; the difference was not statistically significant (*p*=0.868).

CONCLUSIONS: The risk of developing delayed ICH after MTBI in patients on anticoagulation therapy is low. After correction for baseline covariates, the risk does not appear higher compared to non-anticoagulated patients. Thus, a routine control CT scan seems advisable only for patients presenting a clinical deterioration. Larger, prospective trials are required to clarify the safety profile of DOACs *vs.* VKA in MTBI.

Key Words:
Mild traumatic brain injury, Anticoagulation, Direct oral anticoagulants, Intracranial hemorrhage.

Introduction

Traumatic brain injury (TBI) represents one of the most common causes of morbidity and mortality worldwide. In Europe, the incidence rate is 235/100,000, with an average mortality rate of 15/100,000 and an estimated annual cost of 33 billion Euros[1]. Approximately 80% of all TBI are mild (MTBI)[2]. The opportunity to submit patients with MTBI to computed tomography (CT) at admission to the emergency department (ED) is well established[2,3]. However, there is still a lack of consensus on routine CT repeat after a period of clinical observation[3,4]. MTBI commonly occurs in older patients, which have increased fall risk, and commonly need anticoagulation for several clinical conditions[5]. Assumption of long-term oral anticoagulants is traditionally considered an independent risk factor for developing both immediate than delayed intracranial hemorrhage (ICH) after MTBI[6] but not all investigators agree[7]. Moreover, while for patients on vitamin K antagonist (VKA), available data are relatively consistent[8,9], minor evidence exists for patients on Direct Oral Anticoagulants (DOAC)[10-12]. Howev-

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er, current studies suggest that the risk of adverse outcomes following a MTBI could be low for these patients[13].

This study's primary endpoint is to analyze the role of anticoagulants as risk factors for developing delayed ICH after MTBI. The secondary endpoint is to assess the difference in the prevalence rate of delayed ICH in patients on VKA versus those on DOACs.

Patients and Methods

Study Design and Setting

The present paper reports the result of an observational, cross-sectional study conducted in an Emergency Department admitting about 77,000 patients per year, in an urban teaching hospital. The study was conducted over a three-year period between January 1st, 2016 and December 31st, 2018. Our institution serves a metropolitan area, and our hospital is a referral center for several peripheral Emergency Departments, and it is a major trauma center.

Patients Selection and Data Extraction

We performed an automatized search of the ED electronic clinical records based on admission and discharge diagnosis. We included all consecutive records of patients admitted to our ED for MTBI as chief complaint who, after a first negative CT scan at admission, repeated a CT scan 24 hours later. MTBI was defined as TBI with Glasgow Coma Score (GCS) ≥ 13, loss of consciousness < 30 minutes, and post-traumatic amnesia < 24 hours [3].

Our standard ED protocol indicates for all MTBI patient a 6-hour observation. Patients receive a head CT scan at admission, based on emergency physician evaluation. Patients who experience any clinical worsening during the observation period [episode of epilepsy, vomit ≥ 2 episodes, persistence of GCS < 15, prolonged amnesia, persistent headache], are prescribed a prolonged observation and a 24-hour repeat CT scan. All patients on anticoagulant therapy (either VKA or DOAC) get a prolonged observation and a control CT scan at 24 hours from the index control. Control CT scan could be anticipated based on evolving clinical findings.

We excluded from analysis:

- Trauma not classified as MTBI;
- Patients <18 years of age;
- Pregnant women;
- Patients with a known history of inherited coagulation disease;
- Patients that had a positive finding at first CT scan assessment.

For all patients included, we extracted the following data by manually reviewing the clinical records:

- Demographics, including sex and age at the index admission;
- Anticoagulant therapy at the time of injury, including VKA DOACs or low-molecular-weight heparin (either therapeutic or prophylaxis dosing);
- Antiplatelet drug therapy, including aspirin or clopidogrel;
- Presence of comorbidities, including history of neoplasia, neurodegenerative diseases, cerebrovascular diseases, thrombocytopenia, epilepsy, and alcohol abuse;
- Neurological and physical examination data at admission and during the ED observation period.

CT Scan Evaluation

Decision-making to perform CCT was always taken by a board-certified emergency physician based on clinical evaluation and NICE guidelines[4]. Axial CT images were acquired at 2.5 mm slices on a 64 slide CT scan [Revolution CT, GE Healthcare]. Cranial computed tomography scan interpretations were performed in all cases by experienced neuro-radiologists. CT was considered positive if any kind of acute intracranial bleeding was found (regardless of the amount), including subarachnoid hemorrhage, subdural hematoma, epidural hematoma, intra-parenchymal hemorrhage, and cerebral contusion. Results of the CT scans were obtained from radiologists' reports.

Event Adjudication

We evaluated the number of patients that had a positive control CT scan, after an index negative CT assessment in our ED.

Statistical Analysis

Continuous variables are reported as median [interquartile range]. Categorical variables are reported as absolute numbers (%). Statistical univariate comparison with respect of primary study endpoint was assessed by Mann-Whitney U test for continuous variables, and Chi-square test (with Yates correction or Fisher test if appropriate) for categorical variables.

Since this is a retrospective study, and criteria for prescription of anticoagulation therapy include several comorbidities and are often age-dependent, we used a propensity score matching (PSM) analysis to compare non-anticoagulated *vs.* anticoagulated patients in order to adjust the result of our study for these baseline factors. PSM was generated using a logistic regression model on the covariates considered potentially influencing the decision to prescribe anticoagulation and adding any confounding factors identified as significantly associated to hemorrhage. Variable considered for PSM were age, gender, ASA, clopidogrel, LMW heparin, alcohol abuse, malignancy, and high energy trauma. Additional covariates for PSM included factors specifically associated to anticoagulation prescription. Considered factors were coronary artery disease, congestive heart failure, presence of an intra-vascular stent, valvular heart disease, atrial fibrillation, and previous history of pulmonary embolism or deep venous thrombosis. Patients were matched on these propensity scores with a ratio 1:1. An optimal matching with a caliper size of 0.2 was used to avoid poor matches.

Comparison Between VKA and DOACs

To evaluate the secondary endpoint of the study, we restricted the analysis only to patients on anticoagulant therapy. In this sub-group, different anticoagulant therapy and different DOAC were considered a variable regarding the late intra-cranial bleeding. All data were analyzed by SPSS v25® (IBM, Armonk, NY, USA).

Statement of Ethics

The investigation was conducted in accordance with the principles expressed in the Declaration of Helsinki and its later amendments, and it was approved by the local Institutional Review Board. Being a retrospective analysis based on a digital anonymized database, patient's informed consent was waived.

None of the patients or authors received any honorary or economic benefits for participation in this study. This study did not receive any funding or grant from private or public institution.

Results

Globally, 7464 consecutive patients with age ≥ 18 years were evaluated in our ED for MTBI in the study period. After considering including and excluding criteria, we enrolled 685 patients in the study. The median age was 79 years [Interquartile range 64.5-86]; 329 (48%) were males (Table I). Overall, 210 patients (30.7%) were on anticoagulant therapy. Among them, 111 (52.8%) were on VKA and 99 (47.2%) on DOACs. In the DOACs group 23 (11.0%) were on dabigatran, 37 (17.6%) on apixaban, 31 (14.8%) on rivaroxaban and 9 (4.3%) on edoxaban.

Control CT was positive for delayed ICH in 15 (2.2%) cases (Table I).

Of the 15 patients with ICH after MTBI, one refused admission to the ward (no anticoagulant therapy assumed), three were discharged from the ED after a 24-hour clinical control. Of the remaining 11 patients, one underwent neurosurgery for subdural hematoma, 9 were discharged from ward with no surgery, and one developed massive intra-parenchymal bleeding and deceased in the intensive care unit (patients on VKA). Detailed outcomes of delayed positive CT scan patients are reported in Table II.

PSM Population Comparison

After PSM analysis was made, we obtained a population of 350 patients, matched 1:1 being 175 non-anticoagulated and 175 patients anticoagulated, on either VKA or DOACs. The matched population did not present significant differences in terms of age, gender, and comorbidities associated to anticoagulation (Table III).

As expected, we found that anticoagulated patients had a significant less use of ASA/clopidogrel (12.6% *vs.* 40.6%, $p<0.001$), and LMW heparin (0.6% *vs.* 8.0%, $p=0.001$). Patients on VKA or DOACs in this cohort also had fewer malignancies (5.1% *vs.* 16.6%, $p=0.001$) (Table III).

Both groups had similar clinical evolution during observation in terms of post-trauma epilepsy, vomit, and persistent headache. The anticoagulated group showed a significantly reduced incidence of GCS <15 at 6 hours (1.7% *vs.* 6.3%, $p=0.029$).

Delayed ICH after MTBI at control CT scan was found in 4 (2.3%) patients in the anticoagulation group, and in 1 (0.6%) in the non-anticoagulated group. However, this difference was not statistically significant ($p=0.371$) (Table III).

Comparison Between DOACs and VKA

Among the 111 patients on VKA, 5 (4.5%) had a late ICH, compared to 4 out of 99 (4.0%) on DOACs; the difference was not statistically

Table I. Baseline patient in study cohort characteristics, comorbidities, clinical presentation, and outcome. Data are presented for all population and separately for patients with either no anticoagulant therapy, and patients on VKA/DOACs.

	All patients n° 685	No anticoagulant n° 475 (69.3)	DOACs or VKA n° 210 (30.7)	*p*
Baseline characteristics				
Age (years)	79 (64.5-86)	76 (54-85)	83 (78-88)	< 0.001
Sex (male)	329 (48.0)	237 (49.9)	92 (43.8)	0.142
Therapy				
ASA	145 (21.2)	123 (25.9)	22 (10.5)	< 0.001
Clopidogrel	38 (5.5)	33 (6.9)	5 (2.4)	0.016
ASA/Clopidogrel	168 (24.5)	145 (30.5)	23 (11.0)	< 0.001
LMW heparin	25 (3.6)	24 (5.1)	1 (0.1)	0.003
Clinical history				
Malignancy	68 (9.9)	55 (11.6)	13 (6.2)	0.030
Neurodegenerative disease	60 (8.8)	42 (8.8)	18 (8.6)	0.908
Cerebrovascular disease	70 (10.2)	45 (9.5)	25 (11.9)	0.131
Thrombocytopenia	8 (1.2)	7 (1.5)	1 (0.5)	0.263
Alcohol abuse	15 (2.2)	15 (3.2)	0	0.008
Epilepsy	14 (2.0)	11 (2.3)	3 (1.4)	0.642
Other history factors potentially associated with anticoagulation				
Coronary artery disease	61 (8.9)	27 (5.7)	34 (16.2)	< 0.001
Heart failure	38 (5.5)	19 (4.0)	19 (9.0)	0.008
Intra-vascular stent	10 (1.5)	5 (1.1)	5 (2.4)	0.181
Valvular disease	14 (2.0)	0	14 (6.7)	< 0.001
Atrial Fibrillation	43 (6.3)	10 (2.1)	33 (15.7)	< 0.001
Previous DVP/PE	9 (1.3)	4 (0.8)	5 (2.4)	0.103
Clinical evaluation				
High energy trauma	451 (65.8)	309 (65.1)	142 (67.6)	0.514
Episode of epilepsy	11 (1.6)	11 (2.3)	0	0.022
Vomit ≥ 2 episodes at 6 hours	22 (3.2)	20 (4.2)	2 (1.0)	0.032
GCS < 15 at 6 hours	36 (5.3)	33 (6.9)	3 (1.4)	0.002
Persistent headache	149 (21.8)	116 (24.4)	33 (15.7)	0.011
Outcome				
Positive control CT scan	16 (2.3)	7 (1.5)	9 (4.3)	0.025

Abbreviations: DVP (deep venous thrombosis); PE pulmonary embolism; GCS Glasgow coma scale.

significant (p=0.868). Among the four patients on DOACs, we registered 2 ICH among the 23 patients on dabigatran (8.6%) and 2 among the 37 on apixaban (5.4%). No late ICH was registered among the 30 patients on rivaroxaban and among the 9 patients on edoxaban.

Discussion

This is the first study that compared the occurrence of late ICH between anticoagulated and non-anticoagulated patients after adjusting by a PSM the baseline clinical covariates associated with anticoagulation. The main finding is that anticoagulation was not associated to a significant increase in late ICH. Our numbers, however, may be underpowered to evaluate the slightly higher occurrence of late ICH in the anticoagulated cohort (2.3% *vs.* 0.6%, p=0.371). Moreover, we found no significant difference between late ICH in VKA *vs.* DOACs.

Minor Traumatic brain injury is a common complaint of patients evaluated in ED[1,2]. The worldwide aging of the population has led to an evident change in MTBI patient demographics, as the number of older adults evaluated for this condition is rapidly increasing[14,15]. The increased risk of falls in older patients produced a burden of ED access for MTBI in elderly patients[14-16]. Most of the current national guidelines indicate a head CT scan for MTBI patients ≥60/65 years old, regardless of other considerations[17]. Moreover, approximately 6% aged 65-74 and 10% over 75 years are on anticoagulant therapy[18]. The risk of immediate ICH after MTBI for anticoagulated patients older than 65 years was reported to be up to 25%[18,19]. Thus, there is generally a wide con-

Table II. Description of the findings and clinical outcome for the 15 minor head trauma patients that, after a first negative CT, had a positive control CT scan. One patient underwent surgery and was subsequently discharged alive. One patient had a massive intra-parenchymal bleeding and deceased in intensive care unit.

Age	Sex	Anticoagulant therapy	Aspirin/ clopidogrel	Control CT scan findings	Outcome
62	M	No	Yes	Subarachnoid hemorrhage	Refused admission to ward
34	M	No	No	Subdural hematoma	Admitted to ward. Underwent surgery
78	F	No	No	Subarachnoid hemorrhage	Admitted to ward
50	F	No	No	Subarachnoid hemorrhage	Admitted to ward
85	F	No	Yes	Intra-parenchymal hemorrhage	Admitted to ward
80	F	No	Yes	Subdural hematoma	Discharged home from Emergency Department
82	F	VKA	No	Intra-parenchymal hemorrhage	Admitted to ward. Deceased
94	M	VKA	No	Intra-parenchymal hemorrhage	Admitted to ward
82	F	VKA	No	Subarachnoid hemorrhage	Admitted to ward
88	F	VKA	No	Subarachnoid hemorrhage	Admitted to ward
89	F	VKA	No	Subarachnoid hemorrhage	Discharged home from Emergency Department
63	M	DOAC (Dabigatran)	No	Subarachnoid hemorrhage	Admitted to ward
76	M	DOAC (Dabigatran)	No	Subarachnoid hemorrhage	Admitted to ward
86	F	DOAC (Apixaban)	No	Intra-parenchymal hemorrhage	Admitted to ward
88	F	DOAC (Apixaban)	No	Subdural hematoma	Discharged home from Emergency Department

Data are presented for all population and separately for patients with either no anticoagulant therapy, and patients on VKA/DOACs. *Abbreviations:* DVP (deep venous thrombosis); PE pulmonary embolism; GCS Glasgow coma scale.

sensus about submitting anticoagulated patients to CT scan for MTBI, irrespective of their clinical condition[2,5,6,18,19].

On the other hand, the risk for delayed ICH after MTBI in anticoagulated is not well established[19]. Hence, in these patients, it is still debated the need for a control CT scan for those with normal CT findings at admission[5,20]. The possible exponential increase of unnecessary radiological investigations causes concern about costs and radiation exposure[17,21].

In our series of 685 patients, 15 (2.2%) developed a late ICH. In this cohort, the deterioration of clinical condition during observation (GCS <15 at 6 hours, vomit ≥2 episodes, and occurrence of epilepsy) was significantly associated to delayed ICH (Table I). Among the 210 patients on anticoagulation therapy, 9 (4.3%) had a delayed ICH. These results are slightly higher compared to recent studies[19,20], which found the overall incidence of delayed ICH for anticoagulated MTBI to be about 2%. However, other studies reported higher incidences, up to 6%[8]. Moreover, after adjusting the analysis for baseline clinical covariates, we found that delayed ICH was 2.3% in the anticoagulated cohort, in line with most of previous reports[19,20].

Since anticoagulated patients are generally older and more comorbid of non-anticoagulated controls, the real influence of anticoagulation itself on late ICH is hard to estimate by a simple group comparison. The PSM design of our study could help to override some confounding factors. However, we are aware that our adjustment could not correct for some possible negative factors such as dynamic of trauma and characteristics of preinjury antiplatelet therapy[5,20-22]. Actually, since patients on anticoagulation generally have a reduced prescription of ASA/clopidogrel, we cannot fully adjust for the influence of ASA and clopidogrel on late ICH. Indeed, recent reports estimate a higher risk of bleeding following MTBI in patients with concomitant antiplatelet/anticoagulant therapy[23]. Moreover, some authors suggest that while patients on ASA should not undergo a routine control CT scan for late ICH, patients on clopidogrel could have a higher risk[24]. In our cohort, we did not observe late ICH in patients on antiplatelet therapy; thus, we cannot draw definitive conclusions on this point.

Trend in DOACs prescription is rapidly increasing in recent years[15,22-25]. In our series, 99 patients (47.1%) among those on anticoagulant therapy assumed DOACs and 111 (51.7%) were

Table III. Comparison of propensity score matched cohort.

	All patients n° 350	No anticoagulant n° 175	DOACs or VKA n° 175	p
Baseline characteristics				
Age (years)	83 (77-88)	83 (77-88)	83 (77-88)	0.658
Sex (male)	154 (44.0)	79 (45.1)	75 (42.9)	0.667
Therapy				
ASA	82 (23.4)	61 (34.5)	21 (12.0)	<0.001
Clopidogrel	21 (6.0)	16 (9.1)	5 (2.9)	0.013
ASA/Clopidogrel	93 (26.6)	71 (40.6)	22 (12.6)	<0.001
LMW heparin	15 (4.3)	14 (8.0)	1 (0.6)	0.001
Clinical history				
Malignancy	38 (10.9)	29 (16.6)	9 (5.1)	0.001
Neurodegenerative disease	41 (11.7)	24 (13.7)	17 (9.7)	0.245
Cerebrovascular disease	40 (11.4)	21 (12.0)	19 (10.9)	0.737
Thrombocytopenia	1 (0.3)	0	1 (0.6)	0.317
Alcohol abuse	0	0	0	/
Epilepsy	5 (1.4)	2 (1.1)	3 (1.7)	1.000
Other history factors potentially associated with anticoagulation				
Coronary artery disease	47 (13.4)	19 (10.9)	28 (16.0)	0.158
Heart failure	23 (6.6)	10 (5.7)	13 (7.4)	0.518
Intra-vascular stent	7 (2.0)	4 (2.3)	3 (1.7)	0.703
Valvular disease	0	0	0	/
Atrial Fibrillation	21 (6.0)	9 (5.1)	12 (6.9)	0.500
Previous DVP/PE	7 (2.0)	4 (2.3)	3 (1.7)	1.000
Clinical evaluation				
High energy trauma	228 (65.1)	112 (64.0)	116 (66.3)	0.654
Episode of epilepsy	4 (1.1)	4 (2.3)	0	0.123
Vomit ≥ 2 episodes at 6 hours	10 (2.9)	8 (4.6)	2 (1.1)	0.054
GCS < 15 at 6 hours	14 (4.0)	11 (6.3)	3 (1.7)	0.029
Persistent headache	56 (16.0)	29 (16.6)	27 (15.4)	0.771
Outcome				
Positive control CT scan	5 (1.4)	1 (0.6)	4 (2.3)	0.371

Abbreviations: DVP (deep venous thrombosis); PE pulmonary embolism; GCS Glasgow coma scale.

on VKA. Four patients (4%) of DOACs group and 5 (4.5%) of those on VKA developed a delayed ICH. Although slightly higher compared to current literature[3,12,13,25-27], the difference was not statistically significant. The risk of delayed ICH post-MTBI in patients on DOACs is unanimously considered relatively low[13,26-27]. Furthermore, a more favorable safety profile is generally attributed to DOACs if compared to VKA in patients suffering from MTBI[3,12,13,25-27]. Our results confirm that, in the absence of other risk factors, a conservative attitude (observation) could be justified for patients on DOACs with MTBI.

Study Limitations

As for any retrospective study, some limitations are worth considering. First, our institution is the main hub of several peripheral EDs, and for such reason, our population could not represent the MTBI commonly evaluated in general practice. Second, the number of late ICH observed was low, and thus our sample is underpowered to give conclusive clues on the differences between patients on VKA and DOACs. Finally, in our series, there was a considerable use of CT scan in MTBI patients: this might be due to the high median age of patients referring to our ED, many of whom under concomitant anticoagulation therapy.

Conclusions

Our results underline the limited role of anticoagulation therapy as a risk factor for delayed ICH after MTBI. While the clinical observation could be justified for these patients, a control CT scan should be limited to patients experiencing a clinical deterioration.

Further studies and larger cohorts are still needed to clarify the safety profile of DOACs compared to VKA in MTBI.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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References

1) Peeters W, van den Brande R, Polinder S, Brazinova A, Steyerberg EW, Lingsma HF, Maas AI. Epidemiology of traumatic brain injury in Europe. Acta Neurochir (Wien) 2015; 157: 1683-1696.
2) Dewan MC, Rattani A, Gupta S, Baticulon RE, Hung YC, Punchak M, Agrawal A, Adeleye AO, Shrime MG, Rubiano AM, Rosenfeld JV, Park KB. Estimating the global incidence of traumatic brain injury. J Neurosurg 2018; 1: 1-18.
3) Cipriano A, Pecori A, Bionda AE, Bardini M, Frassi F, Leoli F, Lami V, Ghiadoni L, Santini M. Intracranial hemorrhage in anticoagulated patients with mild traumatic brain injury: significant differences between direct oral anticoagulants and vitamin K antagonists. Intern Emerg Med 2018; 13: 1077-1087.
4) National Clinical Guideline- National Institute for Health and Clinical Excellence: Guidance. In Head Injury: triage, assessment, investigation and early management of head injury in children, young people and adults: National Institute for Health and Care Excellence 2014, UK.
5) Campiglio L, Bianchi F, Cattalini C, Belvedere D, Rosci CE, Casellato CL, Secchi M, Saetti MC, Baratelli E, Innocenti A, Cova I, Gambini C, Romano L, Oggioni G, Pagani R, Gardinali M, Priori A. Mild brian injury and anticoagulants: less is enough. Neurol Clin Pract 2017; 7: 296-305.
6) Pieracci FM, Eachempati SR, Shou J, Hydo LJ, Barie PS. Use of long-term anticoagulation is associated with traumatic intracranial hemorrhage and subsequent mortality in elderly patients hospitalized after falls: analysis of the New York State Administrative Database. J Trauma 2007; 63: 519-524.
7) Nishijima DK, Offerman SR, Ballard DW, Vinson DR, Chettipally UK, Rauchwerger AS, Reed ME, Holmes JF; Clinical Research in Emergency Services and Treatment (CREST) Network. Risk of traumatic intracranial hemorrhage in patients with head injury and preinjury warfarin or clopidogrel use. Acad Emerg Med 2013; 20: 140-145.
8) 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: 451-455.
9) Nishijima DK, Offerman SR, Ballard DW, Vinson DR, Chettipally UK, Rauchwerger AS, Reed ME, Holmes JF; Clinical Research in Emergency Services and Treatment (CREST) Network. Immediate and delayed traumatic intracranial hemorrhage in patients with head trauma and preinjury warfarin or clopidogrel use. Ann Emerg Med 2012; 59: 460-468.
10) Beynon C, Potzy A, Sakowitz OW, Unterberg AW. Rivaroxaban and intracranial haemorrhage after mild traumatic brain injury: A dangerous combination? Clin Neurol Neurosurg 2015; 136: 73-78.
11) Spinola MB, Riccardi A, Minuto P, Campodonico P, Motta G, Malerba M, Guiddo G, Lerza R. Hemorrhagic risk and intracranial complications in patients with minor head injury (MHI) taking different oral anticoagulants. Am J Emerg Med 2019; 37: 1677-1680.
12) Cohan CM, Beattie G, Dominguez DA, Glass M, Palmer B, Victorino GP. Routine repeat head CT does not change management in trauma patients on novel anticoagulants. J Surg Res 2020; 249: 114-120.
13) Fuller G, Sabir L, Evans R, Bradbury D, Kuczawski M, Mason SM. Risk of significant traumatic brain injury in adults with minor head injury taking direct oral anticoagulants: a cohort study and updated meta-analysis. Emerg Med J 2020; 37: 666-673.
14) Covino M, Petruzziello C, Onder G, Migneco A, Simeoni B, Franceschi F, Ojetti V. A 12-year retrospective analysis of differences between elderly and oldest old patients referred to the emergency department of a large tertiary hospital. Maturitas 2019; 120: 7-11.
15) Uccella L, Zoia C, Perlasca F, Bongetta D, Codecà R, Gaetani P. Mild traumatic brain injury in patients on long-term anticoagulation therapy: do they really need repeated head CT scan? World Neurosurg 2016; 93: 100-103.
16) Scantling D, Fischer C, Gruner R, Teichman A, McCracken B, Eakins J. The role of delayed head CT in evaluation of elderly blunt head trauma victims taking antithrombotic therapy. Eur J Trauma Emerg Surg 2017; 43: 741-746.
17) Klang E, Beytelman A, Greenberg D, Or J, Guranda L, Konen E, Zimlichman E. Overuse of head CT examinations for the investigation of minor head trauma: analysis of contributing factors. J Am Coll Radiol 2017; 14: 171-176.
18) Grandhi R, Harrison G, Voronovich Z, Bauer J, Chen SH, Nicholas D, Alarcon LH, Okonkwo DO. Preinjury warfarin, but not antiplatelet medications, increases mortality in elderly traumatic brain injury patients. J Trauma Acute Care Surg 2015; 78: 614-621.
19) Minhas H, Welsher A, Turcotte M, Eventov M, Mason S, Nishijima DK, Versmée G, Li M, de Wit

K. Incidence of intracranial bleeding in anticoagulated patients with minor head injury: a systematic review and meta-analysis of prospective studies. Br J Haematol 2018; 183: 119-126.

20) Chauny JM, Marquis M, Bernard F, Williamson D, Albert M, Laroche M, Daoust R. Risk of delayed intracranial hemorrhage in anticoagulated patients with mild traumatic brain injury: systematic review and meta-analysis. J Emerg Med 2016; 51: 519-528.

21) Covino M, Gilardi E, Manno A, Simeoni B, Ojetti V, Cordischi C, Forte E, Carbone L, Gaudino S, Franceschi F. A new clinical score for cranial CT in ED non-trauma patients: definition and first validation. Am J Emerg Med 2019; 37: 1279-1284.

22) DiFiori MM, Lamb LC, Calavan LL, Comey CH, Feeney JM. Readmissions in patients with anticoagulated intracranial hemorrhage: a retrospective review. World Neurosurg 2018; 110: e305-e309.

23) Probst MA, Gupta M, Hendey GW, Rodriguez RM, Winkel G, Loo GT, Mower WR. Prevalence of intracranial injury in adult patients with blunt head trauma with and without anticoagulant or antiplatelet use. Ann Emerg Med 2020; 75: 354-364.

24) Marcia L, Moazzez A, Plurad DS, Putnam B, Kim DY. Utility of repeat head CT in patients on preinjury antithrombotic medications. Am Surg 2018; 84: 1626-1629.

25) Barmparas G, Kobayashi L, Dhillon NK, Patel KA, Ley EJ, Coimbra R, Margulies DR. The risk of delayed intracranial hemorrhage with direct acting oral anticoagulants after trauma: A two-center study. Am J Surg 2019; 217: 1051-1054.

26) Turcato G, Zannoni M, Zaboli A, Zorzi E, Ricci G, Pfeifer N, Maccagnani A, Tenci A, Bonora A. 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. J Emerg Med 2019; 57: 817-824.

27) Fuller GW, Evans R, Preston L, Woods HB, Mason S. Should adults with mild head injury who are receiving direct oral anticoagulants undergo computed Tomography scanning? A systematic review. Ann Emerg Med 2019; 73: 66-75.