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Prevalence of intracranial injury in adult blunt head trauma patients with and without anticoagulant or antiplatelet use

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Abstract

Objective: To determine the prevalence of significant intracranial injury among adults with blunt head trauma who are on preinjury anticoagulant or antiplatelet medications.

Methods: This was a multicenter, prospective, observational, study conducted from December 2007 to December 2015. Patients were enrolled in three emergency departments in the United States. Adults with blunt head trauma who underwent neuroimaging in the emergency department were included. Use of preinjury aspirin, clopidogrel, warfarin was recorded. Data on direct oral anticoagulants was 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 (IQR: 34.7 to 74.3) and 60.7% were male. A total of 1,323 patients (14.6%) were taking antiplatelet medications or warfarin, including 635 taking aspirin alone, 109 clopidogrel alone, and 406 warfarin alone. As compared to patients without any coagulopathy, the relative risk of significant intracranial injury was 1.29 (95% CI: 0.88, 1.87) for patients taking aspirin alone, 0.75 (95% CI: 0.24, 2.30) for those taking clopidogrel alone, and 1.88 (95% CI: 1.28, 2.75) taking warfarin alone.

Author contributions: MP and WM conceived the study. WM obtained research funding. WM, GH, and RR supervised the conduct of the study and data collection. MP, GW, GL and WM provided statistical advice and analyzed the data. MP drafted the manuscript, and all authors contributed substantially to its revision. MP takes responsibility for the paper as a whole.

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Meeting: These results have been presented as an abstract at the American College of Emergency Physicians 2017 research forum.

The relative risk of significant intracranial injury was 2.88 (95% CI: 1.53, 5.42) for patients taking aspirin and clopidogrel in combination.

Conclusions: Patients on preinjury warfarin or a combination of aspirin and clopidogrel were at increased risk for significant intracranial injury, but not those on aspirin alone. Clinicians should have a low threshold for neuroimaging when evaluating patients on warfarin or on a combination of aspirin and clopidogrel.

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 (NICE) on the initial management of traumatic brain injury recommend a non-contrast head computed tomography (CT) scan in 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 due to exclusion of anticoagulated patients from studies conducted to derive clinical prediction instruments for blunt head trauma, e.g. the Canadian Head CT 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/antiplatelet use was not shown to be predictive of traumatic intracranial hemorrhage after adjusted analysis in more recent, prospective studies.[17,18]

Importance

Given how commonly patients with blunt head trauma present to the emergency department (ED) and how often they are taking 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 on specific preinjury anticoagulant or antiplatelet medications, as compared to those without any coagulopathy.

Methods

Study Design and Setting

This was a pre-planned 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 emergency departments (EDs) were located at level 1 urban academic trauma centers, and one was a level 2 suburban community trauma center in California. We obtained institutional review board approval from all participating centers.

Selection of Participants

All adults (age 18 and over) acute blunt head trauma patients 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 those 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 Management

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 prior to CT. (eFigure 1). 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, prior to criterion assessment. Clinicians were asked to complete assessments of the study criteria as soon as possible prior to imaging results becoming available. Specifically, clinicians were queried as to whether the patient in question was taking aspirin, clopidogrel, warfarin, or had any other coagulopathy. “Other coagulopathy” was not strictly defined and could have included factors such as other anticoagulant medications (e.g. heparin) or medical conditions (e.g. severe hepatic dysfunction, hemophilia). Possible responses were “yes”, “no”, or “unknown”. Clinical variables included in the NEXUS-II[16] and Canadian Head CT 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, fall from height >3 feet or five stairs), GCS score of 15, neurologic deficit, amnesia, and level of alertness.

Outcomes

Our primary outcome measure was the presence of significant intracranial injury (ICI) on neuroimaging studies. The definition of significant ICI was based on prior 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 ICI. A list of significant ICIs is shown in eFigure 2 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 >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 1) death due to head injury, 2) craniotomy, 3) elevation of skull fracture, 4) intubation related to head injury, or 5) 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 ICIs. The diagnosis of significant ICI 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. ICI and neurosurgical intervention data was collated with clinical data to form the final study database.

Since we only enrolled patients who underwent neuroimaging, it possible that significant injuries were missed among the unimaged patients. To address this potential verification bias, we conducted 3-month follow-up interviews on 368 consecutive blunt head injury patients 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 ICI, 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 ICIs or injuries requiring neurosurgical intervention that occurred among blunt head trauma patients who were seen but not imaged on their initial presentation.

Statistical Analysis

We performed all analyses using SAS (version 9.3, SAS Institute Inc., Cary, NC). Patient characteristics are reported using descriptive statistics reported as frequencies, medians, and interquartile ranges (IQR). Our sample size calculation was based on the number of imaged head trauma patients estimated to be taking aspirin (~5%). Using the following equation to calculate the lower confidence internal 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 on preinjury aspirin. Thus, we needed to enroll 20 × 370 = 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 using relative risks (RR) with 95% confidence intervals (CI). We then performed a subgroup analysis with the following subgroups: patients 65 years old or older, patients with significant comorbidity, patients with dangerous mechanism of injury, patients with GCS score of 15, and patients 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 1mm 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

Over the 8-year study period, we prospectively enrolled 9,070 adult patients presenting with blunt head trauma undergoing CT scanning of the head (See Figure 1). Median age was 53.8 years (range: 18 to 104, IQR=34.7 to 73.5) and 39% were female. Overall, 1,323 (14.6%) were taking 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 (5.9%) patients with a significant ICI and 297 (3.3%) patients required neurosurgical intervention. Of the 1,323 patients taking antiplatelet or anticoagulant medications, 635 (7.0%) were on aspirin alone, 109 (1.2%) were on clopidogrel alone, 406 (4.5%) on warfarin alone, 85 (0.9%) were on both aspirin and clopidogrel concurrently, and 42 (0.5%) on aspirin and warfarin concurrently. Further coagulopathy data is presented in eTable 1. Of the 368 consecutive patients with blunt head trauma who did not undergo initial neuroimaging, zero reported evidence of a subsequently diagnosed ICI. Review of trauma logs also revealed no evidence of missed ICIs.

Main Results

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

Among patients taking aspirin alone, 9 of 635 required a neurosurgical intervention (1.4%, 95%CI: 0.7, 2.5%); among those taking clopidogrel alone, 1 of 109 required a neurosurgical intervention (0.9%, 95%CI: 0.1, 4.0%); and among those taking warfarin alone, 16 of 406 required a neurosurgical intervention (3.9% 95%CI: 2.3, 6.1%). The prevalence of neurosurgical intervention among patients with no coagulopathy was 85 of 5715 (1.5%, 95%CI: 1.2, 1.8%). The prevalence of neurosurgical intervention among patients taking 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 taking warfarin alone (RR=2.65, 95%CI: 1.57, 4.48) and in those taking aspirin and clopidogrel combined (RR=4.75, 95%CI: 2.13, 10.6). Further data regarding prevalence of neurosurgical intervention is presented in Table 2.

A sensitivity analysis using any traumatic injury as our primary outcome resulted in similar findings, with one notable exception. Aspirin and warfarin combination therapy was

associated with an increased relative risk of traumatic injury (RR=2.08, 95% CI: 1.05, 4.10). See Table 4 for more detail.

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 ICI. Similar results were found in the subgroup of patients with a significant medical comorbidity, with one exception: patients on combination aspirin and clopidogrel were at higher relative risk for significant ICI (RR=2.44, 95% CI: 1.05, 5.64). The increased risk of significant ICI found for patients taking warfarin alone persisted when analyzing the subgroups of patients with a dangerous mechanism, with a GCS of 15, or with a normal level of alertness.

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 on combination aspirin and clopidogrel were at higher relative risk for neurosurgical intervention (RR=2.94, 95% CI: 1.28, 6.76). The increased risk of neurosurgical intervention found for patients taking warfarin persisted when analyzing the subgroups of patients with a dangerous mechanism, and with a GCS of 15, but not with a normal level of alertness. See Table 3 for further subgroup analyses.

Limitations

Our study has certain limitations. Firstly, we do not have specific data on all patients who presented to the study EDs with blunt head trauma but did not undergo neuroimaging. However, our follow-up data on a sample of these un-imaged patients suggest that the rate of missed significant ICI is very low if not near zero. Secondly, we do 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 ICIs discovered at a later time. Thirdly, we did not specifically collect data on the direct oral anticoagulants (DOACs), such as rivaroxaban, dabigatran, apixaban, since these agents were relatively rare at the commencement of our study. Recent clinical data suggests that the risk of bleeding and intracranial bleeding among patients taking these agents is no greater than the risk of bleeding for patients taking warfarin.[22,23] Fourthly, we did not use laboratory analyses (e.g. international normalized ratio, platelet function tests) to verify whether patients were actually taking the antiplatelet or anticoagulant medications. This does mimic real world situations, however, in which clinicians must make imaging decision based on the history provided. Finally, a significant number of patients in our study (roughly one third) had “unknown” medication status limiting the sample size of those who were reportedly on the medications of interest. Despite our large sample size, there were a modest number of significant ICIs in the final dataset (n=532) and a relatively small number in each anticoagulation category.

Discussion

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

Our study did not collect data on DOACs, 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 (US).[24] Use of DOACs has increased substantially in many European countries since approval, including in France, Germany, Austria, Belgium and the Netherlands, while 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 DOAC among patients in the US with atrial fibrillation in 2014, by which time DOACs were as commonly used as warfarin for this indication.[1] More recent data demonstrate that DOACs have surpassed warfarin in both the US and the United Kingdom as the medication of choice to prevent thromboembolism.[30,31] However, as mentioned previously, clinical data suggests that the risk of intracranial bleeding among patients taking DOACs is likely similar to, and apparently no greater than the risk of bleeding among patients taking warfarin.[22,23]

Previous studies assessing the risk of post-traumatic bleeding have been limited by small sample sizes or retrospective design and their attendant biases. Jones et al. in a chart review of 43 patients on clopidogrel and 43 matched controls, found no significant difference in incidence of head injury, only a difference in rates of blood product administration.[8] In another retrospective study looking at 35 patients on preinjury warfarin, compared to controls not on warfarin, Lavoie et al. found that anticoagulated patients had a higher prevalence of severe head injury and mortality.[32] In a larger prospective study of over 1,000 patients with blunt head trauma, Nishijima et al. found that the incidence of immediate

intracranial hemorrhage was higher among patients receiving clopidogrel as compared to those receiving warfarin (12.0% vs. 5.1%).[33] The prevalence of significant ICI among patients on clopidogrel monotherapy was considerably lower in our study (2.6%) while the prevalence among those taking warfarin was similar (6.9%). However, Nishijima et al. did not enroll patients not taking any anticoagulant and antiplatelet medications, thus precluding any comparisons to patients without coagulopathy. The same group published a prospective, observational study enrolling over 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 taking these medications.[17] This study excluded patients under the age of 55 years, which could explain the higher incidence of traumatic intracranial hemorrhage via spectrum bias. Ganetsky et. al. 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% confidence intervals. These findings are in contrast with our results, which showed a higher prevalence of significant ICI in the warfarin alone group. Again, Ganetsky et. al. did not enroll patients not taking 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 ICI associated with these medications.

In summary, our prospective, observational study of adults presenting with blunt head trauma suggests that patients taking preinjury warfarin have a significantly increased risk of immediate significant ICI. An increased risk was also found among those taking a combination of aspirin and clopidogrel. Similar results were not found for those on 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. Since data on direct anticoagulants was 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 taking warfarin or a combination of aspirin and clopidogrel.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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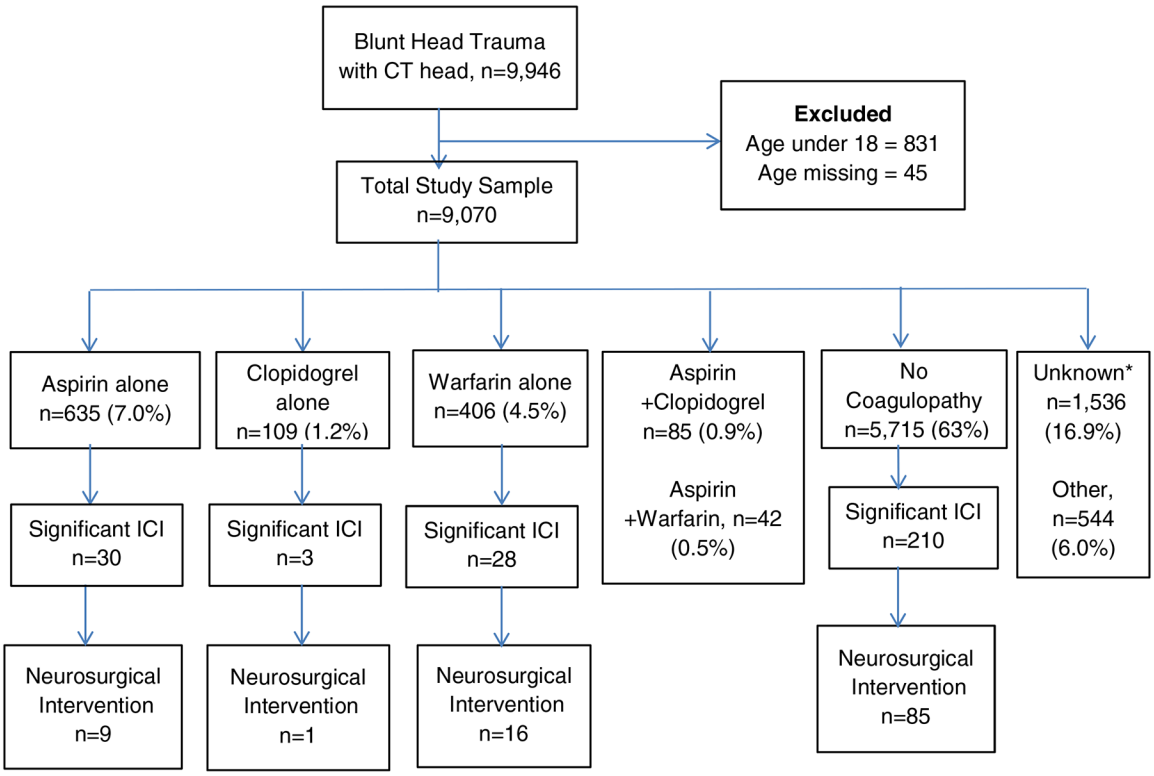

Figure 1.

Patient Flow Diagram

*"Unknown" indicates patients who had "unknown" status for all three medications. "Other" includes patients on a combination of the anticoagulant/antiplatelet medications and patients with "Other Coagulopathy". (These subjects were not included in the primary analysis.)

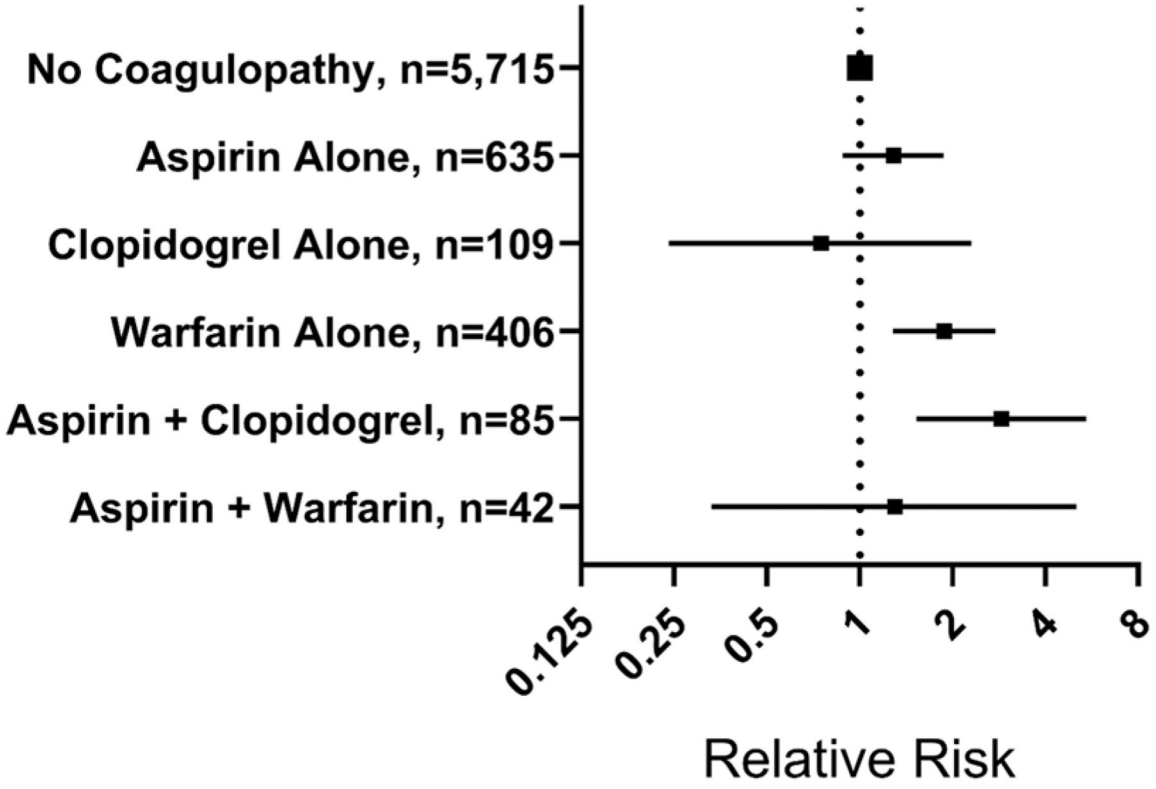

Figure 2:
Relative Risk of Significant Intracranial Injury by Coagulopathy ICI: Intracranial Injury.

Table 1:

Characteristics of Patients Presenting to the Emergency Department with Blunt Head Trauma

Variable	All Patients, N=9,070 N (%)	Aspirin Alone, n=635 n (%)	Clopidogrel Alone, n=109 n (%)	Warfarin Alone, n=406 n (%)	Combination of AC/AP medications n=173, n (%)
Age in years, Median (IQR)	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)
Gender					
-Female	3543 (39.1)	323 (50.9)	58 (53.2)	185 (45.6)	56 (32.4)
-Male	5505 (60.7)	312 (49.1)	51 (46.8)	219 (53.9)	117 (67.6)
-Unknown	22 (0.2)	0 (0.0)	0 (0.0)	2 (0.5)	0 (0.0)
Race/Ethnicity					
-Black	949 (10.5)	40 (6.3)	3 (2.8)	24 (5.9)	7 (4.0)
-White	5520 (60.9)	467 (73.5)	75 (68.8)	308 (75.9)	125 (72.3)
-Hispanic	1325 (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	8538 (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					
-Yes	8773 (96.7)	626 (98.6)	108 (99.1)	390 (96.1)	165 (95.4)
	297 (3.3)	9 (1.4)	1 (0.9)	16 (3.9)	8 (4.6)
Dangerous Mechanism*					
-No	3053 (33.7)	356 (56.1)	64 (58.7)	218 (53.7)	98 (56.6)
-Yes	5221 (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 15					
-No	2041 (22.5)	99 (15.6)	18 (16.5)	60 (14.8)	21 (12.1)
-Yes	7029 (77.5)	536 (84.4)	91 (83.5)	346 (85.2)	152 (87.9)
Significant Vomiting					
-No	8625 (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 (0.0)	1 (0.2)	0 (0.0)
Significant Comorbidity					
-No	4418 (48.7)	289 (45.5)	18 (16.5)	54 (13.3)	23 (13.3)
-Yes	1754 (19.3)	263 (41.4)	61 (56.0)	250 (61.6)	126 (72.8)
-Unknown	2898 (32.0)	83 (13.1)	30 (27.5)	102 (25.1)	24 (13.8)
Signs of basilar/ depressed skull fracture					

Variable	All Patients, N=9,070 N (%)	Aspirin Alone, n=635 n (%)	Clopidogrel Alone, n=109 n (%)	Warfarin Alone, n=406 n (%)	Combination of AC/AP medications n=173, n (%)
-No	8647 (95.3)	616 (97.0)	107 (98.2)	395 (97.3)	169 (97.7)
-Yes	299 (3.3)	13 (2.0)	0 (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	5963 (65.7)	371 (58.4)	59 (54.1)	259 (63.8)	106 (61.3)
-Yes	3043 (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 (0.0)
Neurologic deficit					
-No	7463 (82.3)	569 (89.6)	97 (89.0)	349 (86.0)	153 (88.4)
-Yes	1364 (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)
Abnormal level alertness					
-No	6557 (72.3)	529 (83.3)	90 (82.6)	333 (82.0)	150 (86.7)
-Yes	2418 (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	6982 (77.0)	551 (86.8)	94 (86.2)	351 (86.5)	155 (89.6)
-Yes	1924 (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	6068 (66.9)	477 (75.1)	85 (78.0)	311 (76.6)	143 (82.7)
-Yes	1405 (15.5)	98 (15.4)	9 (8.3)	47 (11.6)	18 (10.4)
-Unknown	1597 (17.6)	60 (9.4)	15 (13.8)	48 (11.8)	12 (6.9)

AC: anticoagulant; AP: antiplatelet; SD: Standard Deviation; sICI: Significant Intracranial Injury; NSx: Neurosurgical; GCS: Glasgow Coma Scale; Dangerous Mechanism defined as pedestrian struck by motor vehicle, occupant ejected from motor vehicle, fall from height >3 feet or five stairs.

Table 2.

Prevalence of Significant Intracranial Injury and Surgical Intervention by Coagulopathy[1]

	Significant Intracranial Injury			Neurosurgical Intervention		
Type of Coagulopathy	**Frequency Count**	**% Prevalence (95% CI)**	**Relative Risk (95%CI)**	**Frequency Count**	**% Prevalence (95% CI)**	**Relative Risk (95%CI)**
No coagulopathy	210/5715	3.7 (3.2, 4.2)	ref	85/5715	1.5 (1.2, 1.8)	ref
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)

SICI: Significant Intracranial Injury. NSx: Surgical Intervention CI: Confidence Interval. Ref: Reference group.

[1]. Unknown treated as Missing data.

Table 3.

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 Relative Risk (95%CI)	Clopidogrel-Alone Frequency count and Relative Risk (95%CI)	Warfarin-Alone Frequency count and Relative Risk (95%CI)	Aspirin and Clopidogrel Combination Frequency count and Relative Risk (95%CI)	Aspirin and Warfarin Combination Frequency count and Relative Risk (95%CI)
Significant Intracranial Injury						
Patients 65 years or older	80/1307	23/537	3/90	23/323	8/74	2/38
	6.1	0.70	0.5	1.2	1.8	0.86
	(4.9, 7.5)	(0.44, 1.1)	(0.18, 1.7)	(0.74, 1.8)	(0.89, 3.5)	(0.22, 3.4)
Patients with significant comorbidity	28/648	12/263	2/61	16/250	6/57	1/33
	4.3	1.1	0.76	1.5	2.4	0.70
	(2.9, 6.1)	(0.55, 2.0)	(0.19, 3.1)	(0.82, 2.7)	(1.05, 5.6)	(0.1, 5.0)
Patients with dangerous mechanism	135/3585	14/239	2/40	15/153	3/33	1/15
	3.8	1.6	1.3	2.6	2.4	1.77
	(3.2, 4.4)	(0.91, 2.6)	(0.34, 5.2)	(1.56, 4.3)	(0.81, 7.2)	(0.26, 11.8)
Patients with GCS of 15	111/4783	19/536	2/91	19/346	7/70	1/60
	2.3	1.5	0.95	2.4	4.3	1.1
	(1.9, 2.8)	(0.95, 2.5)	(0.24, 3.8)	(1.47, 3.8)	(2.1, 8.9)	(0.16, 7.7)
Patients normal level of alertness	104/4518	20/529	0/90	16/328	6/71	0/37
	2.3	1.6	Non-Estimable	2.1	3.7	Non-Estimable
	(1.9, 2.8)	(1.0, 2.6)		(1.3, 3.5)	(1.7, 8.1)	
Neurosurgical Intervention						
Patients 65 years or older	36/1307	7/537	1/90	13/323	6/74	2/38
	2.8	0.47	0.40	1.5	2.9	1.9
	(2.0, 3.7)	(0.21, 1.06)	(0.06, 2.9)	(0.78, 2.7)	(1.28, 6.76)	(0.48, 7.65)
Patients with significant comorbidity	12/648	4/263	1/61	8/250	3/57	1/33
	1.9	0.82	0.89	1.7	2.8	1.6
	(1.0, 3.1)	(0.27, 2.5)	(0.12, 6.7)	(0.72, 4.2)	(0.83, 9.78)	(0.22, 12.21)
Patients with dangerous mechanism	52/3585	4/239	1/40	9/153	2/33	1/15
	1.5	1.2	1.7	4.1	4.2	4.6
	(1.1, 1.9)	(0.42, 3.2)	(0.24, 12.2)	(2.0, 8.1)	(1.06, 16.44)	(0.68, 31.1)
Patients with GCS of 15	30/4783	5/536	0/91	9/346	4/70	1/39
	0.63	1.5	Non-Estimable	4.2	9.1	4.1
	(0.4, 0.9)	(0.58, 3.8)		(1.98, 8.7)	(3.3, 25.17)	(0.57, 29.2)
Patients normal level of alertness	32/4518	5/529	0/90	5/328	4/71	0/37
	0.71	1.3	Non-Estimable	3.4	8.0	Non-Estimable
	(0.5–1.0)	(0.52, 3.4)		(0.84, 5.5)	(2.89, 21.9)	

Table 4:

Prevalence of Any Traumatic Injury by Coagulopathy

Any Traumatic Injury			
Type of Coagulopathy	**Frequency Count**	**% Prevalence - Any Injury (95% CI)**	**Relative Risk - Any Injury (95%CI)**
No coagulopathy	459/5715	8.0 (7.4, 8.8)	Ref
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)

CI: Confidence Interval.