

Early Venous Thromboembolism Prophylaxis in Brain Injury Guidelines 1 and Brain Injury Guidelines 2 Traumatic Brain Injury Patients: A 5-Year Analysis

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OBJECTIVES:	Brain Injury Guidelines (BIG) was developed to reduce hospitalization of patients with mild traumatic brain injury (TBI). Limited data on venous thromboembolism (VTE) prophylaxis for patients were categorized as BIG 1 and BIG 2 hospitalized for non-TBI-related trauma. The aim of this study is to assess safety of early VTE prophylaxis among BIG 1 and BIG 2 patients. We hypothesize that early VTE prophylaxis is safe.
METHODS:	We performed retrospective analysis of 2017–2021 TBI database at our level 1 trauma center and included all adult trauma patients with TBI categorized as BIG 1 or BIG 2 who received thromboprophylaxis. Patients were stratified into EARLY (≤ 24 hours) and LATE (> 24 hours) initiation of VTE prophylaxis. Outcomes were rates of repeat head computed tomography (RHCT) scan for neurological deterioration, mortality, deep vein thrombosis (DVT), and pulmonary embolism. Multivariable logistic regression was performed to identify independent effect of timing of VTE prophylaxis on outcomes.
RESULTS:	A total of 634 met the inclusion criteria. The mean age was 42, 62% were males, the mean systolic blood pressure was 129 mm Hg, and the median ISS was 13. There were 393 patients in EARLY group. Only 20 patients underwent RHCT with no difference between the groups ($p = 0.398$), with no worsening from index head CT. EARLY group had lower incidence of DVT (EARLY: 1% vs. LATE: 5%, $p = 0.020$) but no difference in pulmonary embolism ($p = 0.620$) or mortality ($p = 0.265$). On multivariable regression analysis, early VTE prophylaxis was associated with reducing risk of DVT (adjusted odds ratio, 0.341; 95% confidence interval, 0.121–0.783; $p = 0.043$). However, it was not associated with RHCT ($p = 0.219$) or mortality ($p = 0.653$).
CONCLUSION:	Early thromboprophylaxis for BIG 1 or BIG 2 trauma patients is safe and associated with reducing DVT risk without increasing risk of ICH progression or mortality. Future studies are needed to validate thromboprophylaxis risk-benefit ratio among BIG 1 and BIG 2 patients. (<i>J Trauma Acute Care Surg.</i> 2025;00: 00–00. Copyright © 2025 Wolters Kluwer Health, Inc. All rights reserved.)
LEVEL OF EVIDENCE:	Therapeutic/Care Management; Level III.
KEY WORDS:	Traumatic brain injury; Brain Injury Guidelines; venous thromboembolism; deep vein thrombosis.

In recent years, the management of traumatic brain injury (TBI) has changed significantly since the development of Brain Injury Guidelines (BIG).¹ These were developed to reduce hospitalization, improve resource allocation, and decrease unnecessary neurosurgical consultation of patients with mild TBI.² However, patients with BIG 1 or BIG 2 traumatic brain injuries often require hospital admission for management of other traumatic and/or nontraumatic injuries or medical illnesses. There is also variation

in admission service (e.g., trauma surgery, neurology, medicine, or neurosurgery) and management of pharmacologic prophylaxis to prevent venous thromboembolism (VTEs) in patients with mild TBI,^{3,4} which may impact the timing of initiation of VTE pharmacologic prophylaxis.

Traumatic brain injury is an independent risk factor for the development of thromboembolic events in trauma patients because of prolonged immobility, proinflammatory, and hypercoagulable state after trauma.^{5–9} The incidence of VTE in patients with TBI has been reported to be as high as 30% in some studies.^{6–8} The development of VTE in trauma patients is associated with an increased risk of morbidity and mortality with known long-term consequences such as postthrombotic syndrome, poorer quality of life, and prolonged hospital length of stay.^{5–7} Therefore, the initiation of pharmacologic VTE prophylaxis to decrease the rates of thromboembolic events must be balanced with the risk of intracranial hemorrhage (ICH) progression. The aim of this study is to assess the safety of early VTE prophylaxis among BIG 1 and BIG 2 patients who got admitted to the hospital for non-TBI-related trauma. We hypothesize that early VTE prophylaxis is safe in this patient population.

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METHODS

Study Design and Population

This is a 5-year (2017–2021) retrospective analysis of a prospectively maintained TBI database at our American College of Surgeons–verified Level I trauma center. This study was approved by the institutional review board. We adhered to the STrengthening the Reporting of OBservational studies in Epidemiology guidelines (see Supplemental Digital Content, Supplementary Data 1, <http://links.lww.com/TA/E423>).

Inclusion and Exclusion Criteria

We included all adult (18 years or older) patients who presented with a TBI and were classified based on the Brain Injury Guidelines as BIG 1 or BIG 2. Supplemental Digital Content (Supplementary Data 2, <http://links.lww.com/TA/E424>) demonstrates the criteria for BIG classification.¹ All included patients were admitted for non-TBI-related injuries or medical problems, as per our institution's adherence to the BIG. Patients with isolated TBI and classified as BIG 1 are typically discharged from the ED after a short observation period, while those classified as BIG 2 are admitted to the hospital for observation for no more than 24 hours. While BIG 1 and BIG 2 are distinct classifications, both share key clinical characteristics. Neither group requires neurosurgical consultation, intervention, or routine repeat head CT.

Patient Stratification

Based on the timing of initiation of VTE prophylaxis, patients were stratified into the EARLY group (VTE prophylaxis within 24 hours of admission) and the LATE group (VTE prophylaxis after 24 hours of admission). The 24-hour threshold was chosen based on recent guidelines and previous studies.¹⁰ The timing of initiation of VTE prophylaxis was kept at the discretion of the treating trauma surgeon. While no formal institutional protocol dictated this timing, decisions were likely influenced by multiple factors, including the patient's overall clinical status, perceived risk of ICH progression, hemodynamic stability, and adherence to evolving best practices. Additionally, as these were polytrauma patients, some had concomitant long bone fractures requiring orthopedic intervention, leading to delayed initiation of prophylaxis based on surgical planning. VTE prophylaxis was administered using weight-based low-molecular-weight heparin (enoxaparin) at 0.5 mg/kg with anti-Xa level monitoring to ensure appropriate dosing.

Outcomes

The primary outcome was the rate of repeat head computed tomography (RHCT) scans due to neurological deterioration. Secondary outcomes included rates of clinically significant deep vein thrombosis (DVT) (identified by duplex ultrasound following signs/symptoms), pulmonary embolism, and mortality.

Data Points

We collected multiple data points for each patient. We extracted information related to patient demographics (age, sex), emergency department (ED) vital signs (systolic blood pressure, Glasgow Coma Scale score), injury characteristics (Injury Severity Score [ISS], head–Abbreviated Injury Scale [AIS], abdomen–AIS, chest–AIS, extremity–AIS), blood product transfusion,

neurological examination findings on presentation, intoxication (drug or alcohol), data regarding antiplatelet and anticoagulation therapy, intubation, loss of consciousness, findings from initial CT scan of the head (type and size of ICH), and reasons for and findings from RHCT.

Statistical Analysis

To check the normality of all continuous variables, the Kolmogorov-Smirnov test was performed. We used mean with SDs to report normally distributed variables and median with interquartile ranges (IQRs) for nonnormally distributed variables. Categorical variables were reported as counts and proportions. We performed an independent-sample *t* test to compare continuous normally distributed variables and the Mann-Whitney *U* test for continuous skewed variables. Pearson's χ^2 test was used to compare categorical variables between different groups. Fisher's exact test was used to compare categorical variables when one or more of the expected cell counts were less than five.

Multivariable Logistic Regression Analysis

After adjusting for the potential confounding factors, we performed multivariable binary logistic regression analysis to identify the independent effect of early VTE prophylaxis on outcomes. Potential confounding variables were entered into the model based on existing literature and univariable analysis demonstrating $p < 0.2$. Alpha (α) was set at 5%, and a p value of < 0.05 was considered statistically significant. The odds ratio was obtained and reported with a 95% confidence interval (CI). All statistical analyses were performed using the Statistical Package for Social Sciences (version 29; SPSS, Inc., Armonk, NY).

RESULTS

Study Population

A total of 2,328 TBI patients presented to our trauma center over the study period. Of these, 634 met the inclusion criteria: 370 were BIG 1 and 264 were BIG 2. Nearly two-thirds (62%) of patients comprised the EARLY VTE prophylaxis group. Figure 1 demonstrates the patient flow diagram of the study population.

Baseline Characteristics

Overall, the mean (SD) age was 42 (24), 62% were male, and 60% of the study population were White. On ED presentation, the mean (SD) systolic blood pressure was 129 (20) mm Hg, the mean (SD) heart rate was 90 (22) beats per minute, and the median (IQR) Glasgow Coma Scale was 15 (15). Patients were moderately injured with a median (IQR) ISS of 13 (9–18), the median (IQR) head–AIS score of 2 (2–3), the median (IQR) chest–AIS score of 2 (0–2), the median (IQR) abdomen–AIS score of 2 (0–2), and the median (IQR) extremity–AIS score of 1 (0–1).

Smoking was the most prevalent comorbidity (19%), followed by hypertension (13%), diabetes mellitus (10%), and chronic obstructive pulmonary disease (7%). There was no statistically significant difference between the study groups in terms of demographics, ED vitals, and injury characteristics ($p > 0.05$). The most used thromboprophylaxis among the study

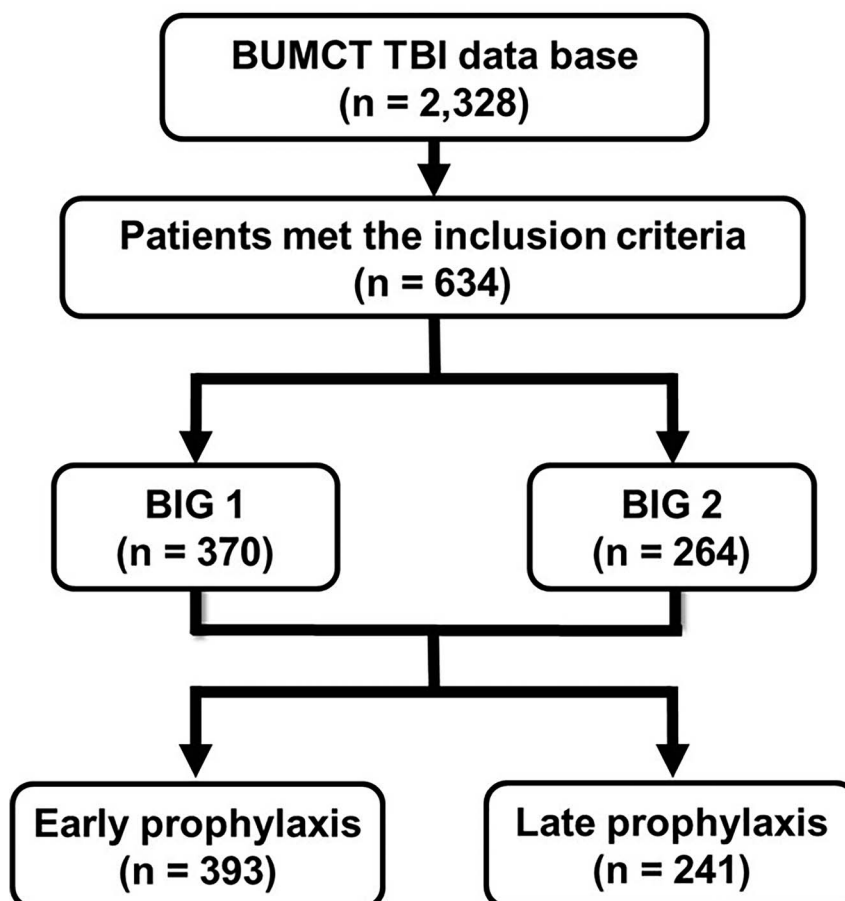


Figure 1. Patient flow diagram.

population was LMWH with 575 patients (91%). Table 1 demonstrates the baseline characteristics of the study cohort.

Univariable Analysis of Outcomes

Only 20 patients underwent repeat head CT with no difference between the two groups ($p = 0.778$). All RHCTs revealed no worsening from the index scan. Patients in the EARLY group had a lower incidence of clinically significant DVT compared with the LATE group (1% vs. 5%, $p = 0.020$). However, there was no significant difference between the groups in terms of pulmonary embolism incidence (0.5% vs. 1%, $p = 0.309$), or rates of mortality (1% vs. 2%, $p = 0.275$). Table 2 demonstrates the univariable analysis for the study population outcomes.

Multivariable Regression Analysis

After adjusting for confounding factors including, patient demographics, ED vitals, ISS, AIS, and patients' comorbidities, on multivariable regression analysis, EARLY VTE prophylaxis was associated with a reduced risk of DVT (adjusted odds ratio [aOR], 0.341; 95% CI, 0.121–0.783; $p = 0.043$). However, it was not associated with repeat head CT (aOR, 0.766; 95% CI, 0.243–3.605; $p = 0.219$) or mortality (aOR, 0.837; 95% CI, 0.386–1.816; $p = 0.653$). Table 3 outlines the independent effect of EARLY VTE prophylaxis on outcomes.

DISCUSSION

In this institutional study, we evaluated 634 patients with traumatic brain injuries classified as BIG 1 or BIG 2 who were admitted for a non-TBI-related diagnosis. We found that receiving early (<24 hours from admission) VTE prophylaxis was safe in this TBI population. By demonstrating a reduction in clinically significant DVTs without an associated increase in bleeding complications or mortality, our findings address a critical clinical dilemma and support the early initiation of VTE prophylaxis.

The occurrence of VTEs during hospitalization is associated with increased morbidity and mortality.^{8,11} Patients with TBI face a unique challenge regarding VTE prophylaxis because of the risk of exacerbating ICH in the limited space within the cranial vault and the potential for cerebral compression and herniation. This emphasizes the importance of identifying a safe window for initiating VTE prophylaxis. While studies have indicated a safe window period for multiple trauma populations regarding the timing of VTE prophylaxis,^{12–14} data specific to TBI remain limited. However, existing evidence demonstrates that early VTE prophylaxis can be safely administered in selected TBI populations, particularly in patients with low-risk injuries. For instance, a study has shown that, in cases of small-volume ICH with radiologic stability confirmed on head CT

TABLE 1. Baseline Characteristics of the Study Population Stratified by Time of Prophylaxis

Variables	Overall (n = 634)	Early Prophylaxis (n = 393)	Late Prophylaxis (n = 241)	p
Demographics				
Age, mean (SD), y	42 (24)	39 (24)	44 (25)	0.243
White race, n (%)	378 (59.6)	236 (60.1)	142 (58.9)	0.778
Male sex, n (%)	391 (61.6)	232 (59.0)	159 (65.9)	0.319
ED vital signs				
SBP, mean (SD), mm Hg	129 (20)	129 (20)	129 (21)	0.168
Heart rate, mean (SD), bpm	90 (22)	89 (22)	92 (21)	0.215
Glasgow Coma Scale, median (IQR)	15 (15–15)	15 (15–15)	15 (15–15)	0.297
Injury characteristics				
Blunt, n (%)	602 (94.9)	373 (94.9)	229 (95)	0.950
ISS, median (IQR)	13 (9–18)	12 (9–16)	17 (13–20)	<0.001
Head-AIS, median (IQR)	2 (2–3)	2 (2–3)	2 (2–3)	0.212
Chest-AIS, median (IQR)	2 (0–2)	2 (0–2)	2 (0–2)	0.628
Abdomen-AIS, median (IQR)	2 (0–2)	2 (0–2)	2 (0–2)	0.253
Extremity-AIS, median (IQR)	1 (0–1)	1 (0–1)	1 (0–1)	0.350
Interventions				
Laparotomy, n (%)	102 (16)	59 (15)	43 (18)	0.346
Long bone fixation, n (%)	57 (8.9)	16 (4)	41 (17)	<0.001
Angioembolization, n (%)	173 (27.3)	110 (28)	63 (26)	0.611
Type of thromboprophylaxis				
LMWH, n (%)	575 (90.7)	357 (90.8)	218 (90.5)	0.872
Comorbidities, n (%)				
HTN	80 (12.6)	50 (12.7)	30 (12.4)	0.919
COPD	45 (7.1)	29 (7.3)	16 (6.6)	0.725
DM	64 (10.1)	41 (10.4)	23 (9.5)	0.718
History of smoking	120 (18.9)	75 (19.1)	45 (18.7)	0.897

*Bold font indicates statistical significance ($p < 0.05$).

bpm, beats per minute; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; HTN, hypertension; SBP, systolic blood pressure.

within 24 hours, prophylaxis can be initiated without causing clinically significant hematoma expansion.¹⁵ These findings are consistent with other recent reports, which also demonstrate the safety of chemoprophylaxis in TBI.^{16–20} However, these studies vary in severity of head injury, time to initiation of chemoprophylaxis, chemoprophylaxis agent, and indications for postinitiation follow-up head CT to assess for hemorrhage progression. Using the BIG, low-risk patients such as those classified as BIG 1 and BIG 2 can be reliably identified for early VTE prophylaxis. Furthermore, repeat head CT scans beyond the initial imaging are unnecessary in this population, simplifying care without compromising safety.

Currently, most guidelines, including those from the Brain Trauma Foundation, do not provide specific recommendations regarding the optimal agent, dosage, or timing for initiating

VTE prophylaxis in patients with TBI.²¹ However, the recent American College of Surgeons Trauma Quality Improvement Program Best Practice Guidelines for TBI recommend initiating VTE prophylaxis within 24 hours in patients with low-risk non-operative TBI, provided that a follow-up head CT shows no progression of intracranial injury. This low-risk category closely aligns with BIG 1 and BIG 2 patients, who have minimal or no ICH and do not require neurosurgical intervention.¹⁰ The Western Trauma Association guidelines emphasize that pharmacologic prophylaxis can be safely initiated in the majority of TBI patients with a stable head CT scan. Specifically, the guidelines recommend the use of enoxaparin as early as 24 hours postinjury in appropriately selected patients, with nearly all TBI patients receiving prophylaxis within 72 hours.²² Importantly, the BIG 1 and 2 criteria may offer a validated framework for identifying low-risk

TABLE 2. Univariable Analysis of Outcomes

Variables	Overall (n = 634)	Early Prophylaxis (n = 393)	Late Prophylaxis (n = 241)	p
Repeat head CT scan, n (%)	20 (3.2)	13 (3.3)	7 (2.9)	0.778
DVT, n (%)	16 (2.5)	4 (1.0)	12 (4.9)	0.020
PE, n (%)	5 (0.8)	2 (0.5)	3 (1.2)	0.309
Mortality, n (%)	9 (1.4)	4 (1.0)	5 (2.1)	0.275

*Bold font indicates statistical significance ($p < 0.05$).

CT, computed tomography; DVT, deep venous thrombosis; PE, pulmonary embolism.

TABLE 3. Multivariable Regression Analysis

Independent Effect of Early VTE Prophylaxis and Outcomes

Variables	aOR	95% CI	<i>P</i>
DVT	0.341	0.121–0.783	0.043
Repeat head CT scan	0.766	0.243–3.605	0.219
Mortality	0.837	0.386–1.816	0.653

*Bold font indicates statistical significance ($p < 0.05$).

CT, computed tomography; DVT, deep venous thrombosis.

TBI patients, supporting the safe initiation of early VTE prophylaxis without increasing the risk of adverse outcomes.

The predominance of LMWH use in nearly 90% of our study population aligns with evidence supporting its safety and efficacy in patients with TBI.¹⁹ Previous studies have demonstrated favorable outcomes associated with LMWH compared with unfractionated heparin in similar patient populations. For instance, a study by Norwood et al.²³ established that LMWH could be initiated within 48 hours of injury in patients with blunt TBI. Furthermore, LMWH was associated with a lower progression rate compared with the unfractionated heparin group.¹⁹ Notably, while timing varies across studies, early initiation of LMWH appears to provide significant benefits without compromising safety. These findings further support the safety profile of LMWH, particularly in low-risk TBI patients such as those classified as BIG 1 and 2 in our cohort. Additionally, the broader adoption of LMWH in our study reflects its growing preference as a standard for early prophylaxis in this population.

Our study is not without limitations. The retrospective nature of the study limits data collection to preexisting data points and suggests correlation rather than causation. Also, because this was a single-institution study, the generalizability of our findings may be limited. Additionally, during our data collection, we were not able to identify the reasons for which VTE prophylaxis was withheld for those patients in the LATE group. This could be due to general concern for a worsening intracranial bleed or other clinical concerns. Furthermore, we did not account for instances where VTE prophylaxis may have been held perioperatively, which could have contributed to differences in VTE rates. Nevertheless, our study provides valuable insights by focusing on a well-defined low-risk population using the established BIG criteria, which enhances the reliability of the findings. Additionally, the large sample size strengthens the evidence supporting early VTE prophylaxis in this TBI population, providing a foundation for future prospective studies.

CONCLUSION

Our study supports the use of BIG 1 and BIG 2 criteria as an objective framework to guide the safe early initiation of VTE prophylaxis in trauma patients with mild TBI. Early administration was associated with a lower risk of DVT without increasing the risk of ICH progression or mortality, and our findings suggest that routine repeat head CT may not be necessary in these patients. Future prospective studies should further validate the safety and efficacy of this approach to refine clinical guidelines for VTE prophylaxis in mild TBI.

AUTHORSHIP

S.V.A., O.H., C.S., L.J.M., and B.J. designed this study. S.V.A., M.A.M., O.H., A.N., F.C.D., M.H.K., and B.J. searched the literature. S.V.A., O.H., F.C.D., M.A.M., C.S., A.N., A.L.S., and B.J. collected the data. S.V.A., M.H.K., L.J.M., A.L.S., and B.J. analyzed the data. All authors participated in data interpretation and manuscript preparation.

DISCLOSURE

Conflicts of Interest: Author Disclosure forms have been supplied and are provided as Supplemental Digital Content (<http://links.lww.com/TA/E425>).

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