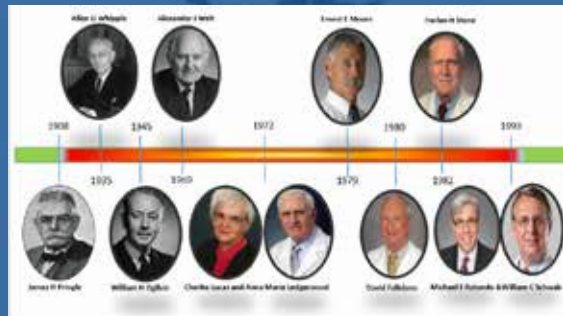




# KOSOVA JOURNAL OF SURGERY

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**Volume 10, Issue 1, Part II:  
Trauma and Critical  
Care Surgery Update:  
Expanding the Evidence  
April 2026  
ISSN: 3027-5008 (Online)  
ISSN: 3027-5016 (Print)**



# Venous Thromboembolism Prophylaxis in Trauma and Critically Ill Patients: A State-of-the-Art Evidence-Based Review

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### Abstract

#### Background:

Venous thromboembolism (VTE), comprising deep vein thrombosis (DVT) and pulmonary embolism (PE), is one of the most frequent and preventable causes of morbidity and mortality in trauma and critically ill patients. These populations present multiple overlapping risk factors, including endothelial injury, venous stasis, systemic inflammation, and prolonged immobilization that create a uniquely high-risk setting. Despite decades of research, variability in practice persists, and the optimal prophylaxis strategy remains debated. The aim of this state-of-the-art review is to provide an updated, evidence-based

review of effective thrombo-prophylaxis strategies in trauma and critically ill patients.

#### Methods:

We performed a state-of-the-art narrative review based on PubMed, Embase, and Cochrane searches (1990–August 2025), complemented by guideline repositories and expert consensus reports. Priority was given to randomized controlled trials, multicenter registries, systematic reviews, and international guideline statements. The review focuses on pharmacologic and mechanical prophylaxis, management of special populations, barriers to implementation, and future directions including anti-Xa-guided dosing, biomarkers, and artificial intelligence (AI).

**Results:**

Low molecular weight heparin (LMWH) has emerged as the pharmacologic gold standard, demonstrating superior efficacy and safety compared to unfractionated heparin (UFH). Early initiation (24–48 hours for most patients, and 24–72 hours post-stable imaging in traumatic brain injury) reduces VTE without significantly increasing bleeding risk. Mechanical prophylaxis remains essential when anticoagulation is contraindicated, and combined strategies (LMWH + intermittent pneumatic compression) provide synergistic benefit. Prophylactic inferior vena cava filters, once widely used, are no longer recommended except in rare cases of absolute contraindication to anticoagulation. Special populations such as spinal cord injury, pelvic fractures, burns, pregnancy, obesity, and cancer require tailored protocols.

**Conclusion:**

VTE prevention in trauma and critical illness patient is evolving from a uniform, protocol-driven approach to a precision-based model. Anti-Xa-guided dosing, biomarker-informed prophylaxis, AI-driven risk prediction,

extended post-discharge strategies, and digital health monitoring represent promising innovations.

**Keywords:** Venous thromboembolism, deep vein thrombosis, pulmonary embolism, trauma, critical illness, thromboprophylaxis, low molecular weight heparin, mechanical prophylaxis, artificial intelligence, precision medicine.

**Introduction**

Venous thromboembolism (VTE), which encompasses both deep vein thrombosis (DVT) and pulmonary embolism (PE), remains one of the leading preventable causes of in-hospital morbidity and mortality worldwide. In trauma and critically ill patients, prevention of VTE has become a cornerstone of patient safety, as these populations are exposed to a unique convergence of risk factors including tissue injury, systemic inflammation, prolonged immobilization, and frequent surgical or interventional procedures.

In the United States alone, VTE affects nearly 900,000 individuals each year, contributing to an estimated

**Table 1: Key Messages in VTE Prophylaxis for Trauma and Critically Ill Patients**

| Domain                           | Key Points   |
|----------------------------------|--|
| <b>Epidemiology</b>              | VTE is common and preventable; without prophylaxis, up to 60% of trauma/ICU patients develop DVT. PE remains a leading cause of preventable in-hospital death.   |
| <b>Pharmacologic Prophylaxis</b> | LMWH is superior to UFH in efficacy and safety. Early initiation (24–48 h in most patients; 24–72 h post-stable imaging in TBI) reduces VTE without excess bleeding.   |
| <b>Precision Dosing</b>          | Anti-Xa-guided or weight-based LMWH dosing is recommended in obese, hypermetabolic, or renally impaired patients to ensure efficacy and safety.  |
| <b>Mechanical Prophylaxis</b>    | IPC is the most effective device; GCS are less effective and often contraindicated (e.g., burns, fragile skin). NMES may serve as adjunct when mobilization is not possible.   |
| <b>Dual Prophylaxis</b>          | Combination of LMWH + IPC provides greater protection than either alone; recommended for very high-risk patients (SCI, pelvic fractures, prolonged immobility).  |
| <b>IVC Filters</b>               | Routine prophylactic use is discouraged. Indicated only in patients with absolute contraindication to anticoagulation and high VTE risk. Retrieval within 30–60 days is essential.   |
| <b>Special Populations</b>       | <ul style="list-style-type: none"> <li>- <b>TBI:</b> Start LMWH 24–72 h after stable CT.</li> <li>- <b>Solid organ injury:</b> Early initiation (24–48 h) safe in stable patients.</li> <li>- <b>SCI:</b> Extended prophylaxis for 8–12 weeks.</li> <li>- <b>Burns:</b> Monitor anti-Xa; avoid cuffs on grafted/burned skin.</li> <li>- <b>Pregnancy:</b> LMWH preferred; continue 6 weeks postpartum if high risk.</li> <li>- <b>Cancer:</b> Higher risk; LMWH inpatient, consider DOACs post-discharge if stable.</li> </ul> |
| <b>Barriers</b>                  | Missed doses, variable institutional protocols, resource shortages (IPC devices, anti-Xa assays), and poor outpatient adherence.   |
| <b>Future Directions</b>         | Precision dosing, AI-driven risk prediction, biomarker panels, extended post-discharge prophylaxis, telemedicine, remote monitoring, and integration into learning health systems.   |

60,000–100,000 deaths annually<sup>1</sup>. The burden is particularly evident in trauma and intensive care unit (ICU) cohorts, where incidence rates range from 18% to 60% in the absence of prophylaxis<sup>2,3</sup>. Autopsy series further suggest that silent or undiagnosed PE may contribute significantly to unexplained mortality, underscoring the hidden impact of this condition<sup>4</sup>. In specific high-risk subgroups, such as patients with spinal cord injury or pelvic fractures, prospective multicenter data have reported baseline VTE rates exceeding 50% when chemoprophylaxis is not administered<sup>5–7</sup>.

In addition to clinical outcomes, the economic burden is significant. In the United States alone, annual costs associated with incident venous thromboembolism (VTE) exceed USD 7 to 10 billion, with readmissions alone accounting for over USD 256 million each year<sup>8</sup>. In Europe, hospitalizations related to VTE represent a cost of EUR 1.5–2.2 billion annually<sup>9,10</sup>. Beyond direct expenses, VTE prolongs hospitalization, delays rehabilitation, and exposes survivors to long-term sequelae such as post-thrombotic syndrome or chronic thromboembolic pulmonary hypertension (CTEPH), both of which compromise functional recovery and quality of life.

The risk–benefit balance of thromboprophylaxis in trauma and critically ill patients is uniquely complex. Acute injuries and surgical procedures elevate bleeding risk, often necessitating temporary suspension of anticoagulation. Meanwhile, the progression from early trauma-induced coagulopathy to later hypercoagulability creates a dynamic physiological environment in which both thrombotic and hemorrhagic hazards evolve over time<sup>11</sup>. This necessitates frequent reassessment of prophylaxis strategies during hospitalization.

Despite decades of research and multiple international guidelines, practice remains highly variable. The Eastern Association for the Surgery of Trauma (EAST), Western Trauma Association (WTA), American College of Chest Physicians (ACCP), American Society of Hematology (ASH), and the UK National Institute for Health and Care Excellence (NICE) all emphasize the importance of early prophylaxis when safe<sup>12–16</sup>. However, their recommendations diverge in key areas, including the preferred first-line agent (low molecular weight heparin vs. unfractionated heparin), the role of anti-Xa monitoring, optimal timing in traumatic brain injury or solid organ injury, and the duration of prophylaxis after hospital discharge. These discrepancies translate into marked heterogeneity across institutions and countries, reinforcing the need for

a comprehensive synthesis of current evidence.

The aim of this state-of-the-art review is therefore to provide an updated, evidence-based overview of effective thromboprophylaxis strategies in trauma and critically ill patients. By integrating data from landmark clinical trials, multicenter registries, systematic reviews, and international guidelines, we highlight both consolidated practices and emerging approaches, with a focus on tailoring interventions to patient-specific risk profiles.

## Methods

This state-of-the-art review was conducted through a structured search of PubMed, Embase, and the Cochrane Library, complemented by guideline repositories and reference lists of relevant articles. Search terms included venous thromboembolism, deep vein thrombosis, pulmonary embolism, trauma, critical illness, intensive care, and thromboprophylaxis. We prioritized evidence from randomized controlled trials, multicenter registries, meta-analyses, and international guideline statements published between 1990 and August 2025. Additional articles were included based on expert consensus relevance, particularly for emerging strategies such as anti-Xa monitoring, artificial intelligence–driven risk prediction, and digital health applications. The aim was not to perform a systematic review but rather to synthesize current knowledge, highlight controversies, and outline future directions in the prevention of VTE among trauma and critically ill patients. Table 1 summarises the main findings of the study

## 1. Pathophysiology and Risk Factors

### Pathophysiologic Basis of VTE in Trauma and Critical Illness

The development of venous thromboembolism (VTE) in trauma and critically ill patients is best understood through Virchow's triad: endothelial injury, venous stasis, and hypercoagulability. In these populations, all three elements are amplified, creating a uniquely high-risk environment. Endothelial injury stems not only from the primary trauma, fractures, and surgical interventions, but also from iatrogenic factors such as central venous catheterization. Disruption of the endothelial glycocalyx, reflected by elevated syndecan-1 levels, has been linked to systemic inflammation, endothelial dysfunction, and worse clinical outcomes, including increased mortality<sup>17,18</sup>. Venous stasis is promoted by prolonged immobilization, sedation, neurological deficits, pelvic or

long-bone fractures, and the use of external fixation devices. In the intensive care unit (ICU), additional contributors include mechanical ventilation, supine positioning, and vasopressor-induced vasoconstriction, all of which impair venous return<sup>6,18–21</sup>. Hypercoagulability is driven by systemic inflammation: cytokines such as interleukin-6 and tumor necrosis factor- $\alpha$ , along with complement activation, promote thrombin generation and fibrin deposition<sup>22,23</sup>. Together, these mechanisms establish a prothrombotic milieu far exceeding that of general medical inpatients.

### Dynamic Nature of Coagulation after Trauma

The coagulation profile of trauma patients evolves dynamically in a biphasic manner. In the immediate phase, many develop acute traumatic coagulopathy (ATC), characterized by hypocoagulability due to protein C pathway activation, hyperfibrinolysis, and clotting factor depletion<sup>17</sup>. Within 24–48 hours, however, most patients transition into a hypercoagulable state, with increased thrombin–antithrombin complex formation, impaired fibrinolysis, and stronger clot formation demonstrated on viscoelastic assays such as rotational thromboelastometry (ROTEM)<sup>21</sup>. This explains why trauma patients remain at significant risk for VTE even after the acute bleeding phase has resolved. An additional factor is acquired antithrombin (AT) deficiency, present in up to 30–50% of patients within the first week of injury. This condition reduces the efficacy of heparin-based prophylaxis and may necessitate dose adjustment or supplementation<sup>23,24</sup>. These temporal changes highlight the importance of repeated reassessment of coagulation status and prophylaxis adequacy during hospitalization.

### Risk Factors and High-Risk Populations

Certain trauma subgroups have been shown to carry particularly high VTE risk. A landmark study by Geerts et al. demonstrated an incidence of 62% in patients with spinal cord injury (SCI) and 61% in those with pelvic fractures when prophylaxis was withheld<sup>6</sup>. Later studies confirmed similarly high rates in patients with traumatic brain injury (TBI), long-bone fractures, and those requiring massive transfusion<sup>19,20,25,26</sup>. Even in non-trauma ICU cohorts, immobility, sepsis, indwelling catheters, and vasopressor therapy substantially increase thrombotic risk. The PROTECT trial reported a 5% incidence of symptomatic VTE despite prophylaxis in medical ICU patients<sup>27</sup>. Collectively, these data underscore that trauma and critical

illness define heterogeneous yet consistently high-risk populations, necessitating tailored prophylactic approaches that carefully balance thrombosis and bleeding risk.

### Risk Stratification Tools

Identifying which patients will derive the greatest benefit from intensified prophylaxis is a cornerstone of VTE prevention.

In trauma and ICU settings, the prevalence of risk factors often results in many patients being automatically categorized as “high risk,” which reduces the effectiveness of conventional assessment tools<sup>28</sup>.

The **Caprini Risk Assessment Model (RAM)** remains the most widely used general tool. Originally designed for elective surgical patients, it incorporates 31 weighted variables including age, BMI, cancer, immobility, and prior VTE. Higher Caprini scores correlate with increased VTE incidence in trauma patients as well<sup>28–30</sup>. Abbreviated versions with only 10 variables demonstrate similar predictive ability, making them more feasible in resource-limited or fast-paced settings<sup>31</sup>. A large systematic review confirmed that VTE risk rises sharply at Caprini thresholds  $\geq 7$ –11 across many surgical and medical specialties, trauma included<sup>32</sup>. However, in polytrauma cohorts, most patients exceed these thresholds, limiting its discriminatory power. Conversely, the Padua Prediction Score (PPS) is commonly used for medical inpatients and has demonstrated reasonable performance among nonsurgical ICU patients; however, it exhibits poor sensitivity in trauma cases<sup>33,34</sup>.

To address these gaps, trauma-specific models have been developed. The **Risk Assessment Profile (RAP)** was one of the first, combining injury site, comorbidities, surgical interventions, and immobilization. It correlated well with venographic DVT in early studies<sup>35</sup>. The **Trauma Embolic Scoring System (TESS)** incorporates age, Injury Severity Score (ISS), Glasgow Coma Scale (GCS), transfusion requirements, and central venous line presence; scores  $\geq 7$  predict high VTE risk, with multicenter validations showing moderate discriminatory ability (AUC  $\sim 0.74$ )<sup>35</sup>. The **Greenfield Risk Assessment Profile** uses similar variables, but its complexity and lack of EMR integration have limited use in contemporary practice<sup>36,37</sup>. The **Risk Assessment Profile for Trauma (RAPT)** integrates injury pattern, comorbidities, vital signs, and anticipated mobility, and has been validated in several U.S. trauma centers<sup>37</sup>.



ICU-specific models have also been explored, integrating immobility, sepsis, vasopressors, indwelling catheters, and illness severity (APACHE II, SOFA). In one multicenter study, adding biomarkers such as D-dimer and fibrinogen improved discrimination, raising the AUC from 0.71 to 0.79<sup>38</sup>. While nearly all ICU patients exceed prophylaxis thresholds, such models may help identify ultra-high-risk subgroups who require strategies like anti-Xa-guided LMWH dosing, combined pharmacologic plus mechanical prophylaxis, or extended prophylaxis duration<sup>39</sup>.

### Artificial Intelligence (AI)-Based Models

More recently, AI and machine learning have been applied to VTE risk prediction in trauma. He et al.<sup>40</sup> demonstrated that combining the Caprini score with EHR-derived data and using a LASSO-random forest model significantly improved prediction accuracy (AUC 0.799) compared with Caprini alone. Liu et al.<sup>41</sup> reported on a national multicenter model for thoracic trauma, which achieved AUROC 0.879 internally and 0.83 in external validation, with potential to reduce unnecessary VTE testing by >90%. A systematic review and pooled analysis by Chiasakul et al.<sup>42</sup> further confirmed that AI-based approaches (neural networks, SVMs, ensemble methods) consistently outperform conventional RAMs, with pooled AUC 0.79 versus 0.61, though the authors stressed the need for external validation and transparency.

### Thrombo-Bleeding Scores: Balancing Two Hazards

A critical challenge in prophylaxis for trauma and ICU patients is finding the right balance between the risk of thrombosis and the equally significant danger of bleeding. Most existing models focus on one dimension and in isolation. Yet trauma-induced coagulopathy (TIC) evolves in a biphasic pattern: initial hypocoagulability with bleeding risk, followed by a hypercoagulable state with high VTE risk<sup>43,44</sup>. This highlights the need for composite **thrombo-bleeding scores**.

The **Trauma-Associated Severe Hemorrhage (TASH) score** estimates the probability of massive transfusion—a surrogate for life-threatening bleeding—based on variables such as systolic blood pressure, hemoglobin, base excess, intra-abdominal fluid, fractures, tachycardia, and sex. It provides a graded risk scale from 0–28 and has demonstrated good discrimination

for transfusion needs<sup>45</sup>. The **Coagulopathy of Severe Trauma (COAST) score**, developed for prehospital use, incorporates variables such as entrapment, hypotension, hypothermia, and suspected intra-abdominal or pelvic injury. In large European validation cohorts, COAST scores  $\geq 3$  predicted acute traumatic coagulopathy with high specificity, though sensitivity was modest. Importantly, positive scores correlated with worse outcomes, including higher transfusion needs, greater surgical intervention, and higher mortality<sup>46</sup>.

The **PATCH trial** explored this balance further, testing prehospital tranexamic acid (TXA) in major trauma with suspected TIC. While TXA reduced 28-day mortality, it did not improve long-term functional outcomes, reflecting the difficulty of achieving a net clinical benefit when both bleeding and thrombosis risks coexist<sup>47,48</sup>.

The risk prediction model for VTE are summarized in table 2.

### Future Directions in Risk Stratification

The future likely lies in dynamic composite models that integrate both thrombotic and bleeding risks, incorporating clinical predictors, laboratory assays (D-dimer, fibrinogen, anti-Xa), and viscoelastic testing (TEG/ROTEM), with repeated reassessment during hospitalization. Advances in AI may allow these tools to continuously update as new patient data become available, offering real-time, individualized guidance. Such thrombo-bleeding scores could mark a pivotal step toward precision medicine in trauma and critical illness, ensuring that prophylaxis decisions weigh competing hazards holistically rather than in isolation.

## 2. Pharmacological Prophylaxis in Trauma and ICU Patients

Pharmacologic prophylaxis remains the cornerstone of VTE prevention in trauma and critically ill patients. Among available agents, **low molecular weight heparin (LMWH)** is generally favored over unfractionated heparin (UFH) because of its superior efficacy, more predictable pharmacokinetics, and lower risk of heparin-induced thrombocytopenia (HIT)<sup>49</sup>. Multiple cohort studies and meta-analyses have consistently shown lower rates of DVT and pulmonary embolism with LMWH compared to UFH, without a corresponding increase in bleeding complications<sup>50</sup>. Nevertheless, UFH retains a role in specific contexts, particularly in patients with severe renal

**Table 2:** Risk prediction models for VTE and bleeding in trauma and ICU patients

| Score / Model  | Type     | Population / Setting                     | Key Variables (examples, not exhaustive)  | Performance (where available)   | Strengths  | Limitations   |
|--|----------|--|---|---|--|---|
| <b>Caprini Risk Assessment Model (RAM)</b>                           | VTE      | Surgical inpatients; applied in trauma   | Age, BMI, prior VTE, cancer, immobility, CVC; 31 items (10-item abbreviated version available)  | Trauma cohorts c-stat $\approx 0.75$ ; abbreviated $\approx 0.75$   | Widely validated; easy bedside scoring; risk scales with score                     | In polytrauma most patients are “high-risk,” limiting discrimination; static snapshot         |
| <b>Padua Prediction Score (PPS)</b>                                  | VTE      | Medical inpatients; sometimes ICU        | Reduced mobility, cancer, prior VTE, recent surgery/trauma, acute infection   | Good in medical wards; variable in ICU  | Simple; validated outside surgery  | Poor sensitivity in trauma; not tailored to injury patterns                                   |
| <b>Greenfield Risk Assessment Profile (RAP / “Greenfield score”)</b> | VTE      | Trauma inpatients                        | Injury site (pelvis, spine), comorbidities, immobilization, operations, venous injury   | Early validation vs. venography; AUROC variably reported  | Trauma-specific; historically influential  | Complex; limited EMR integration; variable modern uptake                                      |
| <b>Trauma Embolic Scoring System (TESS)</b>                          | VTE      | Trauma inpatients                        | Age, ISS, GCS, $\geq 4u$ transfusion first 24h, central venous line   | Multicenter AUROC $\sim 0.74$   | Parsimonious; trauma-focused   | Not designed for bleeding; external performance varies  |
| <b>Risk Assessment Profile for Trauma (RAPT)</b>                     | VTE      | Trauma centers (US)                      | Injury patterns, comorbidities, vitals, anticipated mobility  | Validated; AUROC variably reported  | Practical for trauma workflows   | Many patients still “high-risk”; limited global validation                                    |
| <b>ICU-specific VTE models</b>                                       | VTE      | Mixed medical–surgical ICU               | Immobility, sepsis, vasopressors, CVC, APACHE II/SOFA; $\pm$ D-dimer, fibrinogen  | Adding labs improved AUROC from $\sim 0.71 \rightarrow \sim 0.79$   | Captures ICU-specific drivers; can be updated                                      | Nearly all ICU patients cross prophylaxis threshold; modest discrimination                    |
| <b>AI-based VTE models (ML/AI)</b>                                   | VTE      | Trauma, thoracic trauma, ICU             | EHR features (demographics, injury pattern, labs, imaging, hemodynamics) $\pm$ Caprini  | He et al. (trauma): AUC $\sim 0.80$ (LASSO+RF); Liu et al. (thoracic trauma): AUC 0.88–0.83 (internal/external); Systematic review mean AUC $\sim 0.79$ vs 0.61 for traditional | Better discrimination; dynamic updating; scalable with EMR                         | Need transparent reporting, external validation, bias/missing-data handling; generalizability |
| <b>TASH (Trauma-Associated Severe Hemorrhage)</b>                    | Bleeding | Severe trauma (massive transfusion risk) | SBP, Hb, base excess, intra-abdominal fluid, long-bone/pelvic fractures, HR, sex (0–28 pts)   | Good calibration and discrimination for MT  | Early, bedside prediction of hemorrhagic shock/MT                                  | No thrombosis component; not dynamic  |
| <b>COAST (Coagulopathy of Severe Trauma)</b>                         | Bleeding | Prehospital trauma                       | Entrapment, SBP $<100$ , hypothermia, suspected pneumothorax, pelvic/abdominal injury; extra points for SBP $<90$ or temp $<32^\circ\text{C}$ | European validation AUROC $\sim 0.63$ ; high specificity, low sensitivity   | Identifies patients with coagulopathy and worse bleeding outcomes; prehospital use | Modest sensitivity; region-specific derivation; not thrombo-specific                          |

|   |                        |  |   |   |  |   |
|---|------------------------|--|---|---|--|---|
| <b>BRSS (Bleeding Risk Scoring System for prophylactic anticoagulation)</b> | Bleeding               | Hospitalized trauma patients (in-hospital prophylaxis decisions) | Bedside factors reflecting hemorrhage risk (e.g., TBI/ICH, solid organ injury, coagulopathy indices, platelet count, ongoing bleeding/procedures) | Single-center retrospective; acceptable discrimination; external validation pending | Practical aid to tailor timing/intensity of prophylaxis                      | Emerging tool; variables/weights not yet universally standardized; no VTE dimension |
| <b>MTP (Massive Transfusion Protocol) triggers (institutional)</b>          | Bleeding (operational) | Trauma & ICU   | Shock index, lactate, Hb, SBP, clinician judgment   | Center-specific; not a formal AUROC   | Widely adopted; operationalizes rapid response                               | Heterogeneous criteria; not predictive of thrombosis                                |
| <b>Composite thrombo-bleeding models (emerging)</b>                         | Both                   | Trauma & ICU (concept/prototype)                                 | Combined clinical + lab (D-dimer, fibrinogen, anti-Xa) + viscoelastic (TEG/ROTEM); dynamic reassessment; AI-enabled                               | — (under development)   | Explicitly balances bleeding vs thrombosis; supports precision dosing/timing | Not yet validated; complexity and data needs may limit bedside deployment           |

impairment or in situations where rapid reversibility of anticoagulation is required<sup>51</sup>. Pharmacological prophylaxis is essential for preventing venous thromboembolism (VTE) in trauma and critically ill patients, however, several important issues remain unsettled, including the optimal timing for initiating prophylaxis, the most effective dosing strategies, and the appropriate duration of therapy. These uncertainties highlight the need for individualized approaches to optimize outcomes while minimizing the risks of both thrombosis and bleeding complications.

### The timing of prophylaxis initiation

Evidence supports starting anticoagulation within 24 hours of admission or surgical hemostasis, provided that active bleeding has been controlled<sup>50</sup>. Early initiation has been associated with significant reductions in DVT rates, including in patients with traumatic brain injury (TBI) and solid organ injury, when guided by repeat imaging and ongoing clinical stability<sup>52,53</sup>. Conversely, delaying prophylaxis beyond 48–72 hours markedly increases the risk of VTE<sup>54</sup>.

### Dosing strategies

Dosing remain an area of ongoing debate. Standard fixed-dose regimens, such as enoxaparin 30 mg BID, may provide insufficient anticoagulant effect in obese or hypermetabolic trauma patients. Weight-based protocols (0.5 mg/kg BID) have been shown to improve attainment of prophylactic anti-Xa levels and to reduce breakthrough VTE<sup>55</sup>. The CLOTT-1 registry confirmed

that weight-based enoxaparin more reliably achieved target ranges without increasing bleeding risk<sup>56</sup>. Similarly, anti-Xa-guided titration protocols have demonstrated the ability to individualize dosing and reduce subtherapeutic prophylaxis<sup>57–59</sup>. Despite these advantages, widespread adoption is limited by the costs of monitoring, the requirement for laboratory infrastructure, and the lack of universally standardized thresholds.

### The duration of prophylaxis

The duration of prophylaxis remains less standardized. Most trauma guidelines recommend continuing until the patient is fully ambulatory or discharged, yet certain high-risk populations—including those with spinal cord injury (SCI), pelvic fractures, or severe TBI—may benefit from extended prophylaxis lasting 4–12 weeks after discharge<sup>65–67</sup>. Evidence from orthopedic surgery strongly supports extended prophylaxis up to 35 days, and similar strategies are being increasingly explored in trauma patients. However, adherence to post-discharge regimens remains suboptimal, with compliance rates often below 60%, underscoring the importance of patient education and simplified administration protocols.

### Tailoring Prophylaxis for Special Conditions

Special populations require careful tailoring of prophylaxis. In obese patients, standard dosing often leads to subtherapeutic anti-Xa levels, and therefore weight-based or escalated dosing is recommended<sup>55–57</sup>. In contrast, patients with renal insufficiency exhibit

reduced clearance of LMWH, warranting dose adjustment or substitution with UFH<sup>50</sup>. For patients with TBI, multiple studies support initiation of LMWH within 24–48 hours after a stable CT scan, demonstrating reduced VTE without increased risk of hemorrhagic progression<sup>52</sup>. Similarly, in solid organ injuries, early LMWH initiation following confirmation of hemostasis by imaging has been shown to reduce thrombotic events without increasing the likelihood of failed non-operative management<sup>52</sup>.

### Professional society guidelines

Professional society guidelines converge on the primacy of LMWH when not contraindicated, while differing in specific recommendations. The WTA and EAST recommend enoxaparin 30 mg BID, with escalation or monitoring in selected high-risk groups<sup>12,13,52</sup>. The ACCP supports either LMWH or UFH, with mechanical methods reserved for situations where anticoagulation is

contraindicated<sup>14,53</sup>. The ASH emphasizes individualized risk assessment, balancing thrombosis prevention against bleeding hazards, and the NICE guidelines go further in recommending extended prophylaxis duration in defined high-risk trauma populations<sup>15,16</sup>.

Looking forward, the concept of precision prophylaxis is gaining traction. Future strategies are likely to rely on anti-Xa-guided or weight-adjusted LMWH dosing, supplemented by point-of-care assays for real-time adjustment. Integration of these approaches with electronic medical records (EMRs) could enable automated, patient-specific dosing algorithms. Moreover, advances in artificial intelligence and machine learning offer the potential to dynamically integrate demographics, injury patterns, laboratory results, and imaging data into risk models, providing continuous and individualized optimization of anticoagulant prophylaxis<sup>44</sup>.

Table 3 summarises pharmacologic prophylaxis strategies in trauma and ICU patients.

**Table 3:** Pharmacologic prophylaxis strategies in trauma and ICU patients

| Strategy                                  | Typical dosing (examples)   | Monitoring  | VTE prevention (summary)  | Bleeding / safety   | Pros / Cons & Best use  |
|---|---|---|---|---|---|
| <b>UFH (subcutaneous)</b>                 | 5,000 U q8–12h  | No routine anti-Xa; platelet counts for HIT                                 | Less effective than LMWH for DVT/PE prevention in trauma                                    | Similar major bleeding; higher HIT risk vs LMWH                       | <b>Pros:</b> short half-life, easily reversible, usable in severe renal impairment. <b>Cons:</b> lower efficacy, more injections, variable levels           |
| <b>LMWH fixed-dose (e.g., enoxaparin)</b> | 30 mg q12h (North America); 40 mg q24h (some protocols)                             | Not routine; consider anti-Xa in obesity, ARC, pregnancy, renal dysfunction | Superior to UFH for VTE reduction without excess bleeding                                   | Comparable bleeding to UFH; lower HIT risk                            | <b>Pros:</b> predictable PK, better efficacy, fewer injections. <b>Cons:</b> renally cleared (adjust/avoid in severe impairment), may underdose obesity/ARC |
| <b>LMWH weight-based / escalated</b>      | Enoxaparin <b>0.5 mg/kg q12h</b> (or step-up to 40 mg q12h in obesity)              | Anti-Xa peaks to confirm exposure (see footnote)                            | Higher attainment of target anti-Xa and <b>lower VTE</b> vs fixed dose in high-risk cohorts | No increase in major bleeding reported in registry/center series      | <b>Pros:</b> individualizes dose for obesity/ARC. <b>Cons:</b> needs lab + workflow; thresholds vary across centers   |
| <b>Anti-Xa-guided LMWH protocol</b>       | Start standard dose, <b>titrate</b> in 10 mg (or weight-based) increments to target | <b>Peak anti-Xa</b> after steady state; repeat after dose changes           | Reduces sub-therapeutic prophylaxis; several series show <b>fewer VTE</b>                   | Generally <b>no increase</b> in bleeding with protocolized monitoring | <b>Pros:</b> precision dosing; addresses PK variability. <b>Cons:</b> monitoring costs; requires protocolization/education                                  |
| <b>Renal impairment pathway</b>           | Prefer UFH; or reduced-dose LMWH with monitoring                                    | Anti-Xa (if LMWH used), renal function                                      | Maintains prevention when LMWH contraindicated  | UFH reversible; bleeding risk tied to overall illness/sepsis          | <b>Pros:</b> safety in low CrCl. <b>Cons:</b> less efficacious than LMWH; HIT vigilance   |

*Abbreviations:* UFH, unfractionated heparin; LMWH, low molecular weight heparin; ARC, augmented renal clearance; HIT, heparin-induced thrombocytopenia; PK, pharmacokinetics.

## Key points

- Initiation: start pharmacologic prophylaxis within 24 h of admission or hemostasis when bleeding is controlled (earlier reduction in VTE, including TBI/solid-organ injury with stability). Delays >48–72 h increase risk.
- Anti-Xa targets (prophylaxis): commonly peak 0.2–0.4 IU/mL (draw ~4 h after the 3rd–4th dose); some centers track trough  $\geq 0.1$  IU/mL in very high-risk patients.
- Obesity / ARC: favor weight-based or anti-Xa-guided strategies.
- Severe renal impairment (e.g., CrCl <30 mL/min): consider UFH over LMWH, or reduced-dose LMWH with monitoring.

## 3. Mechanical Prophylaxis and Adjunctive Measures

When pharmacologic prophylaxis must be delayed or is contraindicated, mechanical strategies become a vital component of VTE prevention in trauma and critically ill patients. These modalities, most frequently intermittent pneumatic compression (IPC) devices, and to a lesser extent graduated compression stockings (GCS) or venous foot pumps, reduce venous stasis and stimulate fibrinolysis by applying cyclical or continuous pressure to the lower limbs<sup>69</sup>.

Among the available options, IPC has been the most extensively studied. A Cochrane meta-analysis across surgical and trauma cohorts demonstrated that IPC reduces the risk of DVT by approximately 60% compared with no prophylaxis, although its protective effect remains less potent than that achieved with LMWH<sup>70</sup>. Trauma-specific registry data confirm that IPC lowers the incidence of asymptomatic distal DVT, but protection against PE is limited. Comparative analyses consistently show LMWH to be superior as a single modality, yet IPC confers meaningful added benefit when used in combination with anticoagulation<sup>12,26</sup>.

In clinical practice, the effectiveness of mechanical methods is often compromised by compliance challenges. Observational studies in intensive care units indicate that adherence rates typically fall below 60%, with disruptions arising from patient discomfort, device alarms, conflicts with nursing care, or other pressing clinical priorities<sup>71</sup>. Contraindications such as lower extremity fractures, extensive soft-tissue injury, severe peripheral arterial disease, or significant edema further restrict their applicability. GCS have demonstrated limited efficacy in

trauma patients, with several trials showing no significant reduction in VTE incidence compared to controls<sup>71</sup>. Concerns over skin breakdown, limb ischemia, and poor tolerance have contributed to their progressive decline in clinical use.

## Dual-prophylaxis approach

The strongest evidence now supports a dual-prophylaxis approach, combining IPC with LMWH. Meta-analyses indicate that this strategy provides superior protection compared to either method alone, with reductions in asymptomatic DVT and possible trends toward decreased PE, particularly in polytrauma patients, those with spinal cord injury, pelvic fractures, or prolonged immobility<sup>70–72</sup>. Physiologically, this combined approach is compelling: IPC mitigates venous stasis, while LMWH addresses trauma-induced hypercoagulability. Reflecting this, both the EAST and WTA guidelines endorse dual prophylaxis in very high-risk trauma patients whenever feasible<sup>12,13</sup>. Crucially, IPC should be viewed as a bridge or adjunct, not as a replacement, and must not delay initiation of pharmacologic prophylaxis once bleeding risk is controlled.

## Where does Inferior vena cava filter stand?

The evidence supporting the use of prophylactic filters in trauma remains inconclusive. Early observational studies indicated that high-risk patients who could not receive anticoagulation had lower rates of pulmonary embolism (PE). However, more recent systematic reviews and registry analyses have failed to show a clear survival advantage, with some reports even indicating an increased incidence of deep vein thrombosis (DVT) due to altered venous flow dynamics<sup>74</sup>.

For therapeutic purposes, filters may be appropriate for patients with acute proximal DVT or PE when anticoagulation is contraindicated, as they can help prevent embolization. However, it is important to note that these filters do not eliminate existing clot burdens. Reported complications vary widely, including early issues such as access-site thrombosis, misplacement, and caval perforation. Long-term complications can include filter migration, fracture, recurrent DVT, and chronic caval thrombosis, with occlusion rates reaching as high as 22% in extended follow-up studies<sup>75</sup>. To this end, current guidelines are unanimous in discouraging routine prophylactic IVC filter placement. Both EAST and WTA recommend their use only in exceptional circumstances, namely, very high-risk trauma patients with absolute contraindication to anticoagulation for

at least seven days<sup>12,13</sup>. The ACCP strongly advises against prophylactic filters in patients without acute VTE, restricting their use to those with acute proximal DVT or PE and absolute contraindications to anticoagulation<sup>14</sup>. The Society of Interventional Radiology (SIR) echoes this stance, stressing the importance of timely retrieval, ideally within 30–60 days, to minimize device-related complications<sup>76</sup>. In all cases, insertion should be accompanied by a clearly documented retrieval plan, with reassessment for removal and resumption of anticoagulation as soon as clinically feasible.

Beyond pharmacologic and mechanical prophylaxis, several supportive measures are essential to a comprehensive VTE prevention strategy. Early mobilization remains one of the most effective and cost-free interventions, reducing venous stasis and enhancing endogenous fibrinolysis. In ICU patients with multiple lines, meticulous vascular access care is critical to minimize catheter-related thrombosis. Correcting modifiable prothrombotic factors, such as sepsis, dehydration, and immobilization, further reduces overall thrombotic risk<sup>11,12,26</sup>.

### Emerging Experimental Measures

An emerging but experimental adjunct is antithrombin supplementation. Acquired antithrombin deficiency, which occurs in up to 30–50% of trauma patients during the first week of hospitalization, may impair the efficacy of heparin-based prophylaxis. Although biologically plausible, current evidence does not support routine supplementation outside clinical trials<sup>77</sup>.

Finally, neuromuscular electrical stimulation (NMES) has gained interest as a non-invasive adjunct to mimic the physiologic benefits of active mobilization. By delivering low-frequency impulses that induce visible, tetanic muscle contractions, NMES aims to reduce venous stasis, preserve muscle mass, and maintain strength during prolonged immobilization. Evidence from rehabilitation medicine supports its utility in conditions such as stroke, anterior cruciate ligament reconstruction, knee osteoarthritis, and total knee arthroplasty<sup>78</sup>. In critically ill patients, systematic reviews suggest NMES can maintain or increase muscle mass and strength, shorten the duration of mechanical ventilation, and improve quadriceps function compared to

**Table 4:** Mechanical prophylaxis and adjuncts in trauma and ICU patients

| Modality   | Evidence for VTE prevention  | When to use (typical indications)   | Contraindications & limitations   | Practical notes (monitoring / compliance)  |
|--|--|---|---|--|
| <b>Intermittent pneumatic compression (IPC)</b>        | Reduces DVT vs no prophylaxis; effect smaller than LMWH; additive benefit with pharmacologic prophylaxis.            | When pharmacologic prophylaxis is delayed/contraindicated; as an adjunct to LMWH in very high-risk patients (polytrauma, SCI, prolonged immobility).                              | Lower-extremity fractures or extensive soft-tissue injury preventing sleeve placement; severe PAD; poorly fitting devices; patient intolerance. | Target <b>continuous use ≥18 h/day</b> ; check fit/skin q shift; document device on/alarms; do <b>not</b> delay LMWH once hemostasis achieved. |
| <b>Graduated compression stockings (GCS)</b>           | Less effective than IPC; limited trauma-specific benefit; concern for skin injury in ICU.                            | Rarely as stand-alone in trauma; consider only if IPC not feasible and skin integrity adequate.   | Skin breakdown, edema/bandaging preventing proper sizing, severe PAD, major leg wounds/burns.   | Measure for correct size; reassess skin daily; replace if soiled/wet; avoid as sole strategy in high-risk trauma.                              |
| <b>Venous foot pumps (plantar devices)</b>             | Mixed/limited data; may reduce stasis when calf/ thigh sleeves cannot be used.                                       | Short-term bridge when IPC sleeves cannot be applied (external fixation, wounds).   | Foot/ankle injuries, pain/intolerance; uncertain efficacy vs IPC.   | Ensure correct positioning; use as <b>temporary</b> measure until IPC feasible.  |
| <b>Combination: LMWH + IPC</b>                         | <b>Superior</b> to either alone in high-risk cohorts; lowers asymptomatic DVT and likely PE.                         | Very high-risk patients once bleeding risk acceptable; typical standard in polytrauma centers.  | Device intolerance or contraindications to either component.  | Start LMWH within ~24 h of hemostasis; keep IPC continuous until full ambulation.  |
| <b>Inferior vena cava (IVC) filters — prophylactic</b> | Do <b>not</b> consistently reduce PE or mortality in trauma; device complications (thrombosis, migration, fracture). | <b>Not recommended routinely.</b> Consider only with <b>absolute contraindication to anticoagulation</b> plus ongoing high VTE risk and <b>no near-term reversal</b> anticipated. | Retrieval failures; long-term thrombosis; need for follow-up infrastructure.  | If placed, define <b>retrieval plan (≤30–60 d)</b> ; reassess candidacy for anticoagulation daily.   |

*Abbreviations:* LMWH, low molecular weight heparin; PAD, peripheral arterial disease; SCI, spinal cord injury; PE, pulmonary embolism.

standard ICU care<sup>79</sup>. A more recent network meta-analysis of 23 RCTs involving over 1,300 mechanically ventilated adults found that NMES, particularly when combined with physiotherapy, significantly improved extubation success rates compared to either standard care or NMES alone<sup>80</sup>. However, consistent improvements in ICU length of stay, duration of ventilation, or overall mortality have not yet been demonstrated. While trauma-specific evidence remains limited, NMES appears to be safe, feasible, and potentially beneficial for immobilized patients when early mobilization is not possible. The consensus at present is that NMES should be regarded as a supportive adjunct rather than a replacement for pharmacologic or standard mechanical prophylaxis. Tables 4 and 5 summarize the mechanical prophylaxis devices and adjunctive measures available for clinical implementation.

### Key Points

1. Initiate pharmacologic prophylaxis **as soon as safe** (often  $\leq 24$  h after hemostasis) and keep mechanical methods as a **bridge/adjunct**, not a replacement.
2. Daily device audits (on/fit/skin) improve adherence; real-world IPC compliance in ICU can be **<60%** without active monitoring.
3. Avoid routine **prophylactic IVC filters**; if unavoidable, plan early retrieval and transition to anticoagulation when feasible.

## 4. Special Populations and Clinical Scenarios

The balance between thrombosis and bleeding risk is particularly complex in certain trauma and ICU subgroups. Specific clinical conditions not only amplify thrombotic risk but also complicate decisions around prophylaxis, requiring individualized strategies that extend beyond generic recommendations.

### Traumatic Brain Injury (TBI)

Patients with TBI present one of the most challenging clinical dilemmas. Without prophylaxis, VTE incidence exceeds 50%, yet concerns over intracranial hemorrhage (ICH) progression often delay anticoagulation<sup>81–83</sup>. Multiple cohort studies and meta-analyses demonstrate that initiation of LMWH within 24–72 hours after a stable repeat head CT significantly reduces DVT and PE without substantially increasing clinically relevant hemorrhagic expansion<sup>84–93</sup>. Current EAST and WTA guidelines therefore recommend starting prophylaxis within 24–48 hours of radiographic stability in patients without uncontrolled ICH, with UFH considered as an alternative in renal impairment<sup>11,12,52</sup>. Mechanical prophylaxis should be instituted on admission and continued until pharmacologic agents can be safely initiated.

### Solid Organ Injury (SOI)

The timing of anticoagulation in non-operatively

**Table 5:** Inferior Vena Cava (IVC) Filters in Trauma and Critically Ill Patients

| Aspect                 | Key Points  |
|------------------------|---|
| <b>Rationale</b>       | Prevent major PE when anticoagulation is contraindicated (e.g., active bleeding, high-risk ICH, post-spinal surgery).   |
| <b>Types</b>           | <b>Permanent filters</b> – left in place indefinitely, high late complication rates.<br><b>Retrievable filters</b> – temporary, designed for removal; retrieval success 20–60%, declines after 3–6 months.  |
| <b>Evidence</b>        | Observational studies suggest lower PE incidence, but no survival benefit demonstrated. Some studies show increased DVT due to flow disturbance.  |
| <b>Therapeutic use</b> | Indicated in acute proximal DVT/PE with absolute contraindication to anticoagulation. Do not treat existing clot, only prevent embolization.  |
| <b>Complications</b>   | <b>Early:</b> Access-site thrombosis, misplacement, caval perforation.<br><b>Late:</b> Migration, fracture, recurrent DVT, IVC occlusion (up to 22%).<br><b>Retrieval failure:</b> Due to scar tissue if left >3–6 months.  |
| <b>Guidelines</b>      | EAST/WTA: Avoid routine use; consider only if contraindication $\geq 7$ days.<br>ACCP: Strongly recommend against prophylactic filters; use only with acute proximal DVT/PE and contraindication to anticoagulation.<br>SIR: Similar to ACCP; emphasize early retrieval (30–60 days). |
| <b>Practical tips</b>  | Use only after multidisciplinary discussion. Always document retrieval plan at insertion. Resume anticoagulation as soon as feasible, even with filter in place.  |

PE: pulmonary embolism; ICH: intracranial hemorrhage; DVT: deep vein thrombosis; IVC: inferior vena cava; EAST : Eastern Association for the Surgery of Trauma; WTA: Western Trauma Association; ACCP: American College of Chest Physicians; SIR: Society Interventional Radiology

managed liver, spleen, or kidney injuries remains debated. A landmark multicenter study showed that LMWH started within 48 hours did not increase rates of failed non-operative management (NOM) or transfusion, while reducing VTE compared to initiation beyond 72 hours<sup>94</sup>. Systematic reviews confirm that prophylaxis within 24–48 hours is safe in hemodynamically stable patients<sup>95,96</sup>. Lamb et al. further suggested that starting at 48 hours may balance bleeding and VTE risks, as very early initiation (<48 h) slightly increased NOM failure while reducing DVT<sup>55</sup>. Current recommendations are to begin LMWH once hemoglobin has stabilized and no active bleeding is present. In patients undergoing angioembolization, anticoagulation can often be resumed within 24 hours post-procedure under close monitoring<sup>97</sup>.

### Spinal Cord Injury (SCI)

SCI patients represent one of the highest risk groups, with historical VTE incidence above 60% in the absence of prophylaxis<sup>98</sup>. Modern regimens combining LMWH with IPC have reduced symptomatic VTE to below 10%, yet residual risk persists<sup>99,100</sup>. Extended prophylaxis for at least 8–12 weeks is advised, as immobility continues long after hospital discharge. Mechanical prophylaxis should be applied immediately, with LMWH started once hemostasis is achieved. Higher or weight-adjusted LMWH doses, guided by anti-Xa monitoring, may be required in obese or severely immobilized patients<sup>53,100</sup>.

### Severe Burns.

Patients with major burns develop a distinct hypercoagulable profile, driven by systemic inflammation, endothelial activation, and high levels of circulating procoagulants. Immobility, massive fluid resuscitation, and repeated surgical interventions further increase thrombotic risk<sup>101</sup>. LMWH remains the prophylactic mainstay, but altered pharmacokinetics due to fluid shifts and augmented renal clearance often result in subtherapeutic anti-Xa levels, necessitating frequent monitoring and dose adjustment<sup>102</sup>. Mechanical prophylaxis is often impractical in this group: IPC cuffs should not be applied to burned or grafted areas, while GCS are generally contraindicated because of skin fragility.

### Pregnancy and Postpartum Trauma

Pregnancy increases VTE risk four- to five-fold as a result of hormonal changes, uterine compression causing venous stasis, and reduced mobility. Trauma, especially involving pelvic or lower extremity fractures, further

amplifies this risk<sup>103–105</sup>. LMWH is the agent of choice, as it does not cross the placenta and has a superior safety profile compared to UFH. Warfarin and direct oral anticoagulants (DOACs) are contraindicated due to teratogenicity and fetal bleeding<sup>106</sup>. If anticoagulation is temporarily contraindicated, mechanical prophylaxis should be used until pharmacologic prophylaxis becomes feasible. LMWH dosing should be weight-adjusted, with anti-Xa monitoring in obese or high-risk women. Extended prophylaxis for at least six weeks postpartum is advised in patients with ongoing risk factors<sup>106,107</sup>.

### Oncologic Trauma Patients.

Malignancy is a potent prothrombotic factor, and trauma patients with cancer may have double the baseline risk of VTE compared to those without cancer<sup>108</sup>. LMWH remains the inpatient standard, while DOACs may be considered post-discharge in carefully selected patients with non-gastrointestinal malignancies and stable hemostasis<sup>109</sup>. However, chemotherapy-related thrombocytopenia or mucosal injury increases bleeding risk, underscoring the importance of individualized decision-making in this population.

### Obesity and Renal Impairment.

Obesity not only increases baseline VTE risk but also predisposes to subtherapeutic prophylaxis with standard LMWH doses. Data from the CLOTT-1 registry suggest that weight-based dosing (0.5 mg/kg BID) or anti-Xa-guided adjustments significantly reduce breakthrough VTE<sup>56</sup>. Conversely, patients with renal impairment (CrCl <30 mL/min) may accumulate LMWH, increasing bleeding risk. In this setting, dose-reduced LMWH or low-dose UFH (5,000 IU every 8 h) is preferred<sup>110–112</sup>.

### Orthopedic Trauma and Pelvic Fractures.

Pelvic, acetabular, and long-bone fractures confer some of the highest risks for VTE, with symptomatic rates up to 20–30% in the absence of prophylaxis<sup>113</sup>. Even with LMWH, residual risk remains substantial. Guidelines recommend early and aggressive prophylaxis, often combining LMWH with mechanical measures, and extending prophylaxis for at least four weeks post-discharge in patients with persistent immobility<sup>114</sup>. Aspirin, while widely adopted in elective orthopedic surgery, remains controversial in trauma, with limited supporting evidence<sup>115</sup>.

Table 6 summarises VTE risk and prophylaxis strategies in special trauma and ICU populations.

**Table 6: VTE Risk and Prophylaxis Strategies in Special Trauma and ICU Populations**

| Population                               | VTE Risk Profile   | Prophylaxis Recommendations   | Key Challenges   |
|--|--|---|--|
| <b>Traumatic Brain Injury (TBI)</b>      | VTE incidence >50% without prophylaxis; risk of ICH progression              | Start LMWH within 24–48 h after stable repeat CT; UFH alternative if renal impairment; mechanical prophylaxis immediately | Balancing bleeding vs. thrombosis; need for repeat imaging                   |
| <b>Solid Organ Injury (SOI)</b>          | High VTE risk; bleeding concern in non-operative management                  | LMWH within 24–48 h once hemodynamically stable and Hb stable; safe post-embolization                                     | Risk of delayed bleeding; timing remains debated                             |
| <b>Spinal Cord Injury (SCI)</b>          | Extremely high VTE risk (>60% without prophylaxis); prolonged immobility     | Immediate mechanical prophylaxis + early LMWH; extend prophylaxis 8–12 weeks  | Residual risk despite prophylaxis; need for higher dosing/anti-Xa monitoring |
| <b>Severe Burns</b>                      | Hypercoagulability from inflammation, endothelial activation, fluid shifts   | LMWH with anti-Xa monitoring; mechanical prophylaxis only if skin intact  | Altered pharmacokinetics; skin breakdown limits IPC/GCS use                  |
| <b>Pregnancy &amp; Postpartum Trauma</b> | Pregnancy increases VTE risk 4–5x; trauma amplifies risk                     | LMWH preferred (does not cross placenta); adjust for maternal weight; continue ≥6 weeks postpartum in high-risk cases     | Avoid warfarin/DOACs; bleeding risk during delivery or pelvic trauma         |
| <b>Oncologic Trauma Patients</b>         | Cancer doubles baseline VTE risk; systemic inflammation, tumor procoagulants | LMWH first-line inpatient; consider DOACs post-discharge in selected non-GI cancers                                       | High bleeding risk in thrombocytopenia or mucosal injury                     |
| <b>Obesity</b>                           | Subtherapeutic anti-Xa with fixed-dose LMWH; higher baseline VTE risk        | Weight-based dosing (0.5 mg/kg BID) or anti-Xa monitoring   | Risk of under-dosing vs. bleeding; limited guideline consensus               |
| <b>Renal Impairment</b>                  | Increased bleeding due to LMWH accumulation                                  | Dose-adjust LMWH or use UFH (5,000 IU q8h)  | Monitoring anti-Xa and renal function essential                              |
| <b>Orthopedic/Pelvic Fractures</b>       | Symptomatic VTE up to 30% without prophylaxis                                | Early LMWH ± mechanical prophylaxis; extend prophylaxis ≥4 weeks  | Persistent high risk despite prophylaxis; aspirin use controversial          |
| <b>Critical Illness/ICU</b>              | Risk from sepsis, vasopressors, CVCs, mechanical ventilation                 | LMWH when feasible; mechanical prophylaxis if contraindicated   | Frequent interruptions for procedures; need for dynamic risk reassessment    |

### Future Perspectives

The limitations of a uniform, protocol-based approach to VTE prophylaxis are increasingly evident, particularly in trauma and critically ill populations with highly dynamic physiology. The next frontier in prevention lies in precision medicine and learning health systems, where pharmacology, biomarkers, digital tools, and artificial intelligence converge to provide real-time, individualized guidance. Fixed-dose LMWH regimens often fail to achieve target prophylactic levels in obese patients, those with augmented renal clearance, or highly catabolic trauma patients. Anti-Xa-guided strategies have demonstrated improved attainment of prophylactic ranges and reduced VTE without excess bleeding<sup>116,117</sup> Future advances include

the development of point-of-care assays enabling bedside dose adjustment, and EMR-linked algorithms that automatically integrate anti-Xa results with patient characteristics to suggest personalized dosing in real time.

Traditional scores such as Caprini, RAP, or TESS are static and lack discriminative power in high-risk trauma cohorts. Machine learning models, trained on large trauma registries, have shown AUCs above 0.85 by integrating demographics, injury patterns, laboratory dynamics, mobility metrics, and even free-text clinical notes via natural language processing<sup>118,119</sup>. These approaches promise continuously updated risk estimates but require robust external validation and careful ethical oversight, particularly regarding transparency, bias, and data privacy.

Biomarkers are being increasingly explored to refine VTE risk assessment. D-dimer remains the most established tool, with very high sensitivity (>95%) but poor specificity in trauma, pregnancy, cancer, and postoperative states. Other fibrinogen degradation products (FDPs) add limited incremental value. Novel markers—such as soluble P-selectin, microparticle-associated tissue factor, thrombin–antithrombin complexes (TAT), prothrombin fragment F1+2, and plasmin–antiplasmin complexes (PAP)—provide mechanistic insights into endothelial and platelet activation, coagulation, and fibrinolysis, though most are limited by short half-lives, low specificity, or methodological variability<sup>120</sup>. Endothelial and inflammatory markers such as syndecan-1, endocan, and CRP link systemic inflammation to thrombotic risk, but none are ready for clinical implementation. The emerging strategy is the use of multi-marker panels, potentially combined with AI, to provide dynamic, individualized risk scores that integrate both thrombosis and bleeding risk. Hospital discharge marks a critical period, as many VTE events occur after acute care. Evidence from orthopedic surgery and selected medical populations supports extending LMWH prophylaxis to 28–35 days<sup>121,122</sup>, and ongoing trials aim to clarify its role in trauma. Challenges include adherence and cost; however, long-acting agents and selected DOAC use in stable patients may improve feasibility. Digital innovations offer new opportunities for adherence and follow-up. Wearable devices can monitor patient mobility, triggering reassessment when prolonged inactivity is detected. Smart IPC devices record compliance data and transmit usage reports. Telemedicine and remote patient monitoring (RPM) have demonstrated improved safety, adherence, functional recovery, and reduced readmissions and costs<sup>123,124</sup>. By integrating wearable and RPM data with EMR-linked protocols, health systems can dynamically update VTE risk assessments and prophylaxis plans after discharge, closing a critical gap in continuity of care. The ultimate vision is the development of learning health systems (LHS), in which VTE prevention becomes proactive, adaptive, and continuously refined. Electronic health records (EHRs) play a central role, providing shared patient overviews, structured order sets, and automated decision support. Yet EHRs also pose challenges—administrative burden, information overload, and fragmented communication—that require organizational and cultural adaptation<sup>125,126</sup>. Telemedicine and RPM complement this ecosystem, offering real-time monitoring and patient engagement<sup>123,124</sup>. By combining EHRs,

AI-driven analytics, biomarkers, and digital adherence tools, LHS can transform prophylaxis from a static protocol into a responsive, data-driven process that evolves with each patient and continuously improves through aggregated outcomes.

In summary, the future of VTE prevention in trauma and critical illness lies in precision dosing, AI-based risk prediction, biomarker-guided timing, extended post-discharge strategies, and digital health integration within learning health systems. Such an approach promises not only to optimize individual patient safety but also to create a continuously improving cycle of evidence-based practice.

### Conclusions

Venous thromboembolism events continue to be among the most common, preventable, and persistent complications in trauma and critically ill patients. Over the past three decades, consistent evidence from randomized clinical trials, large registries, and meta-analyses has demonstrated that timely, appropriately dosed, and uninterrupted prophylaxis significantly reduces morbidity and mortality. Low molecular weight heparin (LMWH) is established as the pharmacologic gold standard, outperforming unfractionated heparin (UFH) in terms of efficacy and safety. Early initiation—within 24–48 hours for most patients and within 24–72 hours following radiographic stability in traumatic brain injury—represents the optimal strategy to maximize benefit without unacceptable bleeding risk.

Mechanical prophylaxis, particularly intermittent pneumatic compression (IPC), remains indispensable when anticoagulation is temporarily contraindicated, and offers synergistic benefit when combined with LMWH. However, real-world compliance is often suboptimal, and routine prophylactic use of inferior vena cava (IVC) filters is no longer supported, given the absence of survival benefit and the risk of long-term complications.

Special populations—including those with traumatic brain or spinal cord injury, pelvic and long-bone fractures, severe burns, pregnancy, obesity, renal impairment, or active cancer—require tailored approaches that balance heightened thrombotic risk against bleeding concerns. These groups exemplify the complexity of decision-making, underscoring the limitations of one-size-fits-all strategies.

Persistent barriers to optimal implementation—such as variability in institutional practices, frequent missed

doses, resource limitations, and gaps in provider or patient education—remain a major challenge. Yet successful quality improvement programs demonstrate that standardized protocols, multidisciplinary collaboration, and integration into electronic health systems can markedly improve adherence and outcomes.

Looking ahead, the field is moving towards precision prevention. Anti-Xa-guided and weight-adjusted LMWH dosing, artificial intelligence-based dynamic risk prediction, biomarker-guided timing, extended post-discharge prophylaxis, and digital health monitoring represent emerging tools that will help transform VTE prevention from a static, protocol-driven approach into a proactive, adaptive, and patient-centered paradigm.

The goal is clear: to eliminate preventable VTE in trauma and critical illness, thereby improving survival, functional recovery, and long-term quality of life for this highly vulnerable population.

#### Author Contributions:

Prof. Fausto Catena and Prof. Rifat Latifi contributed equally as senior authors.

#### Conflict of Interest:

The authors have no conflict of interests with this article.

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