The state of the art of the management of anticoagulated patients with mild traumatic brain injury in the Emergency Department

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Abstract

The effects of Oral Anticoagulation Therapy (OAT) in older patients who suffered a mild Traumatic Brain Injury (mTBI) are widely debated but still strong guidelines are lacking and clinical approaches and management are sometimes heterogeneous. Different predictors of adverse outcomes were identified in the literature but their use in the decision-making process is unclear. Moreover, there is no consensus on the appropriate length of stay in the Observation Unit nor on the continuation of OAT, even if the diagnosis of life-threatening delayed post-traumatic Intracranial Hemorrhage is rare. The recurrence of a control CT scan is often needless. This review aims to summarize recent scientific literature focusing on patients with mTBI taking OAT and to identify crucial questions on the topic to suggest a best clinical practice.

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Introduction

Mild Traumatic Brain Injury (mTBI) in patients taking Oral Anticoagulation Therapy (OAT) represents an increasingly common cause of presentation to the Emergency Department (ED), especially among older individuals. The median age of traumatic admission has risen over the years[1] due to increased life expectancy. Low-energy falls are the most common mechanism of injury in the geriatric population.[2] On the other hand, the use of OAT to prevent and treat thromboembolic complications of atrial fibrillation, deep venous thrombosis, valvular heart disease, and surgically placed cardiac valves is constantly growing.[3,4]

Although mTBI has a generally favorable prognosis,[2,3] morbidity and mortality after falls appear to increase with age[5] being associated with a higher risk of Intracranial Hemorrhage (ICH) and a higher mortality rate in patients on OAT.[3,4,6-8] Whilst several guidelines recommend discharging patients who are asymptomatic and stable and whose Glasgow Coma Scale (GCS) score is 15 after 24 hours of observations,[9,10] difficulty in clinical decision-making often persists, since few randomized controlled trials have been performed in this setting, and bleeding risk predictors are not yet clearly identified.

The purpose of this review is to analyze the recent scientific literature for assessing the state of art in the management of adult patients with mTBI taking OAT and giving clinical guidance for diagnosis and treatment to cover clinical questions from the patient's admission to the Emergency Department (ED) discharge.

Materials and Methods

The target of this review is adult patients receiving OAT who suffer mTBI. Both treatments with Direct Oral Anticoagulants (DOACs) and Vitamin K Antagonists (VKAs) were considered. MTBI in defined as blunt head injury associated with a GCS score of 13-15.

PubMed literature research was performed using the MeSH database with the searching tags [traumatic brain injury] and [anticoagulants]. Studies were selected if the following inclusion criteria were met: i) cohort study of adult patients with mTBI; ii) pre-injury use of oral anticoagulation (DOACs vs/or VKAs cohorts); iii) reporting on pre-injury patient demography and comorbidity; iv) reporting on bleeding complications, treatment and outcomes; v) written in English.

For clarity and pragmatism, topical issues were addressed by answering the following questions: i) should all anticoagulated patients with mTBI undergo a head CT scan? ii) Which are the possible predictors of ICH after mTBI? iii) Are DOACs safer than VKAs? iv) Should the head CT scan be repeated?

We also selected some unsolved questions from the literature.

Results

Should all anticoagulated patients undergo a head CT scan?

OAT is considered a risk factor for bleeding complications by several international guidelines (Table 1).[9-13] For this reason, well-established clinical practice suggests performing a head CT scan in all anticoagulated patients with mTBI. Different clinical decision rules for deciding to perform cranial tomography in patients with head trauma exist.[12,14,15] The Canadian CT Head Rule, which is very sensitive for the detection of intracranial pathologies requiring surgical intervention, indicates performing head CT imaging in all patients on OAT.

However, it is notable that, although prior studies and meta-analyses demonstrated an association between traumatic ICH and anticoagulation or antiplatelet agents in patients with head trauma,[16-19] some recent studies did not demonstrate such an association.[20-24]

In a retrospective cohort analysis of 2567 patients, Lampart *et al.* did not find a significant relationship between traumatic ICH and any anticoagulant/antiplatelet agents, although combination therapy was associated with an increase in hospital mortality.[25]

Similarly, Uccella *et al.* found that patients taking OAT with GCS 15 after blunt head trauma did not have a higher risk for intracranial hemorrhage than the general population.[26]

These new observations could be due to the different cohorts of patients. Indeed, when prior studies about TBI in OAT comprehended a more heterogeneous casuistry concerning age and dynamics of trauma, recent literature is often focused on low energy falls in older adults.

Considering these heterogenous data we could conclude that anticoagulation with VKAs and DOACs are possible strong risk factors for post-traumatic ICH with a risk of complication of less than 15%[27,28] depending on the type of anticoagulation. In the next future, the management of these patients could be based on clinical and trauma-related risk factors rather than anticoagulation therapy alone as proposed in some recent trials.[22,29,30]

Which are possible predictors of ICH after mTBI?

A central issue of clinical management of such a growing population is identifying the possible risk factors associated with adverse outcomes (neurosurgery, death, etc.), and providing a decision-making instrument for clinical and radiological monitoring (Table 2).

Some authors even suggest that these predictors could be useful to choose eventually for omitting routine CT head scanning, according to the low prevalence of traumatic ICH, particularly in patients treated with DOACs.[27-29]

Several prediction rules and guidelines for the detection of intracranial lesions and the necessity for neurosurgical intervention after mTBI in adults included items that have been examined for the specific case of anticoagulated subjects as well.

The AHEAD multicenter observational study by Mason *et al.* showed that post-traumatic vomiting, amnesia, headache and loss of consciousness were associated with a greater risk of adverse outcomes in warfarin patients following mTBI.[31]

In a 6-year retrospective analysis, Riccardi *et al*. found a significant increased risk of post-traumatic intracranial bleeding in patients with loss of consciousness, headache, vomiting, or neurological signs.[19]

Post-traumatic amnesia, evidence of trauma above the clavicles, high blood glucose, high blood pressure at arrival to the ED, and low prothrombin activity were predictors for ICH in patients suffering mTBI while OAT in a recent study by Cipriano *et al.*[30]

In a retrospective observational study above patients taking DOACs, Turcato *et al.*[29] found that major dynamics, post-traumatic loss of consciousness, post-traumatic amnesia, GCS<15, post-traumatic headache, and visible trauma above the clavicles were asso-

Table 1. Should all anticoagulated patients with mTBI undergo a Head CT scan?

Evidence		Y	N	Note
GL	EFNS guideline[9]	x		Guidelines and Rules suggest performing a head CT scan in all patients treated with blood thinners within 8 hours of trauma
GL	NICE guideline[10]	x		
GL	NEXUS II[11]	x		
CR	CHIP prediction rule[12]	x		
CR	Canadian CT Head Rule[14]	x		
CR	New Orleans Criteria[15]	x		
RCS	Jeffree *et al.*[18]	x		
SR	Minhas *et al.*[16]	x		
RCS	Riccardi *et al.*[19]	x		
RCS	Lampart *et al.*[25]		?	No relationship between OAT and tICH risk
RCS	Uccella *et al.*[26]		?	Only patients with GCS 15
PCS	Nishijima *et al.*[21]		?	No relationship between OAT and tICH risk
RCS	Alrajhi *et al.*[24]		?	Low bleeding risk in minimal (4.8%) vs minor (21.9%) head trauma in warfarinized patients
PCS	Kuczawski *et al.*[23]		x	
RCS	Turcato *et al.*[22]		x	In absence of predictors

CR: clinical rule; GL: guideline; PCS: prospective cohort study; RCS: retrospective cohort study; SR: systematic review; CT: computed tomography; OAT: oral anticoagulation therapy; tICH: traumatic intracranial hemorrhage; CGS: Glasgow Coma Scale; LOC: loss of consciousness.

ciated with a higher likelihood of ICH.

Nishijima *et al.*[21] recently conducted a prospective multicentric study where history of vomiting, evidence of trauma above the clavicles, or an abnormal GCS score are more predictive of traumatic ICH than anticoagulant or antiplatelet use; mechanism of injury other than ground-fall and a history of loss of consciousness or amnesia were independent risk factors for the incidence of traumatic ICH on initial cranial CT scan as well.

In a recent trial, Turcato *et al.*[22] proposed to collect these predictors in a "decision tree analyses" in which data mining techniques allow the visualization of relationships between many variables by defining explicit rules for their classification and their influence on the dependent variable. Despite this study having a retrospective observational design requiring to be confirmed in prospective trials, the hypothesis that the introduction of these techniques into clinical practice would reduce the number of CT scans for anticoagulated patients with mTBI is intriguing.

Are DOACs safer than VKAs?

In the last years, many authors focused on the comparison between direct anticoagulants and warfarin regarding their effectiveness in preventing thromboembolic illness and their respective hemorrhagic risk. Several studies demonstrated a safer profile of DOACs both in the setting of spontaneous and traumatic ICH (Table 3).[27,29,30,32-40]

A systematic review by Fuller *et al.* of seven observational studies estimates that the prevalence of adverse outcomes (death, intracranial hematoma, or neurosurgery) after mTBI in patients taking DOACs ranged from 0.0% to 8.3%.[27] This value is almost half of the rate of traumatic ICH above patients in OAT with VKAs, as documented in several other studies.[30,34,35,41,42] Further retrospective studies confirmed these data emphasizing the better safety profile compared to warfarin.[42,43]

Conversely, Zeeshan *et al.* found an increased risk of progression, neurosurgical intervention and mortality among the DOAC cohort when compared to warfarin.[44] However, falls caused only 42% of TBI while motor vehicle collisions accounted for a third of patients, leading to a lower GCS at admission. These differences make it difficult to compare Zeeshan's study with others focused on blunt head trauma in the elderly.

In conclusion, the evidence seems to sustain that DOACs are safer than VKAs, but it is also true that warfarin is sometimes the obvious choice for frail patients due to their comorbidities. To rule out the possibility of bias, further studies will be needed to confirm the better safety profile of DOACs even in patients with frailty.

Should the head CT scan be repeated?

The practice of routinely repeating head CT in anticoagulated patients within 24 hours after their first negative CT scan to assess for delayed ICH (dICH) has been widely shared in the past years and it is still currently applied in some countries.[45] Nevertheless, a growing number of evidence suggests that the risk of developing a dICH is very low and when present did not require neurosurgical intervention (Table 4). The prevalence rate of dICH ranges between 1%- 4.5%.[29,30,34,42,46-48]

A similar incidence is described in the subgroup of patients treated with DOACs (0.95%-2.1%).[49,50] In a recent publication by Soleimani *et al.*, only 3 patients above 314 experienced a dICH and they have all been discharged in a week at most.[51] The authors concluded that, in absence of concomitant antiplatelet medication, a confirming head CT scan after initial negative is not necessary.

In a study published in 2019, Cohan *et al.* found that the incidence of dICH in patients on warfarin to those on DOACs was similar (2.6% *vs* 2.1%) and administration of reversal agents, neurosurgical interventions, or deaths never occurred.[50] Even data from a 2020 publication by Savioli *et al.* are in line (3.2% *vs* 1.3%).[42] Many more trials confirmed this evidence in the last period.[52-63] Anyway, comparison between the two categories of oral anticoagulants is hard due to the small number of patients suffering dICH observed. These data do not support routinely obtaining a repeat CT head after a negative initial CT scan since the risk of complications in asymptomatic anticoagulated head trauma patient is negligible when an initial CT scan is negative. In a recent study by Turcato *et al.*,[22] patients without risk factors for bleeding were free from bad outcomes linked to trauma. However, the decision if and when to schedule the control imaging may be influenced by

Table 2. Which are possible predictors of ICH after mTBI?

	Age (yrs)	GCS < 15	EAC	Sk F	PTA	MT	Vom	PTS	LOC	NrlD	HA	Alcool/ Drug	Glc	BP
CHIP[12]	>60													
Canadian[14]	≥65													
New Orleans[15]	>60													
Mason *et al.*[31]					*		*		*		*			
Riccardi *et al.*[19]							*		*	*	*			
Cipriano *et al.*[30]			*		*								*	*
Turcato *et al.*[29]		*	*		*	*			*					
Nishijima *et al.*[21]			*		*	*	*		*					
Lampart *et al.*[25]		*	*	*	*									

In this table, items considered by most used prediction rules (CHIP prediction tule, Canadian CT Head rule, New Orleans Head CT rule) are shown by colored boxes. In lines below, "*" indicates those predictors of tICH for the authors. GCS: Glasgow Come Scale; EAC: evidence of trauma above clavicles; Sk F: skull fractures; PTA: post-traumatic amnesia; MT: major trauma; Vom: vomiting; PTS: posttraumatic seizures; LOC: (post-traumatic) loss of consciousness; Nrl D: neurologic disabilities; HA: (post-traumatic) headache; Glc: elevated blood glucose at arrival; BP: elevated blood pressure at arrival.

the findings of the initial CT, underlying risk factors, and the evolution of neurological examination.

Unsolved questions

How long patient's neurological state should be monitored?

Due to the possibility of developing dICH in anticoagulated mTBI patients with normal initial neurological examination and negative head CT scan, clinical observation for at least 24 hours after the traumatic event is recommended.[52,59,64] However, as already commented, many authors report that diagnoses of ICH in control head CT are rare and rarely require neurosurgical intervention.

At the time of discharge, it is essential to provide mTBI patients with an information sheet on what to do at home and which are the red flags for coming to medical attention. Interestingly, some studies indicate that household observation is effective as the CT in presence of a caregiver and a patient able to understand home instruction.[42,65] These data, along with the very small incidence of dICH, suggest that routinely performing control CT scan in not indicated nor cost-effective and new models of shorter observation should be designed.[66]

Considering the lack of strong evidence supporting the risk of delayed complication in the first 24 hours and some trials reporting the absence (0%) of adverse events in that short period,[22,30] a shorter period of observation, such as 6 hours, after a negative head CT scan performed at least 2-6 hour far from the trauma could be reasonable. This observational period together with clear patients' home information seems to be the best choice in terms of safety and cost-effectiveness.

When and how long to discontinue OAT after mTBI?

Considering risk/benefit balance, it is widely shared that patients without hemorrhagic complications after head trauma will continue to take OAT, as previously indicated. Conversely, the choice to switch oral anticoagulant to subcutaneous antithrombotic prophylaxis, despite being frequently adopted, is without strong evidence-based experiences and is still debated, especially in those subjects with minimal lesions at CT scan. This group of patients has good outcomes and rarely needs surgery. Therefore, switching to Low-Molecular Wight Heparin (LMWH) does not give any benefit in patients premedicated with DOACs since it has a similar duration of action but less evidence of safety and efficacy. Finally, clear indications about the timing to restart OAT are lacking and the incidence of thromboembolic adverse events, while anticoagulation is discontinued, is not clearly described in the literature.

Table 3. Are DOACs safer than VKAs?

Evidence		Y	N	Note
SR	Fuller *et al.*[27]	x		
PCS	Cipriano *et al.*[40]	x		
RCS	Prexl *et al.*[35]	x		
RCS	Spinola *et al.*[34]	x		
RCS	Savioli *et al.*[42]	x		
PCS	Zeeshan *et al.*[44]		x	All TBI; 1/3 motor vehicle crush, only 42% ground falls
PCS	Wilson *et al.*[41]		x	

PCS: prospective cohort study; RCS: retrospective cohort study; SR: systematic review; TBI: traumatic brain injury

Table 4. Should the head CT scan be repeated?

Evidence		Y	N	Note
RCS	Reynolds *et al.*[45]	x		
PCS	Kaen *et al.*[46]		x	Control CT scan NOT indicated if normal neurological exam and in absence of symptoms onset
RCS	Peck *et al.*[52]		x	
PCS	Nishijima *et al.*[53]		x	
SR	Cohn *et al.*[54]		x	
RCS	McCammack *et al.*[61]		x	
SR	Chauny *et al.*[55]		x	
RCS	Uccella *et al.*[56]		x	
RCS	Lim *et al.*[57]		x	
RCS	Campiglio *et al.*[58]		x	
PCS	Huang *et al.*[62]		x	
RCS	Verschoof *et al.*[59]		x	
RCS	Barmparas *et al.*[49]		x	
RCS	Afaneh *et al.*[60]		x	
RCS	Mann *et al.*[48]		x	
PCS	Cipriano *et al.*[30]		x	
RCS	Mourad *et al.*[47]		x	
RCS	Turcato *et al.*[22]		x	
RCS	Cohan *et al.*[50]		x	
RCS	Soleimani *et al.*[51]		x	
SR	Hickey *et al.*[63]		x	

PCS: prospective cohort study; RCS: retrospective cohort study; SR: systematic review; CT: computed tomography.

Discussion

This review aims to collect recent data on patients suffering mTBI while treated with OAT and to suggest a shared model of their clinical management. Our proposal is shown in Figure 1.

Due to the increasing life expectancy, ground-falls in older people are the most common phenotype in this setting. Considering mTBI in the elderly, GCS deserves a particular focus. In fact, despite several authors emphasizing the worse outcome for patients presenting to the ED with GCS less than 15, older patients with traumatic ICH are reported to have higher GCS level compared with younger patients with equivalent injury.[67] Moreover, GCS variation from baseline can be uncertain and slow, and even determining the baseline condition can be difficult in patients with dementia. Recently, new scores for the evaluation of older adults after head trauma such as eTBI[68] have been proposed.

Certain aspects related to trauma such as amnesia, lesions above the clavicles or different dynamics from ground level falls seem to correlate with major risk to develop hemorrhagic complications; further studies will assess if other significant clinical predictors exist.

Strong recommendations for clinical management of anticoagulated patients with blunt trauma after an initial negative head CT scan are still lacking. If the avoidance of a second CT scan in those patients with normal neurological exam and without symptoms is well established in clinical practice, it is not clear how long the observation period should last but a 6 hours period seems safe.

Although rare, dICH can occur several days after trauma. Therefore, the best cost-effective approach seems to be an ultra-short period in Observation Unit, then providing patients and caregivers with clear indications for household monitoring for the next month.

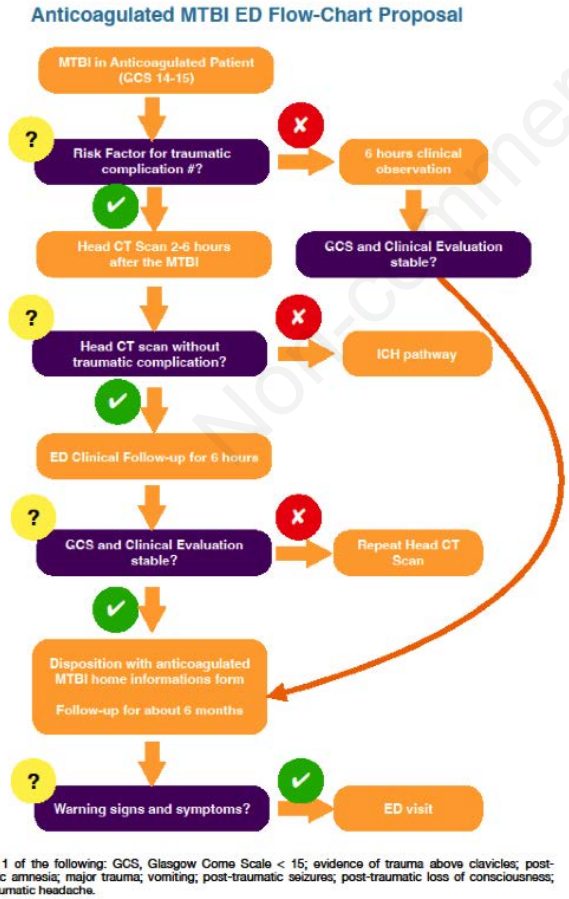

Figure 1. Anticoagulated MTBI ED Flow-chart proposal.

Conclusions

Patients in OAT suffering a TBI require an initial head CT scan to evaluate the presence of traumatic ICH.

DOACs have a better safety profile compared to VKAs. Post-traumatic amnesia, evidence of trauma above the clavicles, major dynamics, post-traumatic loss of consciousness, and GCS<15 are the strongest risk factors for t-ICH.

Delayed ICH is rare and repeating a head CT exam is not indicated unless evolution of the neurological state. For those patients with GCS 15, minor trauma dynamic (e.g., ground falls) and in absence of risk factors a short period of clinical–or even household when possible–observation is recommended.

The present review collects expert opinions in the field of MTBI and OAT. At the same time, we have reviewed the best scientific literature available on this topic, these scientific papers are not all of excellent quality but they are what we currently have available. The main limitation of the study is the potential selection bias. In the next future, randomized controlled trials are required to give strong recommendations in this setting.

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