# DVT PROPHYLAXIS FOR THE NONSURGICAL PATIENT

**Internal Medicine Grand Rounds**

**April 18, 2002**

**Wiley D. Perkins, M.D.**

This is to acknowledge that Wiley Perkins, M.D. has not disclosed any financial interests or other relationships with commercial concerns related directly or indirectly to this program. Dr. Perkins will be discussing off-label uses in his presentation.

Wiley D. Perkins, M.D.
Assistant Professor of Internal Medicine
Division of General Internal Medicine

Interests: Peri/postoperative medical management of the surgical patient, Hospital-based General Internal Medicine, Hypertension, Venous thromboembolic disease

## INTRODUCTION

Prophylactic regimens to decrease the morbidity and mortality associated with venous thromboembolism (VTE), namely the postphlebitic syndrome and pulmonary embolism, are well established in surgical patients. Compared with surgical patients, much less research has been done regarding preventing VTE in hospitalized medical patients. VTE is a definite problem in the nonsurgical setting. The incidence of thromboembolic disease in hospitalized medical patients varies widely, from about 3% in those without pre-existing risk factors to over 50% in those with predisposing factors for deep vein thrombosis. Massive pulmonary embolism accounts for 4-8% of hospitality mortality in medical wards.(1;2) The importance of thromboembolic disease on the medical wards is confirmed by the fact that approximately ¾ of patients that present with pulmonary embolism are nonsurgical. In a retrospective review of autopsies performed between January 1979 and December 1983 at the Royal Hallamshire Hospital, UK it was found that about 10% of autopsies had pulmonary embolism that was thought to have contributed to death. Only 24% of these autopsies that underwent record review had undergone surgery.(3) In the Worchester study, a retrospective survey of 16 short stay hospitals in Massachusetts, 1231 patients were found to be admitted with a diagnosis of acute VTE. Over 80% of patients with pulmonary embolism were nonsurgical. In-hospital mortality with this group of patients was 8.6%. The majority of those with DVT were also nonsurgical as only 19% had surgery reported.(4) In a follow up of nonhospitalized Framingham Heart Study autopsies from 1951-1976 pulmonary embolism was found to be a contributing cause of death in 15.6%. Of these only 18% were postoperative.(5)

Given the significant amount of surgical literature on VTE prophylaxis, it would seem reasonable to assume that this information could be applied to medical patients. However, there are many significant differences between surgical and medical patients that prevent such generalization. Overall, medical patients have lower rates of VTE. Medical patients have more heterogeneous diseases and therefore a wider range of thrombotic risk. They have higher rates of aspirin use (a drug that arguably has some benefit in VTE prophylaxis). Surgical patients have a discrete time frame of risk and this is not usually so of medical patients. The postoperative state is associated with wound activated clotting that further increases DVT rates. These differences preclude the extrapolation of study results from surgical to medical patients.

Over the last ten years there has been a significant increase in the study of VTE prophylaxis in medical patients. A recent consensus statement by the American College of Chest Physicians on VTE prophylaxis(6) has incorporated the results of this ongoing literature into easy to apply guidelines for specific groups of medical patients.

## APPROACHES TO REDUCING VTE IN MEDICAL PATIENTS

There are three main ways to approach VTE in hospitalized patients. One option is to wait for symptomatic DVT or PE to occur, then treat appropriately. This may be cost effective in those at very low risk for VTE, however is not feasible in patients at increased risk. Sudden death due to fatal PE is often the first and only clinical sign of disease.(3) Most patients who die of PE do so within 30 minutes of the acute event, too early for possible therapeutic intervention.(7) Waiting for DVT to occur is also associated with significant morbidity. Almost one third will develop

the postphlebitic syndrome associated with debilitating pain, edema, and venous ulceration. Up to 25% of those with a single episode of DVT, even in association with a transient risk such as recent surgery, will have recurrence in 5 years.(8)

Since the vast majority of patients with fatal pulmonary embolism have previous asymptomatic DVT(3), another option is to use serial surveillance tests to detect asymptomatic DVT in those at risk. Those with DVT found by screening would be treated with full dose anticoagulation to avoid pulmonary embolism. There are also problems with this concept. First, by waiting for DVT to occur before treatment, there is an increased risk of development of the postphlebitic syndrome and PE and their associated morbidity. The economic costs of postthrombotic complications are considerable.(9) Second, the available tests used for screening are either invasive or have low sensitivity in evaluating DVT in asymptomatic patients. Venography is the gold standard for the diagnosis of DVT. It is expensive, invasive, sometimes nondiagnostic, and is not available in many centers. Noninvasive tests include nuclear fibrinogen uptake testing (FUT), impedance plethysmography (IPG), and sonography. Fibrinogen uptake testing was introduced in the early 1970's as an accurate means of detecting asymptomatic DVT. It rapidly became the accepted standard for screening and evaluating prophylaxis measures in hospitalized patients. It is expensive and cumbersome, as it requires almost daily scans to evaluate for increased uptake. Over the last 10 years the accuracy of this test has been in question. In a medline review of studies evaluating FUT with venography in orthopedic and general surgery patients, the pooled sensitivity of FUT for calf vein thrombosis was 55%, all venous thrombosis 45%, and specificity of 92%.(10) Venous thrombi, hematoma, and areas of inflammation can produce abnormal FUT. IPG has high sensitivity and specificity in the evaluation of symptomatic DVT, but does not fare nearly as well in screening for asymptomatic DVT. In a retrospective review by Cruickshank et al(11), a comparison of IPG with venography in patients status post hip surgery showed IPG had a sensitivity of 12.9% and specificity of 98.1%. Agnelli et al(12) also compared IPG with venography after hip surgery. IPG's sensitivity was 19%, specificity 91%, PPV 52%, NPV 70%. Ultrasound (B-mode, duplex doppler, color doppler) is currently the diagnostic test of choice for patients with symptomatic DVT. These tests have shown sensitivity and specificity both in the 97% range. Ultrasound is not nearly as good in evaluating asymptomatic DVT. In a metaanalysis of articles evaluating all forms of venous ultrasound with contrast venography in detecting asymptomatic DVT, ultrasound had an overall sensitivity of 62%, specificity 97%, and a PPV of 66%.(13)

The best way to prevent VTE is to target those at increased risk and apply prophylactic measures. In the surgical literature VTE prophylaxis is also more cost effective than DVT screening.(14;15) Previous studies in general surgery have evaluated the cost effectiveness of VTE prophylaxis, no intervention, and VTE screening with FUT. No intervention and screening with FUT were shown to be 1.2-2.6 and 3.8-8.8 times more expensive respectively than prophylaxis.(16-18)

## WHO BENEFITS FROM VTE PROPHYLAXIS? IDENTIFYING THOSE AT RISK

The risk of VTE in hospitalized patients depends on their underlying illness, history of trauma, planned surgical procedure, and also on pre-existing patient related variables (see Table 1). Advanced age has consistently been found to correlate with an increase risk of VTE in

hospitalized patients. One hospital based prospective autopsy series showed a low incidence of PE in those under 40 years of age, but thereafter the incidence steadily increased with age.(19) In another autopsy study of patients that died from burns and other injuries, isolated venous thrombosis occurred in 47% of those under 45, 62% among those 46-75, and 74% over age 75.(20) In a community wide study in Worcester, Massachusetts, the incidence of DVT and PE increased exponentially with age.(21) Some have questioned whether age is a true independent risk factor for VTE, since other risk factors are also more common with advanced age. A previous multivariate analysis has shown that age is an independent risk factor even after adjusting for other known risks.(22)

**TABLE 1: Known Risk Factors For Venous Thromboembolism In Patients**

| Patient Factors | | Disease / Procedure | |
|---|---|---|---|
| Age | Obesity | Trauma or surgery | Malignancy |
| Varicose veins | Immobility | Heart failure | Myocardial infarction |
| Pregnancy | Puerperium | Paralysis of legs | Infection |
| Oral contraceptives | Previous DVT or PE | Nephrotic syndrome | Polycythemia |
| Thrombophilia | | Paraproteinemia | Homocysteinemia |
| | | Inflammatory bowel disease | Paroxysmal nocturnal hemoglobinuria |

Modified from THRIFT consensus group (23)

A history of prior thromboembolic disease is also is a marker for high risk of recurrent disease. In a previous surgical study, patients without prior VTE had approximately 20% DVT compared with greater than 60% in those with known history of VTE.(22)

Regardless of the cause, immobilization results in prolonged venous stasis in the deep veins of the legs. One autopsy series found an association between bed rest and venous thrombosis.(24) The incidence was only 15% in those confined to bed for less than one week and over 80% for those confined for longer periods. An autopsy series of burned or injured patients yielded similar results of 35% versus 80% respectively.(20) In patients with acute stroke, venous thrombi were detected in 60% of paralyzed lower extremities compared with 7% in the nonparalyzed leg.(25) In another study of acute stroke patients, venography confirmed venous thrombosis in 31% of affected/hemiplegic legs compared with 9% on the unaffected side.(26) This interlimb comparison stresses the relative importance of local paralysis and immobility as a risk for DVT.

Obesity has been suggested as a risk factor for venous thrombosis, however evidence is equivocal. Kakkar et al (22) showed that obesity was an independent risk factor in a series of univariate analyses. 48% of those overweight versus 24% average and underweight had venous thrombosis. However, a data review of patients undergoing general surgery showed that there was no significant increase risk of VTE in obese patients.(27)

Cardiac disease, to include myocardial infarction and CHF, is a significant risk factor for development of VTE. In a study of patients admitted with suspicion of MI, 38% of those with proven MI had DVT compared with 10% of those who were found not to have MI.(28) In a similar study DVT was found in 34% of those with MI compared with 7% of those found not to have MI.(29) CHF is associated with an increased incidence of pulmonary emboli found at autopsy. Harvey and Finch followed 100 CHF patients. 17 of these patients died and autopsy was performed on 12. Of these 8/12 had pulmonary emboli.(30) Anderson and Hull followed 150 CHF patients. 10 of 20 who died had an autopsy performed. 5 had pulmonary emboli at autopsy. Two of those alive had PE diagnosed. This corresponds to at least a 5% incidence of pulmonary emboli in those with CHF.(31)

Many reports have suggested a correlation between VTE and malignancy. The original association was attributed to Trousseau. Coon and Coller found PE twice as common in cancer patients in a postmortem study.(32) In a comparison of patients undergoing laparotomies that did not receive heparin prophylaxis, the incidence of venous thrombosis was 28% in those with benign disease compared to 60% in those with malignancy.(33) There is also an association between cancer and spontaneous venous thrombosis. In a large group of patients referred for confirmation of DVT, long term follow up estimated a five year risk of cancer development in 6.3% of those with confirmed DVT compared with 2.4% of those found not to have DVT ($P<0.01$).(34) Prandoni and colleagues studied the development of cancer in a two-year follow-up of patients referred for treatment of DVT. Of those without obvious cause for DVT 7.6% developed cancer. Only 1.9% of those with an obvious risk factor for DVT developed cancer ($P=0.043$).(35)

Oral contraceptives are well known to be associated with increased risk for VTE. Several recent studies have also suggested an increased risk of VTE with hormone replacement therapy as well. In a double-blind placebo controlled trial, women with coronary artery disease were randomized to estrogen 0.625/progesterone 2.5 mg or placebo and followed over four years for the development of VTE. 2.46% of those on HRT developed VTE versus 0.94% placebo ($P<0.003$). Although this was statistically significant, the yearly number needed to treat for harm was 256.(36)

Based on published data, the degree of risk of VTE in hospitalized medical patients has been summarized by the Thromboembolic Risk Factors Consensus Group (table 2).(23) Medical patients at high risk of thrombosis (incidence of DVT >40%, PE 1-10%) are those with prior thromboembolism or thrombophilia and presenting with a major medical disease. Patients with lower limb paralysis are also included in this group. Those at moderate risk of thrombosis (10-40% DVT, 0-1% PE) are those with history of thrombophilia or thromboembolism and a minor medical condition, or those without thromboembolic history presenting with cardiac or respiratory failure, cancer, inflammatory bowel disease, or severe sepsis. Low risk patients (<10% DVT, <0.1% PE) are those without prior thromboembolism presenting with a minor medical condition. Routine VTE prophylaxis in this low risk group is not justified due to the costs and risks of prophylaxis.(16) Routine prophylaxis in moderate to high-risk patients is advisable and is cost effective.(14;17)

**TABLE 2: Incidence of venous VTE in hospitalized medical patients according to risk group**

| | | DVT | Proximal DVT | Fatal PE |
|---|---|---|---|---|
| Low risk groups | Minor medical illness | <10% | <1% | 0.01% |
| Moderate risk groups | Major medical illness: heart or lung disease, cancer, inflammatory bowel disease, sepsis<br>Minor medical illness with thrombophilia or history of VTE | 10-40% | 1-10% | 0.1-1% |
| High risk groups | Lower limb paralysis, major medical illness with thrombophilia or prior history of VTE | 40-80% | 10-30% | 1-10% |

Modified from THRIFT consensus group(23)

## CURRENT VTE PROPHYLAXIS MODALITIES

### GRADUATED COMPRESSION STOCKINGS (GCS)

Early ambulation to activate the calf muscle "pump" was the first prophylactic modality used to help prevent DVT. This subsequently led to the development of graduated compression stockings (GCS). These stockings compress at approximately 18 mm Hg at the ankle and decrease to about 6-8 mm Hg at the thigh. The main benefit of this modality is no bleeding risk, however GCS has rarely been associated with ischemic leg injury in those with peripheral vascular disease or diabetic neuropathy. This modality has been shown effective to decrease the VTE risk in many surgical subgroups (appendix, figure 1). In a meta-analysis of GCS use in general surgery patients, there was an associated relative risk reduction of 68% for the development of VTE.(37) In medical patients relatively few case reports and small series of GCS use have been evaluated and there has not been enough study to recommend the routine use of GCS in this patient group.

### INTERMITTENT PNEUMATIC COMPRESSION (IPC)

Intermittent pneumatic compression (IPC) is a device that rhythmically compresses the lower extremities. IPC limits venous stasis and decreases the propensity for DVT formation. IPC has also been extensively studied in the surgical literature (appendix, figure 2). As with GCS there is no risk of bleeding, and there may be less risk of leg ischemia given the intermittent nature of IPC. No large randomized trials of IPC use in general medical patients have been performed. There have been two studies(38;39) in stroke patients; only one showed benefit in reducing symptomatic VTE. Venous foot pumps (VFP) are a relatively new mechanical modality for VTE prophylaxis. Reliable studies of their use are limited to orthopedic literature and are few. Two studies in total hip replacement (THR)(40;41) and two studies in total knee replacement (TKR)(42;43) have shown their effectiveness. However, the experience with venous foot pumps in orthopedic patients is small and DVT rates are greater than with anticoagulant prophylaxis. In two other TKR trials, low molecular weight heparins were significantly more effective than venous foot pumps.(44;45) For this reason these mechanical methods have not been

recommended as primary VTE prophylaxis in orthopedic patients. These methods have not been studied in any significant randomized trials in medical patients. Special caution is needed when addressing and interpreting risk reductions of VTE with mechanical means of prophylaxis (GCS, IPC, VFP). Blinding of these studies is not possible. There is also a well-known compliance issue with mechanical prophylaxis modalities. Because of this they are not likely to perform as well in clinical practice as they do in more stringently controlled conditions.

## UNFRACTIONATED HEPARIN (UFH)

Unfractionated heparin (UFH) has been tested extensively in the surgical literature and has been found highly effect in preventing VTE (appendix, figure 3). There is growing literature showing the effectiveness of UFH in medical patients as well. Typical prophylactic doses are 5000 units subcutaneously every 8 to 12 hours. Data comparing these two doses is relatively sparse. In a general surgery meta-analysis higher doses of UFH were slightly more effective.(46) Complications of UFH include bleeding, heparin induced thrombocytopenia, osteoporosis (with long term use), anaphylaxis, urticaria, skin necrosis, and hypoaldosteronism. The incidence of significant bleeding is low in general medical patients. In two separate studies, the bleeding complications associated with UFH were 1.5%(47) and 3.6%(48). Heparin induced thrombocytopenia, as documented by falling platelet counts and positive heparin dependent IgG antibodies, has previously been shown to occur in 2.7% of patients on UFH.(49)

## LOW MOLECULAR WEIGHT HEPARIN (LMWH)

Many low molecular weight heparins have been tested in surgical (appendix, figure 4) and medical patients. Overall LMWH is at least as effect as UFH. In several high-risk groups, such as orthopedics, trauma, and spinal cord injury, LMWH is superior to UFH. Bleeding complications occur, however a meta-analysis of general medical patients showed the bleeding risk of LMWH to be about 52% lower than UFH.(50) LMWH has a lower incidence of injection site hematoma as well. The main limitation of LMWH is its significant increased cost compared with UFH. In select high-risk groups the benefits will outweigh the cost. LMWH is also associated with heparin induced thrombocytopenia, however at a much lower rate than UFH.(49)

## WARFARIN

Anticoagulation with warfarin to a goal INR of 2 to 3 has been shown to be an effective method of VTE prophylaxis. Studies using this regimen have generally been limited to high-risk orthopedic patients (appendix, figure 5). Warfarin has also been used in low dose for catheter related central venous thrombosis prophylaxis. There are no indications for its routine use in VTE prophylaxis in ill medical patients. Warfarin has a delayed onset of action and requires frequent laboratory monitoring. Warfarin's long half-life, concerns for drug-drug interactions in medical patients on complex regimens, and a high incidence of hepatic dysfunction and nutritional variability on the medical wards make other alternatives more attractive.

### ASPIRIN

Aspirin has been studied extensively in VTE prophylaxis. Because of its ease of administration and relatively few side effects, aspirin would appear to be an ideal agent. In a meta-analysis of the Antiplatelet Trialists(51), antiplatelet therapy was shown to significantly reduce the incidence of VTE in surgical and medical patients. This meta-analysis pooled over 30 studies of variable scientific design and quality.(52;53) Many of the individual studies demonstrated no significant benefit of aspirin or showed aspirin to be less effective than other agents. The results of the PEP trial (pulmonary embolism prevention)(54) leaves no doubt that aspirin prevents symptomatic VTE after hip fracture. Aspirin reduced the rate of symptomatic DVT from 1.5% to 1.0% and reduced the rate of pulmonary embolism from 1.2% to 0.7%. The absolute risk reductions were quite small however, resulting in a number needed to treat to reduce DVT and PE of 232 and 195 respectively. In the subgroup of patients who also received LMWH, the frequency of symptomatic DVT and PE were not significantly different. It is also important to note that the prophylactic benefit of aspirin was mainly after the first week, when the majority of patients were discharged and not receiving any other prophylaxis(55). Until aspirin is compared with other proven forms of VTE prophylaxis in randomized large studies using clinical endpoints, aspirin is not recommended over standard therapy. Given its low cost, ease of use, and safety profile, it is reasonable to use aspirin after hospital discharge following orthopedic surgery.

## VTE TRIALS IN MEDICAL PATIENTS

We now have adequate trials in medical patients that make it possible for VTE prophylaxis recommendations. Initial studies were mainly in patients with myocardial infarction and stroke. More recently general medicine and intensive care unit patients have been studied as well. The following studies discussed below have been chosen based on rigorous inclusion criteria defined by the most recent consensus statement on prevention of VTE.(6) This does not represent all available literature on VTE prophylaxis.

### ACUTE MYOCARDIAL INFARCTION

Prophylactic antithrombotic therapy in acute myocardial infarction can be used to prevent VTE, mural thrombi, and systemic arterial emboli. There are three major trials of VTE prophylaxis in acute MI using subcutaneous heparin, two using intravenous heparin followed by warfarin, and one using graduated compression stockings. The first subcutaneous heparin study was performed in 1972 and compared heparin 7500 units subcutaneously twice daily versus no therapy for seven days in an unblinded fashion to patients with acute MI.(56) FUT was performed every other day for two weeks. Of 50 patients enrolled, 23% receiving heparin and 29% in the control group developed DVT ($P>0.7$). There were no significant differences in this study, however there was criticism for small groups, no blinding, and lack of rigorous inclusion criteria. In 1973 a randomized double blind study of heparin 5000 units twice daily versus placebo was performed in patients 40-75 years old and within 12 hours of MI.(57) Treatment was continued for ten days. FUT was used daily to screen for DVT. DVT occurred in 3.2% in the heparin group versus 17.2% in the control group ($P<0.025$). In 1977 Emerson and Marks published a trial of low dose subcutaneous heparin versus control in patients status post MI admitted to a CCU.(58) Treatment was for two weeks. The endpoint was DVT as diagnosed by

every other day FUT. DVT developed in 5% of heparin versus 34% control group (P<0.005). Three patients in the control group developed PE.

In 1973 Wray et al examined prophylactic anticoagulation in prevention of calf vein thrombi after MI.(59) Patients with acute MI and age 70 or less were randomized to 48 hours of high dose IV heparin (40,000 units/day) then adjusted dose warfarin for the duration of the hospital stay, or no treatment. DVT were screened for by daily FUT. DVT developed in 6.5% treatment group and 22% controls (P<0.05). No hemorrhagic complications were noted. In 1973 a cooperative clinical trial evaluated high dose subcutaneous heparin followed by warfarin for PE prophylaxis in patients with acute MI admitted to 12 VA hospitals.(60) The treatment group received subcutaneous heparin 10,000 units twice to three times daily to prolong the clotting time, followed by warfarin for 28 days. Lung scans were performed at 10-14 days and 21-28 days. The treatment group had 2.0% PE versus control 4.8% (P<0.005). There was no significant difference in recurrent MI, death, or CHF between groups.

In 1993 Kierkegaard and Norgren evaluated mechanical prophylaxis with graduated compression stockings(GCS) in those with acute MI.(61) Within 24 hours of presentation, patients were given GCS on one leg and the other leg served as a control. FUT was performed daily for ten days. DVT occurred in no legs with GCS as compared with 10% control legs (P=0.003). Of note venography was done on 6 of 8 with DVT by FUT. Venography confirmed DVT in 5 of 6, and the other had extensive chronic post-thrombotic changes.

In comparing all of the above trials in acute MI, the overall incidence of DVT is around 24% among those not treated with anticoagulant therapy. Both low dose subcutaneous heparin and high dose IV heparin followed by warfarin significantly reduce the rate of DVT. Mechanical prophylaxis with GCS also was of benefit in one study. The current aggressive treatment of MI with thrombolytics, anticoagulants, and antiplatelet agents is likely to further reduce VTE in these patients, however this has not yet been studied.

## ACUTE ISCHEMIC STROKE WITH HEMIPLEGIA

Stroke patients have the highest overall rate of DVT among medical patients. When pooling the control groups of all VTE trials, there is an average 55% rate of DVT in those with acute stroke and hemiplegia. Approximately 5% of early mortality after stroke is attributable to pulmonary embolism. Studies of VTE prophylaxis in acute stroke have used intermittent pneumatic compression (IPC), low dose unfractionated heparin (LDUH), low molecular weight heparin (LWMH), and the heparinoid danaparoid. All have benefit.

In 1982 the first trial of IPC in acute CVA was performed.(38) Those within 72 hours of acute ischemic stroke and with significant lower limb weakness were included. IPC was worn for the first 24 hours then three times daily (for 3 hours) for 9 days. FUT was used to evaluate for DVT. The study groups each had only 13 patients. DVT occurred in 6/13 in both groups. Although there was no difference between groups, the late onset of use of IPC and its unconventional schedule of use leave the results of this study in question. In 1998 IPC was added to conventional unfractionated heparin in ischemic CVA.(39) The heparin group experienced 9.0% DVT and 2.4% PE. The addition of IPC lowered DVT to 0.23% and there were no PE.

Unfortunately the endpoints of this trial were only symptomatic DVT and PE. No asymptomatic DVT screening was performed.

LDUH has been compared with placebo in two trials. The first in 1977 was a pilot study.(62) This pilot study evaluated LDUH 5000 units three times daily for 14 days versus no treatment in a group of patients within 48 hours of acute ischemic stroke. FUT was used for the diagnosis of DVT. DVT was reduced from 75% to 12.5% ($P<0.01$). No hemorrhagic complications were noted. The unusually high DVT rate in the control group was thought due to the particularly extreme severity of stroke in this study. A follow up of this pilot study was done in 1986.(63) The same inclusion criteria and heparin doses were used as in the previous pilot study. DVT was reduced from 72.7% to 22.2% ($P<0.001$). A post-mortem evaluation of 71/84 patients found PE in 33/47 control and 7/24 heparin treated ($P<0.01$). Mortality over twelve weeks was 53/161 control and 31/144 heparin treated ($P<0.05$). Postmortem evaluation showed 9.9% of CVA were hemorrhagic, not significantly different between the two groups.

LMWH and heparinoids were initially tested for VTE prophylaxis in the late 1980's. In 1987 danaparoid, a low molecular weight heparinoid, was compared with placebo in VTE prophylaxis in acute ischemic stroke.(64) Patients randomized were within 7 days of acute stroke. Danaparoid was given at a loading dose of 1000 anti-$X_a$ units IV followed by 750 anti-$X_a$ units subcutaneously twice daily for fourteen days. FUT was done to evaluate for DVT. DVT's were reduced from 28% to 4% ($P=0.005$). Bleeding complications were no different between groups. In 1989 dalteparin (Fragmin), a LMWH, was given to patients within 72 hours of ischemic stroke.(65) Dalteparin dosing was 2500 Anti-$X_a$ units twice daily for fourteen days. FUT was performed daily. There was a reduction in DVT from 50% to 22% ($P=0.05$). In 1990 dalteparin was again tested in a double blind, placebo controlled trial.(66) Patients included were within 72 hours of acute ischemic stroke. The dalteparin dose used was 3000-5500 anti-$X_a$ units given once daily for fourteen days or until discharge. The endpoint was DVT detected by venography of the paretic limb only, on day 10-14. The rates of DVT were 36% with dalteparin and 34% with placebo (NS). There are many possible reasons for the lack of benefit of dalteparin in this trial. It was dosed once daily, whereas the previous study dose was twice daily. There was also the possibility of a false negative result (type 2 error) given the small study size.

LDUH and LMWH/danaparoid have been compared in 4 trials. In 1992 danaparoid was compared with LDUH in a double blind randomized trial.(67) Those included were within 7 days of acute ischemic stroke resulting in leg paralysis. Danaparoid was given at a dose of 750 anti-$X_a$ units subcutaneously twice daily and LDUH was 5000 units twice daily. Both were given for fourteen days or until discharge if earlier. DVT was determined by FUT performed daily. Venography was done to verify positive FUT. 9% danaparoid versus 31% LDUH developed DVT ($P=0.014$). Bleeding episodes occurred in 2% of each group. A similar study in 1994 compared once daily danaparoid with LDUH.(68) Treatment began within 72 hours of stroke, and dosage was 1250 anti-$X_a$ units once daily with danaparoid versus LDUH 5000 units twice daily. FUT was performed daily. Treatment continued on average 9 days. DVT occurred in 14.6% with danaparoid versus 19.8% LDUH ($P=0.392$). In 1999 two abstracts evaluated LDUH with the LMWH enoxaparin. One study, based in seven Finnish hospitals, evaluated enoxaparin 40 mg once daily against LDUH 5000 units three times daily in acute stroke patients with paresis.(69) Treatment was for 10 days or until hospital discharge. DVT was verified by

venography, and PE by lung scan or pulmonary arteriogram. Thromboembolic events occurred in 19.7% with enoxaparin and 34.7% with LDUH (P=0.044). Hemorrhagic infarction occurred in 17.3% enoxaparin and 23.3% LDUH (NS). Harenberg and Schomaker analyzed data from high risk nonsurgical patients given VTE prophylaxis with either enoxaparin 40 mg daily or LDUH 5000 units three times daily.(70) The patients included had respiratory disease, CHF, or acute stroke. Venography was performed for DVT screening. Overall, thromboembolic events occurred in 15.6% enoxaparin and 22.1% LDUH (P=0.04). In subgroup analysis of those with acute ischemic stroke, VTE occurred in 26.5% enoxaparin and 39.7% LDUH. Bleeding events occurred in 1.8% enoxaparin and 3.2% LDUH.

From the above data it is shown that LDUH, LMWH, and danaparoid are all effective at lowering VTE rates in patients with acute ischemic stroke. IPC was effective at lowering symptomatic VTE in one trial. When using asymptomatic DVT as the outcome, both LMWH and danaparoid appear more effective than LDUH. These agents were used for an average of 10 to 14 days after stroke. Continued prophylaxis for longer periods (i.e. rehabilitation) has not been evaluated. In patients with contraindications to anticoagulant therapy, IPC (with or without GCS) can be recommended.

## GENERAL MEDICINE PATIENTS

Patients other than myocardial infarction or stroke who are admitted to a general medical ward service are overall at moderate risk for the development of VTE. The vast majority of patients in prospective studies are those with infections, COPD, or CHF. Combining the control groups of all studies suggests a baseline DVT rate of approximately 16%. A retrospective autopsy review at Addenbrooke's hospital, UK determined the frequency of fatal pulmonary embolism in hospitalized medical patients.(71) Of 200 consecutive medical patient admissions, 31 of these patients died. Only 14 had autopsy, and of these 5 were determined to have died from fatal pulmonary embolism. This correlates to one in forty medical patients having had pulmonary embolism as the cause of death. Since the autopsy rate was only 45%, it is likely that the actual incidence of fatal pulmonary embolism is higher than this.

There are four major studies of LDUH versus placebo in VTE prophylaxis with general medical patients. In 1981 an unblinded randomized study of all medical admissions with CHF or chest infections compared LDUH 5000 units three times daily versus no therapy.(72) Treatment was initiated within 12 hours of admission and continued for 14 days or until discharge. FUT was performed every other day. 26% in the no treatment group versus 4% LDUH group developed DVT (P<0.01). There was no significant difference between groups except for increased hematoma at injection site in the LDUH group. In 1982 a randomized unblinded trial evaluated heparin 5000 units twice daily in general medical ward inpatients.(73) Treatment was started within 12 hours of admission and was continued to discharge or mobilization. The primary outcome was hospital mortality, not DVT. Mortality was 10.9% in the no treatment group and 7.8% LDUH group (P<0.05). In a 1982 ICU VTE prophylaxis study of LDUH versus placebo there was a medical ward comparison group.(74) Heparin 5000 units twice daily or placebo was started within 24 hours of admission and was continued for 10 days. Daily FUT were performed. There were 10% DVT in the placebo group versus 2% in LDUH group (NS). This study had small group sizes that may have contributed to the insignificant results. The last major

study of LDUH done in general medical patients was in 1996.(75) Consecutive patients admitted to infectious disease services at six Swedish hospitals were randomized to receive heparin 5000 units twice daily or no prophylaxis in an unblinded fashion. Treatment was started on average 9 hours after admission and continued for three weeks. Patients were followed for at least three weeks after discharge with a primary endpoint of autopsy verified pulmonary embolism of a size likely to have caused or contributed to death. Mortality was similar between the groups. Mortality secondary to pulmonary embolism occurred in 15/5776 LDUH group versus 16/5917 control group (NS). There was a significant difference between median time from randomization to fatal PE, 28 days in LDUH, versus 12.5 days control (P=0.007). Interestingly, this difference correlated to the duration of heparin therapy. In this study there were concerns that inevitable death may merely have been delayed by heparin prophylaxis. There are also concerns that the study groups were not large enough to be able to show a statistically significant difference in mortality related to pulmonary embolism. It has previously been shown that in order to show a treatment effect of reduction of fatal PE from 0.5 to 0.3% in general surgical patients, approximately 50000 study patients are needed.(51)

Two studies have evaluated LMWH with placebo in VTE prophylaxis in medical patients. In 1986, medical inpatients were enrolled in a randomized double-blind fashion to receive enoxaparin 60 mg daily versus placebo.(76) Treatment started within 10 hours after admission and continued for 10 days. Daily FUT was performed to diagnose DVT. DVT was detected in 9.1% placebo versus 3.0% enoxaparin (P=0.03). Adverse reactions did not differ significantly between the groups. The recent MEDENOX (prophylaxis in medical patients with enoxaparin) trial randomized acutely ill medical patients in a double-blind fashion to receive enoxaparin 20 mg or 40 mg, or placebo.(77) Treatment was started within 24 hours of randomization and continued for 6-14 days. The primary outcome was DVT or pulmonary embolism. Venography was performed for DVT screening. VTE occurred in 14.9% placebo, 15.0% 20 mg enoxaparin, and in 5.5% 40 mg enoxaparin (P<0.001 for 40mg enoxaparin versus others). There was no significant difference in bleeding complications and between mortality at 110 days.

Both LDUH and LMWH are beneficial in VTE prophylaxis in medical patients. A number of trials have compared the two against each other. In 1996 a randomized double-blind study of enoxaparin and LDUH was performed in those with acute medical illness.(78) Enoxaparin 20 mg daily was compared with LDUH 5000 units twice daily. The mean time to start medications was 36 hours, and they were continued for 10 days. The endpoint was DVT by FUT, or pulmonary embolism by perfusion scan. All positive FUT were verified by venography. 4.8% enoxaparin and 4.6% LDUH developed VTE (NS). There were no significant differences in bleeding or adverse reactions. THE PRINCE (thromboembolic prevention in cardiopulmonary disease with enoxaparin) compared enoxaparin 40 mg daily with LDUH 5000 units three times daily in medical patients with cardiopulmonary disorders.(48) DVT was verified by venography. Results showed VTE in 10.4% LDUH and 8.4% enoxaparin (NS). There was significantly more bleeding with LDUH than enoxaparin, 3.6% versus 1.5% respectively. The 1996 PRIME study group compared enoxaparin 40 mg daily with LDUH 5000 units three times daily in high risk medical patients.(79) Treatment began within 12 hours of admission and continued an average of 10 days. Patients were screened for DVT with duplex doppler. The results showed very low rates of VTE in both groups, enoxaparin 0.2% and LDUH 1.4% (NS). Bleeding complications were similar. The overall low rate of thrombosis was thought secondary to the screening test

used. A recent meta-analysis of randomized trials of LDUH and LWMH in medical patients (except MI and stroke) was published in 2000.(50) This meta-analysis found no significant difference in the incidence of DVT, clinical PE, or death between LMWH and LDUH. The overall relative risk reductions with LDUH and LMWH were 56% and 58% respectively. Using LMWH over LDUH reduced the risk of major hemorrhage by 52% (P=0.049).

It can be concluded from these studies that LDUH and LMWH are equally effective at decreasing the risk of thromboembolic events compared with no prophylaxis in general medical patients. LMWH is associated with 52% less risk of major bleeding complications (absolute risk reduction around 1-2%).

### INTENSIVE CARE UNIT PATIENTS

Most critical care patients have multiple risk factors for VTE. Overall there is a paucity of critical care specific data regarding VTE prophylaxis. Previously discussed acute myocardial infarction and acute ischemic stroke are relevant in this setting. There are three major randomized trials of VTE prophylaxis in the ICU. In 1982, medical ICU patients were randomized to LDUH 5000 units twice daily or placebo.(74) Treatment was initiated within 24 hours of admission and continued for 10 days or until patients were ambulatory. DVT was evaluated by FUT. 29% controls and 13% LDUH developed DVT (P<0.05). A double-blind study comparing LDUH with placebo was evaluated in medical ICU patients in 1999.(80) DVT screening was performed with duplex doppler every 72 hours. DVT were found in 31% placebo and 11% LDUH (P=0.001). The third study compared the LMWH nadroparin with placebo in patients with acute COPD exacerbations requiring mechanical ventilation.(81) The average dose of nadroparin was 65 units/kg once daily. Treatment was started within 24 hours of admission and continued for no more than 21 days. DVT were screened by venography. DVT were found in 28.2% controls and 15.5% nadroparin (P=0.045).

Overall, ICU patients are at significantly increased risk for the development of VTE. From the available literature either LDUH or LMWH is recommended for routine VTE prophylaxis in the medical ICU. For those patients at high risk of bleeding, mechanical prophylaxis with IPC and GCS can be used based on few studies in other medical patients and the vast surgical literature.

## SPECIAL CIRCUMSTANCES

### CATHETER RELATED CENTRAL VENOUS THROMBOSIS

The use of central venous catheters is very common in the current management of medical patients, especially those receiving chemotherapy. Complications associated with central venous catheters are the cause of significant morbidity and mortality in the form of catheter infections, tip thrombosis with malfunction, and catheter related central venous thrombosis (CR-CVT). CR-CVT can lead to several clinical problems, to include obstruction, embolism, and development of the postphlebitic syndrome. The incidence of CR-CVT in cancer patients has been investigated in a number of studies.(82) The actual incidence varies from less than 1% to over 50%, and depends on the reason for screening.

The clinical symptoms of CR-CVT are many. The most common problem is in drawing blood or infusing. Symptoms of DVT may occur. There has been no prospective evaluation of CR-CVT and PE, however small series have shown that PE can occur. Prandoni et al evaluated PE in patients with upper extremity DVT.(83) 36% were found to have PE by V/Q scanning or pulmonary arteriogram. One quarter of these had symptoms of PE. Moderate to severe postphlebitic syndrome occurred in 4/15 at two years of follow-up. Monreal et al prospectively evaluated PE in 30 patients with known upper extremity DVT.(84) 20 of these patients had CR-CVT. Perfusion defects were highly suggestive of PE in 4/20 (20%) of those with CR-CVT. It is likely that the occurrence of PE in association with CR-CVT will be approximately 20-30%, however additional studies involving larger numbers of patients needs to be performed to verify this.

Catheter associated infection is also a significant problem. A few studies have suggested that CR-CVT is an independent risk factor for catheter associated infection. Raad et al investigated this in a retrospective case series of autopsy patients with indwelling catheters.(85) Mural thrombi were found in 38% of catheterized veins. 23% of the patients with CR-CVT developed catheter related sepsis. None of the patients without CR-CVT developed catheter related sepsis. These results suggest that CR-CVT is a risk for the subsequent development of catheter related infection, however prospective trials have yet to be done to prove this.

Two major studies have been performed to evaluate therapies to prevent CR-CVT. This presumably would decrease PE and postphlebitic syndrome, and perhaps decrease the rate of catheter sepsis(85). Bern et al evaluated low dose warfarin 1 mg daily in cancer patients with Port-a-Cath subclavian catheters placed for cancer chemotherapy.(86) Warfarin was started 3 days prior to catheter placement and continued daily for the 90 day duration of the study. Venograms were performed at 90 days, or sooner if any symptoms of DVT developed. The rate of CR-CVT in the warfarin group was 10%, and in those without treatment 37% ($P<0.001$). All of those in the warfarin group that had DVT also had symptoms of DVT. Of those not receiving warfarin that had DVT, 2/3 had symptoms of DVT. About 10% of those on warfarin had a transient increase in their prothrombin time. These tended to be the severely cachectic patients. The prothrombin time normalized with vitamin K and treatment was able to be continued. Monreal and colleagues randomized cancer patients receiving Port-a-Cath subclavian catheters to dalteparin (Fragmin) 2500 units once daily or no therapy.(87) The first dose was given 2 hours prior to catheter insertion and the study was continued for 90 days. Venography was performed at 90 days, or earlier if symptoms of DVT appeared. On the recommendation of the Ethics Committee recruitment was terminated early after DVT was found in 6% taking dalteparin versus 62% with no therapy ($P=0.002$). No bleeding complications had developed. Of the 9 upper extremity DVT that were found in this study, 8 had symptoms of DVT (6 had upper extremity symptoms, 2 had evidence of catheter obstruction).

Based on the above well designed studies, patients with long term central venous catheters for chemotherapy should receive prophylaxis with either low dose warfarin or dalteparin to prevent CR-CVT. These treatments are both effective and safe. The cost of therapy may dictate which agent is chosen.

## VTE FROM AIR TRAVEL – "ECONOMY CLASS SYNDROME"

There has been significant scientific attention regarding the concern of VTE after prolong trips, to include air flights. Homans initially described a doctor who developed DVT after a 14-hour flight.(88) This has subsequently been termed "economy class syndrome", because of prolonged sitting in the very limited space of economy class.(89) There is data to implicate the association of prolonged travel with VTE. A cohort study reported that recent travel was noted four times more often in patients with DVT than in controls.(90) In a systematic review of all patients arriving at Charles de Gaulle Airport in France between 11/93 and 12/00, all cases of PE requiring medical care were evaluated.(91) This review showed that prolonged distance over 5000 kilometer (3100 miles) was a significant risk factor to develop PE (1.5/million versus 0.01/million). In those travelling over 10,000 kilometer (6200 miles), the risk was 4.8/million. These incidences are thought to be underestimates secondary to the inability to detect mild cases, missing those who had VTE after leaving the airport, and not including those who died at the airport.

Although overall prevalence of symptomatic DVT and long distance flight is low, this is not so of patients with known risk factors for DVT. The LONFLIT study evaluated the incidence of DVT in low-risk and high-risk subjects after extended flights.(92) Low-risk was defined as no known clinical disease and no drug treatment within 2 weeks of flight. High-risk patients were defined as those with previous DVT, coagulation disorder, severe obesity, limited mobility, neoplastic disease within 2 years, and large varicose veins. The mean age was 46 years in both groups. Flights between 10-15 hours were included. Ultrasound was used to evaluate DVT before and within 24 hours after flights. Low-risk patients had no DVT's found by screening. 2.8% of high-risk subjects had DVT. By including DVT and superficial phlebitis, there were thrombotic events in 4.9% of high-risk subjects. LONFLIT2 evaluated the risk of DVT in high-risk subjects randomized to either elastic compression stocking or no treatment.(92)Average patient age was 44.8. Flights 10-15 hours were included. Ultrasound was used before and within 24 hours after flights to screen DVT. The control group had 4.5% DVT, and the treatment group had 0.24% DVT. ($P<0.02$). Elastic compression stockings decreased the incidence of DVT 18.5 times in high-risk patients undergoing extended flights. LONFLIT3 evaluated aspirin and enoxaparin prophylaxis in high-risk patients undergoing extended flights.(93) The same inclusion criteria for high-risk patients were used as in the previous two LONFLIT trials. Aspirin was used at a dose of 400 mg starting 12 hours before flight and continuing daily for 3 days total. Enoxaparin was given between 2-4 hours before flight at a dose of 100 IU/kg. DVT screening was done with ultrasound before and within 24 hours after flights. DVT occurred in 4.82% controls, 3.6% aspirin group ($P<0.05$), and 0.6% enoxaparin group ($P<0.002$). 13% of patients taking aspirin experienced mild GI symptoms. No side effects were observed in the enoxaparin group. Approximately 60% of all thrombotic events were asymptomatic.

DVT in extended flights is an important safety issue. High-risk subjects are at increased risk of DVT and prophylaxis can be advised. On the basis of these studies elastic compression stockings are the simplest and most cost effective. Aspirin may have a limited benefit. Other measures such as ambulation, exercise, increasing leg space, and maintaining hydration may be of benefit but have not been studied.

## ENDPOINTS IN VTE PROPHYLAXIS TRIALS

There are an abundance of clinical trials of VTE prophylaxis. The evaluation and interpretation of these trial results depends heavily on the diagnostic endpoint used. Clinical diagnosis of DVT is unreliable and should not be used. Measuring the incidence of mortality related to VTE would require a very high autopsy rate, one much higher than is currently attainable in this country. Some consider evidence of reduction in mortality from all causes to be required, however this would require forbiddingly large studies given the overall low incidence of fatal PE. This outcome also dismisses the burden of disease due to symptomatic thromboembolism as well as costs associated with their investigation and treatment. Symptomatic DVT alone is a poor endpoint, as the majority of DVT that occur and embolize are completely asymptomatic. In an autopsy study of deaths secondary to PE, 83% of these patients had leg DVT at autopsy but only 19% had symptoms of DVT prior to death.(3) Because of this most studies have used the endpoints of asymptomatic or symptomatic DVT found by screening tests. This has limitations as well, as some thrombi detected by sensitive screening tests may not be clinically relevant. At this point there are not reliable data that allows us to predict which thrombi will cause an adverse event and which will resolve spontaneously. However, a mounting body of evidence now indicates that venographically determined asymptomatic DVT is not a benign finding. Without treatment isolated calf vein thrombi extend proximally in 28%.(94) DVT may be asymptomatic but still give rise to the postthrombotic syndrome or PE. Therefore, prevention of asymptomatic DVT is a valid therapeutic goal.

Many VTE prophylaxis clinical studies have used noninvasive tests that are admittedly less accurate than venography. How to interpret the results of these studies has been of considerable debate. It has been previously shown that as long as there is no difference in the rate of misclassification of DVT between study and control groups, the study treatment effects actually tend to be underestimated when using noninvasive screening tests. In those studies that followed all positive noninvasive tests with venography (to rid of false positive tests), the estimate of relative treatment effect appears unbiased. (95)

## PHYSICIAN'S USE OF VTE PROPHYLAXIS

There is compelling evidence for efficacy and cost effectiveness of VTE prophylaxis, and straightforward guidelines are available. Every three years since 1986 the American College of Chest Physicians has released comprehensive guidelines on preventing VTE(6). They are the "standard of care" for VTE prophylaxis. Despite this, physicians use of VTE prophylaxis and implementation of these guidelines is less than optimal. In a review of medical records of 20 Oklahoma hospital medicare patients undergoing major general surgery in 1995, it was found that only 38% had any VTE prophylaxis measures implemented. Of those felt to be "high risk" only 39% received any type of prophylaxis.(96) This is contradictory to a 1994 random survey sent to the fellows of the American College of Surgeons. This survey showed that 86% stated they used specific prophylactic measures.(97) In a retrospective review of patients discharged from 16 short stay hospitals in central Massachusetts, 17% of patients were felt to be high risk based on traditional risk factors for VTE. Only 32% of the high-risk patients received any form of prophylaxis. (98) In an article titled "Still Missing the Boat with Fatal Pulmonary Embolism,"

deaths from pulmonary embolism in surgical inpatients of three Scottish regions were identified. Only 44% of these received prophylactic measures. (99) In an effort to see how well physicians were using consensus statement guidelines, Arnold et al identified cases of potentially preventable VTE in a cohort study.(100) Cases of DVT and PE were evaluated to see if appropriate VTE prophylaxis, according to ACCP guidelines at that time, was administered appropriately. 17.4% of all VTE cases were considered potentially preventable, i.e. they were given no prophylaxis or inappropriate prophylaxis. There is clearly a need for improvement in thromboprophylaxis implementation. Educating physicians about the significant risk of VTE in certain hospitalized groups of patients should improve the use of prophylactic measures and lower the morbidity and mortality associated with VTE.

## RECENT DEVELOPMENTS IN VTE PROPHYLAXIS

Data from randomized controlled trials show that even with the most effective anticoagulants currently available, the highest risk medical patients still develop VTE. About 20-25% of acute stroke patients and 10-15% of medical ICU patients develop VTE despite current prophylaxis recommendations. This incidence is even higher in patients undergoing orthopedic surgery, where VTE approaches 30% or more despite prophylaxis with LMWH.(6) Despite their proven efficacy in decreasing VTE, neither LDUH nor LMWH fully eliminates this risk and both have limitations in clinical use. There is a continuing need for the development of novel antithrombotic agents with enhanced benefit to risk ratios, mainly to improve outcomes in select high-risk patients in which current established therapies are insufficient.

Unfractionated heparin is an indirect inhibitor of thrombin. Its anticoagulant effects are in part secondary to its potentiation of two endogenous anticoagulants: antithrombin and heparin cofactor 2. These accelerate inactivation of thrombin and Factor $X_a$.(101) Avenues of research have focused on developing agents with specific antithrombin and anti-$X_a$ effects.

### HIRUDIN CLASS

Hirudin is a natural anticoagulant derived from the medicinal leech. It is the most potent direct thrombin inhibitor identified to date. Hirudin binds irreversibly to both free and clot bound thrombin, inhibiting all of its actions. Recombinant forms of hirudin have been developed for therapeutic use. Desirudin has been studied most extensively in VTE prophylaxis in the patients at highest risk for VTE, namely those undergoing orthopedic surgery for hip and knee replacement. Data so far suggest this agent to be more effect that LMWH and with a similar adverse effect profile. To this date this drug has not yet been evaluated in high-risk medical patients.

Three studies have evaluated desirudin with established VTE prophylaxis. In 1996, a double blind dose ranging trial compared 3 doses of desirudin with LDUH in patients undergoing elective hip replacement.(102) Desirudin was tested at does of 10, 15, and 20 mg subcutaneously twice daily against LDUH 5000 units three times daily. Treatment was started just prior to surgery and continued 8-12 days at which time bilateral venography was performed. Total DVT occurred in 34.2% LDUH, 24% 10 mg (P=0.0113), 19% 15 mg (P=0.003), and

18.2% 20 mg desirudin (P=0.0001). Proximal DVT occurred in 19.6%, 8.5% (P<0.001), 3.1% (P<0.001), and 2.4% (P<0.001) respectively. Bleeding was similar between all groups, but total blood loss was most in the 20 mg desirudin group. Because of this the 15 mg dose was chosen for future studies. In 1997 a second study confirmed the above results. Those undergoing hip-replacement were randomized to receive desirudin 15 mg twice daily or LDUH 5000 units three times daily.(103) Both were initiated just preoperatively, and continued 8-11 days when bilateral venography was performed. Total DVT occurred in 23% LDUH and 7% desirudin (P<0.0001). Proximal DVT occurred in 16% LDUH and 3% desirudin (P<0.0001). There were no differences in bleeding complications between groups. Desirudin is superior to LDUH in VTE prophylaxis in those undergoing hip surgery. However, LMWH is currently the gold standard in these patients, and is significantly more effective than LDUH. Because of this, desirudin was subsequently compared with enoxaparin in hip surgery patients.(104) Doses were desirudin 15 mg twice daily and enoxaparin 40 mg once daily, both started before surgery and given for 8-12 days. Venography was performed at discharge. Total DVT occurred in 25.5% enoxaparin and 18.4% desirudin (P=0.001). Proximal DVT occurred in 7.5% and 4.5% respectively (P=0.01). There was no difference in bleeding complications between the groups.

Based on the above data desirudin is more effect than both LDUH and LMWH in VTE prophylaxis in high-risk orthopedic surgery patients. Desirudin has been licensed for use in VTE prophylaxis in some European countries however it is not yet approved for this indication in the United States. This drug also needs further evaluation in high-risk medical patients.

**PENTASACCHARIDES**

Over twenty years ago a pentasaccharide sequence was identified as the antithrombin binding site in heparin fragments. This pentasaccharide sequence has been chemically synthesized and found to inhibit factor $X_a$.(105) Fondaparinux is the first of this new class of antithrombotic agents. In contrast to heparin, which has many interactions with plasma components, this drug selectively binds antithrombin causing rapid inhibition of Factor $X_a$. Fondaparinux was initially tested in VTE prophylaxis in a dose evaluating study in comparison with enoxaparin after total hip replacement.(106) Doses of 0.75, 1.5,3,6, and 8 mg subcutaneously daily were compared with enoxaparin 30 mg twice daily. Both were started postoperatively and continued 10 days or until discharge. Bilateral venography was then performed. Total DVT occurred in 9.4% enoxaparin and 11.8%, 6.7% (p=0.51), 1.7% (p=0.01), 4.4%, and 0% of those with increasing doses of fondaparinux. The 6 and 8 mg groups of fondaparinux were discontinued secondary to increases in major bleeding, however the other dose groups had similar adverse effects compared with enoxaparin. Three abstracts released in 2000 also showed significant benefit of fondaparinux in orthopedic surgery.(107-109) These three studies, EPHESUS, PENTAMAKS, and PENTATHLON 2000, were all part of a multi-center prospective double-blind randomized cooperative phase 3 study and part of a worldwide VTE prevention program in over 8000 patients undergoing major orthopedic surgery. These three studies showed a relative risk reduction of VTE of 56%, 55%, and 25% of fondaparinux 2.5 mg daily compared with enoxaparin. The results of two trials comparing fondaparinux with enoxaparin in hip fracture and knee surgery were recent published in the New England Journal of Medicine.(110;111). The first compared fondaparinux 2.5 mg once daily starting postoperatively with enoxaparin 40 mg daily starting preoperatively in hip fracture surgery. Treatment was for up to 11 days. Bilateral

venography was performed at discharge. VTE occurred in 19.1% enoxaparin and 8.3% fondaparinux (P,0.001, RRR 56%). There were no significant difference regarding clinically relevant bleeding. Fondaparinux 2.5 mg daily was then compared with enoxaparin 30 mg twice daily, both initiated postoperatively in patients status post major knee surgery. Treatment was for 11 days or until discharge if earlier, and bilateral venography was performed at discharge. VTE occurred in 27.8% enoxaparin and 12.5% fondaparinux (P,0.001, RRR 55%). Bleeding as measured by transfusion requirements occurred more frequently with the fondaparinux group, however there was no difference in bleeding leading to death or reoperation.

The pentasaccharides are an exciting new class of antithrombotic agents. Data so far shows that fondaparinux is superior to the current recommended anticoagulant therapies in patients at highest risk of developing VTE. Fondaparinux (brand name Arixtra) was approved by the FDA on 12/7/01 for use in VTE prophylaxis in patients undergoing hip fracture, hip replacement, and knee replacement surgery. Future studies comparing fondaparinux with the hirudin class of antithrombotic agents and in using both of these novel anticoagulants in medical patients are anticipated.

## CONCLUSION

VTE is at least as common in medical as in surgical patients. Most deaths from pulmonary embolism occur in nonsurgical patients. Based on known risk factors, medical patients at moderate to high risk for thromboembolic disease can be targeted for VTE prophylaxis. Prophylaxis has been shown to decrease complications of VTE, namely PE and the postphlebitic syndrome. These measures are also cost effective. Educating caretakers of the significant problem of VTE and the overall safety and efficacy of prophylactic measures should counter misconceptions of this disease, as well as increase VTE prophylaxis use. Despite adequate prophylaxis, those in high-risk groups still have a significant risk of developing DVT. The study of hirudins and pentasaccharides, and future development of novel antithrombotic agents, will continue to improve the benefit to risk ratio of VTE prophylaxis.

## Appendix

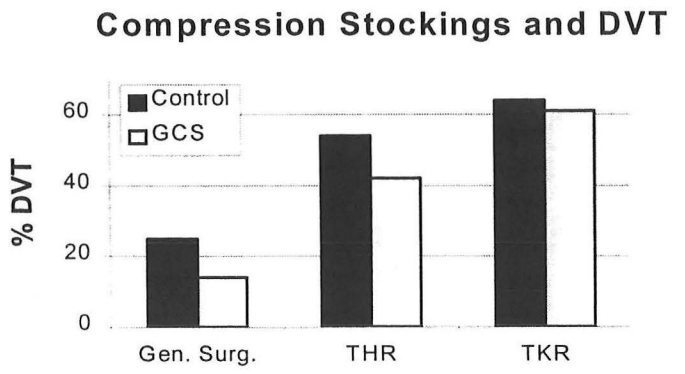


Figure 1

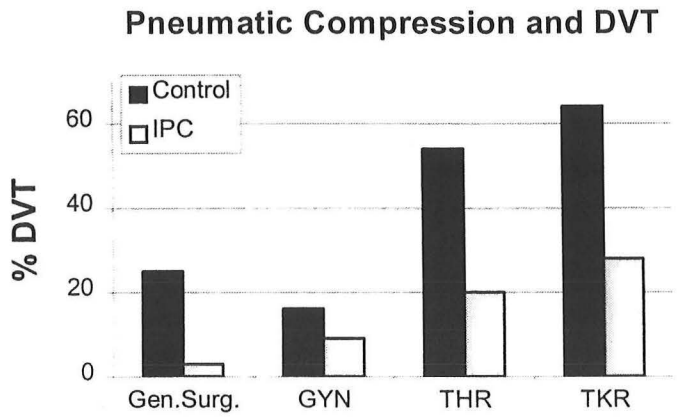


Figure 2

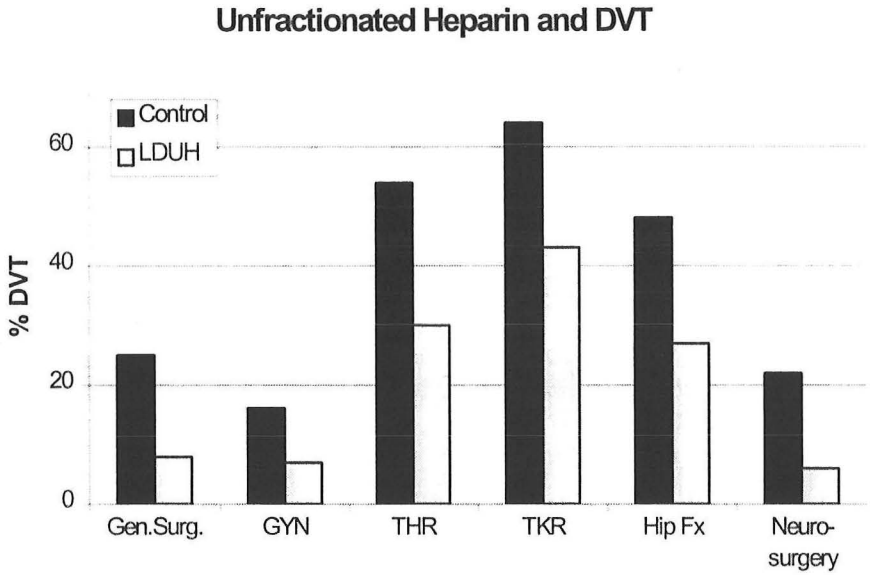


Figure 3

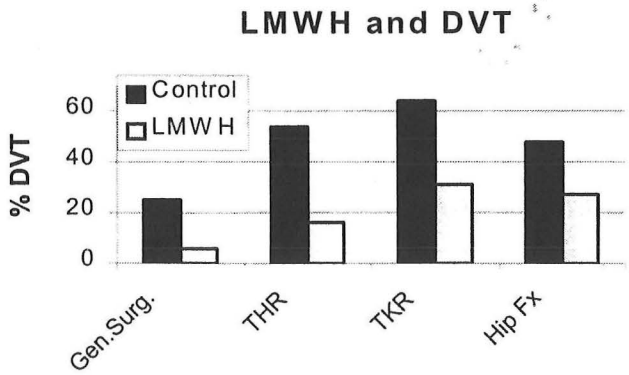


Figure 4

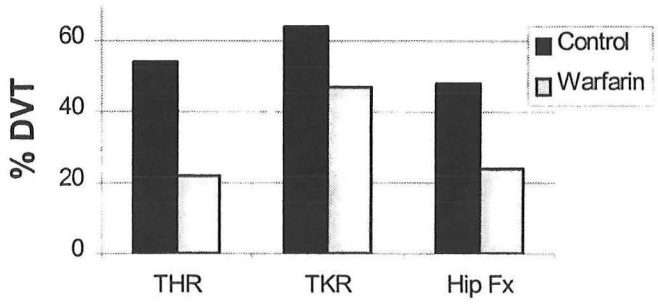


Figure 5

Modified from Geerts, Heit, et al. 2001

Reference List


(1) Gross JS, Neufeld RR, Libow LS, Gerber I, Rodstein M. Autopsy study of the elderly institutionalized patient. Review of 234 autopsies. Arch Intern Med 1988; 148(1):173-176.

(2) Rubinstein I, Murray D, Hoffstein V. Fatal pulmonary emboli in hospitalized patients. An autopsy study. Arch Intern Med 1988; 148(6):1425-1426.

(3) Sandler DA, Martin JF. Autopsy proven pulmonary embolism in hospital patients: are we detecting enough deep vein thrombosis? J R Soc Med 1989; 82(4):203-205.

(4) Anderson FA, Jr., Wheeler HB. Physician practices in the management of venous thromboembolism: a community-wide survey. J Vasc Surg 1992; 16(5):707-714.

(5) Goldhaber SZ, Savage DD, Garrison RJ, Castelli WP, Kannel WB, McNamara PM et al. Risk factors for pulmonary embolism. The Framingham Study. Am J Med 1983; 74(6):1023-1028.

(6) Geerts WH, Heit JA, Clagett GP, Pineo GF, Colwell CW, Anderson FA, Jr. et al. Prevention of venous thromboembolism. Chest 2001; 119(1 Suppl):132S-175S.

(7) Donaldson G, Williams C, et al. A reappraisal of the application of the trendelenburg operation to massive fatal embolism. N.Engl.J.Med. 268, 171-174. 1963.
Ref Type: Generic

(8) Prandoni P, Lensing AW, Cogo A, Cuppini S, Villalta S, Carta M et al. The long-term clinical course of acute deep venous thrombosis. Ann Intern Med 1996; 125(1):1-7.

(9) Bergqvist D, Jendteg S, Johansen L, Persson U, Odegaard K. Cost of long-term complications of deep venous thrombosis of the lower extremities: an analysis of a defined patient population in Sweden. Ann Intern Med 1997; 126(6):454-457.

(10) Lensing AW, Hirsh J. 125I-fibrinogen leg scanning: reassessment of its role for the diagnosis of venous thrombosis in post-operative patients. Thromb Haemost 1993; 69(1):2-7.

(11) Cruickshank MK, Levine MN, Hirsh J, Turpie AG, Powers P, Jay R et al. An evaluation of impedance plethysmography and 125I-fibrinogen leg scanning in patients following hip surgery. Thromb Haemost 1989; 62(3):830-834.

(12) Agnelli G, Cosmi B, Ranucci V, Renga C, Mosca S, Lupattelli L et al. Impedance plethysmography in the diagnosis of asymptomatic deep vein thrombosis in hip surgery. A venography-controlled study. Arch Intern Med 1991; 151(11):2167-2171.

(13) Wells PS, Lensing AW, Davidson BL, Prins MH, Hirsh J. Accuracy of ultrasound for the diagnosis of deep venous thrombosis in asymptomatic patients after orthopedic surgery. A meta-analysis. Ann Intern Med 1995; 122(1):47-53.

(14) Oster G, Tuden RL, Colditz GA. A cost-effectiveness analysis of prophylaxis against deep-vein thrombosis in major orthopedic surgery. JAMA 1987; 257(2):203-208.

(15) Bergqvist D, Matzsch T. Cost/benefit aspects on thromboprophylaxis. Haemostasis 1993; 23 Suppl 1:15-19.

(16) Bergqvist D, Jendteg S, Lindgren B, Matzsch T, Persson U. The economics of general thromboembolic prophylaxis. World J Surg 1988; 12(3):349-355.

(17) Hull RD, Hirsh J, Sackett DL, Stoddart GL. Cost-effectiveness of primary and secondary prevention of fatal pulmonary embolism in high-risk surgical patients. Can Med Assoc J 1982; 127(10):990-995.

(18) Bergqvist D, Lindgren B, Matzsch T. Comparison of the cost of preventing postoperative deep vein thrombosis with either unfractionated or low molecular weight heparin. Br J Surg 1996; 83(11):1548-1552.

(19) Morrell MT, Dunnill MS. The post-mortem incdence of pulmonary embolism in a hospital population. Br J Surg 1968; 55(5):347-352.

(20) Sevitt S, Gallagher NG. Venous thrombosis and pulmonary embolism: A clinicopathological study in injured and burned patients. Br.J.Surg. 48, 475. 1961.
Ref Type: Generic

(21) Anderson FA, Jr., Wheeler HB, Goldberg RJ, Hosmer DW, Patwardhan NA, Jovanovic B et al. A population-based perspective of the hospital incidence and case- fatality rates of deep vein thrombosis and pulmonary embolism. The Worcester DVT Study. Arch Intern Med 1991; 151(5):933-938.

(22) Kakkar VV, Howe CT, Nicolaides AN, Renney JT, Clarke MB. Deep vein thrombosis of the leg. Is there a "high risk" group? Am J Surg 1970; 120(4):527-530.

(23) Risk of and prophylaxis for venous thromboembolism in hospital patients. Thromboembolic Risk Factors (THRIFT) Consensus Group. BMJ 1992; 305(6853):567-574.

(24) Gibbs NM. Venous thrombosis of the lower limbs with particular reference to bedrest. Br.J.Surg. 45, 209. 1957.
Ref Type: Generic

(25) Warlow C, Ogston D, Douglas AS. Deep venous thrombosis of the legs after strokes. Part I--incidence and predisposing factors. Br Med J 1976; 1(6019):1178-1181.

(26) Cope C, Reyes TM, Skversky NJ. Phlebographic analysis of the incidence of thrombosis in hemiplegia. Radiology 1973; 109(3):581-584.

(27) Hills NH, Pflug JJ, Jeyasingh K, Boardman L, Calnan JS. Prevention of deep vein thrombosis by intermittent pneumatic compression of calf. Br Med J 1972; 1(793):131-135.

(28) Nicolaides AN, Kakkar VV, Renney JT, Kidner PH, Hutchison DC, Clarke MB. Myocardial infarction and deep-vein thrombosis. Br Med J 1971; 1(746):432-434.

(29) Murray TS, Lorimer AR, Cox FC, Lawrie TD. Leg-vein thrombosis following myocardial infarction. Lancet 1970; 2(7677):792-793.

(30) Harvey WP, Finch CA. Dicumarol prophylaxis in thromboembolic disease in congestive heart failure. N.Engl.J.Med. 242, 208. 1950.
Ref Type: Generic

(31) Anderson GM, Hull E. The effect of dicumarol upon the mortality and incidence of thromboembolic complications in congestive heart failure. Am.Heart.J. 39, 697. 1950.
Ref Type: Generic

(32) Coon WW, Coller FA. Some epidemiologic considerations of thrombo-embolism. Surg.Gynecol.Obstet. 109, 487-501. 1959.
Ref Type: Generic

(33) Rosenberg IL, Evans M, Pollock AV. Prophylaxis of postoperative leg vine thrombosis by low dose subcutaneous heparin or peroperative calf muscle stimulation: a controlled clinical trial. Br Med J 1975; 1(5959):649-651.

(34) Goldberg RJ, Seneff M, Gore JM, Anderson FA, Jr., Greene HL, Wheeler HB et al. Occult malignant neoplasm in patients with deep venous thrombosis. Arch Intern Med 1987; 147(2):251-253.

(35) Prandoni P, Lensing AW, Buller HR, Cogo A, Prins MH, Cattelan AM et al. Deep-vein thrombosis and the incidence of subsequent symptomatic cancer. N Engl J Med 1992; 327(16):1128-1133.

(36) Grady D, Wenger NK, Herrington D, Khan S, Furberg C, Hunninghake D et al. Postmenopausal hormone therapy increases risk for venous thromboembolic disease. The Heart and Estrogen/progestin Replacement Study. Ann Intern Med 2000; 132(9):689-696.

(37) Wells PS, Lensing AW, Hirsh J. Graduated compression stockings in the prevention of postoperative venous thromboembolism. A meta-analysis. Arch Intern Med 1994; 154(1):67-72.

(38) Prasad BK, Banerjee AK, Howard H. Incidence of deep vein thrombosis and the effect of pneumatic compression of the calf in elderly hemiplegics. Age Ageing 1982; 11(1):42-44.

(39) Kamran SI, Downey D, Ruff RL. Pneumatic sequential compression reduces the risk of deep vein thrombosis in stroke patients. Neurology 1998; 50(6):1683-1688.

(40) Fordyce MJ, Ling RS. A venous foot pump reduces thrombosis after total hip replacement. J Bone Joint Surg Br 1992; 74(1):45-49.

(41) Warwick D, Harrison J, Glew D, Mitchelmore A, Peters TJ, Donovan J. Comparison of the use of a foot pump with the use of low-molecular- weight heparin for the prevention of deep-vein thrombosis after total hip replacement. A prospective, randomized trial. J Bone Joint Surg Am 1998; 80(8):1158-1166.

(42) Wilson NV, Das SK, Kakkar VV, Maurice HD, Smibert JG, Thomas EM et al. Thrombo-embolic prophylaxis in total knee replacement. Evaluation of the A-V Impulse System. J Bone Joint Surg Br 1992; 74(1):50-52.

(43) Westrich GH, Sculco TP. Prophylaxis against deep venous thrombosis after total knee arthroplasty. Pneumatic plantar compression and aspirin compared with aspirin alone. J Bone Joint Surg Am 1996; 78(6):826-834.

(44) Norgren L, Toksvig-Larsen S, Magyar G, Lindstrand A, Albrechtsson U. Prevention of deep vein thrombosis in knee arthroplasty. Preliminary results from a randomized controlled study of low molecular weight heparin vs foot pump compression. Int Angiol 1998; 17(2):93-96.

(45) Blanchard J, Meuwly JY, Leyvraz PF, Miron MJ, Bounameaux H, Hoffmeyer P et al. Prevention of deep-vein thrombosis after total knee replacement. Randomised comparison between a low-molecular-weight heparin (nadroparin) and mechanical prophylaxis with a foot-pump system. J Bone Joint Surg Br 1999; 81(4):654-659.

(46) Clagett GP, Reisch JS. Prevention of venous thromboembolism in general surgical patients. Results of meta-analysis. Ann Surg 1988; 208(2):227-240.

(47) Lechler E, Schramm W, Flosbach CW. The venous thrombotic risk in non-surgical patients: epidemiological data and efficacy/safety profile of a low-molecular-weight heparin (enoxaparin). The Prime Study Group. Haemostasis 1996; 26 Suppl 2:49-56.

(48) Kleber FX, Witt C, Flosbach CW, et al. Study to compare the efficacy and safety of the LMWH enoxaparin and standard heparin in the prevention of thromboembolic events in medical patients with cardiopulmonary diseases [abstract]. Ann.Hematol. 76(suppl 1), A93. 1998.
Ref Type: Generic

(49) Warkentin TE, Levine MN, Hirsh J, Horsewood P, Roberts RS, Gent M et al. Heparin-induced thrombocytopenia in patients treated with low-molecular- weight heparin or unfractionated heparin. N Engl J Med 1995; 332(20):1330-1335.

(50) Mismetti P, Laporte-Simitsidis S, Tardy B, Cucherat M, Buchmuller A, Juillard-Delsart D et al. Prevention of venous thromboembolism in internal medicine with unfractionated or low-molecular-weight heparins: a meta-analysis of randomised clinical trials. Thromb Haemost 2000; 83(1):14-19.

(51) Collaborative overview of randomised trials of antiplatelet therapy-- III: Reduction in venous thrombosis and pulmonary embolism by antiplatelet prophylaxis among surgical and medical patients. Antiplatelet Trialists' Collaboration. BMJ 1994; 308(6923):235-246.

(52) Cohen AT, Skinner JA, Kakkar VV. Antiplatelet treatment for thromboprophylaxis: a step forward or backwards? BMJ 1994; 309(6963):1213-1215.

(53) Collins R, Baigent C, Sandercock P, Peto R. Antiplatelet therapy for thromboprophylaxis: the need for careful consideration of the evidence from randomised trials. Antiplatelet Trialists' Collaboration. BMJ 1994; 309(6963):1215-1217.

(54) Prevention of pulmonary embolism and deep vein thrombosis with low dose aspirin: Pulmonary Embolism Prevention (PEP) trial. Lancet 2000; 355(9212):1295-1302.

(55) Sors H, Meyer G. Place of aspirin in prophylaxis of venous thromboembolism. Lancet 2000; 355(9212):1288-1289.

(56) Handley AJ. Low-dose heparin after myocardial infarction. Lancet 1972; 2(7778):623-624.

(57) Warlow C, Terry G, Kenmure AC, Beattie AG, Ogston D, Douglas AS. A double-blind trial of low doses of subcutaneous heparin in the prevention of deep-vein thrombosis after myocardial infarction. Lancet 1973; 2(7835):934-936.

(58) Emerson PA, Marks P. Preventing thromboembolism after myocardial infarction: effect of low- dose heparin or smoking. Br Med J 1977; 1(6052):18-20.

(59) Wray R, Maurer B, Shillingford J. Prophylactic anticoagulant therapy in the prevention of calf-vein thrombosis after myocardial infarction. N Engl J Med 1973; 288(16):815-817.

(60) Anticoagulants in acute myocardial infarction. Results of a cooperative clinical trial. JAMA 1973; 225(7):724-729.

(61) Kierkegaard A, Norgren L. Graduated compression stockings in the prevention of deep vein thrombosis in patients with acute myocardial infarction. Eur Heart J 1993; 14(10):1365-1368.

(62) McCarthy ST, Turner JJ, Robertson D, Hawkey CJ, Macey DJ. Low-dose heparin as a prophylaxis against deep-vein thrombosis after acute stroke. Lancet 1977; 2(8042):800-801.

(63) McCarthy ST, Turner J. Low-dose subcutaneous heparin in the prevention of deep-vein thrombosis and pulmonary emboli following acute stroke. Age Ageing 1986; 15(2):84-88.

(64) Turpie AG, Levine MN, Hirsh J, Carter CJ, Jay RM, Powers PJ et al. Double-blind randomised trial of Org 10172 low-molecular-weight heparinoid in prevention of deep-vein thrombosis in thrombotic stroke. Lancet 1987; 1(8532):523-526.

(65) Prins MH, Gelsema R, Sing AK, van Heerde LR, den Ottolander GJ. Prophylaxis of deep venous thrombosis with a low-molecular-weight heparin (Kabi 2165/Fragmin) in stroke patients. Haemostasis 1989; 19(5):245-250.

(66) Sandset PM, Dahl T, Stiris M, Rostad B, Scheel B, Abildgaard U. A double-blind and randomized placebo-controlled trial of low molecular weight heparin once daily to prevent deep-vein thrombosis in acute ischemic stroke. Semin Thromb Hemost 1990; 16 Suppl:25-33.

(67) Turpie AG, Gent M, Cote R, Levine MN, Ginsberg JS, Powers PJ et al. A low-molecular-weight heparinoid compared with unfractionated heparin in the prevention of deep vein thrombosis in patients with acute ischemic stroke. A randomized, double-blind study. Ann Intern Med 1992; 117(5):353-357.

(68) Dumas R, Woitinas F, Kutnowski M, Nikolic I, Berberich R, Abedinpour F et al. A multicentre, double-blind, randomized study to compare the safety and efficacy of once-daily ORG 10172 and twice-daily low-dose heparin in preventing deep-vein thrombosis in patients with acute ischaemic stroke. Age Ageing 1994; 23(6):512-516.

(69) Hillbom M, Erila T, Sotaniemi CW, et al. Comparison of the efficacy and safety of the low-molecular-weight heparin enoxaparin with unfraction-ated heparin in the prevention of deep venous thrombosis in patients with acute ischemic stroke [abstract]. Blood 94(suppl 1), 183a. 1999.
Ref Type: Generic

(70) Harenberg J, Schomaker U, Flosbach CW, et al. Enoxaparin is superior to unfractionated heparin in the prevention of thromboembolic events in medical patients at increased thromboembolic risk [abstract]. Blood 94(suppl 1), 399a. 1999.
Ref Type: Generic

(71) Baglin TP, White K, Charles A. Fatal pulmonary embolism in hospitalised medical patients. J Clin Pathol 1997; 50(7):609-610.

(72) Belch JJ, Lowe GD, Ward AG, Forbes CD, Prentice CR. Prevention of deep vein thrombosis in medical patients by low-dose heparin. Scott Med J 1981; 26(2):115-117.

(73) Halkin H, Goldberg J, Modan M, Modan B. Reduction of mortality in general medical in-patients by low-dose heparin prophylaxis. Ann Intern Med 1982; 96(5):561-565.

(74) Cade JF. High risk of the critically ill for venous thromboembolism. Crit Care Med 1982; 10(7):448-450.

(75) Gardlund B. Randomised, controlled trial of low-dose heparin for prevention of fatal pulmonary embolism in patients with infectious diseases. The Heparin Prophylaxis Study Group. Lancet 1996; 347(9012):1357-1361.

(76) Dahan R, Houlbert D, Caulin C, Cuzin E, Viltart C, Woler M et al. Prevention of deep vein thrombosis in elderly medical in-patients by a low molecular weight heparin: a randomized double-blind trial. Haemostasis 1986; 16(2):159-164.

(77) Samama MM, Cohen AT, Darmon JY, Desjardins L, Eldor A, Janbon C et al. A comparison of enoxaparin with placebo for the prevention of venous thromboembolism in acutely ill medical patients. Prophylaxis in Medical Patients with Enoxaparin Study Group. N Engl J Med 1999; 341(11):793-800.

(78) Bergmann JF, Neuhart E. A multicenter randomized double-blind study of enoxaparin compared with unfractionated heparin in the prevention of venous thromboembolic disease in elderly in-patients bedridden for an acute medical illness. The Enoxaparin in Medicine Study Group. Thromb Haemost 1996; 76(4):529-534.

(79) Harenberg J, Roebruck P, Heene DL. Subcutaneous low-molecular-weight heparin versus standard heparin and the prevention of thromboembolism in medical inpatients. The Heparin Study in Internal Medicine Group. Haemostasis 1996; 26(3):127-139.

(80) Kupfer Y, Anwar J, Senenviratne C, et al. Prophylaxis with subcutaneous heparin significantly reduces the incidence of deep venous thrombophlebitis in the critically ill [abstract]. Am.J.Respir.Crit Care Med. 159(suppl), A519. 1999.
Ref Type: Generic

(81) Fraisse F, Holzapfel L, Couland JM, Simonneau G, Bedock B, Feissel M et al. Nadroparin in the prevention of deep vein thrombosis in acute decompensated COPD. The Association of Non-University Affiliated Intensive Care Specialist Physicians of France. Am J Respir Crit Care Med 2000; 161(4 Pt 1):1109-1114.

(82) Bona RD. Thrombotic complications of central venous catheters in cancer patients. Semin Thromb Hemost 1999; 25(2):147-155.

(83) Prandoni P, Polistena P, Bernardi E, Cogo A, Casara D, Verlato F et al. Upper-extremity deep vein thrombosis. Risk factors, diagnosis, and complications. Arch Intern Med 1997; 157(1):57-62.

(84) Monreal M, Lafoz E, Ruiz J, Valls R, Alastrue A. Upper-extremity deep venous thrombosis and pulmonary embolism. A prospective study. Chest 1991; 99(2):280-283.

(85) Raad II, Luna M, Khalil SA, Costerton JW, Lam C, Bodey GP. The relationship between the thrombotic and infectious complications of central venous catheters. JAMA 1994; 271(13):1014-1016.

(86) Bern MM, Lokich JJ, Wallach SR, Bothe A, Jr., Benotti PN, Arkin CF et al. Very low doses of warfarin can prevent thrombosis in central venous catheters. A randomized prospective trial. Ann Intern Med 1990; 112(6):423-428.

(87) Monreal M, Alastrue A, Rull M, Mira X, Muxart J, Rosell R et al. Upper extremity deep venous thrombosis in cancer patients with venous access devices--prophylaxis with a low molecular weight heparin (Fragmin). Thromb Haemost 1996; 75(2):251-253.

(88) Homans J. Thrombosis of the deep leg veins due to prolonged sitting. N.Engl.J.Med. 250, 148-149. 1954.
Ref Type: Generic

(89) Symington IS, Stack BH. Pulmonary thromboembolism after travel. Br J Dis Chest 1977; 71(2):138-140.

(90) Ferrari E, Chevallier T, Chapelier A, Baudouy M. Travel as a risk factor for venous thromboembolic disease: a case- control study. Chest 1999; 115(2):440-444.

(91) Lapostolle F, Surget V, Borron SW, Desmaizieres M, Sordelet D, Lapandry C et al. Severe pulmonary embolism associated with air travel. N Engl J Med 2001; 345(11):779-783.

(92) Belcaro G, Geroulakos G, Nicolaides AN, Myers KA, Winford M. Venous thromboembolism from air travel: the LONFLIT study. Angiology 2001; 52(6):369-374.

(93) Cesarone MR, Belcaro G, Nicolaides AN, Incandela L, De S, Geroulakos G et al. Venous thrombosis from air travel: the LONFLIT3 study--prevention with aspirin vs low-molecular-weight heparin (LMWH) in high-risk subjects: a randomized trial. Angiology 2002; 53(1):1-6.

(94) Lohr JM, James KV, Deshmukh RM, Hasselfeld KA. Allastair B. Karmody Award. Calf vein thrombi are not a benign finding. Am J Surg 1995; 170(2):86-90.

(95) Rodgers A, MacMahon S. Systematic underestimation of treatment effects as a result of diagnostic test inaccuracy: implications for the interpretation and design of thromboprophylaxis trials. Thromb Haemost 1995; 73(2):167-171.

(96) Bratzler DW, Raskob GE, Murray CK, Bumpus LJ, Piatt DS. Underuse of venous thromboembolism prophylaxis for general surgery patients: physician practices in the community hospital setting. Arch Intern Med 1998; 158(17):1909-1912.

(97) Caprini JA, Arcelus JI, Hoffman K, Mattern T, Laubach M, Size GP et al. Prevention of venous thromboembolism in North America: results of a survey among general surgeons. J Vasc Surg 1994; 20(5):751-758.

(98) Anderson FA, Jr., Wheeler HB, Goldberg RJ, Hosmer DW, Forcier A, Patwardhan NA. Physician practices in the prevention of venous thromboembolism. Ann Intern Med 1991; 115(8):591-595.

(99) Gillies TE, Ruckley CV, Nixon SJ. Still missing the boat with fatal pulmonary embolism. Br J Surg 1996; 83(10):1394-1395.

(100) Arnold DM, Kahn SR, Shrier I. Missed opportunities for prevention of venous thromboembolism: an evaluation of the use of thromboprophylaxis guidelines. Chest 2001; 120(6):1964-1971.

(101) Wille-Jorgensen P. The potential role of new therapies in deep-vein thrombosis prophylaxis. Semin Hematol 2001; 38(2 Suppl 5):20-30.

(102) Eriksson BI, Ekman S, Kalebo P, Zachrisson B, Bach D, Close P. Prevention of deep-vein thrombosis after total hip replacement: direct thrombin inhibition with recombinant hirudin, CGP 39393. Lancet 1996; 347(9002):635-639.

(103) Eriksson BI, Ekman S, Lindbratt S, Baur M, Bach D, Torholm C et al. Prevention of thromboembolism with use of recombinant hirudin. Results of a double-blind, multicenter trial comparing the efficacy of desirudin (Revasc) with that of unfractionated heparin in patients having a total hip replacement. J Bone Joint Surg Am 1997; 79(3):326-333.

(104) Eriksson BI, Wille-Jorgensen P, Kalebo P, Mouret P, Rosencher N, Bosch P et al. A comparison of recombinant hirudin with a low-molecular-weight heparin to prevent thromboembolic complications after total hip replacement. N Engl J Med 1997; 337(19):1329-1335.

(105) Lormeau JC, Herault JP. The effect of the synthetic pentasaccharide SR 90107/ORG 31540 on thrombin generation ex vivo is uniquely due to ATIII-mediated neutralization of factor Xa. Thromb Haemost 1995; 74(6):1474-1477.

(106) Turpie AG, Gallus AS, Hoek JA. A synthetic pentasaccharide for the prevention of deep-vein thrombosis after total hip replacement. N Engl J Med 2001; 344(9):619-625.

(107) Lassen MR. The EPHESUS Study: comparison of the first synthetic factor Xa inhibitor with low molecular weight heparin (LMWH) in the prevention of venous thromboembolism (VTE) after elective hip replacement. Blood 96, 490a. 2000.
Ref Type: Generic

(108) Bauer KA. The PENTAMAKS Study: comparison of the first synthetic factor Xa inhibitor with low moledular weight heparin in the prevention of venous thromboembolism (VTE) after elective major knee surgery. Blood 96, 491a. 2000.
Ref Type: Generic

(109) Turpie AG. The PENTATHLON Study: comparison of the first synthetic factor Xa inhibitor with low molecular weight heparin in the prevention of venous thromboembolism (VTE) after elective hip replacement. Blood 96, 491a. 2000.
Ref Type: Generic

(110) Eriksson BI, Bauer KA, Lassen MR, Turpie AG. Fondaparinux compared with enoxaparin for the prevention of venous thromboembolism after hip-fracture surgery. N Engl J Med 2001; 345(18):1298-1304.

(111) Bauer KA, Eriksson BI, Lassen MR, Turpie AG. Fondaparinux compared with enoxaparin for the prevention of venous thromboembolism after elective major knee surgery. N Engl J Med 2001; 345(18):1305-1310.