The Journal of Emergency Medicine, Vol. ■, No. ■, pp. 1–13, 2020

0736-4679/$ - see front matter

https://doi.org/10.1016/j.jemermed.2020.07.036

Clinical Review

INCREMENTAL RISK OF INTRACRANIAL HEMORRHAGE AFTER MILD TRAUMATIC BRAIN INJURY IN PATIENTS ON ANTIPLATELET THERAPY: SYSTEMATIC REVIEW AND META-ANALYSIS

Elisa M. Fiorelli, MD,* Viviana Bozzano, MD,* Mattia Bonzi, MD,† Silvia V. Rossi, MD,† Giorgio Colombo, MD,* Gaia Radici, RN (NURSE),† Tiberio Canini, MD,‡ Hayato Kurihara, MD,§ Giovanni Casazza, PHD,|| Monica Solbiati, MD, PHD,†¶ and Giorgio Costantino, MD†¶

*Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, UOC Medicina Generale–Immunologia e Allergologia, Milano, Italy, †Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, UOC Pronto Soccorso e Medicina d'Urgenza, Milano, Italy, ‡Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Dipartimento di Anestesia-Rianimazione e Emergenza Urgenza, UOSD Chirurgia d'Urgenza, Milano, Italy, §IRCCS Humanitas Research Hospital, UOC Chirurgia Generale, Chirurgia d'Urgenza e del Trauma, Rozzano Milano, Italy, ||Dipartimento di Scienze Biomediche e Cliniche "L. Sacco," Università a degli Studi di Milano, Milano, Italy, and ¶Dipartimento di Scienze Cliniche e di Comunità, Università degli Studi di Milano, Milano, Italy

Reprint Address: Viviana Bozzano, MD, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, UOC Medicina Generale–Immunologia e Allergologia, Via guerrini 8, 20133, Milano, Italy

□ **Abstract—Background: Mild traumatic brain injury (TBI) is a common event and antiplatelet therapy might represent a risk factor for bleeding. Objective: The aim of this study was to evaluate the risk of intracranial hemorrhage (ICH) after mild TBI in patients on antiplatelet therapy through a systematic review and meta-analysis. Methods: We conducted a systematic review and meta-analysis of prospective and retrospective observational studies on patients with mild TBI on antiplatelet therapy vs. those not on any antithrombotic therapy. The primary outcome was the risk of ICH in patients with mild TBI based on the first computed tomography scan. Secondary outcome was the risk of mortality and neurosurgery. Results: Nine studies and 14,545 patients were included. The incidence of ICH ranged from 3.6% to 29.4% in the antiplatelet group and from 1.6% to 21.1% in the control group. Patients on antiplatelet therapy had a higher risk of ICH after a mild TBI compared with patients that were not on antithrombotic therapy (risk ratio 1.51; 95% confidence interval 1.21–1.88). No difference was found in the composite outcome of mortality and neurosurgery. Conclusions: Patients on antiplatelet therapy have an increased risk of ICH after mild TBI compared with patients not on antithrombotic therapy. However, the risk is just slightly increased, and the need to perform a computed tomography scan in patients on antiplatelet therapy after a mild TBI should be evaluated case by case, but always considered in patients with other risk factors.** © **2020 Elsevier Inc. All rights reserved.**

□ **Keywords—mild traumatic brain injury; antiplatelet therapy; intracranial hemorrhage; head CT scan; emergency department**

INTRODUCTION

Traumatic brain injury (TBI) is a common reason for the admission of patients to emergency departments (EDs) (1,2). TBI can occur at any age, but is prevalent in patients aged 15 to 24 years and older than 65 years (3,4). TBI usually resolves without complications, but a minority of patients, mostly with moderate or severe TBI, can develop serious and potentially life-threatening complications (5–7). In mild TBI, intracranial hemorrhage (ICH) and the need for neurosurgery are rare, with head computed tomography (CT) scans being unnecessarily

RECEIVED: 29 February 2020; FINAL SUBMISSION RECEIVED: 5 July 2020;
ACCEPTED: 19 July 2020

implemented, increasing the risk of exposing patients to radiation without a benefit in terms of treatment, as CT scan findings often do not lead to any intervention (8).

Several potential risk factors must be evaluated to identify patients who are at high risk of complications. For example, clinical decision rules have been proposed to stratify the risk of patients (9–11). Antiplatelet therapy represents one of several possible risk factors; however, data remain limited on how this factor contributes in the development of post-traumatic ICH. Various clinical decision rules are available to practitioners in different regions globally, but there is not consensus among them about how to consider patients on antiplatelet therapy. For example, the Canadian CT Head Rule (CCHR) does not consider antiplatelet therapy as a potential bleeding risk factor (9). In comparison, the National Emergency X-Radiography Utilization Study II Criteria identifies "coagulopathy" as a generic risk factor, but does not distinguish the cause (10). Similarly, various guidelines provide few indications on how to treat TBI patients on antiplatelet therapy (6,12–15). Scandinavian and Scottish guidelines identify antiplatelet therapy as a risk factor to patients with TBI. In comparison, the United Kingdom National Institute for Health and Care Excellence Guidelines identify anticoagulation therapy as a bleeding risk factor, stressing the absence of adequate evidence regarding patients on antiplatelet therapy (5,6). The Australian Guidelines identify coagulopathy, particularly supratherapeutic anticoagulant, as a risk factor for intracranial bleeding, but does not mention the possible effects of antiplatelet therapy (12).

The prescription of antiplatelet therapy is increasing, along with the frequent use of new antiplatelet drugs or dual antiplatelet therapy; consequently, more effort is required to determine how these drugs represent potential ICH risk factors to TBI patients, and whether such patients are at higher risk of complications developing, requiring evaluation with head CT scans (16,17). We conducted a systematic review and meta-analysis to evaluate the risk of ICH after mild TBI in patients on antiplatelet therapy compared with patients that were not on antithrombotic therapy.

METHODS

Search Strategy and Study Selection

We conducted a systematic review and meta-analysis according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) statement and the MOOSE (Meta-Analysis Oof Observational Studies in Epidemiology) guidelines (18,19).

Following the PICOS (patient, intervention, comparison, outcome, study) model, we defined the clinical question of our study (P = mild TBI; I = antiplatelet therapy; C = neither antiplatelet therapy nor other antithrombotic therapy; O = ICH detected at first CT scan; S = prospective and retrospective studies). We performed a systematic search on MEDLINE and EMBASE from inception to April 2020. We used combinations of the following terms: (*head trauma* OR *brain injury* OR *cerebral injury* OR *brain trauma* OR *cerebral trauma* OR *brain contusion* OR *cerebral contusion* OR *concussion* OR *craniocerebral trauma*) AND (*antithrombotic* OR *platelet aggregation inhibitor* OR *carbasalate calcium* OR *aspirin* OR *lysine acetylsalicylate* OR *clopidogrel* OR *ticagrelor* OR *dipyridamole* OR *prasugrel* OR *ticlopidine* OR *indobufen* OR *thienopyridine* OR *antiplatelet* OR *acetylsalicylic acid* OR *salicyl**). We consulted the reference sections of all included studies, guidelines, and meta-analysis from the last 5 years to locate any additional primary studies not retrieved from our search. We included both prospective and retrospective English-language studies. We excluded case reports and case series. Inclusion criteria for studies were the following: recruitment of patients 16 years and older reporting mild TBI (based on the definition of the study) and provision of data on the incidence of ICH detected at first CT scan in patients on antiplatelet therapy compared with patients not on antithrombotic therapy. If data on mild TBI could not be separated from moderate TBI, but the latter encompassed < 5% of the study population, we included the study. If moderate TBI exceeded 5%, the study was excluded. We performed a sensitivity analysis without the studies including moderate TBI and, given the lack of a uniform definition of mild TBI and the risk of inclusion of minimal TBI, we performed a sensitivity analysis without studies including minimal TBI. We defined ICH as any type of intracranial bleeding (epidural, subdural, subarachnoid, and intraparenchymal hemorrhage) found at the first head CT scan. We defined first CT scan as the first CT scan performed in the ED, irrespective of the time lag between trauma and CT, and according to the study definition.

Two reviewers (S.V.R. and V.B.) independently screened all titles and abstracts to detect potentially eligible studies and remove irrelevant reports. If the reviewers disagreed on a given study, the study was initially included to increase search sensitivity. We then obtained full texts of the selected articles. Four reviewers (S.V.R., V.B., E.M.F., and M.B.) extracted data on study design, inclusion and exclusion criteria, sample size, clinical characteristics of patients, mechanism of injury, antiplatelet medication, and outcomes of interest using a predefined data extraction form. All reviewers discussed disagreements until a consensus was reached. If the

data could not be retrieved from the selected studies, we contacted the corresponding authors for clarification.

Study Outcomes

The primary outcome of our study was the risk of ICH in mild TBI patients on antiplatelet therapy (any antiplatelet therapy) compared with patients not on antithrombotic therapy (i.e., neither on antiplatelet therapy nor on anticoagulant therapy). The secondary outcomes were the risk of adverse events considered as a composite of mortality and neurosurgery in patients on antiplatelet therapy compared with patients not on antithrombotic therapy and the incidence of mortality and neurosurgery after mild TBI in patients with ICH on antiplatelet therapy.

Quality Assessment

Two reviewers (V.B. and E.M.F.) independently assessed the methodological quality of the selected articles using the Newcastle-Ottawa Scale (NOS) (20). All reviewers discussed disagreements until consensus was reached.

NOS assesses the following components: selection, which consists of four items; comparability, which consists of one item; and outcomes, which consists of three items. Each item is scored with a maximum of one star, except for comparability, which can be scored with two stars. Overall, each article can be assigned a maximum of nine stars. Studies that receive nine stars were rated as having "low risk of bias"; studies that receive seven or eight stars were rated as having "moderate risk of bias"; and studies that receive less than seven stars were rated as having "high risk of bias."

Data Analysis

The categorical data were presented as counts and percentages. Continuous variables were presented as the mean ± standard deviation or as median and interquartile ranges, based on the primary studies. For each included study, we calculated the incidence of the events of interest (ICH, mortality, and neurosurgery) as the proportion of events in the two groups, with their 95% confidence intervals (CIs). We performed the meta-analyses of the incidence of events using a random-effects model, after having applied the Freeman-Tukey double arcsine transformation to the original proportions. The pooled incidence estimates obtained from the meta-analyses were then back-transformed, and the results reported as proportions, with their 95% CIs. We compared the risk of events of patients in antiplatelet and in control group by calculating risk ratios (RRs) for each primary study, with their 95% CIs. We then performed meta-analyses of RRs for primary and secondary outcomes. We performed meta-analyses of RRs using random-effects models when expecting some clinical heterogeneity between studies and fixed-effects models when expecting low clinical heterogeneity between studies. We used the χ^2 test to assess statistical heterogeneity (with $p < 0.1$), which was quantified using the inconsistency index (I^2). We considered heterogeneity to be relevant with an I^2 statistic of > 50% (30–60%: moderate heterogeneity; 50–90%: substantial heterogeneity; and 75–100%: considerable heterogeneity).

Subgroup analyses. We aimed to perform prespecified subgroup analyses to evaluate the risk of bleeding associated with different types of antiplatelet medication (i.e., aspirin, clopidogrel, dipyridamole, prasugrel, ticagrelor, and ticlopidine) and with dual antiplatelet therapy.

Sensitivity analyses. We aimed to perform sensitivity analyses by excluding studies containing data on moderate TBI, studies including patients with minimal TBI, and studies at high risk of bias.

We used Review Manager (release 5.3) and STATA software for data analysis.

RESULTS

Study Selection and Characteristics

A total of 6219 articles were identified from the databases. After removing duplicates, 6146 articles remained, of which 6069 articles were excluded based on the title and abstract. The full texts of the remaining 77 articles were assessed for eligibility. After reading the full texts, we excluded 68 articles that did not meet our inclusion criteria (Figure 1). Nine studies with 14,545 patients (3404 patients in the antiplatelet group and 11,141 patients in the control group) were finally included for qualitative and quantitative analysis (21–29). From each study, we only extrapolated the outcomes data of patients corresponding to our inclusion criteria; patients with mild TBI receiving a head CT scan and taking antiplatelet therapy (3269 patients) vs. patients not taking any antithrombotic therapy as a control group (10,532 patients). Descriptive data are given for the entire population included in the primary studies.

The main characteristics of the selected studies are summarized in Table 1. The studies were performed in Italy (n = 2) (21,25), Spain (n = 1) (29), Canada (n = 1) (28), United States (n = 3) (23,24,27), Switzerland (n = 1) (22), and Israel (n = 1) (26). The studies were published between 2003 and 2020. Four studies were multicenter (23,26–28), five had a retrospective design (21,22,25,28,29), and four had a prospective design (23,24,26,27). Five studies enrolled only patients ≥

55 years (23–26,28) and four enrolled patients ≥18 years old (21,22,27,29). Five studies enrolled patients with mild TBI (21,22,25,28,29), two enrolled patients with mild or moderate TBI (23,26), one study included patients with blunt head trauma but did not exclude patients based on Glasgow Coma Scale (GCS) score (27). The severity of trauma and GCS of patients were not clear in one study (24); however, the authors stated that they excluded patients with major trauma criteria (even if the criteria were not specified) and patients with acute change to baseline neurologic findings. The definition of mild TBI was not uniform across the six studies and it was not always clarified. However, there was consensus on defining mild TBI as GCS ≥ 13. Time from trauma to ED presentation was not specified in two studies (21,22), was less than 30 min in one study (23), between 30 min and 72 h in one study (25), < 2 h in one study (29), and < 24 h in one study (27). In the study by Spektor et al., inclusion criterion was injury less than 1 week before arrival and 50.2% of patients enrolled presented < 3 h after the injury, and in the study by Hamden et al., 76.7% of patients enrolled presented within 6 h (24,26). O'Brien included patients presenting to the ED less than 7 days after the trauma, but did not give a detailed description (28).

Study Outcomes

Intracranial hemorrhage. The incidence of ICH ranged from 3.6% to 29.4% in the antiplatelet group and from 1.6% to 21.1% in the control group (Table 2). The random-effects pooled estimate incidence was 9.9% (95% CI 6.1–14.5%; I^2 = 93%) in the antiplatelet group and 6.4% (95% CI 4.1–9.3%; I^2 = 95%) in the control group (Table 2). Patients on antiplatelet therapy had a higher risk of ICH after a mild TBI compared with patients not on antithrombotic therapy, with a pooled RR of 1.51 (95% CI 1.21–1.88; p = 0.0002; I^2 = 44%) (Figure 2).

Mortality and neurosurgery. The composite outcome of mortality and neurosurgery was available for five studies, but in one study there were no events (21,23,26–28). We found no significant difference in risk of mortality and

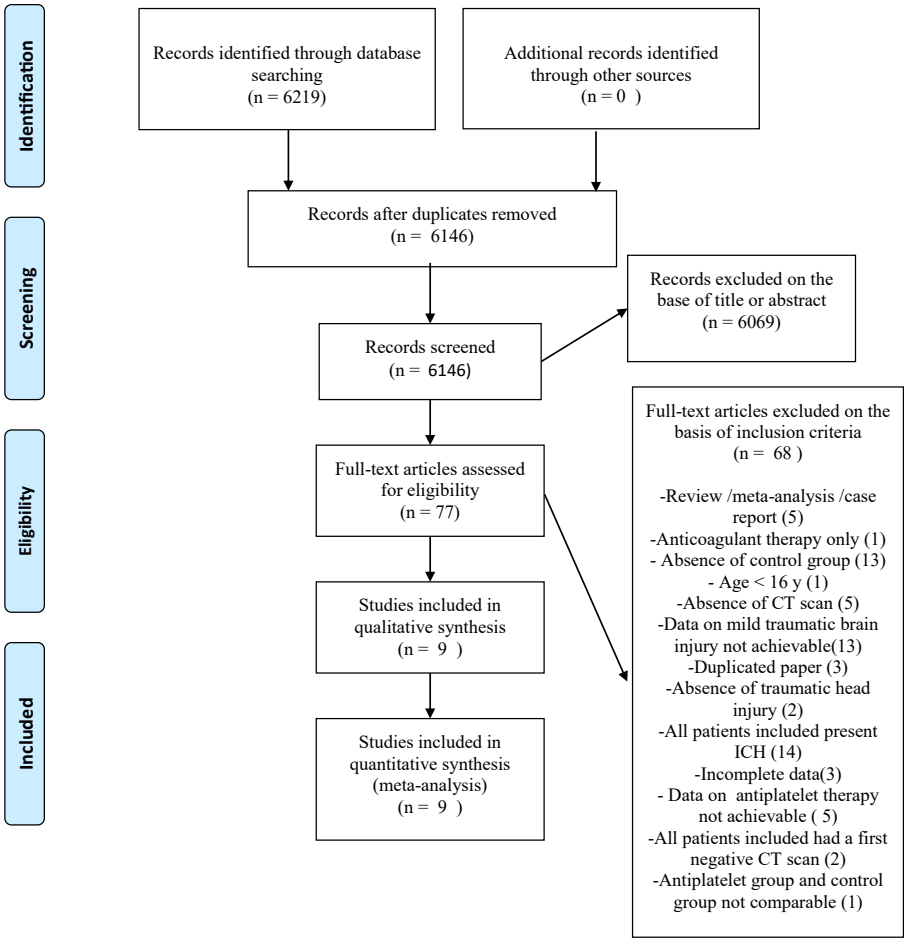

Figure 1. Flow diagram of included studies. CT = computed tomography; ICH = intracranial hemorrhage.

Table 1. Study Characteristics

Study	Data
Spektor, 2003 (26)	
Country	Israel
Single/multicenter	Multicenter
Study design	Prospective
Mild TBI definition	GCS 13–15
Primary outcome	Not specified
Inclusion criteria	Mild (GCS 13–15) or moderate (GCS 9–12) head injury not more than 1 week before arrival at the ED; age ≥ 60 years; taking no anticoagulant medication
Exclusion criteria	Any medication other than low-dose aspirin (100 mg/day), which could affect their coagulation mechanism, hematologic and oncologic diseases
Recruitment time	1995–1997
Patients enrolled, n	231
Age (years), mean ± SD	78 ± NA
Male, n (%)	92 (40)
Time from trauma to ED presentation	<1 week before arrival at the ED 50.2% < 3 h 49.8% > 3 h
Patients enrolled in our meta-analysis, n	103 antiplatelet, 114 control
Aspirin, n	103
Clopidogrel, n	0
Other antiplatelet, n	0
Dual antiplatelet, n	0
Riccardi, 2013 (25)	
Country	Italy
Single/multicenter	Single center
Study design	Retrospective
Mild TBI definition	GCS 14–15 and no neurologic deficits or open injuries
Primary outcome	Any intracranial traumatic findings on CT
Inclusion criteria	Age > 65 years; GCS 15; no dangerous events; no or minor wounds; no neurologic defects, or history of neurologic disease or previous neurosurgical intervention; no history of coagulation disorders, and no assumption of oral anticoagulants; no symptoms after head injury (except pain in site of injury)
Exclusion criteria	GCS < 15; dangerous events; deep wounds or sign of skull fractures; neurologic defects (also related to previous neurologic disorders); history of neurologic disorders (also seizures), previous neurologic intervention; oral anticoagulant, history of coagulopathy; symptoms related to injury (i.e., diffuse headache, vomiting, loss of consciousness after mild head injury, diplopia, amnesia); assumption of alcohol or illicit drugs
Recruitment time	April 2004–April 2010
Patients enrolled, n	2149
Age (years), mean ± SD	81 ± 7.7
Male, n (%)	959 (45)
Time from trauma to ED presentation	Between 30 min and 72 h
Patients enrolled in our meta-analysis, n	617 antiplatelet, 1532 control
Aspirin, n	NA
Clopidogrel, n	NA
Other antiplatelet, n	NA
Dual antiplatelet, n	NA
Hamden, 2014 (24)	
Country	United States
Single/multicenter	Single center
Study design	Prospective
Mild TBI definition	NA
Primary outcome	Not specified
Inclusion criteria	Age ≥ 65 years, presented to the ED with a concern related to a fall, at baseline neurologic status
Exclusion criteria	Major trauma criteria, acute change in baseline neurologic functioning
Recruitment time	16 months (2011–2012)
Patients enrolled, n	799
Age (years), median (IQR)	85 (79–90)
Male, n (%)	265 (33)
Time from trauma to ED presentation	76.7% within 6 h 19.1% > 6 h 4.2% not determined
Patients enrolled in our meta-analysis, n	345 antiplatelet, 298 control
Aspirin, n	345
Clopidogrel, n	0

(*Continued*)

Table 1. Continued

Study	Data
Other antiplatelet, n	0
Dual antiplatelet, n	0
Nishijima, 2018 (23) *	
Country	United States
Single/multicenter	Multicenter
Study design	Prospective
Mild TBI definition	NA
Primary outcome	Presence of ICH on initial cranial CT imaging in the ED based on radiologist interpretation
Inclusion criteria	Age ≥ 55 years with head trauma
Exclusion criteria	Patients transferred by EMS from another receiving facility, patients transported to a nonparticipating hospital, patients with penetrating head trauma, patients for whom we were unable to link hospital data to EMS data
Recruitment time	August 2015 to September 2016
Patients enrolled	1147
Age (years), median (IQR)	73 (63–84)
Male, n (%)	610 (47)
Time from trauma to ED presentation, min, median (IQR)	13 (9–18) from scene to arrival at hospital
Patients enrolled in our meta-analysis, n	368 antiplatelet, 887 control
Aspirin, n	279
Clopidogrel, n	NA
Other antiplatelet, n	NA
Dual antiplatelet, n	NA
Uccella, 2018 (22)	
Country	Switzerland
Single/multicenter	Single center
Study design	Retrospective
Mild TBI definition	GCS 14–15 and LOC/amnesia/disorientation
Primary outcome	ICH after mild TBI in patients on different antithrombotic therapy
Inclusion criteria	Age ≥ 18 years, blunt head trauma with LOC, definite amnesia, or disorientation with a GCS score of 15
Exclusion criteria	Not specified
Recruitment time	January 2014 to December 2016
Patients enrolled	1608
Age (years), mean ± SD	66.9 ± 21.5
Male, n (%)	911 (51)
Time from trauma to ED presentation	NA
Patients enrolled in our meta-analysis, n	547 antiplatelet, 848 control
Aspirin, n	425
Clopidogrel, n	96
Other antiplatelet, n	4
Dual antiplatelet, n	22
Galliazzo, 2019 (21)	
Country	Italy
Single/multicenter	Single center
Study design	Retrospective
Mild TBI definition	GCS 13–15
Primary outcome	ICH after mild TBI with a GCS ≥ 13 in patients treated with different antithrombotic therapy
Inclusion criteria	Age > 18 years, traumatic brain injury, GCS 13–15
Exclusion criteria	Any regimen of low molecular weight heparin
Recruitment time	January 2015–September 2017
Patients enrolled, n	1846
Age (years), median (IQR)	71 (IQR 46–83)
Male, n (%)	926 (50)
Time from trauma to ED presentation	NA
Patients enrolled in our meta-analysis, n	407 antiplatelet, 1222 control
Aspirin, n	NA
Clopidogrel, n	NA
Other antiplatelet, n	NA
Dual antiplatelet, n	NA
Gonzalez, 2020 (29)	
Country	Spain
Single/multicenter	Single center
Study design	Retrospective
Mild TBI definition	NA

(*Continued*)

Table 1. Continued

Study	Data
Primary outcome	To analyze factors associated with post-traumatic ICH after mild TBI
Inclusion criteria	Age > 16 years; recent mild TBI (<2 h); GCS on arrival to the ED of > 14 points; having received a CT scan because of the presence of clinical symptoms, according to the CCHR or NOC
Exclusion criteria	Anticoagulant therapy
Recruitment time	January 2016 to December 2016
Patients enrolled, n	566
Age (years), median (IQR)	55.2 (35–75)
Male, n (%)	329 (58)
Time from trauma to ED presentation	< 2 h
Patients enrolled in our meta-analysis, n	102 antiplatelet 464 control
Aspirin, n	82
Clopidogrel, n	5
Other antiplatelet, n	0
Dual antiplatelet, n	15
O'Brien, 2020 (28)	
Country	Canada
Single/multicenter	Multicenter
Study design	Retrospective
Mild TBI definition	NA
Primary outcome	Clinically significant ICH (defined as any acute ICH that was deemed sufficient to preclude discharge from hospital without further interventions)
Inclusion criteria	Age ≥ 65 years; documented evidence of a blunt head trauma (such as bruising or hematoma) or witnessed head impact; presenting to ED < 7 days following the injury
Exclusion criteria	Any sign or symptoms of TBI (including a deterioration of GCS, LOC post-injury, amnesia, vomiting, confusion, dizziness or vertigo), patients transferred from another hospital, suspected basilar skull fracture, known intracranial anatomic abnormalities such as cancer, previous neurosurgical intervention, chronic subdural hematoma, or with genetic coagulation disorders were excluded, witnessed seizures
Recruitment time	2010–2017
Patients enrolled, n	311
Age (years), mean ± SD	80.1 ± 7.9
Male, n (%)	111 (36)
Time from trauma to ED presentation	< 7 days
Patients enrolled in our meta-analysis, n	86 antiplatelet, 61 control
Aspirin, n	NA
Clopidogrel, n	NA
Other antiplatelet, n	0
Dual antiplatelet, n	NA
Probst, 2020 (27)	
Country	United States
Single/multicenter	Multicenter
Study design	Prospective
Mild TBI definition	NA
Primary outcome	Prevalence of significant intracranial injury on neuroimaging
Inclusion criteria	All adult patients (age > 18 years) with acute blunt head trauma for whom head CT scanning was ordered
Exclusion criteria	Patients with a delayed presentation (>24 h after injury), with penetrating trauma, or with known intracranial injuries who were transferred to a participating center. There were no exclusions based on GCS score
Recruitment time	2007–2015
Patients enrolled, n	9070
Age (years), median (IQR)	53.8 (34.7–74.3)
Male, n (%)	5505 (60.7)
Time from trauma to ED presentation	<24 h
Patients enrolled in our meta-analysis, n	829 antiplatelet, 5715 control
Aspirin, n	635
Clopidogrel, n	109
Other antiplatelet, n	0
Dual antiplatelet, n	85

CCHR = Canadian CT Head Rule; CT = computed tomography; ED = emergency department; EMS = Emergency Medical Services; GCS = Glasgow Coma Scale; ICH = intracranial hemorrhage; IQR = interquartile range; LOC = loss of consciousness; NA = not applicable; NOC = New Orleans Criteria; SD = standard deviation; TBI = traumatic brain injury.

* In this study it was not possible to extrapolate data on mild TBI from data on moderate TBI, but the latter were < 5%. Descriptive data are given for the entire population enrolled in the primary studies.

Table 2. Random-Effects Pooled Estimate Incidence of Intracranial Hemorrhage in Antiplatelet Group and Control Group

	Incidence of ICH			
	Antiplatelet Group*		Control Group†	
Study First Author, Year	n/N	Rate (95% CI)	n/N	Rate (95% CI)
Probst, 2020 (27)	33/829	0.040 (0.028–0.055)	210/5715	0.037 (0.032–0.042)
O'Brien, 2020 (28)	11/86	0.128 (0.066–0.217)	4/61	0.066 (0.018–0.159)
Gonzalez, 2020 (29)	30/102	0.294 (0.208–0.393)	61/464	0.131 (0.102–0.166)
Galliazzo, 2019 (21)	22/387	0.057 (0.036–0.085)	36/787	0.046 (0.032–0.063)
Uccella, 2018 (22)	67/547	0.122 (0.096–0.153)	56/848	0.066 (0.050–0.085)
Nishijima, 2018 (23)	29/253	0.115 (0.078–0.160)	65/713	0.091 (0.071–0.115)
Hamden, 2014 (24)	15/345	0.043 (0.025–0.071)	8/298	0.027 (0.012–0.052)
Riccardi, 2013 (25)	22/617	0.036 (0.022–0.053)	25/1532	0.016 (0.011–0.024)
Spektor, 2003 (26)	22/103	0.214 (0.139–0.305)	24/114	0.211 (0.140–0.297)
Random pooled rate	—	0.099 (0.061–0.145)	—	0.064 (0.041–0.093)

CI = confidence interval; ICH = intracranial hemorrhage.
* Heterogeneity $\chi^2_8 = 119.879$; $p = 0.00$; $I^2 = 93.327\%$.
† Heterogeneity $\chi^2_8 = 167.757$; $p = 0.00$; $I^2 = 95.231\%$.

neurosurgery between patients on antiplatelet therapy compared with the control group (RR 1.16; 95% CI 0.73–1.85; $p = 0.52$; $I^2 = 0\%$) (Figure 3).

The random-effects pooled estimate incidence of the composite outcome of mortality and neurosurgery in patients with ICH was 14.1% (95% CI 1.1–35.4%; $I^2 = 85\%$) in the antiplatelet group and 10.9% (95% CI 0.0–33.3%; $I^2 = 93\%$) in the control group (Table 3).

Quality Assessment

All of the studies were rated as having a moderate risk of bias based on NOS (Table 4). All studies presented an adequate selection quality, as the study populations appeared to be representative of the general population. NOS criteria showed that none of the studies met standard quality for "comparability of cohorts," as analyses adjusted for confounding factors were not performed. Finally, we evaluated that there was not bias in the outcome domain.

Subgroup Analyses

We aimed to perform subgroup analyses to evaluate the bleeding risk associated with different types of antiplatelet medications (e.g., aspirin, clopidogrel, dipyridamole, prasugrel, ticagrelor, and ticlopidine) and with dual antiplatelet therapy; unfortunately, given the lack of data from the original studies, subgroup analyses were possible for aspirin and dual antiplatelet therapy only. RR of ICH for the subgroup of patients taking aspirin alone was 1.27 (95% CI 1.00–1.61; $p = 0.05$; $I^2 = 0\%$), and we found an increased risk of ICH for patients on dual antiplatelet therapy (RR 3.21; 95% CI 2.15–4.76; $p < 0.00001$; $I^2 = 52\%$).

Sensitivity Analyses

We performed a sensitivity analysis removing the study by Nishijima et al. in which moderate TBI could not be separated from mild TBI and the study by Probst et al. in which there were no exclusions based on GCS (23,27). The increased risk of ICH for patients on antiplatelet therapy was confirmed, as an RR of 1.7 (95% CI 1.4–2.05; $p < 0.00001$; $I^2 = 28\%$) was found.

We performed a sensitivity analysis, excluding the studies by Riccardi et al. and O'Brien et al., which included patients with a minimal TBI and the result did not change significantly (RR 1.43; 95% CI 1.22–1.68; $p < 0.0001$; $I^2 = 51\%$) (25,28).

The sensitivity analysis we aimed to perform to exclude studies at high risk of bias was not done because all of the studies were at moderate risk of bias.

DISCUSSION

Our meta-analysis found that patients with mild TBI on antiplatelet therapy have a higher risk of post-traumatic ICH compared with patients not on antiplatelet therapy. This risk was expressed with an RR of 1.51 (95% CI 1.21–1.88). Although wide variability existed in the incidence of ICH among studies, all studies showed an incremental risk of ICH in patients on antiplatelet therapy.

There is a paucity of data on how antiplatelet therapy contributes as a bleeding risk factor in patients with mild TBI; however, from a pathophysiological perspective, these drugs likely contribute to post-traumatic ICH, and this fact is supported by observational studies (30–33). The number of patients receiving antiplatelet therapy is increasing, particularly prescriptions for new antiplatelet drugs and dual antiplatelet therapy.

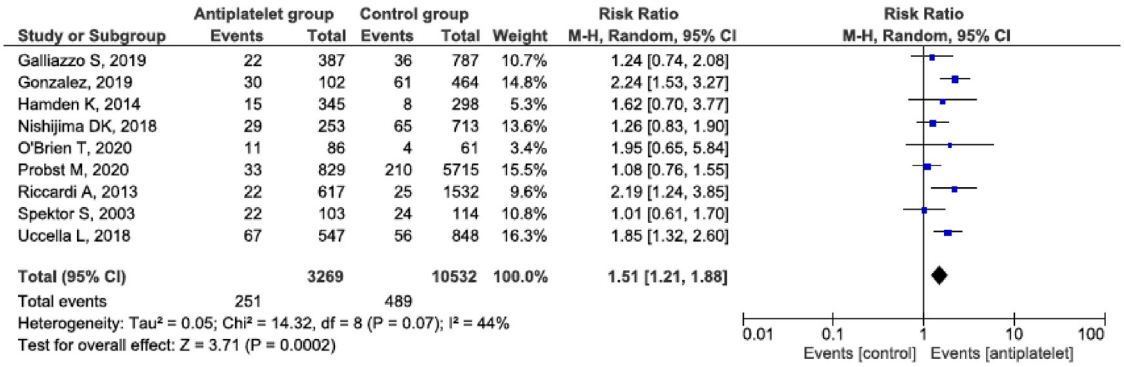

Figure 2. Risk of intracranial hemorrhage in mild traumatic brain injury patients on antiplatelet therapy compared with the control group. CI = confidence interval. M-H = Mantel-Haenszel.

We compared the results of our meta-analysis with data presented in the CCHR (9). The authors identified five high-risk factors (i.e., failure to reach a GCS of 15 within 2 h, suspected open skull fracture, any sign of basal skull fracture, vomiting $\geq$ 2 episodes, and age $\geq$ 65 years) and two medium-risk factors (i.e., amnesia before impact > 30 min and dangerous mechanism of injury) for traumatic ICH in mild TBI, with an OR for increasing risk of brain injury and neurosurgery ranging from 3.6 to 7.3 for high-risk factors and 1.4 to 2.8 for medium-risk factors. The authors recommended that patients with at least one high-risk factor should have a head CT scan, and patients with a medium-risk factor could be managed with careful observation or with a head CT scan, depending on local resources. In comparison, considering that in our meta-analysis patients on antiplatelet therapy had an RR of 1.51 for having an ICH, we speculate that antiplatelet therapy could be compared with the Canadian's medium-risk factors and, as for CCHR medium-risk factor, this implies closer monitoring of patients on antiplatelet therapy. We hypothesize that, as already reported, antiplatelet therapy in association with another risk factor should always be considered to assess the need for CT scan. Particularly considering that antiplatelet therapy is widely prescribed across different populations, its role in ICH development should be evaluated in relation to the characteristics and comorbidities of the patients (13).

We found no difference in the incidence of mortality and neurosurgery between patients on antiplatelet therapy and the control group. Galliazzo et al. documented no deaths and no neurosurgical procedures in both the antiplatelet and control groups (21). In the other studies, the incidence of the composite outcome of mortality and neurosurgery was < 2% (between 1.18% and 1.9%) in the antiplatelet group, except for the study by O'Brien et al., in which the incidence was 2.3% (23–28). However, the number of events was very low, with a larger sample size required to obtain conclusive results.

The data on ICH complications had major implications for patients on antiplatelet therapy because in these patients the detection of minor bleeding is useless, considering that specific antiplatelet antagonists do not exist and neurosurgery is the only treatment of proven benefit. In fact, platelet transfusion is still a matter of debate; several small studies, mainly retrospective, investigated the role of platelet transfusion after ICH in patients on antiplatelet therapy and found contrasting results. Brogi et al., in a recent meta-analysis, found a benefit only in terms of hematoma expansion, although with significant heterogeneity between studies enrolled,

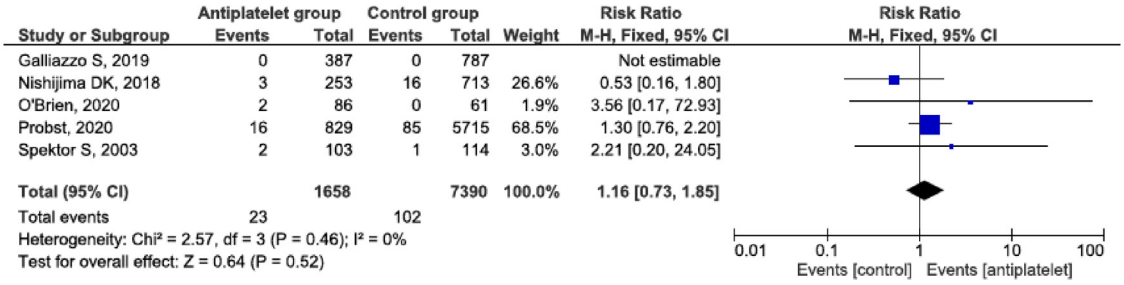

Figure 3. Risk of mortality and neurosurgery in mild traumatic brain injury patients on antiplatelet therapy compared with the control group. CI = confidence interval. M-H = Mantel-Haenszel.

Table 3. Random Pool Estimated Incidence of Composite Outcome Mortality and Neurosurgery in Antiplatelet Group and in Control Group in Patients with Intracranial Hemorrhage

	Incidence of Mortality and Neurosurgery in Patients with ICH			
	Antiplatelet Group*		Control Group†	
Study First Author, Year	n/N	Rate (95% CI)	n/N	Rate (95% CI)
O'Brien, 2020 (28)	2/11	0.182 (0.023–0.518)	0/4	0.000 (0.000–0.602)
Probst, 2020 (27)	16/33	0.485 (0.308–0.665)	85/210	0.405 (0.338–0.474)
Galliazzo, 2019 (21)	0/22	0.000 (0.000–0.154)	0/36	0.000 (0.000–0.097)
Nishijima, 2018 (23)	3/29	0.103 (0.022–0.274)	16/65	0.246 (0.148–0.369)
Spektor, 2003 (26)	2/22	0.091 (0.011–0.292)	1/24	0.042 (0.001–0.211)
Random pooled rate	—	0.141 (0.011–0.354)	—	0.109 (0.000–0.333)

CI = confidence interval; ICH = intracranial hemorrhage.
* Heterogeneity $\chi^2_4 = 26.759$; $p = 0.000$; $I^2 = 85.052\%$.
† Heterogeneity $\chi^2_4 = 59.552$; $p = 0.00$; $I^2 = 93.283\%$.

without finding any significant difference in terms of mortality and severe neurological disability (34).

A recent meta-analysis by Van den Brand et al. evaluated the role of antiplatelet therapy on post-traumatic ICH. The authors included studies that enrolled patients with mild, moderate, and severe TBI and compared ICH risk in patients on antiplatelet therapy with patients not on antiplatelet therapy (35). In contrast to our meta-analysis, the control group contained patients without any antithrombotic therapy and patients on vitamin K antagonists. The authors obtained an OR for increasing risk of ICH after brain injury in patients on antiplatelet therapy of 1.87 (95% CI 1.27–2.74) and an OR of 2.72 (95% CI 1.92–3.85) from the sensitivity analysis, including only patients with mild TBI (GCS score 13–15). Although the population studied in this meta-analysis differs in part from our population, the results obtained from Van den Brand et al. are similar to ours and reaffirm the role of antiplatelet therapy in post-traumatic ICH.

A recent systematic review and meta-analysis of observational studies on the incidence of ICH was conducted in patients with mild TBI on anticoagulant therapy and found a pooled random-effect ICH incidence of 8.9% (95% CI 5–13.8%; $I^2 = 93\%$) (36). Minhas et al. obtained an incidence of ICH similar to that for patients on antiplatelet therapy in our meta-analysis (8.6%; 95% CI 5–13%; $I^2 = 92\%$) (36). This similar incidence in ICH for patients on antiplatelet therapy and patients on anticoagulant therapy suggests that the risk of ICH is similar in these 2 populations. However, focused studies on this topic are needed to obtain robust conclusions.

Our meta-analysis showed wide variability in the incidence of ICH across studies. ICH incidence was much higher in Spektor et al. (around 21% in both groups) compared with other studies (range 1.6% to 12.2%) (26). It is not clear why this variability exists. One explanation is the enrollment of different populations. For example, Riccardi et al. only enrolled patients with mild TBI and no other symptoms (15). In comparison, Uccella et al. enrolled patients with loss of consciousness, post-traumatic amnesia, and other clinical features underlying more severe TBI, although mild according to mild TBI definition (22). Although the incidence of intracranial bleeding varies, all studies showed an incremental risk of ICH and no differences in neurosurgery and mortality were detected, although this result needs to be confirmed in future studies.

Table 4. Newcastle-Ottawa Bias Assessment for Cohort Studies*

Study First Author, Year	Selection	Comparability	Outcome	Quality	Risk of Bias
Probst, 2020 (27)	****	0	***	******	Moderate
O'Brien, 2020 (28)	****	0	***	******	Moderate
Gonzalez, 2020 (29)	****	0	***	******	Moderate
Galliazzo, 2019 (21)	****	0	***	******	Moderate
Uccella, 2018 (22)	****	0	***	******	Moderate
Nishijima, 2018 (23)	****	0	***	******	Moderate
Hamden, 2014 (24)	****	0	***	******	Moderate
Riccardi, 2013 (25)	****	0	***	******	Moderate
Spektor, 2003 (26)	****	0	***	******	Moderate

* A star is awarded for each criterion of the assessment tool that is met. Nine stars = low risk of bias; seven to eight stars = moderate risk of bias; zero to six stars = high risk of bias.

Another interesting aspect is how different types of antiplatelet drugs contribute to the development of posttraumatic ICH. Several antiplatelet drugs exist, with increasing numbers of patients receiving dual antiplatelet therapy. It would be useful to establish whether different drugs cause different effects. Analysis of data from two of the assessed studies found that aspirin has a minor role in ICH developing (22,26). Uccella et al. reported that the number of bleeding events was higher in patients using the new antiplatelet generation (22). Our subgroup analyses found no role of aspirin alone in increasing risk of ICH, and, as expected, we found an increased risk of ICH in patients on dual antiplatelet therapy (RR 3.21; 95% CI 2.15–4.76). However, this result must be considered with caution, as only three studies were included in the subgroup analysis. Probst et al. found an incidence of ICH of 2.7% in patients on clopidogrel; unfortunately, it was the only study in which these data were available and a meta-analysis was not performed (27).

Additional studies are required on this topic for use in clinical practice.

Limitations

The limitations of our study were attributed to the intrinsic limitations of the evaluated articles. For example, one-half of the studies were retrospective, lacking analyses on potential confounding factors when evaluating the risk of ICH (4,9,12). In addition, these articles did not evaluate the risk of ICH in patients who did not receive a CT scan, potentially creating a selection bias. In future studies, it would be interesting to have clinical follow-up for patients not receiving CT scan. Another limit that need to be emphasized is that, considering the lack of consensus on the definition of mild TBI, we could have included patients with minimal TBI rather than mild TBI, underestimating the risk of antiplatelets. We tried to overcome this limit with a sensitivity analysis without studies potentially including patients with minimal TBI, and we obtained similar results. However, we believe that in clinical practice, regardless of the strict definition of minimal or mild TBI, the identification of potential risk factors for bleeding is of pivotal importance to better stratify risk of complication. Finally, we had insufficient data to perform subgroup analyses to evaluate the bleeding risk associated with different types of antiplatelet medication, except for aspirin and dual antiplatelet.

CONCLUSIONS

This study found that patients on antiplatelet therapy have a higher risk of ICH after mild TBI compared with patients not on antiplatelet therapy. Although there was wide variability in the incidence of ICH among studies, all studies found an incremental risk of ICH in patients on antiplatelet therapy. However, the risk is just slightly increased, and the need for performing a CT scan in patients on antiplatelet therapy after a mild TBI should be evaluated case by case, but always considered in patients with other risk factors.

REFERENCES

1. Rutland-Brown W, Langlois JA, Thomas KE, Xi YL. Incidence of traumatic brain injury in the United States, 2003. J Head Trauma Rehabil 2006;21:544–8.
2. Taylor CA, Bell JM, Breiding MJ, Xu L. Traumatic brain injury-related emergency department visits, hospitalizations, and deaths—United States, 2007 and 2013. MMWR Surveill Summ 2017;66(9):1–16.
3. Jagoda AS, Bazarian JJ, Bruns JJ, et al. Clinical policy: neuroimaging and decisionmaking in adult mild traumatic brain injury in the acute setting. J Emerg Nurs 2009;35:5–40.
4. O'Keefe K. Traumatic brain injury. In: Cone D, Brice JH, Delbridge TR, Myers JB, eds. Emergency Medical Services: Clinical Practice and Systems Oversight, 1. Hoboken, NJ: Wiley; 2015:237–42.
5. Rath G, Ray B. Head injury: assessment and early management. Pract Guidel Anesth 2016;2014:53.
6. Powers KS. Head injury: triage, assessment, investigation and early management of head injury in children, young people and adults. Partial update of NICE CG56. Appendices. Natl Clin Guidel Cent 2014;1–618.
7. Albers CE, Von Allmen M, Evangelopoulos DS, Zisakis AK, Zimmermann H, Exadaktylos AK. What is the incidence of intracranial bleeding in patients with mild traumatic brain injury? A retrospective study in 3088 canadian CT head rule patients. Biomed Res Int 2013;2013:453978.
8. Brenner DJ, Hall EJ. Computed tomography—an increasing source of radiation exposure: commentary. N Engl J Med 2007;2277–84.
9. Stiell IG, Wells GA, Vandemheen K, et al. The Canadian CT Head Rule for patients with minor head injury. Lancet 2001;357(9266):1391–6.
10. Mower WR, Hoffman JR, Herbert M, Wolfson AB, Pollack CV, Zucker MI. Developing a decision instrument to guide computed tomographic imaging of blunt head injury patients. J Trauma 2005;59:954–9.
11. Haydel MJ, Preston CA, Mills TJ, Luber S, Blaudeau E, DeBlieux PMC. Indications for computed tomography in patients. N Engl J Med 2000;343:100–5.
12. Reed D. Adult Trauma Clinical Practice Guidelines. Initial Management of Closed Head Injury in Adults. 2nd Edition. North Sydney, NSW, Australia: NSW Ministry of Health; 2011.
13. Unden J, Ingebrigtsen T, Romner B. Scandinavian guidelines for initial management of minimal, mild and moderate head injuries in adults: an evidence and consensus-based update. BMC Med 2013;11:50.
14. Rusticali B, Gili L, Jefferson T, et al. Treatment of minor and severe traumatic brain injury. National reference guidelines. Minerva Anestesiol 2008;74:583–616.
15. SIGN. Early management of patients with a head injury. Scottish Intercoll Guidel Netw 2009;110:84.
16. Williams CD, Chan AT, Elman MR, et al. Aspirin use among adults in the U.S.: results of a national survey. Am J Prev Med 2015;48:501–8.
17. Li L, Geraghty OC, Mehta Z, Rothwell PM. Age-specific risks, severity, time course, and outcome of bleeding on long-term antiplatelet treatment after vascular events: a population-based cohort study. Lancet 2017;390(10093):490–9.
18. Moher D, Liberati A, Tetzlaff J, Altman DG. Academia and clinic annals of internal medicine preferred reporting items for systematic

reviews and meta-analyses: the PRISMA statement. Annu Intern Med 2009;151:264–9.
19. Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology. JAMA 2000;283:2008–12.
20. Wells GA, Shea B, O'Connel D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of non randomised studies in meta-analysis. Available at: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp. Accessed August 9, 2020.
21. Galliazzo S, Bianchi MD, Virano A, et al. Intracranial bleeding risk after minor traumatic brain injury in patients on antithrombotic drugs. Thromb Res 2019;174:113–20.
22. Uccella L. Are antiplatelet and anticoagulants drugs a risk factor for bleeding in mild traumatic brain injury? World Neurosurg 2018;110:e339–45.
23. Nishijima DK, Gaona SD, Waechter T, et al. The incidence of traumatic intracranial hemorrhage in head-injured older adults transported by EMS with and without anticoagulant or antiplatelet use. J Neurotrauma 2018;35:750–9.
24. Hamden K, Agresti D, Jeanmonod R, Woods D, Reiter M, Jeanmonod D. Characteristics of elderly fall patients with baseline mental status: high-risk features for intracranial injury. Am J Emerg Med 2014;32:890–4.
25. Riccardi A, Frumento F, Guiddo G, et al. Minor head injury in the elderly at very low risk: a retrospective study of 6 years in an emergency department (ED). Am J Emerg Med 2013;31:37–41.
26. Spektor S, Agus S, Merkin V, Constantini S. Low-dose aspirin prophylaxis and risk of intracranial hemorrhage in patients older than 60 years of age with mild or moderate head injury: a prospective study. J Neurosurg 2003;99:661–5.
27. Probst MA, Gupta M, Hendey GW, et al. Prevalence of intracranial injury in adult patients with blunt head trauma with and without anticoagulant or antiplatelet use. Ann Emerg Med 2020;75:354–64.
28. O'Brien T, Mitra B, Le Sage N, et al. Clinically significant traumatic intracranial hemorrhage following minor head trauma in older adults: a retrospective cohort study. Brain Inj 2020;34:834–9.
29. Gonzalez GM, Dusseck Brutus R, Garcia-Olloqui A, et al. Role of antiplatelet therapy in the development of intracranial bleeding after mild traumatic brain injury. Med Clin (Barc) 2020;154(2):52–4.
30. Fabbri A, Servadei F, Marchesini G, Bronzoni C, Montesi D, Arietta L. Antiplatelet therapy and the outcome of subjects with intracranial injury: the Italian SIMEU study. Crit Care 2013;17(2):R53.
31. Brewer ES, Reznikov B, Liberman RF, et al. Incidence and predictors of intracranial hemorrhage after minor head trauma in patients taking anticoagulant and antiplatelet medication. J Trauma 2011;70(1):E1–5.
32. Moustafa F, Roubin J, Pereira B, et al. Predictive factors of intracranial bleeding in head trauma patients receiving antiplatelet therapy admitted to an emergency department. Scand J Trauma Resusc Emerg Med 2018;26:50.
33. Nishijima DK, Offerman SR, Ballard DW, et al. Risk of traumatic intracranial hemorrhage in patients with head injury and preinjury warfarin or clopidogrel use. Acad Emerg Med 2013;20:140–5.
34. Brogi E, Corbella D, Coccolini F, et al. The role of platelet transfusions after intracranial hemorrhage in patients on antiplatelet agents: a systematic review and meta-analysis. World Neurosurg 2020; https://doi.org/10.1016/j.wneu.2020.03.216.
35. Van den Brand CL, Tolido T, Rambach AH, et al. Systematic review and meta-analysis: is pre-injury antiplatelet therapy associated with traumatic intracranial hemorrhage? J Neurotrauma 2017;34:1–7.
36. Minhas H, Welsher A, Turcotte M, et al. Incidence of intracranial bleeding in anticoagulated patients with minor head injury: a systematic review and meta-analysis of prospective studies. Br J Haematol 2018;183:119–26.

ARTICLE SUMMARY

1. Why is this topic important?

We believe this study addresses an important topic because emergency physicians often face mild traumatic brain injury in their daily clinical practice and to date there is no consensus on how to manage patients on antiplatelet therapy.

2. What does this review attempt to show?

This review attempts to show the role of antiplatelet therapy in developing intracranial hemorrhage after mild traumatic brain injury.

3. What are the key findings?

Patients on antiplatelet therapy have a slightly increased risk of intracranial hemorrhage after mild traumatic brain injury compared with patients not on antithrombotic therapy. No difference was found in mortality and neurosurgery combined.

4. How is patient care impacted?

We suggest to always consider obtaining a computed tomography scan in patients with mild traumatic brain injury on antiplatelet therapy if they have other risk factors.