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Early Venous Thromboembolism Prophylaxis in Patients with Traumatic Intracranial Hemorrhage: Analysis of the Prospective Multicenter CLOTT Study

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Abstract

Background: The optimal time to initiate venous thromboembolism prophylaxis (VTEp) for patients with intracranial hemorrhage (ICH) is controversial and must balance the risks of VTE with potential progression of ICH. We sought to evaluate the efficacy and safety of early VTEp initiation after traumatic ICH.

Methods: This is a secondary analysis of the prospective multicenter Consortium of Leaders in the Study of Thromboembolism (CLOTT) study. Patients with head AIS > 2 and with immediate VTEp held due to ICH were included. Patients were divided into VTEp ≤ or >48 hours and compared. Outcome variables included overall VTE, deep vein thrombosis (DVT), pulmonary embolism (PE), progression of ICH (pICH), or other bleeding events. Univariate and multivariate logistic regressions were performed.

Results: There were 881 patients in total, 378 (43%) started VTEp ≤48 hours (early). Patients starting VTEp >48 hours (late) had higher VTE (12.4% vs 7.2%, p=.01) and DVT (11.0% vs 6.1%, p=.01) rates than the early group. The incidence of PE (2.1% vs 2.2%, p=.94), pICH (1.9% vs 1.8%, p=.95) or any other bleeding event (1.9% vs 3.0%, p=.28) were equivalent between early and late VTEp groups. On multivariate logistic regression analysis, VTEp >48 hours (OR 1.86), ventilator days >3 (OR 2.00), and risk assessment profile score ≥5 (OR 6.70) were independent risk factors for VTE (all p<0.05), while VTEp with enoxaparin was

associated with decreased VTE (OR 0.54, p<0.05). Importantly, VTEp ≤48 hours was not associated with pICH (OR 0.75) or risk of other bleeding events (OR 1.28) (both p=NS).

Conclusions: Early initiation of VTEp (≤48h) for patients with ICH was associated with decreased VTE/DVT rates without increased risk of pICH or other significant bleeding events. Enoxaparin is superior to unfractionated heparin as VTE prophylaxis in patients with severe TBI.

Level of Evidence: Level IV; Therapeutic/Care management.

Keywords: Traumatic brain injury; intracranial hemorrhage; venous thromboembolism; deep vein thrombosis; pulmonary embolus; chemoprophylaxis

Background

Traumatic brain injury (TBI) is known to be a major and independent risk factor associated with the development of venous thromboembolism (VTE) after trauma [1-4]. The incidence of VTE in TBI patients ranges from 20% to 54% in different studies of TBI or TBI subgroups [5-7]. The underlying pathophysiology of VTE and how it is impacted by TBI is multifactorial and only partly understood at this time. First, immobilization after TBI and associated injuries will cause venous stasis and enhanced clot formation. Second, the post-injury systemic inflammatory response, comprising a series of alteration of coagulation function that frequently culminate in a prothrombotic state, will create an environment for VTE formation [8, 9]. In addition, VTE prophylaxis with anticoagulant medications including unfractionated (UF) or low-molecular weight heparins (LMWH) is frequently delayed or even foregone in patients with intracranial hemorrhage due to the fear of bleeding progression and associated neurologic complications or need for surgical intervention [10, 11].

Both deep vein thrombosis (DVT) and pulmonary embolism (PE) can lead to serious consequences. The acute propagation of DVT to PE or the formation of de novo pulmonary thrombosis can result in significant morbidity or even mortality. Autopsy studies in trauma patients have reported PE as the third leading cause of deaths after 72 hours [12]. The

post-thrombotic syndrome can affect long-term quality of life as well [13]. Timely administration of VTE prophylaxis (VTEp) has been shown to significantly decrease VTE rates, and delayed administration remains a major modifiable risk factor for VTE [10, 14]. However, the optimal VTEp timing for severe TBI patients remains an area of significant debate and wide practice variation. Most available published series have been limited to single center analyses or reviews of large datasets that were not specifically designed for VTE data. The aim of this study was to use a prospective multicenter database specifically designed to examine questions around VTE to evaluate the timing and safety of VTEp in the TBI population. Our hypothesis was that initiating early VTEp for severe TBI patients would reduce the incidence of VTE and would not be associated with progression of intracranial hemorrhage (pICH) or other adverse bleeding events.

Methods

Population data

The original Consortium of Leaders in Traumatic Thromboembolism (CLOTT) was a multicenter prospective observational study designed to address the issue about posttraumatic pulmonary thrombosis. It contained 7,880 deidentified patient data collected during January 2018 to December 2020 from 17 level 1 trauma centers in the United States. The study was funded by Department of Defense so only patients within the typical military deployable age

range (18-40) were involved. Trauma patients admitted to one of the participating centers were included if they were anticipated to stay in the hospital for more than 48 hours and had at least one of the following known risk factors for VTE: pelvic fracture, lower extremity fracture above ankle, head/chest/abdominal injury of Abbreviated Injury Score (AIS) of 3 or greater, required ventilator support for 3 days, shock on admission, spinal cord injury, major vein injury, or requiring major operations on the day of admission. This study was a secondary analysis from the CLOTT database. To identify patients with severe head injury, we selected patients having head AIS 3-5 and length of stay more than 72 hours from the database, and must have 1) no VTEp within 24 hours due to intracranial hemorrhage (ICH), or 2) receiving any emergent neurosurgical interventions, i.e., craniotomy, craniectomy, and intracranial pressure (ICP) monitoring/drain placement. Exclusion criteria included non-survivable head injury (AIS =6), no VTEp or without documentation, and VTEp interruption for reasons irrelevant to concern of bleeding or procedures, e.g., patient refusal or medication administration error.

Data collection and outcome measures

Demographic data, initial vital signs, AIS from different body regions, injury severity score, preexisting condition, use of tranexamic acid, and the timing and methods of VTEp, missing doses and reasons were collected. We used the risk assessment profile score (RAP) to stratify

the risk of VTE [15]. A RAP score greater than 4 was deemed as high risk. The detailed definition of the RAP scoring system is listed in Supplemental Digital Content 1, http://links.lww.com/TA/D72.

Emergent neurosurgical procedures were recorded if patients received a craniotomy, craniectomy, ICP monitoring, or external ventricular drain placement. All eligible patients were then separated into early versus late initiation of VTEp using a cut-off point of 48 hours from admission. Patients were followed until the time of death, transfer to another facility, or discharge. The primary outcome was the development of VTE including DVT, PE, or primary pulmonary thrombosis (PT). As the focus was on the incidence of new VTE after initiation of VTEp, patients with VTE diagnosed prior to 48 hours from admission were not included for analysis since they had VTE before prophylaxis. Secondary outcomes included progression of ICH or any bleeding complications that were deemed to be potentially related to VTEp. The surveillance for VTE and medications for VTEp were utilized at the discretion of treating clinicians from different sites without a universal protocol. DVT was diagnosed by duplex ultrasound or computed tomography. Pulmonary embolism/thrombosis was diagnosed if identified in a computed tomography angiography of the chest.

Statistical analysis

Categorical variables from different groups were compared by Chi-square or Fisher's exact test. Mann-Whitney U test was used for continuous variables when there was non-normal distribution. Missing values were all less than 2% therefore without further imputation. Univariate analysis was conducted to compare the differences between developing VTE or not. Variables with p value <0.2 then proceeded to multivariate logistic regression to identify the independent factors associated with VTE. Confounders were maintained if they were considered relevant to outcome or produced more than 10% change in the odds of association with the outcome of interest. Since our interest was the timing of VTEp, we kept this factor in the final model. Collinearity was checked to ensure variance inflation factors were less than 2. The same method was applied to identify factors associated with pICH or any bleeding events. Statistical significance was set as $p < 0.05$. All statistics were performed using SPSS 28.0 (IBM Corp., Armonk, NY). The study was approved by the Institutional Review Board at our institution and followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guideline (Supplemental Digital Content 2, http://links.lww.com/TA/D72).

Results

There were 881 patients enrolled. The majority were from blunt injury mechanisms (91.8%), with a median injury severity score of 26 (Table 1). VTEp ≤48 hours (early group) accounted for 42.9% of the patients. Of the VTEp >48 hours (late) group, the median initiation time was the 4th day (interquartile range 3-5). Patients with VTEp >48 hours were more severely injured overall than patients with VTEp ≤48 hours and presented with a higher proportion of head AIS of 5 (43.1% vs 28.8%, p<.001), required more neurosurgical interventions (33.4% vs 23.3%, p<.001), and more prolonged mechanical ventilation (49.1% vs 36.2%, p<.001). The incidence of DVT was significantly higher in the VTEp >48 hours group compared to the ≤48 hours group (11.0% vs 6.1%, p=.012), as well as the incidence of overall VTE (12.4% vs 7.2%, p=.012) (Table 2). There was no significant difference in the rates of pICH or other bleeding complications between the early versus late VTEp groups, including hemorrhage from solid organ injury, gastrointestinal or genitourinary bleeding (Figure 1).

The patient characteristics and factors related to VTE, pICH, and any bleeding complications related to VTEp were evaluated (Supplemental Digital Content 3-5, http://links.lww.com/TA/D72) and then entered into a backward stepwise multivariate logistic regression. VTEp >48h (OR 1.86, 95% CI 1.11-3.10), ventilator use >3 days (OR 2.00, 95% CI 1.21-3.31), and RAP score >4 (OR 6.70, 95% CI 2.05-21.94), were

independently associated with an increased VTE rate (Table 3). Use of enoxaparin was associated with lower VTE compared to UF (OR 0.54, 95% CI 0.33-0.88). If using VTEp initiating day as a continuous variable and adjusting with the same variables listed above, the VTEp initiating day had an OR 1.06 (95% CI 1.01-1.11), showing that each day of delay VTEp was related to a 6% increase in odds of VTE. As shown in Table 4, VTEp ≤48 hours (early) was not significantly associated with pICH or any bleeding events after initiation of chemoprophylaxis. There was a significant relationship between pICH and the need for craniectomy (OR 5.41, 95% CI 1.70-17.26). For all the bleeding events after VTEp, only neurosurgical intervention was a significant risk factor (OR 8.31, 95% CI 3.01-22.89). There was no independent association between the early initiation of VTE prophylaxis and bleeding events in all multivariate models.

Discussion

The prevention, early diagnosis, and treatment of post-traumatic VTE remains a cornerstone of inpatient care of the injured patient and represents a major focus of trauma quality initiatives and trauma center verifications programs. However, there is a consistent common tension in both clinical practice and the VTE literature between prioritizing early VTE chemoprophylaxis administration and the fear of resultant bleeding complications. The present study represents one of the only prospective analyses of the associations between

VTEp and outcomes in TBI patients from a database specifically designed to capture data related to thrombotic complications and VTE prophylaxis practices. In this analysis of the CLOTT dataset, we found that early (within 48 hours) initiation of VTE prophylaxis is associated with decreased thromboembolic events and no increase in bleeding complications compared to delayed administration.

Previous studies had shown that the later the VTEp starts, the higher the VTE rate will be [15, 16]. Byrne et al. analyzed 4951 blunt TBI patients and found that each additional day of delay was associated with an 8% increase in odds of VTE (adjusted OR 1.08, 95% CI 1.04-1.12) [16]. Starting VTEp less than 72 hours was proved in several studies to be feasible and effective in decreasing VTE rate [11, 17]. Other studies used an earlier initiating timeline, but the study groups and populations have varied significantly. Meyer et al. included 67 penetrating head injuries and found no difference when starting VTEp at 48 hours compared to later initiation [18]. Coleman et al. analyzed those receiving neurosurgical operations and showed a lower VTE rate when VTEp was initiated within 48 hours from admission [19]. In our study, we included the more severe and higher risk head injuries (head AIS 3-5) with and without neurosurgical interventions and also showed a significant benefit for early prophylaxis. When trying to identify an optimal initiating time, the underlying dynamic coagulation function also needs to be considered. In trauma patients with bleeding, the initial

coagulopathy (if present) generally resolves by 24 hours, and the proportion of patients with hypercoagulable state increases significantly by 48 hours [20, 21]. An analysis of CLOTT-2 database showed that major traumatic brain injury was independently associated with fibrinolysis shut-down at 24 hours [22]. This evidence theoretically supports the importance of VTEp initiation by the 48-hour timepoint. However, it is important to recognize that there is no hard science behind using a cut-off point of 48 hours to define early versus late, and there may be an alternative and even earlier timepoint that would be safe in terms of bleeding and even more effective for prevention of VTE.

In traumatic ICH patients, it is common to see some degree of hemorrhage progression in the first hours after injury (18% - 65%) [23], with most occurring within the first 24 hours [24-26]. Although some degree of ICH progression is relatively common, particularly in moderate to severe traumatic brain injuries, the majority of these do not require any additional neurosurgical interventions. The reported neurosurgical intervention rates for progression of the initial ICH after repeat CT scan has ranged from 1-8% in published studies [23, 27, 28]. Several previous studies have shown that VTEp does not appear to increase the risk of pICH. Kim et al. analyzed 64 TBI patients using UF and found no increase of pICH if starting VTEp at less than 72 hours [29]. In another study by Koehler et al. specifically examining prophylaxis with LMWH, starting VTEp within 72 hours did not increase the

overall pICH rate (1.46% vs 1.54%, p=.912) [30]. However, they excluded patients receiving ICP monitor or external ventricular drain placement and thus the safety remains unproven in that subgroup. Frisoli et al. compared TBI patients starting VTEp <24 hours or >48 hours and did not find a significant difference in pICH rate (18% vs 17%, p=.83), but they similarly excluded patients receiving neurosurgical operations [31]. Since the risk of pICH has a close correlation to higher injury severity [23, 26-28], all severe TBI patients need to be included when trying to evaluate the safety of early VTEp. In this study we used head AIS 3-5, with or without neurosurgical interventions, and "no VTEp within 24 hours due to concern of ICH" as our primary selection criteria. After adjusting for other relevant factors, starting VTEp within 48 hours did not independently raise the risk of pICH.

It is important to note that there are several prior studies that have not supported the safety of early initiation of VTE chemoprophylaxis. Levy et al. found that in 92 patients having pICH in initial follow-up CT, patients who received VTEp had a higher ICH progression rate compared to those without initiation of VTEp [32]. Our analysis included a much larger sample size with significantly greater power for both bleeding and VTE outcomes, and the CLOTT dataset includes detailed data on VTEp administration continuity and missed dosing. The results show that most of the identified bleeding complications after VTEp were pICH, with a much lower incidence of hemorrhage from solid organ injuries, gastrointestinal

bleeding, or genitourinary tract bleeding. Early prophylaxis was found to have no significant association with pICH or any of the other bleeding events. It is also important to note that although these were all defined as bleeding events after initiation of VTEp, there can be no direct causality assumed.

Enoxaparin showed a protective effect on VTE compared to heparin, which has been shown in previous studies. Specific to TBI, Byrne et al. found lower odds of VTE in LMWH compared to UF (OR 0.64, 13 95% CI 0.49-0.84) [16]. While there may be concerns about the risk of bleeding when using LMWH [33], our data showed no significant difference for either pICH or other bleeding events when comparing LMWH to UF.

Although we excluded patients with VTEp interruption due to non-compliance, there were still 30.8% patients who had at least one missing dose. The majority of these patients had only one missing dose (73.8%). Previous literature has identified missing VTEp as a potential risk factor for increased VTE rates, but these analyses are significantly confounded by factors including the number and timing of missed doses, the exact medication utilized, and the reason for the held or missed dose [19, 34]. From the CLOTT dataset with robust information on the reasons and number/timing of missed doses in detail, we found that there was little effect of missed VTEp doses on overall VTE rates or on bleeding risks.

While the overall VTE and DVT incidence was significantly lower in the early VTEp group, the PE rate was not significantly different. This might be partially explained by other interventions to reduce the risk of symptomatic embolic events, such as the use of mechanical prophylactic measures. In the present study, 4.4% of patients in the VTEp >48 hours group had a prophylactic IVC filter placement compared to only 1.1% in VTEp ≤48 hours group. But even with the existing effect of IVC filter factored into the regression analyses, early prophylaxis still showed an overall lower incidence of VTE. A more likely explanation for the difference between DVT and PE/PT rates is that the two entities originate from different etiology and are not always related in trauma patients [35].

We identified that those who required emergent craniectomy had a significantly increased rate of pICH even after adjustment for confounding factors. Although patients receiving craniotomy and ICP monitor had a trend of increased incidence of pICH, only craniectomy remained a significant independent associated factor on multivariate analysis. It may be appropriate to interpret this result as those injury patterns that dictate the need for craniectomy were prone to progress rather than the effect of the craniectomy procedure itself, but this remains speculative. Theoretically patients with more severe head injuries have higher risk of pICH; however, we failed to demonstrate a significant association between head AIS and pICH. A possible explanation is that AIS score does not correlate with the

indications for operations very well. It is also important to mention that pICH rate was relatively low in the CLOTT database because only pICH "after initiating VTEp" was documented, and thus it was not equal to the true overall pICH rate.

One of the major limitations of this study was the lack of details about specific head injury types, detailed CT scans and/or operative findings, and the timing of progression of ICH. The relationship between head injury types and pICH has been elucidated in many studies [38]. Although we focused on severe TBI patients for analysis, variations still existed among the study groups. We did not see a significant difference of PE rate. It is possible that the low incidence of this particular outcome measure results in underpowering of even a large dataset such as CLOTT to detect what could be a potentially significant decrease in incidence with early prophylaxis. Another limitation is that CLOTT was an observational study and thus imaging procedures for VTE and ICH as well as prophylactic measures and their timing were left to the discretion of the treating surgeons leading to interfacility variations. The database did not include the outcome of pICH, so it was unknown whether those findings needed intervention or remained subclinical. Another significant limitation is that this database was designed for inclusion only of relatively younger age patients (age 18-40) per the specifications of the funding agency, and thus extrapolation to more elderly populations and those with existing coagulopathies or on anticoagulant medications cannot be made. Finally,

although the CLOTT dataset is a large and multicenter collection there remain limitations of the sample size and adequate power for analyses of uncommon events and smaller subpopulations.

Conclusion

For severe TBI patients, early initiation of VTE chemoprophylaxis (within 48 hours) after injury was associated with a significant decrease in VTE rates compared to delayed initiation without increasing the incidence of intracranial hemorrhage progression or other extracranial bleeding complication. While DVT rates were lower in the early prophylactic group, pulmonary clots were not, suggesting that risk factors for DVT may be different than those of PE/PT in this population. Further prospective studies in specific high-risk subgroups of pICH are warranted to clarify the ideal timing, medication, and dosing for VTE prophylaxis.

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Figure Legend

Figure 1. The incidence of venous thromboembolism (VTE) and bleeding complications in early (≤48h) or late (>48h) venous thromboembolism prophylaxis patients. DVT, deep vein thrombosis; PE/PT, pulmonary embolism/pulmonary thrombosis; pICH, progression of intracranial hemorrhage.

Supplement Digital Content

Supplement 1. Risk assessment profile (RAS) score

Supplement 2. STROBE Statement

Supplement 3. Univariate analysis of factors related to venous thromboembolism.

Supplement 4. Univariate analysis of factors related to progression of intracranial hemorrhage.

Supplement 5. Univariate analysis of factors related to any bleeding complications.

Figure 1

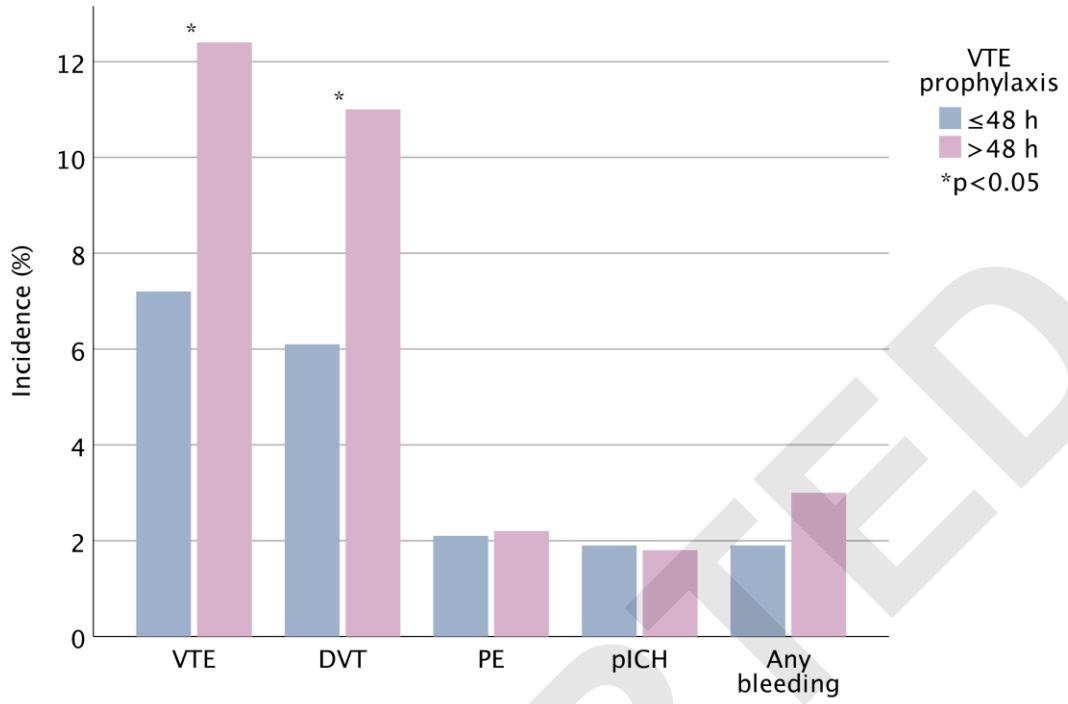


Table 1. Patient characteristics, risk factors related to venous thromboembolism, and prophylaxis methods.

	Total N=881	**VTEp ≤48h N=378**	**VTEp >48h N=503**	**p**
Age (median, IQR)	29, 24-35	29, 24-35	29, 24-35	0.91
Male (%)	680 (77.2)	293 (77.5)	387 (76.9)	0.84
Blunt/penetrating (%)	808/72 (91.8/8.2)	352/26 (93.1/6.9)	456/46 (90.8/9.2)	0.22
Body mass index (median, IQR)	25.4, 22.5-28.9	25.7, 22.9-29.1	25.1, 22.3-28.8	0.23
SBP <90mmHg (%)	65 (7.4)	22 (5.9)	43 (8.6)	0.12
Pulse >120 (%)	160 (18.3)	69 (18.4)	91 (18.2)	0.97
Glasgow coma scale <9 (%)	480 (54.9)	197 (52.8)	283 (56.5)	0.28
Head AIS (%)				<0.01
3	268 (30.4)	134 (35.4)	134 (26.6)	
4	287 (32.6)	135 (35.7)	152 (30.2)	
5	326 (37.0)	109 (28.8)	217 (43.1)	
Chest AIS ≥3 (%)	299 (33.9)	132 (34.9)	167 (33.2)	0.59
Abdomen AIS ≥3 (%)	134 (15.2)	55 (14.6)	79 (15.7)	0.64
Extremity AIS ≥3 (%)	160 (18.2)	63 (16.7)	97 (19.3)	0.32
ISS (median, IQR)	26, 21-34	26, 18-34	27, 21-34	<0.01
RAP ≥5 (%)	643 (76.1)	263 (72.9)	380 (78.5)	0.06
Neurosurgical intervention (%)	257 (29.2)	88 (23.3)	168 (33.4)	<0.01
Craniectomy	141 (16.0)	51 (13.5)	90 (17.9)	0.08
Craniotomy	135 (15.3)	43 (11.4)	92 (18.3)	0.01
ICP monitor	22 (2.5)	13 (3.4)	9 (1.8)	0.12
External ventricular drain	11 (1.2)	3 (0.8)	8 (1.6)	0.37
Ventilator use≥ 4 days (%)	384 (43.6)	137 (36.2)	247 (49.1)	<0.01
Tranexamic acid use (%)	48 (5.4)	19 (5.0)	29 (5.8)	0.63
VTEp medication (%)				<0.01
Heparin	247 (28.0)	132 (34.9)	115 (22.9)	
Enoxaparin	619 (70.3)	239 (63.2)	380 (75.5)	
Others or mixed	15 (1.7)	7 (1.9)	8 (1.6)	
VTEp missing dose (%)	271 (30.8)	104 (27.5)	167 (33.2)	0.07
VTE mechanical prophylaxis (%)	799 (90.7)	340 (89.9)	459 (91.3)	0.51
IVC filter (%)	26 (3.0)	4 (1.1)	22 (4.4)	<0.01

VTEp, prophylaxis of venous thromboembolism; IQR, interquartile range; SBP, systolic blood pressure; AIS, abbreviated injury scale; ISS, injury severity score; RAP; risk assessment profile score; ICP, intracranial pressure; IVC, inferior vena cava.

Table 2. Complications and outcomes

	Total	**VTEp ≤48h**	**VTEp >48h**	**p**
	N=877	**N=376**	**N=501**	
VTE (%)	89 (10.1)	27 (7.2)	62 (12.4)	0.01
Deep vein thrombosis (%)	82 (9.3)	23 (6.1)	55 (11.0)	0.01
Pulmonary embolism/thrombosis (%)	19 (2.2)	8 (2.1)	11 (2.2)	0.94
VTE date (median, IQR)	8, 4-15	11, 4-17	8, 4-15	0.75
Complications (%)				
Hemorrhage from solid organ injury	1 (0.1)	0 (0.0)	1 (0.2)	1
Intracranial bleeding	16 (1.8)	7 (1.9)	9 (1.8)	0.95
Gastrointestinal bleeding	4 (0.5)	0 (0.0)	4 (0.8)	0.14
Genitourinary bleeding	1 (0.1)	0 (0.0)	1 (0.2)	1
Any bleeding	22 (2.5)	7 (1.9)	15 (3.0)	0.28
Length of stay (median, IQR)	13, 7-24	10, 5-21	16, 8-27	<0.01
ICU length of stay (median, IQR)	8, 3-16	6, 3-13	10, 4-18	<0.01
Mortality (%)	44 (5.0)	16 (4.3)	28 (5.6)	0.38

VTEp, prophylaxis of venous thromboembolism; VTE, venous thromboembolism; IQR, interquartile range; ICU, intensive care unit.

Table 3. Risk factors for venous thromboembolism (VTE) on multivariate logistic regression.

	Odds ratio (95% CI)	**p**
VTE prophylaxis initiation >48h	1.86 (1.11-3.10)	0.02
Ventilator use ≥4 days	2.00 (1.21-3.31)	0.01
RAP score ≥5	6.70 (2.05-21.94)	<0.01
VTE prophylaxis with Enoxaparin[1]	0.54 (0.33-0.88)	0.01

[1]Compared to unfractionated heparin.

X^2= 5.192; Hosmer-Lemeshow test= .637; Nagelkerke R square= .119.

RAP, risk assessment profile.

Table 4. Risk factors for progression of intracranial hemorrhage or any bleeding complications after starting prophylaxis of venous thromboembolism (VTE).

	Odds ratio (95% CI)	**p**
Progression of intracranial hemorrhage[1]		
VTE prophylaxis initiation ≤48h	0.75 (0.24-2.29)	0.61
Craniectomy	5.41 (1.70-17.26)	<0.01
Craniotomy	2.60 (0.85-8.00)	0.10
ICP monitor	3.27 (0.73-14.71)	0.12
Body mass index	1.09 (0.99-1.18)	0.07
AIS head		
3	Reference	0.19
4	1.12 (0.95-13.14)	0.93
5	3.83 (0.43-33.92)	0.23
Any bleeding[2]		
VTE prophylaxis initiation ≤48h	1.28 (0.51-3.22)	0.61
Neurosurgical intervention	8.31 (3.01-22.89)	<0.01
Injury severity score	1.03 (0.99-1.08)	0.10

ICP, intracerebral pressure; AIS, abbreviated injury scale.

[1] X^2= 4.177; Hosmer-Lemeshow test= .841; Nagelkerke R square= .209.

[2] X^2= 6.982; Hosmer-Lemeshow test= .539; Nagelkerke R square= .137.

Supplement 1. Risk assessment profile (RAS) score[1]

	Points
Obesity[2]	2
Malignancy	2
Abnormal coagulation[3]	2
History of thromboembolism	3
Femoral venous line	2
Blood transfusion >4 units	2
Major operation >2 h	2
Major venous repair	3
Chest AIS >2	2
Abdomen AIS >2	2
Head AIS >2	2
Spinal fractures	3
Glasgow coma scale <8	3
Severe lower extremity fracture	4
Pelvic fracture	4
Spinal cord injury	4
Age	
≥40 and <60	2
≥60 and <75	3
≥75	4

[1]The original RAS score did not contain the following definition for obesity and coagulation.

[2] Defined as BMI ≥30 in this study.

[3] Normal ranges were defined as INR 0.8-1.5, platelet 140,000-450,000/ul, and fibrinogen 175-425 mg/dl in this study.

Reference: Greenfield LJ, Proctor MC, Rodriquez JL, Luchette FA, Cipolle MD, Cho J. Post-trauma thromboembolism prophylaxis. J Trauma 1997;42:100-3

Supplement 2. STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Relevant text in the manuscript
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	☑☐
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	☑☐
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	☑☐
Objectives	3	State specific objectives, including any prespecified hypotheses	☑☐
Methods			
Study design	4	Present key elements of study design early in the paper	☑☐
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	☑☐
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	☑☐
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	☑☐

Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	☑☐
Bias	9	Describe any efforts to address potential sources of bias	☑☐
Study size	10	Explain how the study size was arrived at	☑☐
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	☑☐
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	☑☐
		(*b*) Describe any methods used to examine subgroups and interactions	☑☐
		(*c*) Explain how missing data were addressed	☑☐
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	Followed til discharge
		(*e*) Describe any sensitivity analyses	
Results			**Relevant text in the manuscript**
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	☑☐
		(b) Give reasons for non-participation at each stage	☑☐
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	☑☐
		(b) Indicate number of participants with missing data for each variable of interest	☑☐ In methods

		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	☑☐
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	☑☐
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	☑☐
		(*b*) Report category boundaries when continuous variables were categorized	☑☐
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	☑☐
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	☑☐
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	☑☐
Generalisability	21	Discuss the generalisability (external validity) of the study results	☑☐
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	☑☐

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

Supplement 3. Univariate analysis of factors related to venous thromboembolism (VTE).

	VTE N=89	No VTE N=788	p
Blunt/penetrating (%)	76/13 (85.4/14.6)	728/59 (92.5/7.5)	.021
Initial shock status (%)	31 (35.2)	168 (21.5)	.004
Risk assessment profile (RAP) (%)			
Age =40	3 (3.4)	22 (2.8)	.734
BMI >30	20 (22.7)	140 (18.1)	.292
Malignancy	0 (0.0)	3 (0.4)	1
History of VTE	0 (0.0)	2 (0.3)	1
Abnormal coagulation	21 (23.9)	125 (16.0)	.062
Head AIS >2	89 (100.0)	788 (100.0)	1
Chest AIS >2	42 (47.2)	255 (32.4)	.005
Abdomen AIS >2	15 (16.9)	117 (14.8)	.616
Spinal cord injury	3 (3.4)	33 (4.2)	1
Pelvic fracture	18 (20.2)	103 (13.1)	.064
Severe lower extremity fracture	21 (23.6)	124 (15.7)	.058
Glasgow coma scale <8	60 (67.4)	378 (48.3)	<.001
Femoral venous line	33 (37.1)	112 (14.2)	<.001
Blood transfusion >4 units	23 (26.1)	94 (11.9)	<.001
Major operations >2 hour	66 (74.2)	472 (59.9)	.009
Major vein injury	5 (5.6)	31 (3.9)	.401
RAP score ≥5	82 (96.5)	559 (73.8)	<.001
Preexisting condition (%)			
Anticoagulant use	0 (0.0)	2 (0.3)	1
Pregnancy	0 (0.0)	8 (1.0)	1
Hormonal medications	2 (2.3)	12 (1.5)	.645
Inflammatory bowel disease	0 (0.0)	3 (0.4)	1
Neurosurgical intervention (%)	38 (42.7)	217 (27.5)	.003
Ventilator use ≥4 days (%)	61 (68.5)	320 (40.6)	<.001
Tranexamic acid use (%)	10 (11.2)	38 (4.8)	.023
VTEp initiation> 48h (%)	62 (69.7)	439 (55.7)	.012
VTEp medication (%)			.002
Heparin	37 (42.5)	209 (26.9)	
Enoxaparin	50 (57.5)	569 (73.1)	
VTEp mechanical (%)	79 (88.8)	717 (91.0)	.492
VTEp missing dose (%)	31 (34.8)	238 (30.1)	.357

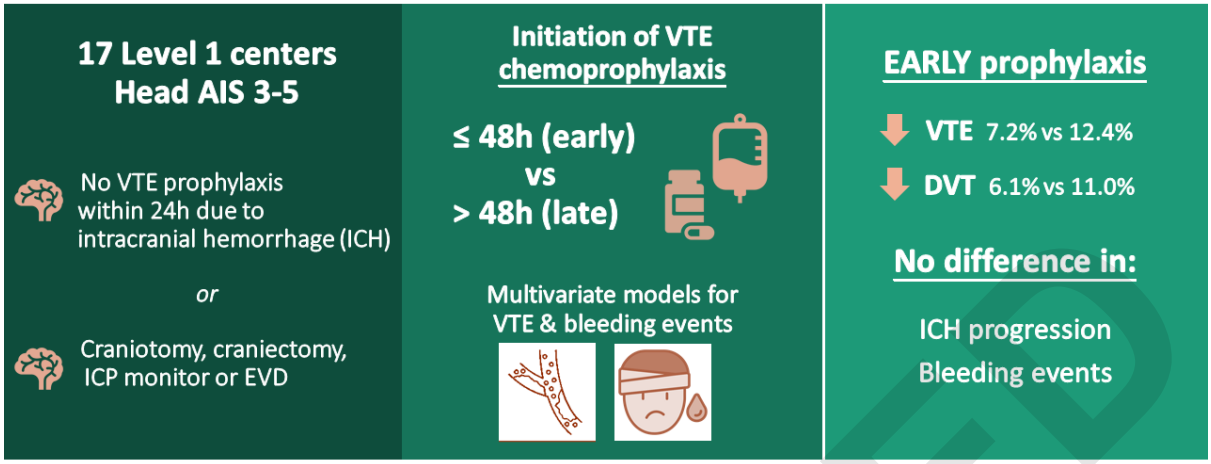
Supplement 4. Univariate analysis of factors related to progression of intracranial hemorrhage.

	pICH **N=16**	**No pICH** **N=865**	**p**
Blunt/penetrating (%)	15/1 (93.8/6.3)	793/71 (91.8/8.2)	1
BMI (median, IQR)	28.2, 22.5-34.2	25.4, 22.5-28.8	.172
Initial shock status (%)	3 (18.8)	197 (23.0)	1
GCS <9 (%)	11 (68.8)	469 (54.7)	.262
Head AIS (%)			.006
3	2 (12.5)	266 (30.8)	
4	2 (12.5)	285 (32.9)	
5	12 (75.0)	314 (36.3)	
Chest AIS ≥3 (%)	4 (25.0)	295 (34.1)	.446
Abdomen AIS ≥3 (%)	1 (6.3)	133 (15.4)	.490
Extremity AIS ≥3 (%)	4 (25.0)	156 (18.0)	.510
Multiple trauma (%)	8 (50.0)	395 (45.7)	.730
Anticoagulant use (%)	0 (0.0)	2 (0.2)	1
Initial coagulopathy (%)	3 (18.8)	145 (16.9)	.743
Neurosurgical intervention (%)	14 (87.5)	242 (28.0)	<.001
Craniectomy	9 (56.3)	132 (15.3)	<.001
Craniotomy	6 (37.5)	129 (14.9)	.025
ICP monitor	3 (18.8)	19 (2.2)	.006
EVD	0 (0.0)	11 (1.3)	1
VTE prophylaxis initiation >48h (%)	9 (56.3)	494 (57.1)	.945
VTEP medication (%)			.773
Heparin	5 (33.3)	242 (28.4)	
Enoxaparin	10 (66.7)	609 (71.6)	
Blood transfusion >4u (%)	3 (18.8)	115 (13.3)	.463

Supplement 5. Univariate analysis of factors related to any bleeding complications.

	Any bleeding	**No bleeding**	**p**
	N=22	**N=856**	
Male (%)	20 (90.9)	658 (76.9)	.121
Blunt/penetrating (%)	21/1 (95.5/4.5)	784/71 (91.7/8.3)	1
BMI (median, IQR)	26.2, 22.7-30.9	25.4, 22.6-28.8	.327
Initial shock status (%)	5 (23.8)	195 (22.9)	1
GCS <9 (%)	17 (77.3)	460 (54.2)	.032
Head AIS (%)			.019
3	2 (9.1)	265 (31.0)	
4	6 (27.3)	280 (32.7)	
5	14 (63.6)	311 (36.3)	
Chest AIS ≥3 (%)	9 (40.9)	288 (33.6)	.477
Abdomen AIS ≥3 (%)	2 (9.1)	130 (15.2)	.559
Extremity AIS ≥3 (%)	5 (22.7)	155 (18.1)	.576
Multiple trauma	13 (59.1)	388 (45.3)	.201
ISS	30, 26-38	26, 21-34	.009
Anticoagulant use	0 (0.0)	2 (0.2)	1
Initial coagulopathy	5 (22.7)	141 (16.6)	.396
Neurosurgical intervention (%)	17 (77.3)	238 (27.8)	<.001
Craniectomy	11 (50.0)	130 (15.2)	<.001
Craniotomy	7 (31.8)	128 (15.0_	.064
ICP monitor	4 (18.2)	18 (2.1)	.002
EVD	0 (0.0)	10 (1.2)	1
VTE prophylaxis initiation >48h (%)	15 (68.2)	485 (56.7)	.281
VTEP medication (%)			.324
Heparin	8 (38.1)	238 (28.3)	
Enoxaparin	13 (61.9)	604 (71.7)	
Blood transfusion >4u	5 (22.7)	111 (13.0)	.196

Early Venous Thromboembolism Prophylaxis in Patients with Trauma Intracranial Hemorrhage: Analysis of the Prospective Multicenter CLOTT Study



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