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Best Practices

Preventing Deep Vein Thrombosis and Pulmonary Embolism

A Practical Guide to Evaluation and Improvement

By

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Rationale

Why is it important to prevent DVT?

Section 1
Venous thromboembolism - the need for prophylaxis

One of the most common causes of death in the hospitalized patient is pulmonary embolism (PE). Routine autopsies estimate that from 10 to 25 percent of all deaths in hospital involve emboli in the lung, many of which are extensive enough to be considered as having caused the death of the patient. In addition, some patients suddenly found dead in bed at home are also thought to be victims of massive, unforeseen PE.

While many of these individuals may have had a terminal illness leading to embolism, a significant number of deaths occur in patients who had comparatively minor ailments and who might otherwise have lived normal and healthy lives.

Death and morbidity

It is estimated that one in 100 patients admitted to a hospital dies because of PE. It appears possible than more than one-half of these at-risk patients could be saved if effective prophylaxis was used. For example, patients undergoing major operations without receiving prophylaxis are put at risk of fatal PE and stand an even greater risk of morbidity from related conditions.

In more than 90 percent of cases of PE, the thrombosis originates in the deep veins of the legs. Deep vein thrombosis (DVT) is itself a distressing but often avoidable condition that leads to long-term complications such as the post-phlebitic syndrome and chronic leg ulcers in a large proportion of patients who have proximal vein thrombosis.

"Pulmonary embolism remains the most common preventable cause of death in hospital"

Morrell MT and Dunnill MS (1968) Br J Surg 55, 347-352

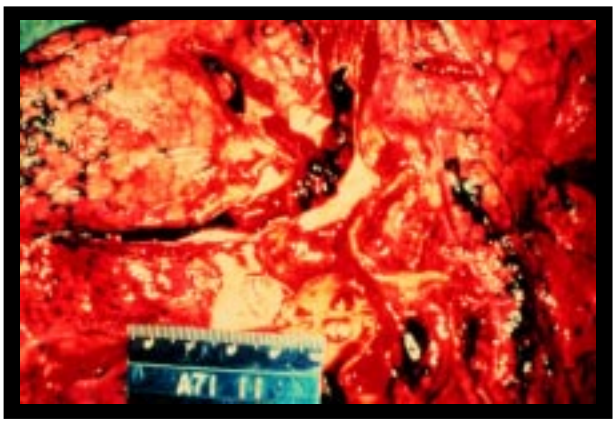

Figure 1.1 Routine autopsy finds pulmonary embolism to be a major contributory factor in 10 to 25 percent of deaths. This major embolism could have been the unforeseen result of otherwise life-saving surgery.

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Table 1.1 Patients at risk of venous thromboembolism

Trauma patients	• Accidental trauma • Surgical patients orthopaedic surgery (hips and knees) major surgery lasting longer than 30 minutes
Additional risk factors	• Age (risk rises steadily from age 40) • Obesity • Malignancy • History of DVT or PE • Immobilization (bed rest, paralysis of legs, plaster casts) • Pregnancy and puerperium • Oral contraceptive use • Extensive dissection at surgery
Clinical disorders predisposing to venous thrombosis	• Varicose veins • Cardiac problems (e.g. cardiac failure and myocardial infarction) • Stroke • Nephrotic syndrome • Thrombocytosis • Primary proliferative polycythaemia • Systemic lupus erythematosus • Infection

Table 1.2 Venous thromboembolism - a serious and common problem that can and should be prevented

A serious problem	• 80% of PE occur without signs • 2/3 of deaths occur within 30 minutes
A common problem	• One in 100 hospitalized patients dies of PE
Can be prevented	• Half of PE, 2/3 of DVT in review of 16,000 patients
Should be prevented	• NIH recommends more extensive use of prophylaxis

Figure 1.2 These pulmonary emboli removed at autopsy look like casts of the deep veins of the leg where they originated.

Figure 1.3 At least 90 percent of pulmonary emboli are thought to orginate in major leg veins. This patient underwent a thrombectomy. The thrombus has been laid over the approximate location in the leg veins where it developed.

Correcting the situation

Despite extensive data documenting the incidence, the risk factors and the measures for preventing venous thromboembolic diseases, the magnitude and seriousness of these problems are not always appreciated. Although physicians in some hospitals are both aware of which patients are at risk of venous thrombosis and adopt a policy of prophylaxis in many of them, physicians in other hospitals do not systematically tackle the problem because of lack of understanding and awareness.

Consequently, patients continue to die and to suffer needlessly. Though doctors may be alert to the signs of venous thromboembolism, they may miss the presence of this condition because more than 80 percent of all deep vein thrombi have no clinical signs; PE too, is often silent. Even objective methods of diagnostic screening may fail to detect the presence of life-threatening thrombi. Clearly, if thrombi can be prevented from occurring in the first place, many of these problems could be overcome.

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"Our review of more than 70 randomized trials in 16,000 patients demonstrated that the perioperative use of sc heparin can prevent about half of all pulmonary emboli and about two-thirds of all DVT"

Collins R et al. (1988) N Engl J Med 318, 1162-1173

Patients at risk

Patients at risk of venous thromboembolism can be identified, and there are methods of prophylaxis available to reduce the incidence of complications in many of these patients.

Prophylaxis is preferred to treatment, as venous thromboembolism can be hard to diagnose and, in the case of PE, there is often no warning that the patient is at risk. Death due to PE is often immediate or occurs within 1 to 2 hours of onset. In high-risk groups of patients, it is more cost effective to protect against DVT and PE than to treat these conditions when they occur.

"Pulmonary embolism originates in the deep veins of the legs in 90 percent or more of cases"

Hull RD, Raskob GE and Hirsh J (1986) Chest 89, 374S-383S

Among the patients at greatest risk of venous thromboembolism are those who have experienced trauma. This can be accidental trauma or the trauma of surgery. Other factors, such as immobility, contribute to increasing risks.

Surgery

In surgery, the risks of venous thromboembolism have been defined and quantified, and the ability to lessen the problem by use of prophylactic measures has been shown in a number of studies. While an individual surgeon may claim to never have known a case of postoperative PE, the statistics prove that this is a problem that is far greater than is generally realized. Often, cases of late fatal PE escape detection, as sudden death at home could be attributed to some other cause. After a patient is discharged from the hospital, a postoperative DVT may go unnoticed by the surgeon, as it is quite likely the patient will be diagnosed and treated by a primary care physician. Even patients who die in the hospital shortly after surgery may not be considered as victims of PE if there has not been a thorough autopsy to establish the cause of death conclusively.

Before any operation, a surgeon is required to weigh the benefits of surgery against the potential risks to the patient. By understanding which types of patients are at risk of venous thromboembolism and why, the surgeon will be able to make the best and most rational use of the currently available forms of prophylaxis, thereby ensuring that the surgery leads to a true improvement in quality of life for the patient.

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Table 1.3 Percentage risks of venous thrombosis

		Deep vein thrombosis	Pulmonary embolism
Trauma (fracture)	Hip	40-60	4-7(fatal)
	Tibia	40-50	
	Multiple injury	35	
Elective surgery	General abdominal	3-51	0.2-1.5(fatal)
	Calf	10-40	
	Proximal	2-10	
	General surgery for cancer	40-70	
	Splenectomy	6	
	Thoracic	20-45	
	Gynecological	7-45	
	Prostatectomy	7-51	
	Peripheral vascular	4-43	
	Neurosurgery	29-43	
	Orthopaedic	17-84	1-5(fatal)
	Calf	40-80	
	Proximal	10-20	
	Knee	17-57	
	Knee replacement	84	
	Calf	50-70	
	Proximal	20	
	Hip replacement	45-60	1-5(fatal)
	Calf	40-50	
	Proximal	20	
	Pregnancy		
	Postpartum	1-3	
	Medical Patients		
	Myocardial infarction	10-38	
	Heart failure	70	
	Stroke	33-60	
	Paraplegia	59-100	

Table 1.4 Major points of the 1986 NIH consensus conference

• DVT and PE constitute major health problems in the United States.
• Groups of high-risk patients have been identified.
• DVT and PE in these patients can be significantly reduced by prophylactic regimens, which should be used more extensively.
• Regimens recommended for prevention of DVT and PE include low-dose heparin, adjusted-dose heparin, dextran and warfarin. Low-dose warfarin, external pneumatic compression and gradient elastic stockings, alone or in combination with heparin or heparin/DHE are also effective in decreasing DVT, which the panel considers to be an indicator of their effectiveness on PE. Aspirin has not been shown to be beneficial.
• None of these preventive measures is ideal but most are relatively simple to use; complications are generally minor and the need for laboratory monitoring is minimal.
• Effective prophylactic regimens differ according to the type of patient at high risk. Prophylactic therapy should be tailored to the patient's disease and degree of risk.
• In some groups of patients, more than one effective prophylatic regimen is available.

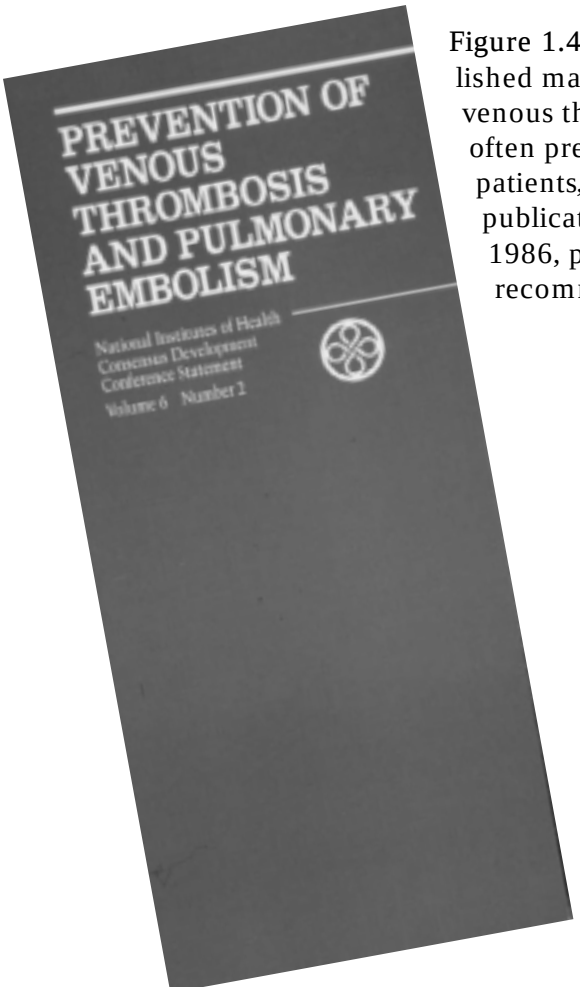

Figure 1.4 There has been a wealth of published material supporting the view that venous thromboembolism is a serious but often preventable complication for many patients, and one of the most authoritative publications was that of the NIH, which, in 1986, produced a consensus document recommending wider use of prophylaxis.

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Section 2
What are we trying to prevent?

The source of most important thromboemboli is deep venous thrombosis in the proximal veins of the legs. It is therefore important to understand the pathogenesis of these thrombi, their formation and eventual embolization.

Postoperative thrombosis is very common but most thrombi lyse spontaneously, particularly those formed in the calf veins. Signs and symptoms will only appear if venous outflow becomes obstructed because of a thrombosis or when a thrombus embolizes into the pulmonary circulation.

Although many thrombi are initially asymptomatic, they are often clinically significant because they can be complicated by **pulmonary embolism** and the post-phlebitic syndrome.

Pulmonary emboli

When PE strikes unexpectedly, it may be the result of the passage of an **asymptomatic thrombus** into the pulmonary circulation. When a large thrombus blocks major pulmonary vessels, cardiogenic shock will occur, followed quickly by circulatory failure and death. Morbidity can also result from smaller thromboemboli reaching the lungs. Small thrombi can lead to blockage of areas of lung vasculature and to **symptomatic pulmonary embolism**, often characterized by shortness of breath. This condition poses dangers to the patient, as a subsequent embolism, small or large, could be fatal.

Deep vein thrombosis

Thrombi in the veins of the legs may also be symptomatic or asymptomatic. Most thrombi originate in distal veins, and some extend to the proximal veins. Generally, proximal vein thrombosis is more serious than distal vein thrombosis, but both are important because of their potential to grow and to embolize. Asymptomatic PE has been observed by routine lung scanning in about 50 percent of patients with documented proximal vein thrombosis and, conversely, asymptomatic venous thrombosis is found at venography in 70 percent of patients presenting with PE, thus emphasizing the close links between these conditions.

The clinical signs and symptoms of DVT are nonspecific and, although most DVTs will be asymptomatic, many will be clinically significant.

The diagnosis of both PE and DVT will be outlined more fully in Section 3.

Table 1.5 The consequences of venous thrombosis

• Distal DVT • Proximal DVT	symptomatic and asymptomatic
• Symptomatic PE	
• Asymptomatic PE	
• Fatal PE	
• Post-phlebitic syndrome	

Other clinical conditions linked with thromboembolism

The post-phlebitic syndrome is thought to be the long-term result of DVT in some patients. Whether the DVT is symptomatic or asymptomatic, specialists now believe that this syndrome, which is characterized by varicose veins, edema, skin pigmentation, induration and ulceration, is often the result of venous valvular damage sustained during an episode of thrombosis.

Pathogenesis of venous thromboemboli

Venous thrombi are different from arterial thrombi, not only in terms of their site of formation but also in their appearance and make-up. Compared with the pale-colored, platelet-rich arterial thrombi, venous thrombi are red, less compact and contain many red blood cells entrapped in a fibrin network. These thrombi can arise in the large venous sinuses of the calf or in the region of valve cusps. Factors which are thought to influence thrombus formation are

- alterations in blood flow (stasis will encourage clot formation),
- changes in the vessel wall (trauma or injury to the vessel wall may trigger coagulation), and
- alterations in the blood (changes in constituents such that coagulation exceeds natural anticoagulant and fibrinolytic systems, or otherwise blood viscosity increases).

Once formed, the fate of a thrombus depends on the persistence of factors involved in its formation. Many will spontaneously lyse or will be reduced in size, but others may extend and embolize, posing a threat to the patient.

Venous stasis

Normally, venous return from the legs is enhanced by contraction of the calf muscles, which help to propel blood towards the heart. But stasis can occur in states of **immobility** when the blood is allowed to pool in the intramuscular sinuses of the calf, which become dilated during prolonged rest.

Autopsy studies have revealed that the prevalence of DVT is high in patients confined to bed for a week or more prior to death. Patients are exposed to these same risks when confined to bed either before or after surgery.

Table 1.6 Virchow's Triad

	Examples
Component change in vessel wall	Femoral vein damage in total hip replacement
Blood flow stasis More time for clotting Small thrombi not washed away Viscosity increased	 Sitting still Limb paralysis Heart failure Varicose veins
Coagulability Increase in tissue factor Presence of activating factors Decrease in coagulation inhibitors	 Surgery Cancer Inherited AT III deficiency

Elderly, bedridden patients, those with varicose veins and pregnant women have a tendency to suffer from venous dilatation in the legs, and this can lead to venous pooling or stasis and, so, to an increased risk of venous thromboembolism.

Venous obstruction is another cause of stasis. Patients who have pelvic tumors or proximal vein thrombosis are prone to stasis and, so, to thrombus formation, as are patients with heart failure.

Increases in blood viscosity in conditions like primary proliferative polycythaemia, erythrocytosis, dysproteinaemia and in some malignant disorders can also lead to stasis.

Vessel wall damage

Damage to vessels contributes to venous thrombosis in patients undergoing both traumatic and elective hip surgery when the femoral vein is likely to be put under strain. Knee surgery, varicose vein stripping, severe burns and lower limb trauma are also associated with vessel damage.

When the endothelium of a vessel is damaged, exposing the subendothelium to blood, platelet adhesion and aggregation are triggered, and tissue-factor is activated, which promotes blood coagulation.

Blood coagulability

Changes in the blood itself can affect coagulability and so promote thrombus formation. With increasing age, we all have increased activation of blood coagulation, but some patients have genetic deficiencies of anti-thrombin III, protein C or protein S that make them particularly susceptible to venous thromboembolism at a young age. Malignancy is also associated with changes in blood coagulability, and patients who have cancers are therefore at high risk of DVT and PE.

Exposure of Factor XII in the blood to collagen, when vessels become damaged, leads to activation of the intrinsic pathway of coagulation, and platelets may also play a role under conditions of tissue damage. Leukocytes migrating into areas of tissue damage and the exposure of blood to tissue thromboplastin are also thought to activate the extrinsic pathway of coagulation through Factor X activation and the intrinsic pathway through Factor IX activation.

The body has certain protective mechanisms to help guard against hypercoagulability. Three plasma proteins have been identified as important modulators of coagulation: antithrombin III, protein C and protein S. The fibrinolytic system, by producing tissue-plasminogen-activator, urokinase and plasminogen-activator-inhibitor, is also important in the physiological control and lysis of thrombi.

In short, any changes that give rise to an increase in active clotting factors, or that decrease the level of inhibitors or the activity of the fibrinolytic system, will disrupt the normal equilibrium. The result will be an increased tendency to form venous thrombi. Clinical risk factors which predispose to venous thromboembolism by activating blood coagulation include extensive surgery, trauma, burns, infusion of Factor II, VI, IX and X, disseminated malignant disease and myocardial infarction.

There may be some merit in performing extensive hematological tests in younger patients who have DVT of uncertain origin.

The implications of not preventing thrombosis

Untreated or inadequately treated venous thrombosis is associated with a high rate of complications. While anticoagulant therapy can be used to treat diagnosed cases of thrombosis, the fact remains that a high percentage of clinically significant thrombi are silent and escape diagnosis. Protecting patients suspected of being in at-risk situations against the occurrence of venous thromboembolism by use of prophylactic measures is preferable to waiting for cases of DVT and PE to occur. Agents and measures exist to provide adequate prophylaxis for a large number of patients.

About 20 percent of untreated, silent calf-vein thrombi and from 20 to 30 percent of untreated, symptomatic, calf-vein thrombi extend into the popliteal vein, and this is associated with a 40 to 50 percent risk of clinically detectable PE. Studies have also found that inadequately treated proximal DVTs have a 47 percent recurrence rate over the next 3 months.

Table 1.7 Thrombogenesis - factors important in stimulation and inhibition

Stimulation	Inhibition
Activation of coagulation	Circulating inhibitors (antithrombin III, protein C, protein S)
Vessel wall damage	Endothelial cell components (heparin sulphate, thrombomodulin)
Stasis	Fibrinolytic system (tPA, PAI-1 plasminogen)

These figures compare poorly with the percentage risk reduction values that are possible when prophylaxis is employed. In recent years, awareness of the long-term problems associated with an episode of DVT has increased. The prevalence of the post-phlebitic syndrome has been estimated to be as high as 2 percent in the general population and occurs in 50 to 70 percent of subjects who sustain proximal vein thrombosis. The syndrome is thought to be caused by venous hypertension resulting from venous valve destruction or persistent obstruction due to thrombosis. The high pressure renders the perforating veins of the calf incompetent, and flow of blood is then directed into the superficial system, leading to edema and impaired viability of subcutaneous tissues or, when severe, to ulceration.

In patients who have thrombi extending into the ileo-femoral veins, swelling persists. Other symptoms or signs of the post-phlebitic syndrome such as calf pain, pigmentation and induration around the lower third of the leg, and ulceration, may not manifest until as late as 5 to 10 years after the initial thrombotic event.

Patients at risk of thrombosis

Clearly, venous thromboembolism in its many guises represents a far greater clinical problem than is widely realized. However, many patients can be identified as being at risk, and prophylactic measures and treatments exist that could be employed to reduce the likelihood of thrombosis in these patients.

In Section 1, Table 1.1, an extensive list of patients at risk of DVT and PE is provided. One particular patient population at risk of thromboembolism, and for whom prophylaxis is very well suited, is surgical patients.

Surgery is a well-recognized risk situation, particularly for patients with additional risk or predisposing factors. In a review of more than 70 randomized trials, involving more than 16,000 patients, it has been shown that the perioperative use of low-dose heparin prophylaxis can prevent

- about half of all PE and
- about two-thirds of all DVT.

This strongly supports the notion that prophylaxis can reduce both morbidity and mortality in surgical patients.

Not all surgery carries the same risks for patients but, by careful categorization of patients into low, moderate, high and very high-risk groups, a surgeon can ensure that those patients in most need of prophylaxis are selected and protected.

Any patient at moderate, high or very high risk is a candidate for thromboembolic prophylaxis because of the high likelihood that he or she will suffer the consequences of a subsequent thrombosis.

Why are surgical patients at risk?

Most patients requiring surgery are unwell to a greater or lesser extent and may have been immobile or inactive because of this. After most types of surgery, patients will also experience a period of enforced bed rest and immobility. In orthopaedic surgery, traction and plaster casts further reduce postoperative movement, and all these factors lead to venous stasis and an increased likelihood of thrombosis. Direct vascular damage can be important. For example, in hip replacement therapy, there may be kinking or twisting of major veins, predisposing the patient to postoperative DVT. Pelvic surgery also carries a high risk because of the pressure on large veins during the dissection.

All operations involve a degree of tissue damage; activated coagulation factor levels in blood following surgery using general anesthesia will be high. The more extensive the damage, the more likely activation of coagulation.

The longer an operation, the greater the risks, and patients undergoing surgery lasting more than 30 to 45 minutes are considered at risk. Recent studies have also suggested that the type of anesthesia employed can influence the degree of thrombosis risk. Spinal and epidural anesthetics seem to be less thrombogenic than general anesthesia.

Patients can be classified according to risk

Low-risk patients

General medical patients and surgical patients younger than 40 years who undergo minor operations (general anesthesia lasting fewer than 30 minutes) appear to be at a low risk for DVT. Early ambulation should provide adequate protection in this group of low-risk patients.

Moderate-risk patients

Surgical patients older than 40 years who undergo major operations requiring anesthesia lasting longer than 30 minutes, but who have no additional DVT risk factors, appear to be at moderate risk of developing postoperative DVT. Adequate protection for these patients can be provided using either graduated compression stockings, low-dose unfractionated heparin b.i.d. or intermittent pneumatic compression.

High-risk patients

Following abdominal surgery, the incidence of DVT is from 16 to 30 percent. Gynecological surgery, particularly in older women, is also associated with significant risk (7 to 45 percent DVT), and the major trauma involved in a Caesarean section carries similar risks. Urological operations, especially transvesical prostatectomy (40 percent risk of DVT), are often performed on older patients and also constitute high risk.

Table 1.8 Reduction in DVT following prophylaxis - results from a review by Collins et al. (1988) of over 16,000 surgical patients given prophylactic heparin

Type of surgery	Risk reduction (±SD)
General	67% (±4)
Orthopaedic	*68% (±7)
Urological	75% (±15)
Any surgery	68% (±3)

*This may be an overestimate, as the end-point used in most studies was fibrinogen leg scan.

Cardiac and thoracic surgery are considered to be of moderate risk although, as described above, the patient may have additional risk factors such as malignancy which bring this surgery into a higher risk category. Another high-risk group are patients undergoing neurosurgery, where the risks of DVT range from 9 to 50 percent. However, in this group, anticoagulant therapy is seldom used for fear that intracerebral or spinal cord hemorrhage might occur.

Any patient undergoing surgery who has any of the medical conditions or other risk factors, listed in Table 1.1 of Section 1, is at risk of thromboembolism and should be assessed for possible prophylaxis.

Adequate protection for high-risk patients can be provided using either low-dose unfractionated heparin, low-molecular-weight heparin or intermittent pneumatic compression. Addition of graduated compression stockings to these measures may provide additional protection.

Very-high-risk surgery

One example of the highest risk surgery is orthopaedic surgery. Common high-risk orthopaedic procedures are hip or knee replacement and hip fracture repair. Hip replacement, both elective and following fracture, may provide patients with a new lease on life but also carries an unacceptably high risk of DVT and of fatal PE, which has led most orthopaedic surgeons to insist that their patients receive the most effective perioperative prophylaxis available.

Many patients undergoing hip or knee surgery are old, and this alone increases the risks of thrombosis. Other risk factors of this form of surgery are major dissection and trauma at operation, torsion of the femoral vein and immobility of the patient both before and after the operation.

Data summarized from the NIH consensus panel show the overall incidence of DVT after elective hip surgery to be from 45 to 70 percent, of clinical PE to be about 20 percent and of fatal PE to be from 1 to 4 percent. The incidence levels are even higher following emergency surgery for fracture.

Other types of very-high-risk surgery are operations to remove malignant tumors in the thoracic region. Patients undergoing thoracic surgery because of malignancy are already in poor health, the surgery may be long and involve extensive dissection and pressure on large veins, and there is an increase in activation of coagulation, all of which put the patient at risk of venous thromboembolism.

In general, adequate protection for very-high-risk patients can be provided using either low-molecular-weight heparin or warfarin. Addition of intermittent pneumatic compression and graduated compression stockings to these agents may provide additional protection. Specific recommendations are provided in Chapter-2.

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Section 3
Approaches to prevention

The results of surveys of surgeons have revealed that, in many hospitals, prophylaxis for deep vein thrombosis and pulmonary embolism is not yet standard practice, despite overwhelming evidence of the benefits to patients when properly used. The reasons for this lack of awareness are many and various. Some surgeons claim that venous thromboembolism is not a problem they encounter, others do not wish to provide prophylaxis to all patients to protect a few, some surgeons fear that methods of prophylaxis carry their own inherent risks for the patient and, at an institutional level, hospitals may lack an organized strategy for thromboprophylaxis or doubt its cost effectiveness. The whole issue of costs will be considered separately in Section 5.

Three approaches are available to address the problem of postoperative venous thromboembolism. These are

- treatment of established DVT/PE
- screening for subclinical disease
- primary prevention

Treating established thrombosis

Clearly, one option is for the surgeon to wait until venous thromboembolism occurs and then to treat aggressively. The treatment of choice is anticoagulant therapy, usually involving continuous IV or sc heparin and oral anticoagulants. Treatment with heparin is usually continued for 5 to 10 days. During this time, daily monitoring of the activated partial-thromboplastin-time is recommended. A course of oral anticoagulants is then prescribed, which the patient may continue to take for months. However, drugs such as warfarin need careful monitoring, and attention should be paid to possible drug interactions during therapy.

A number of randomized controlled trials have demonstrated the safety and efficacy of treating DVT with subcutaneous injections of low-molecular-weight heparin. This new treatment modality provides an opportunity to treat most patients at home. Initial treatment of DVT with low-molecular-weight heparin has become a standard of care in many European countries. This approach seems destined to become the standard in the United States after the FDA approves this indication (probably in 1998).

It is important to ensure that anticoagulants are administered in adequate doses and for adequate periods of time. Patients with proximal vein thrombosis who are treated inadequately have a 40 to 50 percent recurrence of DVT in the following 3 months, and patients with recurrent DVT given anticoagulants for only 3 months are likely to have a 20 percent recurrence of their problem over the next year. A 5-day course of heparin in patients who have calf-vein thrombosis that is not followed by oral anticoagulant therapy will have a 20 percent failure rate in the following 3 months.

In cases of established venous thrombosis or PE in which anticoagulant therapy is contraindicated or has failed, patients may be treated with an inferior vena cava filter, which is inserted either through the jugular or femoral vein by a fairly simple surgical procedure. The idea is that such devices can be used to trap a thrombus which has broken off, thus intercepting it before it embolizes into the lungs.

In cases of massive embolism, thrombolytic therapy with agents such as streptokinase, urokinase or tissue-plasminogen-activator (tPA) may be used to dissolve the PE and so relieve the obstruction. Treatment with thrombolytic agents is expensive and associated with an increased risk of hemorrhage, including hemorrhagic stroke. Therefore, such treatment should be limited to patients who have major PE or underlying cardio-respiratory disease and in whom early lysis is judged to be life-saving.

Limitations of treatment

The most serious problem with the "wait and see" approach to venous thromboembolism is that many patients will suffer serious venous thrombosis or PE as their first manifestation. In the extreme, such a "wait and see" approach could have fatal consequences. Most patients who die from PE do so within 30 minutes of onset, leaving little time for diagnosis or effective intervention.

"... further reductions in mortality from pulmonary embolism must come through systematic prophylaxis in high-risk patients rather than a policy of 'wait and treat'"

Gallus AS (1990) Baillieres Clin Haematol 3, 651-684.

In addition, there is growing awareness that silent DVT can lead, often years later, to the post-phlebitic syndrome, which diminishes quality of life for many otherwise healthy patients. Only by preventing the initial problem - venous thromboembolism - can this major burden on healthcare be avoided.

Screening for DVT

Systematic screening for subclinical venous thromboembolism followed by early treatment to prevent embolism is not feasible in all patients who have recently undergone surgery. In addition, screening programs in high-risk patients may not be possible or affordable in most centers, and, indeed, even in specialized centers, screening is limited to a clinical trial setting.

While screening may not be a suitable approach to DVT and PE prevention for these reasons, it is nevertheless worth reviewing the available methods of diagnosis and screening for thrombosis as they are used in clinical trials of prophylaxis and therapy to establish the efficacy of different regimens.

Diagnosis and screening of venous thromboembolism

The application of diagnostic tests for venous thrombosis and PE differs depending on whether they are used as screening tests in postoperative patients or medical patients at risk, or whether they are used to confirm a diagnosis in patients who have clinical features consistent with venous thrombosis or PE. Only the use of tests for screening is relevant to this discussion. The diagnostic tests used to screen for venous thrombosis are clinical diagnosis, fibrinogen-uptake test (leg scan), impedance plethysmography (IPG), doppler ultrasonography, duplex ultrasound scanning and venography. In the late 1980's, duplex ultrasound scanning became the principal diagnostic screening test for DVT in North American hospitals. The other tests are now primarialy of interest as historic or research methods.

Table 1.9 Hospitalized patients screened for DVT with routine leg scanning or venograph (from original reports)

Patient Category	Screening test(s)	%DVT
Medical		
Myocardial infarction	LS	10-38
Transvenous pacing	LS/P	25
Hemiplegia (stroke)	LS/V	33-53
Paraplegia	LS/V	59-89
Intensive care	LS	13-29
Trauma		
Hip fracture	V	40-49
Tibial fracture	V	45
Multiple injuries	V	35
Elective surgery		
General abdominal	LS/V	3-51
Splenectomy	LS	6
Thoracic	LS	20-45
Gynecologic	LS	7-45
Prostatectomy (open)	LS	29-51
Prostatectomy (closed)	LS	7-10
Aorto-femoral	LS/V	4 -43
Neurosurgery	LS	29-43
Meniscectomy	V	8
Knee surgery	V	17-57
Knee replacement	V	84
Hip replacement	V	30-65
Pregnancy		
Postpartum	LS	1-3

LS = Leg Scan; P = Plethysmography; V = Venogram.

Clinical diagnosis

Clinical diagnosis alone is inaccurate as a screening test because it fails to detect large, clinically important thrombi.

Venography

Venography, or phlebography as it is sometimes called, is the gold standard for the diagnosis of venous thrombosis as it is the only test which is able to detect thrombi in both the calf and the thigh. This test is termed invasive as it involves injecting radiopaque contrast medium into a vein in the dorsum of the foot. The contrast medium then fills the veins, making it possible to visualize the thrombus as a filling defect. The drawback of venography as a screening test is that it is painful and, therefore, cannot be repeated readily. Venography is used for the diagnosis of venous thrombosis in asymptomatic patients and to evaluate the effectiveness of prophylaxis measured in a clinical trial setting.

Impedance plethysmography (IPG)

IPG is a noninvasive test that operates on the principle that changes in blood volume in the leg can be measured as changes in the electrical resistance of tissue as it is monitored on a chart recorder. In this test, patients are asked to lie flat with their feet slightly raised while a cuff is inflated around the leg to a pressure above that normally found in veins. The result is that blood cannot flow back to the heart, and the calf veins fill with blood. Electrodes on the lower leg measure the maximum venous capacity while the cuff is inflated, and the maximum venous outflow can be measured on release of the cuff pressure. These two measurements are reduced from normal levels in patients with an obstructing thrombus. IPG is much less useful as a screening test in asymptomatic patients than it is in diagnosing venous thrombosis in symptomatic patients. This is because the IPG is only sensitive to proximal vein thrombi that produce a critical obstruction. These proximal vein thrombi occur much more frequently in patients who have symptoms of venous thrombosis than in asymptomatic patients. Consequently, the IPG only picks up a minority of asymptomatic proximal vein thrombi and fails to detect most calf-vein thrombi when used as a screening test in high-risk patients.

Doppler ultrasonography

Doppler ultrasonography is another noninvasive method of diagnosing DVT. A beam of ultrasound waves is directed at a vein and is reflected at a frequency that varies according to the rate of movement of red blood cells through that vein. This return signal is detected as an audible tone. As normal blood flow varies with respiration, a low pitch sound can be recorded that disappears as the vein is compressed. As the compression is released, there is an augmented sound if the vein under examination is patent.

This technique, like IPG, is relatively sensitive to obstructing proximal vein thrombi but insensitive to calf-vein thrombi. Therefore, it has limitations when used as a screening test for detecting DVT.

Duplex scanning (B-mode imaging)

This diagnostic test uses the principles of ultrasound to image the deep veins of the leg. The technique is able to identify the proximal veins, including the femoral and popliteal veins, but is limited in its ability to identity calf veins and cannot identify pelvic veins. Therefore as a screening test, duplex scanning has limitations similar to those of IPG and doppler ultrasonography, although recent studies have indicated that it is more sensitive to proximal vein thrombi (including asymptomatic nonocclusive) than IPG. Approximately 60 percent of proximal vein thrombi are detected by this method when it is used to screen patients undergoing hip surgery.

Pulmonary embolism

Patients who show clinical signs of PE usually require urgent investigation and rapid treatment if the diagnosis of PE is confirmed. Symptoms of PE may include dyspnea, chest pain or hemoptysis. As with DVT, clinical examination alone and simple investigations such as chest X ray and ECG are unreliable methods of diagnosis. Patients who may have PE are usually investigated by perfusion lung scanning, since a normal perfusion lung scan excludes the diagnosis. If the perfusion lung scan shows a large defect, then a ventilation lung scan is performed since a normal ventilation scan in the presence of a large perfusion defect is strongly suggestive of the diagnosis of PE. In cases where the perfusion scan is abnormal but only shows a small defect, or if there is a defect seen by

both perfusion and ventilation scanning, a pulmonary angiogram is usually required to either confirm or rule out a diagnosis of PE.

Active prevention

Treatment of established DVT and PE, and screening followed by treatment, are not without their problems. Many surgeons throughout the world today feel that these reactive approaches to postoperative thrombosis are unacceptable given the mounting evidence that prophylaxis around the time of surgery can greatly reduce the chances of thrombosis.

Simple predictions and calculations point to the benefits of general prophylaxis over no prophylaxis and over screening followed by treatment.

"Primary prophylaxis is likely to be more effective, less expensive, and is the prophylaxis of choice in most clinical circumstances. Secondary prevention by screening should never replace primary prophylaxis, and is reserved for those patients in whom effective primary prophylaxis is either contraindicated or unavailable"

Hull RD, Raskob GE and Hirsh J (1986) Chest 89, 3745-3835

Many of the prophylactic measures that can be taken are simple, and newer approaches to prophylaxis are proving that the risks of postoperative thrombosis can be reduced considerably with little risk to the patient.

Not all surgery carries the same risks and not all patients have clear risk factors but, for those patients known to fall into the categories of moderate to very high risk (see Sections 1 and 2), there are strong arguments in favor of employing one or a combination of the prophylactic measures that will be outlined in detail in Section 4.

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Section 4
The available prophylactic measures

Prevention better than treatment

Having identified which patients are at risk of venous thromboembolism, the next choice for the physician is to select the most appropriate prophylactic measure for the patient's circumstances. The ideal primary prophylactic should be effective, free from clinically important side effects, and well accepted by patients, nurses and medical staff. It should be easy to administer, relatively inexpensive and require minimal monitoring.

Over the years, the available methods of thromboprophylaxis have been refined and improved to give maximum risk reduction for patients liable to suffer postoperative, post-traumatic or medical thrombosis. In principle, all prophylaxis is directed either at suppressing activation of blood coagulation or at increasing venous blood flow in the leg veins. There are two general types of prophylaxis - mechanical methods and pharmacological agents.

Mechanical methods

Early mobilization of patients as soon as possible after surgery is thought to reduce the chances of venous thrombosis, and physiotherapy can be categorized as an important mechanical method. The other mechanical methods of prophylaxis act on the same principle as early mobilization, in that they stimulate calf muscles and put pressure on the calf and leg veins, thus discouraging stasis and venous pooling of blood in the lower extremities.

These methods are virtually free of side effects. Graded compression stockings have been shown to be effective in reducing postoperative venous thrombosis in general surgical patients and in neurosurgical patients. The stockings are inexpensive and should be considered in all at-risk surgical patients. However, those that have been most carefully evaluated come in numerous sizes and should be fitted individually to ensure that pressure is correctly graded (highest at the ankle and decreasing in a proximal direction). Intermittent pneumatic leg compression enhances blood flow in the deep veins of the legs. This method is virtually free of side effects and is particularly useful in patients at high risk of bleeding, such as those undergoing neurosurgery, major knee surgery and prostatic surgery. Studies have also shown that compression is as effective as low-dose heparin in patients undergoing abdominal surgery.

Analysis of studies on the use of mechanical methods has shown that general surgery patients on average have about a 9 percent chance of developing deep vein thrombosis (most of which are calf) if stockings or compression are used compared with a 20 to 24 percent chance if no prophylaxis is employed.

Pharmacological agents

Agents include unfractionated heparin (low-dose and adjusted-dose), low-molecular-weight heparins (LMWH's) and heparinoids, warfarin, and dextran. These agents prevent, to differing degrees, thrombus formation after surgery by interfering with blood coagulation (heparin, warfarin) or blood flow and fibrin stability (dextran).

Table 1.10 Measures effective in reducing postoperative DVT

Mechanical methods	
Physiotherapy	• Early mobilization to be encouraged in all patients
Graded elastic compression stockings	• Pressure must be highest at ankle; must be individually fitted
Intermittent pneumatic leg compression	• Relatively inconvenient
Pharmacological agents	
Oral anticoagulants	• Take several days to be effective • Require frequent monitoring • Risk of bleeding higher than with mechanical methods
Low-dose heparin	• Injections 8 or12 hourly (sc) • Small but definite bleeding risk • Limited effect in patients undergoing hip surgery
Low-molecular-weight-heparin (LMWH)	• Once- or twice-daily injection (sc) • Reduced bleeding risk
Dextran	• Anaphylaxis and bleeding may be problems • Risk of volume overload

Table 1.11 Advantages and disadvantages of heparin use

Advantages	Disadvantages
Acts immediately	• Poor sc bioavailability when given in low doses
Proven efficacy in high-risk patients	• Short half-life
Can be neutralized	• Repeated injections
Reference drug	• Risk of thrombocytopenia (minimal with prophylaxis) • Risk of bleeding (minimal) • Not sufficiently effective in very-high-risk groups

“ ... the application of prophylactic measures is much more effective for preventing death and morbidity from pulmonary embolism than is treatment of the established event”

Hull RD, Rascob GE and Hirsh J (1986) Chest 89, 3745-3835

Bleeding is the most common side effect associated with antithrombotic drugs and is the cause of many surgeons rejecting the notion of prophylaxis, particularly prior to surgery. Bleeding can be classified as major and minor. Major bleeding is any overt bleeding associated with a marked fall in hemoglobin, any intracranial or retroperitoneal bleeding, or any situation requiring transfusion or re-operation, whereas minor bleeding could be considered as hematoma at wound sites or other forms of bleeding not associated with a significant fall in hemoglobin.

Clinical trials and large scale studies have measured the effectiveness of each of these types of drugs, sometimes compared with placebo and sometimes compared with each other. In most cases, the trials have not been of sufficient size to provide reliable estimates of the rate of pulmonary embolism, with and without prophylaxis, though the data do support the effectiveness of these agents in preventing DVT.

Unfractionated heparin

Low doses of heparin prevent thrombosis by inhibiting thrombin and Factor Xa. Heparin is a mucopolysaccharide extracted from animal tissues, which is composed of different molecular weight fractions varying in size from 3000 to 30,000 daltons.

Heparin can be administered by subcutaneous injection. When used as prophylaxis, low-dose heparin is usually given at a dose of 5000 U every 8 or 12 hours postoperatively. The first dose may be given 2 hours preoperatively although some surgeons who fear bleeding during surgery may wait until immediately after surgery before giving heparin. Heparin is then usually continued for about 7 days in general surgical patients or until such time as the patient becomes fully ambulatory. Low-dose heparin does not require laboratory monitoring and is simple to use and fairly convenient to administer. It is one of the agents of choice for moderate to high-risk general surgical and medical patients, as it can reduce the risk of venous thromboembolism by 50 to 70 percent.

An overview of more than 70 studies looking at the prophylactic effects of heparin in general and orthopaedic surgery found that DVT, as detected by fibrinogen-uptake scans, could be reduced from approximately

- 22 to 9 percent in general surgery, i.e., a 59 percent risk reduction
- 48 to 24 percent in orthopaedic surgery, i.e., a 50 percent risk reduction
- 41 to 14 percent in urological surgery, i.e., a 68 percent risk reduction.

This same review noted that heparin reduced the frequency of both fatal and nonfatal PE, and in some of the larger trials, (for example, the International Multicentre Trial) this reduction was found to be significant. Mortality was also less in the patients given heparin prophylaxis.

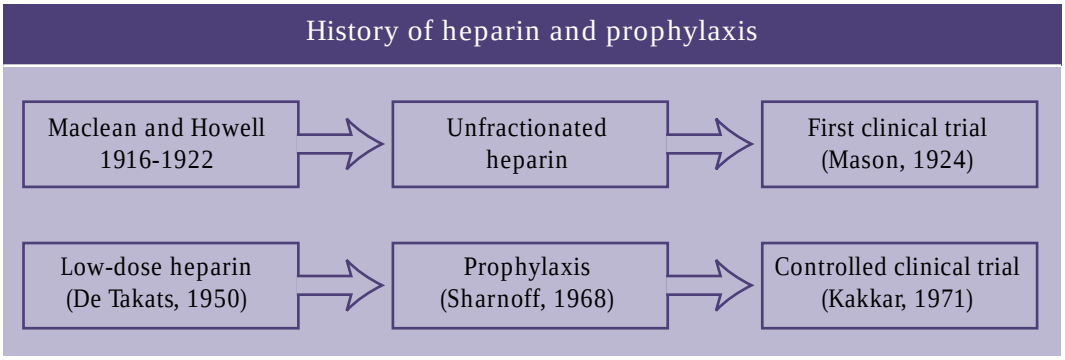
Although low-dose heparin is considered generally to be safe and free from serious bleeding side effects, this agent has some potential to cause minor bleeding, and, so, it should not be used in patients undergoing neurosurgery or eye surgery. It is contraindicated in patients with known heparin sensitivity, patients with a defect in hemostasis, patients with severe hypertension, and when there has been a hemorrhagic accident.

Low-dose heparin is considered to be as effective as dextran in elective hip surgery, where it can reduce the incidence of venous thrombosis by 50 percent. It is, however, less effective than adjusted-dose heparin, oral anticoagulants or LMWH.

Adjusted-dose heparin has been found to be more effective than low-dose heparin in elective hip surgery and in patients who have a spinal cord injury. The adjusted-dose heparin regimen is an 8-hourly regimen of sc heparin that is begun 2 days before surgery. The starting dose of heparin is 3500 U with subsequent dose-adjusted steps of 500 to l000 U to achieve an activated partial-thromboplastin-time (APTT) in the upper normal range 6 hours after injection. This regimen is obviously more complicated and requires more monitoring than low-dose heparin but is more effective in very-high-risk patients.

In this study, the dose of heparin in the adjusted-dose group was increased gradually to an average of 18,900 U/day by the 7th day after surgery (range 13,500-30,000 U for 24 hours). Compared with fixed low-dose heparin prophylaxis using 3500 U sc 8 hourly, the adjusted-dose regimen reduced the overall thrombosis rate in patients having elective hip surgery (measured in the operated leg by venography on days 7 through 9 after surgery) from 39 to 13 percent ($P < 0.01$) without increasing blood loss.

Table 1.12 Heparin has a long history of use in the prevention of thrombosis



Oral anticoagulants (vitamin K antagonists)

Oral anticoagulants, such as warfarin, administered in doses that prolong the prothrombin time (to an international normalized ratio (INR) of between 2.0 to 3.0) are found to be effective in preventing postoperative thrombosis in all risk categories. The prophylaxis can be started preoperatively, at the time of surgery or immediately after surgery, but there is a 3- to 4-day lag before these drugs have their maximum anticoagulant effect.

Oral anticoagulants can be used in two ways:

- Commence with a low dose (3 mg) 10 to 14 days before surgery with the aim of adjusting the INR to 1.3 to 1.5 at the time of surgery and then gradually increase the dose to obtain an INR of 2.0 to 2.5 at 3 to 4 days postoperatively. This approach is relatively safe but impractical because it requires many days of careful monitoring.
- Commence with a dose of 5 mg on the evening of the operation or the first postoperative day, aiming for an INR from 2.0 to 3.0 on the 4th or 5th postoperative day. This approach is more practical and has been shown to be effective and relatively safe but still requires careful laboratory monitoring.

Table 1.13 Advantages and disadvantages of warfarin use

Advantages	Disadvantages
Oral administration	Risk of bleeding
Proven efficacy	Delayed onset of action Delay in neutralizing Frequent monitoring necessary Many drug interactions

The drawbacks to oral anticoagulants are that they require monitoring of prothrombin times and carry a high potential for bleeding complications unless very carefully monitored.

Dextran

Dextran, a glucose polymer available as two fractions of differing molecular weights, dextran-40 and dextran-70, is believed to exert its antithrombotic effects through a number of mechanisms. Dextran is also a plasma volume expanding agent and as such reduces blood viscosity, increases blood flow and reduces venous stasis. It is infused from the time of surgery over a period of 4 to 6 hours and is then given daily for 2 to 5 days postoperatively. The chosen doses of dextran vary greatly. One commonly used regimen is 500 ml dextran-40 daily over the first 3 to 5 days after surgery, followed by additional doses every third day thereafter while the patient remains bedridden. Although dextran is the favored prophylactic agent in some hospitals, studies have shown that it is less effective than warfarin or LMWH in preventing DVT. It has also been associated with allergic reactions or bleeding in some patients, problems that can now be prevented by hapten inhibition, and carries the potential for volume overload. For these reasons dextran has not been widely adopted, at least in North America, as a means of DVT prevention.

Table 1.14 Advantages and disadvantages of dextran use

Advantages	Disadvantages
Effective in high risk surgery	• IV administration inconvenient in postoperative period • Relatively high bleeding risk • Possibility of volume overload • Risk of allergy or anaphylaxis

Low-molecular-weight heparins and heparinoids

Low-molecular-weight heparins (LMWHs) have been introduced as promising prophylactic agents. Interest in LMWHs as potential antithrombotic agents was stimulated by two observations in the mid-1970s and early 1980s. The first was the finding that LMWH fractions prepared from standard unfractionated heparin (UFH) progressively lose their ability to prolong the APTT while retaining their ability to inhibit Factor Xa. The second was the observation that LMWHs produce less bleeding in experimental models for an equivalent antithrombotic effect than the UFH from which they are derived. The LMWHs in clinical use are pro-

duced from UFH by depolymerization and are approximately one-third the molecular size of UFH.

They have a number of advantages over standard heparin preparations and, in clinical trials and major studies throughout the world, have been found to be a highly effective and safe form of prophylaxis in patients undergoing orthopaedic and general surgery, and in stroke patients. They are considered the most effective form of prophylaxis in hip surgery, knee surgery and following major trauma. Studies in both general and orthopaedic surgery have suggested that LMWHs are more effective prophylaxis than standard low-dose heparin. The LMWHs also appear to be superior to dextran. There is evidence that differences between the effects of UFH and LMWH on platelet aggregation or vessel wall permeability may be responsible for the differences in the hemorrhagic properties of these glycosaminoglycans.

A number of different LMWHs have been approved for use in Europe and three are now approved for use in North America: enoxaparin (Lovenox®), dalteparin (Fragmin®) and ardeparin (Normiflo®). The LMWHs have a longer half-life than standard heparin and are highly effective and safe when used for prophylaxis in surgical patients.

At least eight randomized studies compared LMWH with standard heparin in patients undergoing abdominal surgery. A number of the early trials evaluating prophylactic LMWH reported excessive bleeding, which, in the light of subsequent experience, was probably due to use of excessively high doses of LMWH. In two large studies, the incidence of thrombosis was significantly lower in the LMWH group, but there was no difference detected in the rate of bleeding between the LMWH and UFH groups. In a recent study in general surgical patients, comparing LMWH with no treatment, patients randomized into the LMWH group had significantly lower total mortality and thromboembolic mortality.

LMWH has also proved to be very effective in reducing postoperative venous thrombosis in patients who have undergone elective hip surgery. In most studies using LMWH, the agent was given preoperatively and then once daily postoperatively; however, a double blind placebo-controlled trial in which a LMWH was given twice daily starting 12 to 24 hours after hip replacement found that venous thrombosis could be markedly reduced - from 42 percent in the control group to 12 percent in the LMWH group. Proximal vein thrombosis was reduced from 23 percent in the control group to 4 percent in the LMWH group in this same trial, without excessive bleeding. Other studies, using the preoperative regimen and then once-daily LMWH, have reported similarly low rates of venous thrombosis after hip surgery, and a recent study found that LMWH was significantly more effective than adjusted-dose heparin in reducing the incidence of proximal vein thrombosis.

In another recent study comparing a LMWH with dextran in hip surgery, a relative risk reduction of 70 percent was seen for the LMWH group. Patients received either 40 mg/day enoxaparin 12 hours before surgery and for 8 days thereafter, or 500 ml infusions of dextran during surgery, on the day of surgery and on days 1 and 3 after surgery. The rate of DVT was 22 percent in the dextran group but was considerably lower in patients who received enoxaparin - just 6 percent.

Three recently published randomized studies in patients undergoing total knee replacement have shown similar favorable results using LMWH, which is now considered the prophylaxis of choice following knee replacement surgery.

Fewer studies have been performed in medical patients at risk of thrombosis. However, the results for LMWHs look promising. Two studies in stroke patients suggest from 60 to 80 percent relative reduction in thrombosis risk can be achieved by administering LMWHs prophylactically, and a third study in elderly bedridden patients points to a similar risk reduction for DVT following administration of LMWH.

A number of different LMWHs have been developed. All are produced from UFH by depolymerization techniques that differ from manufacturer to manufacturer. Although often described collectively, each LMWH has different properties. While, as a group, these agents can be said to exhibit certain prophylactic properties that compare well with other methods of prophylaxis, the clinical trial results obtained with one LMWH should not be extrapolated to predict the effect of another LMWH. They differ in dosage and in their effects on blood parameters. The dosing schedule and administration of enoxaparin illustrate the advantages of this class of prophylactic drug.

Enoxaparin has a half-life of approximately 4.4 hours and is 90 percent bioavailable. Unlike standard heparin, which has to be administered two or three times a day, a once or twice daily sc injection of enoxaparin affords the patient adequate protection against the risks of thrombosis. It is therefore convenient to use and is well accepted by physicians, nurses and patients.

Two different dosing regimens are available for use in either very-high-risk patients or high-risk patients. In a very-high-risk situation, such as orthopaedic surgery, enoxaparin is given at a dose of 30 mg twice a day, with the first dose administered 12 hours after surgery, and doses repeated twice daily thereafter until the risk of thrombosis is considered to have passed. There is currently much interest in continuing to administer LMWHs for a longer period after surgery to protect against the longer-term threat of thrombosis.

In high-risk general surgical patients enoxaparin is given in a dose of 40 mg once a day, with the first dose given 2 hours before surgery and then repeated once daily until the risk of thrombosis is thought to have diminished.

It is assumed that many of the contraindications to the use of heparins will apply to the use of LMWHs, but there is evidence that the risks of heparin-induced thrombocytopenia are lower with LMWHs.

Combined prophylactic modalities

There is a lack of good data comparing combinations of prophylactics with agents or methods used alone. However, almost all surgical patients are thought to benefit from the use of stockings or compression in addition to a pharmacological agent.

Using the current methods of prophylaxis

There is still some debate as to exactly when and for how long prophylaxis for venous thrombosis should be given. Even established agents, such as low-dose and adjusted-dose heparin, are used earlier and longer by some doctors than by others. Should pharmacological prophylaxis begin pre- or postoperatively? How long should a course of prophylaxis last? Are there differences in the type, dose and duration of prophylaxis to be used in different risk groups?

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Table 1.15 Summary of efficacy of various prophylactic approaches in elective hip surgery with venography as the endpoint (Salzman and Hirsh, 1987)

Agent	No. of patients	Thrombosis(%)	Risk % reduction
Aspirin	309	40	13
Dextran	123	17	57
Warfarin	208	25	48
Low-dose heparin	301	22 (pooled analysis)	57
Control	979	47	-
LMWH (enoxaparin)	50	12 (single studies)	72

Choice of prophylaxis in different patient groups

Most often, the decision to use prophylaxis is based on the presence of one or more of the risk factors known to predispose patients to postoperative or medical thrombosis. There have been attempts to refine this process by adding laboratory tests to the clinical risk factors and deriving formulae in which risks are weighed to yield a predictive index for a given patient. Most of these indices have not proved helpful, and, consequently, the best approach is still for doctors to rely on their knowledge of risk factors and to weigh the benefits of prophylaxis for each patient.

All patients suspected of being at risk of venous thrombosis should be encouraged to keep mobile.

Indeed, in all general surgery and medical patients, early ambulation and graduated compression stockings should be considered automatically. Patients in high-risk groups should receive, in addition, pharmacological prophylaxis.

The choice of prophylaxis has widened since 1986 when the consensus statements on methods of prophylaxis in at-risk patients were first issued. Since the advent of LMWHs, many experts now believe that the efficacy and ease of use of these compounds make them the *prophylaxis of choice* in most very-high-risk patients.

Patients at high risk should receive either low-dose heparin or intermittent pneumatic compression, while patients at very-high-risk should receive LMWH or oral anticoagulants.

Orthopaedic surgery, for example hip surgery, carries a very high risk of thrombosis and all patients should receive prophylaxis with either LMWH, adjusted-dose heparin, or oral anticoagulants. Results from studies in orthopaedic surgery suggest that LMWHs have a profile that makes them the *prophylaxis of choice*. Major knee surgery is another area where LMWHs have become the favored method of prophylaxis. Genitourinary surgery and neurosurgery are procedures

following which intermittent pneumatic compression may be the safest, most effective form of prophylaxis.

Medical patients, such as those who have suffered myocardial infarction or hemiplegia, may also benefit from thrombosis prophylaxis. Information is sparse about the success of preventive measures. Heparin prophylaxis may have some role in post-myocardial infarction patients, and may also prevent DVT in patients who have recently suffered a stroke.

The greater safety margin of LMWHs has sparked interest in their possible use in ischemic stroke for the prevention of thrombosis. Bedridden patients suffering from complaints such as pneumonia or heart failure are known to be at increased risk of venous thromboembolism, and both low-dose heparin and LMWH appear to achieve substantial risk reductions in these patients.

Prophylaxis: pre- or postoperative?

Many North American surgeons do not wish to begin prophylaxis, even with LMWHs, preoperatively and prefer instead to begin with the first dose of heparin or LMWH 12 hours after surgery, especially when spinal anesthesia was used.

For how long should prophylaxis continue?

Studies using both standard heparin and LMWH often state that prophylaxis was continued for about 7 days after surgery, or until such time as the patient became mobile. However, no one actually knows how long the danger of venous thromboembolism persists after surgery, and there is much debate currently over when to stop prophylaxis.

A recent study of patients after their discharge from the hospital following major surgery confirmed that the risks of developing thromboembolic disease can extend beyond the patient's stay in the hospital. Once patients return home, they may be even less mobile than they were in the hospital. Of 57 patients studied, 13 developed DVT during the 6 weeks after surgery, despite having shown no signs of this complaint while in the hospital.

Many patients receive heparin or LMWH for about one week after surgery and are then switched to oral anticoagulants for several weeks to provide some continuing protection. However, the apparent high safety margin and excellent efficacy of LMWHs has led doctors in some hospitals to suggest that daily injections continue for longer periods including periods after the patient has returned home. Because of the ease of injection, surgical patients in Europe are now often asked to continue their LMWH prophylaxis at home by self-administration. In North America and Europe there is growing enthusiasm for treating acute DVT at home with LMWHs. This has led to the wide adoption of home treatment protocols by managed care organizations and hospitals. While this development should make it easier to implement continued DVT prophylaxis with LMWHs at home, at least in 1997, the price of LMWHs in North America was considerably higher than the price of oral anticoagulants. Thus, the most cost-effective approach to long-term DVT prophylaxis appears to be LMWHs for one to two weeks followed by oral anticoagulants if longer protection seems warranted.

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Section 5
The cost effectiveness of prophylaxis

There is now a fairly extensive body of literature on the relative efficacy and safety of the various available forms of prophylaxis. In contrast, there are very few definitive reports on the economic implications of prophylaxis. The reluctance of many hospitals to adopt an organized strategy for the prevention of venous thromboembolism is sometimes blamed on the fact that this information is not forthcoming. However, there have been reviews of cost effectiveness that clearly identify those patients who will benefit clinically and financially from prophylaxis, as distinct from those in whom prophylaxis would have no overall benefits.

"... the decision to use prophylaxis should be based not on economic grounds but on avoiding the tragic and unnecessary loss of life due to massive pulmonary embolism"

Hull RD, Raskob GE and Hirsh J (1986) Chest 89, 374S-383S

In any calculation of cost effectiveness, it is difficult to quantify the cost of time lost through illness or indeed the cost of death. Similarly, the morbid long-term effects of venous thromboembolism cannot easily be measured in monetary terms. But, it is possible to compare the costs of a course of prophylaxis with the costs of diagnosis, treatment and hospital care involved in dealing with a thrombosis once it has occurred. A study performed in Sweden compared the cost effectiveness of three alternatives in patients 40 years and older who underwent general surgery, surgery for cholelithiasis or elective hip surgery:

- no prophylaxis
- general prophylaxis with low-dose heparin
- selective therapy following screening with fibrinogen-uptake alone or with venography.

Three different categories of surgery were chosen to represent the different degrees of risk to patients in different groups.

"in elective hip and general surgery, at least, treatment costs can be minimized with the general prophylaxis alternatives"

Bergqvist et al. (1988) World J Surg 12, 349-355

When calculating the costs of treatment, general hospital costs, such as those for room and board were kept separate from those for medication, diagnosis, monitoring, treatment of complications and prolonged hospitalization due to re-admission or complications. There was also no concession made for the costs of lost productive capacity during illness.

From this study, it emerged that general prophylaxis was the best option in terms of reducing the frequency of venous thrombosis - a reduction of 70 percent. General prophylaxis was also the best approach to reducing patient mortality after surgery.

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Table 1.16 Expected costs (SEK Swedish crowns) per patient for three alternatives in three different categories of surgery

Study population	General surgery	Surgery for cholelithiasis	Elective hip surgery
No prophylaxis	1511	662	2944
General prophylaxis	1199	1073	1600
Selective treatment following fibrinogen test fibrinogen and venography	 4542 3984	 2123 1932	 8382 7256

"General prophylaxis will also minimize hospital costs per patient"

Bergqvist et al. (1988) World J Surg 12, 349-355

When costs were analyzed, it became clear that, both in elective hip surgery and general surgery, the most cost-effective alternative is general prophylaxis, while in surgery for cholelithiasis, the general prophylaxis option was not quite as cost effective as no prophylaxis, given the rate of complications.

The prophylaxis chosen, that is, low-dose heparin, was associated with an increased frequency of hemorrhagic complications, as compared with the alternative of not using prophylaxis.

"This is an unusual finding – interventions that save both lives and health care dollars are relatively uncommon"

Oster G, Tuden RL and Colditz GA (1987) JAMA 257, 203-208

Both deep vein thrombosis and pulmonary embolism were significantly reduced by general prophylaxis in this study. Selective treatment after screening was shown to be the least effective option in terms of both clinical outcome and cost.

Thus, in very-high-risk (orthopaedic) and high-risk (general) surgery, prophylaxis is both clinically and financially worthwhile. The case for prophylaxis in low-risk (cholelithiasis) surgery cannot be made on financial grounds, even though there will be a reduction in the patient's risk of postoperative thrombosis.

"Our results do suggest that the failure to use any method of prophylaxis may be difficult to justify on grounds of concern over either the outcome or cost of care"

Oster G, Tuden RL and Colditz GA (1987) JAMA 257, 203-208

Another study confirming the cost effectiveness of prophylaxis in orthopaedic surgery was performed in the USA. Several different types of prophylaxis including warfarin, low-dose heparin, graduated compression stockings, intermittent pneumatic compression and heparin plus stockings were compared with no prophylaxis. As well as reducing the number of fatalities by about 50 percent, prophylaxis was also found to be cost effective.

When the costs of diagnostic tests to confirm DVT and PE in patients who had not received prophylaxis were calculated and added to the costs of treatment and hospital time spent managing established thrombosis, it was clear that, in this very-high-risk group of patients, prophylaxis was justified not only on the grounds that it reduces morbidity and mortality but also because it was more cost effective. Prophylaxis could reduce average costs of care by $19 to $182 per patient.

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