Trauma-induced pulmonary thromboembolism: What's update?

Yu-Hong Mi*, Ming-Ying Xu

Emergency and Critical Care Center, Beijing Anzhen Hospital, Capital Medical University, Beijing Institute of Heart, Lung and Blood Vascular Disease, Beijing, 100029, China

A R T I C L E   I N F O

Article history:
Received 22 June 2021
Received in revised form 28 July 2021
Accepted 2 August 2021
Available online 5 August 2021

Keywords:
Wounds and injuries
Pulmonary thromboembolism
Venous thromboembolism
Deep venous thrombosis
Etiology
Treatment
Prevention

A B S T R A C T

Trauma-induced pulmonary thromboembolism is the second leading cause of death in severe trauma patients. Primary fibrinolytic hyperactivity combined with hemorrhage and consequential hypercoagulability in severe trauma patients create a huge challenge for clinicians. It is crucial to ensure a safe anticoagulant therapy for trauma patients, but a series of clinical issues need to be answered first, for example, what are the risk factors for traumatic venous thromboembolism? How to assess and determine the status of coagulation dysfunction of patients? When is the optimal timing to initiate pharmacologic prophylaxis for venous thromboembolism? What types of prophylactic agents should be used? How to manage the anticoagulation-related hemorrhage and to determine the optimal timing of restarting chemoprophylaxis? The present review attempts to answer the above questions.

I n t r o d u c t i o n

Trauma patients who survive the initial injury are at a high risk of secondary multiple organ dysfunction and thromboembolic events, both of which are major contributors to subsequent morbidity and mortality.1–3 Venous thromboembolism (VTE), clinically presenting as pulmonary thromboembolism (PTE) and deep venous thrombosis (DVT), is a life-threatening but potentially preventable complication after trauma. Trauma as a strong trigger factor for VTE is a leading cause of global death and disability.4–7 Severe trauma patients faced a double threat of post-traumatic bleeding and post-traumatic thrombotic events, as pulmonary embolism (PE) is commonly PTE, which will be focused in this review.

Acute trauma-induced coagulopathy is inevitable following severe trauma such as shock, low perfusion and vascular injury.8–10 Fröhlich et al.11 reported that one in every four patients with severe trauma at admission had abnormal blood clotting with laboratory defined signs of coagulopathy. The therapeutic focus is to identify bleeding and hypercoagulability as soon as possible and give targeted treatment.12,13

Base on that trauma-induced coagulopathy is a potentially preventable and controllable disease,13 this review focuses on the pathogenesis, risk factors, diagnosis and preventative strategies for post-traumatic VTE, so as to reduce the incidence of trauma-related thromboembolic events. Patients who survive the initial injury are thought to emerge from dysfunctional or exaggerated responses to major tissue damage and shock, exacerbated by iatrogenic factors such as transfusion and surgical intervention.14,15

Epidemiological characteristics of post-traumatic VTE

Incidence of post-traumatic VTE

The incidence of post-traumatic VTE can be up to 13 times more than that of non-traumatic patients.16 Base on the sample size, types of trauma, diagnostic methods, and means of VTE prevention during trauma treatment, the incidence of post-traumatic VTE varies greatly among different study designs: from 0.27% to 65% and remains high after major traumas even with the initiation of prophylactic antithrombotic therapy within 48 h. Study of Bahloul et al.17 showed that 60% of patients with an injury severity score ≥45 developed hypercoagulability within 1 h of injury and these patients were four times more likely to die than those without clotting abnormalities (46.0% vs. 10.9%). Once post-traumatic PTE occurs, the mortality will be greatly increased.18 VTE can occur in hospitalized patients with acute
trauma as well as in the community where the incidence of VTE following trauma is 12%.21

Characteristics of post-traumatic VTE

The peak period and duration of traumatic VTE

Patients are at a risk of hypercoagulability early after traumatic injury, although the highest risk appears at one week after trauma. Lots of PTE is diagnosed within the first few days, and a significant number of PTE is found as early as the first 24 h after injury; and the hypercoagulable state persisted even after patient discharge.20,22 A recent study shows that the occurrence of PTE in trauma patients within 72 h accounts for 41.5% of total PTE, and the mortality rate of PTE patients are significantly higher than that of non-PTE patients after 72 h.22 A retrospective study23 enrolled 267,743 trauma patients including pelvic fractures, vertebral fractures, and spinal cord injuries (SCIs) showed that the incidence of VTE was the highest within 3 months and decreased to normal after 12–15 months. This study also found that the decrease of VTE risks differs over time based on the types of trauma. It is showed that the VTE risk decreases more rapidly in patients with pelvic fractures and vertebral fractures than in those with spinal cord injuries. The recurrence of VTE occurred mostly in 6–12 months, and the recurrence risk lasted for at least 10 years for previous VTE. The patients with neurological disease, local paralysis, or malignancy are at a higher risk of recurrence than others. It is worth mentioning that regardless of the types of injury, trauma-induced coagulopathy generally resolves within 24 h of trauma, and hypercoagulability becomes more common.

The features of traumatic DVT

Traumatic DVT can occur on either injured extremity or uninjured lower extremity, preoperatively or postoperatively. A study24 enrolled 1454 patients with lower extremity fractures found that the incidence of preoperative DVT in the uninjured lower extremity was 9.63% whereas the postoperative incidence was 20.29%. Age and female were independent risk factors for preoperative DVT in the uninjured lower extremity. They found that 5.39% of patients with preoperative peripheral DVT presented no thrombosis postoperatively; conversely, 34.73% of patients with no preoperative thrombosis developed postoperative peripheral DVT (33.83%), central (0.30%), or mixed DVT (0.60%), respectively. Another study25 enrolled 1179 patients with tibial plateau fractures and showed that 192 of them (16.3%) had a preoperative DVT, with the incidence rate of proximal DVT being 1.0% and distal DVT being 15.3%. The average interval between fracture occurrence and diagnosis of DVT was 3.5 days (median, 2 days), range 0–19 days. DVT involved the injured extremity in 166 (86.4%) patients, both extremities (injured and uninjured) in 14 patients (7.3%) and the uninjured extremity alone in 12 patients (6.3%). This study also identified six risk factors to be associated with DVT, respectively gender (male vs. female), hypertension, open fracture, alkaline phosphatase > 100 u/L, sodium concentration < 135 mmol/L, and D-dimer > 0.5 mg/L.

The relation between types of trauma and risk of VTE

Compared with the severity of trauma, the types of trauma have greater influence on VTE although Tan et al.’s26 meta-analysis did not support the same conclusion. Major orthopedic trauma has the highest incidence of VTE. The incidence of VTE in pelvic fracture, traumatic brain injury (TBI), SCI, and lower limb fracture was 32.7%, 25.0%, 11.0%, and 9.2%, respectively.11,27–29 The onset of thrombotic events is more common after TBI because of the rich tissue factors (TF) in the brain. The risk of VTE is further increased when TBI patients have intracranial hemorrhage or multiple cranioencephalic injury.30 Patients with multiple fractures have a higher risk of VTE than those with single fractures, meanwhile pelvic fracture patients are more likely to develop PTE than those with single tibial or femoral fractures.31 Blunt injuries are accompanied with a higher incidence of VTE than sharp injuries. Patients with severe abdominal injuries, vascular injuries, and younger patients are at higher risks for VTE, and those with neurological diseases, local paralysis, or malignancy are at higher risks of recurrent VTE than others.32

The relation between pathophysiology of acute traumatic coagulopathy and the mechanisms of traumatic VTE

Pathophysiology of acute traumatic coagulopathy

Acute traumatic coagulopathy consists of traumatic coagulopathy caused by primary endogenous immediately after trauma such as hypoperfusion, shock, tissue injury, trauma, etc. and iatrogenic coagulopathy, which is aggravated in further sequelae, such as dilution (hemodilution) or anticoagulants.33,34 In recent years, however, experts have pointed out that activation of the protein C pathway is associated with tissue hypoperfusion/shock. Combined trauma and hypoperfusion/shock may lead to a hypercoagulable state via formation of an anticoagulant complex (thrombomodulin complex), which converts protein C into activated protein C, leading to an inactivation of the coagulation factors V and VIII. The activated protein C in surplus also consumes plasminogen activator inhibitor-1, which may lead to an increase in tissue plasminogen in the context of severe trauma.35,36

Acute traumatic coagulopathy is divided into three stages. In the first stage, multiple hemostasis pathways are activated immediately after trauma, with fibrinolytic hyperactivity associated with tissue damage and/or tissue hypoperfusion. The second phase deals with factors related to resuscitation therapy. The third stage is the pre-thrombosis state associated with the acute phase reaction.37 The consumption of protein C associated with tissue injury, the increase of thromboregulatory protein level and the decrease of factor V level indicate the important role of protein C pathway in acute traumatic coagulopathy. The hypoperfusion of tissue in the early stage of trauma may change the function of thrombin from promoting fibrin formation to activating the protein C system and generating systemic anticoagulant response. Hypoxia, acidosis, low temperature and other factors affect the function of platelets and thrombin, and then aggravate fibrinolytic hyperactivity. Tissue damage itself activates the immune system and further activates the clotting pathway through protein degradation and oxidative stress, which aggravates tissue damage. Non-standard resuscitation and traumatic bleeding can lead to dilution of coagulation factors and aggravate acute traumatic coagulopathy.5,10

Mechanisms of traumatic VTE

Clinically VTE is the result of multifactorial interactions (gene–gene and/or gene-environment). When the threshold is exceeded, the onset of VTE will be triggered.22,38 Venous stasis following injury was already described by Rudolf Virchow in 1856 as one of the main etiologic factors for VTE.22 The occurrence of VTE is closely related to three aspects: blood stasis, vascular endothelial injury and onset of blood hypercoagulability rapidly after trauma. Immobilization was required for all the trauma patients with TBI, SCI, pelvic fracture/long bone fracture, etc., which results in venous blood stasis. In addition, the significantly reduced capability of calf muscle pump further slows down the rate of venous return in the lower extremities. For trauma patients, the exogenous coagulation pathway will be initiated by TFs released after tissue injury. TFs
bind to activated factor VII and further activates factor X, to promote the activation of prothrombin into thrombin, which converts fibrinogen into fibrin and activates platelets to promote thrombosis. In general, TFs are expressed in cardiomyocytes, bronchial and alveolar epithelial cells, brain astrocytes, etc., and are separated from blood circulation. Inflammation and hypoxia after vascular endothelial injury in trauma patients can promote the expression of TFs released by neutrophils and macrophages. Once these organs are injured, TFs will be released into the blood and trigger clotting. It has been found that progressive trauma-induced coagulopathy is often associated with microparticles and increased thrombin production, in addition to TFs. Cheng et al.\(^4\) reported that the TF pathway inhibitor, thrombin, Xa-TF pathway inhibitor were involved in the occurrence of hypercoagulability in trauma patients. Interestingly, platelets are involved in the thrombus of trauma patients (both hemostatic and innate immune responses against injured tissue), such as offering a wide array of cell surface receptor at a high density, enabling rapid reaction to a range of stimuli, making sure close endothelial contact and can be deployed rapidly and simultaneously by possessing a diverse toolkit of molecular effectors. This dual regulation of inflammation and thrombosis, known as immunothrombosis, plays a key role in understanding the response to injury.\(^1\) Cardenas et al.'s study\(^2\) has indicated similar associations between trauma-induced impairment in platelet aggregation and fibrinolytic shutdown phenotypes. Obviously, acute trauma coagulopathy creates favorable conditions for thrombotic events which involve multiple factors.

**Risk factors for traumatic VTE**

There are several risk factors that affect the occurrence of VTE in trauma patients. Obesity and advanced age were found to be independent risk factors for VTE after discharge.\(^40\) Age and smoking can increase the risk of VTE.\(^46\) and a meta-analysis\(^47\) showed that the risk of VTE was nearly doubled in people over 60 years old. The acute physiology and chronic health evaluation II score on intensive care unit admission, ventilator-acquired pneumonia, heart failure, history of hypertension, duration of surgery and bed rest, cancer, diabetes, varicose veins, obesity, or blood transfusion of more than 5 units can all contribute to VTE. Patients with a history of VTE had a more than 5-fold increased risk of developing post-traumatic VTE. A 5-year study\(^48\) of the incidence of trauma-related VTE on 662 patients diagnosed with DVT and 258 with acute PTE found that 84 of these patients were trauma-related, i.e. 56 (8.5%) with DVT and 29 (10.9%) with PTE. The majority were diagnosed as inpatients (64.3% vs. 28.6%; \(p = 0.002\)), compared to DVT where a significantly higher proportion was constituted by outpatient diagnosis (71.4% vs. 35.7%; \(p = 0.002\)). Patients diagnosed with PTE were more likely to have a history of recent surgery (51.9% vs. 28.6%; \(p = 0.03\)), immobilization (25.0% vs. 8.9%; \(p = 0.04\)), and a prior PTE (7.4% vs. 0.0%; \(p = 0.03\)) as compared to those with DVT. Studies also found that the comorbidity of obesity, hypertension, diabetes mellitus, and hypercholesterolemia in VTE patients (52.9%, 25.0%, 17.9% and 17.9%, respectively) was high than that in non-VTE group, despite no significant difference was observed between the two groups.\(^48,49\)

**Diagnosis of traumatic VTE**

**Clinical manifestations and probability assessment system**

Up to now, there are not any ideal scoring systems for traumatic VTE patients. The Wells score is important in the differential diagnosis of non-high-risk PTE patients,\(^50,51\) but its predictive value in trauma patients is limited.\(^52\) The trauma embolic scoring system (TESS) for VTE may be an objective measure of classifying VTE risk for patients with trauma. Studies suggest that an optimal high-risk cut-off value of TESS \(\geq 7\) demonstrates a high sensitivity in predicting VTE.\(^53,54\)

**Laboratory tests**

**PT/INR ratio**

Although a prolonged PT alone may indicate the presence of traumatic coagulopathy, studies showed that PT/INR >1.2 was clearly associated with not only traumatic hemorrhagic shock-related mortality, but also VTE and all-cause mortality.\(^55,56\)

**D-dimer level**

D-dimer has an important value of excluding VTE, whose level is closely related to the occurrence of traumatic VTE.\(^57\) Masuda et al.\(^58\) indicated the best time to detect D-dimer was 2 weeks after SCI, with a cutoff value of 0.016 mg/L (sensitivity 77.3%, specificity 69.2%). Whereas other studies showed that the highest value of D-dimer should be detected within 2 days or 1 week after trauma.\(^59,60\) Due to the presence of injury and bleeding in trauma itself, the predictive value of D-dimer is limited.\(^61\) A new study showed that the measurement of D-dimer level should be complemented by routine color doppler ultrasound for detecting DVT within 6 months post-SCI. D-dimer screening alone for DVT detection revealed a better effect with the duning of >6 months, compared with that within the periods of 3 weeks—3 months and 3—6 months.\(^62\)
Soluble fibrin monomer complex (SFMC)

SFMC can reflect the early changes of thrombus formation and can be increased within 1 day after the occurrence of trauma or even increased before the formation of thrombus. SFMC level will decline the first day after thrombus formation. Studies have shown that the combination of SFMC and D-dimer will improve the sensitivity of VTE diagnosis.

Platelet monitoring

As a sensitive and reversible indicator of bleeding, coagulation and inflammation, platelet has obtained great attention. Dynamic monitoring of both the count and function of platelets plays an important guiding role in understanding the overall changes of patients and helping clinicians to make treatment decisions timely.

Thromboelastogram (TEG)

TEG have been proved to be useful in many studies because it can reflect the complete changes of coagulation and fibrinolysis system in the process of blood clot formation, and can reflect the function of coagulation factors, fibrin, platelet and fibrinolysis. TEG can help clinicians to estimate the clotting status of trauma patients: the more complex the clotting status, the more detailed information TEG can offer. Unfortunately, TEG has limited guidance in the presence of shock, hypothermia, and coagulation disorders in patients with severe trauma. The comprehensive view of TEG (Fig. 1) and the main parameters of TEG such as reaction time (R), coagulation time (K)/(k), platelet function and fibrinolytic function and its significance have been shown in Table 1.

Imageological diagnosis

Venous ultrasound of lower limbs

Venous ultrasound has been widely used as a diagnosis method for DVT in trauma patients for its non-invasive, repeatable and bedside property. At the same time, venous ultrasound can identify the nature of lower limb thrombus, i.e. fresh thrombus, old thrombus, etc. It is worth noting that ultrasound diagnosis is more sensitive to embolism in the femoral and popliteal veins, but less sensitive to those in the proximal iliac and distal intermuscular veins. Weekly venous compression duplex should be considered in patients at a high risk of VTE who is unable to start or maintain on pharmacologic prophylaxis as this is associated with a reduced PE rate.

Computed tomography pulmonary angiogram (CTPA) and lung perfusion/ventilation scan

Intravenous pulmonary angiography used to be a gold standard for the diagnosis of DVT, but it has been rarely used now because of its several disadvantages, such as high price, many contraindications, and invasion, etc. CTPA or lung perfusion/ventilation scan has become an alternative to pulmonary angiography for the diagnosis of PTE. Low doses of CTPA can be safely used in trauma patients even in pregnancy. CTPA is more sensitive to the main and sub-segmental parts of pulmonary artery, whereas lung perfusion/ventilation scan is more suitable and meaningful for the diagnosis of PTE below the subsegment level of pulmonary artery.

The machine learning predictors

Improved risk stratification may not only prevent unnecessary invasive testing in patients for whom DVT cannot be ruled out using the existing methods, but also allow for more targeted use of prophylactic anticoagulants, as well as earlier diagnosis and treatment, preventing the development of pulmonary emboli and other sequelae of DVT. The machine learning predictors can be obtained for DVT risk prediction on hospitalized patients at 12-h and 24-h windows.

Treatment and prevention of trauma VTE

The treatment of trauma-induced VTE is the same as other causes. A therapeutic dose of anticoagulants should be used timely if there is no anticoagulant contraindication (Table 2). Systematic thrombolytic therapy, such as, recombinant tissue type plasminogen activator (r-tPA), 50 mg intravenous infusion for 2 h, is recommended only for patients at a high risk of PTE. For trauma patients with contraindications to systemic thrombolysis, pulmonary interventional thrombolysis, or thrombus aspiration can be considered, even under the condition that extracorporeal membrane oxygenation was needed for help. While unfractionated heparin and the low molecular weight heparin (LMWH), enoxaparin, is most commonly dosed at 5000 units every 8 h and 30 mg every 12 h, respectively. In TBI evaluation, the anti-factor Xa assay allows for assessment of LMWH within a targeted range without increased risk of intracranial hemorrhage progression.

The prevention methods of VTE include mechanical prophylaxis and chemical prophylaxis. This review focuses on primary prophylactic anticoagulation for trauma patients, such as (1) how to assess? (2) The means of prophylaxis? (3) The optimal timing, frequency, and duration of prophylaxis? (4) Who should be delayed in pharmacologic prophylaxis? (5) The initial dose, etc.

Relevant guidelines suggest an important basis for active assessment of patients’ blood coagulation state and early prophylaxis. However, patients with intracranial injury tend to receive a delayed chemoprophylaxis. Severe trauma patients face the dual threat of traumatic bleeding and hypercoagulable thrombus.

Table 1

| Parameters | Normal range | Significance |
|------------|--------------|--------------|
| Reaction time (R) | 4–9 min | It indicates that there is no fibrin formation in the sample, which reflects the coagulation state. An increase in R indicates a prolonged clotting time, which can be corrected by fresh frozen plasma. Whereas, the decline in R shows hypercoagulability, and thus anticoagulant therapy is need. |
| Coagulation time (K)/k | 1–3 min/53–73 | It indicates that fibrin begins to form in the tested sample. Decline in K or increase in k indicates a high fibrinogen level and the need for anticoagulant therapy. An increase in K or a decrease in k indicates a low fibrinogen level, which can be treated with fresh frozen plasma or cryoprecipitation. |
| Platelet function (MA) | 50–70 mm | MA suggests the maximum size of thrombosis. A decrease in MA indicates low platelet function and the need for platelet transfusion. An elevated MA indicates the use of antplatelet drugs. |
| Fibrinolytic function (LY30/EPL) | 0–8%/0–15% | It shows the fibrinolytic function. Elevated LY30 and/or EPL both indicate fibrinolytic hyperactivity, which requires the combination of MA (MA > 70 mm, secondary fibrinolytic hyperactivity; MA < 50 mm, primary fibrinolytic hyperactivity); Hyperfibrinolysis occurs within 24 h in patients with severe trauma, and LY30 > 3% is usually used as an important basis for tranexamic acid in patients with traumatic bleeding. |

MA: maximum amplitude.
events. Unfortunately, there are still many uncertainties about how to safely and effectively use the thromboprophylaxis in severe trauma patients, even with the updated medical progress. It is difficult to decide the optimal strategy for VTE prevention because trauma patients may have real or perceived contraindications to prophylaxis, which affects the timing of preventive measures. A meta-analysis showed that the optimal plan for the prevention of traumatic VTE has not been reached, due to many factors such as the poor study quality, study design, population characteristics, outcome definition, etc. Chemical anticoagulation has clear therapeutic effects, but there is an unavoidable risk of bleeding. Therefore, although hypercoagulability may appear in severe trauma patients within 24 h, how to prevent its development safely and effectively still needs to be further explored, due to each trauma modality has different complications. A recent study from the Netherlands and USA indicated that more early commencement protocol (chemical prophylaxis started within 48 h after arrival) resulted in reduced thrombosis events almost twice as much compared with a delayed initiation of treatment. However, most episodes of VTE developed while receiving recommended prophylaxis. Early chemical thromboprophylaxis appears to be safe if started early, not significantly increasing the bleeding complications. Studies also indicated that except for spine and intracranial surgery, almost no existing data demonstrate that continuing chemoprophylaxis without interruption leads to increased bleeding complications. In patients with a low risk of bleeding complications and a high risk of VTE, chemoprophylaxis should be continuously used.

**Mechanical prophylaxis**

Mechanical prophylaxis is recommended for patients with moderate to high risks of VTE no matter concurrent pharmacologic prophylaxis or not. Mechanical prophylaxis includes stretch socks, intermittent pneumatic compression, and inferior vena cava (IVC) filters, which can be used alone or combined with chemoprophylaxis. Indications and contraindications for mechanical prophylaxis need to be carefully evaluated in order to avoid the occurrence of complications, e.g. mechanical compression devices may lead to local soft tissue injury, bleeding and patient non-compliance. IVC filters may migrate, causing IVC occlusion or penetrating the vessel wall. Application of these techniques must be appropriately utilized even if it can be life-saving. Intermittent pneumatic compression lowers the DVT incidence if no pharmacologic prophylaxis is initiated and therefore is recommended for patients with contraindication to pharmacologic prophylaxis. But intermittent pneumatic compression in critically ill patients who received pharmacologic prophylaxis failed to effectively reduce the incidence of DVT, although the DVT rate in this study was low and only 8% of the population were trauma patients. It was found that a mobility protocol is safe in trauma patients and may reduce the rate of traumatic VTE. On the contrary, prolonged maintenance of spinal precautions is associated with an increased immobility-associated DVT rate and physicians should focus on prompt, definitive care and early mobilization.

**Chemoprophylaxis**

Geerts et al. determined that the DVT rate without pharmacologic prophylaxis was 58% in severely injured trauma patients who undergo serial impedance plethysmography with lower extremity contrast venography. More recently, a systematic review from 2020 evaluated 17 studies, and concluded that early chemoprophylaxis between 24 h and 72 h after injury is associated with a reduced VTE incidence without increasing intracranial hemorrhage in TBI patients, confirmed by a stable repeat head CT.

**How to assess VTE risk?**

An appropriate assessment of VTE risk will assist in determining which patients require pharmacologic prophylaxis. Patients with a TESS ≥7 is at a high risk of VTE and should receive prophylaxis earlier. Studies have shown that an ISS ≥10 suggests that pharmacologic prophylaxis should be initiated as soon as possible, whereas patients with an ISS<10 are at a lower VTE risk and may not require pharmacologic prophylaxis. Patients with minor trauma may not require pharmacologic prophylaxis. Pharmacologic prophylaxis may need to be appropriately delayed for those patients with an active bleeding, coagulopathy, hemodynamic instability, solid organ injury, TBI, or spinal trauma.

**Optimal timing to initiate VTE prophylaxis and types of prophylactic agents**

What needs to be emphasized is that a continuous prophylaxis therapy is crucial once initiated. Interruption of VTE prophylaxis for a period of 24 h or even missing a single dose is closely related to an increased risk of VTE. Pharmacological prophylaxis should be continued or only stopped for significant or potentially significant bleeding events, development of heparin-induced thrombocytopenia, severe hemorrhage and recent spine or intracranial surgery.

**Optimal timing of VTE prophylaxis**

VTE prophylaxis should be given to trauma patients at medium to high risks. Anticoagulant therapy should be synchronized with surgery in patients with pelvic fractures. Due to the rich TFs and other factors in the brain tissue of TBI

---

**Table 2**

| Anticoagulant | Therapeutic dose | Prophylactic dose | Special considerations |
|---------------|-----------------|------------------|-----------------------|
| UFH           | 80 unit/kg IV bolus, followed by an 18-unit/kg/h infusion every 8 h | 5000 units 30 mg every 12 h | Caution of heparin-induced thrombocytopenia |
| Enoxaparin    | 1 mg/kg subQ BID | — | Caution of heparin-induced thrombocytopenia |
| Fondaparinux  | <50 kg: 5 mg subQ daily | — | Initiate warfarin within 72 h and give concomitantly for at least 5 days. |
|               | 50–100 mg: 7.5 mg subQ daily | >100 kg: 10 mg subQ daily | — |
| Edoxaban      | 60 mg po once daily; 30 mg once daily if body weight <60 kg | — | Not for use in patients with CrCl >95 mL/min. Dose after 5–10 days of initial therapy with a parenteral anticoagulant |
| Rivaroxaban   | 15 mg po twice daily for 3 weeks, then 20 mg once daily at least 6 months | — | Take food to improve absorption |
| Dabigatran    | 150 mg po BID; 110 mg BID for patients ≥80 years old | — | Dose after 5–10 days of initial therapy with a parenteral anticoagulant Reduce dose to 110 mg BID for patients ≥80 years or ≥75 years with at least one bleeding risk factor. |

UFH: unfractionated heparin; subQ: subcutaneously; BID: twice a day; CrCL: creatinine clearance; IV: intravenous injection; po: profess to convinced.
patients, the risk of VTE greatly increases. Therefore, anticoagulant therapy should be started within 24–48 h after cerebral hemorrhage event has been excluded, and chemoprophylaxis is the first choice for patients without contraindications. Additional stratification of TBI patients into moderate-risk and high-risk groups follows with a 72-h delay in VTE prophylaxis initiation and consideration of an IVC filter, respectively.101

Pharmacologic prophylaxis. Patients with severe trauma have a high risk of both hemorrhage and thrombus; it is a key issue to ensure the safety of anticoagulant therapy.102 After deciding to start pharmacologic prophylaxis, the non-oral anticoagulants and initial dose should be determined individually. Many trauma patients require dose adjustment after initiating enoxaparin. Compared with LMWH may be superior for its more specific inhibitor of Xa. Both low dose unfractionated heparin (5000U Q12H) and LMWH (30 mg Q12H) enoxaparin administered after trauma can effectively prevent the occurrence of VTE and be safely adjusted based on the anti-Xa levels.72,103 Weight-based and blood for the anti-Xa testing should be typically drawn 4 h after the third dose of enoxaparin, that with the target prophylactic levels falling in the range of 0.2–0.4 IU/mL (the target for therapeutic full anticoagulation is > 0.5 IU/mL) is recommended. But one larger retrospective study104 reported no decrease in VTE rates with an anti-Xa-based regimen. As an inhibitor of the factor Xa, fondaparinux has been shown to be more effective in preventing VTE than LMWH in trauma patients.105 Other studies have shown that fondaparinux is not inferior to LMWH in preventing post-traumatic VTE and does not increase the risk of bleeding.106 However, fondaparinux has a long half-life and is metabolically cleared by the kidney, and once dose accumulation occurs, the risk of bleeding will be increased.91 A multicenter, double-blind, randomized, controlled trial involved 3424 patients experienced total hip or knee arthroplasty shown that after received 5 days of rivaroxaban prophylaxis, extended prophylaxis with aspirin was not significantly different from rivaroxaban in the prevention of symptomatic venous thromboembolism.107

Duration of prophylactic anticoagulant therapy

The optimal postdischarge dose and duration of pharmacologic prophylaxis after trauma are not well defined. By now, the duration of pharmacologic prophylaxis may be considered for up to 4 weeks after the date of admission. For those who undergo major orthopedic surgery, pharmacologic prophylaxis may be extended up to 35 days from the date of surgery.91 Trauma patients with TBI, orthopedic or spinal injuries, and those who undergo major surgeries are at a particular VTE risk and should be considered for postdischarge pharmacologic prophylaxis. A recent study108 showed that prolonged thromboprophylaxis for more than 28 days with LMWH significantly reduces the risk of VTE compared to thromboprophylaxis during hospital stay only, without increasing bleeding complications or mortality after major abdominal or pelvic surgery. The highest VTE risk occurs during the first 3 months after injury with approximately 1 year required until the VTE risk rate returns to that of general population.109,110 Direct oral anticoagulants may also be considered for post discharge pharmacologic prophylaxis after isolated orthopedic injury.107 Prophylactic anticoagulant therapy for SCI patients should be extended or even continued into the recovery period. Once VTE is present, anticoagulant therapy should be performed for at least 3 months.111 Severe trauma patients with risk assessment profile score >10 have a >25% rate of VTE despite receiving prophylactic anticoagulation.111 Studies show that the patients received tranexamic acid can significantly reduce the fibrinolytic activity and not increase the risk of VTE, even TEG, or other blood coagulation indexes within 24 h of admission shows the coming state of hypercoagulation status.3,112 But a recent systemic review113 indicated the use of tranexamic acid and fibrinogen concentrate was associated with the development of thromboembolic complications.

Management of anticoagulation-related bleeding

Determination of major bleeding and minor bleeding

The classification of bleeding has been simplified as major or nonmajor.114 The former refers to bleeding that is associated with hemodynamic instability, requires transfusion (>2 units of packed red blood cells) or results in a hemoglobin drop >20 g/L, occurs in an anatomically critical site such as intracranial hemorrhage and other central nervous system bleeds (e.g., intraocular, spinal). Thoracic, airway, pericardial, intra-abdominal, retroperitoneal, intra-articular, and intramuscular bleedings are considered critical as they may cause severe disability and necessitate surgical procedures for hemostasis. Intraluminal gastrointestinal bleeding is not considered a critical site bleeding; however, it can result in hemodynamic compromise. All the other bleedings are classified as minor bleeding.115,116

Management of major bleeding and minor bleeding

There is no indication to discontinue medication for minor bleeding, and studies have shown that minor bleeding during anticoagulation has no predictive value for major bleeding.115–117 Stop the chemoprophylaxis once major bleeding is confirmed, maintain vital signs, and blood transfusion or specific reversal agents are recommended if necessary (Table 3).118–123

The optimal timing of restarting anticoagulation

The timing to restart anticoagulation is different, depending on the exact sites of anticoagulation-related bleeding, for example, 4–7 days after the stop of gastrointestinal bleeding (a multidisciplinary decision is required to restart anticoagulation), whereas, 4–8 weeks for intracranial hemorrhage and recheck by cranial CT.

| Anticoagulant | First line reversal agent | Alternative reversal agent(s) |
|---------------|--------------------------|------------------------------|
| UFH           | Protamine sulfate        |                              |
| LMWH          | Protamine sulfate        |                              |
| VKA           | 4F-PCC                   |                              |
| Dabigatran    | Idarucizumab             |                              |
| Direct oral factor-Xa inhibitors | Andexanet alfa PCC |                              |
| Fondaparinux factor | Villa aPCC               | Andexanet alfa               |

UFH: Unfractionated heparin; LMWH: low molecular weight heparin; VKA: vitamin K antagonist; 4F-PCC: 4-factor prothrombin complex concentrate; FFP: fresh frozen plasma; PCC: prothrombin complex concentrate. aPCC: activated prothrombin complex concentrate.
The optimal timing of restarting chemoprophylaxis in trauma patient remains uncertain and ranges between 24 h and 72 h. There are no clear data to guide the decision making until now.124

**Vena cava filter**

IVC filters may be considered in the setting of proximal DVT or PE when there is a contraindication to appropriate therapeutic anticoagulation. The use of prophylactic IVC filters in trauma patients is controversial, but should be considered in trauma patients at a very high-risk of VTE who cannot receive chemoprophylaxis for a long period because of the increased bleeding risk.123–125 The IVC filters should be removed as soon as protection is no longer needed or the patient can safely receive chemoprophylaxis or therapeutic anticoagulation, to avoid long-term complications related to IVC filters.126,127

But there is study showed that a prophylactic IVC filter did not lower the incidence of PE or mortality, which established the lack of utility of early prophylactic placement of an IVC filter in this population.128

**Take home messages**

1. The mechanisms of traumatic coagulopathy are complex, severe trauma patients faced a double threat of post-traumatic bleeding and post-traumatic thrombotic events soon after injury.

2. Hypercoagulability exists early after the traumatic injury, although one week after trauma is the time-point with a higher risk of VTE. A significant number of VTE cases have been reported to be diagnosed as early as the first 24 h after injury and the hypercoagulable state persisted even after discharged.

3. TESS > 7 or ISS ≥ 10 suggests that pharmacologic prophylaxis should be initiated as soon as possible. Patients with higher acute physiology and chronic health evaluation II score on intensive care unit admission, ventilator-acquired pneumonia, heart failure, history of hypertension, duration of surgery and bed rest, cancer, diabetes, varicose veins, obesity, or blood transfusion of more than 5 units may all contribute to VTE incidence. A rapid and timely diagnosis and treatment is necessary.

4. Effective monitoring (such as TEG and anti-Xa levels) and the optimal timing for mechanical and/or chemoprophylaxis are the most effective means to prevent venous thrombus events. Non-oral anticoagulants are routinely recommended for primary prophylaxis, whereas oral anticoagulants were used for secondary prevention if there are no anticoagulation contraindications and should not be interrupted within 3 months.

5. Pharmacological prophylaxis should only be held or stopped for significant or potentially significant bleeding events. The optimal timing of restarting anticoagulants depends on the specific condition of the patient.

**Funding**

This study was funded by Chaoyang District Bureau of Science and Technology and Information Technology (Bureau of Big Data). Contract no. CYSF 2049. The fund provider had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

**Ethical statement**

Not applicable.

**Declaration of competing interest**

The authors declare no conflicts of interest or financial interests.

**Author contributions**

Yu-Hong Mi is responsible for data analysis and manuscript composition. Ming-Ying Xu did data collection. Both the two authors approved the drafting, editing and publication of this article.

**References**

1. Sauaia A, Moore EE, Johnson JL, et al. Temporal trends of postinjury multiple-organ failure: still resource intensive, morbid, and lethal. J Trauma Acute Care Surg. 2014;76:582–592. https://doi.org/10.1097/JTA.0000000000000147.

2. Lord JM, Midwinter MJ, Chen YF, et al. The systemic immune response to trauma: an overview of pathophysiology and treatment. Lancet. 2014;384:1455–1465. https://doi.org/10.1016/S0140-6736(14)60687-5.

3. Van Haren RM, Valle EJ, Thorsen CM, et al. Hypercoagulability and other risk factors in trauma intensive care unit patients with venous thromboembolism. J Trauma Acute Care Surg. 2014;76:443–449.

4. Haagsma JA, Graetz N, Bolliger I, et al. The global burden of injury: incidence, mortality, disability-adjusted life years and time trends from the Global Burden of Disease study 2013. Inj Prev. 2016;22:3–18.

5. CDC. 10 Leading Causes of Death by Age Group. United States; 2014. accessed http://www.cdc.gov/injury/wisqars/leadingcauses.html. Accessed May 23, 2016.

6. WHO. World Health Statistics. Monitoring Health for the SDGs; 2016. accessed http://www.who.int/gho/publications/world_health_statistics/en/. Accessed May 23, 2016.

7. James SL, Castle CD, Dingels ZV, et al. Global injury morbidity nd mortality from 1990 to 2017: results from the Global Burden of Disease Study 2017. Inj Prev. 2020;26:96–114, 10.1136.

8. Spahn D, Bouillon B, Cerny V, et al. The European guideline on management of major bleeding and coagulopathy following trauma: fifth edition. Crit Care. 2019;23:98. https://doi.org/10.1186/s13054-019-2347-3.

9. Simmons JW, Powell MF. Acute traumatic coagulopathy: pathophysiology and resuscitation. Br J Anaesth. 2016;117:i31–i43. https://doi.org/10.1093/bja/aew328.

10. Maegle M. The diagnosis and treatment of acute traumatic bleeding and coagulopathy. Dtsch Arztebl Int. 2019;116:799–806. https://doi.org/10.3238/arztebl.2019.0799.

11. Frohlich M, Mutschler M, Caspers M, et al. Trauma-induced coagulopathy upon emergency room arrival: prevention, recognition, awareness and management? Eur J Trauma Emerg Surg. 2019;45:115–124. https://doi.org/10.1007/s00068-017-0884-5.

12. Kornblith LZ, Moore HB, Cohen MJ. Trauma-induced coagulopathy: past, present and future. J Thromb Haemostasis. 2019;17:852–862. https://doi.org/10.1111/jth.14450.

13. Schoeneberg C, Schilling M, Hussmann B, et al. Preventable and potentially preventable deaths in severely injured patients: a retrospective analysis including patterns of errors. Eur J Trauma Emerg Surg. 2017;43:481–489. https://doi.org/10.1007/s00068-016-0670-9.

14. Cabrera CP, Manson J, Shepherd JM, et al. Signatures of inflammation and impending multiple organ dysfunction in the hyperacute phase of trauma: a prospective cohort study. PLoS Med. 2017;14:e1002352.

15. Huber-Lang M, Lambris JD, Ward PA. Immune immune responses to trauma. Nat Immunol. 2018;19:329–341. https://doi.org/10.1038/s41590-018-0064-8.

16. Hamada SR, Espina C, Guedj T, et al. High level of venous thromboembolism in critically ill trauma patients despite early and well-driven thromboprophylaxis protocol. Ann Intensive Care. 2017;7:97. https://doi.org/10.1186/s13637-017-0315-0.

17. Bahloul M, Diela M, Bouchala K, et al. Post-traumatic pulmonary embolism: incidence, physiopathology, risk factors of early occurrence, and impact outcome. A narrative review. Am J Cardiovasc Dis. 2020;10:432–443.

18. Zhang M, Parikh B, Dirlikov B, et al. Elevated risk of venous thromboembolism among post-traumatic brain injury patients requiring pharmacological immobilization. J Clin Neurosci. 2020;75:66–70. https://doi.org/10.1016/j.jocn.2020.03.028.

19. Heit JA, O’Fallon WM, Petterson TM, et al. Relative impact of risk factors for deep vein thrombosis and pulmonary embolism: a population-based study. Arch Intern Med. 2002;162:1245–1248. https://doi.org/10.1001/archinte.162.11.1245.

20. Coleman J, Zarzaur BL, Katona CW, et al. Factors associated with pulmonary embolism within 72 hours of admission after trauma: a multicenter study.
34. Upadhyaya GK, Iyengar KP, Jain VK, et al. Evolving concepts and strategies in trauma-induced coagulopathy. J Trauma Acute Care Surg. 2012;73:416-424. https://doi.org/10.1097/TA.0b013e31822664c8.

35. Caspers M, D€olich M, Ohlich M, et al. How do external factors contribute to deep vein thrombosis in polytrauma patients. J Orthop Sci. 2009;14:374-381. https://doi.org/10.1007/s00776-008-1745-y.

36. Dobson GP, Letson HL, Sharma R, et al. Mechanisms of early trauma-induced coagulopathy: the chicken or the egg? J Trauma Acute Care Surg. 2015;79:301-309. https://doi.org/10.1097/TA.0000000000000729.

37. Varga EA, Kujovic JL. Management of inherited thrombophilia: guide for genetics professionals. Clin Genet. 2012;81:7-17. https://doi.org/10.1111/j.1399-0004.2011.01763.x.

38. Bagot CN, Atya R, Virechow and his triad: a question of attribution. Br J Haematol. 2008;143:180-190. https://doi.org/10.1111/j.1365-2141.2008.07123.x.

39. Cheng Y, Liu B, Qian H, et al. BAY11-7082 inhibits the expression of tissue factor and plasminogen activator inhibitor-1 in type-II alveolar epithelial cells following TNF-a stimulation via the NF-kB pathway. Exp Ther Med. 2021;21:177. https://doi.org/10.3892/etm.2020.8608.

40. Cognasse F, Laradi S, Berthelin P, et al. Platelet inflammatory response to stress. Front Immunol. 2019;10. https://doi.org/10.3389/fimmu.2019.01478.

41. Vollayn P, Kornblith LZ, Kornblith S, et al. Platelets retain inducible alpha granule markers after major trauma: adaptive or maladaptive? Platelets. 2021;32:295-304. https://doi.org/10.1080/09537104.2021.1781633.

42. Dyer MR, Alexander W, Hassoune A, et al. Platelet-derived extracellular vesicles released after trauma promote hemostasis and contribute to MHC class I up-regulation. J Thromb Haemostasis. 2019;17:173-1745. https://doi.org/10.1111/jth.14563.

43. Miyazawa B, Trivedi A, Togaratti PP, et al. Regulation of endothelial cell permeability by platelet-derived extracellular vesicles. J Trauma Acute Care Surg. 2018;86:31-38. https://doi.org/10.1097/TA.0000000000002230.

44. Cardenas JC, Wade CE, Cotton BA, et al. TEG lysis shutdown represents coagulopathy in bleeding trauma patients: analysis of the pro/coag process. Shock. 2018;51:273-283. https://doi.org/10.1097/HSH.0000000000001690.

45. Park MS, Perkins SE, Spears GM, et al. Risk factors for venous thromboembolism after acute trauma: a population-based case-cohort study. Thromb Res. 2016;144:40-45. https://doi.org/10.1016/j.thromres.2016.03.026.

46. Darzi AJ, Karam SG, Charide R, et al. Prognostic factors for VTE and bleeding in hospitalized medical patients: a systematic review and meta-analysis. Blood. 2017;130:1711-1722. https://doi.org/10.1182/blood-2016-08-760580.

47. Strandvik G, EliMenyar A, Asim M, et al. Clinical characteristics, management practices, and in-hospital outcomes among trauma patients with venous thromboembolism. J Emergencies, Trauma, Shock. 2020;13:124-130. https://doi.org/10.1016/j.jetsaco.2019.100202.

48. Spinella PC, Carroll CI, Staff I, et al. Duration of red blood cell storage is associated with increased incidence of deep vein thrombosis and in hospital mortality in patients with traumatic injuries. Crit Care. 2009;13:R51. https://doi.org/10.1186/cc7120.

49. Wells PS, Owen C, Doucette S, et al. Does this patient have deep vein thrombosis? J Am Med Assoc. 2006;295:199-207. https://doi.org/10.1001/jama.2006.12919.

50. Al Dandan O, Hassan A, Alnasr A, et al. The use of clinical decision rules for pulmonary embolism in the emergency department: a retrospective study. Int J Emerg Med. 2020;13:23. https://doi.org/10.1186/s12245-020-00281-1.

51. Kim YJ, Choi DH, Lee ES, et al. Utility of the simplified Wells and revised Geneva scores to exclude pulmonary embolism in femur fracture patients. Am J Emerg Med. 2017;35:1131-1135. https://doi.org/10.1016/j.ajem.2017.03.023.

52. Rogiers K, Shackford SR, Horst MA, et al. Determining venous thromboembolic risk assessment for patients with trauma: the Trauma Embolic Scoring System. J Trauma Acute Care Surg. 2012;73:511-515. https://doi.org/10.1097/TA.0b013e3182588504.

53. Vulliamy P, Schobel S, Caruso JD, et al. Trauma Embolic Scoring System in military trauma: a sensitive predictor of venous thromboembolism. Trauma Acute Care Open. 2019;4:e000367. https://doi.org/10.1136/trauma-2019-000367.

54. Hagemoen JS. Prehospital diagnosis of traumatic coagulopathy. J Trauma. 2013;52:488-515. https://doi.org/10.1097/TA.0b013e318289d8a9.

55. Suehiro E, Koizumi H, Fujiyama Y, et al. Predictors of deterioration indicating a requirement for surgery in mild to moderate traumatic brain injury. Clin Neurophysiol. 2014;127:97-100. https://doi.org/10.1016/j.clinphys.2013.09.007.

56. Lieu JT, Desai K, Temple J, et al. Deployment of the activated protein C resistance test in patients with severe trauma: incidence, risk factors and outcome. J Trauma. 2012;73:67-73. https://doi.org/10.1097/TA.0b013e31824973db.

57. Dyer MR, Alexander W, Hassoune A, et al. Platelet-derived extracellular vesicles released after trauma promote hemostasis and contribute to MHC class I up-regulation. J Thromb Haemostasis. 2019;17:173-1745. https://doi.org/10.1111/jth.14563.

58. Dyer MR, Alexander W, Hassoune A, et al. Platelet-derived extracellular vesicles released after trauma promote hemostasis and contribute to MHC class I up-regulation. J Thromb Haemostasis. 2019;17:173-1745. https://doi.org/10.1111/jth.14563.
70. Konstantinides SV, Meyer G, Becattini C, et al. 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS): the task force for the diagnosis and management of acute pulmonary embolism of the European Society of Cardiology (ESC). Eur Respir J. 2019;54:1901647. https://doi.org/10.1183/13993003.01647-2019.

71. Ryu J, Longo LA, Patel A, et al. A machine learning approach to predict deep vein thrombosis among hospitalized patients. Clin Appl Thromb Hemost. 2021;27, 1076029621991185. http://doi.org/10.1177/1076029621991185.

72. Panahian L, Iudea C, Horasan R, Hosemann M. Review of medical text for the management of pulmonary embolism. Medicina (Kaunas). 2021;57:1100019. https://doi.org/10.3390/medicina57020110.

73. FDA highlights of prescribing information unfractionated heparin. accessed https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/170295s140b1l. pdf. Accessed May 23, 2016.

74. Smythe MA, Prizioja J, Dobesh PP, et al. Guidance for the practical management of the heparin anticoagulants in the treatment of venous thromboembolism. J Thromb Thrombolysis. 2016;41:165–186. https://doi.org/10.1007/s11239-015-1315-2.

75. Sebaaly J, Covert K. Enoxaparin dosing at extremes of weight: literature review and dosing recommendations. Ann Pharmacother. 2018;52:898–905. https://doi.org/10.1177/1060028018780440.

76. Janssen Pharmaceuticals. Xarelto (Rivaroxaban) Package Insert. Beerse, Belgium: Janssen Pharmaceuticals Inc.; 2020.

77. Boehringer Ingelheim Pharmaceuticals Inc. (Dabigatran) Package Insert. CT, USA: Boehringer Ingelheim: Ridgefield; 2020.

78. Rodier SG, Kim M, Moore S, et al. Early anti-Xa Assay-Guided low molecular weight heparin prophylaxis is safe in adult patients with acute traumatic brain injury. Am Surg. 2016;82:369–370. https://doi.org/10.1177/1072150416662570.

79. Anderson DR, Morgano GP, Bennett C, et al. American Society of Hematology 2019 guidelines for management of venous thromboembolism: prevention of venous thromboembolism in surgical hospitalized patients. Blood Adv. 2019;3:3898–1944. https://doi.org/10.1182/bloodadvances.2019000957.

80. Raksin PB, Harrop JS, Anderson PA, et al. Congress of neurological surgeons in injury: is delaying venous thromboembolism chemoprophylaxis worth the risk? J Neurosurg. 2019;131:2044–2055. https://doi.org/10.3171/2019/18.14363-360. https://doi.org/10.1016/j.jns.2019.03.063.

81. Joseph B, Friesse RS, Sadoun M, et al. The big (brain injury guidelines) project: defining the management of traumatic brain injury by acute care surgeons. J Trauma Acute Care Surg. 2014;76:965–969. https://doi.org/10.1097/TA.0000000000000702.

82. Dow N, Coleman JR, Moore H, et al. Dense and dangerous: the tissue plasminogen activator-resistor fibrinolysis shutdown phenotype is due to abnormal fibrin polymerization. J Trauma Acute Care Surg. 2020;88:258–265. https://doi.org/10.1097/TA.0000000000002486.

83. Rahkra S, Martin EL, Fitzgerald M, et al. ATLANTIC study: anti-Xa guided dosing of enoxaparin with venous thromboembolism after trauma. JAMA Surg. 2018;153:144–149. https://doi.org/10.1001/jamasurg.2017.3787.

84. El-Daly I, Reidy J, Culpan P, et al. Thromboprophylaxis in patients with pelvic and acetabular fractures: a short review and recommendations. Injury. 2013;44:1710–1720. https://doi.org/10.1016/j.injury.2013.04.030.

85. Rodier SG, Bukur M, Moore S, et al. Weight-based enoxaparin with anti-factor Xa assay-based dose adjustment for venous thromboembolic event prophylaxis in adult trauma patients results in improved prophylactic range targeting. Eur J Trauma Emerg Surg. 2021;47:145–151. https://doi.org/10.1007/s00068-019-01215-0.

86. Anderson DR, Dunbar M, Murriagah J, et al. Aspirin or Rivaroxaban for VTE prophylaxis after hip or knee arthroplasty. N Engl J Med. 2018;378:699–707. https://doi.org/10.1056/NEJMoa1712746.

87. Felder S, Rasmussen MS, King R, et al. Prolonged thromboprophylaxis with low molecular weight heparin for abdominal or pelvic surgery. Cochrane Database Syst Rev. 2015;3, CD004318. https://doi.org/10.1002/14651858.CD004318.pub4.

88. Godat LN, Kobayashi I, Chang DC, et al. Can we ever stop worrying about venous thromboembolism after trauma? J Trauma Acute Care Surg. 2015;78:18–28. https://doi.org/10.1097/JTA.0000000000000566.

89. Huo MH, Muntz J. Extended thromboprophylaxis with low-molecularweight heparin after hospital discharge in high-risk surgical and medical patients: a review. Clin Therapeut. 2009;31:1129–1141. https://doi.org/10.1016/j.clinthera.2009.06.002.

90. Rattan R, Parreco J, Eidelson SA, et al. Hidden burden of venous thromboembolism after trauma: a national analysis. J Trauma Acute Care Surg. 2018;85:899–906. https://doi.org/10.1097/TA.0000000000002580.

91. CRASH-2 trial collaborators, Shukur H, Roberts I, et al. Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomised, placebo-controlled trial. Lancet. 2010;376:23–32. https://doi.org/10.1016/S0140-6736(10)60835-5.

92. Wirtz MR, Schalkers DV, Goslings JC, et al. The impact of blood product ratio and procoagulant therapy on the development of thromboembolic events in severely injured hemorrhaging trauma patients. Transfusion. 2020;60:1873–1882. https://doi.org/10.1111/trf.15917.

93. Schulman S, Angeras U, Bergqvist D, et al. Definition of major bleeding in clinical investigations of anestheticmpharmacological medicinal products in surgical patients. J Thromb Haemost. 2006;4:202–204.

94. Tomaselli GF, Mahaffey KW, Cuker A, et al. 2017 ACC expert consensus decision pathway on management of bleeding in patients on oral anticoagulants. J Am Coll Cardiol. 2017;70:3042–3067. https://doi.org/10.1016/j.jacc.2017.05.085.

95. Tomaselli GF, Mahaffey KW, Cuker A, et al. 2020 ACC expert consensus decision pathway on management of bleeding in patients on oral anticoagulants. J Am Coll Cardiol. 2020;76:694–722. https://doi.org/10.1016/j.jacc.2020.04.053.
117. Heidbuchel H, Verhamme P, Alings M, et al. Updated European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist anticoagulants in patients with non-valvular atrial fibrillation. Europace. 2015;17:1467–1507. https://doi.org/10.1093/europace/euv309.
118. Chai-Adisaksopha C, Hillis C, Siegal DM, et al. Prothrombin complex concentrates versus fresh frozen plasma for warfarin reversal. A systematic review and meta-analysis. Thromb Haemostasis. 2016;116:879–890.
119. Pollack Jr CV, Reilly PA, van Ryn J, et al. Idarucizumab for dabigatran reversal—full cohort analysis. N Engl J Med. 2017;377:431–441. https://doi.org/10.1056/NEJMoa1707278.
120. Connolly SJ, Milling Jr TJ, Eikelboom JW, et al. Andexanet alfa for acute major bleeding associated with factor Xa inhibitors. N Engl J Med. 2016;375:1131–1141. https://doi.org/10.1056/NEJMoa1607887. Epub 2016 Aug 30.
121. Britt RB, Brown JN. Characterizing the severe reactions of parenteral vitamin K1. Clin Appl Thromb Hemost. 2018;24:5–12. https://doi.org/10.1177/1076029616674825.
122. Sarode R, Milling Jr TJ, Refaai MA, et al. Efficacy and safety of a 4-factor prothrombin complex concentrate in patients on vitamin K antagonists presenting with major bleeding: a randomized, plasmacontrolled, phase IIIb study. Circulation. 2013;128:1234–1243. https://doi.org/10.1161/CIRCULATIONAHA.113.002283.
123. Milling TJ, Refaai MA, Sarode R, et al. Safety of a four-factor prothrombin complex concentrate versus plasma for vitamin K antagonist reversal: an integrated analysis of two phase IIIb clinical trials. Acad Emerg Med. 2016;23:466–475.
124. Steffel J, Verhamme P, Potpara TS, et al. The 2018 European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation. Eur Heart J. 2018;39:1330–1393. https://doi.org/10.1093/eurheartj/ehy136.
125. McEnulty PG, Salyers Jr WJ, Joshi A. Vena cava filter complications: aortic pseudoaneurysm presenting as a gastrointestinal bleed. Kans J Med. 2019;12:53–54.
126. Garcia-Godoy F, Collins T, Sacks D, et al. Retrieval of inferior vena cava filters after prolonged indwelling time. Arch Intern Med. 2011;171:1953–1955. https://doi.org/10.1001/archinternmed.2011.526.
127. Charlton-Ouw KM, Afaq S, Leake SS, et al. Indications and outcomes of open inferior vena cava filter removal. Ann Vasc Surg. 2018;46(205):e5–e11. https://doi.org/10.1016/j.avsg.2017.05.038.
128. Ho KM, Rao S, Honeybul S, et al. A multicenter trial of vena cava filters in severely injured patients. N Engl J Med. 2019;381:328–337. https://doi.org/10.1056/NEJMoa1806515.