Consensus Development Recommendations for the Role of LMWHs in Prophylaxis of Venous Thromboembolism: An Indian Perspective

R Parakh*, A Somaya**, SK Todi***, SS Iyengar****, For Consensus Development Guidelines Panel+

Abstract
Despite the availability of effective prophylactic and therapeutic options, venous thromboembolism (VTE) continues to be underdiagnosed and undertreated. Awareness level among Indians is particularly low in regard to this potentially life-threatening killer disease. It has to be however noted that, contrary to popular belief, the incidence of DVT in India is comparable to that in the Western countries. The clinically silent nature of the disease, makes the diagnosis of this condition even more challenging.

These clinical practice guidelines provide recommendations for the continued management of patients with VTE. The purpose of the consensus/guidelines is to address specifically the risk stratification of VTE, and the appropriate use of low molecular weight heparins (LMWHs) in the prophylactic management of this condition. They are intended to assist physicians, intensivists, vascular surgeons, orthopedicians, surgeons and practitioners in the proper evaluation and prophylaxis of patients with symptoms suggestive of this condition. The diagnostic and prophylactic strategies are supported by the best available evidence and expert opinion. The application of these principles with carefully reasoned clinical judgment would significantly aid in the effective management of VTE.

Rapid strides have been taken in the field of deep vein thrombosis (DVT) prophylaxis. Most studies have compared unfractionated heparin (UFH) and LMWHs. The latter have almost revolutionized the treatment of DVT, and their indications continue to expand by the day. The medical fraternity needs to be made aware of the advantages of using LMWHs and their immense role in significantly reducing, or even completely eliminating, the need for hospitalization, thereby making them the most cost-effective treatment for DVT.

© OVERVIEW OF VENOUS THROMBOEMBOLISM

Definition of terms
Venous thromboembolism (VTE) is a common potentially life-threatening complication that incorporates signs and symptoms of two inter-related but distinct clinical conditions, deep vein thrombosis (DVT) and pulmonary embolism (PE). This is often a silent yet potentially fatal disease. When symptoms do occur, they are often nonspecific and the first manifestation may be fatal PE. Long-term morbidity is a consequence of VTE since unrecognized and untreated thromboembolic episodes predispose patients to recurrent events.

VTE is a serious preventable cause of morbidity and mortality in the western world. It is estimated that 20 million cases of lower extremity DVT occur in United States alone. Undiagnosed and untreated DVT of the lower extremities accounts for the vast majority of the 600,000 cases of PE in United States each year. DVT and PE are distinct but related aspects of VTE. Approximately one third of patients with symptomatic VTE manifest PE, whereas two thirds manifest DVT alone. Despite treatment, VTE recurs frequently in the first few months after the initial event, with a recurrence rate of 7% at 6 months. Death occurs in 6% of DVT cases and 12% of PE cases within 1 month of diagnosis. VTE is a major cause of death among hospitalised patients, with PE causing or contributing to up to 240,000 deaths each year in hospitalized patients in the United States. Results from autopsy studies conducted in European
hospitals suggest that up to 10% of the deaths that occur in hospitals are due to PE.\(^4\)\(^5\)

Acutely ill non-surgical or ‘medical’ patients represent 60% of hospital admissions and 75% of all fatal PEs occur in this patient population.\(^6\) In a recent review, approximately 54% of patients with symptomatic VTE were either general medical or non-surgical oncology in-patients.\(^7\) PE is a serious cause of mortality in both surgical and non surgical patients. PE is the most common preventable cause of death in hospitalized patient. PE is the primary cause of death in 1,00,000 patients annually and a contributing cause of death in another 1,00,000 patients.\(^8\) Based on these various factors, primary prevention of VTE may have a significant impact on reducing the morbidity and mortality associated with hospitalized, acutely ill medical patients.\(^10\)

**DVT AND PE: THE STRONG ASSOCIATION**

VTE is often silent and difficult to diagnose because approximately 80% of all DVTs are silent (Fig. 1). DVT often goes under-diagnosed as it is frequently asymptomatic. When symptoms do occur they are non-specific (pain in the calves or thigh muscles and swelling). Similar symptoms can occur with simple muscle strains or streptococcal infections. Often, a definitive diagnosis can only be reached when tests for diagnosis of VTE are performed. Silent VTE may develop into PE which itself may go unrecognized. PE is often asymptomatic and even when symptoms do appear they may be difficult to recognize. Consequently, less than half of all cases of fatal PE are detected prior to death.\(^11\)

90% of PE is the result of DVT. A recent study showed that 82% of patients with acute PE had detectable DVT at the time PE was diagnosed.

A prospective, open, randomized study was conducted by to assess the incidence of postoperative DVT among Indian patients and to evaluate the safety and efficacy of LMWHs. A total of 104 adult patients were recruited, of whom 35.6% (n = 37) underwent total hip arthroplasty, 46.1% (n = 48) had total knee arthroplasty and 18.3% (n = 19) had fracture fixation involving the proximal femur. One subset of the study fraction received thromboprophylaxis with dalteparin sodium and the other subset did not receive any prophylaxis whatsoever. Results showed that patients who received dalteparin sodium had a considerably lower incidence of DVT, 43.2% as opposed to 60% in those who did not receive any prophylaxis (\(p < 0.05\); chi-square test). Venographically proven DVT in different categories of major orthopedic surgeries was as follows: 72.2% and 42.9% of patients undergoing total knee arthroplasty and total hip arthroplasty developed DVT. This study concluded that DVT is more common among Indians than commonly reported and that the use of LMWH (dalteparin) once daily for prophylaxis led to a decrease in the incidence of DVT, which was statistically significant.\(^12\)

Thromboembolism remains a major preventable cause of postoperative mortality and morbidity in the Western world; very little attention has been given to this condition in the Indian patients. The present study was a prospective randomized study carried out in 104 Indian patients undergoing major orthopaedic lower limb surgery. The aim of the study was to determine the incidence of venographically proved deep vein thrombosis, the distribution of the thrombi and their significance. Group A consisting of patients treated prophylactically with LMWH showed a 43.2% incidence of deep vein thrombosis. Group B consisting of patients without any prophylaxis showed an incidence of 60% postoperatively. The incidence was high in patients undergoing total knee arthroplasty. Majority of the thrombi were distal, involving a short segment of the ipsilateral leg. Clinical signs and symptoms proved unreliable for diagnosing this condition.\(^13\)

**Symptoms of DVT**

Many patients are asymptomatic; however, the history may include the following:

- Edema, principally unilateral, is the most specific symptom. Massive edema with cyanosis and ischemia (phlegmasia cerulea dolens) is rare.
- Leg pain occurs in 50%, but this is entirely nonspecific. Pain can occur on dorsiflexion of the foot (Homans’ sign).
- Tenderness occurs in 75% of patients but is also found in 50% of patients without objectively confirmed DVT. The pain and tenderness associated with DVT does not usually correlate with the size, location, or extent of the thrombus.
- Clinical signs and symptoms of pulmonary embolism as the primary manifestation occur in 10% of patients with confirmed DVT.
- Warmth or erythema of skin can be present over the
No single physical finding or combination of symptoms and signs is sufficiently accurate to establish the diagnosis of DVT. The following is a list outlining the most sensitive and specific physical findings in DVT:

- Edema, principally unilateral
- Tenderness, if present, is usually confined to the calf muscles or over the course of the deep veins in the thigh.
- Pain and/or tenderness away from these areas is not consistent with venous thrombosis and usually indicates another diagnosis.
- Homans’ sign: Discomfort in the calf muscles on forced dorsiflexion of the foot with the knee flexed at 30° has been a time-honored sign of DVT. However, this sign is present in less than one third of patients with confirmed DVT. The Homans’ sign is found in more than 50% of patients without DVT and, therefore, is very nonspecific (Fig. 2).
- Bancroft’s sign is tenderness on anteroposterior, but not on lateral compression of the calf.
- Louvel sign denotes worsening of pain along the course of a thrombotic vein by coughing and sneezing.
- Lowenberg sign is present if, after inflation of sphygmomanometer cuff around each calf, pain is experienced in the affected calf at a lower pressure than in the unaffected one.
- Venous distension and prominence of the subcutaneous veins. Superficial thrombophlebitis is characterized by the finding of a palpable, indurated, cordlike, tender subcutaneous venous segment. Patients with superficial thrombophlebitis without coexisting varicose veins and with no other obvious etiology (e.g., IV catheters, IV drug abuse, soft tissue injury) are at high risk because associated DVT is found in as many as 40% of these patients. Patients with superficial thrombophlebitis extending to the saphenofemoral junction are also at higher risk for associated DVT.
- Fever: Patients may have a fever, usually low grade. High fever is usually indicative of an infectious process such as cellulitis or lymphangitis.
- Phlegmasia cerulea dolens: Patients with venous thrombosis may have variable discoloration of the lower extremity. The most common abnormal hue is reddish purple from venous engorgement and obstruction. In rare cases, the leg is cyanotic from massive iliofemoral venous obstruction. This ischemic form of venous occlusion was originally described as phlegmasia cerulea dolens or painful blue inflammation. The leg is usually markedly edematous, painful, and cyanotic. Petechiae are often present.
- Phlegmasia alba dolens: Painful white inflammation was originally used to describe massive iliofemoral venous thrombosis and associated arterial spasm. The affected extremity is often pale with poor or even absent distal pulses. The physical findings may suggest acute arterial occlusion, but the presence of swelling, petechiae, and distended superficial veins point to this condition.
- Clinical findings of pulmonary embolism: These findings are the primary manifestation in about 10% of patients with DVT. In patients with angiographically proven pulmonary embolism, DVT is found in 45-70%. In the vast majority of these patients, the DVT is clinically silent.14

**Pathophysiology**

Venous thrombi are intravascular deposits composed of cellular material (red and white blood cells and platelets) bound together with fibrin strands. A thrombus can occur in any vein in the body but usually forms in the veins of the lower limbs, including the superficial large veins, deep veins of the calf, and deep veins above the knee, including the proximal and popliteal veins. Venous thrombi of the larger veins above the knee often break off to form PE. More than 95% of pulmonary emboli originate as thrombi in the deep-venous circulation of the lower extremities.15

Many acquired and inherited factors increase the risk for developing venous thromboembolism. The basic factors implicated in thrombus formation - hypercoagulability, vascular injury, and circulatory stasis – is represented as Virchow’s triad to illustrate the overlap between these factors (Fig. 3).

Hypercoagulability or activation of blood coagulation can be initiated by many factors, including tissue or vascular injury and inflammation. Vascular wall injury occurs as a result of mechanical or chemical trauma, which subsequently triggers an inflammatory response known as phlebitis. Circulatory stasis may be due to a reduced or altered blood flow through the deep veins of the lower limbs and is a critical component of thrombus formation in many patients. Circulatory stasis enhances the activation of blood coagulation by
impairing the clearance of clotting factors, allowing them to concentrate locally.15,16

In practical terms, reduction of blood flow leads to a state of hypercoagulability. Endothelial injury can expose collagen, causing platelet aggregation and tissue thromboplastin release. When stasis or hypercoagulability is present, it triggers the coagulation mechanism. This explains why the most successful prophylactic regimens are anticoagulation and minimizing venous stasis.17

DVT of the lower extremity usually begins in the deep veins of the calf around the valve cusps or within the soleal plexus. Tissue thromboplastin, when released, forms thrombin and fibrin that trap RBCs and propagate proximally as a red or fibrin thrombus, which is the predominant morphologic venous lesion (the white or platelet thrombus is the principal component of most arterial lesions). Anticoagulant drugs (e.g., heparin, the coumarin compounds) can prevent thrombi from forming or extending. Antiplatelet drugs, despite intensive study, have not proved effective for prevention.18

Studies have suggested that isolated calf vein thrombi are smaller and do not cause significant morbidity or mortality if they embolize. However contradictory evidence from several other studies have indicated that isolated calf vein thrombi do embolize and suggests that propagation proximally may occur rapidly and that fatal PE arising from isolated calf vein DVT is a significant risk.17

**RISK FACTORS FOR VTE**

Most hospitalized patients have one or more risk factors for VTE (Table 1).19-24 These risk factors are generally cumulative.25 For example, patients with fractures of the hip are at particularly high risk for VTE because they are usually in the elderly age group, the presence of a proximal lower extremity injury as well as its operative repair, and the frequent marked reduction in mobility for weeks after surgery. If cancer is also present, the risk is even greater. Without prophylaxis, the incidence of objectively confirmed, hospital-acquired DVT is approximately 10 to 40% among medical or general surgical patients and 40 to 60% following major orthopedic surgery (Table 2).26,27 One quarter to one third of these thrombi involve the proximal deep veins, and these thrombi are much more likely to produce symptoms and to result in PE.

In many of these patient groups, VTE is the most common serious complication.26-35 Approximately 10% of hospital deaths are attributed to pulmonary embolism.

---

**Fig 3: Virchow’s triad**

---

### Table 1: Risk Factors for VTE

<table>
<thead>
<tr>
<th>Category</th>
<th>Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Circulatory Stasis</strong></td>
<td>Atrial fibrillation</td>
</tr>
<tr>
<td></td>
<td>Left ventricular dysfunction from cardiomyopathy, congestive heart failure, or myocardial infarction</td>
</tr>
<tr>
<td></td>
<td>Immobility or paralysis (e.g., stroke, spinal cord injury)</td>
</tr>
<tr>
<td></td>
<td>Venous insufficiency or varicose veins</td>
</tr>
<tr>
<td></td>
<td>Venous obstruction from tumor, obesity, or pregnancy</td>
</tr>
<tr>
<td><strong>Hypercoagulable State</strong></td>
<td>Malignancy</td>
</tr>
<tr>
<td></td>
<td>Pregnancy and Peripartum period</td>
</tr>
<tr>
<td></td>
<td>Estrogen Therapy</td>
</tr>
<tr>
<td></td>
<td>Trauma or Surgery of lower extremity, hip, abdomen, or pelvis</td>
</tr>
<tr>
<td></td>
<td>Inflammatory bowel disease</td>
</tr>
<tr>
<td></td>
<td>Nephrotic Syndrome</td>
</tr>
<tr>
<td></td>
<td>Protein C or S deficiency</td>
</tr>
<tr>
<td></td>
<td>Resistance to activated</td>
</tr>
<tr>
<td></td>
<td>Protein C</td>
</tr>
<tr>
<td></td>
<td>Sickle cell Anemia</td>
</tr>
<tr>
<td><strong>Vascular Wall Injury</strong></td>
<td>Trauma or surgery</td>
</tr>
<tr>
<td></td>
<td>Venipuncture</td>
</tr>
<tr>
<td></td>
<td>Chemical irritation (e.g., intravenous potassium)</td>
</tr>
<tr>
<td></td>
<td>Chloride or vancomycin</td>
</tr>
<tr>
<td></td>
<td>Heart valve disease</td>
</tr>
<tr>
<td></td>
<td>or replacement</td>
</tr>
<tr>
<td></td>
<td>Atherosclerosis (coronary artery or disease or cerebrovascular disease)</td>
</tr>
<tr>
<td><strong>Vascular Wall Injury</strong></td>
<td>Acute Myocardial Infarction</td>
</tr>
<tr>
<td><strong>Hypercoagulable State</strong></td>
<td>Indwelling catheters</td>
</tr>
</tbody>
</table>

---

### Table 2: Absolute Risk of DVT in Hospitalized Patients*

<table>
<thead>
<tr>
<th>Patients Group</th>
<th>DVT Prevalence, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical Patients</td>
<td>10-20</td>
</tr>
<tr>
<td>Cardiac Surgery</td>
<td>15-40</td>
</tr>
<tr>
<td>Major Gynecologic Surgery</td>
<td>15-40</td>
</tr>
<tr>
<td>Major Urologic Surgery</td>
<td>15-40</td>
</tr>
<tr>
<td>Neurosurgery</td>
<td>15-40</td>
</tr>
<tr>
<td>Stroke</td>
<td>20-30</td>
</tr>
<tr>
<td>Hip or Knee arthroplasty, hip fracture surgery</td>
<td>40-60</td>
</tr>
<tr>
<td>Major Trauma</td>
<td>40-50</td>
</tr>
<tr>
<td>Spinal Cord injury</td>
<td>60-80</td>
</tr>
<tr>
<td>Critical Care Patients</td>
<td>10-20</td>
</tr>
</tbody>
</table>

*Study based on objective diagnosis for DVT in patients not receiving thromboprophylaxis.
For example, among 1,234 hospitalized patients who died and underwent autopsy within 30 days of a surgical procedure, the rate of PE was 32%, and PE was considered to be the cause of death in 29% of these cases. In a second study of 51,645 hospitalized patients, the prevalence of acute PE was 1%, and PE was believed to have caused or contributed to death in 37% of these cases. Although improved patient care may have attenuated some of the risk factors for VTE, patients currently in the hospital may well be at greater risk than those studied in the past because of their more advanced age, greater prevalence of cancer and intensive cancer therapy, more extensive surgical procedures, and prolonged stays in a critical care unit. Table 3 shows the risk stratification score card for the evaluation of VTE risk.

## Complications Of DVT

Asymptomatic VTE results in permanent vascular damage and in some instances the post-phlebitic syndrome. The risk of post-phlebitic syndrome is about 30% by 5 years and even in asymptomatic patients the post-phlebitic syndrome occurs in 25% of these patients.

### Fatal PE

Fatal PE is the most dramatic effect of VTE, and it remains the most common preventable cause of death in hospitalized patients. The mortality rate from PE is as high as 32%. PE accompanied by hypotension or shock, severe hypoxemic respiratory failure, acute right-sided heart dysfunction, or obstruction of the pulmonary vasculature that exceeds 50% as demonstrated by angiogram or ventilation-perfusion (V/Q) scan. Depending on the series and the method of diagnosis, 40% to 80% of patients with acute PE, end up having fatal PE as defined here. Unfortunately, 75% of patients...
who die of PE do so within 1 hour of symptom onset. Rapid evaluation and intervention are critical (Fig. 4).

Chronic thromboembolic pulmonary hypertension

Chronic thromboembolic pulmonary hypertension (CTPH) is associated with considerable morbidity and mortality. But its incidence after PE and associated risk factors are not well documented. CTPH is associated with progressive dyspnea and progressive heart failure and could be highly fatal. A prospective, long-term, follow-up study was done to assess the incidence of symptomatic CTPH in consecutive patients with an acute episode of PE but without prior VTE. CTPH was considered to be present if systolic and mean pulmonary artery pressures exceeded 40 mm Hg and 25 mm Hg, respectively; pulmonary-capillary wedge pressure was normal; and there was angiographic evidence of disease. The cumulative incidence of symptomatic CTPH was 1.0% (95% confidence interval) at six months, 3.1% (95% confidence interval) at one year, and 3.8% (95% confidence interval) at two years. It was concluded that CTPH is a relatively common, serious complication of PE. Diagnostic and therapeutic strategies for the early identification and prevention of CTPH are needed.

CONCLUSIONS

● Deep Vein Thrombosis (DVT) is an important problem in India and should be diagnosed early to prevent the associated mortality and long-term morbidity.

● Fatal PE is the most dramatic effect of VTE, and it remains the most common preventable cause of death in hospitalized patients.

REFERENCES


4. Lindblad B, Sternby NH, Bergqvist D. Autopsy-verified pulmonary embo
lism among hospitalized patients at Brigham and Women’s Hospital. Chest 1989;82:203/g25905.


DVT – Available Diagnostic Modalities

Accurate and timely diagnosis of DVT is critical in making appropriate treatment decisions. Careful patient assessment, combined with objective testing, improves the accuracy of the diagnosis and reduces the likelihood of inappropriate treatment. Venography remains the reference standard for the diagnosis of DVT but is expensive, invasive, and prone to inducing complications. When used alone, none of the noninvasive methods is sufficiently sensitive for the evaluation of asymptomatic patients. The diagnostic strategy used should be based on whether the patient is symptomatic or asymptomatic, whether the event is a first one or is recurrent, and a careful clinical assessment. Accurate diagnosis of deep vein thrombosis relies on both testing and patients assessment. There are a host of options available for diagnosing DVT and PE and it is vital for the treating physician to choose the appropriate one. This chapter not only gives the advantages and disadvantages of the different diagnostic modalities but also gives the management protocols for the management of this condition, especially in the Indian setting.

DVT – Available Diagnostic Modalities

Contrast Venography: Venography should be performed whenever noninvasive testing is non-diagnostic or impossible to perform. Venography appears to be the most sensitive test for calf DVT. However, it provides inadequate visualization of the deep venous system in 20 to 25% of patients and is difficult to perform in non-ambulatory patients. Besides, the radiographic contrast media can cause complications like allergy, CHF, acute renal insufficiency and venous thrombosis.1

Color Doppler Sonography: The combination of compression ultrasound with Doppler technology to assess blood flow is referred to as duplex ultrasound, and the addition of color mapping of the Doppler energy is termed power Doppler.

At present, there is no evidence that Doppler techniques provide additional benefits as long as compressibility of the deep veins during ultrasound imaging is used as the major diagnostic criterion. However, the sensitivity and specificity of duplex for proximal vein thrombosis is 98%. It helps to differentiate venous thrombosis from hematoma, Baker’s cyst, abscess, other causes of leg pain and edema.2

Impedance Plethysmography: Impedance plethysmography (IPG) is a sensitive method for evaluating the rate of venous return from the lower extremities. This technique detects increased venous outflow resistance in the deep veins of the proximal lower extremities. It has been demonstrated that the sensitivity and specificity of IPG for detecting proximal DVT is dependent on adherence to the validated protocol.

This procedure is safe, non-invasive, rapid, inexpensive, has no radiation hazard and can diagnose symptomatic proximal DVT. On the flip side, it is operator-dependent, and cannot diagnose asymptomatic proximal DVT, calf DVT and non-obstructing thrombi (Fig. 5).3,4

Radio Isotope Venography: Technetium-99m-labeled red blood cells or macro-aggregated albumin can be used to detect DVT. Venography using labeled macro-aggregated albumin can be performed in conjunction with lung perfusion scanning. Scintigraphy using autologous labeled platelets can detect active DVT sites that are not readily evaluated by ultrasonography.

Radionuclide scintigraphy using labelled peptides that attach to activated platelets is currently being evaluated for the detection of acute DVT. A labeled peptide scan may complement a negative or equivocal ultrasound study, particularly in patients who have undergone surgery, patients with intermediate or low-probability lung scans and patients with active deep venous thrombosis in the calf and/or pelvis region.5

There are certain limitations to it, viz., it does not provide direct information on the cause of venous obstruction, is unreliable in the calf due to presence of multiple vessels, cannot differentiate intrinsic from extrinsic obstruction and its accuracy decreases markedly in patients with previous DVT or congenital duplication of deep venous system above the knee.6

Radio labeled Fibrinogen Uptake: Fibrinogen uptake radionuclide scanning was used extensively in the 1960s. It is more sensitive for DVT in the calves than in thighs. In view of the greater risk of pulmonary embolism with DVT of the thighs than of the calves, the value of fibrinogen uptake scanning is limited. Besides, it is time consuming and gives many false-positive results.

CT Venography: Indirect Venography is performed
in spiral CT by volumetric acquisition from the upper abdomen to the popliteal fossa. Combined CT venography and pulmonary angiography (CTVPA) is a single examination that combines multidetector CT pulmonary angiography (CTPA) and CT venography (CTV) of the abdomen, pelvis, and lower extremities, providing “one-stop shopping” for venous thromboembolism without additional venepuncture or i.v. contrast, and it adds only a few additional minutes to scanning time. CTVPA rapidly and accurately examines the deep veins, reveals the presence, absence, and extent of deep venous thrombosis, serves as a baseline, and helps guide patient management.

**INDICATIONS**

- Orthopedic patients after major surgery for limb and trauma.
- ICU patients, intubated and in whom one cannot assess the leg symptoms, dressing, trophic changes, lack of mobility in these patients may interfere.
- Obese patients with moderate to severe leg swelling.
- No symptoms in high risk patients for DVT and PTE.
- To detect calibre and patency of IVC, particularly when interventions like filter placement are considered.

CT Venography is a safe, specific, easily available and relatively fast procedure. Its limitations are that it is expensive, not portable and needs contrast bolus comparable to angiogram.

**MR Venography**: MRI directly images thrombi, and can image non-occlusive clots. It does not rely on compression or other adjunctive techniques. Recently, investigators have studied the accuracy of MRI in diagnosing DVT. Early research suggests that it is between 87%-100% sensitive to DVT—depending on the location of the blood clot and thus comparable to venography. A 1992 study found that MRI is best at detecting clots in the thigh and pelvis (100%), but slightly less sensitive to clots in the calf (87%). It may have a role in evaluating DVT in pregnancy. This procedure is sensitive, specific, safe, available and can diagnose pelvic/IVC DVT and upper extremity DVT. But it is expensive, not portable and cannot diagnose calf DVT.

**D-Dimer Assay**: The D-dimer test provides 93% sensitivity to proximal DVT but only 70% sensitivity to distal DVT. D-dimer assays are dependent on the size of clot and are not “clot specific”. Several studies have shown that D-dimer assay to have a high negative predictive value but poor specificity when used in the detection of VTE. Yet in the emergency room setting, the D-dimer test may be useful if a detailed risk factor analysis for each patient is included in the diagnosis.

The combination of testing for the presence of D-dimer and impedance plethysmography was found to be very effective in diagnosing or excluding deep venous thrombosis (DVT). When both tests were normal, only 1.5% of patients had DVT; when only one was abnormal, 33% had DVT; and when both were abnormal, 93% had DVT. Thus, this combination of tests is useful in making decisions regarding anticoagulation in patients with suspected DVT.

Thermography: Preliminary assessment of clinically suspected DVT of the lower limb by thermography avoids the need for over one third of venograms or duplex Doppler ultrasound scans. Clinical diagnosis of DVT is notoriously unreliable, hence the need for an accurate means of clinical investigation.

Thermal imaging is quick, simple, non-invasive, risk-free, cost-effective and highly sensitive in the initial investigation of suspected DVT; a negative thermogram excludes DVT and avoids the necessity for further investigation. Thermal imaging is, however, non-specific; a positive thermogram has a number of possible causes and is an indication for further assessment by venography or Doppler ultrasound to confirm or exclude DVT. Thermography should be considered the initial investigation of choice in clinically suspected DVT, proceeding to venography or Doppler ultrasound only when thermography is positive.

**Management of DVT**

The Wells Clinical Prediction score provides a reliable estimate of the pretest probability of DVT (Table 4), which should, in turn, guide the interpretation of subsequent diagnostic tests. The value of various diagnostic tests and imaging studies in predicting the presence of DVT depends on the likelihood of disease in each risk group. For example, the same test may rule out disease when it is negative in a low-probability patient but not when it is negative in a high-probability patient. Because many patients have an intermediate probability of venous thromboembolism, clinical judgment continues to be an important factor in making the decision to treat. Table 5 shows the diagnostic path way for the prophylaxis of DVT.

**PE - AVAILABLE DIAGNOSTIC MODALITIES**

**Radioisotope Lung Scintigraphy**: The ventilation-perfusion (V/Q) scan has long been considered the pivotal diagnostic test in acute PE. Unfortunately, the V/Q scan is diagnostic in minority of cases; that is, it is rarely interpreted as normal or high probability. Most lung diseases affect pulmonary blood flow to some extent as well as ventilation, thus decreasing the specificity of the V/Q scan. Concordance between clinical suspicion and VP scan result improves the predictive value.

Combination of a high clinical suspicion and high
probability scan have a positive predictive value of 96% for PTE (PIOPED). Combination of low clinical suspicion and low probability scan has a negative predictive value of 96% for PTE.

CT Pulmonary Angiography: Spiral CT technique enables rapid scanning with continuous volume acquisitions obtained during a single breath hold. Diagnosis of pulmonary embolism with spiral volumetric CT was based on the direct visualization of intraluminal clots. Spiral CT has the greatest sensitivity for emboli in the main, lobar, or segmental pulmonary arteries. CT pulmonary angiography (CTPA) is increasingly being used as an adjunct and, more recently, as an alternative to other imaging modalities, and is clearly superior in specificity to V/Q isotope scanning. CTPA is now the recommended initial lung imaging modality for non-massive PE.

Patients with a good quality negative CTPA do not require further investigation or treatment. CTPA has the advantages of direct demonstration of clot in involved vessels and documentation of non-thromboembolic abnormalities of the lung, heart or mediastinum. However, it provides demonstration up to fourth order vessels only, and is less accurate for detecting subsegmental thrombus. Technical failures are another limitation in 1-4% of cases.

Catheter Pulmonary Angiography: Pulmonary angiography for purpose of diagnosing acute PE is unnecessary when the perfusion scan is normal. Relative contraindications to the procedure include significant bleeding risk and renal insufficiency. Pulmonary angiography has traditionally been the “gold standard” for accuracy in diagnosing pulmonary embolism. A positive result on a pulmonary angiogram provides nearly 100% certainty that a blockage exists, while a negative result gives greater than 90% certainty in ruling out a pulmonary embolus.

**Indications**
- In patients with unresolved suspicion of PTE
- When VP Scan is at variance with the clinical probability of PE
- In massive pulmonary embolism, as a prelude to embolectomy, vena cava filter insertion or thrombolytic therapy.
- When identification of subsegmental emboli is regarded as vital, usually in patients with severely limited cardio pulmonary reserve.

The advantage of using catheter pulmonary angiography is that direct visualization of thrombus within the pulmonary arteries is possible, whereas its limitations are that it only provides vascular morphology pertaining to vessel lumen and concentric thrombus in chronic PTE and other mural changes are not evaluated. Cost, expertise and immediate availability are other concerns.

**Electrocardiography**: While electrocardiographic abnormalities may develop in the setting of acute PE, they are generally nonspecific and include T-wave changes, ST segment abnormalities, and left or right axis deviation. The low frequency of specific electrocardiogram (ECG) changes associated with PE was confirmed in the PIOPED (Prospective Investigation of Pulmonary Embolism Diagnosis) study.

**Echocardiography**: Right ventricular failure is the ultimate cause of death in patients who succumb to acute PE. Dysfunction of the right ventricle frequently accompanies massive PE, and this finding has been shown to correlate not only with larger emboli but also with recurrence of PE. Visualization of large emboli within the main pulmonary artery has been reported with surface echocardiography, but this appears to be unusual. At the present time, the role of surface echocardiography for the diagnosis of acute PE remains undefined. Until level 1 data become available, echocardiography cannot be considered a primary diagnostic test for the investigation of clinically suspected acute PE.

**Arterial Blood Gas Analysis**: Hypoxemia is common in acute PE, but is not universally present. Young patients without underlying lung disease may have a
normal PaO2. In a retrospective analysis of hospitalized patients with proven PE, the PaO2 was greater than 80 mm Hg in 29% of patients less than 40 yr old, compared with 3% in the older group.

Ultrasonography of The Leg: Leg ultrasound has been used in suspected PE as an initial test in those with a clinical DVT, as an initial test in all patients to reduce the need for lung imaging, and after lung imaging, particularly isotope lung scanning, has given inconclusive information.

Management of PE

Wells clinical prediction rule for PE produces a point score based on clinical features and the likelihood of diagnoses other than PE. Other clinical prediction rules include the Geneva rule and the rule developed in the Prospective Investigative Study of Acute Pulmonary Embolism Diagnosis (PISA-PED). However, the Geneva rule requires an arterial blood gas measurement and a chest radiograph, while the PISA-PED rule requires an ECG. One investigative team has developed rules for explicit use with D-dimer tests, and Wells rule has been simplified for use with D-dimer tests. The diagnostic pathway for the management of PE is shown in Table 6.

No consensus has emerged on the best clinical prediction rule for PE or the criteria that should be used to judge the performance of the various rules. Table 7 below shows the Wells clinical prediction rule to help guide physicians when D-dimer testing is not available. This prediction rule is one of the oldest and most frequently used decision rules. A low probability based on the combination of a prediction rule and a negative D-dimer test significantly reduces the probability of PE; however, the development of PE protocols awaits empiric validation.

Table 7: Wells Clinical Prediction Scoring System for PE

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strong Clinical Suspicion of PE + Suspected DVT</td>
<td>3</td>
</tr>
<tr>
<td>Alternative Diagnosis is less likely than PE</td>
<td>3</td>
</tr>
<tr>
<td>HR &gt; 100/min</td>
<td>1.5</td>
</tr>
<tr>
<td>Immobilization of Surgery in previous 4 weeks</td>
<td>1.5</td>
</tr>
<tr>
<td>Previous DVT or PE</td>
<td>1.5</td>
</tr>
<tr>
<td>Hemoptysis</td>
<td>1.5</td>
</tr>
<tr>
<td>Malignancy</td>
<td>1.5</td>
</tr>
<tr>
<td>(Treatment within past 6 months or ongoing or palliative)</td>
<td></td>
</tr>
</tbody>
</table>

No consensus has emerged on the best clinical prediction rule for PE or the criteria that should be used to judge the performance of the various rules. Table 7 below shows the Wells clinical prediction rule to help guide physicians when D-dimer testing is not available. This prediction rule is one of the oldest and most frequently used decision rules. A low probability based on the combination of a prediction rule and a negative D-dimer test significantly reduces the probability of PE; however, the development of PE protocols awaits empiric validation.

Conclusions

- Accurate and timely diagnosis of DVT is critical in making appropriate treatment decisions.
- Venography should be performed whenever noninvasive testing is non-diagnostic or impossible to perform.
- CT Venography is a safe, specific, easily available and relatively fast procedure.
- The combination of testing for the presence of D-dimer and impedance plethysmography was found to be very effective in diagnosing or excluding deep venous thrombosis (DVT).
- Wells clinical prediction rule for PE produces a point score based on clinical features and the likelihood of diagnoses other than PE.

References

Venous thromboembolism in elderly and special populations

Venous thromboembolism (VTE), a condition which includes both deep vein thrombosis (DVT) and its primary complication, pulmonary embolism (PE), is a very important condition for health professionals who provide care for the elderly (Table 8). Venous thromboembolism (VTE) is often a clinically silent disease that can result in significant morbidity and mortality. Increasing age is a strong risk factor for venous thromboembolism. Below age 40, the annual incidence of VTE is approximately 1 per 10,000 while, over the age of 75, the risk is almost 1 per 100 per year. Some of this age-related risk is due to an increased prevalence of major surgery, malignancy, stroke and other medical illnesses in the elderly. However, thrombosis risk increases with age independent of these additional factors (Table 9). Aging is associated with increased levels of procoagulant molecules, reduced levels of endogenous clotting inhibitors and evidence of increased thrombin generation. Therefore, even the healthy elderly have an acquired prothrombotic state.

VTE is more dangerous for the elderly than for younger patients. The case fatality rate for PE has been shown to depend on the size of the embolus and the underlying cardiorespiratory reserve (often reduced in the elderly), as well as on advancing age. It has been seen that the incidence of VTE is the highest at the age of 80-85 years. According to Anderson et al., the risk increases by 1.9 per 10-year increase in age. Therefore, one has to be cautious in treating elderly patients. VTE prophylaxis might be needed in these patients (Fig. 6).
Although there is an increased risk of bleeding in geriatric patients, the risk for thrombosis is high. There is also a widespread perception that the risk of bleeding is increased in geriatric patients. This concern is certainly appropriate when full-dose oral anticoagulants are used but not for heparin or low molecular weight heparins. Clinical bleeding complications are very uncommon with use of anticoagulant prophylaxis both in controlled trials and in clinical practice.

Prevention of Venous Thrombosis and Thromboembolism

A strategy for prevention of venous thromboembolic complications for older adults is recommended for every hospital. The incidence, morbidity, and mortality of DVT and PE in the older surgical patient population, particularly those undergoing gynecological, urological, major general, and major orthopedic procedures, and in the medically ill, is sufficient to warrant general recommendations for prevention of venous thrombosis and thromboembolism.

Since it is not possible to predict whether or not a specific patient will develop a clinically-important thromboembolic event related to hospitalization, the prevention of VTE is essential for elderly patients at risk. Patients with chronic, degenerative diseases or cognitive impairment should also be strongly considered for thromboprophylaxis.

How does one decide whether or not to provide prophylaxis for such patients? The rule is as follows: if one would investigate an elderly, severely impaired patient for clinically-suspected DVT or PE and treat him/her if acute thromboembolism is found, then it is appropriate to provide effective prophylaxis both to reduce the morbidity and mortality of thromboembolism and because screening for asymptomatic DVT is ineffective at preventing VTE.

Furthermore, primary prophylaxis has repeatedly been demonstrated to be more cost-effective than case-finding or investigation and treatment of clinically-suspected cases. Many older adults have several risk factors, and the risk is cumulative. Antithrombotic prophylaxis or therapy must be used with extreme caution in all patients undergoing a spinal puncture for diagnosis, therapy, or regional anesthesia or analgesia with an epidural catheter (Grade 1C+).

Options for Thromboprophylaxis

Low-dose heparin (LDH)

Low-dose, unfractionated heparin, started 1-2 hours pre-operatively and then continued every 8 or 12 hours after surgery, decreases the relative risk of DVT and fatal PE in a variety of surgical and medical scenarios by at least 60%, without increasing the risk for major bleeding. These properties and low cost make LDH the prophylaxis agent of choice for most elderly patients undergoing general, urologic and gynecologic surgery and for medical patients with additional thromboembolic risk factors.

Low Molecular Weight Heparins (LMWHs)

These derivatives of heparin have a number of pharmacologic properties that increase their effectiveness (up to 80% compared with placebo) and safety and therefore make them attractive prophylaxis options, especially for high risk patients. In patients with moderate thromboembolic risks (Table 10), LDH and LMWH have comparable efficacy and safety while, in higher risk patients, LMWHs are clearly superior.

Oral Anticoagulants

Oral anticoagulation is substantially more difficult and is associated with increased risks of bleeding in the elderly because of increased sensitivity to warfarin, greater number of comorbid diseases and increased potential for drug interactions. However, short-term thromboprophylaxis with oral anticoagulants in geriatric patients can be both safe and effective, as long as the clinician is experienced in the use of these agents in the elderly and is committed to providing careful supervision during the period of prophylaxis. The only situation where this may arise is following major hip and knee surgery or for long-term prophylaxis after major trauma—for these groups there are alternatives which have greater efficacy and safety, and are much simpler to use.

Antiplatelet Agents

Because alternative methods of prophylaxis consistently demonstrate superior protection compared with aspirin or other antiplatelet agents, we believe there is no role for these drugs in the prevention of VTE.

Graduated Compression Stockings (GCS) and Pneumatic Compression Devices (PCD)

Mechanical prophylaxis with elastic stockings and/
or intermittent pneumatic compression devices has the advantage of not producing bleeding. For this reason, these methods are preferred for situations in which the risks for and the consequences of bleeding are high such as in neurosurgery, hemorrhagic stroke, traumatic intracranial bleeding and open prostate surgery. However, for many patients (especially those in the high-risk group), the efficacy of these devices is inferior to anticoagulant prophylaxis and compliance with the pump devices is generally poor. There is evidence that the combination of pharmacologic and mechanical prophylaxis provides greater protection than does either alone. Therefore, combined prophylaxis may be particularly advantageous for patients with a greater than usual thromboembolic risk. Mechanical prophylaxis, followed in a few days by anticoagulant prophylaxis, should also be considered in patients with a high bleeding risk that diminishes overtime (for example, following a major surgical procedure or hemorrhagic stroke).

**SPECIAL POPULATIONS**

### VTE in Congestive Heart or Respiratory Failure

The burden of venous thromboembolic disease in hospitalized patients is especially significant; with certain medical conditions (like congestive heart failure, respiratory failure), and systemic infection-being associated with an elevated risk for thromboembolic disease.

### VTE in Cardiac Rehabilitation after CABG

According to a recent study, there was a high rate of DVT in patients after CABG. Clots were surprisingly more often localized in legs contralateral to the saphenous vein harvest site. On multivariate analysis, female sex (p<0.001) and length of stay in the unit > 8 days (p<0.05) were independently associated with risk of DVT. Efficacy of routine prophylaxis against VTE after CABG and the need for its use in well defined patient population are debatable. Wearing unilateral graded compression stockings post CABG had limited efficacy.²⁹

**Trauma**

Major trauma patients have the highest risk of VTE with elderly trauma patients having a particularly high risk.³⁰ For patients with traumatic intracranial bleeding or active, uncontrolled bleeding, mechanical prophylaxis, at least for the first 5 days of admission, is recommended.²⁹ For the majority of trauma patients, it is safe to commence LMWH within 36 hours after injury if primary hemostasis has occurred.³⁰ Patients with complete spinal cord injury should be given aggressive prophylaxis with LMWH, generally followed by full-dose oral anticoagulation until they are released from rehabilitation.

**CONCLUSIONS**

- Elderly patients with CHF, respiratory failure, sepsis and ischemic stroke have a significantly higher risk of DVT.
- LMWH reduces the incidence of VTE in acutely ill and elderly (>65 years) hospitalized patients with a low risk of bleeding.

**REFERENCES**

Thromboprophylaxis in Orthopedic Surgery

The risk of venous thromboembolism (which includes the clinical conditions deep vein thrombosis and pulmonary embolism) increases with age and is extremely high when older patients undergo major orthopedic surgery without adequate thromboprophylaxis. Effective and well-tolerated prophylaxis against venous thromboembolism is available and should be employed in all patients undergoing major orthopedic surgery of the lower limb. Uncertainty remains regarding the optimal time to commence pharmacological prophylaxis, and the optimal duration also remains to be established, although there is good evidence to suggest that 7 to 10 days of prophylaxis is adequate in the majority of patients. Modified thromboprophylactic strategies may be required in patients considered to be at high risk of bleeding, particularly those undergoing hip fracture surgery.

Deep vein thrombosis most commonly arises in the deep veins of the calf or, less often, in the proximal deep veins of the thigh. If left untreated, up to 30% of calf thrombi extend into the more proximal veins of the thigh. If proximal leg vein thrombi are left untreated, they are associated with a 50% risk of pulmonary embolism or recurrent venous thrombosis and a 5 to 10% risk of fatal pulmonary embolism. Despite modern surgical techniques and early postoperative mobilisation, the incidence of venous thromboembolism during major orthopedic surgery remains high in the absence of adequate prophylaxis. In addition, although many perioperative deep vein thrombi remain clinically silent, there is a high incidence of asymptomatic pulmonary embolism coincident with tourniquet deflation during knee arthroplasty. Furthermore, there is a risk of venous thromboembolism after hospital discharge.

In patients undergoing hip or knee arthroplasty, prophylactic strategies can reduce the risk of venous thromboembolism by 50% or more. As the risks and costs of thromboprophylaxis are relatively small, strong recommendations can be made regarding their use in the ‘average’ patient. Similarly, in patients undergoing surgery for hip fracture, risk reductions associated with the use of thromboprophylaxis are in the order of 40 to 50%. However, estimates of the risk of bleeding in these patients, even in the absence of pharmacological thromboprophylaxis, are higher than in elective hip and knee arthroplasty, and the balance between risk and benefit may, therefore, be less certain in the individual patient. Nevertheless, given the high risk of venous thromboembolism in patients undergoing orthopedic surgery, some form of thromboprophylaxis is indicated in all patients, although the precise strategy may need to be modified in patients who are considered to be at increased risk of bleeding.

Vascular Events and Mortality after Major Orthopedic Surgery

Major orthopedic surgery, such as total hip replacement (THR), increases the mortality rate, which has been estimated to be 6.5 excess deaths per 1000 operations within the 0th postoperative day when compared with that of the first postoperative year. The 90-day mortality rate is 2.5-fold higher than that of comparable periods in the remainder of the year (Fig. 7). Trauma of major orthopedic surgery results in local and systemic activation of coagulation and the resulting hypercoagulable state increases the risk of venous thromboembolism.

Studies have confirmed dramatic reductions in the venous capacitance of the lower limbs and in the venous outflow after hip arthroplasty. During dislocation of the hip joint and the insertion of the prosthesis, venography has shown torsion and complete occlusion of the femoral vein. Further, knee arthroplasty involves the use of a tourniquet on the thigh and flexion of the knee for a prolonged time that leads to vascular problems. Injury to the venous endothelium as a result of operative...
positioning, manipulation and thermal injury from bone cement may result in foci of vascular damage that provide a nidus for thrombosis. Thrombin clots that develop in the peripheral veins of the calf, thigh and pelvis, propagate proximally, thereby increasing the risk of pulmonary embolism.

Methods of Thromboprophylaxis

The goal of thromboprophylaxis is to prevent both the occurrence and the consequences of deep vein thrombosis. General measures to reduce the risk of venous thromboembolism in older patients undergoing major orthopedic surgery include optimal surgical and anesthetic techniques to minimise the extent of tissue injury and duration of patient immobility. These general measures should be combined with 1 or more specific methods of thromboprophylaxis according to the needs of the individual.

Mechanical methods of venous thromboprophylaxis (Table 1) are simple to use, noninvasive and free of bleeding risk. The utility of these measures may, however, be limited by non-use during physical therapy and by patient intolerance. In practice, mechanical methods are usually used in combination with pharmacological strategies for thromboprophylaxis.

Pooled data indicate that graduated compression stockings alone reduce the risk of deep vein thrombosis following total hip arthroplasty by 25%, and intermittent pneumatic compression devices (of the calf alone, or calf and hip) reduce the incidence of deep vein thrombosis following hip and knee arthroplasty by 57 and 82%, respectively. There is also preliminary evidence suggesting that plantar compression devices may be effective in preventing venous thromboembolism following major orthopedic surgery of the lower limbs.

Antiplatelet Agents: Results from a meta-analysis indicate that antiplatelet therapy [most commonly aspirin (acetylsalicylic acid)] reduces the incidence of deep vein thrombosis by 30% and pulmonary embolism by 65% (statistically significant compared with placebo) in patients undergoing elective orthopedic surgery. Antiplatelet therapy was associated with a small but statistically significant increase in the risk of nonfatal major bleeds and minor bleeds. However, other data suggest that aspirin is relatively ineffective compared with other prophylaxis regimens.

Unfractionated Heparin: Although low dose unfractionated heparin may be less effective than adjusted-dose unfractionated heparin at reducing the risk of deep vein thrombosis in patients undergoing hip or knee arthroplasty, it is more commonly used. This is because of the need for laboratory monitoring during therapy with dose-adjusted unfractionated heparin as well as the inconvenience of 3 times daily administration and frequent dose adjustment.

Low dose unfractionated heparin (usually 5000 IU every 8 or 12 hours) started preoperatively reduces the risk of deep vein thrombosis by 31 to 39% compared with placebo or control in patients undergoing hip or knee arthroplasty, and it is not associated with an increased risk of major bleeding. Low dose unfractionated heparin is also effective in reducing the risk of deep vein thrombosis in patients undergoing surgery for hip fracture (44% risk reduction).

Adjusted-dose unfractionated heparin is associated with a 78% risk reduction of deep vein thrombosis compared with placebo or control following hip arthroplasty and appears to be more effective than low dose unfractionated heparin with a comparable tolerability profile.

Low molecular weight heparin: Low molecular weight heparin (LMWH) preparations are more convenient to use than dose-adjusted unfractionated heparin or dose-adjusted warfarin. The major practical advantages of LMWH are that no laboratory monitoring or dose adjustment is required as there is a predictable anticoagulant effect when these preparations are administered in a fixed bodyweight adjusted dose.

Although it has been suggested that LMWH preparations may not be clinically interchangeable, there is currently no evidence to suggest that there are clinically important differences between individual LMWH preparations for the prevention of venous thromboembolism in patients undergoing major orthopedic surgery.

LMWH preparations are associated with a 49 to 71% reduction in the risk of deep vein thrombosis following hip or knee arthroplasty compared with placebo or control, and a 44% risk reduction in patients undergoing surgery for hip fracture. LMWHs have also been shown to be as effective as, or superior to, dose-adjusted unfractionated heparin following hip arthroplasty.

LMWH preparations are at least as effective as dose-adjusted warfarin in preventing venous thromboembolism in patients undergoing hip or knee arthroplasty and more effective in patients undergoing total hip replacement. However, they may be associated with a higher risk of minor bleeding complications than dose-adjusted warfarin. LMWH preparations may also be more effective than dose-adjusted unfractionated heparin in preventing venous thromboembolism in patients undergoing total hip replacement.

Dose-Adjusted Warfarin: Dose-adjusted warfarin [target international normalised ratio (INR) 2.0 to 3.0] is widely used and is thought to be highly effective for thromboprophylaxis following major orthopedic surgery of the lower limbs. It is associated with a 50% reduction in the risk of deep vein thrombosis in patients undergoing surgery for hip fracture compared with placebo or control.
**Direct Thrombin Inhibitors**: Direct thrombin inhibitors seem to be effective and well tolerated in the prevention of venous thromboembolism following orthopedic surgery. Randomised controlled trials have shown that subcutaneous administration of recombinant hirudins is more effective than both low dose unfractionated heparin and LMWH following hip arthroplasty. Furthermore, in a phase II study bivalirudin was shown to be well tolerated and effective for the prevention of venous thromboembolism following hip or knee arthroplasty. However, direct thrombin inhibitors are not approved for use in venous thromboembolism prophylaxis in all countries.

The optimal timing of commencement of thromboprophylaxis is not clear. The main drawback to preoperative administration of antithrombotic drugs is the risk of bleeding. Low dose unfractionated heparin and low dose warfarin are commonly used preoperatively without an excess of major bleeding complications. However, it is unclear whether this also results in a lower risk of thromboembolism.

LMWH appears to be more effective and associated with a lower risk of bleeding when commenced preoperatively rather than postoperatively. However, concerns regarding the risk of epidural or spinal haematoma has led to reluctance to use LMWH preoperatively in patients undergoing regional anaesthesia (spinal or epidural) for major lower limb orthopedic procedures.

Although the optimal duration of thromboprophylaxis following major lower limb orthopedic surgery remains uncertain, it has been clearly demonstrated that the risk of symptomatic venous thromboembolism in patients undergoing hip or knee arthroplasty and who receive at least 7 to 10 days of LMWH or dose-adjusted warfarin is relatively low. As it remains to be demonstrated that extended thromboprophylaxis beyond hospital discharge further reduces the risk of developing symptomatic venous thromboembolism, it would seem reasonable to recommend that thromboprophylaxis should be continued for 7 to 10 days in these patients. However, prolonged therapy with LMWH preparations beyond 10 days can be given safely and is effective in reducing the risk of asymptomatic venous thromboembolism after hospital discharge and may be considered in patients who have ongoing venous thromboembolism risk factors (e.g. prolonged immobility).

**7TH ACCP RECOMMENDATIONS**

**Elective Hip Arthroplasty**
- For patients undergoing elective total hip replacement (THR), the guideline developers recommend the routine use of one of the following three anticoagulants: (1) LMWH (at a usual high-risk dose, started 12 hours before surgery or 12 to 24 hours after surgery, or 4 to 6 hours after surgery at half the usual high-risk dose and then increasing to the usual high-risk dose the following day); (2) fondaparinux (2.5 mg started 6 to 8 hours after surgery); or (3) adjusted-dose vitamin K antagonist (VKA) started preoperatively or the evening after surgery (international normalized ratio [INR] target, 2.5; INR range, 2.0 to 3.0) (all Grade 1A). Underlying values and preferences: The guideline developers have not recommended the use of fondaparinux over LMWH and VKA, or the use of LMWH over VKA, because they place a relatively low value on the prevention of venographic thrombosis and a relatively high value on minimizing bleeding complications.
- The guideline developers recommend against the use of aspirin, dextran, LDUH, GCS, IPC, or venous foot pump (VFP) as the only method of thromboprophylaxis in these patients (Grade 1A).

**Elective Knee Arthroplasty**
- For patients undergoing elective total knee replacement arthroplasty (TKA), the guideline developers recommend routine thromboprophylaxis using LMWH (at the usual high-risk dose), fondaparinux, or adjusted-dose VKA (target INR, 2.5; INR range, 2.0 to 3.0) (all Grade 1A). Underlying values and preferences: The guideline developers have not recommended fondaparinux over LMWH and VKA, or LMWH over VKA, because they place a relatively low value on the prevention of venographic thrombosis and a relatively high value on minimizing bleeding complications.
- The optimal use of IPC is an alternative option to anticoagulant prophylaxis (Grade 1B).
- The guideline developers recommend against the use of any of the following as sole methods of thromboprophylaxis: aspirin (Grade 1A); LDUH (Grade 1A); or VFP (Grade 1B).

**Knee Arthroscopy**
- The guideline developers suggest clinicians do not use routine thromboprophylaxis in these patients, other than early mobilization (Grade 2B).
- For patients undergoing arthroscopic knee surgery who are at a higher than usual risk, based on preexisting VTE risk factors or following a prolonged complicated procedure, the guideline developers suggest thromboprophylaxis with LMWH (Grade 2B).

**Hip Fracture Surgery**
- For patients undergoing hip fracture surgery (HFS), the guideline developers recommend the routine use of fondaparinux (Grade 1A), LMWH at the usual high-risk dose (Grade 1C+), adjusted-dose VKA (target INR, 2.5; INR range, 2.0 to 3.0) (Grade 2B).
The guideline developers recommend against the use of aspirin alone (Grade 1A).

If surgery will likely be delayed, the guideline developers recommend that prophylaxis with either LDUH or LMWH be initiated during the time between hospital admission and surgery (Grade 1C+).

The guideline developers recommend mechanical prophylaxis if anticoagulant prophylaxis is contraindicated because of a high risk of bleeding (Grade 1C+).

### Other Prophylaxis Issues in Major Orthopedic Surgery

For major orthopedic surgical procedures, the guideline developers recommend that a decision about the timing of the initiation of pharmacologic prophylaxis be based on the efficacy-to-bleeding tradeoffs for that particular agent (Grade 1A).

For LMWH, there are only small differences between starting preoperatively or postoperatively, and both options are acceptable (Grade 1A).

The guideline developers recommend against the routine use of Doppler ultrasonography (DUS) screening at the time of hospital discharge in asymptomatic patients following major orthopedic surgery (Grade 1A).

The guideline developers recommend that patients undergoing THR, TKA, or HFS receive thromboprophylaxis with LMWH (using a high-risk dose), fondaparinux (2.5 mg daily), or a VKA (target INR, 2.5; INR range, 2.0 to 3.0) for at least 10 days (Grade 1A).

The guideline developers recommend that patients undergoing THR or HFS be given extended prophylaxis for up to 28 to 35 days after surgery (Grade 1A). The recommended options for THR include LMWH (Grade 1A), a VKA (Grade 1A), or fondaparinux (Grade 1C+). The recommended options following HFS are fondaparinux (Grade 1A), LMWH (Grade 1C+), or a VKA (Grade 1C+).

### Isolated Lower Extremity Injuries

The guideline developers suggest that clinicians not use thromboprophylaxis routinely in patients with isolated lower extremity injuries (Grade 2A).

### Trauma

The guideline developers recommend that all trauma patients with at least one risk factor for VTE receive thromboprophylaxis, if possible (Grade 1A).

In the absence of a major contraindication, the guideline developers recommend that clinicians use LMWH prophylaxis starting as soon as it is considered safe to do so (Grade 1A).

The guideline developers recommend that mechanical prophylaxis with IPC, or possibly with GCS alone, be used if LMWH prophylaxis is delayed or if it is currently contraindicated due to active bleeding or a high risk for hemorrhage (Grade 1B).

The guideline developers recommend DUS screening in patients who are at high risk for VTE (e.g., the presence of a spinal cord injury [SCI], lower extremity or pelvic fracture, major head injury, or an indwelling femoral venous line), and who have received suboptimal prophylaxis or no prophylaxis (Grade 1C).

The guideline developers recommend against the use of inferior vena cava filters (IVCFs) as primary prophylaxis in trauma patients (Grade 1C).

The guideline developers recommend the continuation of thromboprophylaxis until hospital discharge, including the period of inpatient rehabilitation (Grade 1C+). The guideline developers suggest continuing prophylaxis after hospital discharge with LMWH or a VKA (target INR, 2.5; INR range, 2.0 to 3.0) in patients with major impaired mobility (Grade 2C).

In North America, the initial LMWH dose is generally administered 12 to 24 h after surgery. However, in Europe, the first LMWH dose is usually administered the evening (10 to 12 h) before surgery. One review suggested that any difference in efficacy between preoperative and postoperative commencement of LMWH prophylaxis was likely to be small, while a recent meta-analysis concluded that preoperative initiated LMWH was significantly more effective than postoperative initiated LMWH. Hull et al, who have shown that LMWH prophylaxis administered close to surgery is more effective, corroborate this view.

### Conclusions

- Patients at the highest risk of development of VTE are those undergoing THR, TKA and hip and pelvic fracture surgery.
- Prolonged out-of-hospital LMWH prophylaxis is recommended for high-risk patients by the ACCP consensus guidelines.
- VTE prophylaxis with both pharmacotherapeutic and mechanical devices can be adopted.

### References

abdomen, pelvis and lower extremities and malignancy play a key role in the causation of DVT. Besides, it must however be remembered that factors related to the procedure itself, including the site, technique, and duration of the procedure, the type of anesthetic, the presence of infection and the degree of postoperative immobilization, could be solely responsible for DVT in the patient. The levels of thromboembolism risk in surgical patients without prophylaxis is shown in Table 11.2

Pharmacologic Options of VTE in Major Surgery Patients

Most commonly used pharmacologic agents for thromboprophylaxis and treatment of thromboembolic events include unfractioned heparin (UFH) – standard (SH), low-dose (LDUFH), or adjusted-dose, low molecular weight heparin (LMWH), oral anticoagulants such as warfarin and antiplatelet agents for arterial events.

Low Dose Unfractioned Heparin (LDUFH)

LDUFH was the first antithrombotic agent investigated in large randomized trials. Treatment with SC heparin (5,000 IU) was usually started 2 h before operation and continued every 8 or 12 h after surgery, for 7 days or until patients were ambulatory or discharged from the hospital. It has been found that the use of LDUFH consistently reduces serious end points like PE and DVT. The overall reduction of incidence of DVT from 25% to 8% and 50% reduction in fatal PE is observed with LDUFH prophylaxis. The beneficial effect of LDUFH was also observed in trials in which patients with malignant disease were studied.34

Low Molecular Weight Heparin (LMWH)

Extensive clinical studies have been conducted to compare the antithrombotic efficacy of LMWH, dalteparin sodium with that of UFH in surgical thromboprophylaxis, treatment of established DVT and the anticoagulation of patients undergoing hemodialysis and hemofiltration. In majority of trials, patients receiving thromboprophylactic heparin perioperatively have shown similar efficacy of dalteparin sodium and UFH in the prevention of DVT and PE, although 2 groups of investigators reported superior antithrombotic potency for dalteparin sodium.

Dalteparin sodium is notable for its improved pharmacokinetic characteristics (i.e., chiefly increased bioavailability). Extensive clinical studies have been conducted to compare the antithrombotic efficacy of LMWH, dalteparin sodium with that of UFH in surgical thromboprophylaxis, treatment of established DVT and the anticoagulation of patients undergoing hemodialysis and hemofiltration. In majority of trials, patients receiving thromboprophylactic heparin perioperatively have shown similar efficacy of dalteparin sodium and UFH in the prevention of DVT and PE, although 2 groups of investigators reported superior

| Table 11 Levels of Thromboembolism Risk in Surgical Patients Without Prophylaxis |
|-----------------|-----------------|-----------------|-----------------|
| Level of Risk Examples | Low risk | Moderate risk | High risk |
| Low risk | Minor surgery in patients <40 yrs, no additional risk factors | 2 | 10-20 | 20-40 |
| Moderate risk | Minor surgery in patients with additional risk factors; non major surgery in patients aged 40-60 yrs with no additional risk factors; major surgery in patients >60 yrs with no additional risk factors | 10-20 | 20-40 | 20-40 |
| High risk | Minor surgery in patients >60 yrs or with additional risk factors; major surgery in patients >40 yrs with additional risk factors | 40-80 | 20-40 | 40-80 |
| Highest risk | Major surgery in patients >40 yrs plus prior VTE, cancer, or lower limb amputation, hip fracture surgery; major trauma; spinal cord injury | 40-80 | 20-40 | 40-80 |

VTE in Major Surgery

Deep vein thrombosis (DVT) is one of the common causes of morbidity and mortality in surgical patients. The overall incidence of thromboembolic end points in general surgical patients was calculated by pooling data from the control groups of published English-language trials of thromboprophylaxis. Almost all patients were older than 40 years. The overall incidence of DVT, as assessed by the fibrinogen uptake test (FUT), in surgical patients with thromboprophylaxis: the need for careful consideration of the evidence from randomised trials. BMJ 1994;309:1215-7.

Patients

Most commonly used pharmacologic agents for thromboprophylaxis and treatment of thromboembolic events include unfractioned heparin (UFH) – standard (SH), low-dose (LDUFH), or adjusted-dose, low molecular weight heparin (LMWH), oral anticoagulants such as warfarin and antiplatelet agents for arterial events.

Low Dose Unfractioned Heparin (LDUFH)

LDUFH was the first antithrombotic agent investigated in large randomized trials. Treatment with SC heparin (5,000 IU) was usually started 2 h before operation and continued every 8 or 12 h after surgery, for 7 days or until patients were ambulatory or discharged from the hospital. It has been found that the use of LDUFH consistently reduces serious end points like PE and DVT. The overall reduction of incidence of DVT from 25% to 8% and 50% reduction in fatal PE is observed with LDUFH prophylaxis. The beneficial effect of LDUFH was also observed in trials in which patients with malignant disease were studied.34

Low Molecular Weight Heparin (LMWH)

Extensive clinical studies have been conducted to compare the antithrombotic efficacy of LMWH, dalteparin sodium with that of UFH in surgical thromboprophylaxis, treatment of established DVT and the anticoagulation of patients undergoing hemodialysis and hemofiltration. In majority of trials, patients receiving thromboprophylactic heparin perioperatively have shown similar efficacy of dalteparin sodium and UFH in the prevention of DVT and PE, although 2 groups of investigators reported superior antithrombotic potency for dalteparin sodium.

Dalteparin sodium is notable for its improved pharmacokinetic characteristics (i.e., chiefly increased bioavailability). Extensive clinical studies have been conducted to compare the antithrombotic efficacy of LMWH, dalteparin sodium with that of UFH in surgical thromboprophylaxis, treatment of established DVT and the anticoagulation of patients undergoing hemodialysis and hemofiltration. In majority of trials, patients receiving thromboprophylactic heparin perioperatively have shown similar efficacy of dalteparin sodium and UFH in the prevention of DVT and PE, although 2 groups of investigators reported superior antithrombotic potency for dalteparin sodium.
antithrombotic potency for dalteparin sodium. These properties enable the drug to be given subcutaneously as a single daily dose, compared with the 8 to 12 hourly regimens necessary with UFH. Dalteparin sodium also appears to exert a greater inhibitory effect than UFH on plasma activity of coagulation factor Xa relative to its effects on clotting times [usually expressed as activated partial thromboplastin time (APTT)] and activity of factor IIa. One distinct advantage of LMWH is that it can be administered once daily. LMWH is also less likely to cause heparin induced thrombocytopenia and thrombosis than standard heparin preparations.

LMWH is effective in the prevention of postoperative VTE and it has been found to be safer than standard heparin. A multicentre randomised trial was done with 3809 patients undergoing major abdominal surgery (1894 LMWH, 1915 UFH) heparin was given preoperatively and continued for at least 5 postoperative days.

Patients were assessed in the postoperative period and were followed up for at least 4 weeks, the emphasis being on safety. Follow-up was done on 91% of 3699 evaluable patients.

Major bleeding events occurred in 69 (3.6%) patients in the LMWH group and 91 (4.8%) patients in the UFH group (relative risk 0.77, 95% confidence interval 0.56-1.04; p = 0.10) Fig. 1). 93 indices of major bleeding were observed in the 69 LMWH patients and 141 in the UFH patients. (p = 0.058). Severe bleeding was less frequent in the LMWH group (1.0% vs. 1.9%; p = 0.02), as was wound hematoma (1.4% vs. 2.7%; p = 0.007). The two drugs were of similar efficacy. The primary end point, the frequency of major bleeding, showed a 23% reduction in the LMWH group. The secondary safety end points revealed that LMWH was significantly better than UFH (Fig. 8).5

**Warfarin**

Warfarin is given at a dose of 10 mg beginning the day of the surgery. Daily INR is adjusted to 2-3 and continue the same, from the second post operative day upto 4-6 weeks. The onset of action of warfarin is delayed, the treatment is cumbersome because it requires frequent laboratory monitoring, and it is subject to bleeding complications if not closely monitored. Because of these shortcomings and the availability of other effective options, there is little rationale for using warfarin in general surgery patients.

**Aspirin**

Aspirin is considered as an ideal antithrombotic agent to prevent VTE as it is inexpensive, easy to administer and has fewer side effects. However, it has been found to be ineffective in preventing VTE in general surgery patients, and is not recommended by ACCP as an appropriate strategy.

**Extended Prophylaxis in Major Surgery Patients**

Patients undergoing major abdominal surgery, particularly for malignancy are at increased risk of venous thromboembolism. Hemostatic markers of coagulation are raised for several weeks after surgery. It has been seen that LMWH given at a higher dose is more effective in preventing post-surgical VTE in patients with cancer with no compromise on bleeding.

Four week’s of thromboprophylaxis with the LMWH, dalteparin is superior to standard (1 week) thrombo-prophylaxis in preventing proximal DVT. A meta-analysis study comparing 4 week’s with 1 week of Thromboprophylaxis showed that prolonged thrombo-prophylaxis with LMWH following major abdominal surgery for malignancy significantly reduces the risk of late occurring DVT.

A study was done to evaluate the safety criteria in regard to the bleeding complications on using the dalteparin sodium in surgical patients. The study comprised of 165 and 178 patients for prolonged and short-term thromboprophylaxis respectively. The incidence of VTE, 28 days after major abdominal surgery was 7.3% and 16.2% respectively for prolonged TP and short-term TP. The RRR was 55% and 95% respectively and the confidence interval was 15% and 76% respectively. The results are shown in the Fig. 9. This

![Fig. 8](image-url): Incidence of major bleeding in patients on LMWH.

![Fig. 9](image-url): Incidence of all VTE, 28 days after major abdominal surgery.
study concluded that 4 weeks of dalteparin is effective and safe in preventing late VTE.6

**VTE IN CANCER PATIENTS**

Venous thromboembolism (VTE) is a common complication in cancer patients and an important cause of morbidity and mortality. Development of VTE is associated with a poor prognosis in cancer patients. Patients with concurrent VTE and malignancy have a greater than threefold higher risk of recurrent thromboembolic disease and death (from any cause) than patients with VTE without malignancy.7 One in every seven hospitalized cancer patients who die do so from a pulmonary embolism (PE). Of the patients who die from a PE, 60% have localized cancer or limited metastatic disease, which would otherwise have allowed for reasonably long survival in the absence of a fatal PE.

The association between VTE and cancer appears to be two way: cancer patients are at a greater risk for thrombotic episodes,9 while idiopathic VTE may be the first sign of occult malignancy.10 Abnormalities as manifested by changes in hemostatic parameters are frequently encountered in cancer patients. These include elevations in markers of activity, including factor VIIa, thrombin-antithrombin complex, and the initiator of blood coagulation tissue factor. These abnormalities are not predictive of thrombosis risk.9

Cancer patients undergoing surgical procedures have at least twice the risk of postoperative DVT and more than 3 times the risk of fatal PE than non cancer patients undergoing similar procedures. Thromboembolic disease affects approximately 15% of all cancer patients. In a retrospective analysis of a total of 1068 patients from three prospective studies referred for evaluation of clinically suspected DVT, patients with cancer constituted 29.9% (59 of 197) of all cases of objectively diagnosed DVT. The diagnosis of cancer within 1 year of venous thromboembolism is associated with poor prognosis.

Patients with cancer are more likely to develop VTE than patients without malignancy. The risk varies with different tumor types and is thought to be highest in tumors of the ovary, pancreas, and central nervous system.11 Many factors are thought to contribute to the risk of VTE, including the primary tumor site, age, immobility, and type of therapeutic intervention.12,13 For example, operations for cancer are associated with a higher risk of VTE and fatal PE than noncancer surgery.14 Chemotherapy, particularly when combined with hormone therapy, also increases the risk of VTE.15 A high risk of thrombosis has been reported in patients with indwelling central venous catheters.15,16

On the basis of long term follow up data on patients with thrombosis, those with cancer have a 4 to 8 fold higher risk of dying after an acute thrombotic event than patients without cancer. Sorensen and colleagues found that, the one year survival rate for patients with cancer and thrombosis was 12% compared with 36% in control patients (p<0.001).

**Risk Factors for VTE in Cancer**

Cancer risk is related to cancer type and stage, with greater risk in advanced disease. Certain cancers can be rated as high risk for development of VTE, including cancers of the brain and pancreas and colorectal, ovarian, prostate, cervical, and esophageal/ gastric cancers. Medical and surgical experts believe that cancers that were associated with a greater than 20% risk of VTE include brain and pancreatic cancers.

Certain procoagulant substances, which have been isolated from human tumor also considered to increase risk of VTE. Other factors like age, immobilization, reinfection, surgery and drugs such as asparaginase and tamoxifen also play a part.

### VTE in Cancer and Death

Paul Thodiyil and Ajay K. Kakkar conducted a retrospective study of approximately 10 million patient episodes from the Medicare system, described death within 183 days of initial hospital admission and described this outcome for four categories of patients: those without malignant disease, those with VTE but no cancer, those with cancer but no VTE, and those with concurrent VTE and malignant disease. In patients with both VTE and cancer, the probability of death was much greater than for patients in the other three groups and more than two-fold greater than that observed among patients with cancer but no VTE. These data suggest that the development of VTE can impact adversely on the survival of patients with cancer and that intervention to prevent or effectively treat VTE may improve their outcome. (Fig. 10).

The role of hereditary thrombophilia in patients with cancer and thrombosis is still unclear, and screening for this condition in cancer patients is not indicated. The most common malignancies associated with thrombosis are those of the breast, colon, and lung reflecting the prevalence of these malignancies.
in the general populations. When adjusted for disease prevalence, the cancers most strongly associated with thrombotic complications are those of the pancreas, ovary, and brain, idiopathic thrombosis can be the first manifestation of an occult malignancy.17

Recurrent VTE in Cancer

In the Tasman and Columbus study, a total of 1,303 patients were available for analysis, of which 264 were known to have malignant disease. During treatment with vitamin K antagonists, a total of 35 recurrent episodes of venous thromboembolism (31 DVT and 4 PE) were observed. Of these, 14 were among patients with malignancy, and 21 were among patients without malignancy. It was seen that the overall incidence of recurrent VTE was increased among patients with malignancy (27.1 per 100 patient-years; 95% CI, 14.8 to 45.4) compared with patients without malignancy (9.0 per 100 patient-years; 95% CI, 5.6 to 13.8). This difference in incidence is statistically significant (rate ratio 3.0; 95% CI, 1.5 to 5.9; \( P = .003 \)).18

**Pharmacological Options of VTE in Cancer Patients**

The treatment options of acute VTE in cancer patients are:

- Oral anticoagulants
- LMWH

**Oral Anticoagulants**

The use of oral anticoagulant (OAC) therapy is associated with a significant risk of recurrent VTE and bleeding in patients with cancer. Maintenance of the international normalised ratio (INR) and longterm prevention of recurrent VTE with OAC can be problematic in the patient with cancer due to unpredictable changes in dose response as a result of poor nutrition, infection, concomitant medications or impaired hepatic function. In addition, temporary cessation of OAC therapy may be needed to accommodate chemotherapy induced thrombocytopenia and invasive procedures.

**LMWH**

LMWH (dalteparin) is effective in the treatment and prevention of thromboembolic disease in patients with cancer. In addition, other anticancer effects of LMWHs, such as inhibition of coagulation proteases, which affect tumor biology contribute to an improved outcome. It was also noted that LMWH has an advantage in providing long-term survival for patients with pelvic (ovarian or uterine) cancer. A study was done to compare the effects of prolonged and short-term thromboprophylaxis in regard to the bleeding complications on using the dalteparin sodium in cancer patients (Table 12).19

<table>
<thead>
<tr>
<th>Type of Surgery</th>
<th>Prolonged TP (%)</th>
<th>Short-term TP (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Curative</td>
<td>61(67%)</td>
<td>77(71%)</td>
</tr>
<tr>
<td>Palliative</td>
<td>30(33%)</td>
<td>30(29%)</td>
</tr>
</tbody>
</table>

**The CLOT Trial**

CLOT trial is a randomized comparison of LMWH (dalteparin) versus Oral Anticoagulant Therapy for Long Term Anticoagulation in Cancer Patients with Venous Thromboembolism. It was done to find out whether long term LMWH therapy is more effective and safer than oral anticoagulant therapy in treating cancer patients with venous thromboembolism. 1303 patients who met the inclusion criteria, 439 also met one or more of the exclusion criteria and were not considered. Of the 676 consenting patients, 338 were allocated to receive dalteparin and 338 were assigned to oral anticoagulant therapy, each for 6 months. Patients in the two groups had similar base line characteristics.20

The hazard ratio for recurrent thromboembolism in the dalteparin group as compared with the oral anticoagulant group was 0.48 (95% confidence interval, 0.30-0.77; \( P=0.002 \)) over the six month study period. The Kaplan-Meier estimate of the probability of recurrent thrombosis at six months was 9% in the dalteparin group, as compared with 17% in the oral anticoagulant group. (Fig. 11).

It was seen that 19 of 338 patients in the dalteparin group (6%) and 12 of 335 patients who received oral anticoagulant therapy (4%) had major bleeding (\( P=0.27 \)).

![Fig. 11: Recurrent VTE.](image-url)
The respective rates of any bleeding were 14% and 19% (P=0.09). During the six-month study period, 130 patients died in the dalteparin group and 136 patients in the oral-anticoagulant group. The respective mortality rates at 6 months were 39% and 41% (P=0.53). 90% of the deaths in each group were due to progressive cancer. (Fig. 12). It was later concluded that in cancer patients with acute VTE:

- Long-term dalteparin therapy substantially reduced the risk of symptomatic, recurrent VTE compared with OAC therapy
- Long-term dalteparin therapy was not associated with an increase in bleeding
- No difference in mortality was detected between dalteparin and OAC therapy

The FAMOUS Trial

Fragmin Advanced Malignancy Outcome Study (FAMOUS) was the first double-blind, randomised, placebo controlled trial in patients with advanced cancer to determine any potential survival benefit after administration of chronic LMWH. This trial has investigated the safety and efficacy of 5000 IU of dalteparin administered once-daily, against a placebo control, in increasing survival in patients with advanced malignancy.

The FAMOUS trial randomised 385 patients to receive either dalteparin or placebo for 1 year and assessed 1 year mortality. A trend towards improved survival was seen in the dalteparin group (46% vs. 41%). In a subgroup of 102 patients with a better prognosis, who survived beyond 17 months, there was a significant increase in median survival from 24 to 43 months (P=0.03). These data are supported by a subgroup analysis of survival of patients in the CLOT study (Fig. 13).

CONCLUSIONS

- LMWH (dalteparin) is effective in the prevention of postoperative VTE and it has been found to be safer than standard heparin.

A meta-analysis of studies comparing 4 week’s with 1 week of thromboprophylaxis showed that prolonged thromboprophylaxis with LMWH (dalteparin) following major abdominal surgery for malignancy significantly reduces the risk of late occurring DVT.

- VTE is one of the most common complications seen in cancer patients and may be due to the hypercoagulable state of malignancy and/or to its treatment including surgery, chemotherapy, radiotherapy, and central venous lines.

- LMWH (dalteparin) provided an advantage in long-term survival for patients with pelvic (ovarian or uterine) cancer.

- Long-term dalteparin therapy substantially reduced the risk of symptomatic, recurrent VTE in cancer patients when compared with OAC therapy.

REFERENCES

The rationale for thromboprophylaxis is based on the high prevalence of venous thromboembolism (VTE) among hospitalized patients, the clinically silent nature of the disease in the majority of patients, morbidity, cost, and potential mortality associated with thrombi.

7th ACCP Guidelines

According to the guidelines2,3 issued by the seventh American College of Chest Physicians (ACCP) Conference on antithrombotic and thrombolytic therapy,

- In acutely ill medical patients who have been admitted to the hospital with congestive heart failure or severe respiratory disease, or who are confined to bed and have one or more additional risk factors, including active cancer, previous VTE, sepsis, acute neurologic disease, or inflammatory bowel disease, the guideline developers recommend prophylaxis with LDUH (Grade 1A) or LMWH (Grade 1A).

DVT in Acute Myocardial Infarction

Prior to the introduction of routine antithrombotic therapy (aspirin, thrombolysis, anticoaguants) patients with acute myocardial infarction had a risk of asymptomatic DVT of about 24%, and a risk of clinical PE of 2.6-9.4%. The risk increases with age and in the presence of heart failure.4-6

The Scottish Intercollegiate Guidelines Network (SIGN) guidelines7 endorse the routine use of aspirin (and thrombolytic therapy) in selected patients in clinically suspected evolving acute myocardial infarction, because both interventions reduce mortality.

According to these guidelines

- Heparin should not be used routinely in addition to aspirin in acute MI, but reserved for patients at increased thromboembolic risk (and for certain patients undergoing thrombolysis).

- Patients with acute, established MI at increased risk of systemic or pulmonary thromboembolism due to:
  - Large anterior Q-wave infarction
  - Severe left ventricular dysfunction
  - Congestive heart failure
  - History of systemic or PE or thrombophilia
  - Echocardiographic evidence of mural thrombus
  - Persistent atrial fibrillation
  - Prolonged immobilisation
  - Marked obesity

should be considered for anticoagulation with full-dose heparin (target aPTT ratio 2.0, range 1.5-2.5) followed (if indicated by continuing risk) with warfarin (target INR 2.5, range 2.0-3.0) for up to three months, depending upon the physician’s estimate of the risk: benefit ratio in the individual patient.

In other patients with acute MI, and in patients as
defined above in whom the bleeding risks of full-dose anticoagulation are judged to outweigh the benefits, prophylaxis of VTE with low-dose subcutaneous heparin (7,500 IU 12-hourly) for seven days or until ambulant, should be considered.

**LMWH In Acute Myocardial Infarction**

Low molecular weight heparin, given subcutaneously twice daily without monitoring, is an attractive potential alternative to conventional UFH in the treatment of AMI. Initial animal experiments comparing LMWHs with UFH in combination with fibrinolytic therapy in animal thrombosis models showed higher patency rates and reduced infarct size with LMWHs with equivalent or lower bleeding rates. Clinical studies of LMWHs in AMI have largely focused on safety when combined with fibrinolytic therapy, dosing, and infarct-related artery patency.

The FATIMA (Fraxiparin Anticoagulant Therapy in Myocardial Infarction Study Amsterdam) trial enrolled 30 patients with AMI. In this study, a weight-adjusted initial bolus and subsequent twice-daily subcutaneous injections of nadroparin were administered with t-PA. At angiography, a patent infarct-related artery was present in 24 of the 30 patients (80%). No major bleeding complications occurred, although minor bleeding complications were observed in two patients. Anti-Xa activity was within the prespecified range in 88% of cases.

The BIOMACS-II (Biochemical Markers in Acute Coronary Syndromes) trial was the first randomized, placebo controlled pilot trial evaluating the effect of an LMWH, dalteparin, as an adjuvant to thrombolysis in patients with AMI. The primary end points were the proportion of patients with successful reperfusion, recurrent ischemia, and patency at 24 hours. In 101 patients, dalteparin 100 IU/kg or placebo was given just before streptokinase. A second injection of dalteparin, 120 IU/kg, or placebo was administered 12 hours following the initial dose. Dalteparin added to streptokinase tended to provide a higher rate of TIMI grade 3 flow in the infarct-related artery compared with placebo, 68% versus 51% (P = 0.10). There were also fewer recurrent ischemic episodes 6 to 24 hours after the start of treatment, as evaluated by continuous ECG monitoring in the dalteparin group, 16% versus 38% (P = 0.04).

In FRAMI (Fragmin in Acute Myocardial Infarction), dalteparin significantly reduced left ventricular thrombus formation in acute anterior myocardial infarction but was associated with increased hemorrhagic risk. Patients were randomized to either subcutaneous dalteparin (150 IU/kg body weight every 12 hours during the hospital period) or placebo. Thrombolytic therapy and aspirin were administered in 91.5% and 97.6% of patients, respectively. Echocardiographic evidence of left ventricular thrombus, the primary end point, was found in 59 (21.9%) of 270 patients in the placebo group and 35 (14.2%) of 247 in the dalteparin group (P = 0.03). The risk reduction of thrombus formation associated with dalteparin treatment was 0.63 (95% CI 0.43-0.92, P = 0.02). Dalteparin was associated with an increased risk of hemorrhage: major in 11 patients in the dalteparin group (2.9%) versus 1 patient in the placebo group (0.3%, P = 0.006); minor in 52 patients in the dalteparin group (14.8) versus 8 patients in the placebo group (1.8%, P = 0.001).

The HART-II (Heparin Aspirin Reperfusion Trial) pilot study enrolled 20 patients with AMI, who received aspirin and t-PA. Patients were randomly allocated to either enoxaparin (30 mg intravenous bolus followed by subcutaneous injections of 0.75 mg/kg three times a day for 24 hours and twice a day for the following 24 to 48 hours) or UFH (5000 IU intravenous bolus followed by 15 IU/kg/h) titrated to a prespecified aPTT range. The purpose of this study was to examine the anti-Xa and anti-IIa effect of enoxaparin in the presence of a thrombolytic agent. Enoxaparin had no effect on the aPTT except at 30 minutes following the first intravenous dose and the bolus dose of t-PA. Anti-Xa levels values were consistently within the presumed therapeutic range throughout the observation period. UFH had its greatest effect on anti-IIa activity, with wide variations in aPTT levels despite frequent dose adjustments.

The HART-II study compared the safety and efficacy of enoxaparin with UFH in 404 patients with acute ST-segment elevation myocardial infarction treated with t-PA. The primary end points were infarct-related artery patency 90 minutes following initiation of therapy and adverse bleeding events. Patients were randomized to either enoxaparin (30 mg intravenous bolus, then subcutaneous injections of 1.0 mg/kg every 12 hours for 72 hours) or UFH to achieve a target aPTT of at least two times control. Ninety-minute TIMI 2/3 flow grade was 80.1% for enoxaparin and 75.1% for UFH. The relative increase among patients who received enoxaparin was attributable mainly to an increase in the rate of TIMI 3 flow. Preliminary data analysis suggested no difference in clinical event rates or bleeding complications in the two treatment arms.

**DVT in Ischemic Stroke**

Stroke patients have a high risk of DVT in the paretic or paralyzed lower extremity with a pooled DVT incidence of 55%. Approximately 5% of early deaths following stroke are attributed to PE.

A multi-centre, double-blind, randomized study was conducted in which patients of ischemic stroke resulting in lower limb paralysis lasting for at least 24 hours and necessitating bed rest, were randomized within 48 hours of the onset of stroke, and treated with enoxaparin (40
mg OD SC) or UFH (5000 IU SC thrice daily) for a period of 10-12 days. Main outcome measures were deep-vein thrombosis, pulmonary embolism (PE), death from any cause, intracranial hemorrhage including hemorrhagic infarction, or any other major bleeding.

Outcome events occurred within 3 months of stroke in 37.7% patients treated with enoxaparin and 49.1% patients treated with UFH. Fewer patients treated with enoxaparin (13.2%) than with UFH (18.9%) had evidence of hemorrhagic transformation of ischemic stroke. The authors concluded that enoxaparin administered subcutaneously once daily was as safe and effective as subcutaneous UFH given thrice daily in the prevention of thromboembolic events in patients with lower limb paralysis caused by acute ischemic stroke.

The MEDENOX Study

The objective of this study was to identify the need for prophylaxis of VTE in medical patients with LMWH and also to determine the optimal dose in patients immobilized with severe chest (cardiopulmonary) disease. This trial was designed as a Phase III, multicentric, randomized, double blind, placebo controlled study, consisting of three parallel groups. Enoxaparin 20 or 40mg once daily vs placebo, were administered subcutaneously for 6 to 14 days. DVT was detected by routine bilateral ascending venography. The patients were followed up after 3 months. The incidence of total, proximal and distal DVT was significantly reduced (upto 63%) with enoxaparin 40 mg compared with placebo. This was achieved without an increase in adverse events, in particular hemorrhage or thrombocytopenia, as compared with placebo.

The PRINCE II Study

The PRINCE II trial, which was a multi-centre and randomized, controlled study done in 333 patients with heart failure (NYHA III / IV), to compare the efficacy of LMWH and UFH. Patients were diagnosed by phlebography, lung scan or angiography. It was found that LMWH (Enoxaparin) was effective in preventing DVT and/or PE. Also, significantly fewer patients treated with LMWH had adverse events (51.8% vs 59.7% p=0.02).

The PREVENT Trial

A new paradigm for thromboprophylaxis in medical patients is embraced in the Prospective Evaluation of Dalteparin Efficacy for Prevention of Venous Thromboembolism in Immobilised Patients Trial (PREVENT). This study was designed to investigate the efficacy and safety of the LMWH dalteparin in the prevention of thromboembolism in hospitalized medical patients and is important because it is the first study to utilize clinically relevant endpoints in this patient population. The primary endpoint in PREVENT is a composite of objectively confirmed symptomatic DVT, fatal or non-fatal PE, asymptomatic proximal DVT and sudden death.

This study is of sufficient size (over 3700 patients enrolled) to address the impact of dalteparin on these clinically relevant endpoints. PREVENT is also the first study to use compression ultrasonography (CUS) rather than venography as the primary diagnostic method for DVT. Use of CUS more closely approximates clinical practice, and clinicians in many countries have largely abandoned venography in favour of CUS. Diagnosis of symptomatic PE in PREVENT was verified by: ventilation–perfusion scintigraphy, pulmonary angiography, chest computed tomography, magnetic resonance imaging or autopsy. The figure below summarises key elements of the PREVENT trial design.

Incidence of VTE in the PREVENT Trial

Data from this large, randomised, prospective, double-blind study, with clinically relevant endpoints, in patients who received dalteparin 5000 IU once daily, showed a 45% relative risk reduction in DVT/PE and sudden death versus placebo at day 21 and 51% relative risk reduction in secondary end point of DVT (proximal and symptomatic distal) versus placebo at day 21 as shown in Fig. 15. These risk reductions were maintained for 90 days. This should provide ample evidence to encourage appropriate thrombo-prophylaxis use in medical patients. It was found that the incidence of bleeding and thrombocytopenia were relatively less with dalteparin.

CONCLUSIONS

- Low molecular weight heparin, given subcu-
taneously twice daily without monitoring, is an attractive potential alternative to conventional UFH in the treatment of AMI.

- The PREVENT Study showed that the incidence of bleeding and thrombocytopenia were relatively less with dalteparin.

Acknowledgement
This initiative would not have been possible without a continued medical educational grant by Pfizer.

REFERENCES