CHAPTER **45**

CURRENT CONCEPTS IN DEEP VENOUS THROMBOSIS PROPHYLAXIS

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INTRODUCTION

Development of deep venous thrombosis (DVT) in the postoperative setting is a significant concern for foot and ankle surgeons. Such an untoward event is one of the greatest concerns of a surgeon, adding significant morbidity, mortality, and cost to patient care. DVT affects approximately two million people in the United States each year with 600,000 developing a pulmonary embolism (PE) as a consequence. Subsequent deaths from PE range from 50,000-100,000.[1-3] There is a wealth of information in the medical literature regarding the incidence of DVT and PE following major orthopedic surgeries of the lower extremities (particularly total joint replacement and trauma) as well as general surgery. However, statistics regarding occurrence after foot and ankle surgery have been sparse and recommendations regarding prophylaxis are not clearly identified.[4-6] The reported incidence of DVT following foot and ankle surgery has ranged from 0.22% to 3.5% with non-fatal PE being 0.15%.[4,5] Differences in study design and criteria may add to the disagreement in prevalence. Also, it is important to appreciate that not all of those who develop DVT are symptomatic, and not all will require treatment or progress to PE. In this light, the foot and ankle surgeon is left to face the question of prophylaxis against DVT and PE without solid scientific evidence. This combined with current trends in health care management, litigation, and the risks inherent not only with the surgery itself but to both preoperative co-morbidities and postoperative convalescence enhance the need to explore prophylaxis against DVT and PE. Therefore, the most clinically relevant questions are: What is the risk of thromboembolism following surgery? Is routine thromboprophylaxis indicated? What are the current recommendations for prophylaxis?

RISK FACTORS AND PATHOGENESIS

Several risk factors have been clearly defined for the development of DVT postoperatively and these are cumulative in nature. As the number of co-morbid conditions increase, so does risk of DVT. Categorized risk factors are any conditions described by following within Virchow's triad of a hypercoagulable state, endothelial damage, and stasis (Figure 1). Any one or a combination of these may predispose to the development of a thrombus.[11] Some of the generalized factors include: acquired coagulopathies, age, immobilization, history of DVT, recent major orthopedic surgery, prolonged surgery, obesity, tourniquet use, malignancy and trauma (Table 1).[1,3,5-7] Specifically in hospitalized patients, the most common risk factors have been found to be age, recent major surgery, immobilization, cardiopulmonary disease and obesity.[8,9] Detailed recommendations for prophylaxis with antithrombotic and thrombolytic therapy have been defined out by the American College of Chest Physicians and grades assigned to each level of evidence- based medicine (Table 2).[10,11]

Congenital ~~Acquired~~ coagulopathies include disorders such as factor V Leiden mutation, as well as protein C and S deficiencies. In addition to these acquired etiologies, increasing age may be a factor due to decreased elasticity of veins with valvular incompetence resulting in varicosities and stasis. Immobilization, though not clearly defined (i.e., non-ambulatory versus. non-weightbearing with a short- or long- leg cast) has been shown to have an effect on development of DVT.[1,3,6] Immobilization prevents movement at the ankle joint and activity of the posterior muscles of the leg, which in turn creates stasis of blood in the calf.[3,12] If a short- leg cast is inadvertently applied to far proximal, a mechanical irritation to the popliteal fossa may result in over-constriction, chronic inflammation, and soft tissue injury. History of DVT advances the patient into a high risk category and therefore a strategic plan for DVT prophylaxis should be employed.[3]

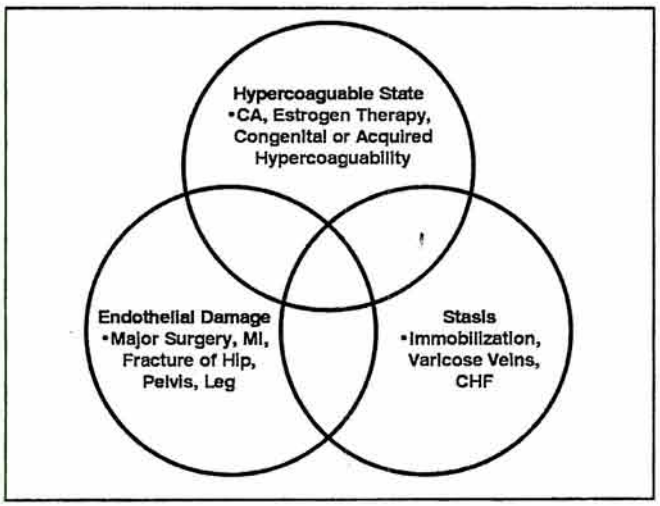

Figure 1. Virchow's Triad.

Table 1

RISK FACTORS FOR DEVELOPMENT OF DVT

- Recent Surgery
- Prolonged Surgery
- Increasing Age
- Immobilization
- History of DVT
- Obesity
- Malignancy
- Tourniquet Use
- Cardiopulmonary Disease
- Inherited Coagulopathies

Table 2

ACCP GUIDELINES FOR PROPHYLAXIS

	Low Risk	Moderate Risk	High Risk	Very High Risk
	Minor Sx in patients <40 y.o. with no clinical risk factors	Major and minor Sx in patients 40 to 60 y.o. with no other clinical risk factors Major Sx in patients <40 y.o. with no additional risk factors Minor Sx in patients with risk factors	Major surgery in patients > 60 y.o. who have additional risk factors; patients with MI and medical patients with risk factors	Major Sx in patients >40 y.o. with previous VTE or malignant dz or hypercoagulable state; patients with elective major lower extremity orthopedic surgery or hip fx; patients with stroke multiple trauma or spinal cord injury
Distal DVT (%)	2	10 to 20	20 to 40	40 to 80
Proximal DVT (%)	0.4	2 to 4	4 to 8	10 to 20
Clinical PE (%)	0.2	1 to 2	2 to 4	4 to 10
Fatal PE (%)	0.002	0.1 to 0.4	0.4-1.0	1 to 5
Successful preventive strategies	No specific measures	LDUFH (every 12h) LMWH, IPC and ES	LDUFH (every 8 hr) LMWH and IPC	LMWH, oral anticogulants, IPC (+LDUFH or LMWH) and ADH

Most proximal clots are thought to originate from smaller emboli in the cusps of the valves in deep calf veins, which grow to occlude the lumen and induce an inflammatory reaction.[12] This nidus can remain asymptomatic and resolve spontaneously or migrate proximally. While most DVT's are asymptomatic, a few may manifest as a PE as their first clinical presentation. A DVT may be asymptomatic and clinically silent potentially making one of its first manifestations a PE. The PE results from a dislodged clot entering the right side of the heart and subsequently is pumped into the pulmonary arteries where it can become lodged. This in turn results in a ventilation/perfusion defect within a section of the affected lung. This tissue then suffers from a decrease perfusion while normal ventilation is maintained. Ultimately right-sided heart failure and death can result from an inability to overcome the resultant increased vascular resistance.[12]

Post-thrombotic syndrome is another possible complication of DVT resulting from recanalization of the occluded vein and ambulatory venous hypertension affecting up to 25% of patients.[11] Valve destruction and loss of muscular pump activity can cause reversal of blood flow from superficial to deep veins, resulting in edema, pain, hyperpigmentation of skin, and potentially ulceration.

PREVALENCE OF DEEP VENOUS THROMBOSIS

The incidence of DVT postoperatively following foot and ankle surgery has been found to be significantly lower than that after other orthopedic procedures. Mizel et al in a multicenter study of over 2,700 patients, found that frequency of DVT was 0.22% with resultant PE in 0.15% following foot and ankle surgery.[44] They found that only two factors correlated with thromboembolism; post operative non-weightbearing and immobilization. When combined, these variables increase the relative risk by 0.04%. They suggested that routine prophylaxis is not necessary due to the low incidence of DVT, in conjunction with costs, potential complications, and limited gain. This study's implications were limited due to its design. First, the use of prophylaxis was determined by the treating physician therefore DVT in an untreated population is still unknown. Second, ancillary studies to detect DVT were utilized only in symptomatic patients. It has been documented that many DVTs are asymptomatic, making clinical exam unreliable and often equivocal, again underestimating the prevalence of DVT.[1,4,7]

Solis and Saxby performed a prospective study of 209 patients undergoing surgery of the foot and ankle with an ultrasound of the legs at the first postoperative visit.[55] In this study, no patients were treated prophylactically unless they had a history of DVT or PE (in which case they were excluded, leaving a population of 201). Their protocol was to evaluate all patients via ultrasound, regardless of symptomatology. If a clot was present (3.5% of patients) the ultrasound was repeated in one week. Lack of progression resulted in no treatment, and ultimately none of the patients required treatment in this series. The authors found that DVT formation was associated with hindfoot surgery with or without immobilization, increase in age, and tourniquet time. A small cohort in addition to the lack of sensitivity for diagnostic ultrasound (48-57%) in the calf, limits the significance of their findings. Again, this study may serve to underestimate the true incidence of DVT post operatively.

These rates are in contrast to other orthopedic surgeries of the lower extremities with much higher incidence of DVT. Examples include total hip arthroplasty which causes development of DVT in 35-60% with 16% of those progressing to PE.[4,7] A recent study that evaluated the prevalence of DVT following total knee replacement (TKR), bilateral TKR, and total hip replacement (THR) (in which all patient received chemical and mechanical prophylaxis) found rates of 8.9%, 25.6%, and 36.9%, respectively.[13] The prevalence of DVT in knee arthroscopy is 17.9%, and that of lower extremity trauma is 28% (tibial plateau – 42.9%, Femoral shaft – 40.0%, Tibial Shaft – 22.2%, Tibial plafond – 12.5%).[77]

DVT GUIDELINES

The American College of Chest Physicians (ACCP) provides a comprehensive systematic review of the literature related to risks of venous thromboembolism (VTE) and its prevention. They have compiled guidelines for thromboprophylaxis therapy for lower extremity surgery consisting of elective hip and knee arthroplasty, hip fracture, and isolated lower extremity injuries. (Table 3). Although most of these procedures do not have specific relevance for foot and ankle surgeons, their recommendations can be used as a reference in decision-making. ACCP in 2001 published guidelines (Table 2) based on the type of operation (minor or major), age group (<40 years, 40-60 years, and >60 years), and the presence of additional risk factors (e.g., cancer, surgery, or previous DVT) but because there is not sufficient clinical evaluation to apply an individualized approach to prophylaxis, they believe group-specific prophylaxis (e.g., elective hip arthroplasty, isolated

Table 3

ACCP GUIDELINES FOR THROMBOPROPHYLAXIS THERPY FOR LOWER EXTREMITY SURGERY PROPHYLAXIS

Procedure	Treatment
Elective hip arthroplasty	1. LMWH: Started at high risk dose at 12h before surgery or 12-24h after surgery, or 4-6h after surgery at the usual high risk dose and then increase to the usual high-risk dose the following day 2. Fondaparinux: 2.5mg started 6-8h after surgery Arixtra SC qd x 5-9 d 3. Adjusted-dose Vitamin K Antagonist (VKA): Start pre-operatively (2-5mg) or the evening after surgery with combination of LMWH or LDUH for 4-5 days until target INR (2-3) is reached (weekly lab work is necessary to monitor INR)
Elective knee arthroplasty	1. LMWH: Start at high risk dose 2. Fondaparinux 3. Adjusted-dose VKA: (INR target 2.5)
Knee Arthroscopy	1. Do not suggest routine thromboprophylaxis 2. Early mobilization 3. Note: If increase risk factors (i.e. previous VTE, they suggest LMWH)
Hip Fracture Surgery	1. Fondaparinux 2. LMWH: high-risk dose 3. adjusted-dose VKA: Target INR 2.5
Isolated Lower Extremity Fracture	Do not suggest routine thromboprophylaxis

Note: Recommend mechanical prophylaxis for all patients
Modified from Guyatt 2004

lower extremity injuries, etc.) is more reliable.[10,11] The following section provides insight to multiple treatment options, including new antithrombolytic agents.

MECHANICAL TREATMENT

Mechanical methods of DVT prophylaxis consisting of graduated compression stockings (GCS), intermittent pneumatic compression (IPC) device, and venous foot pump (VFP) are all beneficial adjuncts to pharmacological treatment. Because most trials are not blinded and real world compliance is difficult to measure, they should not be used as sole DVT prophylaxis unless the patient has risk of excessive bleeding and cannot take pharmacological prophylaxis.[10]

PHARMACOLOGICAL TREATMENT

Currently, low-dose unfractionated heparin (LDUH), low molecular weight heparins (LMWH), and warfarin, vitamin K antagonist ~~have been the treatments for~~ are the main stay in DVT prophylaxis. Recently, fondaparinux, has been released it to the market, and two others drugs, idraparinux and ximelaigratan have shown promising results in phase II and III trials, respectively.[14]

Heparin was first discovered by McLean in 1916 and gained its popularity over the last several decades. It is a long chain pentasaccharide that inhibits factor IIa, Xa and potentiates the effects of antithrombin III. The length as well as the sequence of the polysaccharide determines its antithrombin III inhibition tendency. A longer polysaccharide chain yields a greater tendency for factor IIa inhibition while the sequence of the chain

determines its anti-factor Xa efficacy. Intuitively, LMWH, a smaller chain pentasaccharide would have less anti-IIa activity than that of LDUH, thus less bleeding and the need for monitoring is not required. LDUH and to a lesser extent LMWH also have an affinity to platelets and can induce thrombocytopenia, a life-threatening reaction.[15]

LMWH's have gained greater usage than LDUH because of their decrease risk of thrombocytopenia and the need for no monitoring, which contributes in decreasing healthcare cost. There are a variety of different LMWH's on the market, each prepared by different fragmentation methods, therefore in theory they would have different affinities to factors IIa, Xa, antithrombin, and platelets. However, there has not been many prospective, double-blind studies that have shown differences in efficacy.[15]

Fondaparinux is a synthetic analog of heparin and LMWH. It has a half-life of 17 hours, thus it can be used once daily. Fondaparinux does not cause heparin-induced thrombocytopenia since it does not have any affinity to platelets to cause aggregation. However, it also fails to interact with protamine sulfate and its only antidote is recombinant factor VIIa, which is not available in most hospitals. Therefore, it can potentially cause thrombotic complications.[14] The ACCP recognizes fondaparinux as an acceptable treatment for DVT prophylaxis in the lower extremity and has provided it in their guidelines.[8]

Phase III trials, comparing fondaparinux with enoxaparin for thromboprophylaxis in patients undergoing surgery for hip fracture, elective hip or knee arthroplasty, found a reduction in the risk of venous thromboembolism in the patient group using fondaparinux by approximately 55% compared with that of enoxaparin. Differences in increased risk of bleeding with resultant death was not found to be significant between the two groups.[14]

A second study evaluated the efficacy of extended fondaparinux thromboprophylaxis undergoing surgery for hip fracture.[16] All patients received daily 2.5 mg fondaprinux subcutaneously for seven days postoperatively. Patients were then randomized into two groups: fondaparinux 2.5 mg once daily? or placebo subcutaneously for an additional 3 weeks. The results based on routing venography showed that the group utilizing the 4 week regimen of fondaparinux decreased the risk of thrombosis from 35% to 1.4% compared with placebo. More importantly, the rate of symptomatic venous thrombo-embolic events was reduced from 2.7 to 0.3%.[14]

Idraparinux is a derivative of fondaparinux. It has a half-life of 130 hours, and it has a higher affinity to antithrombin. Because of its long half-life it can be administered once weekly. Idraparinux is a derivative of fondaparinux, therefore it has the similar efficacy and risks.[14]

For idraparinux, no phase III trials have been published to date. However, phase II trials, comparing idraparinux to warfarin therapy in proximal DVT have shown similar outcomes in compression ultrasound and perfusion lung scan findings. In these trials, they found that idraparinux, at doses higher than 5 mg can cause fatal bleeding. The group who received 2.5 mg of idraparinux showed similar therapeutic results as those who received warfarin while the risk of bleeding was less in the idraparinux group than than in the warfarin group.[17]

Warfarin therapy was introduced 60 years ago and until recently, has been the only oral anticoagulant on the market. Warfarin inhibits binding of vitamin K to the coagulation factors II, VII, XI, and X, and the natural anticoagulant proteins C and S. Warfarin has many side effects and drug and food interactions. Furthermore, warfarin does not have a predictable anticoagulant response, requiring regular coagulation monitoring via blood tests and is often cumbersome to patients. Although the cost of the drug is less than other newer agents, the costs of blood tests need to be taken into account when considering the overall healthcare cost. It is also important that warfarin must be discontinued 4-5 days before surgery to allow for the INR to drift below.[18] If anticoagulation is needed, LDUH or LMWH can be given, with discontinuation of LMWH 24 hours before surgery and discontinuation of LDUH at least 6 hours before surgery.

Ximelagatran is an oral anticoagulant on the horizon that has showed promising results. Ximelagatran, once absorbed, undergoes biotransformation to melagatran. It has a plasma half-life of 3-4 hours and is administered twice daily. It has a predictable anticoagulant response therefore coagulation monitoring is not necessary. There have not been any reports of foods or drugs that influence the absorption of ximelagatran.[14]

Eriksson et al reported 3 studies showing favorable results using ximelagatran in orthopedic surgery. The first study (METHRO II) with 1,876 participants compared subcutaneous ximelagatran (administered preoperatively and twice daily for 1-3 days postoperatively) followed by oral ximelagatran therapy (in various doses) with subcutaneous dalteparin therapy in patients undergoing elective hip or knee arthroplasty. The frequency of DVT was 15.1% in the ximelagatran/ximelagatran group compared with 28.2% in the dalteparin group.[19] METHRO III trial compared post-operative administration of melagatran/ximelagatran to enoxaparin. Rates of venograhically detected proximal DVT and symptomatic PE were similar in both groups. However the rate of total venous thromboembolism was slightly higher in the melagatran/ximelagatran group

(31%) than the enoxaparin group (27.3%).[20] Lastly, the EXPRESS study compared subcutaneously administered melagatran (given immediately prior to surgery, a second dose given the evening after surgery, followed by oral administration of ximelagatran daily) to enoxaparin (given once daily starting the evening before surgery). The total incidence of DVT was 20.3% in the melagatran/ximelagatran group compared with 26.6% in the enoxaparin group. More bleeding was observed in the melagatran/ximelagatran group compared to the enoxaparin group, but rates of fatal bleeding, critical-site bleeding and bleeding requiring re-operation did not differ between the two groups.[21]

In September 2004 the FDA turned down approval of ximelagatran because of evidence of liver damage in patients taking ximelagatran long-term. Ximelagatran had shown transient increase in liver enzymes in short-term usage with values returning to normal shortly after discontinuation. Therefore it is unknown at this time if ximelagatran will be approved for short-term use.

DISCUSSION

It is understood that any patient undergoing reconstructive lower extremity surgery requiring non-weightbearing and immobilization is at risk for DVT. Therefore, the foot and ankle surgeon should be diligent in identifying additional risk factors during the preoperative period. Additional risk factors would further increase potential morbidity and mortality such as: age over 40, obesity, use of a tourniquet, or other chronic systemic illnesses. Any patient undergoing surgery with anticipated post-operative immobilization possesses two risk factors for DVT and the podiatric surgeon must therefore critically evaluate them for other potential risks. The addition of age >40 years, obesity, use of a tourniquet, or any other co-morbidities should clue one in to the need for prophylaxis. Reconstructive surgery, fracture management and certain other procedures of the leg, ankle, and foot most certainly merit evaluation and possible appropriate consultation if patients are at very high risk. Although to date the medical literature may be limited in its assessment regarding prevalence, and equivocal in its recommendations in prophylaxis for DVT after lower extremity surgery. It is the authors' belief that routine prophylaxis hasis merited in major reconstructive foot and ankle surgeries and in the face of a changing medico-legal environment, justified.

At our institution a three-step approach is taken to evaluate risk and implement prophylactic DVT prophylaxis measures. Step 1 is to perform the initial risk assessment based upon the patient's history, which includes review of the factors included in Table 1. Step 2 adds the clinical assessment, and finally Step 3 is assigning the level of risk as "Low, Moderate, High, Very High." All of our patients receive either compressive stocking/wrap or intra-operative sequential compression devices on the contralateral limb. Low to Moderate risk patients receive enoxaparin (Lovenox, company name, location) 30 mg subcutaneously in the preoperative setting. Moderate to High risk patients receive the above therapy with an additional 30 mg of Lovenox postoperatively and, based on risk assessment, 2-4 weeks of daily subcutaneous 40 mg. Very High risk patients, especially with the history of DVT/PE or coagulation abnormality, are referred for further consultation to their primary care physician or hematologist before progressing with surgical intervention.

The authors' clinical experience suggests that the actual prevalence of this disorder may be higher than what is reported in the literature. Although the reported risk for development of DVT associated with lower extremity surgery is low in the limited medical literature, the benefits of prophylaxis against this potential surgical complication easily outweigh the risks in its implementation.

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