When is it safe to start venous thromboembolism prophylaxis after blunt solid organ injury? A prospective American Association for the Surgery of Trauma multi-institutional trial

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BACKGROUND: The optimal time to initiate venous thromboembolism (VTE) chemoprophylaxis (VTEp) after blunt solid organ injury remains controversial, as VTE mitigation must be balanced against bleeding promulgation. Evidence from primarily small, retrospective, single-center work suggests that VTEp ≤48 hours is safe and effective. This study was undertaken to validate this clinical practice.

METHODS: Blunt trauma patients presenting to 19 participating trauma centers in North America were screened over a 1-year study period beginning between August 1 and October 1, 2021. Inclusions were age older than 15 years; ≥1 liver, spleen, or kidney injury; and initial nonoperative management. Exclusions were transfers, emergency department death, pregnancy, and concomitant bleeding disorder/anticoagulation/antiplatelet medication. A priori power calculation stipulated the need for 1,158 patients. Time of VTEp initiation defined study groups: Early (≤48 hours of admission) versus Late (>48 hours). Bivariate and multivariable analyses compared outcomes.

RESULTS: In total, 1,173 patients satisfied the study criteria with 571 liver (49%), 557 spleen (47%), and 277 kidney injuries (24%). The median patient age was 34 years (interquartile range, 25–49 years), and 67% (n = 780) were male. The median Injury Severity Score was 22 (interquartile range, 14–29) with Abbreviated Injury Scale Abdomen score of 3 (interquartile range, 2–3), and the median American Association for the Surgery of Trauma grade of solid organ injury was 2 (interquartile range, 2–3). Early VTEp patients (n = 838 [74%]) had significantly lower rates of VTE (n = 28 [3%] vs. n = 21 [7%], $p = 0.008$), comparable rates of nonoperative management failure (n = 21 [3%] vs. n = 12 [4%], $p = 0.228$), and lower rates of post-VTEp blood transfusion (n = 145 [17%] vs. n = 71 [23%], $p = 0.024$) when compared with Late VTEp patients (n = 301 [26%]). Late VTEp was independently associated with VTE (odd ratio, 2.251; $p = 0.046$).

CONCLUSION: Early initiation of VTEp was associated with significantly reduced rates of VTE with no increase in bleeding complications. Venous thromboembolism chemoprophylaxis initiation ≤48 hours is therefore safe and effective and should be the standard of care for patients with blunt solid organ injury. (*J Trauma Acute Care Surg.* 2024;96: 209–215. Copyright © 2023 American Association for the Surgery of Trauma.)

LEVEL OF EVIDENCE: Therapeutic and Care Management; Level III.

KEY WORDS: Venous thromboembolic event; venous thromboembolic prophylaxis; missed doses; solid organ injury; nonoperative management.

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Venous thromboembolic events, consisted of deep vein thromboses (DVTs) and pulmonary emboli (PEs), are an important cause of morbidity and mortality among trauma patients.[1] As a result of myriad postinjury factors including a hypercoagulable state,[2] fibrinolysis shutdown,[3] and immobility,[4] trauma patients are at high risk for venous thromboembolism (VTE). Existing literature emphasizes the benefit of early initiation of venous thromboembolism chemoprophylaxis (VTEp) to mitigate the risk of thromboembolism.[1,5,6] However, trauma patients present the competing concern of hemorrhage exacerbation from injured solid organs after early VTEp.[7] This may necessitate additional blood transfusion or even lead to failure of nonoperative management. Therefore, it is critical for optimal patient care to establish the ideal time to initiate VTEp after solid organ injury.

Existing literature on this subject is consisted primarily of small, single-center, retrospective studies,[8–13] with one prospective study,[14] three large retrospective studies,[15–17] and several systematic reviews or meta-analyses summarizing these works.[18–20] Taken together, these studies indicate that VTEp initiation within 48 hours of hospital arrival is both safe and effective at preventing VTEs, with VTEp initiation ≤48 hours associated with VTE rates of approximately 2% as compared with 5% with VTEp initiation >48 hours.[10,11,17] Prospective multi-institutional validation of these existing studies is warranted.

The aim of this study was to determine if early VTEp initiation (≤48 hours of hospital arrival) was associated with reduced VTE rates among patients with blunt solid organ injury managed nonoperatively. Secondarily, this study endeavored to demonstrate that early VTEp did not lead to clinically significant bleeding, defined as the need for postprophylaxis blood product transfusion and/or failed nonoperative management. We hypothesized that early VTEp initiation would reduce VTE rates and would not be associated with clinically significant bleeding.

PATIENTS AND METHODS

This was a multi-institutional prospective observational study sponsored by the American Association for the Surgery of Trauma (AAST). Nineteen trauma centers in North America were enrolled, and each screened patients over a 365-day study period beginning on dates ranging from August 1, 2021, to October 1, 2021. Patients were screened and assessed for study criteria within 24 hours of presentation to the emergency department (ED). Inclusions were age older than 15 years; ≥1 abdominal solid organ injury, defined as the liver, spleen, and/or kidney; and an initial plan for nonoperative management, defined as the absence of laparotomy within the first 4 hours after admission and an expressed plan for nonoperative management by the admitting trauma surgeon. Exclusions were transfers from another institution, ED death, pregnancy, comorbid bleeding disorder, and preinjury anticoagulation/antiplatelet medication use. Angioembolization as part of the nonoperative management of these patients was not an exclusion criterion. Institutional review board approval was obtained by the coordinating site and each participating site, with a waiver of informed consent granted because of the observational nature of the study. Data were deidentified and uploaded to an electronic data entry form. The STrengthening the Reporting of OBservational studies in Epidemiology guidelines were used to ensure proper reporting of *Patients and Methods*, *Results*, and *Discussion* (Supplemental Digital Content 1, http://links.lww.com/TA/D327).

Variables collected were patient demographics (age, sex, race/ethnicity, comorbidities, home medications); ED arrival date/time and first ED vital signs; injury data (mechanism of injury, Injury Severity Score, Abbreviated Injury Scale [AIS] score by body region, solid organ AAST grade of injury); ED discharge disposition; performance of catheter-based angiography with or without embolization and date/time; VTEp data (type, dosing, schedule, date/time of first dose, missed doses of VTEp, reason for delay if first dose given >48 hours from arrival); nonpharmacological VTE prophylaxis data, that is, hospital day of first ambulation and the use of sequential compression devices; center approach to VTE screening (protocolized vs. symptom driven); and outcomes.

The primary outcome was in-hospital development of VTE. Secondary outcomes included post-VTEp initiation blood transfusion; failure of nonoperative management, defined as the need for exploratory laparotomy >4 hours after admission; hospital length of stay (LOS, days); intensive care unit LOS; ventilator days; and in-hospital mortality.

Time of VTEp initiation defined study groups: Early VTEp (≤48 hours of admission) versus Late VTEp (>48 hours). An a priori power calculation stipulated the need for 1,158 patients, based upon an α of 0.05, β of 0.2, and the anticipated difference in primary outcome (VTE rate) between Early versus Late VTEp based on existing literature (approximately 1.8% vs. 4.9%[10,11,17]). Bivariate analysis compared patient demographics, clinical and injury data, VTEp data, and outcomes between groups. Continuous variables are given as median [interquartile range] and compared with the Mann-Whitney U test and independent-sample t test. Categorical variables are given as number (percentage) and compared with the Pearson χ^2 test and Fisher's exact test. Missed doses of VTEp were coded into a binary variable based on receiver operating characteristic curve results as <30% or ≥30% of anticipated doses not administered. Multivariable analysis with logistic regression examined factors independently associated with VTE. Covariates were selected for inclusion in the regression model based on clinical relevance and those that differed by $p < 0.2$ on univariate analysis. Logistic regression results are presented as odds ratios (ORs) with 95% confidence intervals. Subgroup analyses of Very Early VTEp (≤24 hours) and of high AAST grade (≥4) solid organ injuries were planned and performed. Statistical significance was defined as $p < 0.05$. IBM SPSS, version 28.0 (SPSS Inc., Chicago, IL), was used for statistical analyses.

RESULTS

In total, 1,173 patients satisfied the study criteria: 838 patients (74%) with Early VTEp and 301 patients (26%) with Late VTEp. Thirty-four patients did not receive a single dose of VTEp during admission and were not analyzed further. The reported rationale for Late VTEp initiation, when used, was concern for exacerbation of solid organ bleeding (30%), concern for exacerbation of intracranial bleeding (29%), concern for exacerbation of other bleeding (20%), or other/unspecified/combined (19%). Although many centers had formal or informal VTEp initiation protocols encouraging early VTEp administration, only five

TABLE 1. Patient Demographics, Clinical Data, and Injury Data

	Early VTEp (n = 838 [74%])	Late VTEp (n = 301 [26%])	*p*
Patient demographics			
Age, y	34 [25–48]	36 [27–51]	0.153
Sex, male	549 (66%)	213 (71%)	0.097
Race/ethnicity			
Non-Hispanic White	337 (40%)	121 (40%)	0.027
Hispanic	201 (24%)	74 (25%)	
Non-Hispanic Black	142 (17%)	30 (10%)	
Non-Hispanic Asian	16 (2%)	5 (2%)	
Non-Hispanic other	48 (6%)	22 (7%)	
Unknown	94 (11%)	49 (16%)	
BMI	27 [23–31]	26 [22–29]	0.004
First ED vital signs			
SBP	127 [114–143]	120 [105–140]	0.002
SBP <90	41 (5%)	30 (10%)	0.002
HR	93 [79–106]	97 [82–114]	<0.001
HR >120	71 (9%)	48 (16%)	0.001
GCS	15 [14–15]	14 [7–15]	<0.001
GCS <9	60 (7%)	81 (27%)	<0.001
Mechanism of injury			0.071
MVC	424 (51%)	146 (48%)	
MCC	111 (13%)	45 (15%)	
AVP	97 (12%)	40 (13%)	
GLF	79 (9%)	18 (6%)	
Assault	26 (3%)	11 (4%)	
Fall from height	23 (3%)	18 (6%)	
Other	78 (9%)	23 (8%)	
Injury severity			
ISS	19 [14–27]	27 [18–34]	<0.001
ISS >15	585 (70%)	252 (84%)	<0.001
Median AIS			
Head	0 [0–2]	2 [0–3]	<0.001
Face	0 [0–1]	0 [0–1]	0.002
Neck	0 [0–0]	0 [0–0]	<0.001
Chest	3 [0–3]	3 [2–3]	0.001
Abdomen/pelvis	3 [2–3]	3 [2–4]	<0.001
Spine	0 [0–1]	0 [0–2]	<0.001
Upper extremities	0 [0–1]	0 [0–2]	0.039
Lower extremities	0 [0–2]	1 [0–3]	<0.001
External	0 [0–1]	0 [0–1]	0.909
Severe injuries (AIS ≥3)			
Head	108 (13%)	113 (38%)	<0.001
Face	9 (1%)	7 (2%)	0.149
Neck	34 (4%)	26 (9%)	0.002
Chest	457 (55%)	189 (63%)	0.013
Abdomen/pelvis	437 (52%)	178 (59%)	0.037
Spine	21 (3%)	34 (11%)	<0.001
Upper extremities	25 (3%)	23 (8%)	<0.001
Lower extremities	155 (19%)	83 (28%)	<0.001
External	3 (<1%)	3 (1%)	0.192
Solid organ injury data			
Liver	417 (41%)	154 (41%)	0.884
AAST injury grade	2 [2–3]	3 [2–4]	0.065
Spleen	403 (39%)	154 (41%)	0.543
AAST injury grade	2 [2–3]	2 [2–3]	0.641
Kidney	209 (20%)	68 (18%)	0.353
AAST injury grade	3 [2–3]	3 [2–4]	0.074
Multiple (≥2) SOI	176 (21%)	65 (22%)	0.829
AAST grade ≥4 SOI	178 (21%)	88 (29%)	0.005

Continuous variables are presented as median [interquartile range]. Categorical variables are presented as number (percentage).

AAST, American Association for the Surgery of Trauma; AIS, Abbreviated Injury Scale score; AVP, auto versus pedestrian; BMI, body mass index; ED, emergency department; GCS, Glasgow Coma Scale; GLF, ground level fall; HR, heart rate in beats per minute; ISS, Injury Severity Score; MCC, motorcycle crash; MVC, motor vehicle crash; SBP, systolic blood pressure in mm Hg; SOI, solid organ injury; VTE, venous thromboembolism. VTEp, VTE chemoprophylaxis.

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institutions (26% of centers) had protocols explicitly specifying VTEp initiation timing after solid organ injury (three centers specifying initiation as <24 hours, one as <48 hours, and one as <72 hours).

Patient age and sex were comparable between groups (Table 1). Body mass index was slightly higher among Early VTEp patients (27 vs. 26, $p = 0.004$). Mechanism of injury did not vary between groups ($p = 0.071$), with motor vehicle collisions as the most frequent mechanism in both Early and Late VTEp patients (51% vs. 48%). Injury Severity Scores (19 vs. 27, $p < 0.001$) and the proportion of patients with severe (AIS score, ≥3) head injury (13% vs. 38%, $p < 0.001$) were lower after Early VTEp than Late VTEp. Solid organ injury type and AAST grade did not vary between groups (Table 1), although a greater proportion of patients in the Late VTEp group had high grade (AAST grade, ≥4) solid organ injuries (29% vs. 21%, $p = 0.005$).

In terms of VTEp agent and dosing schedules, enoxaparin was the most frequently used agent in both Early and Late VTEp groups (82% vs. 73%), with 30 mg administered subcutaneously every 12 hours as the most common dose and schedule (Table 2). Unfractionated heparin was used for VTEp more commonly among Late than Early VTEp patients (10% vs. 4%, $p < 0.001$). Sequential compression devices were used among Late VTEp patients more frequently than Early VTEp patients (93% vs. 87%, $p = 0.008$). Although ambulation occurred sooner among Early VTEp patients, the difference was not significant (hospital day 2 vs. 4, $p = 0.094$). The proportion of patients with ≥30% missed doses of VTEp was comparable between groups (11% vs. 9%, $p = 0.449$).

The VTE rate was lower after Early VTEp as compared with Late VTEp (3% vs. 7%, $p = 0.008$) (Fig. 1; Table 3). Venous thromboembolism rates by time of VTEp initiation are demonstrated in Figure 2. One percent of Early VTEp patients developed a DVT as compared with 5% of Late VTEp patients ($p = 0.001$) (Table 3), with venous duplex scans as the most common method of DVT diagnosis in both Early and Late VTEp groups (92% vs. 80%, $p = 0.605$). Two percent of Early and Late VTEp patients developed a PE ($p = 0.260$), with computed tomography pulmonary angiography as the most common method for diagnosis among both Early and Late VTEp patients (94% vs. 89%, $p = 1.000$). Two centers routinely screened asymptomatic patients for DVT with duplex scans within the first 48 hours of admission

TABLE 2. Venous Thromboembolism Prophylaxis Data

	Early VTEp (n = 838 [74%])	Late VTEp (n = 301 [26%])	*p*
VTE chemoprophylactic agent and dosing			<0.001
Enoxaparin	685 (82%)	220 (73%)	
30 mg Q12H	429 (63%)	143 (65%)	
40 mg Q12H	174 (25%)	44 (20%)	
40 mg Q24H	47 (7%)	29 (13%)	
Weight-based dosing	35 (5%)	4 (2%)	
Other low-molecular-weight heparin	96 (11%)	46 (15%)	
Unfractionated heparin	32 (4%)	29 (10%)	
Other/unspecified	25 (3%)	6 (2%)	
VTE nonchemoprophylaxis			
Sequential compression devices	728 (87%)	280 (93%)	0.008
Hospital day of first ambulation	2 [1–4]	4 [2–8]	0.094
Missed doses ≥30%	88 (11%)	27 (9%)	0.449

Continuous variables are presented as median [interquartile range]. Categorical variables are presented as number (percentage).

Q12H, every 12 hours; Q24H, every 24 hours.

VTE, venous thromboembolism; VTEp, VTE chemoprophylaxis; Q12H, every 12 hours; Q24H, every 24 hours.

and then weekly thereafter. All other centers investigated for DVT and PE based on symptomatology.

Post-VTEp blood transfusion occurred more frequently after Late VTEp initiation (23% vs. 17%, $p = 0.024$) (Fig. 1; Table 3). The number of post-VTEp initiation units transfused by blood component type was similar between groups (Table 3). Failure of nonoperative management occurred with comparable frequency (3% vs. 4%, $p = 0.228$) (Fig. 1; Table 3). In-hospital mortality was greater among Late VTEp patients (5% vs. 2%, $p = 0.022$). Hospital LOS (12 vs. 5 days, $p < 0.001$) and intensive care unit LOS (3 vs. 0 days, $p < 0.001$) were longer among Late VTEp patients.

Subgroup analysis of AAST grade ≥4 solid organ injuries demonstrated comparable rates of post-VTEp transfusion after Early versus Late VTEp (21% vs. 22%, $p = 0.880$) and similar volumes of component therapy transfusion post-VTEp initiation as well (Supplemental Digital Content, Table 1, http://links.lww.com/TA/D328). Failure rates of nonoperative management were comparable between groups (3% vs. 8%, $p = 0.131$). Venous thromboembolism rates were also similar (5% vs. 10%, $p = 0.107$).

After adjustment for age, sex, body mass index, injury severity, angiography, severe head injury, severe lower extremity injury, hospital day of first ambulation, and missed doses of VTEp ≥30%, VTEp initiation >48 hours was significantly associated with increased odds of VTE (OR, 2.251; $p = 0.046$) (Table 4). Head AIS score of ≥3 was not associated with increased odds of VTE (OR, 0.366; $p = 0.068$). On subgroup analysis examining the impact of Very Early VTEp, after adjusting for the same covariates, VTEp initiation >24 hours was associated with increased odds of VTE (OR, 5.128; $p = 0.009$) (Supplemental Digital Content, Table 2, http://links.lww.com/TA/D328).

DISCUSSION

This study demonstrated that VTEp initiation ≤48 hours of arrival is both effective and safe for patients with blunt solid organ injury managed nonoperatively. In terms of effectiveness, the study findings show that early VTEp is associated with reduced risk of VTE in this patient population, supporting findings from existing literature on blunt solid organ injuries.[20] In terms of safety, early initiation of VTEp did not increase the need for postprophylaxis blood transfusion nor have any impact on the failure rate of nonoperative management, even on subgroup analysis of patients with AAST grade ≥4 solid organ injuries. Taken together, these findings suggest that early VTEp does not result in clinically relevant bleeding and therefore that this concern should not prevent early initiation of VTEp.

After adjusting for potential confounders, our study found that initiation of VTEp beyond 48 hours was independently associated with increased odds of VTE. Odds of VTE were even higher when VTEp was started beyond 24 hours, suggesting that VTE mitigation from early VTEp initiation may be most impactful when VTEp is started within the first day of admission. These findings align with published recommendations from

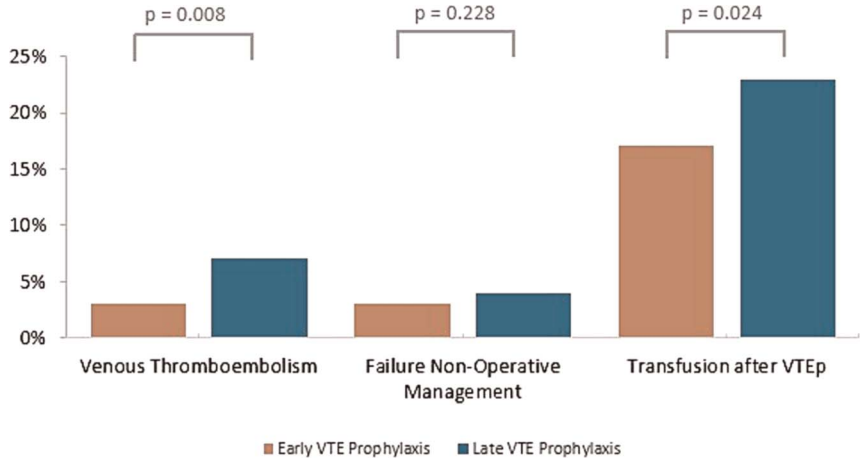

Figure 1. Primary and key secondary outcomes between Early versus Late VTEp patients.

TABLE 3. Primary and Key Secondary Outcomes: VTE and Bleeding Data

	Early VTEp (n = 838 [74%])	Late VTEp (n = 301 [26%])	*p*
VTE	28 (3%)	21 (7%)	0.008
DVT	12 (1%)	15 (5%)	0.001
Hospital day of diagnosis	5 [2–9]	6 [2–11]	0.928
Symptomatic DVT	3 (25%)	4 (27%)	0.646
PE	16 (2%)	9 (3%)	0.260
Hospital day of diagnosis	5 [3–13]	9 [6–11]	0.704
Symptomatic PE	12 (75%)	8 (89%)	0.621
Post-VTEp transfusion, any	145 (17%)	71 (23%)	0.024
Post-VTEp transfusion, U			
pRBCs	1 [0–2]	1 [0–2]	0.198
Whole blood	0 [0–0]	0 [0–0]	0.381
Plasma	0 [0–0]	0 [0–0]	0.063
Platelets	0 [0–0]	0 [0–0]	0.197
Failed NOM	21 (3%)	12 (4%)	0.228
Time to laparotomy, h	52 [14–222]	57 [30–232]	0.627

Continuous variables are presented as median [interquartile range]. Categorical variables are presented as number (percentage).

DVT, deep vein thrombosis; NOM, nonoperative management; pRBC, packed red blood cell; VTE, venous thromboembolism. VTEp, VTE chemoprophylaxis.

major trauma societies about VTEp initiation after blunt splenic and liver injury.[21,22]

One important injury associated with solid organ trauma is traumatic brain injuries (TBIs). Traumatic brain injuries are an especially relevant potential confounder in this study because the presence of a TBI increases VTE risk[23] and may also influence clinician decisions on the timing of VTEp initiation.[23,24] Literature on the optimal time for VTEp initiation after TBI is not yet definitive,[24] and there is evidence of associated harm from excessively early initiation.[25] Because of the enclosed space imparted by the skull, minimal increases in intracranial bleeding volumes can be clinically significant and potentially catastrophic. In this study, the concurrence of TBI was provided as a rationale for delaying VTEp initiation beyond 48 hours in one third of patients in the Late VTEp group. When we examined the impact of head injury on odds of VTE in the multivariable analysis, we did not find severe head injuries to be independently associated with increased odds of VTE in this patient population. Further need persists for examination of ideal timing of VTEp initiation after TBI.

The study limitations must be explicitly acknowledged. First, a fundamental limitation of prospective observational study is its inherent inability to establish causation as opposed to association, which hinders our complete understanding of this subject. Second, because of the inclusion of centers with differing approaches to VTE prophylaxis initiation and screening, there is heterogeneity in the data, which may have been a source of bias. For example, VTE screening is known to increase VTE detection rate,[26] and therefore, inclusion of centers that do and do not screen routinely is likely to have impacted our study results. Third, the inclusion of patients with TBI may have been another source of bias, although attempts were made to control for this with the multivariable analysis. Next, the possibility that some patients received inadequate VTEp based on specific agents and dosing (e.g., non–weight-based dosing of enoxaparin or the administration of unfractionated heparin) must be acknowledged, and this may have interplayed with VTE risk. Late VTEp patients were more severely injured and had longer hospital stays. Therefore, their intrinsic VTE risk may have been higher, and/or they may have been screened for DVT more frequently. Particularly with these differential risk factors for VTE, the possibility of unmeasured confounding exists in this study and should be considered in the interpretation of the study results. In addition, patients who did not receive any doses of VTEp during admission are problematic from a methodologic standpoint. These patients are largely those who had brief hospital stays after minor injury or, conversely, after significant injury and death that occurred before VTEp initiation. To preserve the integrity of the Early and Late VTEp groups, we did not analyze these patients in this study. We did not capture tranexamic acid administration or the volume of pre-VTEp initiation blood product transfusion, both of which may influence baseline VTE risk. Lastly, as in existing studies on this subject, high-grade (AAST grade, ≥4) solid organ injuries were underrepresented in this

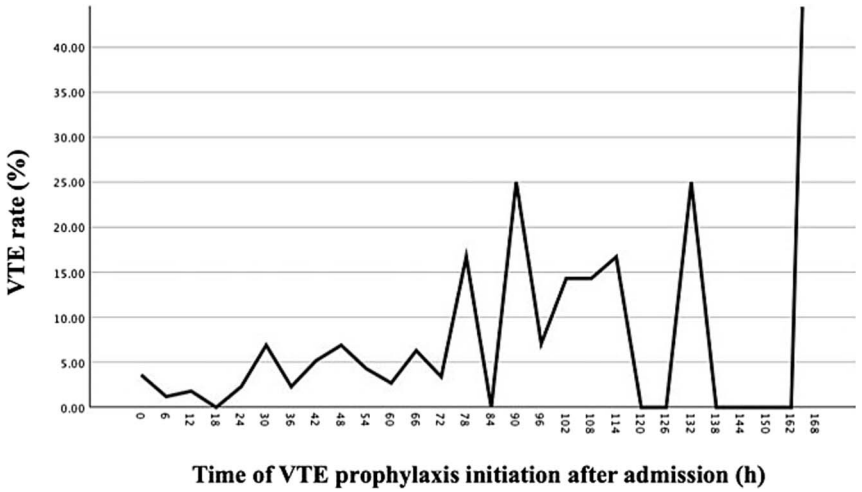

Figure 2. Venous thromboembolism rates by time of VTEp initiation.

TABLE 4. Multivariable Analysis of Independent Factors Associated With VTE

			95% CI	
	p	OR	Lower	Upper
Age, y	0.038	1.023	1.001	1.046
Male sex	0.026	3.128	1.147	8.533
BMI	0.200	1.021	0.989	1.054
ISS	0.015	1.047	1.009	1.086
Catheter-based angiography	0.206	0.527	0.195	1.423
Head AIS ≥3	0.068	0.366	0.125	1.077
Lower extremity AIS ≥3	0.084	2.084	0.905	4.799
Hospital day of first ambulation	0.023	1.002	1.000	1.004
Missed doses of VTEp ≥30%	0.908	1.077	0.307	3.774
Heparin chemoprophylaxis	0.919	0.923	0.198	4.304
Late VTEp (>48 h)	0.046	2.251	1.014	5.000

Multivariable analysis with logistic regression. Test for collinearity was performed before analysis (AUROC, 0.789; 95% CI, 0.716–0.863).

AIS, Abbreviated Injury Scale score; AUROC, area under the operating characteristic curve; BMI, body mass index; CI, confidence interval; ISS, Injury Severity Score; VTE, venous thromboembolism; VTEp, VTE chemoprophylaxis.

study, likely owing to an increased need for immediate surgical intervention in these patients. Although subgroup analysis of these patients did not demonstrate an increase in bleeding complications among Early VTEp patients, caution should still be exercised with early VTEp initiation after high-grade solid organ injuries.

To conclude, this prospective multicenter study of patients with blunt solid organ injuries demonstrated that VTEp initiated within 48 hours of arrival was associated with reduced rates of VTE without any observed increase in clinically relevant bleeding. The best available evidence therefore supports the routine adoption of this management strategy to reduce VTEs after trauma without encouraging bleeding.

AUTHORSHIP

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DISCLOSURE

Conflict of Interest: Author Disclosure forms have been supplied and are provided as Supplemental Digital Content (http://links.lww.com/TA/D329).

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