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Early versus late venous thromboembolism: A secondary analysis of data from the PROPPR trial

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ABSTRACT

Background: Factors predicting timing of post-traumatic venous thromboembolism (VTE) remain incompletely understood. Because the balance between hemorrhage and thrombosis is dynamic during a patient's hospital course, early and late VTE may be physiologically discrete processes. This secondary analysis of the Pragmatic, Randomized Optimal Platelet and Plasma Ratios (PROPPR) trial aims to explore whether certain risk factors are associated with early versus late VTE.

Methods: The PROPPR trial investigated post-traumatic resuscitation with platelets, plasma, and red blood cells in a 1:1:1 ratio compared with a 1:1:2 ratio. Multinomial regression based on a threshold determined by cubic spline analysis tested the association of clinical variables with early or late VTE, a composite of deep vein thrombosis and pulmonary embolus, adjusting for predetermined confounders.

Results: Of the 87 patients (13%) with VTE, pulmonary embolus was predominant in the first 72 hours. A statistically determined threshold at 12 days corresponded to change in odds of early versus late events. Variables associated with early VTE included plasma transfusion (risk ratio [RR] 1.14; 95% confidence interval, 1.00, 1.30; $P = .05$), sepsis (RR 0.05; 95% confidence interval, 1.40, 6.64; $P = .01$), pelvic or femur fracture (RR 2.62; 95% confidence interval, 1.00, 6.90; $P = .05$). Late VTE was associated with dialysis (RR 7.37; 95% confidence interval, 1.59, 34.14; $P = .01$), older age (RR 1.02; 95% confidence interval 1.00, 1.04; $P = .05$), and delayed resuscitation approaching ratios of 1:1:1 among patients randomized to 1:1:2 therapy (RR 2.06; 95% confidence interval, 0.28, 3.83; $P = .02$). Cyroprecipitate increased risk of early (RR 1.04, 95% confidence interval, 1.00,1.08; $P < .03$) and late VTE (1.05; 95% confidence interval, 1.01, 1.09; $P = .01$). Prolonged lagtime (coeffcient 0.06, 95% confidence interval, 0.02, 0.10; $P < .01$) and time-to-peak thrombin generation (coeffcient 0.04, 95% confidence interval, 0.02, 0.07; $P < .01$) were associated with increased risk of early VTE.

Conclusion: Early and late VTE may differ in their risk factors. Defining temporal trends in VTE may allow for a more individualized approach to thromboprophylaxis.

Approximately 50% to 60% of early trauma-related deaths are attributed to hemorrhage,[1] making the initial focus on hemostasis a priority after injury. However, trauma patients are at high risk of thrombotic complications, and thus balancing hemorrhage control with pro-thrombotic states remains an ongoing challenge. Although seminal studies such as the Pragmatic, Randomized, Optimal Platelet and Plasma Ratio (PROPPR) trial[2,3] have improved resuscitation strategies, further investigations are needed to address how altered coagulation profiles contribute to post-traumatic morbidity. Specifically, trauma induced coagulopathy can exacerbate significant bleeding and lead to clotting factor depletion and augmented clot breakdown. Despite this, venous

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thromboembolic events (VTEs) are common after severe injury, with as many as 25% of severely injured patients experiencing VTEs after trauma even with pharmacologic prophylaxis.[4–6] In addition, the use of hemostatic adjuncts may further contribute to dysregulation of fibrinolysis and coagulation and trigger complications such as VTEs.[7,8] Offsetting the risks of either extreme (ie, hemorrhage versus thrombosis) requires an appreciation that coagulation profiles change over time. A subset of VTEs occur within the initial hours or days of presentation after injury, and, as such, the temporality of VTEs may signal that early and late events are physiologically discrete processes or have unique predictors. Identifying biologic differences indicated by chronologic variation will motivate future investigations aimed at refining risk stratification systems.

Models predicting VTEs such as the risk assessment profile (RAP)[9] and the trauma embolic scoring system (TESS)[10] aid in clinical decision making. Unfortunately, these instruments are often underutilized,[11] fail to distinguish the level of prophylaxis needed for a specific risk category, do not reflect the relative weight that specific factors contribute to overall risk, and disregard a "very high risk" category that likely exists. In addition, none of these scoring systems address how clotting and bleeding risk change over a patient's recovery course. As such, factors predicting VTE timing remain incompletely understood. To date, investigations into time-to-VTE have been insufficient in that they are from nontrauma literature and have used arbitrary cutoffs to designate early and late events.[12,13] As a first step in addressing this gap in knowledge, we conducted a secondary analysis of the PROPPR trial data. We hypothesized that unique predictors and risk factors may distinguish early from late VTEs. Ultimately, understanding chronologic thresholds and temporal trends in VTEs will allow for the development of a more individualized approach to prophylaxis and reduce the rate of this serious complication.

Methods

We conducted a secondary analysis of data from the PROPPR trial to test the hypotheses that early VTEs are physiologically distinct from late VTEs. We aimed to identify a threshold that could distinguish between early and late events and could be used to detect differences in risk factors based on temporality.

Study design

The PROPPR trial was a multicenter, pragmatic, randomized trial to compare the effectiveness of transfusion with a 1:1:1 versus 1:1:2 ratio of blood products on the primary outcomes of death at 24 hours and 30 days.[14] Patients randomized to resuscitation with a 1:1:1 ratio of blood products received 1 dose of platelets (the equivalent of 6 whole blood-derived units), 6 units of plasma, and 6 units of red blood cells (RBCs).[15] Those who were randomized to a 1:1:2 ratio received an initial cooler containing 3 units of plasma and 6 units of RBCs. During the investigation, patients had blood samples drawn at admission and then serially at 2, 4, 6, 12, 24, 48, and 72 hours after admission. Thromboelastography, which was used to assess whole blood coagulation, included time to clot initiation (R-value), time to 20-mm clot displacement (K-value), rate of clot formation (α-angle), clot strength (maximum amplitude [MA]), and clot lysis at 30 minutes (LY30) and 60 minutes (LY60). Thrombin generation assays included lag time, endogenous thrombin potential, peak, time to peak, and velocity index. Samples were also assessed for coagulation factor activity and fibrinogen levels.

Patient characteristics

Patients from 12 level-1 trauma centers who were at least 15 years of age, presented directly from the scene of injury as the highest trauma level activation, required at least 1 unit of blood product within the first hour of arrival and were predicted to require massive transfusion were eligible for inclusion. Exclusion criteria involved lethal traumatic brain injury, incarceration or pregnancy, >5 minutes of cardiopulmonary resuscitation, >20% total body-surface area burn, inhalation injury, or >3 units of RBC transfusion before arrival.

Outcomes

Our primary outcome of interest was VTEs, defined as a composite outcome that included pulmonary embolism (PE) and deep vein thrombosis (DVT). DVT was diagnosed by duplex ultrasound, whereas PE was diagnosed by CT angiography, pulmonary angiography, or ventilation perfusion scan. PE, but not DVT, was classified as either symptomatic (ie, diagnosis precipitated by clinical suspicion) or asymptomatic (ie, diagnosis after screening). Secondary outcomes included association of trial site with VTE diagnoses (participating institutions were variable regarding screening protocols), effect of delayed resuscitation (ie, resuscitation approaching ratios of 1:1:1 among patients randomized to 1:1:2 therapy) on timing of VTEs, and differences in coagulation assay parameters between early or late and no VTEs.

Statistical analysis

To our knowledge there are no standardized or clinically accepted definitions to discriminate between early and late VTEs. Univariate analyses were performed to assess crude associations between variables and timing of VTEs. We defined very early events a priori as occurring within 72 hours of presentation. Stepwise regression was utilized to select covariates included in a multinomial regression model exploring differences in risk factors for very early VTEs and VTEs that occurred after hospital day 7 compared with no VTEs. We accounted for the competing risk of death in all analyses, using an inverse probability weight of mortality.[16] A logistic regression analysis predicting risk of death was generated adjusting for multiorgan failure, demographics, blood product requirement, need for vasoactive agents, admission hemodynamics, acute renal insufficiency, need for hemostatic agents, injury severity and mechanism. Once probability of death was assessed, the contribution of VTEs to the overall population was weighted against the probability of dying using inverse probability weighting.

To determine a data-driven threshold for early and late events, we first plotted VTE distribution over time. A cubic spline analysis was used to identify the threshold that corresponded to a change in odds of experiences early versus late VTEs accounting for death. Reclassification of VTEs as a categorical variable was used to distinguish whether the event was absent, occurred early, or occurred late. We performed a multinomial regression to define clinical variables significantly associated with early and late VTEs compared with no VTEs accounting for death and adjusting for confounders including quantity of blood products for 24 hours, cryoprecipitate, sepsis, pelvic or femur fracture, traumatic brain injury (TBI), dialysis, age, and intensive care unit (ICU) duration of stay. As screening practices were variable among institutions that participated in the PROPPR trial, logistic regression was used to ascertain individual site effect on VTEs versus no VTEs adjusting for the same confounders included in the multinomial regression used to distinguish between early and late events. Screening practices of

Table I
Characteristics of patients who experienced VTE

Variable	No VTE n = 593	DVT alone n = 38	PE alone n = 38	DVT and PE n = 11	*P* value*
Pelvic/femoral fracture, *n* (%)	118 (20)	9 (23)	11 (28)	3 (30)	.60
Female sex, *n* (%)	118 (20)	7 (18)	7 (18)	2 (20)	1.00
Penetrating mechanism, *n* (%)	284 (48)	13 (33)	18 (46)	6 (60)	.35
Age, median (IQR)	34 (24–51)	38 (25–47)	39 (29–51)	41.5 (25–47)	.38
Acute kidney injury, *n* (%)	128 (22)	10 (26)	16 (41)	5 (50)	.23
Sepsis, *n* (%)	139 (24)	15 (38)	26 (67)	10 (100)	.02
Tobacco, *n* (%)	120 (20)	12 (31)	7 (18)	1 (10)	.29
ISS, median (IQR)	26 (17–38)	34 (21–43)	24 (16–41)	24 (16–34)	.07
TBI, *n* (%)	60 (10)	0 (0)	2 (5)	0 (0)	.49
AIS chest	230 (39)	11 (28)	21 (54)	5 (50)	.04
Intervention, *n* (%)	299 (51)	18 (46)	19 (49)	6 (60)	1.00
Death, *n* (%)	160 (27)	0 (0)	3 (8)	1 (10)	.24
Day of diagnosis, median (IQR)	—	8 (4–17)	6 (3–10)	8 (4–17)	.17

IQR, interquartile range; *ISS*, injury severity score.
* *P* value refers to test of difference in variables between patients who experienced PE alone compared with those who experienced DVT alone.

participating institutions (Table I, Supplementary Online Content), which were not included in the initial data set, were obtained by contacting each site individually.

Coagulation assays including thrombin generation, thromboelastography, plasmin-antiplasmin, and D-dimer assays were also assessed to determine whether differences existed between early and late events. Finally, postrandomization resuscitation strategies in patients who had initially received a 1:1:2 ratio of blood products were evaluated to determine whether delayed resuscitation approaching a ratio of 1:1:1 was associated with timing of VTEs using a univariate analysis. All statistical analyses were performed using STATA 15 (Stata Corporation, College Station, TX).

Results

Of the 680 patients enrolled in the PROPPR trial, 87 patients (13%) had a documented VTE (Table I). DVT alone occurred in 38 patients (6%). Symptomatic events accounted for 22 of the 38 isolated PEs that were observed. Eleven patients experienced both DVT and PE. Eleven of the patients (28%) who experienced only PE were diagnosed within 72 hours compared with 4 of the patients (10%) who experienced DVT alone (Fig 1). Nearly half of the PEs diagnosed within this early time frame were symptomatic.

Univariate analyses demonstrated that covariates changed in significance and degree of risk over time (Table II in Supplementary Online Content). Trial site (as a surrogate for differences in VTE screening policies) was not associated with diagnosis of VTEs (odds ratio [OR] 0.97; 95% confidence interval [CI], 0.89–1.05; $P = .48$) after adjusting for blood product administration, sepsis, pelvic or femur fracture, TBI, need for dialysis, age, or ICU duration of stay. Plasma to RBC ratio in the first 24 hours postinjury (risk ratio [RR] 6.48; 95% confidence interval [CI], 1.36–30.92; $P = .02$) and pelvic or femur fracture (RR 3.89, 95% CI, 0.96–15.92; $P = .05$) were associated with increased risk of very early VTEs, defined a priori as events occurring within 72 hours of admission while tobacco use (RR 2.12; 95% CI, 0.97–4.66; $P = .05$) and sepsis (RR 4.82; 95% CI, 2.26–10.29; $P < .001$) were associated with events after 72 hours (Tables II and III).

After plotting VTE distribution over time, cubic spline analysis established a threshold at 12 days corresponding to a change in odds of early (ie, before day 12) versus late (ie, day 12 and after) events (Fig 2). Multinomial regression revealed differences between early and late VTEs. Risk factors associated with early but not late VTEs included plasma transfusion (binary variable) in the first 24 hours postinjury (ie, before delayed resuscitation in the postintervention phase), sepsis, and pelvic or femur fracture (Table IV). Platelet transfusion in the first 24 hours postinjury was associated with a lower risk of early but not late VTEs (RR 0.93; 95% CI, 0.87–1.00; $P = .04$). In contrast, late VTEs were predicted by dialysis, increased age, and ICU duration of stay (Table IV). Cryoprecipitate increased risk of early (RR 1.04, 95% CI, 1.00–1.08; $P = .03$) and late VTE (1.05; 95% CI, 1.01–1.09; $P = .01$). Symptoms inciting clinical suspicion for PE and consequent diagnostic imaging were not significantly associated with early versus late events. Area under receiver operative curves (AUROC) was 0.69 and 0.70 for early and late VTE models, respectively (Fig 1 in Supplementary Digital Content).

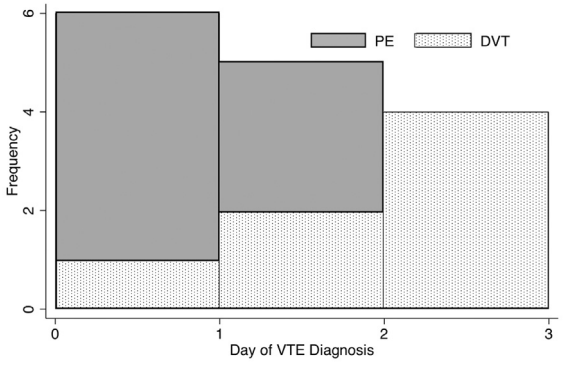

Fig 1. Venous thromboembolic events that occurred within 72 hours of admission.

In the design of PROPPR, postprotocol resuscitation was administered at clinician discretion, which resulted in a significant number of patients who received less plasma and platelets up front to receive additional transfusion of these products after the protocol based resuscitation was completed.[1] Strikingly, delayed resuscitation approaching ratios of 1:1:1 for plasma, platelets, and RBCs among patients randomized to 1:1:2 therapy was a risk factor for late (RR 2.06; 95% CI, 0.28–3.83; $P = .02$) but not early VTE.

Coagulation assays also differed between early and late VTEs (Table IV). Prolonged lag time (RR 1.06, 95% CI, 1.02–1.10; $P = .003$) and time to peak thrombin generation (RR 1.04; 95% CI, 1.02–1.07; $P = .001$) were associated with increased risk of early VTEs alone. There were no significant differences in thromboelastography parameters, plasmin-antiplasmin, or D-dimer assays for early or late VTEs compared with no VTEs.

Table II
Factors associated with VTE in the first 72 hours (very early) and after hospital day 7 compared with no VTE

Variable	Very early VTE		VTE after hospital day 7	
	RR (95% CI)	*P* value	RR (95% CI)	*P* value
24-h plasma: RBC ratio	6.48 (1.36–30.92)	0.02	3.41 (0.91–12.80)	.07
24-h platelet: RBC ratio	0.76 (0.40–1.44)	0.40	0.72 (0.42–1.23)	.24
Tobacco use	0.56 (0.11–2.91)	0.50	2.12 (0.97–4.66)	.05
Sepsis	0.97 (0.24–3.98)	0.97	4.82 (2.26–10.29)	<.001
Pelvic/femur fracture	2.89 (0.95–15.93)	0.05	1.01 (0.41–2.49)	.99
Penetrating mechanisms	0.80 (0.19–3.37)	0.77	1.81 (0.73–4.52)	.20

Table III
Factors associated with early VTE (before 12 days) and late VTE (day 12 or later)

Variable	Early VTE		Late VTE	
	RR (95% CI)	*P* value	RR (95% CI)	*P* value
Cryoprecipitate	1.04 (1.00–1.08)	.03	1.05 (1.01–1.09)	.01
24-h blood product administration				
Red blood cells	0.95 (0.88–1.02)	.18	0.97 (0.89–1.05)	.45
Platelets	0.93 (0.87–1.00)	.04	0.94 (0.86–1.03)	.19
Plasma	1.14 (1.00–1.30)	.05	1.1 (0.96–1.26)	.16
Sepsis	3.05 (1.40–6.64)	.01	2.97 (0.99–10)	.08
Pelvic/femur fracture	2.62 (1.00–6.90)	.05	2.93 (0.90–9.58)	.08
Traumatic brain injury	0.55 (0.21–1.42)	.22	0.21 (0.04–1.10)	.06
Dialysis	2.63 (0.42–16.36)	.30	7.37 (1.59–34.14)	.01
Age	1.00 (0.96–1.05)	.71	1.02 (1.00–1.04)	.05
ICU duration of stay	1.00 (0.96–1.05)	.79	1.08 (1.03–1.13)	.002

ICU, intensive care unit.
Variables included in multinomial regression models were selected based on stepwise regression (threshold of 0.5).

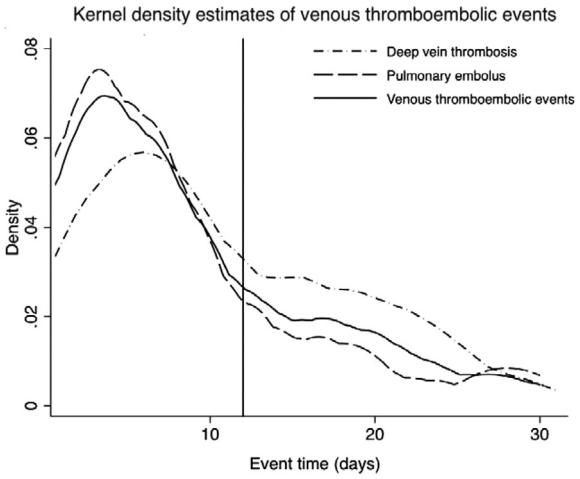

Fig 2. Distribution of venous thromboembolic events as estimated by kernel density plots.

Discussion

This study aimed to address timing of VTEs after traumatic injury accounting for competing risk of death. Our findings reflect that VTEs ocurring immediately postinjury may be pathophysiologically distinct from events that arise later. Specifically, almost a third of PEs were diagnosed within 72 hours after trauma compared with only 10% of DVTs, indicating that very early posttraumatic PE may represent in-situ thrombosis separate from mechanisms that promote DVT formation.[17–19] Although PE detected as a consequence of admission CT may raise concern over surveillance bias given that imaging is not customarily obtained for DVT initially postinjury, the considerable portion (45%) of these early posttraumatic PEs, which were symptomatic and diagnosed as a result of nonroutine testing, substantiate the concept that DVT may be a separate entity.

Univariate analyses suggest that certain factors such as administration of reversal agents, pelvic or femur fracture, acute kidney injury, initial hemodynamic instability, female sex, penetrating mechanism, chest trauma, and chemical paralysis may be associated with increased risk of early VTEs but that this risk might dissipate over time. On the other hand, cryoprecipitate, increased age,[20] INR elevation, TBI,[21] and sepsis may be associated with increasing risk over time. Based on a statistically identified threshold of 12 days, sepsis, femur or pelvic fracture, and plasma transfusion were all risk factors for early VTEs. In contrast, dialysis, age, and ICU duration of stay were risk factors for late VTEs. Although the mechanisms require further elucidation, it is plausible that proinflammatory drivers associated with late VTEs, for example, age and sepsis, induce prolonged dysregulation and delayed hemostasis in a manner different from other risk factors for hypercoagulability associated with critical illness and injury.[22,23] Although we recognize that the risk factors identified in this analysis might be considered nonspecific insofar as they are highly related to injury severity, acuity, and consequent morbidity, the significant differences identified in our analysis demonstrate that physiologic insults vary in their degree and duration of effect on coagulopathy. Future studies aimed at determining more specific, and perhaps clinically applicable factors, could guide decisions regarding timing and frequency of screening and implementation of extended prophylaxis. In addition, individuals who experience clinically silent (ie, without hemodynamic compromise) early VTEs resulting from the acute systemic response to injury may not be at risk for subsequent thrombotic events after resolution of the posttraumatic inflammatory state. In these patients, an argument may be made for reconsidering therapeutic anticoagulation if the risk of bleeding complications prevails over preventative benefits.

Table IV
Association of thrombin generation assay parameters with early versus late VTE using a multinomial regression model

Assay	Early VTE		Late VTE	
	Coefficient (95% CI)	*P* value	Coefficient (95% CI)	*P* value
Lag time	0.06 (0.02–0.10)	<.01	0.02 (−0.05 to 0.10)	.55
Endogenous thrombin potential	−0.00005 (−0.0007 to 0.0006)	.87	0.00006 (−0.0008 to 0.0009)	.88
Peak	−0.004 (−0.005 to 0.00006)	.06	−0.0004 (−0.005 to 0.004)	.85
Time to peak	0.04 (0.02 to 0.07)	<.01	0.004 (−0.05 to 0.06)	.90
Velocity index	−0.003 (−0.008 to 0.001)	.19	−0.0005 (−0.008 to 0.007)	.90

Although late resuscitation did not bestow significant survival benefit,[1] our findings demonstrate that increased volume of delayed resuscitation may increase risk of late VTEs, as has been suggested previously.[24] Administration of cryoprecipitate increased the risk of VTEs, as has been previously suggested,[24–26] independent of onset time. Early VTEs were associated with prolonged lagtime and time-to-peak thrombin generation assay parameters, suggesting that mechanisms occurring during the initiation and amplification phase of thrombin generation are different for early versus late VTEs.

Despite being a potentially preventable source of morbidity and mortality, VTEs remain common after traumatic injury.[27] The high incidence of VTEs reflects both underutilization[28] of standardized thromboprophylactic regimens and also an incomplete understanding how injury and resuscitation affect the risk of posttraumatic VTEs over time. Importantly, the observation of a significant number of very early pulmonary thrombi, which may not necessarily represent embolic events, raises the question as to whether all VTEs after injury can be considered preventable.[29] Because VTE risk is dynamic during a patient's recovery course,[9] prevention requires re-evaluation and modification of prophylaxis regimens as clinical circumstances change. Current risk assessment models, such as the RAP,[30] the TESS,[31] and the Caprini score[32] do not accommodate variation in risk profiles over time. Our models for early and late VTEs exhibit AUROCs of 0.69 and 0.70, respectively. In comparison, AUROC for the RAP ranges from 0.74 to 0.80[33,34] in the literature and between 0.71 to 0.89[10,35] for TESS. Although the predictive ability of our models is lower than that of the RAP or TESS, and data limitations restricted our ability to directly calculate and compare these risk stratification systems within our specific cohort, our findings substantiate future investigations aimed at identifying risk factors that distinguish early from late VTEs. In addition, existing guidelines for prevention of VTEs recommend the use of extended postdischarge prophylaxis for patients at high risk for VTEs, such as those with active malignancy.[36–39] There is, however, no uniformity regarding the length of these extended prophylaxis regimens, which can be costly, inconvenient to patients, and associated with increased bleeding risk.[21] Lack of data to identify the precise risk factors that predispose patients to late VTEs make it difficult to specify which patients would benefit from prolonged VTEs prophylaxis.

To date, there have been relatively few investigations into temporal distributions of VTEs, and none of these have been performed in the trauma population. Motivated by the fact that 28.6% of VTEs after liver surgery occur postdischarge, Tzeng et al conducted a retrospective analysis of patients who underwent hepatectomy between 2005 to 2010 using the American College of Surgeons-National Surgical Quality Improvement Program database to determine risk factors for early (predischarge) versus late VTEs (postdischarge). Although different from the variables included in our model, this study detected differences in risk factors for early and late events, which included demographics, transfusion rates, and infectious complications, among others.

We determined the threshold to distinguish between early and late events at 12 days. Tzeng et al found postoperative day 9 to be the median day of any VTE, with early events occurring at a median of 6 days postoperatively and late events occurring at a median of 14 days postoperatively. In general surgery patients, one prospective observational study reported that 40% of VTEs occurred after postoperative day 21.[40] Accordingly, chronologic thresholds discriminating between early and late VTEs may vary depending on type of surgery, whether the patient had a traumatic insult, and severity of injury.[2] In our study, ≈20% of VTEs were experienced after 2 weeks posttrauma, indicating the importance of interventions aimed at timely DVT prophylaxis and possibly extended prophylaxis regimens. In addition, these data suggest that data censored by hospital discharge may not accurately reflect VTE rates because a large proportion of late events may fail to be captured.[41] Accomodating postdischarge and lengthier follow-up for assessment of thrombotic complications will be paramount to precise risk evaluation in future investigations.

Previous studies have shown that patients who experience VTEs after trauma may have delayed onset of recovery for platelet dysfunction and coagulopathy. Although others have demonstrated that TEG may be predictive of VTEs,[42] in our analysis, which assessed longitudinal temporal changes in TEG over the first 72 hours after admission, parameters were not shown to discriminate between early and late events. In a previous secondary analysis of the PROPPR trial, McCully et al found that patients with VTEs who survived >24 hours and were not prescribed prehospital anticoagulants had TEG parameters consistent with hypercoagulability at admission (ie, decreased K time, increased α angle, and increased MA at admission) but shortly thereafter exhibited hypocoagulability (ie, increased R and K time, decreased α angle, and MA).[43] Our analysis demonstrated that the lagtime and time-to-peak thrombin generation are prolonged in patients who experience early VTEs, indicating that they may initially be hypocoagulable soon after injury. This finding suggests that variability in coagulation profiles among individuals who experience posttraumatic VTEs may be consequential to differences in the pathophysiology of early and late events.

Limitations

As a secondary analysis of prospectively collected data, this study is limited in the parameters that could be evaluated. Data regarding prehospital anticoagulation, DVT at site of central line placement or vessel trauma, and initiation and timing of VTEs prophylaxis are incomplete. Despite attempting to adjust for confounding in a multivariate analysis, biases likely remain. Timing of certain covariates (eg, sepsis, vasoactive agents, etc) is ambiguous. In particular, although the association between sepsis and VTEs has been documented elsewhere,[44] it is difficult from our analysis to discern the precise nature of the association or causality between sepsis and VTEs. In addition, we were unable to assess the relative influence of risk factors based on effect size and further studies are

necessary to determine whether clinically significant variables presented in this study are independently associated with early versus late VTEs. Future investigations are necessary to develop a cohesive and validated risk stratification system that not only distinguishes between early versus late VTEs, but that can provide comparison regarding predictive ability of temporally related models and existing ones such as the RAP and TESS. The small sample size of patients who experienced PE or DVT limits our power to detect a significant association between certain factors and early versus late VTEs. Although recent studies substantiate that DVT and PE may be separate or unrelated processes,[45–47] our restricted sample size and low event rate constrain our ability to analyze DVT and PE as discrete entities or perform subgroup analyses. In addition, we were underpowered to perform subgroup analyses to examine heterogeneity of effects in patients who experienced PE versus DVT or symptomatic versus asymptomatic PE. Having previously been accepted as standard practice, we recognize the limitations associated with VTEs as a composite outcome. We advocate that forthcoming investigations consider PE and DVT separately as the field more precisely characterizes the pathophysiologic differences between them. Finally, because there was no standardization of screening for VTEs among participating institutions, those that did screen routinely may have contributed to selection bias by detecting events earlier than would occur had screening not been implemented.[48–50] Although we attempted to account for site effect by using site number (ie, 1–12), which was included as part of the initial data set, identity of the site corresponding to each number was unknown owing to blinding practices. For these reasons, we were not able to accommodate individual screening practices within our analysis. Although differences between centers' approaches to screening compromises the conclusions of our analyses, we maintain that the overall concept that early and late thromboembolisms are physiologically discrete processes with different risk factors holds merit.

VTEs remain common after traumatic injury despite standardized thromboprophylactic regimens. The frequency of this complication can in part be attributed to an incomplete understanding how injury and resuscitation affect the risk of posttraumatic VTEs over time. Our study has demonstrated that early and late thromboembolic events may differ in their pathophysiology and clinically relevant risk factors. Defining chronologic thresholds and clinical markers associated with temporal trends in VTE distribution may allow for a more individualized approach to thromboprophylaxis, which is a step toward minimizing the occurrence of this serious complication.

Conflict of interest

Dr Neal is an external scientific advisor to Janssen Pharmaceuticals. The remaining authors have no disclosures.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.1016/j.surg.2019.04.014.

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