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To Clot or Not to Clot—Advancements in VTE Prophylaxis in the Trauma Patient

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- The presenters have no real or perceived conflicts of interest related to this presentation

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Learning Objectives

At the end of this session, participants should be able to:

1. Identify factors that lead to the increased risk of thromboembolism in the acute trauma population.
2. Recognize inconsistencies that traditionally existed regarding optimal pharmacologic VTE prophylaxis strategies.
3. Recall strategies to develop and manage a safe and effective trauma population-specific pharmacologic thromboembolism prophylaxis protocol based on current literature.

Physiology & Risk

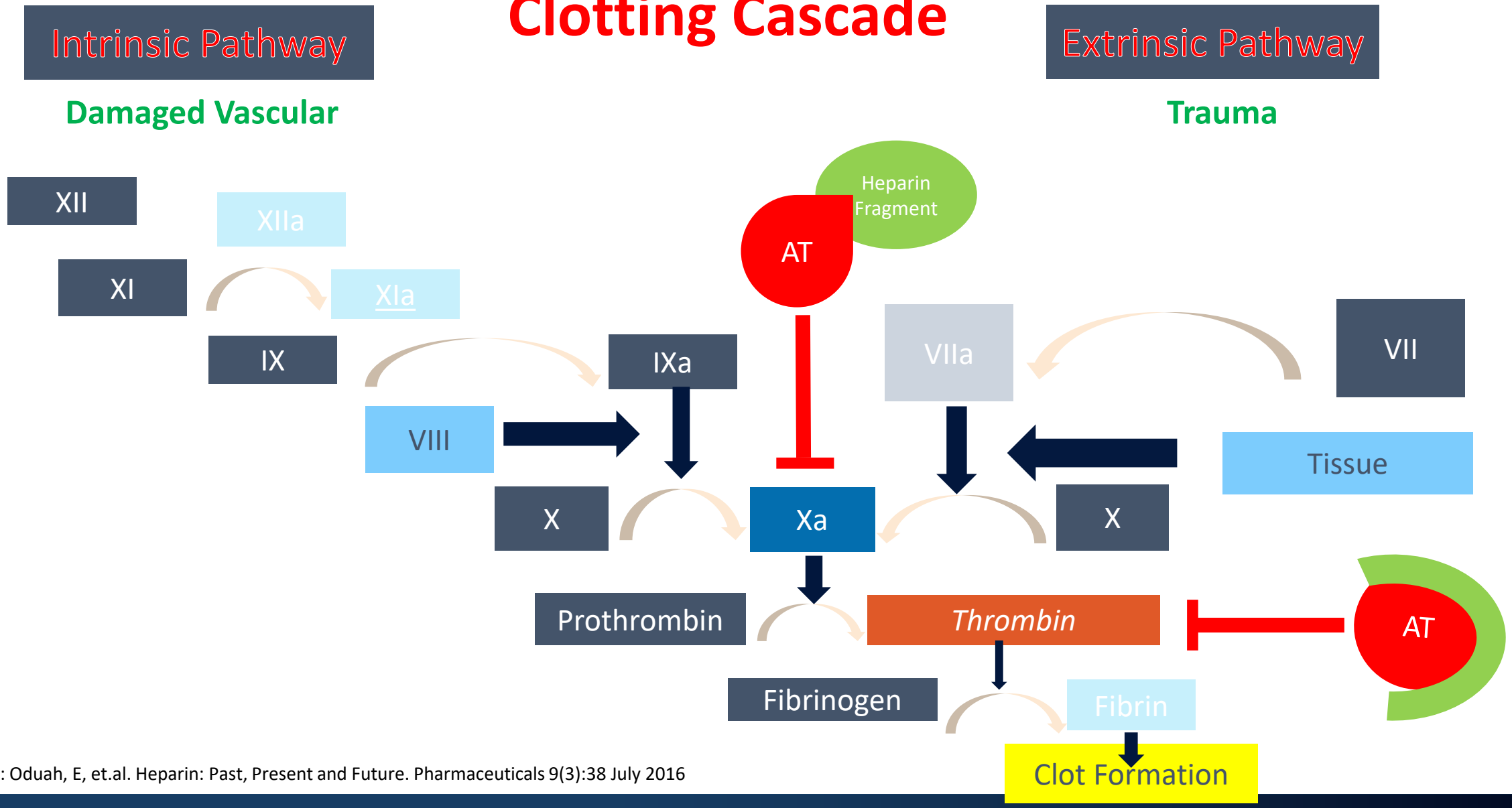
Carol Barthel, PharmD, BCPS

4 Stages of Hemostasis (process of clot formation)

1. Creation of platelet plug consequent from disruption of vascular endothelium
   - Injuries due to diabetes, HTN, smoking, vascular wall tear, etc.
   - Following damage to vascular wall, VWF is released which mediates platelet adhesion and aggregation
2. **Propagation of clots by activation of various proenzymes to their active form**
   - **Clotting cascade initiated by the extrinsic pathway and propagated via intrinsic pathway**
3. Termination of clot formation and the antithrombin control mechanism
   - Designed to prevent and mediate extent of clot formation, preventing processes that lead to thrombosis, ensures fluidity of blood
4. Removal of clot by fibrinolysis

Source: Umerah Co, Momodu II. Anticoagulation. [Updated 2022 Jul 18].

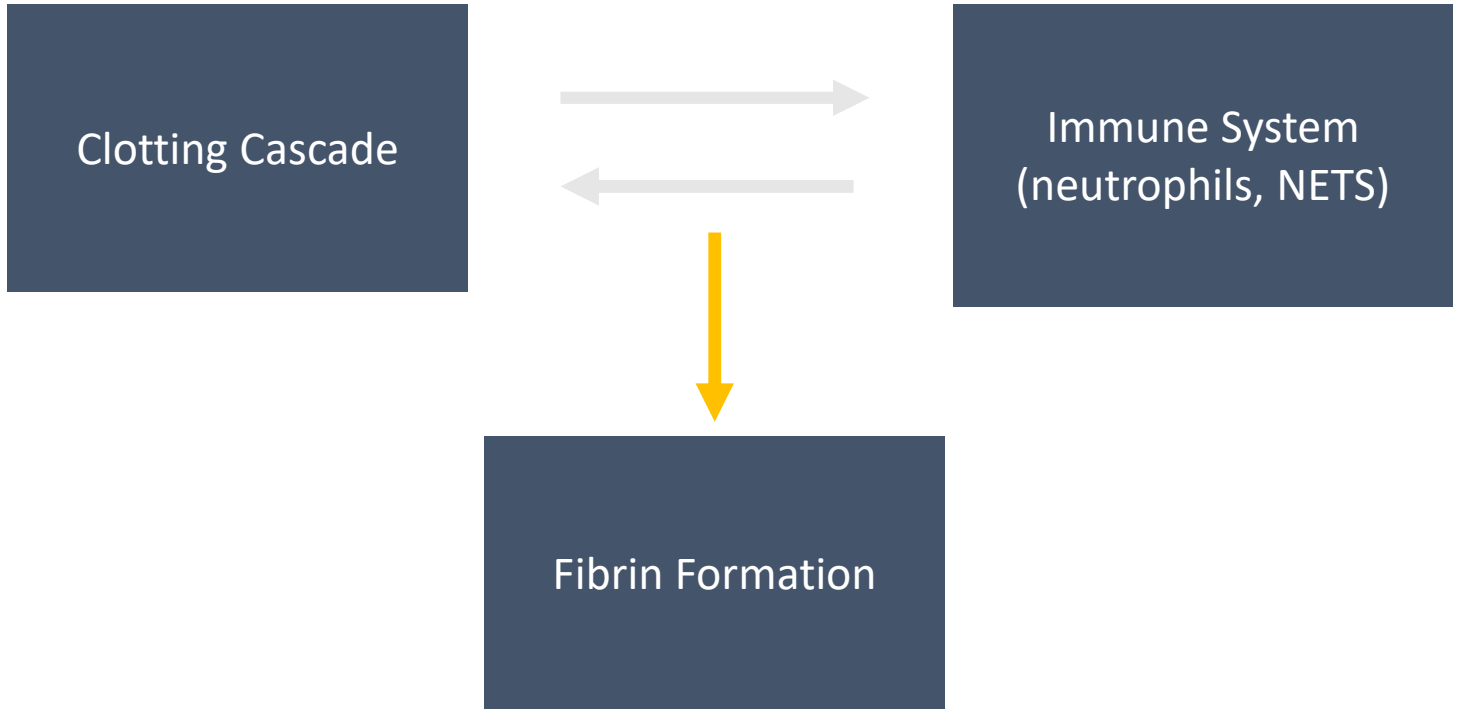
Clotting Cascade



Source: Oduah, E, et.al. Heparin: Past, Present and Future. Pharmaceuticals 9(3):38 July 2016

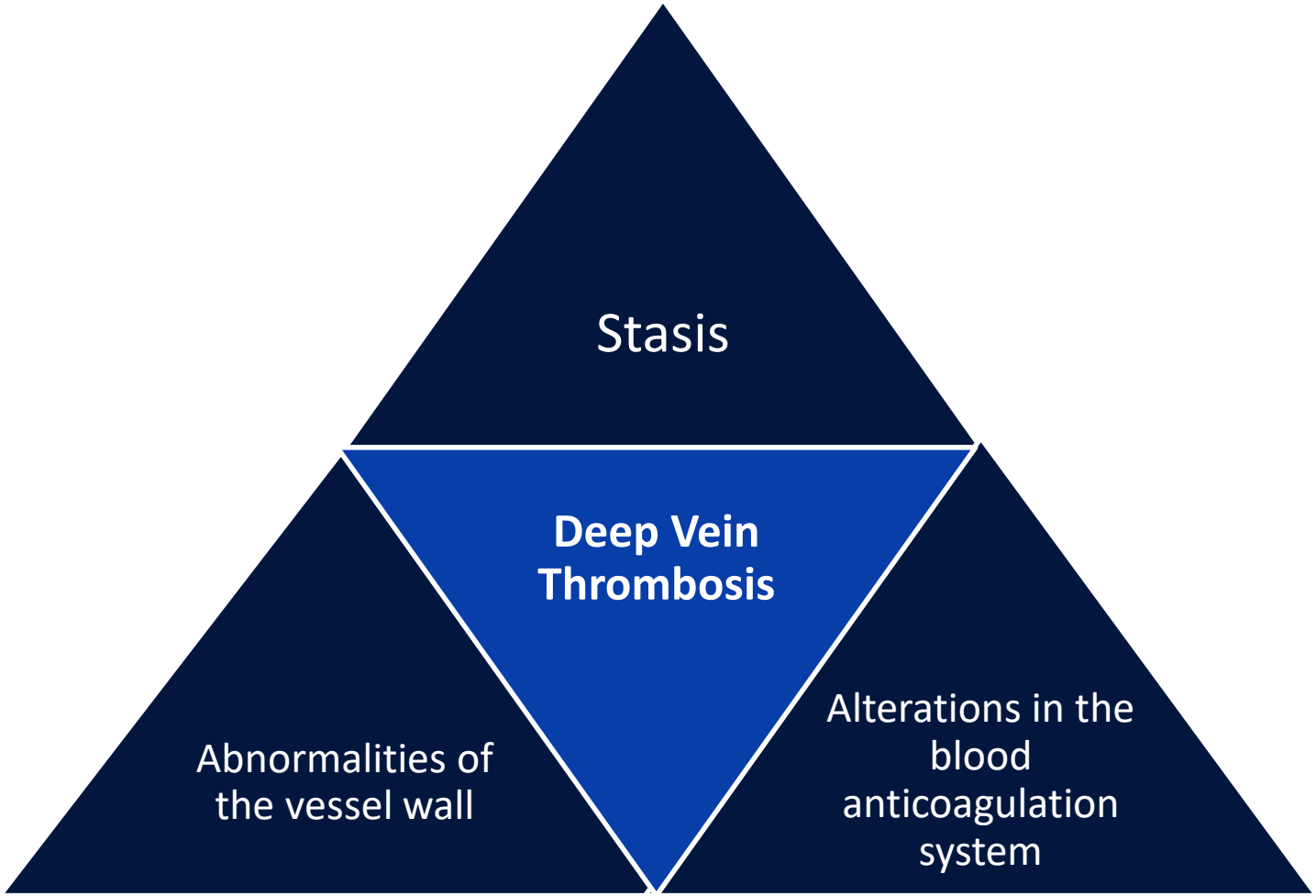
Immunothrombosis

- Complex interplay between anticoagulation and inflammation
- Immune cells contribute to thrombus formation = immunothrombosis



Source: Khan, F, et al. Venous thromboembolism. Lancet. 2021 Jul 3;398910294):64-77.

Virchow’s Triad (circa 1800s)



Source: Wolberg AS, et al. Procoagulant activity in hemostasis and thrombosis: Virchow's triad revisited. Anesth Analg. 2012 Feb;114(2):275-85.

Components of Virchow's Triad

Factors below have been correlated with venous and/or arterial coagulopathies

- Abnormal levels of pro- and anticoagulant proteins
- Thrombin generation
- Clotting Factor activity
- Resistance to inactivation
- Markers of vascular cell damage or activation
- Fibrinolysis inhibitors

Source: Wolberg AS, et al. Procoagulant activity in hemostasis and thrombosis: Virchow's triad revisited. Anesth Analg. 2012 Feb;114(2):275-85

Venous Thromboembolism (VTE) Epidemiology

- Comprises both Deep Vein Thrombosis (DVT) and Pulmonary Embolism (PE)
- Chronic illness that affects 10 million people worldwide
- Annual incidence is 1–2 cases per 1,000 population
- Strong provoking risk factors can be transient or persistent
- Strong *transient* provoking risk factors:

Major surgery
Active cancer
Prolonged immobilization
Major Trauma

Accounts for 20% of all venous thromboembolism episodes

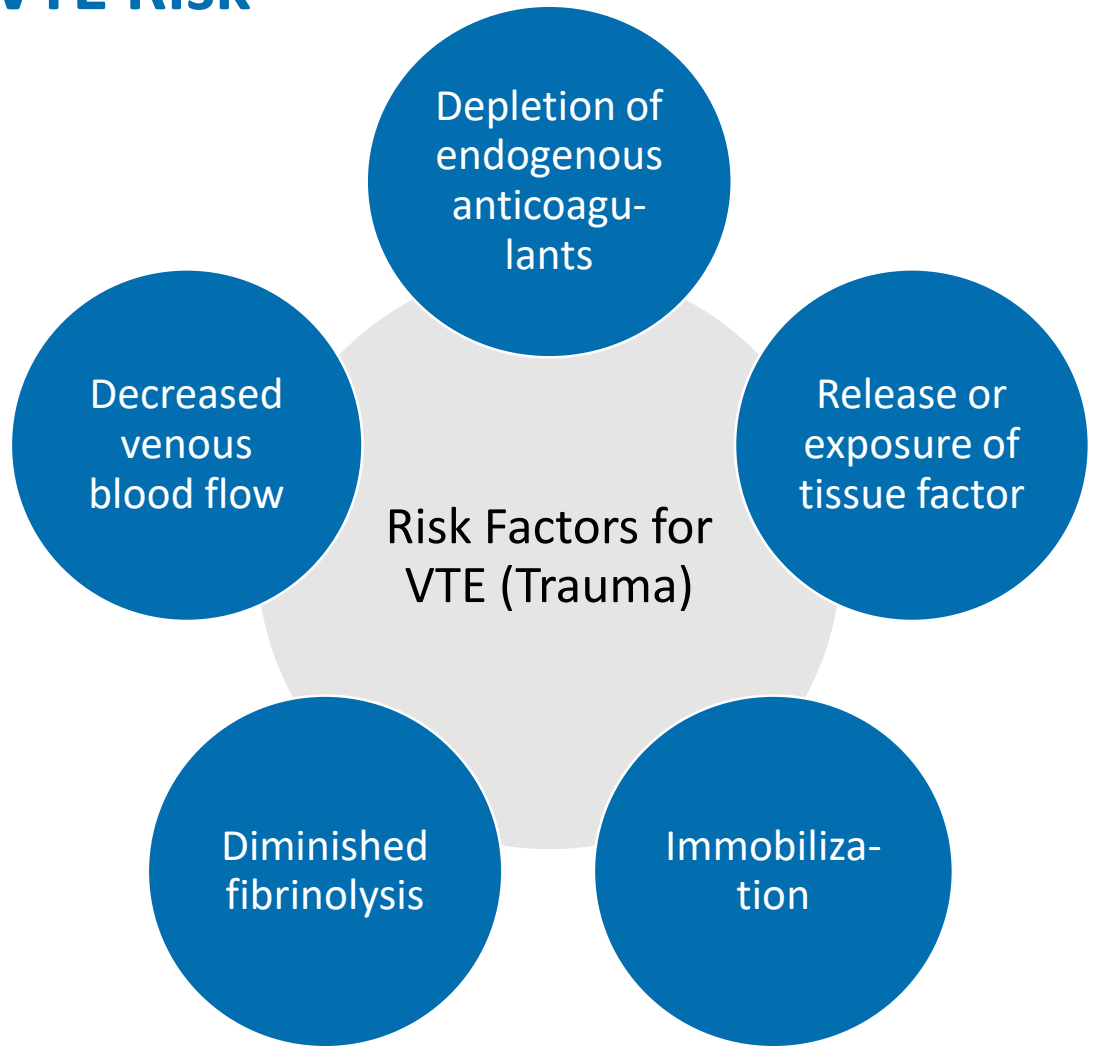
Source: Khan, F, et al. Venous thromboembolism. Lancet. 2021 Jul 3;398910294):64-77.

Trauma & VTE Risk

- Traumatic injuries remain leading cause of death among young adults in the United States with more than 60,000 deaths yearly
- VTE is a common and preventable complication following traumatic injury
- The most severely injured patients are at especially significant risk of VTE
- Risk factors in the trauma patient can lead to VTE rates as high as 58% in the absence of adequate prophylaxis
  - Clotting cascade activation with markedly elevated thrombin within first 24 hours following injury
  - Increased injury severity score (ISS)
  - Immobilization
  - Multiple transfusions
  - Need for operations

Source: Hecht JP, et al. Early Chemoprophylaxis in Severely Injured Trauma Patients Reduces Risk of Venous Thromboembolism. Am Surg. 2020 Sep;86(9):1185-1193.

Trauma & VTE Risk



Source: Yorkgitis BK, et al. AAST/ACS. -Committee on Trauma Clinical Protocol for inpatient venous thromboembolism prophylaxis after trauma. J Trauma Acute Care Surg. 2022 Mar 1;92(3):597-604.

Engelman, D.T., et al.

- Attempted to identify early alterations in the endogenous coagulation and fibrinolytic systems that may contribute to hypercoagulability in the multiple trauma patient
- Looked for a relation between injury severity and laboratory evidence of a hypercoagulable state
- Small prospective, single-site study
- Factors associated with hypercoagulability were measured

Source: Engelman DT, et al. Hypercoagulability following multiple trauma. World J Surg. 1996 Jan;20(1):5-10.

Engelman, D.T., et al.

- **Inclusion**: All adult patients with multiple trauma significant enough to warrant admission to the trauma resuscitation room
- **Exclusions**: Pediatrics, isolated head injuries, patients with documented DVT or PO, any unresuscitatable patients
- **Factor levels associated with hypercoagulability**:

Factor	Hypercoagulable changes
Tissue plasminogen activator (tPA)	Decreased
Plasminogen activator inhibitor (PAI-1)	Increased
Serum antithrombin III (SAT)	Decreased
Protein C antigen (PrC)	Decreased
Functional protein C (FPrC)	Decreased
Protein S Antigen (PrS)	Decreased
D-Dimer	Increased
Prothrombin fragment 1.2 (PF1.2)	Increased

Source: Engelman DT, et al. Hypercoagulability following multiple trauma. World J Surg. 1996 Jan;20(1):5-10.

Engelman, D.T., et al.

- **Results**:
  - 85% of the patients had one or more hypercoagulable values
  - Significantly elevated levels of D-dimer and decreased levels of FPrC were seen in the more severely injured group compared to the values for the less severely group
- **Discussion**:
  - Traumatic shock has been found to cause an AT-III deficiency
  - Heparin (endothelial or exogenous) causes 1000-fold increase in AT-III activity
  - Heparin cannot work without AT-III, therefore deficiency could eliminate effectiveness of subQ heparin injections for VTE prophylaxis

Source: Engelman DT, et al. Hypercoagulability following multiple trauma. World J Surg. 1996 Jan;20(1):5-10.

Post-Op Spinal

- Incidence of postoperative spinal thromboembolic events varies from 0.3% to 31 % (poorly defined, gathered from small, heterogenous studies)
- Risk of developing VTE in post op period influenced by:
  - Patient's comorbidities
  - Need for anticoagulation for other medical problems
  - Type and length of surgery
- Risk of venous thromboembolism greatest during the first 12 weeks after injury when flaccidity, paralysis, or immobilization of extremities allow "stasis" component of Virchow's triad to predominate
- Spinal cord injuries may also lead to autonomic dysregulation, ultimately increasing coagulability through changes in hemostatic and fibrinolytic cascades
- Risks associated with anticoagulation include epidural hematomas and other hematologic complications

Source: Alvarado AM, et al. Venous Thromboprophylaxis in Spine Surgery. Global Spine J. 2020 Jan;10(1 Suppl):65S-70S.
Nimmons, et al. Design and Retrospective Applicaton of a Spine Trauma DVT Prophylaxis Protocol on Level 1 Trauma Center Patient database. Global Spine. J. 2022 Sep;12 (7): 1321-1329

Inconsistencies in Practice

Inconsistencies in Practice

- Few published prospective, randomized clinical trials
- Optimal dose
- Optimal timing
- When to initiate, hold and resume therapy before and after surgery or epidural dose
- Variability in practice amongst providers involved in the multidisciplinary care of trauma patients
  - Trauma Provider
  - Orthopedic Surgeons
  - Spine Surgeons
  - Neurosurgeons

Source: Yorkgitis BK, et al. AAST/ACS. -Committee on Trauma Clinical Protocol for inpatient venous thromboembolism prophylaxis after trauma. J Trauma Acute Care Surg. 2022 Mar 1;92(3):597-604.

Lim, et al. | A Web-based Survey

- **Rationale:** Recommendations exist for elective orthopaedic procedures and some extremity trauma, but guidelines regarding VTE prophylaxis in patients who sustain various types of pelvic trauma, a cohort at high risk for VTE, do not exist
- **Goal**: identify current practices and rationales of orthopaedic surgeons regarding VTE prophylaxis for pelvic and acetabular (P&A) fractures
- **Design:** 5-item web-based questionnaire made available to all Orthopaedic Trauma Association (OTA) members on the OTA website
- Analysis of data completed after 3 month study period

Source: Lim, Philip K. MD; et. al. A. MD, MA. Venous Thromboembolism Prophylaxis After Pelvic and Acetabular Fractures: A Survey of Orthopaedic Surgeons' Current Practices. Journal of the merican Academy of Orthopaedic Surgeons 28(18):p 750-755, September 15, 2020.

Lim, et al. | A Web-based Survey (Conclusion)

- LMWH remains agent of choice for both nonsurgical and surgical P&A fractures
  - Most important factor in selection was effectiveness, followed by compliance/route of administration, then by bleeding/infection
- Routine VTE screening was not performed by most surgeons
- Weight-bearing status or need for surgical intervention did not have a notable impact on the modality or duration of the VTE prophylaxis
- Of note, findings indicate that surgeons do not feel that current literature provides adequate guidelines for how they should manage VTE prophylaxis in patients with P&A trauma

Source: Lim, Philip K. MD; et. Al. A. MD, MA. Venous Thromboembolism Prophylaxis After Pelvic and Acetabular Fractures: A Survey of Orthopaedic Surgeons' Current Practices. Journal of the American Academy of Orthopaedic Surgeons 28(18):p 750-755, September 15, 2020. .

Timing is Everything

Photo Source: Carol Barthel. Do not reprint without permission.

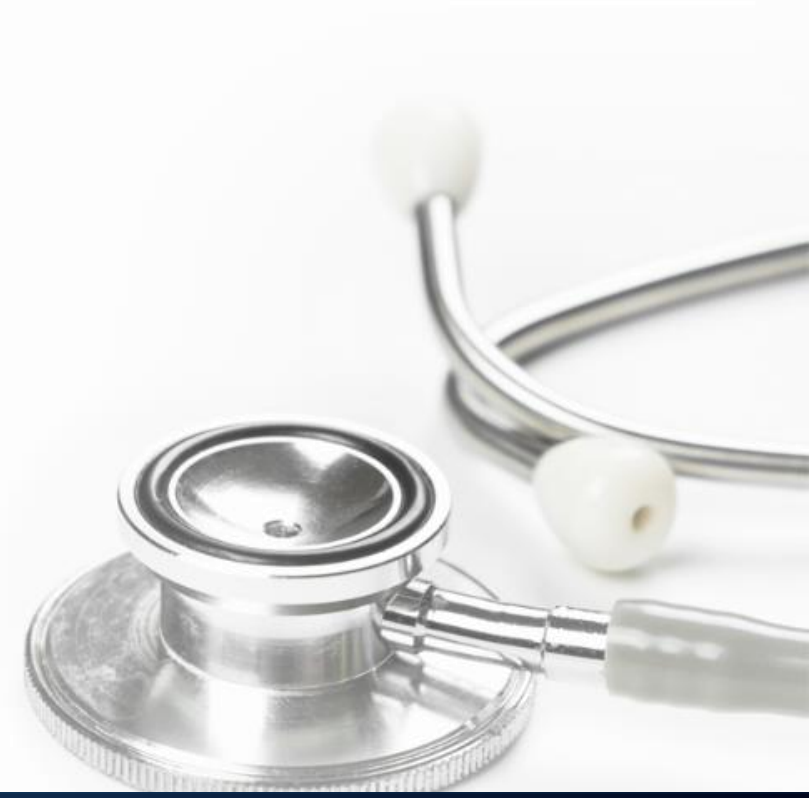
Timing of Chemoprophylaxis

- Retrospective cohort study evaluated impact of initiating early (< 48 hours) versus late (> 48 hours) chemoprophylaxis in trauma patients undergoing operative intervention
- 23.3% received early prophylaxis and 76.7% received late prophylaxis (N = 206)
- There was no incidence of epidural hematoma or excessive postoperative bleeding requiring intervention
- 6.2% developed VTE (92% were in late group)
- Age (>45) and traumatic brain injury were associated with increased risk of VTE events
- Authors concluded VTE prophylaxis within 48 hours of operative fixation were not associated with increased risk of bleeding or neurological complications.

Source: Alvarado AM, et al. Venous Thromboprophylaxis in Spine Surgery. Global Spine J. 2020 Jan;10(1 Suppl):65S-70S.

Timing of Chemoprophylaxis, *continued*

- Study evaluated VTE-related events in 195 patients undergoing spinal surgery for fractures
- Found that compared with other patients undergoing spine surgery, patients with spinal fractures were more likely to receive chemoprophylactic anticoagulation and also experienced higher rates of VTE events
- Found that within 30 days of surgery, estimated blood loss, and comorbid cardiac disease predicted VTE events in patients with spinal fractures
- Authors concluded timing of VTE prophylaxis must be evaluated on an individual patient basis with thorough consideration of underlying medical comorbidities and risk factors
- Limited evidence suggests that patients with spinal cord injury may have a VTE risk and thus warrant earlier chemoprophylaxis treatment to negate effects of venous stasis



Source: Alvarado AM, et al. Venous Thromboprophylaxis in Spine Surgery. Global Spine J. 2020 Jan;10(1 Suppl):65S-70S.

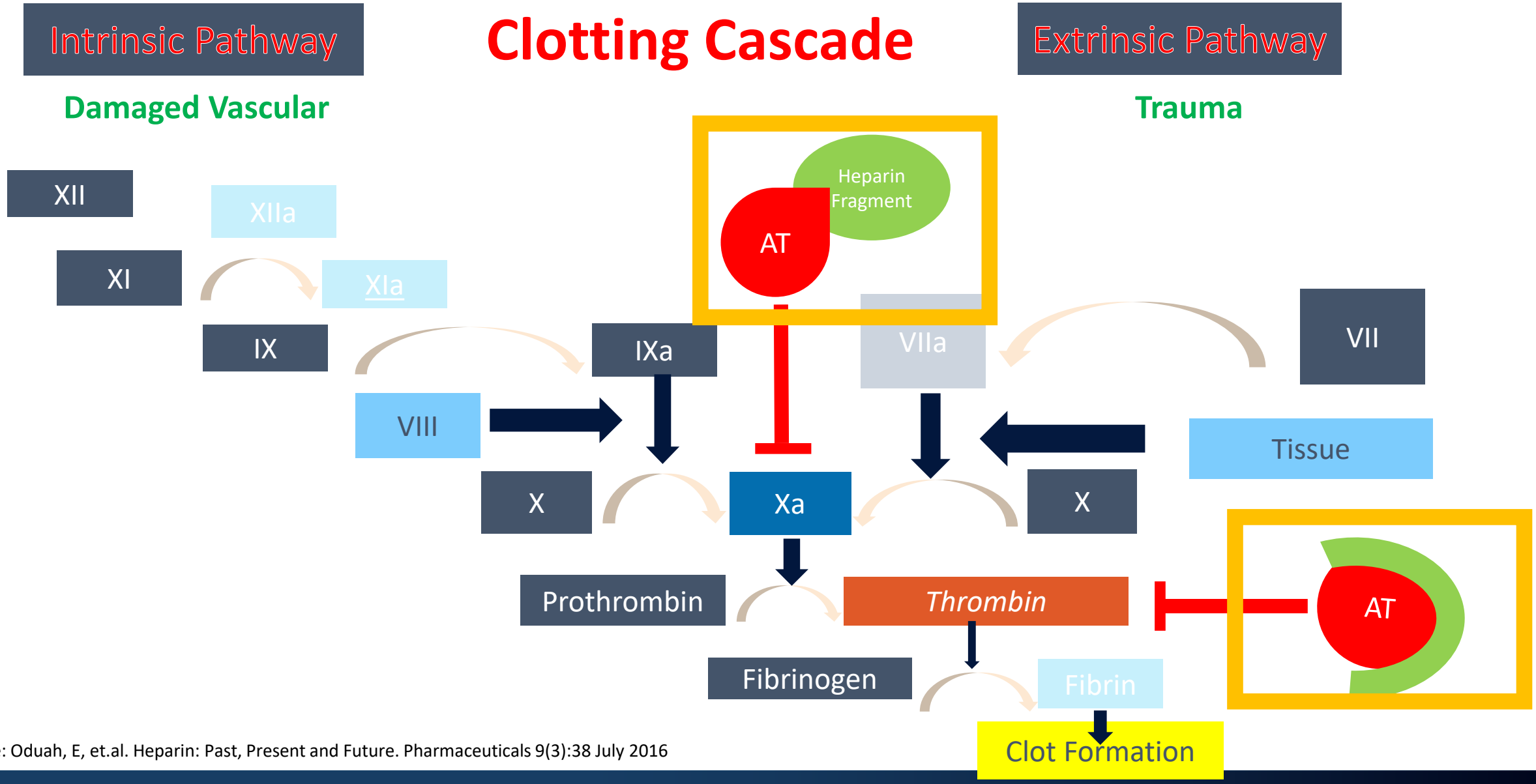
Pharmacological Thromboprophylaxis

Heparin

- Interacts with plasma protein Antithrombin III to induce a conformational change which enhances protease activity of Antithrombin III, thereby inhibiting the activated coagulation factors involved in the clotting sequence, particularly Xa and IIa
  - Small amounts of heparin inhibit Factor Xa, larger amounts inhibit thrombin (Factor Iia)
  - Heparin prevents formation of stable fibrin clot by inhibiting action of fibrin stabilizing factor
  - Highly bound to antithrombin, fibrinogens, globulins, serum proteases, lipoproteins
  - Heparin is mainly cleared by liver and reticuloendothelial cells mediated uptake into the extravascular space
  - Plasma half-life is dose-dependent and ranges from 0.5 to 2 hours

Source: Heparin package insert. Hikma Pharmaceuticals. NJ, January 2020

Clotting Cascade



Source: Oduah, E, et.al. Heparin: Past, Present and Future. Pharmaceuticals 9(3):38 July 2016

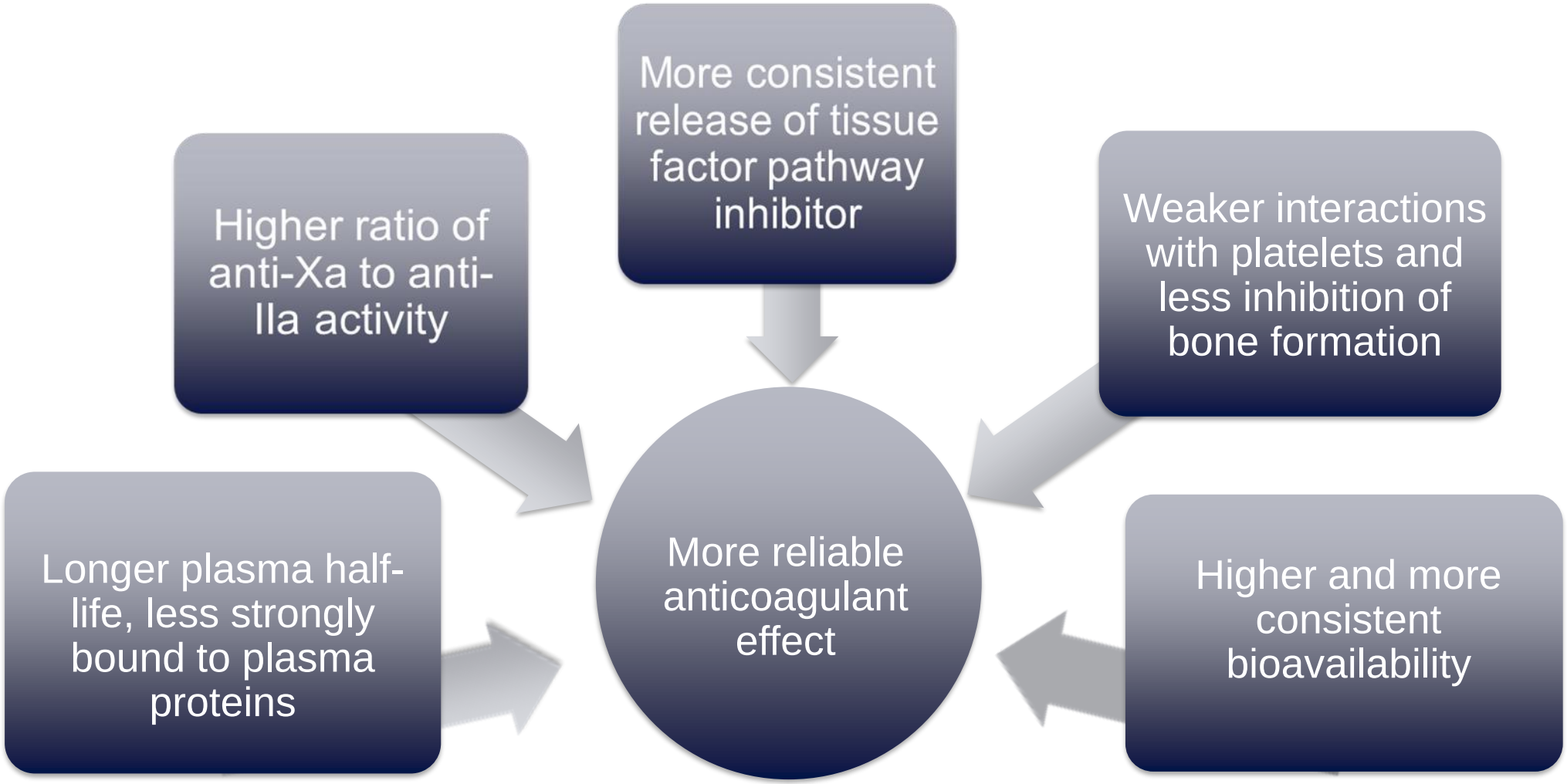
Enoxaparin

Enoxaparin is a low molecular weight heparin that exerts its anticoagulation effect by binding antithrombin and exerting a conformational change which accelerates inactivation of factor Xa.

- Half life based on anti-Factor Xa activity 4.5 to 7 hours
- Primarily metabolized in the liver by desulfation and/or depolymerization
- Renal clearance of active fragments represent 10% of active dose and total renal excretion of active and non-active fragments 40% of the dose
- Decreased clearance of enoxaparin in patients with reduced renal function
  - Anti-Xa exposure represented by AUC is marginally increased in mid/moderate renal impairment and significantly increased in severe renal impairment (creatinine clearance < 30 mL/min)

Source: Lovenox package inset, Sanofi-Aventis, U.S. LLC, NF, 2017

Why is enoxaparin preferred over heparin?



Source: Fareed J, Hop. Pharmacodynamic and pharmacokinetic properties of enoxaparin : implications for clinical practice. Clin Pharmacokinet. 2003;42(12):1043-57.

Unfractionated Heparin (UFH) vs. Enoxaparin

Unfractionated Heparin	Enoxaparin
Large molecule with mean molecular weight of 15 kDa leads to varied anticoagulant activity. Profile is influenced by chain length of molecules and clearance is influenced by molecular size	LMWH has **shorter polysaccharide chains** with average molecular weight in range of 3-7 kDa
UFH exhibits complex **mixed-order kinetic behavior** due to additional exogenous interactions such as binding to proteins and vascular sites: no clear dose-response relationship→ periodic monitoring of drug and dosage adjustments required	Enoxaparin exhibits **first order kinetics** where the endogenous microbiological effects (anti-Xa and anti-Xa) are dosage and time dependent: More predictable, dosage be can adjusted for optimization of clinical outcome
UFH highly **variable bioavailability** after SubQ administration (may be explained by mixed-order kinetics)	LMWH has **shorter polysaccharide chains** with average molecular weight in range of 3-7 kDa

Source: Fareed J, Hop. Pharmacodynamic and pharmacokinetic properties of enoxaparin : implications for clinical practice. Clin Pharmacokinet. 2003;42(12):1043-57.

UFH vs. Enoxaparin, *continued*

Unfractionated Heparin	Enoxaparin
Almost 95% of heparin components exhibit both anti-Xa and anti-IIa actions. Ratio of **anti-Xa: anti-IIa** is **lower** and **does not change** over time	Less than 30% of molecules show both anti-Xa and anti-IIa actions but relative presence of oligosaccharides exhibiting sole anti-Xa activity much high. The **anti-Xa:IIa ratio is higher than heparin (4:1) and increases** over period of time; (higher ratio may be associated with less tendency to cause bleeding)
UFH may be **less effective** in situations where there is significant platelet activation	Enoxaparin has **lower tendency to cause bleeding** due to weaker platelet inhibition. Reduced interaction with platelets may be linked to reduced incidence of HIT
Both UFH and enoxaparin lead to release of Tissue Factor Pathway Inhibitor which has inhibitor effects on coagulation cascade, however after 5 days of administration of UFH, **total TFPI activity is partially depleted**	**No depletion of total Tissue Factor Pathway Inhibitor** following subcutaneous dosing of Enoxaparin: further explanation of more predictable anticoagulation effect

Source: Fareed J, Hop. Pharmacodynamic and pharmacokinetic properties of enoxaparin : implications for clinical practice. Clin Pharmacokinet. 2003;42(12):1043-57.

Heparin vs. Enoxaparin | Geerts, W. H., et al.

Primary Objective: Compare the efficacy of low-dose heparin with that of low-molecular-weight heparin in patients with major trauma

Secondary Objective: Assess the safety of beginning prophylaxis with anticoagulants early after an injury

Exclusions: ISS < 9, likely to survive or remain in hospital < 7 days, intracranial bleeding on CT scan (patients w/ cerebral contusion, localized petechial hemorrhages, or diffuse axonal damage were not excluded), bleeding that remained uncontrolled 36 hours after injury, systemic coagulopathy (PT > 3 seconds above control or Platelet count < 50,000, needed therapeutic anticoagulation, could not undergo venography due to contrast allergy, renal failure, pregnant, venous access could not be achieved because of amputation or a major foot injury

Methods: Patients stratified by presence or absence of lower-extremity fracture. Consenting patients randomized to either heparin 5000 units or Enoxaparin 30mg q12 in a blinded fashion

Source: Geerts WH, et al. A comparison of low-dose heparin with low-molecular-weight heparin as prophylaxis against venous thromboembolism after major trauma. N Engl J Med. 1996 Sep 5;335(10):701-7. .

Geerts, W. H., et al. | Rates of thrombosis in the Study Patient

Group and Outcome	Low-Dose Heparin	Enoxaparin	Statistics
All Patients			
All deep-vein thrombosis	60/136 (44.1)	40/129 (31.0)	RRR 0.3; 95% CI 4-50; P = 0.014
Proximal-vein thrombosis	20/136 (14.7)	8/129 (6.2)	RRR 0.58; 95% CI 12-87; P = 0.012
Patients with leg fractures			
All deep-vein thrombosis	43/88 (48.9)	31/80 (38.8)	RRR 0.21
Proximal-vein thrombosis	16/88 (18.2)	4/80 (5)	RRR 0.73
Patients without leg fractures			
All deep-vein thrombosis	17/48 (35.4)	9/49 (18.4)	RRR 0.48
Proximal-vein thrombosis	4/48 (8.3)	4/49 (8.2)	RRR 0

Source: Geerts WH, et al. A comparison of low-dose heparin with low-molecular-weight heparin as prophylaxis against venous thromboembolism after major trauma. N Engl J Med. 1996 Sep 5;335(10):701-7. .

Geerts, W. H., et al., *continued*

Results

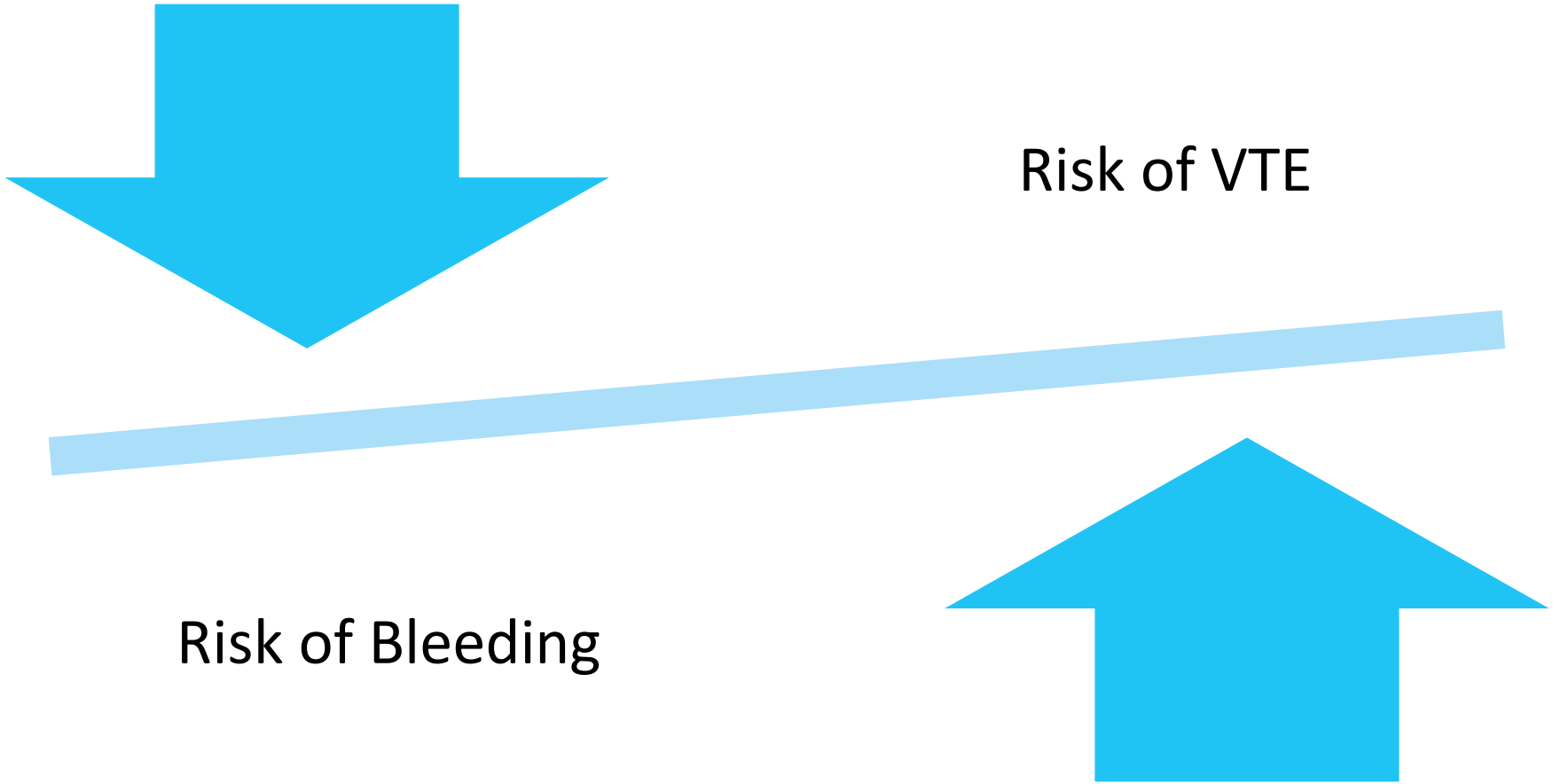
- Heparin decreases rate of DVT and proximal vein thrombosis by only 19% and 12%, respectively. The risk reductions with enoxaparin were 43% and 65%, respectively.
- No significant difference in regard to major bleeding with one episode in the heparin group (0.6%) and five episodes in the enoxaparin group (2.9%) P = 0.12

Author's Conclusion:

- Patients with major trauma are at very high risk for venous thromboembolism
- Enoxaparin is efficacious in preventing thromboembolic events in major trauma patients
- Low-dose heparin is relatively ineffective as prophylaxis in this population of patients
- Risk of major bleeding in low in both groups, even when anticoagulant therapy is initiated within 36 hours of the injury

Source: Geerts WH, et al. A comparison of low-dose heparin with low-molecular-weight heparin as prophylaxis against venous thromboembolism after major trauma. N Engl J Med. 1996 Sep 5;335(10):701-7. .

Finding the Proper Balance



Finding the Proper Balance

- Pharmacologic thromboprophylaxis is associated with a low, but clearly quantifiable, bleeding risk in the range of 1% to 3%, depending on the agent used
- Provider has to balance the risk of bleeding with the risk of VTE and the perceived benefit of thromboprophylaxis
- Ability of provider to assess the risks and benefits might be limited, particularly when caring for patients at high risk for both bleeding and VTE
- The inability of providers to define the risks and benefits of prophylaxis may promote them to simply delay in the initiation of pharmacologic VTE prophylaxis until the bleeding risk has sufficiently abated

Source: Practice of Venous Thrombembolism Prophylaxis in Major Trauma Patient, J Trauma 2007;62:557-563.

Inflammation & Host Response to Injury Trial

- Incidence of venous thromboembolism (VTE) without prophylaxis as high as 80% after major trauma
- Multicenter prospective cohort study designed to evaluate clinical outcomes in adults with hemorrhagic shock after injury
- Purpose was to evaluate:
  - Timing of pharmacologic prophylaxis
  - The effects of delayed prophylaxis in a severely injured cohort of patients admitted to the ICU
- Rate of VTE was estimated as a function of the time to initiation of pharmacologic prophylaxis
- Multivariate stepwise logistic regression model used to evaluate factors associated with late initiation

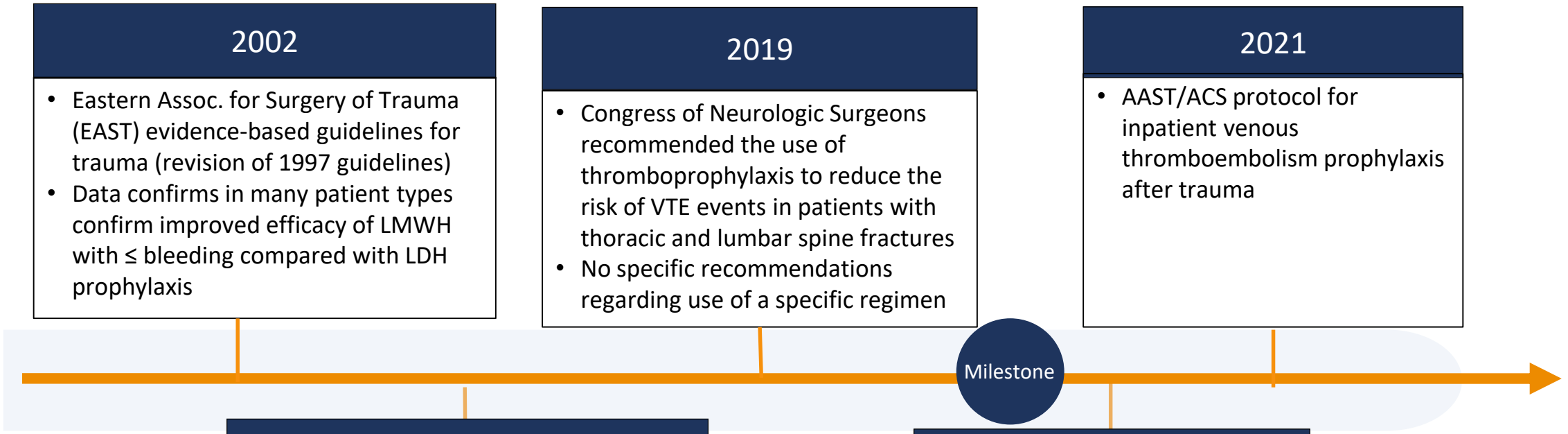
Source: Nathens AB, et al. The practice of venous thromboembolism prophylaxis in the major trauma patient. J Trauma. 2007 Mar;62(3):557-62.

Inflammation & Host Response to Injury Trial, *continued*

- **Primary objective** is to evaluate the relationship between the inflammatory response to injury and posttraumatic multiple organ failure
- Exposure represented the time to pharmacologic VTE prophylaxis and the primary outcome was development of VTE within 28 days of injury
- Of the 315 patients evaluated, 34 (11%) had a diagnosis of VTE
- Pharmacologic prophylaxis was initiated within 48 hours of injury in one-quarter of all patients, and another one-quarter went without prophylaxis for at least 7 days after injury
- Early prophylaxis was associated with a 5% risk of VTE, whereas a delay beyond 4 days was associated with three times that risk (RR: 3, 95% CI [1.4-6.5])

Source: Nathens AB, et al. The practice of venous thromboembolism prophylaxis in the major trauma patient. J Trauma. 2007 Mar;62(3):557-62.

Guidance

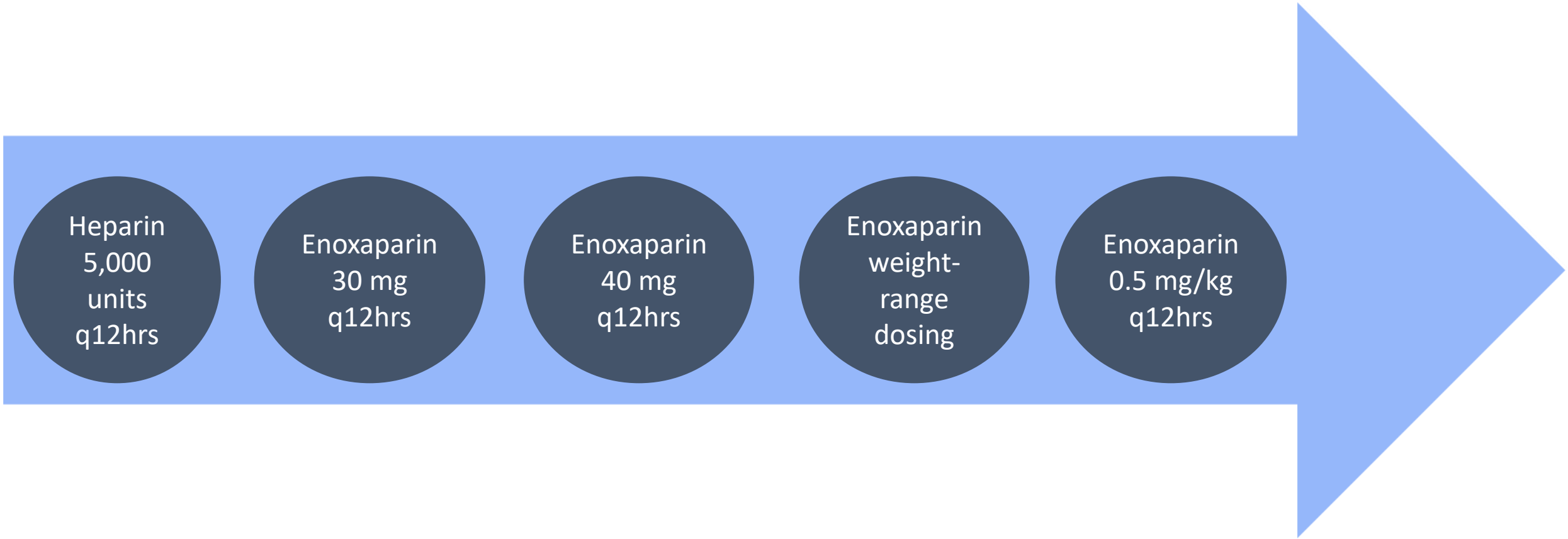


Source: Yorkgitis BK, W, Ley EJ, Napolitano L, Costantini TW. AAST/ASurgeons-Committee on Trauma Clinical Protocol for inpatient venous thrombo-embolism prophylaxis after trauma. *J Trauma Acute Care Surg.* 2022 Mar 1;92(3):597-604.

Dosing & Monitoring

Scott Rhude, PharmD

Dosing Strategies for Prophylaxis | A Historical Progression



Enoxaparin 30 mg SQ q12 hours

- Rationale: compared heparin 5000 units SQ q12 hours to enoxaparin 30 mg SQ q12 hours for efficacy and safety
- Method: randomized, double-blind controlled trial in trauma patients > 18 yoa with ISS ≥ 9 and no intracranial hemorrhage started within 36 hours of injury
- Results: rate of DVT was less in the enoxaparin group (31%) versus the heparin group (44%) p = 0.014
- Conclusion: enoxaparin was more effective at preventing VTE than heparin

Source: Geerts, et al. A comparison of low-dose heparin with low-molecular weight heparin as prophylaxis against venous thromboembolism after major trauma. N Engl J Med. 1996; 335(10): 701-707.

A Comparison of Low-dose Heparin With Low-molecular Weight Heparin as Prophylaxis Against Venous Thromboembolism After Major Trauma

- 344 patients enrolled with 265 completing the trial
- 136 received heparin and 129 received enoxaparin
- No significant differences in demographics or injury types between the two groups
- Prophylaxis initiated within 36 hours of injury
- Venography performed between days 10–14
- VQ scan performed to rule out PE if symptomatic
- Primary measure was proved VTE between the two groups

Source: Geerts, et al. A comparison of low-dose heparin with low-molecular weight heparin as prophylaxis against venous thromboembolism after major trauma. N Engl J Med. 1996; 335(10): 701-707.

A Comparison of Low-dose Heparin With Low-molecular Weight Heparin as Prophylaxis Against Venous Thromboembolism After Major Trauma, *continued*

Variable	Heparin 5,000 units q12 hours	Enoxaparin 30 mg q12 hours
DVT	60/136 (44.1%)	40/129 (31%)
Patients with leg fractures	43/88 (48.9%)	31/80 (38.8%)
Major bleeding	1	5

Source: Geerts, et al. A comparison of low-dose heparin with low-molecular weight heparin as prophylaxis against venous thromboembolism after major trauma. N Engl J Med. 1996; 335(10): 701-707.

Enoxaparin 40 mg SQ q12 hours

- Rationale: to test if enoxaparin 40 mg q12 hours would improve peak anti-Xa levels and reduce VTE
- Methods: retrospective review of trauma patients receiving prophylactic enoxaparin and peak anti-Xa levels. Patients were divided into two groups: (A) 30 mg q12 hours and (B) 40 mg q12 hours
- Results: 33% of group A had sub-prophylactic anti-Xa levels while 9% of group B had sub-prophylactic anti-Xa levels
- Conclusion: higher dosing leads to improved anti-Xa levels but did not have statistical decrease in VTE

Source: Kopelman, et al. Alternative dosing of prophylactic enoxaparin in the trauma patient: is more the answer? Am J Surg. 2013 Dec; 206(6); 911-15.

Alternative Dosing of Prophylactic Enoxaparin in the Trauma Patient: *Is more the answer?*

- 124 patients included
- 90 patients received enoxaparin 30mg q12 hours (group A)
- 34 patients received enoxaparin 40mg q12 hours (group B)
- Demographics similar in both groups except group B had significantly higher average body weight ($p < 0.001$)
- No significant difference in start time of prophylaxis
- Inadequate peak level defined as < 0.2 IU/mL

Source: Kopelman, et al. Alternative dosing of prophylactic enoxaparin in the trauma patient: is more the answer? Am J Surg. 2013 Dec; 206(6); 911-15.

Alternative Dosing of Prophylactic Enoxaparin in the Trauma Patient:

Is more the answer?

Variable	Group A 30mg q12 hours	Group B 40mg q12 hours	P value
Peak level < 0.2 IU/mL	30/90 (33%)	3/34 (9%)	0.01
VTE rate	6/47 (13%)	2/22 (9%)	NS

Source: Kopelman, et al. Alternative dosing of prophylactic enoxaparin in the trauma patient: is more the answer? Am J Surg. 2013 Dec; 206(6); 911-15.

Stratified Dosing of Enoxaparin

- Rationale: 30mg SQ q12 hour dosing may be inadequate for many patients.
- Method: 275 trauma patients were retrospectively reviewed for variables affecting initial anti-Xa levels. This led to development of a new dosing protocol with three weight-defined categories that might provide a higher percentage initial anti-Xa levels within the desired range (0.2-0.4 IU/ml) of which 145 patients were enrolled.
- Results: 29.5% of the pre-intervention group had initial anti-Xa levels within the desired range. 74.5% of the post-intervention group had initial anti-Xa levels within the desired range.
- Conclusion: Weight-based dosing improves the in-target anti-Xa levels on initial assessment.

Source: Berndston, et al. If some is good, more is better; an enoxaparin dosing strategy to improve pharmacologic venous thromboembolism prophylaxis. J Trauma Acute Care Surg. 2016; 81(6): 1095-1100.

If Some Is Good, More Is Better

An enoxaparin dosing strategy to improve pharmacologic venous thromboembolism prophylaxis

- Most patients started on enoxaparin 40 mg SQ q12 hours
- Peak anti-Xa level was checked 3-5 hours after at least three serial doses
- Goal anti-Xa range of 0.2 to 0.4 IU/mL
- Patients included if > 50 kg and CrCL ≥ 30 mL/min
- 68% of patients had subprophylactic anti-Xa levels on initial assessment
- Study was not powered to compare VTE rates between groups

Source: Berndston, et al. If some is good, more is better; an enoxaparin dosing strategy to improve pharmacologic venous thromboembolism prophylaxis. J Trauma Acute Care Surg. 2016; 81(6): 1095-1100.

Stratified Dosing for Enoxaparin

Weight	Dose
50-60 kg	30 mg SQ q12 hours
61-99 kg	40 mg SQ q12 hours
>/= 100 kg	50 mg SQ q12 hours

Adjust by +/- 10 mg q12 hours based upon anti-Xa levels

Source: Berndston, et al. If some is good, more is better; an enoxaparin dosing strategy to improve pharmacologic venous thromboembolism prophylaxis. J Trauma Acute Care Surg. 2016; 81(6): 1095-1100.

If Some Is Good, More Is Better

An enoxaparin dosing strategy to improve pharmacologic venous thromboembolism prophylaxis

Variable	Pre-intervention	Post-intervention	P-value
Sub-prophylactic level on initial draw	68%	20.7%	< 0.001
Level within the desired range on initial draw	29.5%	74.5%	< 0.001

Source: Berndston, et al. If some is good, more is better; an enxoparin dosing strategy to improve pharmacologic venous thromboembolism prophylaxis. J Trauma Acute Care Surg. 2016; 81(6): 1095-1100.

Enoxaparin 0.5 mg/kg q12 hours

- Rationale: weight-based dosing would result in appropriate prophylaxis more reliably than fixed dosing
- Methods: A prospective adjusted-dosing group was compared to a retrospective uniform-dosing group. Adjusted dosing began at 0.5 mg/kg SQ q12 hours and adjusted based upon peak anti-Xa levels in +/- 10mg increments. The uniform group received 30mg SQ q12 hours without adjustment.
- Results: More patients were sub-prophylactically dosed in the uniform-dosing group relative to the adjusted-dosing group (25% vs 5%)
- Conclusion: Weight based prophylactic dosing with anti-Xa dose adjustments improve prophylactic range targeting compared to uniform dosing.

Source: Rodier, et al. Weight-based enoxaparin with anti-factor Xa assay-based dose adjustment for venous thromboembolic event prophylaxis in adult trauma patients results in improved prophylactic range targeting. Eur J Trauma Emerg Surg. 47, 145-151 (2021)

Weight-based Enoxaparin

With anti-factor Xa assay-based dose adjustment for venous thromboembolic event prophylaxis in adult trauma patients results in improved prophylactic range targeting

Patient weight	Enoxaparin dose
< 69.9 kg	30 mg q12 hours
70-89.9 kg	40 mg q12 hours
>/= 90 kg	50 mg q12 hours

Source: Rodier, et al. Weight-based enoxaparin with anti-factor Xa assay-based dose adjustment for venous thromboembolic event prophylaxis in adult trauma patients results in improved prophylactic range targeting. Eur J Trauma Emerg Surg. 47, 145-151 (2021)

Weight-based Enoxaparin, *continued*

With anti-factor Xa assay-based dose adjustment for venous thromboembolic event prophylaxis in adult trauma patients results in improved prophylactic range targeting

- Initial dose was 0.5 mg/kg rounded to the nearest 10 mg
- Initial maximum dose of 50 mg q12 hours with final maximum adjusted dose of 60 mg q12 hours
- Initial minimum dose of 30 mg q12 hours with final minimum adjusted dose of 20 mg q12 hours
- Peak anti-Xa level measured 4 hours after the 3rd dose
- Prophylactic range defined as 0.2 – 0.5 IU/mL
- Not powered to detect VTE rates between the groups

Source: Rodier, et al. Weight-based enoxaparin with anti-factor Xa assay-based dose adjustment for venous thromboembolic event prophylaxis in adult trauma patients results in improved prophylactic range targeting. Eur J Trauma Emerg Surg. 47, 145-151 (2021)

Weight-based Enoxaparin, continued

With anti-factor Xa assay-based dose adjustment for venous thromboembolic event prophylaxis in adult trauma patients results in improved prophylactic range targeting

Variable	Uniform dosing	Adjusted dosing	P value
Mean peak anti-Xa level	0.26	0.32	0.009
Sub-prophylactic initial level	25%	5%	0.03
Desired range after 1 adjustment	75%	100%	0.003

Source: Rodier, et al. Weight-based enoxaparin with anti-factor Xa assay-based dose adjustment for venous thromboembolic event prophylaxis in adult trauma patients results in improved prophylactic range targeting. Eur J Trauma Emerg Surg. 47, 145-151 (2021)

Anti-Xa Monitoring | Questions That Need an Answer

- In whom should levels be drawn?
- At what point in therapy should a level be checked?
- What is the target level or range?

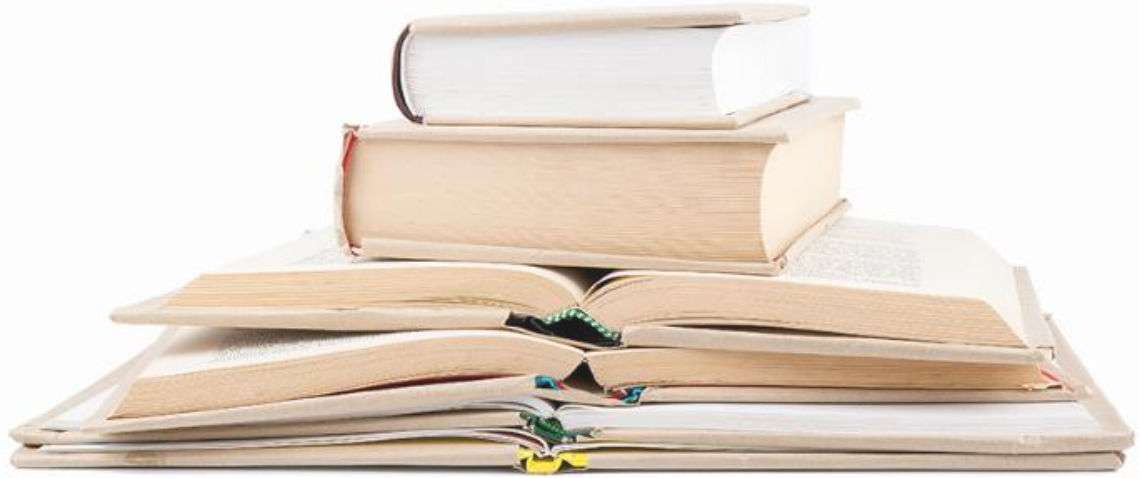
In whom should levels be drawn?

- Malinoski et al reported a DVT rate of 37% in patients with anti-Xa peak levels ≤ 0.1 IU/mL
- Many patients will require dose adjustments based upon anti-Xa levels

Sources: Malinoski, et al. Standard prophylactic dosing leads to inadequate anti-Xa levels and increased deep venous thrombosis rates in critically ill trauma and surgical patients. J Trauma. 2010' Apr; 68(4):874-880
Ley, EJ, et al. Updated guidelines to reduce venous thromboembolism in trauma patients: A Western Trauma Association critical decisions algorithm. J Trauma Acute Care Surg. 2020 Nov;89(5):971-981.
Yorkgitis BK, et al. **AAST/ACS-Committee on Trauma Clinical Protocol for inpatient venous thromboembolism prophylaxis after trauma**. *J Trauma Acute Care Surg.* 2022 Mar 1;92(3):597-604.

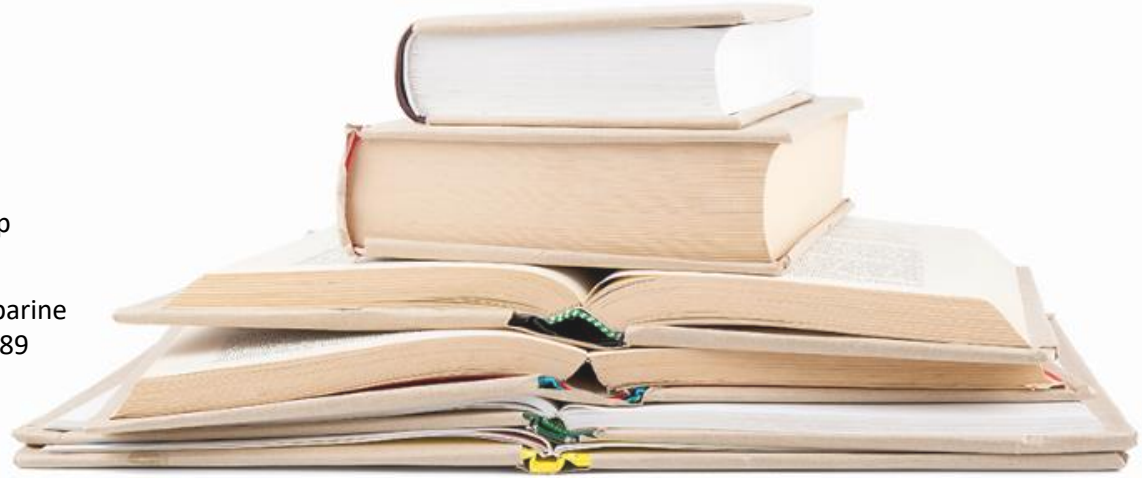
At what point in therapy should a level be checked?

- Anti-Xa levels should be drawn after the 3rd consecutive dose
- Peak anti-Xa levels should be drawn 3–5 hours after the dose is administered



What is the target level or range?

- Malinoski et al reported a DVT rate of 37% in patients with anti-Xa peak levels ≤ 0.1
- Range of 0.2 – 0.5 originally derived from orthopedic literature
- Many studies have used a peak range of 0.2 – 0.4
- Some literature suggests a range of 0.3 – 0.5



Sources: Malinoski, et al. Standard prophylactic dosing leads to inadequate anti-Xa levels and increased deep venous thrombosis rates in critically ill trauma and surgical patients. J Trauma. 2010; Apr; 68(4): 874-880.

Levine et al. The relationship between anti-factor Xa level and clinical outcomes in patients receiving enoxaparine low molecular weight heparin to prevent deep vein thrombosis after hip replacement. Thromb Haemost. 1989 Nov 24;62(3):940-4.

Kopelman eta al. Goal directed enoxaparin dosing provides superior chemoprophylaxis against deep vein thrombosis. Injury. 2017 May;48(5): 1088-1092.

Western Trauma Association (WTA) Critical Decisions Algorithm – 2020

- Who should receive prophylaxis?
- When should prophylaxis be initiated?
- Which agent should be used?
- How should agents for prophylaxis be dosed?
- How should regimens be monitored?
- How should regimens be adjusted?

WTA Algorithm | Who should receive prophylaxis?

- Trauma patients are at high risk of developing VTE with a rate as high as 58% in severe trauma
- Trauma patients with an ISS >/= 10 should be initiated on prophylaxis as soon as possible
- Other scoring systems such as the Greenfield Risk Assessment Profile or the TESS can assist in calculating VTE risk

Source: Ley, et al. Updated guidelines to reduce venous thromboembolism in trauma patients: A Western Trauma Association critical decisions algorithm. J Trauma Acute Care Surgery. 2020; 89(5): 971-981.

WTA Algorithm | Other Considerations

- Pelvic/spinal fractures
- Repair of venous injuries
- Prior history of VTE
- Inherited clotting disorders
- Increasing age
- Obesity
- Lower extremity fractures
- Combination any of the above

Source: Ley, et al. Updated guidelines to reduce venous thromboembolism in trauma patients: A Western Trauma Association critical decisions algorithm. J Trauma Acute Care Surgery. 2020; 89(5): 971-981.

WTA Algorithm | Cause for Pause

- Active bleeding – hemoglobin drop > 2 g/dL in under 12 hours
- Coagulopathy – platelet count < 50,000 per cubic millimeter
- Solid organ injury (grades 4-5)
- Traumatic brain injury (requires stabilization of CT)
- Spinal cord injury (may require 48-hour delay post operative fixation)

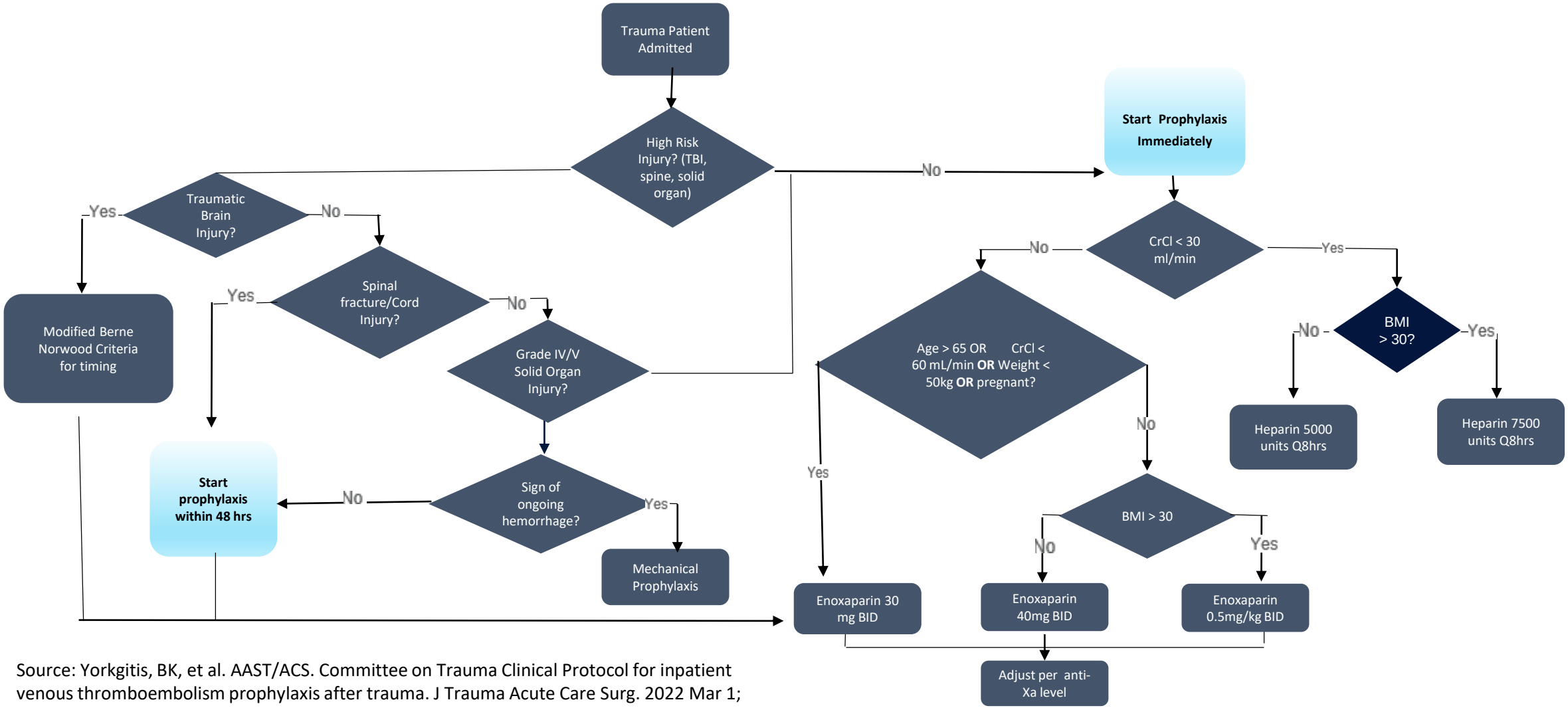
Source: Ley, et al. Updated guidelines to reduce venous thromboembolism in trauma patients: A Western Trauma Association critical decisions algorithm. J Trauma Acute Care Surgery. 2020; 89(5): 971-981.

WTA Algorithm | When to Start Prophylaxis

- In most cases prophylaxis may be started within 24 hours of the injury
- Withholding prophylaxis for 12–24 hours before planned surgical procedures is almost always unnecessary
- Some trauma injuries require special attention

Source: Ley, et al. Updated guidelines to reduce venous thromboembolism in trauma patients: A Western Trauma Association critical decisions algorithm. J Trauma Acute Care Surgery. 2020; 89(5): 971-981.

Inpatient Trauma VTE Prophylaxis Algorithm



Source: Yorkgitis, BK, et al. AAST/ACS. Committee on Trauma Clinical Protocol for inpatient venous thromboembolism prophylaxis after trauma. J Trauma Acute Care Surg. 2022 Mar 1; 92(3):597-604.

When to Start Prophylaxis

Scoring systems used to determine VTE risk in the trauma population

Scoring Systems Used to Categorize the Risk of VTE

- Injury severity score (ISS)
- Risk assessment profile (RAP)
- Trauma embolic scoring system (TESS)
- AAST for blunt injury scoring
- Modified Berne-Norwood criteria

Injury Severity Score (ISS)

- Divides the body into six anatomical regions
- Each injury is assigned a value based upon severity
- The sum of the values added together provides the score
- The maximum score is 75
- ISS of >/= 10 puts a patient at an elevated risk of VTE
- Not calculated in real time
- Used to standardize the study of trauma patients

Source: Injury Severity Score (ISS) – MDCalc; accessed April 2023

Greenfield Risk Assessment Profile

- Published in 1997
- Simple means of stratifying patients within the 1st 24 hours of admission for the potential of development of a DVT
- Considers factors such as: pre-injury conditions, iatrogenic factors, injury related factors and age
- Score of >/= 5 are at high risk of DVT formation
- Has a sensitivity of 82% and a specificity of 57% for predicting VTE

Source: Greenfield, et al. Posttrauma Thromboembolism Prophylaxis. The Journal of Trauma: Injury, Infection and Critical Care. 42(1): p 100-103, January 1997.

Trauma Embolic Scoring System (TESS)

- Considers factors such as: Age, ISS, BMI, ventilator days and presence of lower extremity fractures
- Scores can range from 0 to 14
- Score = 7–14 is indicative of moderate to high risk for VTE
- Has a sensitivity of 81.6% and a specificity of 84% for predicting VTE

Source: Rogers, et al. Determining venous thromboembolic risk assessment for patients with trauma: The Trauma Embolic Scoring System. Journal of Trauma and Acute Care Surgery. 73(2). 2012.

Special Types of Traumatic Injuries

- Solid organ injury (SOI)
- Traumatic brain injury (TBI)
- Spinal cord injury (SCI)

When to Initiate Prophylaxis | Solid Organ Injury

- American Association for the Surgery of Trauma (AAST) injury scoring system
- Used in blunt solid organ injuries
- Evaluates the injury to each organ (kidney, liver, spleen and pancreas)
- Grades can be 1 (least severe) through 5 (most severe)
- Grades 1–3 – Begin prophylaxis within 24 hours
- Grades 4–5 – Use caution

Source: Yorkgitis, BK, et al. **AAT/ACS-Committee on Trauma Clinical Protocol for inpatient venous thromboembolism prophylaxis after trauma**. *J Trauma Acute Care Surg*. 2022 Mar 1;92(3):597-604.

When to Initiate Prophylaxis | Traumatic Brain Injury

- Modified Berne-Norwood criteria
- Used for scoring traumatic brain injury (TBI)
- Stratifies patients into one of three categories: low, medium and high
- Low risk = Begin prophylaxis if CT stable at 24 hours
- Medium risk = Begin prophylaxis if CT stable at 72 hours
- High risk = Consider IVC filter placement

Source: Yorkgitis, BK, et al. **AAT/ACS-Committee on Trauma Clinical Protocol for inpatient venous thromboembolism prophylaxis after trauma**. *J Trauma Acute Care Surg.* 2022 Mar 1;92(3):597-604.

When to Initiate Prophylaxis | Traumatic Brain Injury, *continued*

- Cerebral contusion, petechial hemorrhage and diffuse axonal injury – No delay in prophylaxis
- For other TBI (intracerebral hemorrhage) – Hold until follow-up CT reveals no progression
- Progression can occur in almost 10% of patients with stable follow-up CT
- Majority may be started on prophylaxis within 24 hours of stable CT
- Nearly all TBI patients should receive prophylaxis within 72 hours of the time of injury

Source: Ley, et al. Updated guidelines to reduce venous thromboembolism in trauma patients: A Western Trauma Association critical decisions algorithm. J Trauma Acute Care Surgery. 2020; 89(5): 971-981.

When to Initiate Therapy | Spinal Cord Injuries

- The optimal timing is controversial
- When started within 48 hours there is a reduced incidence of VTE
- When delayed beyond 72 hours there is a substantial increase of VTE
- Intraspinal hemorrhage is of concern

Source: Ley, et al. Updated guidelines to reduce venous thromboembolism in trauma patients: A Western Trauma Association critical decisions algorithm. J Trauma Acute Care Surgery. 2020; 89(5): 971-981.

WTA Algorithm | What is the appropriate regimen of enoxaparin?

- Most patients will start with enoxaparin 40 mg SQ q12 hours
- Stratified dosing and weight-based dosing may also be appropriate

Source: Ley, et al. Updated guidelines to reduce venous thromboembolism in trauma patients: A Western Trauma Association critical decisions algorithm. J Trauma Acute Care Surgery. 2020; 89(5): 971-981.

WTA Algorithm | What is the appropriate regimen of enoxaparin?

Weight	Dose
50–60 kg	30 mg SQ q12 hours
61–99 kg	40 mg SQ q12 hours
≥ 100 kg	50 mg SQ q12 hours
0.5 mg/kg SQ q12 hours	

Source: Ley, et al. Updated guidelines to reduce venous thromboembolism in trauma patients: A Western Trauma Association critical decisions algorithm. J Trauma Acute Care Surgery. 2020; 89(5): 971-981.

WTA Algorithm | When to Begin With 30 mg q12 Hours

- Patient weight < 50kg
- Age > 65 years
- CrCL = 30–60 mL/min
- Patients with TBI
- Patients with SCI

Source: Ley, et al. Updated guidelines to reduce venous thromboembolism in trauma patients: A Western Trauma Association critical decisions algorithm. J Trauma Acute Care Surgery. 2020; 89(5): 971-981.

WTA Algorithm | What about heparin?

- Heparin 5,000 units q8 hours if CrCL < 30 mL/min

Source: Ley, et al. Updated guidelines to reduce venous thromboembolism in trauma patients: A Western Trauma Association critical decisions algorithm. J Trauma Acute Care Surgery. 2020; 89(5): 971-981.

WTA Algorithm | How to Monitor

- Majority of trials followed peak levels
- Consensus range is 0.2 – 0.4 IU/mL
- Some literature suggests 0.3 – 0.5 IU/mL

Source: Ley, et al. Updated guidelines to reduce venous thromboembolism in trauma patients: A Western Trauma Association critical decisions algorithm. J Trauma Acute Care Surgery. 2020; 89(5): 971-981.

WTA Algorithm | How to Monitor

- Trough levels may also be used
- Trough range is 0.1 to 0.2 IU/mL

Source: Ley, et al. Updated guidelines to reduce venous thromboembolism in trauma patients: A Western Trauma Association critical decisions algorithm. J Trauma Acute Care Surgery. 2020; 89(5): 971-981.

Polling Question 1

What do these five movies have in common?

- Back to the Future
- Bad Boys
- Fast and Furious
- Home Alone
- Matrix

Polling Question 1

a) Michael J. Fox stars in all 5 movies

b) All of the movies are foreign films

c) Each movie had a sequel

d) Each movie had a high speed car chase

American Association for the Surgery of Trauma/ American College of Surgeons – Committee on Trauma Clinical Protocol for Inpatient Venous Thromboembolism Prophylaxis After Trauma

- Enoxaparin 40 mg SQ q12 hours
- Same recommendations for enoxaparin 30 mg SQ q12 hours
- BMI > 30 begin enoxaparin at 0.5 mg/kg SQ q12 hours
- For CrCL < 30 ml/min begin heparin 5,000 units SQ q8 hours
- For CrCL < 30 and BMI > 30 begin heparin 7,500 units SQ q8 hours

Source: Yorkgitis, et al. American Association for the Surgery of Trauma/American College of Surgeons-Committee on Trauma Clinical Protocol for inpatient venous thromboembolism prophylaxis after trauma. J of Trauma and Acute Care Surg. 2022 Mar 1; 92(3): 597-604.

Looking Beyond the Horizon

- Further trials investigating the connection between antithrombin III and anti-Xa levels
- Use of thromboelastography to guide chemoprophylaxis
- Extending thromboprophylaxis to the outpatient setting

Source: Teichman, et al. Approaches for optimizing venous thromboembolism prevention in injured patients: Findings fro mthe consensus conference to implement optimal venous thromboembolism prophylaxis in trauma. J of Trauma and Acut Care Surgery. 2023; 94(3): 469-478.

Assessment Question 1

The following factor(s) may lead to an increased risk of thromboembolism in the acute trauma population:

a) Decreased venous blood flow
b) Increased endogenous anticoagulants
c) Immobilization
d) a & c
e) All of the above

Assessment Question 1 | Answer…

The following factor(s) may lead to an increased risk of thromboembolism in the acute trauma population:

a) Decreased venous blood flow

b) Increased endogenous anticoagulants

c) Immobilization

d) a & c

e) All of the above

Assessment Question 2

Which of the following inconsistencies traditionally existed regarding pharmacologic VTE prophylaxis strategies?

a) Optimal dose
b) Optimal timing
c) Parenteral versus oral therapy
d) Differences in practice amongst trauma specialists

Question 2 | Answer…Assessment

Which of the following inconsistencies traditionally existed regarding pharmacologic VTE prophylaxis strategies?

a) Optimal dose

b) Optimal timing

c) Parenteral versus oral therapy

d) Differences in practice amongst trauma specialists

Assessment Question 3

Based on current literature, which of the following dosing strategies would not be recommended as a starting therapy for trauma patients?

a) Enoxaparin 30 mg SQ Daily

b) Enoxaparin 40 mg SQ BID

c) Enoxaparin 0.5 mg/kg SQ BID

d) Heparin 5,000 units SQ TID in renal failure

Assessment Question 3 | Answer…

Based on current literature, which of the following dosing strategies would not be recommended as a starting therapy for trauma patients?

a) **Enoxaparin 30 mg SQ Daily**

b) Enoxaparin 40 mg SQ BID

c) Enoxaparin 0.5 mg/kg SQ BID

d) Heparin 5,000 units SQ TID in renal failure

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- Kopelman eta al. Goal directed enoxaparin dosing provides superior chemoprophylaxis against deep vein thrombosis. Injury. 2017 May:48(5): 1088-1092
- https://Source: Injury Severity Score (ISS) – MDCalc; accessed April 2023

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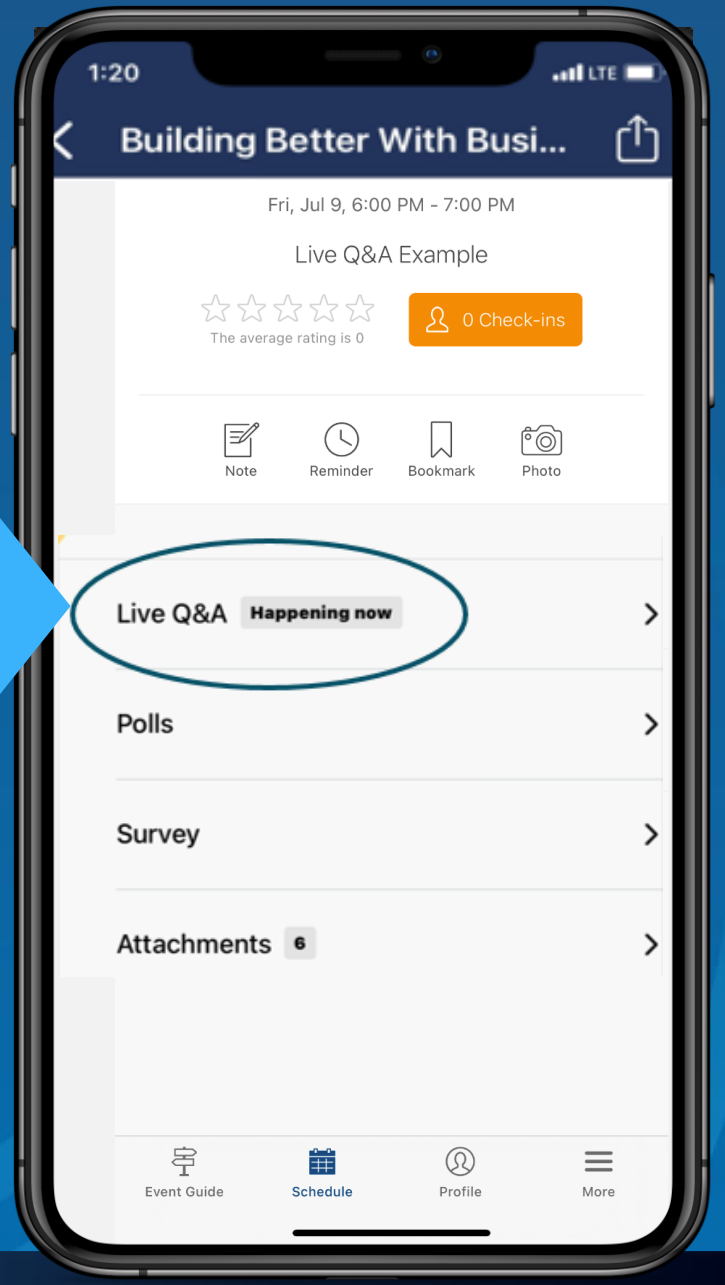
- Send in any time; Qs will be held until the end of the session



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