Prevalence of Intracranial Injury in Adult Patients With Blunt Head Trauma With and Without Anticoagulant or Antiplatelet Use

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Study objective: We determine the prevalence of significant intracranial injury among adults with blunt head trauma who are receiving preinjury anticoagulant or antiplatelet medications.

Methods: This was a multicenter, prospective, observational study conducted from December 2007 to December 2015. Patients were enrolled in 3 emergency departments (EDs) in the United States. Adults with blunt head trauma who underwent neuroimaging in the ED were included. Use of preinjury aspirin, clopidogrel, and warfarin was recorded. Data on direct oral anticoagulants were not specifically recorded. The primary outcome was prevalence of significant intracranial injury on neuroimaging. The secondary outcome was receipt of neurosurgical intervention.

Results: Among 9,070 patients enrolled in this study, the median age was 53.8 years (interquartile range 34.7 to 74.3 years) and 60.7% were men. A total of 1,323 patients (14.6%) were receiving antiplatelet medications or warfarin, including 635 receiving aspirin alone, 109 clopidogrel alone, and 406 warfarin alone. Compared with that of patients without any coagulopathy, the relative risk of significant intracranial injury was 1.29 (95% confidence interval [CI] 0.88 to 1.87) for patients receiving aspirin alone, 0.75 (95% CI 0.24 to 2.30) for those receiving clopidogrel alone, and 1.88 (95% CI 1.28 to 2.75) for those receiving warfarin alone. The relative risk of significant intracranial injury was 2.88 (95% CI 1.53 to 5.42) for patients receiving aspirin and clopidogrel in combination.

Conclusion: Patients receiving preinjury warfarin or a combination of aspirin and clopidogrel were at increased risk for significant intracranial injury, but not those receiving aspirin alone. Clinicians should have a low threshold for neuroimaging when evaluating patients receiving warfarin or a combination of aspirin and clopidogrel. [Ann Emerg Med. 2020;75:354-364.]

Please see page 355 for the Editor's Capsule Summary of this article.

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INTRODUCTION

Background

Antiplatelet and anticoagulant medications are commonly used in North America for a variety of indications.[1-5] It is widely believed that preinjury use of these medications increases the risk of traumatic intracranial injury and worsens clinical outcomes after blunt head trauma.[6-9] This belief is based largely on biological plausibility and retrospective cohort studies.[10,11] Current guidelines from the American College of Emergency Physicians (ACEP) and the National Institute for Health and Care Excellence on the initial management of traumatic brain injury recommend a noncontrast head computed tomography (CT) scan for all patients with coagulopathy.[12,13] However, these guidelines do not provide guidance for individual medications such as aspirin or other antiplatelet agents. Both cite a paucity of evidence on this topic partly because of exclusion of anticoagulated patients from studies conducted to derive clinical prediction instruments for blunt head trauma (eg, the Canadian CT Head Rule and the New Orleans Criteria).[14,15] Other attempts to assess the increased risk of intracranial injury associated with coagulopathy have included this as one variable without separating different subtypes of coagulopathy based on individual medications.[16] Contrary to common belief, anticoagulant and antiplatelet use was not shown to be predictive of traumatic intracranial hemorrhage after adjusted analysis in more recent, prospective studies.[17,18]

Editor's Capsule Summary

What is already known on this topic

Anticoagulant and antiplatelet therapies are risk factors for intracranial bleeding among head injury patients, but this concept has been based mainly on retrospective studies.

What question this study addressed

What is the risk for intracranial injury (defined as bleeding, brain edema, or complicated skull fracture) for head injury patients receiving aspirin, clopidogrel, or warfarin?

What this study adds to our knowledge

This prospective multicenter study of 9,070 patients found that warfarin use increased risk compared with nonuse. Aspirin and clopidogrel alone were not clearly risk factors but the combined use did increase risk.

How this is relevant to clinical practice

Although this study did not include patients receiving direct oral anticoagulants, warfarin and combination antiplatelet therapy were risk factors for intracranial injury. Imaging should be strongly considered for patients receiving anticoagulant or combination antiplatelet medication.

Importance

Given how commonly patients with blunt head trauma present to the emergency department (ED) and how often they are receiving anticoagulant or antiplatelet medication, it is important to know what the actual magnitude of this increased risk is, if any, for specific agents such as warfarin, aspirin, and clopidogrel.

Goals of This Investigation

Our objective was to determine the prevalence of significant intracranial injury and neurosurgical intervention after acute blunt head trauma in ED patients receiving specific preinjury anticoagulant or antiplatelet medications compared with those without any coagulopathy.

MATERIALS AND METHODS

Study Design and Setting

This was a preplanned secondary analysis of data from a large, multicenter, observational study that was conducted to derive and validate a clinical decision instrument to predict significant intracranial injury among patients presenting with blunt head trauma.[19] Two of the participating EDs were located at Level I urban academic trauma centers, and one was a Level II suburban community trauma center in California. We obtained institutional review board approval from all participating centers.

Selection of Participants

All adult patients (≥18 years) with acute blunt head trauma for whom head CT scanning was ordered between December 2007 and December 2015 were eligible for inclusion. Patients with a delayed presentation (>24 hours after injury), with penetrating trauma, or with known intracranial injuries who were transferred to a participating center were excluded. There were no exclusions based on Glasgow Coma Scale (GCS) score. The decision to obtain CT imaging was based on the clinical judgment of the treating physician and was not dictated by study protocol. Other methodological details have been published previously.[20]

Data Collection and Processing

Research assistants were trained to approach the treating clinicians and collect demographic, clinical, and medication information on each patient, using a standardized data collection form before CT (Figure E1, available online at http://www.annemergmed.com). For those deemed unstable, determined by the clinician as any patient who might be harmed by a delay in imaging, data collection was bypassed and immediate imaging was obtained before criterion assessment. Clinicians were asked to complete assessments of the study criteria as soon as possible before imaging results becoming available. Specifically, clinicians were queried about whether the patient in question was receiving aspirin, clopidogrel, or warfarin, or had any other coagulopathy. "Other coagulopathy" was not strictly defined and could have included factors such as other anticoagulant medications (eg, heparin) or medical conditions (eg, severe hepatic dysfunction, hemophilia). Possible responses were yes, no, or unknown. Clinical variables included in the National Emergency X-Radiography Utilization Study–II[16] and Canadian CT Head Rule[14] were prospectively collected as well, including significant vomiting, dangerous mechanism of injury (defined as pedestrian struck by motor vehicle, occupant ejected from motor vehicle, and fall from height >3 feet or 5 stairs), GCS score of 15, neurologic deficit, amnesia, and level of alertness.

Outcome Measures

Our primary outcome measure was the presence of significant intracranial injury on neuroimaging studies. The

definition of significant intracranial injury was based on previous work involving experts in neurosurgery, neuroradiology, and emergency medicine.[21] Isolated linear or basilar skull fractures, single small cerebral contusions, and coincidental or congenital abnormalities were not considered to represent a significant intracranial injury. A list of significant intracranial injuries is shown in Figure E2 (available online at http://www.annemergmed.com) and includes injuries such as subarachnoid hemorrhage, subdural and epidural hematoma, depressed or complex skull fracture, intracerebral hematoma, diffuse cerebral edema, intraventricular hemorrhage, cerebral contusions greater than 2 cm in diameter, diffuse cerebral edema, pneumocephalus, and diastasis of the skull. Our secondary outcome was the need for neurosurgical intervention, defined in previous studies specifically as death caused by head injury, craniotomy, elevation of skull fracture, intubation related to head injury, and intracranial pressure monitoring, within 7 days of head injury.[14]

Copies of all final radiology reports were collected and abstracted by trained research assistants to determine the presence or absence of significant intracranial injuries. The diagnosis of significant intracranial injury was based on final radiologic interpretations of all imaging studies as read by board-certified radiologists. Investigators determined final injury classification while blinded to information about clinical and medication variables. Intracranial injury and neurosurgical intervention data were collated with clinical data to form the final study database.

Because we enrolled only patients who underwent neuroimaging, it is possible that significant injuries were missed among the unimaged patients. To address this potential verification bias, we conducted 3-month follow-up interviews with 368 consecutive patients with blunt head injury who presented between July 2011 and March 2015 at one study center. Follow-up interviews assessed whether each patient had received neuroimaging, a diagnosis of intracranial injury, or a neurosurgical intervention at another facility during a subsequent visit. We also reviewed case logs and trauma logs to identify any instances of significant intracranial injuries or injuries requiring neurosurgical intervention that occurred among patients with blunt head trauma who were treated but did not receive imaging on their initial presentation.

Primary Data Analysis

We performed all analyses with SAS (version 9.3; SAS Institute, Inc., Cary, NC). Patient characteristics are reported with descriptive statistics presented as frequencies, medians, and interquartile ranges. Our sample size calculation was based on the number of imaged head trauma patients estimated to be receiving aspirin (≈5%). Using the following equation to calculate the lower confidence interval (CI) of a proportion, $0.99=N/(N+F\ 0.05,2,2N)$, we derived that our necessary sample size would be 370 patients undergoing head CT imaging and receiving preinjury aspirin. Thus, we needed to enroll $20\times370=7{,}400$ patients overall. Our final sample size of 9,070 exceeded this number. We did not specifically power the study to examine the effects of warfarin or clopidogrel.

We compared the prevalence of primary and secondary outcome measures across specific anticoagulant or antiplatelet medication groups, including aspirin alone, clopidogrel alone, warfarin alone, aspirin and clopidogrel combined, aspirin and warfarin combined, and other coagulopathy. Prevalences were compared by using relative risks (RRs) with 95% CIs. We then performed a subgroup analysis with the following subgroups: patients aged 65 years or older, those with significant comorbidity, those with dangerous mechanism of injury, those with GCS score of 15, and those with a normal level of alertness. We also performed a sensitivity analysis using "any traumatic injury" as the primary outcome, which included findings such as a small solitary contusion, isolated linear skull fracture, and localized subarachnoid blood less than 1 mm thick, all in neurologically intact patients. Responses of "unknown" were treated as missing data, and no data imputation was performed.

RESULTS

Characteristics of Study Subjects

During the 8-year study period, we prospectively enrolled 9,070 adult patients presenting with blunt head trauma and undergoing CT scanning of the head (Figure 1). Median age was 53.8 years (range 18 to 104 years; interquartile range 34.7 to 74.3 years) and 39% were women. Overall, 1,323 patients (14.6%) were receiving at least one antiplatelet or anticoagulant medication. Most patients (77.5%) had a GCS score of 15, a dangerous mechanism of injury (57.6%), and a normal level of alertness (72.3%). Further clinical and demographic data are presented in Table 1. Overall, there were 532 patients (5.9%) with a significant intracranial injury, and 297 (3.3%) required neurosurgical intervention. Of the 1,323 patients receiving antiplatelet or anticoagulant medications, 635 (7.0%) were receiving aspirin alone, 109 (1.2%) were receiving clopidogrel alone, 406 (4.5%) were receiving warfarin alone, 85 (0.9%) were receiving aspirin and clopidogrel concurrently, and 42 (0.5%) were receiving aspirin and warfarin concurrently. Further coagulopathy data are presented in Table E1, available online at

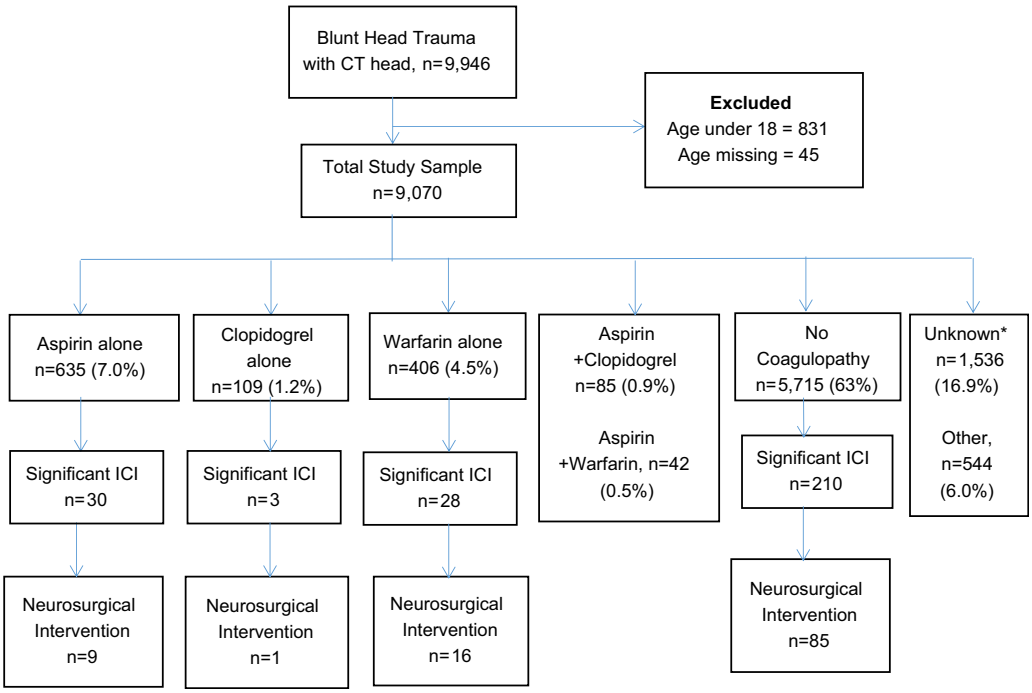

Figure 1. Patient flow diagram. *"Unknown" indicates patients who had unknown status for all 3 medications. "Other" includes patients receiving a combination of the anticoagulant/antiplatelet medications and patients with other coagulopathy. (These subjects were not included in the primary analysis.) *ICI*, Significant intracranial injury.

http://www.annemergmed.com. Of the 368 consecutive patients with blunt head trauma who did not undergo initial neuroimaging, zero reported evidence of a subsequently diagnosed intracranial injury. Review of trauma logs also revealed no evidence of missed intracranial injuries.

Main Results

Among patients receiving aspirin alone, 30 of 635 had a significant intracranial injury (4.7%; 95% CI 3.3% to 6.6%); among those receiving clopidogrel alone, 3 of 109 had a significant intracranial injury (2.8%; 95% CI 0.7% to 7.0%); and among those receiving warfarin alone, 28 of 406 had a significant intracranial injury (6.9%; 95% CI 4.7% to 9.6%). The prevalence of significant intracranial injury among patients not receiving any of the above agents and without any other coagulopathy (labeled "no coagulopathy" in Table 2) was 210 of 5,715 (3.7%; 95% CI 3.2% to 4.2%). The prevalence of significant intracranial injury among patients receiving aspirin alone or clopidogrel alone was not significantly different than among those with no coagulopathy (Table 2). There was a statistically significant increase in risk of significant intracranial injury in patients receiving warfarin alone (RR=1.88; 95% CI 1.28 to 2.75), as well as aspirin and clopidogrel combination therapy (RR=2.88; 95% CI 1.53 to 5.42). Further data in regard to the RR of significant intracranial injury are presented in Table 2 and Figure 2.

Among patients receiving aspirin alone, 9 of 635 required a neurosurgical intervention (1.4%; 95% CI 0.7% to 2.5%); among those receiving clopidogrel alone, 1 of 109 required a neurosurgical intervention (0.9%; 95% CI 0.1% to 4.0%); and among those receiving warfarin alone, 16 of 406 required a neurosurgical intervention (3.9%; 95% CI 2.3% to 6.1%). The prevalence of neurosurgical intervention among patients with no coagulopathy was 85 of 5,715 (1.5%; 95% CI 1.2% to 1.8%). The prevalence of neurosurgical intervention among patients receiving aspirin alone or clopidogrel alone was not significantly different than among those with no coagulopathy. There was a statistically significant increase in risk of requiring a neurosurgical intervention in patients receiving warfarin alone (RR=2.65; 95% CI 1.57 to 4.48) and in those receiving aspirin and clopidogrel combined (RR=4.75; 95% CI 2.13 to 10.6). Further data in regard to prevalence of neurosurgical intervention are presented in Table 2.

A sensitivity analysis using any traumatic injury as the primary outcome resulted in similar findings, with one notable exception. Aspirin and warfarin combination therapy was associated with an increased RR of traumatic injury (RR=2.08; 95% CI 1.05 to 4.10). See Table 3 for more detail.

Table 1. Characteristics of patients presenting to the ED with blunt head trauma.

Variable	All Patients, N=9,070, No. (%)	Aspirin Alone, n=635, No. (%)	Clopidogrel Alone, n=109, No. (%)	Warfarin Alone, n=406, No. (%)	Combination of AC/AP Medications, n=173, No. (%)
Age, median (IQR), y	54.8 (34.7–74.3)	81.0 (70.5–87.3)	81.3 (69.3–88.3)	80.0 (68.0–87.3)	80.7 (70.0–87.2)
Sex					
Women	3,543 (39.1)	323 (50.9)	58 (53.2)	185 (45.6)	56 (32.4)
Men	5,505 (60.7)	312 (49.1)	51 (46.8)	219 (53.9)	117 (67.6)
Unknown	22 (0.2)	0	0	2 (0.5)	0
Race/ethnicity					
Black	949 (10.5)	40 (6.3)	3 (2.8)	24 (5.9)	7 (4.0)
White	5,520 (60.9)	467 (73.5)	75 (68.8)	308 (75.9)	125 (72.3)
Hispanic	1,325 (14.6)	30 (4.7)	9 (8.3)	22 (5.4)	9 (5.2)
Asian	499 (5.5)	34 (5.4)	7 (6.4)	19 (4.7)	10 (5.8)
Other	777 (8.5)	64 (10.1)	15 (13.7)	33 (8.0)	22 (12.7)
Significant ICI					
No	8,538 (96.7)	605 (95.3)	106 (97.2)	378 (93.1)	161 (93.1)
Yes	532 (5.9)	30 (4.7)	3 (2.8)	28 (6.9)	12 (6.9)
NSx intervention					
No	8,773 (96.7)	626 (98.6)	108 (99.1)	390 (96.1)	165 (95.4)
Yes	297 (3.3)	9 (1.4)	1 (0.9)	16 (3.9)	8 (4.6)
Dangerous mechanism of injury*					
No	3,053 (33.7)	356 (56.1)	64 (58.7)	218 (53.7)	98 (56.6)
Yes	5,221 (57.6)	239 (37.6)	40 (36.7)	153 (37.7)	61 (35.3)
Unknown	796 (8.8)	40 (6.3)	5 (4.6)	35 (8.6)	14 (8.1)
GCS score 15					
No	2,041 (22.5)	99 (15.6)	18 (16.5)	60 (14.8)	21 (12.1)
Yes	7,029 (77.5)	536 (84.4)	91 (83.5)	346 (85.2)	152 (87.9)
Significant vomiting					
No	8,625 (95.1)	612 (96.4)	108 (99.1)	392 (96.6)	171 (98.8)
Yes	354 (3.9)	22 (3.5)	1 (0.9)	13 (3.2)	2 (1.2)
Unknown	91 (1.0)	1 (0.2)	0	1 (0.2)	0
Significant comorbidity					
No	4,418 (48.7)	289 (45.5)	18 (16.5)	54 (13.3)	23 (13.3)
Yes	1,754 (19.3)	263 (41.4)	61 (56.0)	250 (61.6)	126 (72.8)
Unknown	2,898 (32.0)	83 (13.1)	30 (27.5)	102 (25.1)	24 (13.8)
Signs of basilar/depressed skull fracture					
No	8,647 (95.3)	616 (97.0)	107 (98.2)	395 (97.3)	169 (97.7)
Yes	299 (3.3)	13 (2.0)	0	7 (1.7)	3 (1.7)
Unknown	124 (1.4)	6 (0.9)	2 (1.8)	4 (1.0)	1 (0.6)
Scalp hematoma					
No	5,963 (65.7)	371 (58.4)	59 (54.1)	259 (63.8)	106 (61.3)
Yes	3,043 (33.6)	257 (40.5)	48 (44.1)	144 (35.5)	67 (38.7)
Unknown	64 (0.7)	7 (1.1)	2 (1.8)	3 (0.7)	0
Neurologic deficit					
No	7,463 (82.3)	569 (89.6)	97 (89.0)	349 (86.0)	153 (88.4)
Yes	1,364 (15.0)	51 (8.0)	8 (7.3)	51 (12.6)	16 (9.2)
Unknown	243 (2.7)	15 (2.4)	4 (3.7)	6 (1.5)	4 (2.3)

Table 1. Continued.

Variable	All Patients, N=9,070, No. (%)	Aspirin Alone, n=635, No. (%)	Clopidogrel Alone, n=109, No. (%)	Warfarin Alone, n=406, No. (%)	Combination of AC/AP Medications, n=173, No. (%)
Abnormal level of alertness					
No	6,557 (72.3)	529 (83.3)	90 (82.6)	333 (82.0)	150 (86.7)
Yes	2,418 (26.7)	97 (15.3)	17 (15.6)	71 (17.5)	22 (12.7)
Unknown	95 (1.0)	9 (1.4)	2 (1.8)	2 (0.5)	1 (0.6)
Abnormal behavior					
No	6,982 (77.0)	551 (86.8)	94 (86.2)	351 (86.5)	155 (89.6)
Yes	1,924 (21.2)	75 (11.8)	10 (9.2)	50 (12.3)	16 (9.2)
Unknown	164 (1.8)	9 (1.4)	5 (4.6)	5 (1.2)	2 (1.2)
Amnesia >30 min					
No	6,068 (66.9)	477 (75.1)	85 (78.0)	311 (76.6)	143 (82.7)
Yes	1,405 (15.5)	98 (15.4)	9 (8.3)	47 (11.6)	18 (10.4)
Unknown	1,597 (17.6)	60 (9.4)	15 (13.8)	48 (11.8)	12 (6.9)

AC, Anticoagulant; *AP*, antiplatelet; *IQR*, interquartile range; *NSx*, neurosurgical.
*Dangerous mechanism of injury is defined as pedestrian struck by motor vehicle, occupant ejected from motor vehicle, or fall from height greater than 3 feet or 5 stairs.

Our subgroup analysis revealed that in the subgroup of patients aged 65 years and older, none of the medications, as monotherapy or in combination, were statistically significantly associated with prevalence of significant intracranial injury. Similar results were found in the subgroup of patients with a significant medical comorbidity, with one exception: patients receiving combination aspirin and clopidogrel were at higher RR for significant intracranial injury (RR=2.44; 95% CI 1.05 to 5.64). The increased risk of significant intracranial injury found for patients receiving warfarin alone persisted when the subgroups of patients with a dangerous mechanism of injury, with a GCS score of 15, or with a normal level of alertness were analyzed.

Our subgroup analysis revealed that in the subgroup of patients aged 65 years and older, none of the medications were statistically significantly associated with an increase in neurosurgical intervention, with one exception: patients receiving combination aspirin and clopidogrel were at higher RR for neurosurgical intervention (RR=2.94; 95% CI 1.28 to 6.76). The increased risk of neurosurgical intervention found for patients receiving warfarin persisted when the subgroups of patients with a dangerous mechanism of injury and with a GCS score of 15, but not with a normal level of alertness, were analyzed. See Table 4 for further subgroup analyses.

LIMITATIONS

Our study has certain limitations. First, we did not have specific data on all patients who presented to the study EDs with blunt head trauma but did not undergo

Table 2. Prevalence of significant intracranial injury and surgical intervention by coagulopathy.*

Type of Coagulopathy	Significant Intracranial Injury			Neurosurgical Intervention		
	Frequency Count	% Prevalence (95% CI)	RR (95% CI)	Frequency Count	% Prevalence (95% CI)	RR (95% CI)
No coagulopathy	210/5,715	3.7 (3.2–4.2)	1 [Reference]	85/5,715	1.5 (1.2–1.8)	1 [Reference]
Aspirin monotherapy	30/635	4.7 (3.3–6.6)	1.29 (0.88–1.87)	9/635	1.4 (0.7–2.5)	0.95 (0.48–1.88)
Clopidogrel monotherapy	3/109	2.8 (0.7–7.0)	0.75 (0.24–2.3)	1/109	0.92 (0.1–4.0)	0.62 (0.09–4.39)
Warfarin monotherapy	28/406	6.9 (4.7–9.6)	1.88 (1.3–2.8)	16/406	3.9 (2.3–6.1)	2.65 (1.57–4.48)
Aspirin+clopidogrel	9/85	10.6 (5.7–18.9)	2.88 (1.5–5.4)	6/85	7.1 (3.3–14.6)	4.75 (2.13–10.6)
Aspirin+warfarin	2/42	4.8 (0.13–15.8)	1.30 (0.33–5.0)	2/42	4.8 (0.13–15.8)	3.2 (0.81–12.6)

*Unknown treated as missing data.

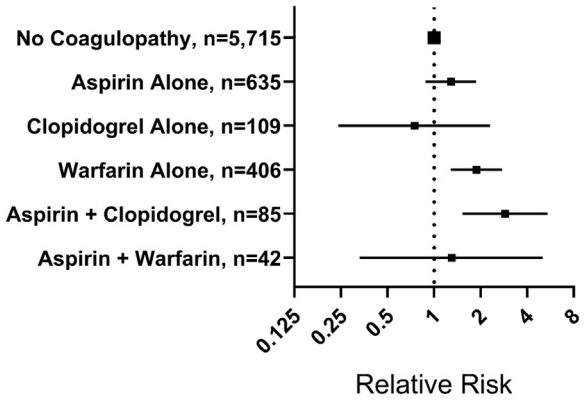

Figure 2. RR of significant intracranial injury by coagulopathy.

neuroimaging. However, our follow-up data on a sample of these unimaged patients suggest that the rate of missed significant intracranial injury is very low, if not near zero. Second, we did not have any data pertaining to rates of delayed intracranial hemorrhages, only data based on initial neuroimaging during the index visit. Thus, some of the patients in our study may have had significant intracranial injuries discovered later. Third, we did not specifically collect data on the direct oral anticoagulants, such as rivaroxaban, dabigatran, and apixaban, because these agents were relatively rare at the commencement of our study. Recent clinical data suggest that the risk of bleeding and intracranial bleeding among patients receiving these agents is no greater than the risk of bleeding for patients receiving warfarin.[22,23] Fourth, we did not use laboratory analyses (eg, international normalized ratio, platelet function tests) to verify whether patients were actually receiving the antiplatelet or anticoagulant medications. This does mimic actual situations, however, in which clinicians must make imaging decisions based on the history provided. Fifth, a significant number of patients in our study (approximately one third) had unknown medication status, limiting the sample size of those who were reportedly receiving the medications of interest. Despite our large sample size, there were a modest number of significant intracranial injuries in the final data set (n=532) and a relatively small number in each anticoagulation category.

Table 3. Prevalence of any traumatic injury by coagulopathy.

Type of Coagulopathy	Frequency Count	% Prevalence, Any Injury (95% CI)	RR, Any Injury (95% CI)
No coagulopathy	459/5,715	8.0 (7.4–8.8)	1 [Reference]
Aspirin monotherapy	55/635	8.7 (6.7–11.1)	1.08 (0.82–1.41)
Clopidogrel monotherapy	10/109	9.2 (5.1–16)	1.14 (0.63–2.08)
Warfarin monotherapy	48/406	12 (9.0–15)	1.49 (1.13–1.97)
Aspirin+clopidogrel	14/85	16 (10–26)	2.05 (1.26–3.34)
Aspirin+warfarin	7/42	17 (8.3–31)	2.08 (1.05–4.10)

DISCUSSION

In this large, prospective study examining the prevalence of significant intracranial injury after blunt head trauma in patients receiving anticoagulant and antiplatelet medications, we found that patients receiving preinjury warfarin monotherapy were at significantly higher risk of both significant intracranial injury and neurosurgical intervention compared with those without any known coagulopathy (Table 2). This increased risk persisted in most, but not all, of our subgroup analyses (Table 3). Neither aspirin monotherapy nor clopidogrel monotherapy was associated with a significantly greater RR of significant intracranial injury, although the point estimate of the RR was slightly greater than 1 in the aspirin alone group. There are several possible explanations for such findings. For one, the antiplatelet effect of aspirin and clopidogrel, although conferring benefit for cardiovascular outcomes, may not actually affect platelet function enough to have a clinically significant effect on risk of significant intracranial injury. Alternatively, this lack of association may be explained by the fact that patients receiving antiplatelet agents have a lower threshold to seek care, and similarly, their treating clinicians have a lower threshold to obtain neuroimaging after head trauma. This would increase the number of otherwise "lower-risk" patients presenting to the ED and undergoing neuroimaging, and thus deflate the prevalence of significant intracranial injury. However, in our subgroup analyses, examining only the subgroup of patients with a dangerous mechanism of injury, we found the same results (ie, a nonsignificant trend toward increased risk of significant intracranial injury in patients with individual preinjury antiplatelet medication use). The lack of association between aspirin and warfarin dual therapy and increased prevalence of significant intracranial injury should be interpreted with caution, given the relatively small number of patients in this subgroup (n=42).

Our study did not collect data on direct oral anticoagulants, which limits the utility of our findings, given that this class of medications has become increasingly common since the approval of dabigatran in 2008 in Europe and Canada, and 2010 in the United States.[24] Use of direct oral anticoagulants has increased substantially in many European countries since approval, including in France, Germany, Austria, Belgium, and the Netherlands, whereas use of warfarin has decreased.[25-27] Similar trends have been observed in the United States[1,28] and in Alberta, Canada.[29] Rivaroxaban was the most commonly prescribed

Table 4. Subgroup analysis for significant intracranial injury and neurosurgical intervention by coagulopathy.

Subgroup	No Coagulopathy, Frequency Count and Prevalence (95% CI)	Aspirin Alone, Frequency Count and RR (95% CI)	Clopidogrel Alone, Frequency Count and RR (95% CI)	Warfarin Alone, Frequency Count and RR (95% CI)	Aspirin and Clopidogrel Combination, Frequency Count and RR (95% CI)	Aspirin and Warfarin Combination, Frequency Count and RR (95% CI)
Significant intracranial injury						
Patients ≥65 y	80/1,307 6.1 (4.9–7.5)	23/537 0.70 (0.44–1.1)	3/90 0.5 (0.18–1.7)	23/323 1.2 (0.74–1.8)	8/74 1.8 (0.89–3.5)	2/38 0.86 (0.22–3.4)
Patients with significant comorbidity	28/648 4.3 (2.9–6.1)	12/263 1.1 (0.55–2.0)	2/61 0.76 (0.19–3.1)	16/250 1.5 (0.82–2.7)	6/57 2.4 (1.05–5.6)	1/33 0.70 (0.1–5.0)
Patients with dangerous mechanism of injury	135/3,585 3.8 (3.2–4.4)	14/239 1.6 (0.91–2.6)	2/40 1.3 (0.34–5.2)	15/153 2.6 (1.56–4.3)	3/33 2.4 (0.81–7.2)	1/15 1.77 (0.26–11.8)
Patients with GCS score 15	111/4,783 2.3 (1.9–2.8)	19/536 1.5 (0.95–2.5)	2/91 0.95 (0.24–3.8)	19/346 2.4 (1.47–3.8)	7/70 4.3 (2.1–8.9)	1/60 1.1 (0.16–7.7)
Patients normal level of alertness	104/4,518 2.3 (1.9–2.8)	20/529 1.6 (1.0–2.6)	0/90 Nonestimable	16/328 2.1 (1.3–3.5)	6/71 3.7 (1.7–8.1)	0/37 Nonestimable
Neurosurgical intervention						
Patients ≥65 y	36/1,307 2.8 (2.0–3.7)	7/537 0.47 (0.21–1.06)	1/90 0.40 (0.06–2.9)	13/323 1.5 (0.78–2.7)	6/74 2.9 (1.28–6.76)	2/38 1.9 (0.48–7.65)
Patients with significant comorbidity	12/648 1.9 (1.0–3.1)	4/263 0.82 (0.27–2.5)	1/61 0.89 (0.12–6.7)	8/250 1.7 (0.72–4.2)	3/57 2.8 (0.83–9.78)	1/33 1.6 (0.22–12.21)
Patients with dangerous mechanism of injury	52/3,585 1.5 (1.1–1.9)	4/239 1.2 (0.42–3.2)	1/40 1.7 (0.24–12.2)	9/153 4.1 (2.0–8.1)	2/33 4.2 (1.06–16.44)	1/15 4.6 (0.68–31.1)
Patients with GCS score 15	30/4,783 0.63 (0.4–0.9)	5/536 1.5 (0.58–3.8)	0/91 Nonestimable	9/346 4.2 (1.98–8.7)	4/70 9.1 (3.3–25.17)	1/39 4.1 (0.57–29.2)
Patients normal level of alertness	32/4,518 0.71 (0.5-1.0)	5/529 1.3 (0.52–3.4)	0/90 Nonestimable	5/328 3.4 (0.84–5.5)	4/71 8.0 (2.89–21.9)	0/37 Nonestimable

direct oral anticoagulant among patients in the United States with atrial fibrillation in 2014, by which time direct oral anticoagulants were as commonly used as warfarin for this indication.[1] More recent data demonstrate that direct oral anticoagulants have surpassed warfarin in both the United States and the United Kingdom as the medication of choice to prevent thromboembolism.[30,31] However, as mentioned previously, clinical data suggest that the risk of intracranial bleeding among patients receiving direct oral anticoagulants is likely similar to and apparently no greater than the risk of bleeding among patients receiving warfarin.[22,23]

Previous studies assessing the risk of posttraumatic bleeding have been limited by small sample sizes or retrospective design and their attendant biases. Jones et al,[8] in a chart review of 43 patients receiving clopidogrel and 43 matched controls, found no significant difference in incidence of head injury, only a difference in rates of blood product administration. In another retrospective study examining 35 patients receiving preinjury warfarin compared with controls not receiving warfarin, Lavoie et al[32] found that anticoagulated patients had a higher prevalence of severe head injury and mortality. In a larger prospective study of greater than 1,000 patients with blunt head trauma, Nishijima et al[33] found that the incidence of immediate intracranial hemorrhage was higher among patients receiving clopidogrel compared with those receiving warfarin (12.0% versus 5.1%). The prevalence of significant intracranial injury among patients receiving clopidogrel monotherapy was considerably lower in our study (2.6%), whereas the prevalence among those receiving warfarin was similar (6.9%). However, Nishijima et al[33] did not enroll patients not receiving any anticoagulant and antiplatelet medications, thus precluding any comparisons to patients without coagulopathy. The same group published a prospective, observational study enrolling greater than 1,300 older adults (>55 years) with and without anticoagulation or antiplatelet use and found that the incidence of traumatic intracranial hemorrhage (11%), after adjusted analysis, was not increased in those receiving these medications.[17] This study excluded patients younger than 55 years, which could explain the higher incidence of traumatic intracranial hemorrhage by spectrum bias. Ganetsky et al[18] studied a cohort of 939 patients with head trauma after ground-level fall and found that the prevalence of traumatic intracranial hemorrhage was higher in the aspirin alone group (4.6%) than in the warfarin alone group (2.1%), with overlapping 95% CIs. These findings are in contrast with our results, which showed a higher prevalence of significant intracranial injury in the warfarin alone group. Again, Ganetsky et al[18] did not enroll patients not receiving any anticoagulant and antiplatelet medications, thus precluding any comparisons with patients without coagulopathy. Our multicenter study, with a large sample of prospectively collected data on patients with and without coagulopathy, may represent the largest and most rigorous attempt to date to determine the increased risk of significant intracranial injury associated with these medications.

In summary, our prospective, observational study of adults presenting with blunt head trauma suggests that patients receiving preinjury warfarin have a significantly increased risk of immediate significant intracranial injury. An increased risk was also found among patients receiving a combination of aspirin and clopidogrel. Similar results were not found for patients receiving preinjury aspirin alone or clopidogrel alone. Our results should be interpreted in the context of other prospective studies on this topic and should be confirmed in future studies. Because data on direct anticoagulants were not specifically collected, our study cannot shed light on the potentially increased risks of traumatic injury associated with these medications, but the risk of intracranial injury is likely to be similar to, or at least no greater than, the risk associated with warfarin. Our study findings suggest that clinicians evaluating ED patients with blunt head trauma would be prudent in maintaining a low threshold for neuroimaging for those receiving warfarin or a combination of aspirin and clopidogrel.

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