Patients with moderate and severe traumatic brain injury: Impact of preinjury platelet inhibitors and anticoagulants

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Running head: Preinjury antithrombotic medication in traumatic brain injury

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Abstract

Object: We aimed to examine the effect of preinjury antithrombotic medication on clinical and radiological neuroworsening in TBI, and also study the effect on outcome.

Methods: 185 consecutive patients ≥50 years old with moderate and severe TBI admitted to a level 1 trauma center were included. Neuroworsening was assessed clinically by using Glasgow Coma Scale (GCS) score and radiologically by using Rotterdam CT score on repeated time points. Functional outcome was assessed with the Glasgow Outcome Scale Extended (GOSE) at 6 months postinjury.

Results: The platelet inhibitor group (mean age 77.3, n=43) and the anticoagulation group (mean age 73.5, n=21) were significantly older than the non-user group (mean age 63.7, n=121, p< 0.001). 74% in the platelet inhibitor and 86% in the anticoagulation group were injured by falls. Platelet inhibitors were not significantly associated with clinical or radiological neuroworsening (p=0.37-1.00), while anticoagulants increased the frequency of worsening in GCS score (p=0.002-0.028) and Rotterdam CT score (p=0.004). In-hospital mortality was higher in the platelet inhibitor group (28%, p=0.030) and the anticoagulation group (52%, p<0.001) compared to the non-user group (13%). Platelet inhibitors did not predict mortality or worse outcome after adjustment for age, preinjury disability, GCS score and Rotterdam CT score, while anticoagulants predicted both mortality and worse outcome.

Conclusion: In this study, preinjury platelet inhibitors did not cause neuroworsening or predict higher mortality or worse outcome. In contrast, preinjury anticoagulation caused neuroworsening and was an independent risk factor for mortality and worse outcome at 6 months. Hence, fall prevention measures and liberal use of CT examinations is important in this patient group.

Introduction

Traumatic brain injury (TBI) is an important cause of death and disability and has the third highest share of injury-related health care costs in Europe.[1] The incidence of TBI peaks in the youngest and elderly age groups[2] and is increasing amongst the oldest.[3] Age is known to be one of the most important prognostic factors in TBI.[4] Elderly patients have more co-occuring diseases and higher consumption of medications that might increase the risk of bleeding, such as antithrombotic medication. Antithrombotic medication, i.e. platelet inhibitors and anticoagulants, are usually prescribed as primary and secondary prophylaxis of cardiovascular disease. A report from the Norwegian registry of prescriptions showed that 32 % of Norwegians > 65 years of age were prescribed acetylsalicylic acid in 2011, making it the most commonly prescribed drug in this age group. Warfarin was the tenth most prescribed drug used by 9 % of the population >65 years of age.[5] In a national multicenter study of severe TBI in Norway, 60 % of patients > 65 years of age used antithrombotic medication at the time of injury.[6]

Several studies have addressed the effect of preinjury platelet inhibitors on intracranial bleeding, mortality and outcome after TBI. In 2009, McMillian et al. concluded in a review that although the studies included were limited, there seemed to be an increased risk of complications and possibly higher mortality in patients on preinjury platelet inhibitors. However, the studies were inconclusive and did not address whether platelet inhibitors contributed to neuroworsening in the acute phase. [7] A recent, large study by Cull et al. found increased in-hospital mortality in patients on platelet inhibitors with an Injury Severity Score (ISS) > 20. However, they were unable to tease out whether the higher mortality resulted from the use of platelet inhibitors or a higher comorbidity in this patient group. They suggested studies of older and more severely injured patients to better assess the effect of platelet inhibitors. [8] A recent study of patients with moderate and severe TBI found that both platelet inhibitors and anticoagulants were associated with hemorrhagic progression of contusions in univariable, but not in multivariable, analyses.[9]

Effects of anticoagulants, and especially warfarin, prior to TBI have been more studied, and it is well established that anticoagulants increase mortality after TBI. [10-12] The effect of anticoagulants on neuroworsening from the scene of accident is, however, a less explored

area, as is functional outcome after 6 months. Hence, the primary aim of this study was to examine the effect of platelet inhibitors and anticoagulants on clinical and radiological neuroworsening as evaluated by worsening of the Glasgow Coma Scale (GCS) score and CT findings in TBI patients defined as moderate and severe at admission. A second aim was to examine the effect of preinjury platelet inhibitors and anticoagulants on mortality and functional outcome after adjusting for other well-established prognostic factors.

Material and methods

Patient population

All patients with moderate-to-severe TBI (according to the Head Injury Severity Scale [HISS] classification[13]) admitted to St.Olavs Hospital, Trondheim University Hospital, Norway, during the time period from October 2004 - October 2013, were prospectively and consecutively included and registered in a database (Trondheim TBI study, n=500). The hospital is the only Level 1 trauma center in a region of 680,000 habitants (2013). Due to infrequent use of antithrombotic medication in younger patients (0.8 % of the patients < 50 years), only patients ≥ 50 years were included in this study. A total of 198 patients met the inclusion criteria (Figure 1), but 6 were excluded due to death from other injuries within the first 24 hours, 4 were excluded due to missing preinjury medication lists, and 3 did not consent to follow-up, leaving 185 patients (93 %) for further analyses.

Glasgow Coma Scale (GCS) scores

GCS scores were registered at the scene of accident in 159 patients (86 %) (36 were intubated at the scene). 57 patients (31 %) were primarily admitted to a local hospital, and GCS score was registered (8 of these patients were intubated at scene, 35 were intubated at local hospital). GCS score was registered at admission to the university hospital in 109 patients (71 patients were already intubated at scene of accident or local hospital). For 5 patients exact GCS score was impossible to assess because of alchohol intoxication or postictal status after epileptic seizures. Clinical neuroworsening was defined as ≥ 1 point decrease in GCS score. Such neuroworsening could not be assessed after sedation and intubation.

The following GCS scores were used when evaluating clinical neuroworsening:

- GCS score closest to the scene of accident (hereafter denoted *field GCS score*), i.e. the GCS score from the scene of accident, or GCS score from local hospital if score from scene of accident was missing.
- GCS score closest to admission to the university hospital (hereafter denoted *admission GCS score*), i.e. the GCS score from admission or from local hospital if the

patient was already intubated at admission to the university hospital or if impossible to assess for other reasons at university hospital.

- The GCS score obtained after any clinical deterioration after admission to the university hospital (hereafter denoted *final GCS score*).

Other Injury Variables

Preinjury and in-hospital injury related variables were prospectively collected during the study period. Injury severity was estimated at admission using the HISS, the Abbreviated Injury Scale Head (AIS head) and the Injury Severity Score (ISS). [13-15] Pupillary abnormalities were registered at admission to the University Hospital.

Registration of Preinjury Antithrombotic Medication

Preinjury antithrombotic medication, defined as either platelet inhibitors or anticoagulants, was prospectively registered during the study. To specify the type of antithrombotic drug and dose of platelet inhibitors, a quality check of the database and medical records was retrospectively performed (MHT). Blood samples including pt-INR (prothrombin time - international normalized ratio) was obtained at admission for the anticoagulation group, pt-INR was defined as supratherapeutic if > 3.5.

Preinjury disability

Preinjury disability was prospectively registered and classified as yes or no, stating if the patient had any disability prior to injury that affected daily functioning at the time of injury. Pre-injury disability was further sub classified into alcohol-and drug-abuse, psychiatric history, neurological disease or developmental disorders and severe somatic disease including cancer and heart- and lung disease.

Classification of head CT

A head CT at admission (first CT) and a second scan were obtained in all patients. All CT scans were reviewed by a radiologist or resident in neurosurgery or radiology in cooperation with three neuroradiologists. The Rotterdam CT score (scoring 1-6, 6 being worst) was estimated. [16] This is a point-based classification system shown to have a prognostic value in TBI, and components of this scoring system are signs of raised intracranial pressure (e.g.

compressed basal cisterns and midline shift), traumatic intraventricular or subarachnoid hemorrhage and epidural hematoma of a certain size (mass lesions [defined as hematomas > >25 ml] or evacuated hematomas, reducing the score with 1 point). Radiological neuroworsening was defined as ≥ 1 point increase in Rotterdam CT score.

Mortality and functional outcome

In-hospital mortality was defined as death during the university hospital stay or before transfer to other wards for other conditions or rehabilitation. 6 months mortality included all deaths within 6 months after injury. Functional outcome was assessed as the brain-injury related outcome, using the structured interview for the Glasgow Outcome Scale Extended (GOSE). This is an 8 –category scale measuring a patient´s overall functioning (1=death, 8=upper good recovery). The interview was performed at 6 months postinjury by telephone or personal contact. 6 patients (3 %) were lost to follow-up.

Statistical Analyses

Data are presented as numbers with percentages, mean with standard deviations (SD), and median with interquartile ranges (IQR). Pearson's chi square test or Fisher exact test were used for comparisons of proportions. Continuous variables were tested for normality distribution (by QQ-plots and the one-sample Kolmogorov–Smirnov test). If data were normally distributed, Student's t-test were used, otherwise, Kruskal–Wallis and Mann–Whitney U-tests were used. The platelet inhibitor group and the anticoagulation group were compared with the non-user group. The effect of platelet inhibitors or anticoagulation medication on mortality and functional outcome was further explored in more advanced logistic regression models, presented with odds ratio (OR) and 95% confidence intervals (CI). In one model, mortality was the dependent variable (multiple binary logistic regression model). In the other model, GOSE score was the dependent variable (multiple ordinal logistic regression model). In the ordinal logistic regression model, the GOSE scores were inverted to give OR >1, making them more intuitive to interpret. For both models, platelet inhibitors or anticoagulation and other clinically well-established prognostic factors served as independent variables. First, all variables were analyzed in univariable regression models

(unadjusted OR), and only variables with a significance level below 0.1 were added to the multivariable regression models (adjusted OR). The *first adjusted model* included the Rotterdam CT score obtained from the first CT scan and the first GCS score registered (mainly field GCS score but admission GCS score was used in cases where field GCS score was missing). To further explore the effect of platelet inhibitors and anticoagulation medication on outcome, we also performed a second regression analysis; the *worst adjusted model* included the Rotterdam CT score obtained from the worst CT scan and the final GCS score. All statistical tests are two-sided and results were considered statistically significant at 5% level ($P<0.05$). The statistical analyses were carried out using IBM Statistical Package for the Social Sciences (SPSS), version 22 (IBM, Armonk, NY). For the ordinal regression analyses STATA/SE (version 13.1; Stata LP, College Station, TX) was used.

Ethics

The study was approved by the Regional Committee for Medical Research. Written informed consent was obtained from surviving patients or, for incapacitated individuals, their next of kin. Use of data from deceased individuals without consent was approved by the Regional Committee for Medical Research and the Norwegian Directorate of Health.

Results

Patient characteristics and injury-related variables

Of the 185 patients included in the study, 43 (23 %) were in the platelet inhibitor group, 21 (11 %) in the anticoagulation group and 121 (65 %) were in the non-user group. Patients were significantly older in both the platelet inhibitor group (77.3 years) and the anticoagulation group (73.5 years) compared to the non-user group (63.7 years, Table 1).

In the platelet inhibitor group 40 patients (Figure 1) were treated with ASA (acetylsalicylic acid) at doses below 75 mg (n=3), 75 mg (n=15) or 160 mg (n=16). In the anticoagulation group the mean pt-INR was 2.2 (SD 1.15, n=19), only one patient had supratherapeutic p-t-INR (measured at 6.0). The anticoagulation group had a higher rate of fall (86%), higher ISS and AIS head scores than the non-user group. The presence of mass lesions and surgical evacuation of these were more frequent in the anticoagulation group than in the non-user group, but no such differences were observed for the platelet inhibitor group (Table 1).

Clinical neuroworsening assessed with Glasgow Coma Scale (GCS) score

There was no significant difference in worsening of GCS score between the platelet inhibitor and the non-user group (Table 2). In the anticoagulation group significant more patients had worsening of the GCS score from field to admission (52 % versus 18%, p = 0.002) and after admission (29 % versus 10 %, p =0.028) than in the non-user group. The anticoagulated patients had higher field GCS scores (p=0.002) and tended to have a lower final GCS score (p=0.063) than the non-user group.

Radiological neuroworsening assessed with computed tomography (CT) findings

There was no significant difference in worsening of Rotterdam CT score between the platelet inhibitor and the non-user group (Table 3). In the anticoagulation group the worst CT score was significantly higher than in the non-user group (p=0.004, Table 3), and significantly more patients had worsening in CT score (38 % versus 11%, p=0.004). AIS head was worse in the anticoagulation group (5, Table 1) than the platelet inhibitor group (4) and the non-user group (4), but there was no significant difference in the first Rotterdam CT score between any of the groups.

Mortality and functional outcome

In-hospital and 6 months mortality was significantly higher both in the platelet inhibitor (45 % at 6 months) and the anticoagulation group (62 %) than in the non-user group (21 %) (Table 4). Functional outcome at 6 months was worse in both the platelet inhibitor and anticoagulation group compared to the non-user group. Analyzing only the patients who survived the hospital stay, the proportion of patients with GOSE score 5-8 was 37 % (n=10) in the platelet inhibitor group, 56 % (n=5) in the anticoagulation group and 74 % (n=72) in the non-user group (Table 4).

A multivariable binary logistic regression model: *first model* (adjusting for age, preinjury disability and first GCS and Rotterdam CT scores) demonstrated that use of anticoagulants, but not platelet inhibitors was a predictor of mortality at 6 months (p=0.011, Table 5). In the *worst model* (adjusting for age, preinjury disability and the final GCS and worst Rotterdam CT scores), anticoagulants did not predict mortality.

Similar multiple ordinal regression models demonstrated in the *first model* (adjusting for age, preinjury disability, the first GCS and Rotterdam CT scores) that platelet inhibitors were not an independent predictor of worse functional outcome (Table 6). Anticoagulants predicted worse functional outcome (p=0.003). In the second *worst model* (adjusting for age, preinjury disability, the final GCS and worst Rotterdam CT score), neither platelet inhibitors nor anticoagulants predicted worse functional outcome.

Discussion

In this prospective study we found no higher frequency of neuroworsening in moderate and severe TBI patients who were on platelet inhibitors than in patients with no antitrombotic medication. However, the frequency of both clinical and radiological neuroworsening was higher for patients using anticoagulants. Patients were older and had higher mortality in both the platelet inhibitor and anticoagulation groups compared to non-users. Higher mortality for patients on platelet inhibitors could not be ascribed to the medication, while use of anticoagulants independently predicted 6 months mortality and also worse functional outcome when adjusting for other well-established prognostic factors.

Clinical neuroworsening assessed with Glasgow Coma Scale score

In the platelet inhibitor group, GCS scores did not decrease from field to after admission. In the anticoagulation group, we found a significantly higher frequency of clinical neuroworsening, both from field to admission and after admission, as reflected in the final GCS score. To our knowledge, this is the only study examining the change in GCS score from the scene of accident in patients admitted with moderate to severe TBI with preinjury antithrombotic medication. When comparing GCS scores at the respective time points, the field GCS score was higher in the anticoagulation group than in the platelet inhibitor and non-user group. This is consistent with previous studies demonstrating a high risk of intracranial hemorrhage in anticoagulated patients, even after minor traumas like falls. [17,18] Falls were also more often the cause of injury in our anticoagulation group suggesting anticoagulated patients who fall run a high risk of deterioration even with initial high GCS scores.

Radiological neuroworsening assessed with computed tomography findings

We found no higher frequency of radiological neuroworsening in the platelet inhibitor group than in the non-user group. Three former studies investigating platelet inhibitors found similar results. [19-21] However, in contrast to our findings, Fabbri et al. showed that platelet inhibitors more than doubled the risk of radiological worsening when comparing CT images at 6 and 24 hours postinjury in a large multicenter study. [22]

In contrast to the results in the platelet inhibitor group, we found that the anticoagulation group had significantly increased frequency of worsening of the Rotterdam CT score. This is in accordance with Peck et al. who concluded that warfarin increased the risk of both progression and new development of intracranial hematoma in subsequent CT scans. [21] Also Grandhi et al. found a tendency of more frequent progression of intracranial hemorrhage in the anticoagulation group. [12] On the other hand, Fabbri et al. did not find anticoagulants to be independently associated with radiological neuroworsening. However, the authors concluded that exclusion of patients with initial mass lesions from the analyses might explain their negative result[22]. This explanation is also supported by our finding of poorer Rotterdam first and worst CT scores in the anticoagulation group.

Mortality and functional outcome

We found higher in-hospital mortality and worse functional outcome at 6 months in both the platelet inhibitor and anticoagulation group compared to the non-user group. However, use of platelet inhibitors did not predict 6 months mortality or worse functional outcome when adjusting for other prognostic factors, such as age.

Previous studies of preinjury platelet inhibitors and mortality and functional outcome show conflicting result. In a meta-analysis, preinjury platelet inhibitors did not significantly increase the risk of death.[23] A review concluded that preinjury platelet inhibitors seem to increase risk of mortality and morbidity, and severe TBI patients seem to be at particular risk of the negative effects of platelet inhibitors.[24] Fabbri et al. found in their study of all TBI severities but exclusion of patients with initial mass lesions, that platelet inhibitors were predictors of poor outcome at 6 months after adjusting for age, Marshall CT score, GCS score and intracerebral hemorrhage / contusion.[22]

The increased mortality in TBI patients on preinjury anticoagulants observed in our study is well known [11,12] and was also observed in a meta-analysis where the common odds ratio for death was over doubled for the warfarin anticoagulated patients.[10] However, the long-term functional outcome in anticoagulated patients is more uncertain. Peck et al. found in a study including all severities of TBI (≥55 years), that anticoagulated patients were more likely to be discharged to a care facility.[21] In contrast, Fabbri et al. did not find anticoagulants to be

predictive of poor outcome 6 months after injury. [22] However, they did not report whether the analysis was adjusted for the CT at 6 or 24 hours. Any adjustment for the 24 hour-CT might conceal the early effect of anticoagulants on outcome, since, if detrimental, the medication will already have resulted in enlargement of hematomas, hence captured by the model as a higher CT score. Similarly, this is a concern in the study of Grandhi et al., where the multivariable analysis adjusts for both hemorrhage progression and surgical intervention.[12] Hence, in our study we fitted two multivariable models, one adjusting for the first GCS and CT scores, and one adjusting for the final GCS score and worst CT score. Anticoagulants predicted a worse outcome only in the *first model,* consistent with our hypothesis.

The worse 6 months functional outcome in the anticoagulation group, however, could be explained by the high mortality in this group. With only 8 surviving patients, we were not able to compare their function with that of patients from the other groups. It should be noted that all but one of the patients in the anticoagulation group were on warfarin. In a recent study, the authors observed a markedly worse outcome in patients on warfarin compared to the new oral anticoagulants (NOAC).[25] The high mortality in our group of patients receiving warfarin is concerning, and more studies are needed to elucidate the possible benefit of the NOACs.

Strengths and limitations

The main strength of our study was the prospective study design and our selection of patients with moderate and severe TBI specifically. We propose that the inclusion of mild TBI entails the inclusion of a large patient group with sparse findings, which might conceal trends amongst the patients with moderate and severe TBI. The injury severity was well documented through GCS scores at multiple time points and with initial and subsequent CT examinations classified with the Rotterdam CT score.

One limitation in the study is the small sample size in the anticoagulation group. One might also discuss if a quantitative volumetric measure of intracranial hematomas and contusions would be better in detecting more subtle changes than different CT scoring methods like

Rotterdam CT score. However, we wanted to use a scoring algorithm that is more likely to be used by clinicians in their daily routine. One should also bear in mind that TBI in itself can alter the hemostatic balance with unknown consequences for outcome and therefore difficult to adjust for.[26]

Conclusions

In this study, preinjury platelet inhibitors prior to moderate and severe TBI neither increased the risk of clinical or radiological neuroworsening, nor mortality or functional outcome 6 months post injury. Anticoagulants, on the other hand, increased the risk of clinical and radiological deterioration, mortality and worse functional outcome at 6 months. This increased risk of deterioration in anticoagulated patients supports liberal use of control CT examinations. Because almost all patents were injured by falls (86%), prophylactic fall prevention for this group could be of importance.

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Figure legend

FIGURE 1. Flowchart of study population.
ASA = acetylsalicylic acid

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TABLE 1. Patient characteristics and injury-related variables

	Non-user group (n= 121)	Platelet inhibitor group (n=43)	p Value (*)	Anticoagulation group (n=21)	p Value (**)
Mean age (SD)	63.7 (9.9)	77.3 (10.0)	**<0.001**	73.5 (10.4)	**<0.001**
Male, n (%)	80 (66)	29 (67)	0.848	15 (71)	0.633
Mechanism of Injury					
- *Vehicle accident, n (%)*	34 (28)	9 (21)	0.345	2 (10)	0.071
- *Fall, n (%)*	74 (61)	32 (74)	0.110	18 (86)	**0.030**
- *Other, n (%)*	9 (7)	1 (2)	0.294	0 (0)	0.356
Severe TBI, n (%)	45 (37)	18 (43)	0.540	9 (43)	0.621
Pupil size, bilateral dilation, n (%)	3 (2)	1 (2)	1,000	2 (10)	0.158
unilateral dilation, n (%)	18 (15)	7 (16)	0.7881	7 (33)	0.059
Median AIS head (IQR)	4 (3-5)	4 (4-5)	0.482	5 (5-5)	**0.002**
Median ISS (IQR)	24 (16-26)	25 (16-25)	0.861	25 (25-31)	**0.039**
Any mass lesion, n (%)	32 (27)	15 (35)	0.322	16 (76)	**<0.001**
Evacuation of mass lesion, n (%)	32 (26)	7 (16)	0.179	10 (48)	0.050
Mean length of hospital stay (SD)	11.6 (1.1)	8.7 (1.2)	0.114	5.9 (1.2)	**0.008**

SD: standard deviation. IQR: interquartile range. TBI: traumatic brain injury.

AIS: abbreviated injury scale. ISS: injury severity score.

* Platelet inhibitor group versus non-user group

** Anticoagulation group versus non-user group

TABLE 2. Clinical neuroworsening assessed with Glasgow Coma Scale (GCS) score

	n	Non-user group (n= 121)	Platelet Inhibitor group (n=43)	p Value (*)	Anticoagulation group (n=21)	p Value (**)
Field GCS score, median (IQR)	171	11 (6.5-13)	10 (6-13.5)	0.971	14 (12.5-15)	**0.002**
Admission GCS score, median (IQR)	180	11 (6-13)	9.5 (6-12)	0.441	12 (5-13)	0.686
Final GCS score, median (IQR)(°)	180	10 (6-13)	9 (6-12)	0.484	6 (3-12.5)	0.063
GCS score worsening from field to admission, n (%)	167	22 (18)	11 (26)	0.366	11 (52)	**0.002**
GCS score worsening from admission to final, n (%)(°)	178	12 (10)	4 (9)	1.000	6 (29)	**0.028**
GCS score worsening from field to final, n (%)(°)	166	31 (26)	14 (33)	0.416	13 (62)	**0.001**

GCS: Glasgow Coma Scale. IQR: Interquartile range.

°Includes worsening after admission

* Platelet inhibitor group versus non-user group

** Anticoagulation group versus non-user group

TABLE 3. Radiological neuroworsening assessed with Rotterdam CT score

		Non-user group (n= 121)	Platelet inhibitor group (n=43)	p Value (*)	Anticoagulation group (n=21)	p Value (**)
First Rotterdam CT score						
Mean (IQR)		3 (3-4)	3 (3-4)	0.596	4 (3-5)	0.095
n (%)	1	1 (1)	0		0	
	2	20 (17)	6 (14)		3 (14)	
	3	55 (45)	20 (47)		6 (29)	
	4	25 (21)	9 (21)		6 (29)	
	5	18 (15)	8 (19)		4 (19)	
	6	2 (2)	0		2 (10)	
Worst Rotterdam CT score						
Mean (IQR)		3 (3-4)	3 (3-5)	0.689	4 (3.5-5)	**0.004**
n (%)	1	1 (1)	0		0	
	2	19 (16)	6 (14)		1 (5)	
	3	48 (40)	18 (42)		4 (19)	
	4	25 (21)	8 (19)		7 (33)	
	5	25 (21)	9 (21)		6 (29)	
	6	3 (2)	2 (5)		3 (14)	
Any worsening of Rotterdam CT score, n (%)		13 (11)	5 (12)	1.000	8 (38)	**0.004**

IQR: Interquartile range.

* Platelet inhibitor group versus non-user group

** Anticoagulation group versus non-user group

TABLE 4. Mortality and functional outcome

		Non-user group (n= 121)	Platelet Inhibitor group (n=43)	p Value (*)	Anticoagulation group (n=21)	p Value (**)
Mortality in-hospital, n (%)		16 (13)	12 (28)	**0.03**	11 (52)	**<0.001**
Mortality 6 months, n (%)		25 (21)	19 (45)	**0.002**	13 (62)	**<0.001**
GOSE score at 6 months						
Mean (IQR)		5 (3-7)	3 (1-4.5)	**<0.001**	1 (1-5)	**0.002**
n (%)	*1*	21 (19)	17 (44)		12 (60)	
	2	2 (2)	0		0	
	3-4	18 (16)	12 (30)		3 (15)	
	5-6	38 (31)	4 (10)		1 (5)	
	7-8	34 (30)	6 (15)		4 (20)	

GOSE = Glasgow Outcome Scale Extended.

GOSE score: n = 172 (6 (3%) lost to follow up and 7 (4%) died from other causes)

* Platelet inhibitor group versus non-user group

** Anticoagulation group versus non-user group

TABLE 5. Multivariable binary logistic regression models predicting 6 months mortality

	First adjusted model (n=177, R^2* =0.414)			Worst adjusted model (n=172, R^2*=0.478)		
Variable	**OR**	**95% CI**	**p Value**	**OR**	**95% CI**	**p Value**
Age	1.12	(1.06; 1.72)	**<0.001**	1.36	(1.07; 1.20)	**<0.001**
First GCS score	0.83	(0.73; 0.94)	**0.003**			
Final GCS score				0.73	(0.62; 0.85)	**<0.001**
Rotterdam CT score, first CT	2.21	(1.35; 3.63)	**0.002**			
Rotterdam CT score, worst CT				1.80	(1.04; 3.09)	**0.033**
Preinjury disability**	8.03	(3.08; 20.94)	**<0.001**	6.59	(2.38; 18.26)	**<0.001**
Antithrombotics Non-user group	ref					
Platelet inhibitor group	1.02	(0.33; 3.14)	0.969	0.95	(0.28; 3.19)	0.939
Anticoagulation group	5.74	(1.50; 21.96)	**0.011**	1.79	(0.43; 7.46)	0.426

GCS: Glasgow Coma Scale. OR: Odds ratio. CI: Confidence interval. NA: Non applicable. Ref: reference.

*Explained variance is calculated with McFadden´s R^2.

** Any disability prior to injury that would interfere with function

TABLE 6. Multivariable ordinal logistic regression models predicting 6 months outcome (GOSE category)*

		First adjusted model (n=166, R^2*=0.165)			Worst adjusted model (n=161, R^2*=0.202)		
Variable		**OR**	**95% CI**	**p Value**	**OR**	**95% CI**	**p Value**
Age		1.04	(1.01; 1.08)	**0.009**	1.05	(1.02; 1.09)	**0.004**
First GCS score		0.81	(0.75; 0.89)	**<0.001**			
Final GCS score					0.77	(0.70; 0.84)	**<0.001**
Rotterdam CT score, first CT		2.13	(1.53; 2.95)	**<0.001**			
Rotterdam CT score, worst CT					1.93	(1.41; 2.64)	**<0.001**
Preinjury disability**		4.85	(2.46; 9.56)	**<0.001**	3.91	(1.95; 7.86)	**<0.001**
Antithrombotics	Non-user group	ref					
	Platelet inhibitor group	1.88	(0.81; 4.34)	0.142	1.92	(0.79; 4.67)	0.153
	Anticoagulation group	5.79	(1.85; 18.12)	**0.003**	1.87	(0.59; 5.94)	0.286

GOSE: Glasgow Outcome Scale Extended. GCS: Glasgow Coma Scale.

OR: Odds ratio. CI: Confidence interval. NA: Non applicable. Ref: reference.

* Explained variance is calculated with McFadden´s R^2.

**Any disability prior to injury that would interfere with function

Figure 01

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