

DISCLAIMER: These guidelines were prepared jointly by the Surgical Critical Care and Medical Critical Care Services at Orlando Regional Medical Center. They are intended to serve as a general statement regarding appropriate patient care practices based upon the available medical literature and clinical expertise at the time of development. They should not be considered to be accepted protocol or policy, nor are intended to replace clinical judgment or dictate care of individual patients.

## DEEP VEIN THROMBOSIS PROPHYLAXIS IN THE CRITICALLY ILL

### SUMMARY

Critically ill patients are at significant risk for deep vein thrombosis (DVT) as a result of inactivity, immobilization, vascular injury, and/or hypercoagulable states. DVT may progress to thrombophlebitis or pulmonary embolism (PE) with increased morbidity and mortality. Appropriate DVT prophylaxis varies with the patient's risk factors and physiologic state.

### RECOMMENDATIONS

- **Surgery (General / Vascular / GYN / Urology / Non-Trauma Neurosurgery)**
  - **Level 1**
    - Patients at moderate or high-risk for DVT should receive prophylaxis using low dose unfractionated heparin (LDUH).
  - **Level 2**
    - Patients at low-risk for DVT require only early ambulation.
    - Patients at risk for bleeding should receive mechanical prophylaxis with intermittent pneumatic compression devices (IPC) or venous foot pumps (VFP).
    - Patients at very high-risk for DVT should receive LDUH combined with IPC or VFP.
- **Trauma**
  - **Level 1**
    - Patients should receive DVT prophylaxis using low molecular weight heparin (LMWH) as soon as is clinically safe.
  - **Level 2**
    - If LMWH prophylaxis is contraindicated, IPC should be used.
    - Inferior vena cava filter (IFC) insertion is not recommended for primary prophylaxis (see IVC Filter guideline).
  - **Level 3**
    - LMWH, started 24 hours after injury or craniotomy, may be safely used for prophylaxis in patients with intracranial hemorrhage.
    - When using LMWH, dose adjustment and/or anti-Xa monitoring should be considered for weight < 45 kg, obesity, or renal impairment ( $Cr_{Cl} < 30$  mL/min).
- **Medical**
  - **Level 1**
    - Patients with congestive heart failure, severe respiratory disease or who are confined to bed AND have 1 or more additional risk factors should receive LMWH.
  - **Level 2**
    - Mechanical prophylaxis using IPC or VFP is indicated for patients with a contraindication to anticoagulant prophylaxis.

### EVIDENCE DEFINITIONS

- **Class I:** Prospective randomized controlled trial.
- **Class II:** Prospective clinical study or retrospective analysis of reliable data. Includes observational, cohort, prevalence, or case control studies.
- **Class III:** Retrospective study. Includes database or registry reviews, large series of case reports, expert opinion.
- **Technology assessment:** A technology study which does not lend itself to classification in the above-mentioned format. Devices are evaluated in terms of their accuracy, reliability, therapeutic potential, or cost effectiveness.

### LEVEL OF RECOMMENDATION DEFINITIONS

- **Level 1:** Convincingly justifiable based on available scientific information alone. Usually based on Class I data or strong Class II evidence if randomized testing is inappropriate. Conversely, low quality or contradictory Class I data may be insufficient to support a Level I recommendation.
- **Level 2:** Reasonably justifiable based on available scientific evidence and strongly supported by expert opinion. Usually supported by Class II data or a preponderance of Class III evidence.
- **Level 3:** Supported by available data, but scientific evidence is lacking. Generally supported by Class III data. Useful for educational purposes and in guiding future clinical research.

## OVERVIEW

Venous thromboembolism (VTE) is associated with significant morbidity and mortality as well as an enormous economic expense. Approximately 200,000 cases of VTE occur annually of which one third involve pulmonary embolism (PE) accounting for 10% of hospital deaths (1). Hospitalization for an acute medical illness increases the risk of VTE almost 8-fold (2). The 30-day mortality of deep venous thrombosis (DVT) is 6% and that of PE is 12% (3). The annual economic burden of VTE is estimated at \$1.5 billion per year. Critically ill patients are at significant risk for the development of DVT as a result of inactivity, immobilization, vascular injury, and/or hypercoagulable states. DVT prophylaxis is indicated in the majority of critically ill patients with the appropriate therapy being determined by the patient's risk factors and physiologic state.

### **DVT PROPHYLAXIS SHOULD BE CONSIDERED IN ALL CRITICALLY ILL PATIENTS AND INITIATED AT THE TIME OF IMMOBILITY**

## ***SURGERY (GENERAL / VASCULAR / GYN / UROLOGY / NON-TRAUMA NEUROSURGERY)***

### **Introduction**

The overall incidence of DVT in post-surgical patients is 19-29% with patients with malignancy being at highest risk. PE is clinically recognized in 1.6% of patients with an additional 0.9% being recognized only post-mortem. Knowledge of specific risk factors forms the basis for appropriate prophylaxis. The rationale for thromboprophylaxis is based on the high prevalence of DVT among hospitalized patients, the clinically silent nature of the disease in the majority of patients, and the morbidity, costs, and potential mortality associated with DVT (4,5).

### **Clinical risk factors for DVT and PE in the NON-TRAUMA SURGICAL patient**

- Prolonged immobility
- Age > 40 years
- Stroke
- Paralysis
- Previous DVT
- Malignancy and its treatment
- Major surgery (particularly involving the abdomen, pelvis, and lower extremities)
- Obesity
- Varicose veins
- Cardiac dysfunction
- Indwelling central venous catheters
- Inflammatory bowel disease
- Nephrotic syndrome
- Pregnancy or estrogen use
- Congenital and acquired thrombophilic disorders (factor V Leiden, Lupus anticoagulant, protein C/S deficiency, etc...)

In many patients, multiple risk factors may be present with the total risk being cumulative. For surgical patients, the incidence of DVT is proportional to the risk factors present and the risk associated with the procedure itself. Procedure-related risks include: the location, technique, and duration of the procedure; the type of anesthetic; the presence of infection; and the degree of postoperative immobilization.

### **Prophylactic Agents and Literature Review**

<p>Low dose unfractionated heparin (LDUH)</p> <p>Cost: \$2 / day</p>	<p>LDUH thromboprophylaxis in surgical patients has been evaluated in numerous meta-analyses. LDUH (5,000 units SQ q 8 to 12 hours) is usually started 2 hours before operation and continued for 7 days postoperatively, until patients are ambulatory, or discharged from the hospital. The overall incidence of DVT may be reduced from 25% to 8% using prophylactic LDUH therapy (3). There are no randomized trials comparing q 8 hour vs. q 12 hour dosing, however, one meta-analysis suggested that LDUH administered every 8 hours was more efficacious. The beneficial effect of LDUH has also been observed in trials of patients with malignant disease. LDUH therapy reduces the more serious end points of proximal DVT, clinically diagnosed PE, and fatal PE diagnosed at autopsy. The overall risk reduction in fatal PE using LDUH prophylaxis is 89% (7-9).</p>
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<p>Low molecular weight heparin (LMWH)</p> <p>Cost: \$ 16 / day</p>	<p>The advantages and disadvantages of LMWH in general surgery have been clarified by a number of large trials, as well as by meta-analyses in which LMWH and LDUH were compared. LMWH and LDUH appear to be equally efficacious in preventing DVT in surgical patients. In general surgery patients, there appears to be no adverse consequences of giving the first dose of LMWH 2 hours pre-op, and there may be an additional benefit in preventing DVT from developing during surgery or in the immediate postoperative period. When higher doses of LMWH are used in high-risk general surgery patients, treatment with the drug should generally be commenced 10 to 12 hours before operation to avoid excessive intra-operative bleeding. Given the approximate equivalence in efficacy and safety, cost becomes an important determinant in the choice between these drugs. LMWH is 2 to 10 times more expensive than LDUH. Cost-effectiveness analyses performed in abdominal and colorectal surgery patients have concluded that prophylaxis with LDUH is more economical (10,11).</p>
<p>Intermittent pneumatic compression devices (IPC)</p> <p>Cost: \$50 / admission</p>	<p>IPC is an attractive method of prophylaxis because of the lack of hemorrhagic complications. Several small studies have demonstrated that IPC is effective in reducing DVT in general surgery patients and in surgical patients with malignant disease. In trials comparing IPC with LDUH, both agents produced similar reductions in DVT (12). However, compliance with these devices is low and it is not proven that IPC prevents PE (or even proximal DVT) in general surgery patients.</p>
<p>Graded compression elastic stockings (ES)</p>	<p>ES (e.g., Jobst® stockings NOT TED hose) reduce the incidence of leg DVT and enhance the protection provided by LDUH. Insufficient data exists to assess their effect on proximal DVT and PE however. Combining ES with other prophylactic agents, such as LDUH, appears to give better protection against DVT than either approach alone (13,14).</p>
<p>Venous foot pumps (VFP)</p> <p>Cost: \$ 50 / admission</p>	<p>Intermittent plantar compression, using VFP, produces hemodynamic effects on lower extremity emptying similar to that of IPC while also stimulating fibrinolytic activity (12).</p>

### **Discussion and Recommendations**

An appropriate preventive strategy takes into account the risk of DVT, the effectiveness of the various agents, and the expense and possible complications incurred by their use (Table 1) (15-17).

**Table 1: Non-Trauma Surgery Patient: Risk Stratification and Therapeutic Recommendations**

<b>Risk Category</b>	<b>Patient Example</b>	<b>Appropriate Therapy</b>
<b>Low</b>	Minor procedure with no additional risk factors	<b>No specific measures Early mobilization</b>
<b>Moderate</b>	Minor procedure with additional risk factors <i>OR</i> Major procedure with no additional risk factors	<b>LDUH q 12 hours <i>OR</i> LMWH +/- IPC / VFP</b>
<b>High</b>	Major procedure with additional risk factors	<b>LDUH q 8 hours <i>OR</i> LMWH +/- IPC / VFP</b>
<b>Very high</b>	Any procedure with 2 or more risk factors	<b>LDUH q 8 hours + IPC / VFP <i>OR</i> LMWH + IPC / VFP</b>

## **TRAUMA SURGERY**

### **Introduction**

PE is the third most common cause of death in trauma patients who survive beyond the first day (18). Without prophylaxis, patients with multi-system or major trauma have a risk for DVT that exceeds 50%, and a risk of fatal PE of approximately 0.4 - 2.0%. The traumatically injured are at high risk for developing DVT and PE as a result of endothelial injury and prolonged immobility. DVT is seen in 69% of lower extremity fractures, 62% of spine fractures, 54% of major head injuries, and 40% of patients with blunt thoracoabdominal trauma (18). Patients with single-system, non-orthopedic injuries have a lower risk of DVT than those with multiple injuries or with lower extremity fractures.

### **Risk factors independently associated with DVT in the TRAUMA patient**

- Spinal cord injury
- Lower extremity or pelvic fracture
- Need for a surgical procedure
- Increasing age
- Femoral venous line or major venous repair
- Prolonged immobility
- Duration of hospital stay

Routine use of thromboprophylaxis in trauma was first recommended 50 years ago. Because of the high thrombosis risk in the traumatically injured, recommendations for prophylaxis have been made using information from the limited studies in this specific group combined with extrapolation from other high-risk groups (15,19,20). Although the risk of DVT increases with age, young trauma patients may develop major DVT and fatal PE; thromboprophylaxis should therefore not be withheld simply because of youth (21,22).

### **Prophylactic Agents and Literature Review**

<p>Low dose unfractionated heparin (LDUH)</p> <p>Cost: \$2 / day</p>	<p>LDUH is not effective in the trauma patient and has been shown to be equivalent to <u>no prophylaxis</u> in high-risk trauma patients (23,24). LDUH should not be used for DVT prophylaxis in trauma patients.</p>
<p>Low molecular weight heparin (LMWH)</p> <p>Cost: \$24 / day</p>	<p>LMWH (e.g., enoxaparin 30 mg SQ q 12 hours) started within 36 hours of injury in major trauma patients without frank intracranial hemorrhage has been demonstrated to be superior to LDUH in preventing proximal DVT (6% vs. 15%) with a risk reduction of 58% (p=0.01) (25). The overall rate of major bleeding was 2% with no significant differences between the two drugs. The use of LMWH, started when primary hemostasis has occurred, is the simplest and most efficacious method of achieving DVT prophylaxis in most high-risk trauma patients.</p> <p>Current contraindications to early initiation of LMWH prophylaxis include the following:</p> <ul style="list-style-type: none"> <li>• Intracranial hemorrhage</li> <li>• Incomplete spinal cord injury with associated peri-spinal hematoma</li> <li>• Ongoing-uncontrolled hemorrhage</li> <li>• Uncorrected coagulopathy</li> </ul> <p>The presence of head injury without frank hemorrhage, complete spinal cord injuries, lacerations or contusions of internal organs such as the lungs, liver, spleen or kidneys, or the presence of retroperitoneal hematoma associated with pelvic fracture do not by themselves contraindicate the use of LMWH prophylaxis as long as the patient has no evidence of active bleeding. Recent Class II and III data suggests that LMWH can be safely used for DVT prophylaxis in patients with intracranial hemorrhage within 24 hours of hospital admission or craniotomy (26,27).</p> <p>The rates of total and proximal DVT after hip fracture are 50% and 25%, respectively, without thromboprophylaxis. In a population-based autopsy</p>

<p>Low molecular weight heparin (LMWH) (continued)</p> <p>Cost: \$24 / day</p>	<p>study of 581 patients who died after hip fracture from 1953 to 1992, PE was the fourth most common cause of death, accounting for 14% of all deaths (28). In a multivariate analysis, the risk of death following hip fracture was significantly reduced among patients receiving pharmacologic thromboprophylaxis (29). Although lower extremity fractures are very common, the risk of DVT has been poorly studied in this patient group. Among 76 patients with tibial fractures, Hjelmstedt and Bergvall found a 45% incidence of DVT overall, with extensive DVT in 16% and proximal DVT in 8% of patients. The risk of chronic leg swelling after these fractures and its association with post-injury DVT are unknown. Limited data demonstrate that DVT rates can be reduced by routine administration of LMWH in these patients (30).</p>
<p>Intermittent pneumatic compression devices (IPC)</p> <p>Cost: \$50 / admission</p>	<p>IPC cannot be recommended as routine prophylaxis in trauma, due to a lack of data. IPC may be beneficial as the initial prophylaxis in patients with intracranial hemorrhage or other injury who are at high risk for bleeding and can be utilized until anticoagulants, such as LMWH, may be safely initiated (31).</p>
<p>Graded compression elastic stockings (ES)</p>	<p>ES (e.g., Jobst® stockings NOT TED hose) cannot be recommended as routine prophylaxis in trauma, due to a lack of data. They may be beneficial as the initial prophylaxis in patients with intracranial hemorrhage or other injury who are at high risk for bleeding and can be utilized until anticoagulants, such as LMWH, may be safely initiated (31).</p>
<p>Venous foot pumps (VFP)</p> <p>Cost: \$ 50 / admission</p>	<p>The efficacy of these devices has been called into question by a randomized trial showing DVT rates three times greater with VFP compared to IPC. A recent cohort study demonstrated a venographically proven DVT rate of 57% in major trauma patients receiving prophylaxis with bilateral VFP. Compliance with these devices is poor. At the present time, VFP cannot be recommended in trauma patients (31).</p>

### **Discussion and Recommendations**

LMWH should be considered the agent of choice for DVT prophylaxis in the trauma patient without ongoing hemorrhage or uncontrolled coagulopathy. For patients with contraindications to LMWH prophylaxis, IPC should be initiated upon admission with institution of LMWH prophylaxis once primary hemostasis has been established. Although the optimal duration of prophylaxis is not known, therapy should generally continue until discharge from the hospital (4).

Standard dosing of enoxaparin (30 mg SQ q 12 hours) for DVT prophylaxis may not be optimal in several patient populations (32). For patients weighing less than 45 kg, some clinicians recommend using 0.5 mg/kg SQ q 12 hours. For obese patients, higher doses may be warranted. Due to the potential for delayed elimination in patients with renal impairment (creatinine clearance < 30 mL/minute), dose adjustment to 30 mg SQ q 24 hours is recommended. Dosing information for patients undergoing hemodialysis is lacking. Anti-Xa levels have been used to guide therapy (32). However, there is a relative lack of outcome data supporting this practice and the target range is not well-established. Despite these limitations, monitoring anti-Xa activity may be useful in populations where dosing is not well-established and the use of unfractionated heparin is not feasible. If obtained, levels should be drawn four hours after the third or fourth dose. The goal anti-Xa level for DVT prophylaxis is 0.1 to 0.3 IU/mL (33).

### **ENOXAPARIN DOSING IN TRAUMA PATIENTS**

Although several dosing strategies exist for DVT prophylaxis with enoxaparin (30 mg SQ q 12 hours and 40 mg SQ q day), the use of 40 mg SQ q day has not been well studied in the trauma population. Class I evidence demonstrates that enoxaparin 30 mg SQ q 12 hours decreases the incidence of DVT in major

trauma patients when compared to low-dose unfractionated heparin (25). This regimen has also been used in several other clinical trials (34-36). The use of enoxaparin 40 mg SQ q day has been evaluated in patients with multiple trauma (37,38) as well as those with spinal cord injuries (39). However, these studies are only available in abstract form at this time. There are currently no published trials comparing the two dosing regimens in trauma patients. Given the class I data supporting the efficacy of enoxaparin 30 mg SQ q12 hours and the lack of published data evaluating 40 mg SQ q 24 hours, a dose of 30 mg SQ q12 hours is recommended in the trauma population.

**MEDICINE**

**Introduction**

Fifty to 70% of symptomatic thromboembolic events and 70-80% of fatal PE currently occur in non-surgical patients (4). Over 96% of hospitalized adult medical patients have one risk factor and 40% have 3 or more risk factors for VTE (40). VTE risk increases in proportion to the number of risk factors present (40). Failure to prevent DVT can result in delayed hospital discharge, readmission, and postthrombotic syndrome, which can in turn lead to leg ulcers and leg swelling.

**Risk factors independently associated with DVT in the MEDICAL patient**

- Prolonged immobility
- Age > 40 years
- Stroke
- Paralysis
- Previous DVT
- Malignancy and its treatment
- Congestive heart failure
- Obesity
- Varicose veins
- Cardiac dysfunction
- Indwelling central venous catheters
- Inflammatory bowel disease
- Nephrotic syndrome
- Pregnancy
- Estrogen-containing oral contraception or hormone replacement therapy
- Selective estrogen-receptor modulators
- Myeloproliferative disorders
- Paroxysmal nocturnal hemoglobinuria
- Smoking
- Congenital and acquired thrombophilic disorders (factor V Leiden, Lupus anticoagulant, protein C/S deficiency, etc...)

**Prophylactic Agents and Literature Review**

<p>Low dose unfractionated heparin (LDUH)  Cost: \$2 / day</p>	<p>LDUH is not effective in the medical patient and has been shown to be equivalent to <u>no prophylaxis</u> (41). LDUH should not be used for DVT prophylaxis in medical patients.</p>
<p>Low molecular weight heparin (LMWH)  Cost: \$24 / day</p>	<p>LMWH (e.g., enoxaparin 40 mg SQ q 24 hours) has been demonstrated to be superior to placebo in preventing proximal DVT (5.5% vs. 14.9%) with a risk reduction of 63% (p&lt;0.001) (42). There was no statistically significant difference between enoxaparin 20 mg and placebo with respect to VTE.</p> <p>LMWH (enoxaparin 40 mg SQ q 24 hours) has been demonstrated to be equivalent to LDUH (5000 IU SQ q 8 hours) in preventing DVT in several large, prospective, randomized trials. In addition, enoxaparin was associated with fewer deaths, less bleeding, and fewer adverse events (4,43,44).</p>
<p>Low-intensity warfarin (target INR 1.5-2.0)</p>	<p>Long-term, low-intensity warfarin (target INR 1.5-2.0) has been demonstrated to be superior to placebo in preventing recurrent VTE with a risk reduction of 64% (p&lt;0.001) (45).</p>

Intermittent pneumatic compression devices (IPC) Cost: \$50 / admission	IPC cannot be recommended as routine prophylaxis in medical patients as no studies have been performed to determine their efficacy in preventing VTE. IPC may have a role in patients at high risk of bleeding or in combination with pharmacologic prophylaxis in very high-risk patients.
Venous foot pumps (VFP) Cost: \$ 50 / admission	VFP cannot be recommended as routine prophylaxis in medical patients as no studies have been performed to determine their efficacy in preventing VTE. VFP may have a role in patients at high risk of bleeding or in combination with pharmacologic prophylaxis in very high-risk patients.

### **Discussion and Recommendations**

LMWH should be considered the agent of choice for DVT prophylaxis in the acutely ill medical patient with congestive heart failure, severe respiratory disease, or who is confined to bed and have 1 or more additional risk factors including active cancer, previous VTE, sepsis, acute neurologic disease or inflammatory bowel disease. LMWH is associated with fewer deaths, less bleeding, and fewer adverse events compared to LDUH. VTE prophylaxis with LMWH is cost-effective compared with no prophylaxis and is cost-neutral or the dominant strategy compared with prophylaxis with LDUH. In medical patients in whom there is a contraindication to anticoagulant prophylaxis, the use of mechanical prophylaxis with IPC or VFP should be considered.

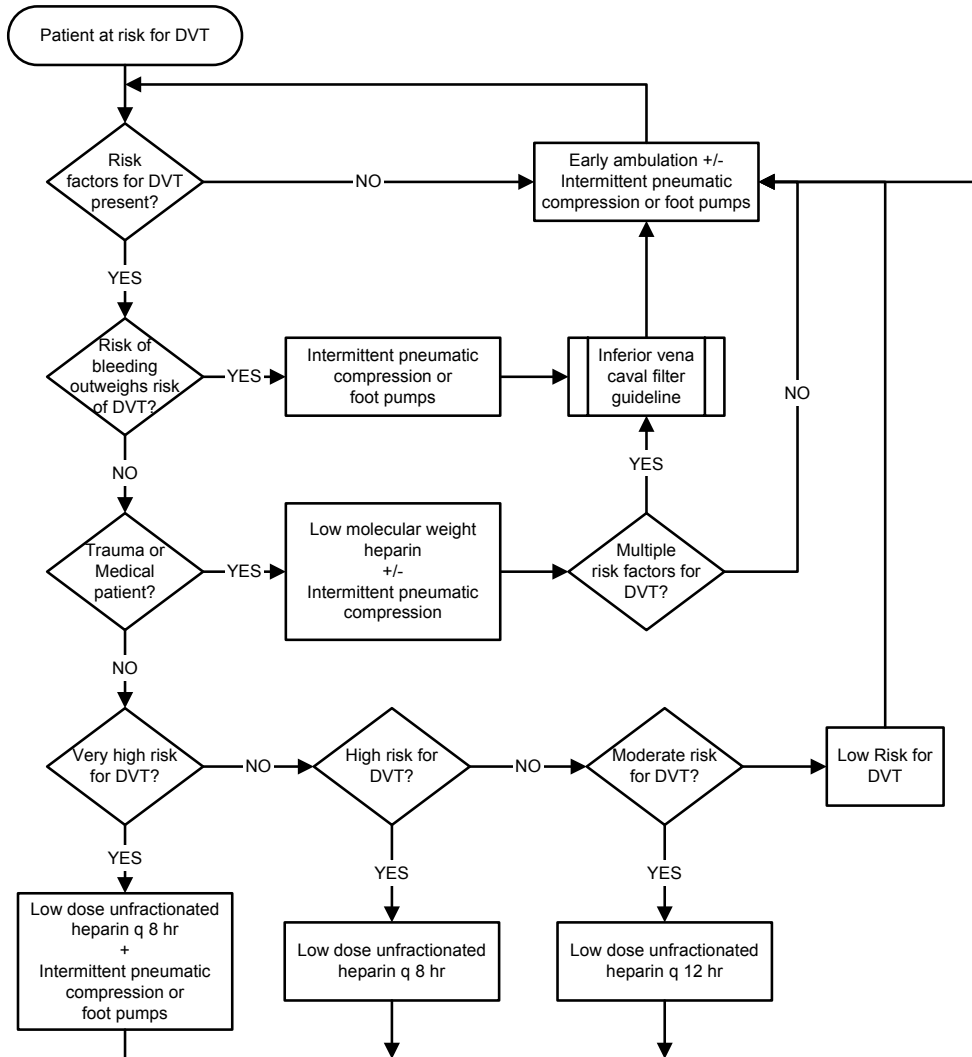
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## DEEP VENOUS THROMBOSIS (DVT) PROPHYLAXIS IN THE CRITICALLY ILL



- Risk Factors for DVT**
- Age > 40
  - Prolonged immobility / Spinal cord injury / Lower extremity or pelvic fracture
  - Stroke / Paralysis
  - History of previous venous thrombosis
  - Malignancy
  - Major surgery involving the abdomen, pelvis, lower extremities
  - Obesity
  - Congestive heart failure
  - Varicose veins
  - Cardiac dysfunction
  - Indwelling central venous catheters
  - Inflammatory bowel disease
  - Nephrotic syndrome
  - Pregnancy, estrogen use, hormone replacement therapy
  - Myeloproliferative disorders
  - Paroxysmal nocturnal hemoglobinuria
  - Smoking
  - Congenital or acquired thrombophilic disorders (e.g., factor V Leiden, lupus anticoagulant, Protein C or S deficiency)

<b>Surgical Risk Stratification</b>	
Low Risk	Minor procedure with no additional risk factors
Moderate Risk	Minor procedure with additional thrombosis risk factors OR Major surgery with no additional risk factors
High Risk	Major surgery with additional risk factors
Very High Risk	Any procedure with 2 or more risk factors