Venous thromboembolism in the trauma patient

Stephen M M Tai
Pranai Buddhdev
Aroon Baskaradas
Nishanth Sivarasan
Nigel R M Tai

Abstract
Deep vein thrombosis (DVT) is a common complication amongst patients who sustain major trauma. Whilst DVT may result in long-term morbidity, it is the potential for the fatal consequences of acute pulmonary embolism (PE) that remain a significant cause for concern in the severely injured patient. The incidence and risk factors for venous thromboembolism (VTE) are discussed. The aetiology of thrombus formation in trauma is reviewed in depth.

Multiple methods of thromboprophylaxis exist, both pharmacological and mechanical. Inferior venal caval filters, on the other hand, aim to prevent the emboli from DVTs that have already formed lodging within the pulmonary vasculature. All modalities have potential advantages and disadvantages.

The likelihood of DVT can potentially be predicted by scoring systems, whilst numerous methods of DVT detection can be employed. Once DVT has been diagnosed, treatment should be commenced.

Major trauma patients may sustain a vast array of injuries, and prevention and treatment of VTE in specific injury patterns are reviewed. However, further evidence in the form of multi-centre, randomized controlled trials must be obtained before a standardized protocol for thromboprophylaxis in major trauma can be produced.

Keywords deep vein thrombosis; prophylaxis; pulmonary embolism; trauma; venous thromboembolism

Introduction
It is well recognized that significant multisystem trauma is a risk factor for deep venous thrombosis (DVT) and pulmonary embolism (PE): an observation that was first made nearly 80 years ago.1 Whilst DVT may cause long-term morbidity, it is the potentially fatal consequences of acute PE that pose particular risks to the trauma patient. Hence, commencement of appropriate thromboprophylaxis is an essential step in the management of the multiply injured patient. There are a number of methods of thromboprophylaxis available in the armamentarium of the clinician caring for trauma victims. However, the decision as to which of these to use, coupled with the timing of their commencement, has been long debated: the risk of thromboembolism must be balanced against the complications associated with the use of thromboprophylaxis.

Incidence
The reported frequency of DVT after trauma varies according to a number of factors, including patient demographics, the nature, site and severity of injury, and the method of detection. Without thromboprophylaxis, however, the incidence of DVT in trauma victims may be more than 50%.2 DVT may be clinically silent and although DVT itself is not a life-threatening condition, subsequent PE has significant mortality.3

Complications of acute DVT
Pulmonary embolism
PE is the most important complication of DVT. Approximately 30% of untreated PEs will cause fatality.3 It is the third most common cause of death in patients that survive the first 24 h after trauma.2-4 Proximal lower limb DVTs are probably the source of the majority of PE’s.5

Post-thrombotic syndrome
Also known as post-phlebitic syndrome, it is a late complication associated with DVT. Clinically it may manifest as pain, oedema, eczema, hyperpigmentation or ulceration, usually around the medial malleolus. Severe cases may result in venous claudication.

Acute recurrent DVT — any patient who has a proximal vein thrombosis must receive adequate treatment, otherwise they have a 47% chance of recurrent thrombus formation over 3 months. Conversely, in patients in whom adequate anticoagulation is achieved, the recurrence rate is 2–4% during the subsequent 3 months.6

Risk factors for VTE in trauma patients
A number of risk factors for VTE after major trauma have been put forward. These include increasing age, lower limb, pelvic or head injury, prolonged immobility, ventilatory support, haemodynamic instability and subsequent surgical intervention7 (Table 1).

The Eastern Association for the Surgery of Trauma (EAST) has published proposed risk factors for DVT in trauma patients. The guidelines state the level of evidence associated with each specific risk factor according to the US Preventive Services Task Force ranking system. The evidence for patients with spinal cord injuries or spinal fractures is most compelling, with Level 2 evidence that the following risk factors are associated with the development of DVT: older age, higher injury severity score (ISS), blood transfusion rate, long bone fractures, pelvic fractures and head injuries, severe chest injuries and the requirement for mechanical ventilatory support (Table 2).8
Pathogenesis of DVT in major trauma

In 1856, Rudolf Ludwig Karl Virchow proposed a principle for delineating the pathogenesis of venous thrombosis.9 This came to be known as Virchow’s Triad. The theory postulates that vascular endothelial injury, alterations in the constitution of the blood, and alterations in venous blood flow or stasis may precipitate thrombus formation. Whilst the pathogenesis of DVT in major trauma is a highly complex, multifactorial process, involving both acquired risk factors and genetic pre-disposition,10 the principle of Virchow’s triad remains a valid concept (Figure 1).

Venous stasis

Impairment of the usual laminar flow of blood through the venous system can occur in a number of ways. Venous obstruction, increased venous pressure, increased blood viscosity and venous dilation may all cause stasis.6 Immobilization secondary to spinal protection, limb stabilization, anaesthesia, pain or functional impairment will diminish the ‘calf pump’ and contribute to stasis.11 Inability to stand means that the pedal venous pump, triggered on weight bearing through the plantar arch, is abolished.12 Venous stasis may also be encouraged by the inability of the immobile patient to weight bear. When venous stasis does occur, activated clotting factors can accumulate locally, leading to a prothrombogenic state.13 Even if venous stasis can be avoided, local trauma may result in eddy currents and vortices within venous valve pockets that in turn may promote platelet deposition and thrombus formation.14

Vascular injury

Vascular endothelial Injury may result from direct trauma, low oxygen tension, thrombin release or cytokines (IL-1/TNF).6 If endothelial injury occurs, subendothelial cells are exposed to the circulating blood with expression of tissue factor (TF) that may also be produced by leukocytes attracted to the site of the vessel wall damage. Expression of Von Willebrand’s Factor and fibronectin results in platelet aggregation and complementary activation of the clotting cascade.10 Tissue damage may impede fibrinolysis, normally mediated by endothelial cell derived plasminogen activator inhibitor-1.15

Hypercoagulability

Although in the acute phase the significantly injured patient may develop a hypocoagulable state due to shock and iatrogenic fluid administration, once stabilized, trauma patients are prone to entering a state of hypercoagulability.16 Imbalanced activation of the clotting cascade appears to be the most important factor in the development of acute deep vein thrombosis.10 The clotting cascade is a complex pathway, which ultimately results in the formation of a cross-linked fibrin clot. Disruption of the endogenous coagulation or fibrinolytic systems may therefore contribute to a hypercoagulable state in the multiply injured patient. Tissue factor and markers of thrombin generation increase after trauma,16,17 whilst endogenous anticoagulants are reduced.18 Tissue plasminogen activator (tPA) activity has been found to be suppressed in the multiply injured trauma victim, thus leading to a state of hypofibrinolysis, which may in turn result in venous thromboembolism.19

The EAST practice management guidelines for the prevention of venous thromboembolism in trauma patients

Level I:

- Patients with spinal cord injuries or spinal fractures are at high-risk of venous thromboembolism following trauma

Level II:

- Older age is an increased factor for venous thromboembolism, but it is not clear at which age the risk increases substantially.
- Increasing injury severity score and blood transfusion appear to be associated with a high-risk of venous thromboembolism in single institution studies, but on meta-analysis these factors this effect did not reach significance.
- Likewise traditional risk factors such as long bone fractures, pelvic fractures or head injuries in many studies may constitute a high-risk patient population in single institution studies but on meta-analysis it did not prove of major significance.

Risk factors associated with VTE in trauma patients

- Age ≥ 40 years
- Pelvic fracture
- Lower extremity fracture
- Spinal cord injury with paralysis
- Head injury (abbreviated injury score ≥ 3)
- Ventilator days > 3
- Venous injury
- Shock on admission (BP < 90 mmHg)
- Major surgical procedure

Table 1

Table 2

Figure 1 Virchow’s triad.
PAI-1 and it is the post-traumatic increase in PAI-1, rather than direct tPA suppression, that is thought to result in hypercoagulability. Antithrombin III is synthesized in the liver, and is a glycoprotein inhibitor of thrombin, factor Xa and Xla and may be reduced in trauma.\(^1\) Protein C is an endogenous anticoagulant, inhibiting the activated clotting factors Va and VIIIa. Decreased levels of Protein C antigen have been demonstrated in patients immediately following multiple trauma.\(^2\) Von Willebrand Factor (vWF) is produced constitutively in endothelium, megakaryocytes and subendothelial connective tissue and binds factor VIII (thus preventing its rapid degradation in the circulation), facilitating platelet adhesion to endothelium and thus, formation of a platelet plug. In experiments with rat models with traumatic brain injuries, plasma vWF levels were significantly elevated when compared with controls, peaking at day 3 post-injury.\(^3\)

**Prevention of DVT in the trauma patient**

Without thromboprophylaxis, overall DVT rates in the multi-system trauma patient exceed 50%,\(^4\) making prevention a crucial part of trauma patient care. The diversity of methods of thromboprophylaxis may suggest that the optimum way of preventing DVT formation has not yet been established. Thromboprophylaxis can be broadly divided into pharmacological or mechanical modalities and inferior vena caval filters (Figure 2). While inferior vena caval filters do not prevent DVT, they can prevent the most significant complication of DVT — pulmonary embolism.

**Pharmacological anticoagulation**

All types of pharmacological thromboprophylaxis aim to prevent the formation of a clot either through the inhibition of formation of the platelet plug, or by preventing progression of the clotting cascade. The cascade and points at which the various pharmacological agents act is illustrated in Figure 3.

**Low dose unfractionated heparin (LDUH)**

Heparin was first discovered in 1916. It is a naturally occurring anticoagulant produced by mast cells and basophils that inhibits thrombin. It has been used extensively for DVT prophylaxis in the elective surgical setting. However, little evidence exists regarding the benefit of using LDUH for DVT prophylaxis in trauma.\(^5\) Indeed, doubt has been cast over the efficacy of prophylactic LDUH in the trauma patient.\(^6\) Furthermore, the risk of haemorrhage with LDUH has not been determined.\(^7\) In their evidence-based clinical practice guidelines, the American College of Chest Physicians (ACCP) highlight the fact that some studies show LDUH to be no more effective than no prophylaxis at all.\(^8\) LDUH may however, prove to be beneficial when used in conjunction with mechanical prophylaxis, especially in those patients with a high-risk of bleeding, in whom the option of protamine reversal may need to be considered.\(^9\) In such instances the LDUH and the additional prophylactic measures, for example pneumatic compression devices, are commenced together and used throughout the duration of the patient’s hospitalization.\(^10\)

**Low molecular weight heparins (LMWH)**

LMWH is synthesized from the de-polymerization of unfractionated heparin, reducing its size, charge and weight.\(^11\) Like unfractionated heparin, LMWH inhibits thrombin. In comparison to unfractionated heparin, LMWH has an increased bioavailability and half-life, with fewer incidences of heparin induced thrombocytopenia (HIT) and a more predictable dose-dependent response.\(^12\)

Despite the obvious pharmacological advantages of LMWH there is mixed evidence supporting their use over unfractionated heparin in trauma victims.\(^13\) Furthermore, whilst LMWH preparations are traditionally administered as non-weight adjusted doses, the altered pharmacokinetics experienced in severely injured patients may lead to a variable response to LMWH (as measured by anti-Xa levels).\(^14\) This would suggest that the principle of using non-weight adjusted doses of LMWH for thromboprophylaxis in trauma patients requires further analysis in the form of randomized trials.

LMWH can be administered once or twice daily. However, whilst twice daily injections of LMWH have been shown to be an effective means of thromboprophylaxis with few associated complications,\(^15\) the optimal dosing and frequency itself remains undetermined. There appears to be little difference in the incidence of DVT when once daily administration of LMWH is compared with twice daily dosing.\(^16\) Further large-scale trials are required before the dosing of LMWH can be standardized.

The timing of commencement and duration of prophylaxis with LMWH also remains unclear. Intuition might suggest that bleeding complications are more frequent the earlier anticoagulation is commenced after the initial injury and that clinicians should withhold anti-coagulant prophylaxis until they feel the risk of significant haemorrhage has subsided.\(^17\) However, there is little evidence to support this theory and guidelines produced by the ACCP suggest that all major trauma patients at risk of DVT should be commenced on LMWH within 36 h of the injury, assuming haemostasis has been achieved.\(^18\) If surgical management is to be considered, with the correct protocol, the trauma surgeon can “operate through” systemic thromboprophylaxis.\(^19\) This prophylaxis should be continued until hospital discharge and until the patient becomes fully mobile.\(^20\)

Many trauma surgeons tend to delay the commencement of LMWH in the presence of head injury, massive blood transfusion, or multiple medical co-morbidities.\(^21\) However, the only absolute contraindications to early commencement of LMWH...
DVT prophylaxis are intraocular haemorrhage, intracranial bleeding, incomplete spinal cord injury associated with paraspinal haematoma, ongoing uncontrolled bleeding and uncorrected coagulopathy. LMWH should not be used when epidural catheters are placed or removed (Table 3).

Clinicians may be concerned by the side effects associated with LMWH use. The rate of major bleeding associated with LMWH use in trauma patients is well documented, with a pooled incidence of 3.1% reported. However, when compared with other modalities of thromboprophylaxis, LMWH demonstrates equivalent bleeding rates. Heparin Induced Thrombocytopenia (HIT) is another risk associated with the use of LMWH. It is an immune-mediated condition that results in platelet aggregation, thrombocytopenia and potentially the development of arterial and venous thrombosis. It may manifest as thromboembolism (DVT/PE) or haemorrhage, and has been defined as occurring when the platelet count decreases inexplicably by more than 50%. Hence, together with the presence of HIT antibodies in the serum, platelet count can be utilized in the diagnosis of the condition. However, heparin induced thrombocytopenia is a rare complication of LMWH use, with a pooled rate of HIT reported as 0.4%. Although the risk of HIT is small, the prescribing clinician should regularly check an injured patient’s platelet level after commencement on LMWH for DVT prophylaxis.

Oral vitamin K antagonist anti-coagulants
Vitamin K antagonists are not commonly used as a means of thromboprophylaxis, as they come with several considerable disadvantages. They have a delayed onset of action, require regular laboratory monitoring, have effects that can be difficult and slow to reverse in the event of a surgical procedure, create concern about the risk of bleeding and cannot be used in patients with

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**Figure 3** The clotting cascade and points of action of chemical thromboprophylaxis.

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**Figure 3** The clotting cascade and points of action of chemical thromboprophylaxis.
Impaired gastrointestinal function. Furthermore, interaction with other medications may result in a prolonged or accentuated effect.

**Aspirin**
Aspirin has been reported as a useful adjunct to thromboprophylaxis following hip fracture, but is either not addressed or not recommended in contemporary thromboprophylaxis guidelines. Its use may be complicated by gastrointestinal side effects, allergy and post-operative haematoma formation. These risks, coupled with uncertainty regarding the dosage at which it can be effective, have prevented widespread use of aspirin as thromboprophylaxis in the trauma patient.

**New anticoagulant therapies**
The search is currently being conducted for agents with various combinations of increased efficacy, oral administration, and decreased side effect profiles.

**Synthetic pentasaccharides:** Fondaparinux is a non-heparin synthetic pentasaccharide that potentiates the antithrombin III mediated inhibition of factor Xa. Potential benefits over LMWH include once daily dosing and a reduced risk of heparin induced thrombocytopenia (HIT). Fondaparinux has been used for thromboprophylaxis in post-operative orthopaedic and abdominal surgery patients with good results, however it has yet to be used or trialled extensively in trauma patients.

**Direct thrombin inhibitors:** Hirudin has been shown to be more effective than low dose heparin and LMWH for the prevention of venous thrombosis in elective orthopaedic surgery. Another direct thrombin inhibitor, Dabigatran, has shown efficacy and safety levels similar to those of Enoxaparin. Direct thrombin inhibitors have yet to be used or trialled extensively in trauma patients.

**Inhibitors of activated factor V and activated factor VIII:** recombinant thrombomodulin, which modulates thrombin production by binding thrombin and activating Protein C, has been trialled as DVT prophylaxis in the elective orthopaedic environment with initially promising results. However, none of these new-generation medications have been trialled on a large-scale basis in trauma patients.

**Mechanical prophylaxis**
Mechanical prophylaxis can be utilized with ease and can be started early in trauma patients. Mechanical thromboprophylactic devices fall into one of two categories: compression devices and motion devices. Compression devices increase the velocity of blood flow through the venous system by narrowing the diameter of the blood vessel lumen whilst motion devices mimic the calf venous pump. Inferior vena caval filters do not prevent DVT but can prevent the most significant complication of DVT — pulmonary embolism.

**Compression devices**
**Graduated compression stockings:** the exact mechanism by which Graduated Compression Stockings (GCS) function is unknown. Some evidence suggests that GCS exert a circumferential graded pressure (~18 mmHg at the ankle to ~8 mmHg at the thigh — Figure 4), milking venous blood from distal to proximal. It is postulated that this effectively increases the velocity and volume of blood flow in the deep system thereby potentially preventing thrombosis. Within the significantly injured trauma population, however, no data currently exists on their efficacy.

**Intermittent pneumatic compression/sequential compression devices:** intermittent pneumatic compression (IPC) and sequential compression devices (SCDs) use an air pump to periodically and/or sequentially inflate and deflate bladders located within a sleeve that is fitted around an extremity. In the lower limb, the devices can be fitted around the calf or simply around the foot. The mechanism of action by which these compression devices work is debatable, although increased femoral vein blood flow velocity is likely. Furthermore, significant increases in the levels of tissue plasminogen activator-plasminogen activator inhibitor complex and lowered levels of plasminogen activator inhibitor-1 have also been noted, suggesting adjustment of the coagulation and fibrinolytic pathways.

The current evidence regarding the use of pneumatic compression in the trauma victim is contradictory and, as a result, the sole use of SCDs as a means of thromboprophylaxis in the multiply injured patient should be questioned.
have been shown to be significantly superior to venous foot pumps in preventing DVT in trauma patients, but overall there is a lack of supporting evidence for the use of IPCs in the traumatically injured patient. Poor compliance has been proposed as a reason for lack of effect: pneumatic compression devices have a short-lived antithrombotic effect and medical staff must ensure that patients are fully compliant with this prophylaxis in order to achieve the maximum desired effect. Thus the true benefits of SCDs and ICP devices in the multiple trauma patient remain unknown and they should be seen as an adjunct to, rather than the mainstay of, thromboprophylaxis.

Venous foot pumps: in the sole of the foot a venous plexus fills and empties by gravity and upon weight bearing, therefore increasing femoral blood flow without the aid of the muscle pump. The venous foot pump (VFP) mimics the action of weight bearing and has been shown to increase blood flow within the popliteal vein by 250%. The major advantage of VFPs over other forms of compression device is that they require access to the foot only; hence, they can potentially be used in patients with casts and external fixators. Furthermore, in patients who have casts or have had operations for traumatic lower extremity injuries, the use of VFPs has been shown to significantly decrease pain, swelling, and compartment pressure measurements in the affected limb. The exclusive use of venous foot pumps for preventing DVT after major trauma has been shown to be ineffective. However, if a clinician is reluctant to commence chemical prophylaxis early after trauma, the use of VFPs with a delayed commencement of LMWH can be as effective as early initiation of LMWH alone.

Complications of compression devices: compression devices are considered to be safer than chemical thromboprophylaxis, as they minimize the risk of bleeding-associated complications. Although the reported side effects are rare, they may be significant. Subcutaneous tissue perfusion may be impaired, especially in patients with peripheral vascular disease. Focal pressure can result in peroneal nerve palsy and the potentially disastrous complication of compartment syndrome has been reported in association with intermittent pneumatic compression devices, although there have been no such cases documented in trauma patients.

Motion devices

Muscle electrostimulation: electrical stimulation of the muscles of the lower limb can prevent venous stasis by mimicking the action of the muscle pump and increasing venous flow, with short-term electrical foot stimulation at least as effective as knee-high IPC in increasing popliteal and femoral blood flow velocity. Current evidence would suggest that muscle electrostimulation is not effective in decreasing DVT rates in major trauma patients.

Continuous passive motion: like muscle electrostimulation, mechanical devices that perform continuous passive motion (CPM) imitate muscle contractions, increasing venous flow and decreasing venous stasis. Venous stasis is a thrombotic risk factor identified by Virchow, hence, the absence of muscular contraction in the immobilized trauma patient may predispose these patients to DVT. Unless the site or severity of injury prevents its use, CPM seems to be a reasonable addition to a thromboprophylaxis regimen in high-risk patients who have sufficient joint range of motion to permit the repetitive flexion–extension cycle of the machine.

Inferior vena cava filters

Inferior vena cava filters do not prevent the formation of a deep vein thrombus. Instead, their function is to prohibit the most significant sequel of DVT, namely pulmonary embolus. They have been reported as preventing PE in the presence of established lower limb DVT in 98% of cases. The concept of interrupting the flow in the inferior vena cava (IVC) to prevent PE originated many years ago. Numerous surgical procedures were subsequently devised based upon this concept: interruption of the IVC with ligation, plastic clips, staples, and balloons, as well as femoral vein ligation, have all been utilized historically in an attempt to prevent PE.

Insertion and type of filter: filters are typically inserted in a percutaneous fashion via the femoral or internal jugular veins. A small number of designs may be inserted via the basilic vein in the antecubital fossa. The ideal position in most patients is in the infra-renal IVC, thus providing prophylaxis against infra-renal thrombosis as well as PE. Filters may be either permanent, which cannot be removed percutaneously, or non-permanent. Compared to permanent filters, which are not retrievable, non-permanent filters are becoming an increasingly attractive option. Non-permanent filters offer the prospect of immediate PE prophylaxis, but can be removed when necessary, helping to avoid the long-term complications associated with permanent filter insertion.

The indications for insertion of IVC filter in trauma patients are potentially wide-ranging. A specific set of recommendations regarding the insertion of IVC filters in the trauma patient have been published by the Eastern Association for the Surgery of Trauma (Table 4).

Contraindications to filter placement include patients in whom there is restricted access to the IVC, and in those who have a chronic IVC thrombosis.

Figure 5 Intermittent compression devices can be used in conjunction with graduated compression stockings.
Insertion of an IVC filter is an invasive procedure and as such has a number of recognized complications related to the initial insertion, such as vessel damage, and longer-term sequelae including filter migration, fracture, IVC thrombosis and recurrent DVT. However, with the high incidence of venous thromboembolism in trauma patients, coupled with the potential haemorrhagic complications associated with chemical thromboprophylaxis, there has been a rise in the use of IVC filters for PE prophylaxis in high-risk trauma patients. As with other modes of prophylaxis, the evidence for the use of IVC filters in trauma victims is contradictory. As a result of this ambiguity in evidence, together with their associations with both short and long term complications (Table 5), it is not recommended that IVC filters should be used as a routine means of prophylaxis against thromboembolism in trauma patients. Perhaps their use should be reserved for high-risk patients in whom both mechanical and pharmacological means of thromboprophylaxis are contraindicated. Where IVC filters are utilized, associated complications would suggest that their use should be discontinued if and when traditional means of thromboprophylaxis are no longer contraindicated.

A suggested thromboprophylaxis algorithm for trauma patients is displayed in Figure 6.

### Diagnosis and detection of DVT

The symptoms and signs of DVT may include localized tenderness along the course of the deep venous system, thigh and calf swelling, erythema, pitting oedema, unilaterally dilated superficial veins and pain on dorsiflexion of the ankle (Homan’s sign). However, as few as 1.5% of patients diagnosed with venography-confirmed DVT have such characteristics.

### Diagnostic tests

**Venography:** venography is the “gold standard” in DVT diagnosis. However, its use is often impractical in trauma patients, particularly those with soft tissue wounds of the extremities, significant lower limb swelling or long bone fractures. Furthermore, venography may be over-sensitive, detecting small valve cusp thrombi that are clinically insignificant, it may induce DVT and, although rare, may also be associated with allergic reactions and renal failure. The associated complications and logistical problems make it less attractive than non-invasive diagnostic modalities. As such, perhaps venography is best reserved for patients in whom other diagnostic tests are equivocal for the presence of DVT.

**Ultrasound:** duplex Doppler Ultrasound (DDU) has become a primary tool of DVT detection. It employs real time B-mode imaging in addition to Doppler ultrasound, providing two-D image information on venous anatomy, clot structure and venous flow. The accuracy of ultrasound in the detection of DVT in the non-trauma patient is well documented, with a specificity reaching more than 90%. However, when compared with venography, a sensitivity of only 62% was reported. In the asymptomatic high-risk trauma patient, significant oedema, cast and other immobilization devices can impede ultrasound visualization of the venous system. Therefore, it may be suggested that the primary value of duplex ultrasonography should be reserved for symptomatic patients only. However, as the sophistication of DDU and DDU training improves, surveillance scanning is a more feasible option in high-risk patients unable to receive prophylaxis.

**Magnetic resonance imaging (MRI):** MRI has demonstrated up to 91.5% sensitivity and 94.8% specificity for the detection of DVT. However, this modality is frequently not a practical choice for DVT diagnosis, particularly in ventilated trauma patients, those with pacemakers, metallic foreign bodies or with certain surgical or orthopaedic implants.
D-dimer: D-dimer is the final fragment of the enzyme-mediated breakdown of cross-linked fibrin and, as such, is a unique marker of fibrin degradation. Elevated levels of D-dimer may therefore be noted in any condition in which fibrin is formed and then degraded (Table 6). Therefore, numerous conditions including trauma can cause an elevated D-dimer level and therefore the specificity of this test in predicting DVT is as low as 23%, even in a cohort of non-trauma patients.59 In contrast, the negative predictive value is high in the presence of a normal D-dimer value. A negative D-dimer can be as diagnostically useful as a negative CT in excluding PE or a negative ultrasound in excluding DVT.60

Predictive score indices: a number of predictive tests exist to aid in the diagnosis of DVT, with the best known of these being the Wells score (Table 7). This score takes into account a patient’s signs, symptoms and risk factors to generate a likelihood score for the presence of DVT. If a patient has a high Wells score, this has been shown to reflect a high likelihood of DVT and indicates that definitive diagnostic imaging should be performed.61 It has been suggested that patients with a low Wells score and a negative ultrasound can safely be assumed to have had DVT excluded, whilst a low pre-test probability coupled with a negative D-dimer assay can identify those patients who do not require ultrasonography.62

The risk assessment profile (RAP) (Table 8) is another means by which an individual’s risk of DVT can be stratified. The RAP should be determined within 24 h of admission and examines four factors: underlying conditions, iatrogenic factors, injury-related factors, and age. Unlike the Well’s score, the RAP score is a tool that is designed to be used in adult trauma patients only.63 Patients with a high RAP score have been shown to be three times more likely to develop thromboembolism than those patients with a score of less than 5.22 Furthermore the RAP score has been reported to have a strong

**Figure 6** Multiple trauma victim DVT prophylaxis algorithm.

**Table 6**

<table>
<thead>
<tr>
<th>Conditions which cause elevated D-dimer levels</th>
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<tbody>
<tr>
<td>Thromboembolism</td>
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<td>Trauma</td>
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<tr>
<td>Thermal injury</td>
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<tr>
<td>Surgery</td>
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<tr>
<td>Cancer</td>
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<tr>
<td>Infections</td>
</tr>
<tr>
<td>Vascular disease (IHD, CVA, aortic aneurysm/dissection)</td>
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<tr>
<td>Chronic inflammatory diseases</td>
</tr>
<tr>
<td>Pregnancy</td>
</tr>
</tbody>
</table>

**Table 8**
negative predictive value, with no DVTs being detected amongst patients classified as low-risk with the RAP score, leading to the proposition that thromboprophylaxis and DVT screening protocols can be withheld in patients with a RAP score of less than 5. In contrast to these findings, one study found a DVT rate of 13.3% in patients classed as “low-risk” by the RAP scoring system, with regression analysis demonstrating a poor correlation between magnitude of score and incidence of DVT. Given the demonstrable variation in the predictive accuracy of RAP scoring, it would be impossible to recommend withholding thromboprophylaxis in all patients classified as “low-risk” with the RAP score, leading to the proposition that thromboprophylaxis and DVT screening protocols can be withheld in patients with a RAP score of less than 5.

Treatment of DVT in trauma

In 2008, the American College of Chest Physicians published a set of evidence-based clinical practice guidelines on antithrombotic therapy for venous thromboembolic disease. In the presence of confirmed DVT, the guidelines recommend the commencement of a vitamin K antagonist (VKA) with additional antithrombotic cover in the form of LMWH, unfractionated heparin or subcutaneous Fondaparinux until the INR is ≥2 for 24 h. IVC filters should be reserved for patients in whom acute DVT is confirmed, but anticoagulation is not possible. Formal anticoagulation should be commenced once the risk of bleeding has subsided.

Trauma patients’ risk factors for DVT are most often transient, and in such patients, VKA therapy should be continued for three months. Patients diagnosed with acute DVT should, where appropriate, be mobilized at the earliest possible opportunity.

Specific considerations

Isolated lower limb injuries (distal to knee): patients who sustain orthopaedic injuries have been reported to be at risk of developing DVT, perhaps due to the trauma itself, cast application, immobilization or subsequent surgery. The incidence of DVT in patients with isolated lower limb fractures who do not receive thromboprophylaxis can be as high as 45%, and the risk of DVT after Achilles tendon rupture may be at least as high as that following fracture. In some European countries, prophylaxis with LMWH has become commonplace in such patients. However, the lack of a clear, evidence-based protocol on thromboprophylaxis for patients with lower limb cast immobilization reflects the ambiguity in published data and it may be that there is no significant reduction in the incidence of DVT rates when LMWH is prescribed for thromboprophylaxis in lower limb injuries. Given the uncertainty as to whether LMWH reduces the rate of clinically significant thromboembolism in below knee injury, coupled with the recognized haemorrhagic complications associated with LMWH, there seems to be little evidence to support the routine use of chemical thromboprophylaxis in isolated below knee injuries. Patients who require a prolonged period of lower limb immobilization should therefore be stratified for DVT risk on an individual basis and local and/or national guidelines should be followed.

Pelvic and acetabular fractures: patients with pelvic trauma are at high-risk of DVT. The incidence of proximal deep vein thrombosis

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### The Wells score

<table>
<thead>
<tr>
<th>Clinical characteristics</th>
<th>Score</th>
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<tbody>
<tr>
<td>Active cancer (treatment within last 6 months or palliative)</td>
<td>1</td>
</tr>
<tr>
<td>Paralysis, paresis, or recent cast immobilization of lower extremities</td>
<td>1</td>
</tr>
<tr>
<td>Recently bedridden &gt;3 days, or major surgery requiring regional or general anaesthetic in past 12 weeks</td>
<td>1</td>
</tr>
<tr>
<td>Localized pain along distribution of deep venous system</td>
<td>1</td>
</tr>
<tr>
<td>Swelling of entire leg</td>
<td>1</td>
</tr>
<tr>
<td>Calf swelling &gt;3 cm compared to asymptomatic side (measured 10 cm below tibial tuberosity)</td>
<td>1</td>
</tr>
<tr>
<td>Pitting oedema confined to symptomatic leg</td>
<td>1</td>
</tr>
<tr>
<td>Collateral superficial veins (non-varicose)</td>
<td>1</td>
</tr>
<tr>
<td>Previous documented DVT</td>
<td>1</td>
</tr>
<tr>
<td>Alternative diagnosis at least as likely</td>
<td>−2</td>
</tr>
<tr>
<td>A score of 2 or higher indicates probability of DVT is likely</td>
<td></td>
</tr>
<tr>
<td>A score of less than 2 indicates probability of DVT is unlikely</td>
<td></td>
</tr>
<tr>
<td>In bilateral leg symptoms, the more symptomatic leg is used</td>
<td></td>
</tr>
</tbody>
</table>

#### Table 7

#### The risk assessment profile score

<table>
<thead>
<tr>
<th>Clinical characteristic</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Underlying condition</td>
<td></td>
</tr>
<tr>
<td>• Obesity</td>
<td>2</td>
</tr>
<tr>
<td>• Malignancy</td>
<td>2</td>
</tr>
<tr>
<td>• Abnormal coagulation</td>
<td>2</td>
</tr>
<tr>
<td>• History of thromboembolism</td>
<td>3</td>
</tr>
<tr>
<td>Iatrogenic factors</td>
<td></td>
</tr>
<tr>
<td>• Femoral Venous Line</td>
<td>2</td>
</tr>
<tr>
<td>• Transfusion &gt;4u</td>
<td>2</td>
</tr>
<tr>
<td>• Operation &gt;2 h</td>
<td>2</td>
</tr>
<tr>
<td>• Major Venous Repair</td>
<td>3</td>
</tr>
<tr>
<td>Injury-related factors</td>
<td></td>
</tr>
<tr>
<td>• Chest AIS&gt;2</td>
<td>2</td>
</tr>
<tr>
<td>• Abdomen AIS&gt;2</td>
<td>2</td>
</tr>
<tr>
<td>• Head AIS&gt;2</td>
<td>2</td>
</tr>
<tr>
<td>• Spinal fractures</td>
<td>3</td>
</tr>
<tr>
<td>• GCS &lt;8</td>
<td>3</td>
</tr>
<tr>
<td>• Severe lower extremity fracture</td>
<td>4</td>
</tr>
<tr>
<td>• Pelvic fracture</td>
<td>4</td>
</tr>
<tr>
<td>• Spinal cord injury</td>
<td>4</td>
</tr>
<tr>
<td>Age</td>
<td></td>
</tr>
<tr>
<td>• 40, &lt;60</td>
<td>2</td>
</tr>
<tr>
<td>• 60, &lt;75</td>
<td>3</td>
</tr>
<tr>
<td>• ≥75</td>
<td>4</td>
</tr>
</tbody>
</table>

(AIS — Abbreviated Injury Score; GCS — Glasgow Coma Scale).
may be as high as 35% in patients with pelvic trauma, with PE occurring in 2–10% of patients. 76 Given the potential frequency of DVT in this patient cohort, early commencement of LMWH should be considered. 83,70 The presence of a retroperitoneal haematoma in pelvic fractures is not a contraindication to commencement of chemical thromboprophylaxis, presuming that there is nothing to suggest ongoing haemorrhage. 23 For detection of DVT in this high-risk group, the trauma clinician should consider surveillance screening with serial duplex ultrasonography, 71 particularly in those patients who are not able to receive optimal chemoprophylaxis. 23 It should be remembered that ultrasound may miss a proportion of DVTs that originate within the pelvis and as such alternative methods of diagnosis may need to be considered. 72

**Burns victims:** the physiological changes that occur in burns patients would appear to place them at great risk of DVT, as all elements of Virchow’s triad are met. A hypercoagulable state may be induced by dehydration, extended periods of immobility, repeated wound coverage procedures and the insertion of numerous venous lines. Platelet count, fibrinogen, and factors V and VIII can all be dramatically increased, 75 whilst antithrombin III and protein C are decreased following thermal injury. 74 Although the incidence of VTE in thermally injured patients may be as low as 2.9% in the absence of thromboprophylaxis, 75 contemporary figures suggest that thermally injured patients are at much greater risk of DVT. 76 However, there is little high-quality evidence regarding the incidence of DVT in burns patients. The efficacy of thromboprophylaxis in this group remains unexplored and recommendations are based on extrapolations from other patient groups. In burns patients with additional risk factors for DVT, LMWH or LDUH should be commenced as soon as it is safe to do so. In patients in whom the bleeding risk is high, mechanical thromboprophylaxis should be utilized if the burn pattern permits. 23

**Paediatric and adolescent trauma patients:** to date, no prospective randomized study exists examining the need for thromboprophylaxis in younger trauma victims but limited data would suggest that the incidence of DVT in paediatric and adolescent trauma patients is extremely low, even in the absence of thromboprophylaxis. 77 Given the complications associated with thromboprophylaxis, it is therefore recommended not to routinely use thromboprophylaxis in this group. Despite this, a survey of trauma management practices demonstrated that 13% of centres often or always use LMWH for thromboprophylaxis in 11–15 year-olds. 78 Beyond patients who fall into the high-risk category (ISS ≥ 25, GCS ≤ 8, or spinal cord injury), currently there would seem to be little rationale to support this practice.

**Head injury:** significant head injury is a well-described and independent risk factor for DVT. 22,27 The incidence of DVT in traumatic head injury in the absence of prophylaxis is estimated to be 20%. 79 Various methods of thromboprophylaxis have been shown to successfully decrease the risk of VTE in head injury. Clinicians who are reluctant to commence pharmacological prophylaxis in the presence of head injury can be reassured by studies demonstrating mechanical thromboprophylaxis devices to be effective in preventing DVT in traumatic brain injury (TBI) patients, when compared with no prophylaxis at all. 79 Given the potential for LMWH to exacerbate the consequences of any traumatic intracranial haemorrhage, clinicians may be wary of commencing chemical thromboprophylaxis. Whilst LMWH use in TBI may be effective and safe, 80 one recent retrospective analysis of 342 patients with TBI reported that pharmacological thromboprophylaxis was associated with a 1.3-fold increase in the risk of intracranial haemorrhage (ICH) progression in individuals who already demonstrate early progression of a bleed. 81 If head injury is associated with intracranial haemorrhage, the decision to start LMWH at the 24-h mark does not provide a significant advantage 82 and it is important that patients with traumatic head injury undergo relevant and adequate imaging to ensure that there is no evidence of ongoing intracranial haemorrhage before commencing LMWH later on.

The evidence concerning the efficacy of thromboprophylaxis in traumatic brain injury is frequently contradictory. As such, in one of the most comprehensive evidence-based publications to date, “Guidelines for the Management of Severe Traumatic Brain Injury”, 83 no level 1 or level 2 recommendations could be made. Level 3 recommendations included: use of graduated compression stockings and/or intermittent compression devices until patient is ambulatory; LMWH or LDUH should be used in combination with mechanical prophylaxis, (with increased risk for expansion of intracranial haemorrhage). The authors caveat these guidelines by stating that there is insufficient data to support recommendations regarding preferred agent, dose, or timing of commencement of pharmacological prophylaxis for DVT.

Delaying the initiation of prophylaxis may be associated with increased risk of DVT, 71 whilst the use of anticoagulation prophylaxis in the presence of intracranial haemorrhage may lead to clinically significant progression of the TBI. 82

**Spinal cord injury:** published literature, including the EAST guidelines, highlight the evidence for spinal fractures and SCI as major risk factors for DVT. 9 Without prophylaxis, patients with SCI are reported to have one the highest incidences of DVT amongst all hospitalized groups: in Geerts et al.’s 1994 landmark study, 7 trauma patients were not given thromboprophylaxis and bilateral contrast venography was performed 14–21 days after admission. In this study, the small cohort of patients with SCI had a frequency of DVT of 17/25 (68%) with the odds ratio of DVT in SCI calculated at 8.59 (95% C.I).

Once again, the evidence supporting the use of chemoprophylaxis is mixed. There is evidence of successful use of both unfractionated heparin 84 and LMWH in SCI, 21 whilst others report equivalent safety and efficacy of LMWH and UFH in preventing DVT in SCI patients. 85 However, even with the use of pharmacological thromboprophylaxis, rates of DVT can be as high as 66% in SCI. 24

The ambiguity in the available evidence surrounding thromboprophylaxis was reflected in a 2002 survey of the 13 regional and national spinal injury referral centres within the British Isles, which reported a wide variation in the method of thromboprophylaxis used amongst these centres. 86 Attempts have been made to standardize the thromboprophylactic regime in SCI patients. Recently published guidelines from NICE recommend that a combination of mechanical and chemical (either LMWH or low dose UFH) thromboprophylactic methods should be used. 87 However, no specific combination of these modalities is
suggested. Both ACCP and EAST guidelines recommend the use of LMWH to be commenced as soon as is safe to do so after injury. In contrast to NICE, neither endorses the addition of GCS or IPC to this chemical prophylaxis, advising that mechanical prophylaxis should be reserved for patients in whom anticoagulation is contraindicated because of high bleeding risk early after injury. The specific complication that may preclude anticoagulation in SCI patients is that of incomplete SCI associated with suspected or proven spinal haematoma. This complication should be ruled out at an early stage by review of MRI and/or CT scans performed as part of the initial SCI work-up. In patients in whom chemical prophylaxis is delayed, screening for DVT with ultrasound could be considered.

Venous thromboembolism may also occur during the rehabilitation phase after a SCI, and hence the continuation of ultrasound could be considered. When chemical prophylaxis is delayed, screening for DVT with scans performed as part of the initial SCI work-up. In patients in whom chemical prophylaxis is delayed, screening for DVT with ultrasound could be considered. However, with blunt splenic injury, the early use of LMWH in trauma is not associated with an increased rate of blood transfusion requirements or an increased rate of failure of non-operative management. Likewise, early commencement of LMWH after significant blunt hepatic injury is also reported to be safe and delaying thromboprophylaxis can increase the risk of thrombosis, without reducing the need for transfusion or operative therapy. Therefore, in the absence of ongoing bleeding, LMWH can be commenced for thromboprophylaxis, even if there is contusion or laceration of the spleen, liver or kidneys.

**Blunt abdominal injury:** as with traumatic brain injury, clinicians may defer from early administration of chemical thromboprophylaxis in patients with solid organ injury because of a perceived risk of haemorrhage. However, with blunt splenic injury, the early use of LMWH in trauma is not associated with an increased rate of blood transfusion requirements or an increased rate of failure of non-operative management. Likewise, early commencement of LMWH after significant blunt hepatic injury is also reported to be safe and delaying thromboprophylaxis can increase the risk of thrombosis, without reducing the need for transfusion or operative therapy. Therefore, in the absence of ongoing bleeding, LMWH can be commenced for thromboprophylaxis, even if there is contusion or laceration of the spleen, liver or kidneys.

**Conclusion**

It has long been recognized that the severely injured patient is at significant risk of VTE. The pathogenesis of thrombus formation may be explained according to Virchow’s triad — blood vessel damage, alteration in blood constituents and venous stasis. Trauma victims may fulfill all three requisites of this classic triad. Hence, DVT is a major cause for concern amongst multiple trauma victims owing to the potentially fatal consequences associated with PE.

Thromboprophylaxis is therefore at the forefront of sound and appropriate clinical management in trauma patients once they have been stabilized. This fact is reflected in the large volume of studies, reviews and guidelines that have been written on the subject. Despite this, however, doubt remains regarding the most effective and appropriate form of thromboprophylaxis in major trauma victims. There exists a lack of unanimity in current research, together with a shortfall in prospective studies exploring prophylaxis in this patient cohort. Perhaps this is representative of the fact that trauma encompasses a large number of mechanisms of injury, and as a result, patients may suffer a huge variety of injuries. The diverse nature of injuries sustained by major trauma victims dictates that no single thromboprophylaxis protocol can be applied to this cohort of patients.

Currently however, unless contraindicated, LMWH should form the mainstay of DVT prophylaxis — a fact reiterated in published guidelines (notably, ACCP, EAST and NICE). The dose and timing of commencement of LMWH are controversial. Mechanical prophylaxis should be strongly considered, either as an adjunct to chemical thromboprophylaxis or in patients in whom chemical thromboprophylaxis is contraindicated. Clearly the exact mode of mechanical prophylaxis must be tailored according to the individual’s pattern of injuries. If all other means of prophylaxis are contraindicated, placement of a VCF may be appropriate in high-risk patients who are likely to be immobilized for a prolonged period of time.

Evidently, there is a paucity of high-quality, randomized prospective studies exploring prophylaxis in major trauma patients. As a result, it is possible that we are under-using alternative therapies that may prove to be effective in managing the polytrauma victim. Future randomized controlled trials will play a vital role in addressing this shortfall and it is likely that we will regularly see the introduction of new or updated management protocols. Until such time, it is impossible to produce a universal guideline for all patients and clinicians are therefore encouraged to use their clinical expertise to adapt the currently available protocols to address the needs of the individual trauma patient.

**REFERENCES**


42 Slavik RS, Chan E, Gorman SK, et al. Dalteparin versus enoxaparin for venous thromboembolism prophylaxis in acute spinal cord injury and


