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 VENOUS THROMBOSIS PROPHYLAXIS IN SURGICAL PATIENTS

SUMMARY

Critically ill patients are at significant risk for deep venous 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 / Trauma / Vascular / GYN / Urology)**
  - **Level 1**
    - **Patients should receive DVT prophylaxis using low molecular weight heparin (LMWH) as soon as is clinically safe.**
  - **Level 2**
    - **Patients at low-risk for DVT require only early ambulation.**
    - **Patients at high-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 LMWH combined with IPC or VFP.**
    - **Inferior vena cava filter (IFC) insertion is not recommended for primary prophylaxis (see IVC Filter guideline).**
  - **Level 3**
    - **When using LMWH, dose adjustment and/or anti-Xa monitoring should be considered for weight < 45 kg, morbid obesity, or renal impairment (Cr_{Cl}<30 mL/min).**
- **Neurosurgery**
  - **Level 1**
    - **Patients at moderate or high-risk for DVT should receive prophylaxis using low dose unfractionated heparin (LDUH) due to easier reversibility.**
  - **Level 2**
    - **If chemoprophylaxis is contraindicated, IPC or VFP should be used.**
  - **Level 3**
    - **LDUH may be safely used for early prophylaxis in patients with non-worsening intracranial hemorrhage.**

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

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.

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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 PATIENTS AND INITIATED AT THE TIME OF IMMOBILITY*****

The overall incidence of DVT in 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).

PE is the third most common cause of death in trauma patients who survive beyond the first day (6). 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% (8-11). 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 (6). Patients with single-system, non-orthopedic injuries have a lower risk of DVT than those with multiple injuries or with lower extremity fractures.

Clinical risk factors for DVT and PE in the 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
- Spinal cord injury
- Lower extremity or pelvic fracture
- Need for a surgical procedure
- Increasing age
- 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…)
- Femoral venous line or major venous repair
- Prolonged immobility
- Duration of hospital stay

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.

Despite appropriate DVT prophylaxis, surgical patients may still develop both DVT and PE. A recent case-control study identified five independent predictors of in-hospital DVT despite chemoprophylaxis (12). These included hospitalization for cranial surgery, intensive care unit admission, admission leukocyte count >13,000/mm^3, presence of an indwelling central venous catheter, and admission from a long-term care facility. In the presence of such risk factors, aggressive efforts to achieve DVT prophylaxis should be maintained.

Alhazzani et al. recently performed a systematic review of studies involving medical-surgical ICU patients who received either any form of heparin [low dose unfractionated heparin (LDUH) or low molecular weight heparin (LMWH)] or no anticoagulant prophylaxis evaluating the incidence of DVT, pulmonary embolism, major bleeding , or mortality (13). Any heparin prophylaxis compared with no prophylaxis reduced rates of

DVT (relative risk [RR] 0.51; p<0.0001) and PE (RR 0.52; p=0.04). Major bleeding (RR 0.82; p=0.32) and mortality (RR 0.89; p=0.09) rates were not significantly increased. Compared with LDUH, LMWH reduced rates of symptomatic PE (RR 0.58); p=0.04), but not symptomatic DVT (RR 0.87; p=0.44), major bleeding (RR 0.97; p=0.83), or mortality (RR 0.93; p=0.20).

PROPHYLACTIC AGENTS AND LITERATURE REVIEW

Low dose unfractionated heparin (LDUH) – Cost: $5 per day

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 endpoints of proximal DVT, clinically diagnosed PE, and fatal PE diagnosed at autopsy. The overall risk reduction in fatal PE using LDUH prophylaxis is 89% (14-16).

LDUH is not effective in the trauma patient and has been shown to be equivalent to no prophylaxis in high-risk trauma patients (17). LDUH should not be used for DVT prophylaxis in trauma patients.

Low molecular weight heparin (LMWH) - Cost: $5-8 / day

The advantages and disadvantages of LMWH in surgery have been evaluated in a number of large trials as well as by meta-analyses comparing LMWH with LDUH. LMWH and LDUH appear to be equally efficacious in preventing DVT in surgical patients (13). In general surgery patients, there appear 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.

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 DVT and PE (18-20). The overall rate of major bleeding is no different 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. Current contraindications to early initiation of LMWH prophylaxis include the following:

- Active intracranial hemorrhage
- Incomplete spinal cord injury with associated peri-spinal hematoma
- Ongoing, uncontrolled hemorrhage
- Uncorrected coagulopathy

Although several dosing strategies exist for DVT prophylaxis with enoxaparin (30 mg SQ q 12 hours and 40 mg SQ q day), 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.

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 (21,22). LMWH may be more difficult to reverse than LDUH should intracranial hemorrhage worsen, however. At Orlando Regional Medical Center, the

neurosurgical team advocates early use of LDUH 5000 units q 8 hrs at the time of admission (in the absence of active intracranial hemorrhage) for the first seven (7) of prophylaxis after which time the patient may be switched to LMWH. For patients with contraindications to LDUH / LMWH prophylaxis, IPC should be initiated upon admission with institution of chemoprophylaxis once primary hemostasis has been established. Although the optimal duration of chemoprophylaxis 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 such as the under- and over-weight (23). For obese patients (BMI > 30), 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 (23). 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 (24).

Intermittent pneumatic compression devices (IPC) - Cost: $50 / admission

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 (25). However, compliance with these devices is low and it is not proven that IPC prevents PE (or even proximal DVT) in general surgery patients.

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 (26).

Graded compression elastic stockings (ES)

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 (27,28). ES 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 (26).

Venous foot pumps (VFP) - Cost: $50 / admission

Intermittent plantar compression, using VFP, produces hemodynamic effects on lower extremity emptying similar to that of IPC while also stimulating fibrinolytic activity (25). 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 (29). At the present time, VFP cannot be recommended in trauma patients.

Table 1: Surgical Patients: Risk Stratification and Therapeutic Recommendations

Population	Recommendation	Alternatives
High Risk (Polytrauma, VTE history, obesity, critical illness)	CrCl > 30 mL/min Enoxaparin 30 mg BID ($$) CrCl< 30 min Enoxaparin 30 mg daily ($)	Heparin 5000 units q 8 hrs ($) Fondaparinux 2.5 mg daily ($$$$) (for patients with history of heparin induced thrombocytopenia; contraindicated in patients with CrCl < 30 mL/min)
General Surgery Abdominal/Pelvic Surgery Cardiothoracic Surgery Trauma Surgery Orthopedic Surgery	CrCl > 30 mL/min Enoxaparin 40 mg daily ($) CrCl< 30 min Enoxaparin 30 mg daily ($)	
Neurosurgery Spine Surgery	Heparin 5000 units q 8 hrs ($)	

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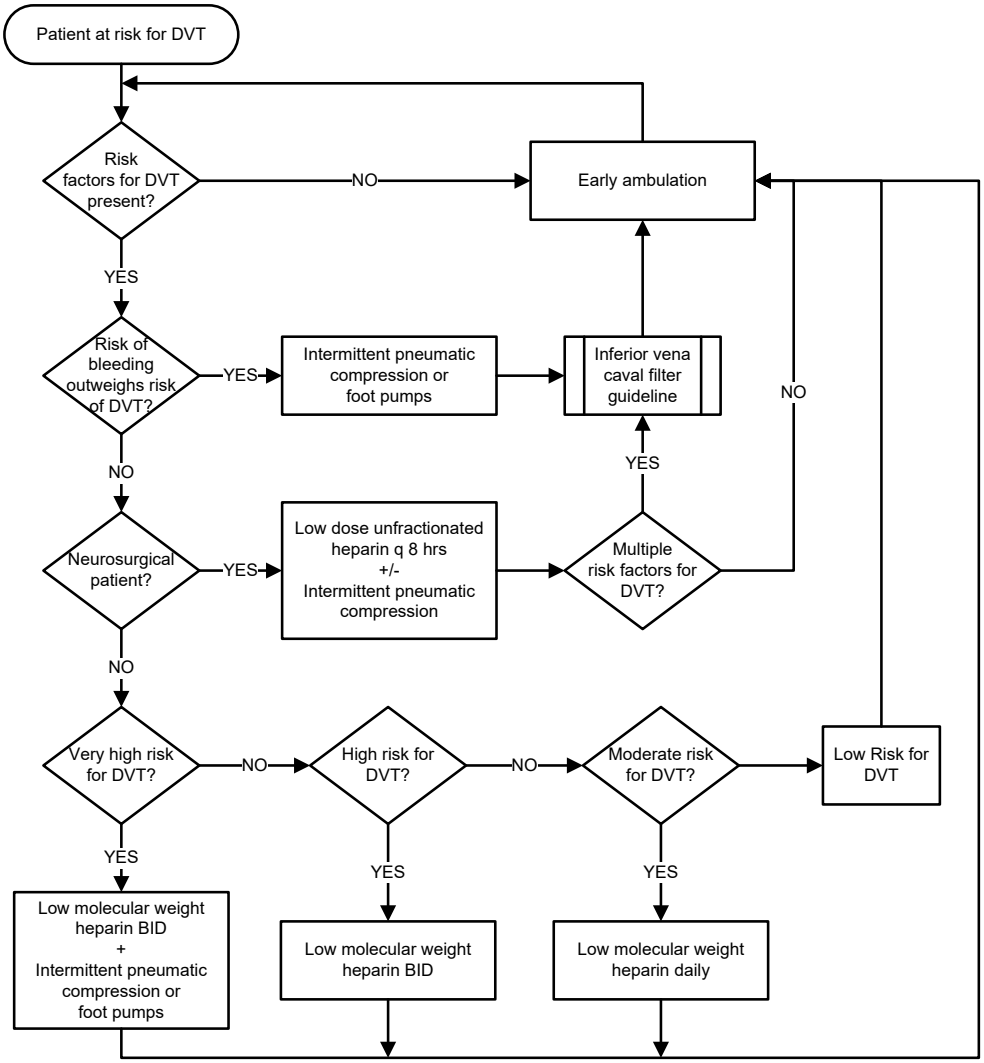
DEEP VENOUS THROMBOSIS (DVT) PROPHYLAXIS IN THE SURGICAL PATIENT



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)

Surgical Risk Stratification

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

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