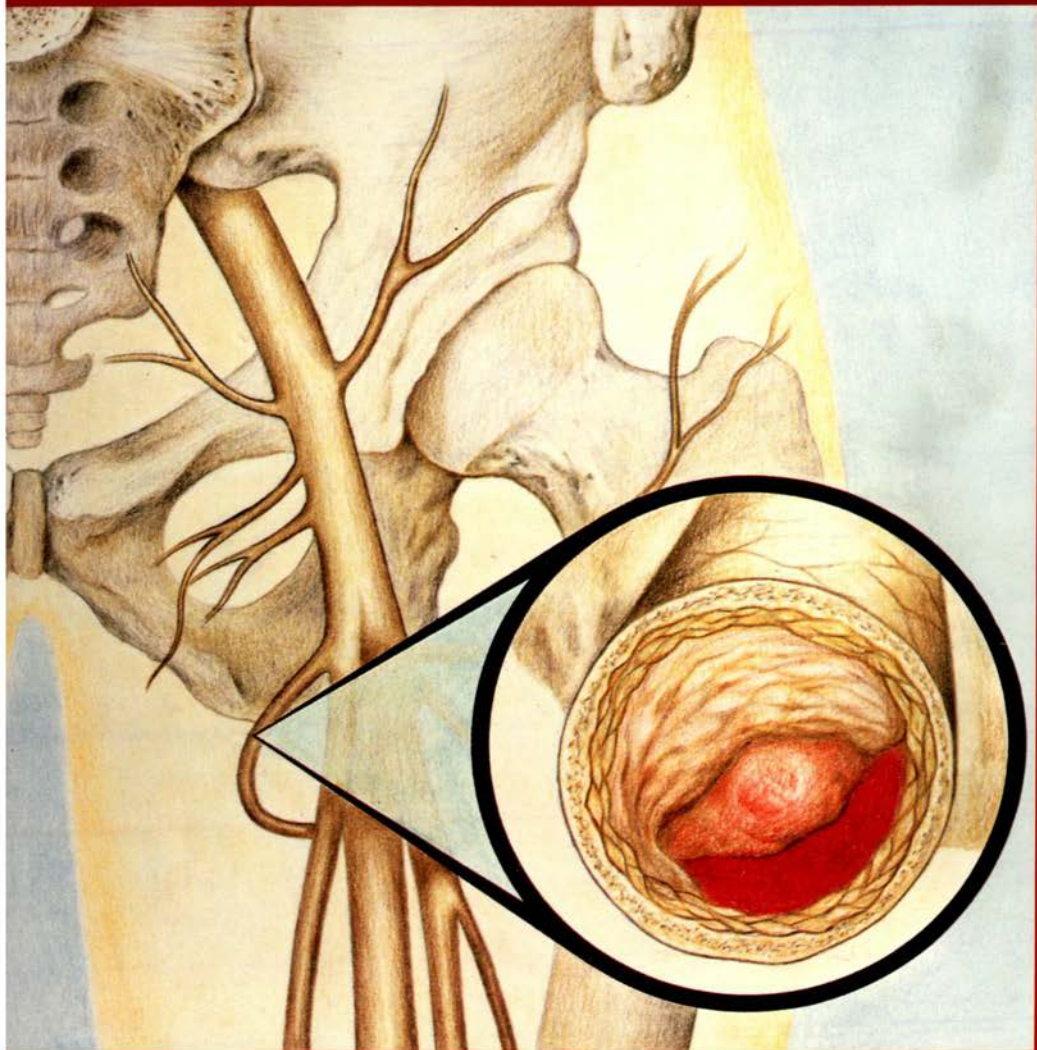


# DEEP VEIN THROMBOSIS AND PULMONARY EMBOLISM



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No 114 in a series of papers on current health problems published by the Office of Health Economics. Copies are available at £7.50. For previous papers see inside back cover.

Cover illustration shows the condition known as deep vein thrombosis which has led to the formation of a blood clot (thrombus) in a subsidiary vein of the larger common iliac vein. Copyright Science Photo Library.

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ISSN 0473 8837

Printed by White Crescent Press Ltd, Luton.

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# 1 Glossary

<b>Antithrombin III</b>	a plasma protein which inhibits certain blood coagulation factors.
<b>Calf vein thrombosis</b>	a thrombus in the veins of the calf.
<b>Cutaneous ulceration</b>	formation or development of a skin ulcer.
<b>Deep vein thrombosis</b>	a thrombus which has formed in the veins beneath the deep fibrous tissue of the leg.
<b>Dermatitis</b>	inflammation of the skin.
<b>Dyplasminogemia</b>	defective release of plasminogen activator.
<b>Factor V (Leiden)</b>	deficiency of this factor, an autosomal recessive trait, leads to a rare haemorrhagic tendency, which varies greatly in severity.
<b>Haemoptysis</b>	the spitting up of blood from the lower air passages. The blood is usually coughed up, it may be in mouthfuls at a time and is bright red and frothy.
<b>Indurated cellulitis</b>	hard, brawny induration of the skin of the lower leg.
<b>Incidence</b>	the number of new cases within a given population within a given period.
<b>Lysis</b>	the process of dissolution of a thrombus or the loosening of adhesions.
<b>Oedema</b>	swelling due to the presence of abnormally large amounts of fluid in the intercellular tissue of the body.
<b>Phlebogram</b>	x-ray of the veins of the leg in which x-ray contrast media is injected into the vein.
<b>Plasminogen</b>	converts fibrin to soluble products.
<b>Pleuritic/pleurisy</b>	inflammation of the membrane enclosing the lungs.
<b>Popliteal cysts (Baker's cysts)</b>	a cyst occurring at the back of the knee.
<b>Post phlebitic syndrome</b>	dilated and varicose veins frequently occur months to years after deep vein thrombosis. Many patients also develop further changes which may include oedema, pigmentation, recurrent indurated cellulitis, stasis dermatitis (often intensely itchy) and cutaneous ulceration.

<b>Prevalence</b>	the number of cases present in a given population at a given time.
<b>Protein C</b>	a vitamin K dependent plasma protein that, when activated inhibits blood coagulation. Deficiency results in recurrent venous thrombosis.
<b>Protein S</b>	a vitamin K dependent plasma protein that inhibits blood coagulation by acting as a co-factor for activated Protein C.
<b>Proximal vein thrombosis</b>	a thrombus in the proximal veins (veins found around the femur and the hip bones). A more serious disorder than calf vein thrombosis, as the thrombi tend to be larger. May be found in association with calf thrombi which have extended proximally from the calf.
<b>Puerperium</b>	period which elapses after the birth of a child until mother is again restored to her normal health. Generally held to be one month.
<b>Pulmonary thromboembolism</b>	a thromboembolism of the lungs.
<b>Pulmonary embolism</b>	most serious complication of DVT. Massive obstruction of the circulation of oxygen in the lungs may result in sudden death and multiple small emboli may lead to pulmonary hypertension.
<b>Stasis</b>	slowing or stoppage in the flow of blood.
<b>Syncope</b>	fainting.
<b>Thrombus</b>	a semi-solid mass, formed from components of the blood, which has developed in the bloodstream.
<b>Thrombosis</b>	the disease which results from thrombus formation.
<b>Thromboembolism</b>	detachment of thrombus from the site of its formation and subsequent passage in the blood vessels until it reaches a smaller vessel which it then obstructs.
<b>Venous thromboembolism</b>	in this situation the embolism is detached from the thrombus (usually in the proximal veins of the thigh) and ends up obstructing the pulmonary arteries and therefore producing a pulmonary embolism (see above).

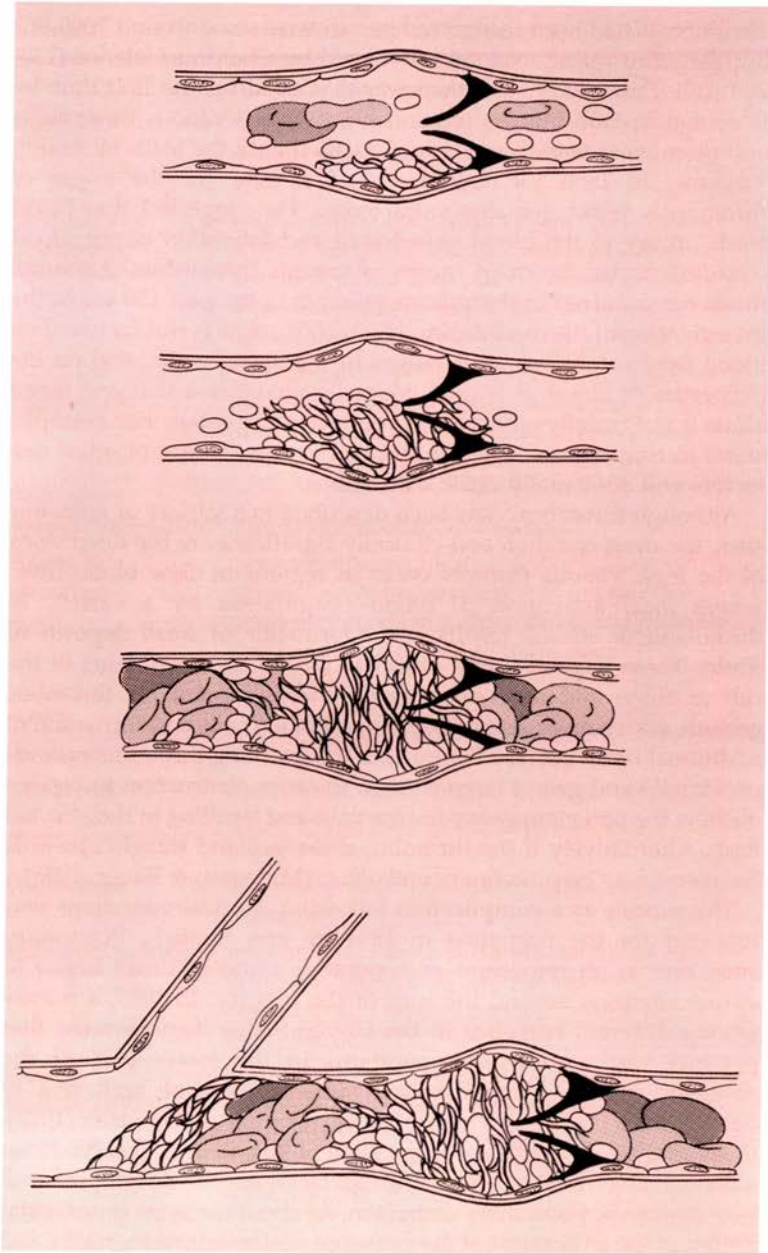
## 2 Introduction

Thrombosis had been recognised as a disease since around 2000 BC, but the word thrombosis was first used by Claudius Galenos (130-200 AD). Pulmonary embolism was described for the first time by Wiseman in 1676 but the relationship between venous thrombosis and pulmonary embolism was not clarified until the 1840s by Rudolf Virchow. In 1856 Virchow described a triad for the origin of thrombosis which remains valid today. He suggested that blood stasis, injury to the blood vessel wall and alteration of the blood constituents are the main causes of venous thrombosis. Although much has occurred in thrombosis research in the past 150 years, the investigation of the mechanism by which it arises is still focussed on blood flow conditions, on changes in the vessel walls, and on the properties of blood. It is now generally recognised that one factor alone is not usually sufficient to produce a thrombus. For example, stasis during normal sleep or bed rest in the absence of other risk factors will not usually cause a thrombus.

Although thrombosis has been described in a variety of anatomic sites, the most common and clinically significant are the deep veins of the legs. Venous thrombi occur in regions of slow blood flow, where local activation of blood coagulation by a variety of thrombogenic stimuli results in the formation of small deposits of fibrin. These deposits often originate within the deep veins of the calf or thigh and may serve as the starting point for thrombus growth, with subsequent entrapment of blood cells and formation of additional fibrin gel (see Figure 1). If the evolving thrombus extends proximally and grows large enough to cause obstruction to venous outflow the patient may experience pain and swelling in the affected limb. Alternatively if the thrombus dislodges and travels upwards the result may be pulmonary embolism (Millensen & Bauer, 1996).

Thrombosis as a complication following surgical operations was reported for the first time in 1894 by von Strauch. Pulmonary embolism as an important postoperative cause of death began to attract attention around the turn of the century. In 1905, a survey among different surgeons in the United States demonstrated that patients who underwent operations in the lower part of the abdomen and/or gynaecological surgery were at high risk of developing a postoperative thrombosis (Cordier, 1905). Lister (1927), in an analysis of the then current state of knowledge, observed that advancing age was an important risk factor for the development of post-traumatic pulmonary embolism. At about the same time Gustaf Petren made an analysis of the causes of postoperative mortality and

Figure 1 The development of a deep vein thrombosis





concluded: 'The often unexpected and unforeseeable occurrence of deaths from pulmonary embolism, their increased number and our, in the main, helplessness in the face of them, both prophylactically and therapeutically, make pulmonary embolism the greatest crux of present day practical surgery'.

Unfortunately, although our knowledge of the causes of deep vein thrombosis and the therapeutic and prophylactic measures available to treat and prevent venous thromboembolic diseases have increased, it continues to be of great importance in surgery today and is still a major cause of postoperative death.

This paper sets out what is currently known about venous thromboembolic diseases:

- describes the incidence and prevalence of the condition;
- discusses the associated risk factors and their relative importance;
- relates the difficulties that exist in making an accurate diagnosis of deep vein thrombosis;
- considers the regimens which exist to both treat and prevent deep vein thrombosis and their relative cost effectiveness using published economic evaluations;
- looks at the cost to the NHS of deep vein thrombosis in 1993/94 and calculates the potential costs and lives saved if adequate prophylaxis had been used; and
- concludes by asking what might be done to ensure that all patients at risk of developing a deep vein thrombosis receive adequate prophylaxis.

### 3 Epidemiology

Deep vein thrombosis (DVT) of the lower limb and its acute complication, pulmonary embolism (PE), are major causes of death and disability. In the general population, clinically recognised DVT and/or PE occurs in about 2 in 1000 persons each year. In the hospitalised population DVT and PE are much commoner. This is probably due to the contribution of acute injury, surgery or medical illness (which cause pooling of blood in the deep leg veins, within which activated clotting factors produce fibrin rich thrombi) (SIGN, 1995).

A recent study in Sheffield (Thromboembolic Risk Factors (THRIFT) Consensus Group, 1992), found that 9 per cent of patients admitted to a general hospital died and that 10 per cent of these deaths (0.9 per cent of all admissions) were due to pulmonary embolism. This is approximately 77,000 deaths in 1992 (in 1995 it is estimated that the number of hospital deaths due to PE will have risen to 80,000; OHE, 1995).

#### Clinical diagnosis

The clinical diagnosis of DVT and PE has always been unreliable (Sharnoff, 1980), particularly with regard to physical symptoms and signs.

Some of the physical symptoms and signs of DVT include pain and tenderness in the calf muscles, swelling of the calf or thigh and palpation of vein cords in the leg and thigh muscles, increase in temperature and skin discoloration (cyanosis). Objective tests have shown that the clinical physical signs are only 50 per cent or less accurate, with a frequent false-positive diagnosis (Weinmann and Salzman, 1994). Not only are some of these tests of limited sensitivity but a major difficulty is that other conditions besides deep vein thrombosis can cause a painful, swollen leg. In a study of 87 consecutive patients with clinically suspected deep vein thrombosis, who had a normal phlebogram (see Box 1), it was found that only 34 actually had a DVT. Of the remainder, 37 had a musculoskeletal cause, 12 had impaired venous or lymphatic flow, and 4 had popliteal cysts (Baker's cysts) (Hull et al, 1981). Therefore a diagnosis suspected on clinical grounds must be confirmed by a sensitive diagnostic test.

The diagnosis of pulmonary embolism is also frequently inaccurate both clinically and radiographically. The most common clinical signs are dramatic, sudden collapse, air hunger, cyanosis and shock. Less common are pleuritic chest pain, apprehension, cough,



haemoptysis, syncope and substernal chest pain in that order of frequency. It is often a medical catastrophe and frequently the most rapid death known to man (Sharnoff, 1980).

The principal aim of any clinical investigation into venous thromboembolic disease should be to prevent the mortality and morbidity associated with pulmonary embolism. Carter et al (1987) suggest that DVT can be used 'as a substitute end point for the study and prevention of pulmonary embolism..., since treated venous thromboembolism is not a fatal condition but is of high frequency in the hospital population and, with the exception of postphlebotic syndrome, carries a relatively low morbidity'. A natural extension of this approach would be to try to identify those patients at risk of developing DVT and to initiate appropriate prophylaxis in order to prevent any possible future development of a pulmonary embolism.

### **Tests for DVT**

The objective techniques for the diagnosis of deep vein thrombosis may be divided into invasive and non-invasive methods. The invasive method most commonly used is venography. Among the more commonly used non-invasive methods for the demonstration of deep vein thrombosis are the Doppler ultrasound flowmeter method, impedance plethysmography and thermography. These techniques are more fully discussed in Box 1. Unfortunately, these techniques are not suitable for use outside the hospital setting. Consequently, the extent of the problem of venous thrombosis and the identification of risk factors is better defined for the hospital population than for the general population.

### **The incidence and prevalence of deep vein thrombosis**

Estimates of the incidence and prevalence of DVT vary. In a community study undertaken in west London (Franks et al, 1992) a random sample of 2103 patients aged between 35 and 70 years of age, registered with three general practices, were invited to complete a questionnaire to assess the prevalence of venous disease. Of this sample 1,338 (64 per cent) responded. The study reported that three per cent of the sample had had a thrombosis, four per cent in the leg and one per cent in the lung. This gave an overall prevalence of six per cent for a history of thrombosis or embolism.

The incidence of venous thrombosis in specific circumstances, for example in the post operative period, has been defined with some degree of precision but official figures are either non-existent or unreliable in DVT due to the inability to make a diagnosis by clinical signs alone. The unreliability of clinical examination for the

## **BOX 1 Objective techniques for the diagnosis of deep vein thrombosis**

### **Invasive techniques**

#### **Venography**

Venography is the gold standard reference test for the diagnosis of deep vein thrombosis. Performed correctly, ascending venography outlines the deep venous system of the lower extremities, including the external and common iliac veins in most patients. The aim of venography is to outline clearly the deep venous system of the leg by injecting radiopaque contrast medium into a distal dorsal foot vein. Radiographic films can then be taken of the whole leg to ascertain whether a thrombus is present.

In general, venography, is not a suitable screening test for asymptomatic venous thromboembolism because it is invasive and therefore cannot be repeated. However, it is the most accurate method for diagnosing asymptomatic thrombi. Its routine use, before hospital discharge, could be justified in patients who have had major orthopaedic surgery where there is a relatively high incidence of thrombosis even where prophylaxis is used (Lensing et al, 1994).

Venography is an invasive procedure that may cause discomfort during injection or as a result of adverse reactions to the contrast agent. It is contraindicated in patients with an allergy to iodine and acute or chronic renal failure, a history of a reaction to contrast material, or an obvious local infection of the foot. If venography is required in a pregnant woman, it should be performed with the foetus shielded from radiation by covering the patient's abdomen with a lead lined apron.

#### **Non-invasive techniques**

Four non-invasive diagnostic techniques have been evaluated in properly designed clinical studies: impedance plethysmography; real-time compression ultrasonography; Doppler ultrasonography; and <sup>125</sup>I-fibrinogen leg scanning.

#### **Impedance plethysmography**

Plethysmography is a non-invasive technique that detects volume changes in the leg. The principle of the method is based on the observation that changes in blood volume in the calf, produced by inflation and deflation of a pneumatic thigh cuff, result in changes in electrical resistance (impedance). These changes are reduced in patients with thrombosis.

The problem with this technique is that it detects only thrombi that produce obstruction to venous outflow. It therefore does not detect most calf vein thrombi, most asymptomatic proximal vein thrombi (because they are usually non-occlusive), and some symptomatic non-occlusive proximal thrombi. The test also cannot distinguish between thrombotic and non-thrombotic obstruction to venous outflow.

#### **Real-time compression ultrasonography**

An image is obtained by real-time computation of the reflected signals from an array of ultrasound sources, resulting in two-dimensional images. The reflections are due to boundaries between adjacent (micro) structures with different acoustic properties. The test using vein compressibility as the single

diagnostic criterion (compression ultrasound), is sensitive and specific for proximal vein thrombosis.

Compression ultrasound is more accurate than impedance plethysmography for the detection of proximal vein thrombosis in asymptomatic patients at high risk for venous thromboembolism (Ginsberg et al, 1991).

#### **Doppler ultrasonography**

In expert hands, Doppler ultrasound is a sensitive method for detecting proximal vein thrombosis but is less sensitive to calf vein thrombosis. The Doppler ultrasound flow-velocity detector contains an oscillator that activates a piezoelectric crystal in a hand held probe, so that it emits an ultrasound beam. This beam is directed percutaneously at an underlying vein, where it is reflected from blood cells. If the blood is moving, then the beam is reflected and a sound is emitted, if the blood is stationary no sound will be recorded.

Advantages of this technique are that it can be performed rapidly and that it is inexpensive. The major limitation, however, is that the interpretation of the Doppler signal is subjective, resulting in considerable observer variation (Lensing et al, 1994).

#### **<sup>125</sup>I-fibrinogen leg scanning**

The diagnosis of venous thrombosis by radioiodine-labeled fibrinogen scanning is based on the incorporation of circulating labeled fibrinogen as fibrin into the thrombus, which is then detected by measuring the increase of overlaying surface radioactivity with an isotope detector (Lensing et al, 1994). This method has been evaluated to a limited extent as a screening test in general and orthopaedic surgical patients, and was accepted as an accurate test in high risk patients (Field et al, 1972), however, results of recent studies have cast doubts on its accuracy (Fauno et al, 1990). This point is moot, since <sup>125</sup>I-labeled fibrinogen has been withdrawn from the market for fear of transmission of viruses (Weinmann & Salzman, 1994).

#### **Other**

Other diagnostic techniques, including other forms of plethysmography, thermography, and various isotopic methods, have been evaluated to a limited extent (Barnes et al, 1972; Cooke & Pilcher, 1974; Johnson et al, 1974; Tibutt et al, 1975). Sensitive blood tests that detect intravascular fibrin formation and lysis have also been evaluated (Wilde et al, 1989) but are of limited value.



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detection of DVT has been demonstrated repeatedly (see Box 1). Many patients present no signs to indicate the presence of thrombosis (Ogston, 1987). Therefore it is likely that the frequency of venous thrombosis will be greatly underestimated when the detection is based on physical examination alone. Equally, up to half of the patients presenting with symptoms suggestive of DVT are found to have no objective evidence of thrombosis. For example, in a study by Hull et al (1983), 183 patients out of 270 referred with the clinical diagnosis of acute DVT were found to have negative impedance plethysmography and negative <sup>125</sup>I-fibrinogen scans.

The prevalence of DVT has also been examined in a number of post-mortem studies. Not surprisingly, given the differences in the extent and technique of vein dissection and in the type of patient involved, these studies have shown wide variations. Gibbs (1957) dissected the veins of the lower limbs, the iliac veins and the inferior vena cava in 253 cases following bed rest and found thrombi in 149 (59 per cent). In a consecutive series of 108 patients dying in medical and surgical wards of a Glasgow hospital, Roberts (1963) found venous thrombosis of the lower limbs in 58 (54 per cent). Havig (1977) carried out a complete dissection of the veins of both lower limbs in 261 randomized post mortems that were claimed to give a representative cross-section of the total deaths in Oslo; large thrombi were found in 161 (62 per cent), while a further 23 had microscopic thrombi, giving a total prevalence in the series of 72 per cent.

### **The incidence and prevalence of pulmonary embolism**

Estimates of the incidence of pulmonary embolism which are based on diagnosis using clinical or radiological methods are also unreliable. Pulmonary emboli occur more frequently than those cases diagnosed by these methods. In one study on 61 consecutive postoperative patients using ventilation-perfusion lung scintigraphy (V/Q scanning), Rodzynek et al (1985) found an incidence of 11.5 per cent for symptomless postoperative pulmonary embolism, while that of symptomatic embolism was 6.5 per cent. Estimates using post mortem findings clearly will be more precise, but unless special techniques are used, post mortem may fail to detect other than large emboli in major vessels. Morrell and Dunnill (1968) examined 263 right lungs by a method which allowed very small cut vessels to be seen by eye, with vessels containing an embolus being identified more easily; the technique was considered to provide an estimate of the true incidence of pulmonary embolism. Emboli were found in 51.7 per cent of the right lungs. In contrast, only 11.8 per cent of the left lungs were found to have emboli when examined by



pathologists using a routine method. Partly for this reason, and partly because of differences in the clinical background of the subjects, the incidence of pulmonary embolism at post-mortem has varied widely in reported series.

In a study to investigate the status of pulmonary embolism as a cause of death in a general hospitals patient population, a five year retrospective analysis of all autopsy reports and associated hospital records was undertaken (Sandler & Martin, 1989). Pulmonary embolism was thought to be the cause of death in 239 of 2338 autopsies (10 per cent): 15 per cent of these patients were aged less than 60 years of age and 68 per cent did not have cancer (see page 25). Of these patients 83 per cent had deep vein thrombosis in the legs at autopsy, of whom only 19 per cent had symptoms of DVT prior to death. However, only three per cent of patients who had DVT at autopsy had undergone an investigation for such before death. Twenty four per cent of patients had undergone surgery a mean 6.9 days before.

The finding of pulmonary emboli, however, may be incidental to the cause of death (Ogston, 1987). In a study by Havig (1977) on 508 randomised post mortems the total incidence of pulmonary embolism was 69 per cent, but in only 18 per cent was a pulmonary embolism judged to be the cause of death, that is another condition was considered to be the principal cause.

## 4 Risk factors

The development of objective means of diagnosing venous thromboembolism and the relatively high incidence of venous thrombosis in various groups of hospitalised patients has enabled the careful study of both individual and multiple risk factors for the development of venous thrombosis in this population. The results are summarised in Box 2 and discussed below.

<b>BOX 2 Risk Factors for Deep Vein Thrombosis</b> (Adapted from Weinmann & Salzman, 1994)		
<i>RISK FACTOR</i>	<i>COMMENT</i>	<i>REFERENCE</i>
<b>Advancing age</b>	Exponential increase above the age of 40 years.	Morrell & Dunnill, 1968; Sevitt & Gallagher, 1961.
<b>Immobilization</b>	Increased risk in paralysed limbs of patients with stroke; Increased risk in both legs of patients with paraplegia; Prolonged bed rest of more than a week; Long haul air travel.	Warlow et al, 1976; Bors et al, 1954; Gibbs, 1957; Sevitt & Gallagher, 1961; Sigel et al, 1974; Milne, 1992.
<b>Previous Deep Vein Thrombosis</b>	Risk is increased two to three fold if DVT is confirmed by objective diagnostic methods.	Anderson et al, 1991; Nicolaidis & Irving, 1975.
<b>Surgery</b>	High risk in major abdominal operations (general, vascular, urological, gynaecological), major orthopaedic surgery, neurosurgery, and surgery for multiple injuries; Low risk in minor, brief and uncomplicated operations, such as transurethral or transvaginal operations, arthroscopy of knee.	Collins et al, 1988; Walsh et al, 1974; Sue-Ling et al, 1986; Olin et al, 1993; Walsh et al, 1974; Mebust et al, 1989; Stringer et al, 1989.

<b>Other trauma</b>	<p>Increased risk following fractures of lower leg; Increased in incidence in patients with fractured neck of femur (27-83 per cent);</p> <p>Increased incidence in burn patients.</p>	<p>Hjelmstedt &amp; Bergvail, 1968; Montrey et al, 1983; Morris &amp; Mitchell, 1976; Sevitt &amp; Gallagher, 1961; Sevitt &amp; Gallagher, 1961</p>
<b>Pregnancy</b>	<p>Increased risk in the post-partum period as compared with the normal risk during pregnancy.</p>	<p>Drill &amp; Calhoun, 1968; Kierkegaard, 1983</p>
<b>Cardiac Disease</b>	<p>Increased incidence following myocardial infarction of between 20 and 40 per cent reported. But not proven to be an independent risk factor since treatment of MI in these studies involved prolonged bed rest.</p>	<p>Maurer et al, 1971; Murray et al, 1970; Carter et al, 1987.</p>
<b>Malignant Disease</b>	<p>Whilst some studies have reported up to a three fold increase in DVT in patients with cancer others have found that when other risk factors such as age and immobilisation are taken into account the difference disappears.</p> <p>However, a recent European multicentre study support a probable causal association between cancer and venous thrombosis.</p>	<p>Kakkar et al, 1970; Rosenber et al, 1975; Walsh et al, 1974; Nicolaidis &amp; Irving, 1975</p> <p>Prandoni et al, 1992.</p>
<b>Hypercoagulable states due to genetic abnormalities of coagulation inhibitors</b>	<p>Increased risk in patients with antithrombin III deficiency;</p> <p>Increased risk in patients with Protein C deficiency, both inherited and acquired;</p> <p>Increased risk in patients with Protein S deficiency.</p> <p>Increased risk in patients who are carriers of Factor V (Leiden) mutation.</p>	<p>Thaler &amp; Lechner, 1981; Egeberg, 1965; Gitel et al, 1979; Griffin et al, 1981; Broze &amp; Miletich, 1994;</p> <p>Comp et al, 1984; Broze &amp; Miletich, 1994. Davie and Fujikawa, 1975.</p>

Box 2 continued

<b>Dysplasminogenemia</b>	Increased risk in patients with defective release of plasminogen activator.	Paramo et al, 1985; Scharrer & Hach, 1986; Taberero et al, 1989.
<b>Oral Contraceptives</b>	Evidence appears to suggest that there is an increased risk for users of oral contraceptives. In these older generation OC's the risk seems to be related to the level of oestrogen content. Recent research into the new OC's, in particular those containing gestodene and desogestrel, suggest that the risk of thrombosis is twice as high in current users of these OC's than users of other OC's.	Petitti et al, 1978; RCGP, 1978; Inman & Vessey, 1968; Vessey & Doll, 1968; Stolley et al, 1975. WHO, 1995; Jick et al, 1995; Bloemkamp et al, 1995.
<b>Obesity</b>	Unproven. Some studies have shown a higher risk; others have not been able to demonstrate that obesity is a significant factor.	Kakkar et al, 1970; Coon, 1976; Hills et al, 1972; Sigel et al, 1974.
<b>Varicose veins</b>	Studies have examined the relationship between varicose veins and thrombosis but do not provide convincing evidence that varicose veins are a positive risk factor for the development of post-operative venous thromboembolism.	Kakkar et al, 1970; Nicolaides & Irving, 1975; Sigel et al, 1974.
<b>Post-menopausal hormone replacement</b>	Unproven. Two small studies found an association but two larger case control studies were unable to confirm findings.	Gow & MacGillivray, 1971; Moore, 1976; Boston Collaborative Drug Surveillance Program, 1974
<b>Sex</b>	Taking other risk factors into account, there appears to be no sex difference.	Ogston, 1987; Nordstrum et al, 1992.
<b>Smoking</b>	No influence, may even be protective.	Doll & Peto, 1976; Handley & Teather, 1974; Marks & Emerson, 1974.



## **Age**

Advancing age has consistently been found to be associated with an increased incidence of venous thromboembolic disease. The Tecumseh, Malmo, and Worcester studies (Coon et al, 1973; Anderson et al, 1991; Nordstrum et al, 1992 (all showed a strong correlation between increasing age and venous thrombosis development. The effect was found to be most marked after the fifth decade.

One hospital based prospective autopsy study showed the incidence of pulmonary embolism to be relatively low in patients under the age of 40 years, but thereafter the incidence increased steadily (Morrell & Dunnill, 1968). In another autopsy survey among people who had died from burns and injuries, isolated venous thrombosis occurred in 47 per cent of patients under 45 years of age, 62 per cent among patients aged 46 to 75, and 74 per cent in those aged over 75 (Sevitt & Gallagher, 1961).

Two hospital based surveys of surgical patients in which leg scanning was used showed increasing age to be a major risk factor (Kakkar et al, 1970; Nicolaidis & Irving, 1975). In the second study, this increased risk was shown to persist even after adjustment for other concomitant risk factors such as type of surgery and previous thrombosis.

## **Sex**

After taking account of such risk factors as pregnancy, the puerperium and the use of oral contraceptives, it appears unlikely that a sex difference exists in the incidence of venous thrombosis.

## **Prolonged immobility**

Studies have shown that, in the absence of calf muscle contraction, prolonged venous stasis occurs in the soleal veins, the area in which thrombi are most commonly found. It is therefore not surprising that diseases or situations which paralyse or immobilise the lower limbs are associated with a high incidence of venous thrombosis.

Gibbs (1957) in an autopsy series of 253 patients found an association between bedrest and venous thrombosis, the incidence being only 15 per cent for those confined to bed for less than a week but more than 80 per cent for those confined for longer periods. Other studies have confirmed his findings (Sevitt & Gallagher, 1961; Sigel et al, 1974).

Situations such as air travel, which involve sitting still for long periods have also been anecdotally associated with deep vein thrombosis. There are plausible reasons why air travel might

predispose towards venous thromboembolism. Physical triggers to thrombosis include sitting in cramped conditions which directly compress the leg veins, dehydration caused by low humidity air in aircraft and drinking alcohol as well as possibly the low atmospheric pressure in passenger aircraft (Milne, 1992).

The reports of a link between air travel and venous thromboembolism are to date purely anecdotal and there has been no epidemiological study to assess the risks for particular modes of travel and for particular groups of people, which would require a controlled study. However, that there is an association would appear to be borne out by the experience in London during the blitz. In 1940, in a classic observational study, Simpson reported an association between sitting overnight on deck-chairs in air raid shelters and death from pulmonary embolism. In September/October 1939 he diagnosed at autopsy four cases of pulmonary embolism in the same month the following year he diagnosed 24 cases, 21 of which had occurred in, or soon after leaving air-raid shelters. He attributed these to 'obstruction, stasis, oedema and thrombosis' as a result of sitting for long periods and observed: 'It is noteworthy that cases of fatal pulmonary embolism are already decreasing again, concurrently with the provision of bunks for sleeping'.

### **Prior thromboembolism**

A clinical history of previous venous thromboembolic disease has been shown to be associated with an increased frequency of venous thrombosis (Carter et al, 1987) and one study has indicated that a history of venous thrombosis was an independent risk factor (Nicolaidis & Irving, 1975).

### **Surgery**

Interest in the aetiology of venous thromboembolism was stimulated primarily by clinical observations of the unexpected development of venous thrombosis or pulmonary embolism in both medical and surgical hospital patients. In a postmortem study of surgical patients dying in Malmö, Sweden, over the period 1951 to 1980, 49 per cent being postoperative patients, 1274 of the 5477 who died had demonstrable pulmonary emboli, and in 349 this was assessed to be the cause of death with a further 353 in whom it was considered to have contributed to death (Bergqvist & Lindblad, 1985).

Through the use of objective diagnostic criteria, such as autopsy examination, <sup>125</sup>I-fibrinogen leg scanning and venography, reliable



information has been gathered on the frequency of postoperative venous thrombosis and pulmonary embolism in general abdominal, urological, and orthopaedic surgery and following trauma to the lower limbs (Gallus et al, 1976). There have been very few studies in which an objective measurement has been made to exclude thrombosis prior to surgery, and the majority of studies assume that the thrombosis has developed in the intraoperative and postoperative periods.

A number of factors have been identified as influencing the risk of postoperative thrombosis, including the age of the patient, the length of the operation, the nature of the operation and the underlying disease (Ogston, 1987). Operations for malignant conditions are associated with a higher incidence of postoperative thromboembolism than similar operations for benign conditions (Walsh et al, 1974). Reported incidences of venous thrombosis after various operations in patients in whom specific preventative measures were not used are summarised in Table 1. The incidence of postoperative thrombosis may be overestimated since a number of researchers have found that a significant number of patients have demonstrable thrombi prior to operation (Rodzynek et al, 1983). Postoperative venous thrombosis have also been found to be frequent even when prophylactic measures have been used. Cade et al (1983) reported that of 49 patients undergoing thoracotomy for carcinoma of the lung or oesophagus and receiving low dose heparin and intraoperative calf stimulation 16 developed a venous thrombosis in the postoperative period (32 per cent).

Hip replacement is associated with a particularly high incidence of postoperative thromboembolic complication. Hampson et al (1974) using a combination of leg scanning, ultrasound and confirmatory venography in selected cases, found that 54 per cent of patients developed venous thrombosis within two weeks of elective hip surgery. Other studies have reported incidences of around 35 per cent (Hume et al, 1976; Harris et al, 1976). Hume et al (1976) reported the overall incidence of venous thrombosis to be ten times higher in the operated limb. In the study by Hampson et al (1974) in which calf and femoral vein thrombi were reported separately, it was observed that the femoral thrombi occurred almost exclusively in the operated limb, but calf vein thrombi were equally distributed. This suggests that the operative procedure or the trauma itself is a risk factor independent of more general risk factors such as bedrest.

The incidence of fatal pulmonary embolism after hip surgery, based on clinical diagnosis or postmortem assessment, has been reported to be between 0.3 per cent and 10 per cent (Salzman &

Table 1 Deep vein thrombosis following surgery or trauma<sup>1</sup>

Type of surgery	Incidence
General surgery	25%
Urology	
Transurethral	10%
Transvesical	35%
Gynaecology	
Vaginal hysterectomy	5%
Abdominal hysterectomy	10%
Malignancy	35%
Orthopaedic	
Hip fracture	>50%
Hip arthroplasty	>50%
Knee arthroplasty	>50%
Neurosurgery	
Craniotomy	25%
Trauma	
Hip fracture	>50%
Femur fracture	50%
Tibial fracture	50%
Acute spinal cord injury	>50%

Source: Adapted from Becker, 1986

Harris, 1976). It is important to note that the three highest reported incidences of 6.6 per cent (Zekert, 1975), 7 per cent (Eskeland et al, 1966) and 10 per cent (Sevitt & Gallagher, 1959) were all based on a series of at least 100 patients and had autopsy rates of between 83 and 100 per cent. This suggests that some of the other reported figures might be underestimates. Interestingly, among the deaths which were autopsied in less than 50 per cent was the cause attributed to the pulmonary embolism.

The length of the operation appears to be an important determinant of the risk of postoperative thromboembolism and, as shown by isotope scanning, thrombosis first develops during the operation in approximately half of the total number of affected patients undergoing elective surgery (Flanc et al, 1968).

In a study by Scurr (1990) it was found that the risk factors which occur immediately after major general surgery persist for several weeks. It was found that in the six weeks after discharge from hospital 13 of 51 patients, who had not developed a DVT during their hospital stay, did so. Diagnoses were made by Doppler ultrasound, <sup>125</sup>I-fibrinogen scanning, plethysmography and venography. In a study to assess the risk of DVT after hospital discharge in patients having undergone total hip replacement (Planes et al, 1996) it was found at 21 days that 17 out of 89 patients, who had not developed a DVT during their hospital stay had done so.

### **Other Trauma**

The risk of thromboembolism following a lower limb fracture has long been recognised (McCartney, 1934; Vance, 1934) particularly when compared to other situations such as the postoperative period or the puerperium. In a survey of the literature Shackford and Moser (1988) found reported incidences for venous thrombosis in patients with trauma of between 18 per cent and 90 per cent, average incidence 42 per cent. The incidence of pulmonary embolism was reported to be between four and 22 per cent, average incidence 10 per cent.

Thrombosis following fractured neck of femur has received particular attention and the incidence has been assessed using clinical examination alone, <sup>125</sup>I-fibrinogen scanning, venography and vein dissection at necropsy. Using the aforementioned techniques various studies have reported incidences of between 27 per cent and 83 per cent (Montrey et al, 1983; Culver et al, 1970; Morris & Mitchell, 1976; Sevitt & Gallagher, 1961).

Pulmonary embolism is a frequent cause of death following fractures of the hip. For example, Fitts et al (1964) found that pulmonary embolism was the cause of death in 61 of the 161 patients in whom necropsy was performed after hip fracture.

The incidence of thromboembolism after fractures of the lower bones of the leg is also considerable. Hjelmstedt and Bergvall (1968) examined 76 patients who had sustained a tibial fracture using venography and found an overall incidence of thrombosis of 45 per cent. Of the 36 patients with a thrombosis 12 had clinical signs of embolism.

Other forms of trauma such as burns are also associated with a high risk of thrombosis. In a necropsy study an incidence of venous thrombosis of 60 per cent was found in burned patients (Sevitt & Gallagher, 1961).



## **Pregnancy and the puerperium**

Historically, pregnancy and the puerperium have been regarded as high risk conditions for the development of venous thromboembolic disease. However, all of the reported major studies were conducted prior to the widespread use of oral contraceptives (see page 26) or the development of objective techniques for the diagnosis of venous thrombosis. Consequently, the results of these studies should be treated with caution.

Thrombotic risks in pregnancy can be usefully divided on clinical grounds into those of the antepartum and postpartum period. Antepartum risks reflect the physiological changes of pregnancy, such as changes in venous stasis in the lower limbs, whereas postpartum risks reflect tissue breakdown plus an additional traumatic or surgical component, such as prolonged labour, caesarian section or infection.

In an extensive summary of clinically diagnosed thrombosis in pregnancy Drill and Calhoun (1968) made comparisons between the rates of venous thrombosis in the antepartum period, post partum period and nonpregnant female population of childbearing age. The reported monthly incidence (as adjusted by Carter et al, 1987) per 1000 pregnancies in the antepartum period ranged from 0.08 to 0.15. These figures are similar to the 0.07 to 0.25 per 1000 nonpregnant women of childbearing age. In contrast, the reported monthly incidences of postpartum thrombosis per 1000 pregnancies ranged from 2.7 to 20. The postpartum period was consistently found to be a higher risk period than the antepartum period.

In a more recent study of the incidence of deep vein thrombosis among a group of 14,869 pregnant women, clinical diagnosis was confirmed by ascending venography (Kierkegaard, 1983). In this study the antepartum incidence was found to be 0.13 per 1000 and the postpartum incidence to be 0.61 per 1000. It appears likely that studies using clinical diagnosis alone have overestimated the incidence of deep vein thrombosis in pregnancy and the puerperium.

In summary, the antepartum period does not appear to be associated with excess risk of venous thrombosis, but the postpartum period does, and this results in a higher observed incidence of venous thrombosis for the whole pregnancy compared with age-matched, nonpregnant female population.

## **Cardiac disease**

A number of postmortem studies have identified that the incidence of venous thromboembolic disease is markedly increased in patients

with cardiac disease and, in particular, those with congestive heart failure. Anderson and Hull (1950) followed 150 patients with congestive heart failure; ten of the 20 patients who died were autopsied of whom five had macroscopic pulmonary emboli. In addition, among the survivors, two were clinically diagnosed with emboli. Since there is a tendency to underestimate or misdiagnose pulmonary embolus by clinical methods it is probable that the overall incidence of emboli was in excess of the 5 per cent recorded in the study.

Several studies have demonstrated an increased risk of venous thromboembolism, as assessed by clinical examination, following myocardial infarction. In a series of descriptive studies using leg-scan positivity to diagnose venous thrombosis in patients who had undergone a myocardial infarction an incidence of 20 to 40 per cent have been shown over a period of 10 to 14 days (Carter et al, 1987). Studies using the <sup>125</sup>I-fibrinogen technique have found similar results and are summarised in Box 2.

Among patients with acute myocardial infarction, the incidence of pulmonary embolisms not known, but post mortem examination have found emboli in approximately eight per cent of cases on average. This figure is similar to that of other postmortem surveys of hospital patients (Hume et al, 1970).

### **Malignant disease**

Several anecdotal type reports have suggested an association between clinical venous thrombosis and malignancy. In a postmortem study (Coon & Coller, 1959) found that pulmonary embolism was twice as common in those with cancer as in others. More recently, the presence of cancer has been associated with an increased rate of postoperative venous thrombosis, detected by leg-scanning, but the presence of other confounding factors such as age, extent of surgery, and preoperative and postoperative management make it difficult to assess the real role of malignancy in the aetiology of venous thrombosis. Kakkar et al (1970) reported a significant threefold increase in venous thrombosis among patients with malignancy. However, another study (Nicolaidis & Irving, 1975), while observing a trend towards increased venous thrombosis in association with malignancy, found that the difference disappeared when other risk factors were taken into account.

### **Biochemical abnormalities**

Abnormalities in some of the natural inhibitors of coagulation have been reported to be associated with an increased risk of thrombosis.

These are decreased antithrombin III activity, protein C deficiency, protein S deficiency, Factor V (Leiden) and dysplasminogenemia. These disorders are important since patients with these conditions who have a thromboembolic episode must receive lifelong anticoagulation therapy and must receive adequate prophylaxis when exposed to conditions known to predispose to thrombosis, such as pregnancy, surgery and trauma (Carter et al, 1987).

### **Obesity**

Much of the available evidence suggests that obesity represents a major risk factor for the development of venous thromboembolic disease. This evidence has been obtained from clinical studies, postmortem studies and studies using objective diagnostic techniques such as the <sup>125</sup>I-fibrinogen uptake technique in the postoperative situation.

In a postmortem survey, Coon (1976) noted that 21.9 per cent of those more than 20 per cent overweight had pulmonary emboli compared with 14.4 per cent in the non-obese subjects. The incidence of embolism, however, was not significantly greater in the group who were more than 30 per cent overweight. Using the <sup>125</sup>I-fibrinogen technique, Kakkar et al (1970) found the incidence of deep vein thrombosis following elective surgery to be 47.9 per cent in overweight patients compared with 27.2 per cent for those of average weight and 22.9 per cent for underweight patients. However, Hills et al (1972), using the same technique, were unable to demonstrate an effect of obesity on the development of postoperative deep vein thrombosis. In a prospective epidemiological study on 2877 patients undergoing elective surgery body build was not found to be a significant risk factor for postoperative deep vein thrombosis (Sigel et al, 1974).

The evidence to justify the inclusion of obesity as a direct risk factor in the causation of venous thrombosis is not conclusive (Ogston, 1987).

### **Use of oral contraceptives and other hormonal preparations**

In the 1960's a series of case reports of unusual venous thromboses in young women drew attention to the possibility of a causal relationship between oral contraception and thrombosis (FDA, 1968). Despite these early reports, due to the efficacy and utility of oral contraceptives, their use has increased. Since the overall frequency of thrombotic events is low, the initial comparative studies on venous thromboembolism and oral contraceptives were classic case-control studies.



An early British study (Inman & Vessey, 1968) used death certificate information in women of child-bearing age, mentioning thrombosis or pulmonary embolism as the source for their cases. These cases were classified as 'idiopathic' or 'non-idiopathic' based on the current ideas on causation of venous thrombosis. Family practitioners' records were used to determine the use of oral contraceptives by the cases. These same records were also used as the source of controls. Among the cases of 'idiopathic' thrombosis there were 26 deaths attributed to pulmonary embolism. Sixteen of these cases were taking oral contraceptives immediately prior to death. The expected exposure to oral contraceptives, based on the control group of similar age and parity, was 4.2. These figures mean that oral contraceptive users' are 8.3 times more likely than non-users to die of pulmonary embolism. This figure is statistically significant.

When the association between 'non-idiopathic' cases of fatal pulmonary embolism and oral contraceptives was examined, the relationship was less clear. Of 49 cases only nine were users of the pill, compared with an expected usage of 6.8. This odds ratio of 1.4 is not statistically significant.

A second British study (Vessey & Doll, 1968) was reported in the same year. For this study the source of the cases was the hospital admission codings for idiopathic pulmonary embolus or venous thrombosis. Unfortunately, objective diagnostic tests were not widely available in the 1960's and therefore most of the diagnoses were made on clinical grounds. In this study each of the 84 cases was matched with two hospital controls. Forty of the cases had been taking oral contraceptives compared with only 23 of the 168 controls, resulting in a highly significant odds ratio of 6.4. Other studies conducted in the late 1960's and early 1970's in the United States have confirmed the relationship between oral contraceptive use and idiopathic pulmonary embolism and venous thrombosis (Sartwell et al, 1969; Boston Collaborative Drug Surveillance Program, 1973).

In 1975, Stolley et al addressed the issue of oestrogen dosage. Of the 103 analysable cases of idiopathic thromboembolism there were 58 users of oral contraceptives. Thirty-five used medications containing less than 100g of ethinyloestradiol or its equivalent, 23 used medications with 100g or more. The respective relative risks for thromboembolic disease were 4.7 and 10.1. This information, together with that of an earlier British study (Inman, 1970), supports the concept that oestrogen dosage is an important determinant of thromboembolic risk.

The low overall incidence of venous thromboembolism amongst oral contraceptive users has tended to discourage the performance

of prospective cohort studies. However, despite this constraint two extensive cohort studies have been performed. The larger was The Royal College of General Practitioners' Oral Contraceptive Study (1978). Twenty-three thousand women taking oral contraceptives were prospectively followed for one year together with a similar cohort of non-users. There were 30 episodes of deep vein thrombosis among the contraceptive users compared to 9 among the non-users. This is a standardized relative risk of 4.2 and is statistically significant. Although this was a prospective study it was not blinded and the possibility of a diagnostic bias exists, particularly since clinical diagnoses were used in most instances (Carter, 1992).

The second study was the Walnut Creek Contraceptive Drug Study (Petitti et al, 1978). This study was started in 1969 and was designed to assess the long term effects of oral contraception on various health issues. A cohort of around 16,000 caucasian, middle-class women aged between 18 and 54 was recruited. Information concerning events was obtained by a variety of means including hospital records, death certificates and questionnaires. A monthly record of events and oral contraceptive exposure was kept. The relative risk for oral contraceptive users for venous thromboembolism was approximately 7.0 for current users with no effect observed in past users.

To summarise the above studies, the majority of the evidence suggests that oral contraceptives predispose towards venous thromboembolism and that thrombogenicity appears to correlate strongly with the oestrogen content. However, all the above studies preceded the introduction of medications containing less than 5ug of oestrogen and the 'third generation' preparations.

However, in 1995, publicity in newspapers and on television in the UK raised a question about the safety, in respect of unexpected fatal and nonfatal venous thromboembolic events, of 'third generation' oral contraceptives. The results of studies reported by the World Health Organisation (WHO, 1995), Jick et al (1995), and Bloemenkamp et al (1995) conclude that women taking a 'third generation' oral contraceptive, that is one containing as its progestogen component either desogestrel or gestodene, are at particularly high risk. Each of these studies was large and each came to the same conclusion: that there was approximately a two-fold difference in risk between current users of 'third generation' OC's and other OC's. The association persisted after adjustments for several risk factors for venous thromboembolism that might have influenced the choice of OC, for example; age, weight, smoking, parity and varicose veins.

The increased risk of venous thromboembolic disease attributable to use of a 'third generation' OC, beyond the risk of an earlier OC, seems to be about 10-15 per 100,000 women years of use. If the typical case-fatality was about 1 per cent, the increased rate of fatal venous thromboembolism would be 1-1.5 per million women years (Weiss, 1995).

Recent evidence therefore appears to suggest that there is an association between the use of oral contraceptives containing the progestogens desogestrel or gestodene and the development of venous thromboembolic disease. However, more needs to be known about other health issues in order that both doctors and women can make individually appropriate and informed choices on the basis of relative risk. Unfortunately, little is known about the risks and benefits of any serious health outcome other than venous thromboembolism. But it appears possible that 'third generation' OC's are associated with lower risk of myocardial infarction and diabetes mellitus than the older OC's.

In contrast, it has not been possible to identify a causal relationship between postmenopausal oestrogen replacement therapy (HRT) and venous thromboembolism. Whilst two small descriptive studies detailed an association (Gow & MacGillvray, 1971; Moore, 1976) a larger case control study did not confirm these findings (Boston Collaborative Drug Surveillance Program, 1974). It is not known whether the absence of a relationship is dose related but 0.625 mg of natural conjugated oestrogen may be the oestrogenic equivalent of only 5 mg of ethinyloestradiol.

## **Smoking**

The relationship between cigarette smoking and an increased mortality and morbidity from coronary artery disease is well documented. In contrast, smoking appears to have no influence, or in certain situations a protective effect, on the development of venous thrombosis. In the study by Doll and Peto (1976) of mortality in relation to smoking among British doctors, no association was found between mortality from venous thromboembolism and smoking.

A protective influence of cigarette smoking on venous thromboembolic disease has also been noted after myocardial infarction and surgery. In a study of the factors affecting the risk of deep vein thrombosis (as detected by <sup>125</sup>I-fibrinogen) after myocardial infarction, Handley and Teather (1974) found that the incidence of thrombosis in the patients who gave a history of regular cigarette smoking within the month before admission was



significantly lower than that of non-smokers. Other studies have confirmed this finding (Marks & Emerson, 1974;1977).

Prescott et al (1978) determined the incidence of deep vein thrombosis, again using the <sup>125</sup>I-fibrinogen technique, in a series of 300 newly admitted patients to medical wards and 201 patients scheduled to undergo abdominal surgery. Increasing levels of cigarette smoking were found to be associated with a reduced incidence of deep vein thrombosis, although statistical significance was not achieved.

### **Opportunities for behavioural change**

The evidence on causality is so limited and the risk factors so multifactorial and interdependent that any opportunities for encouraging behavioural changes are likely to have only minimal effect on the number of cases of DVT and PE.

## 5 Treatment of deep vein thrombosis and thromboembolism

The appropriate management of patients suspected of having a lower limb deep vein thrombosis (DVT) is a complex clinical issue. Patients with DVT should be treated to prevent pulmonary embolism, and those without DVT should be spared the morbidity, expense and inconvenience of anticoagulation therapy. Because the diagnosis of DVT by history of physical examination is imprecise an objective diagnostic test (see Box 1, page 12) should be used to evaluate patients suspected to have DVT.

Having established the presence of a deep vein thrombosis, there are four therapeutic approaches which can be used to prevent death by pulmonary embolism:

- anticoagulant therapy<sup>2</sup>
- thrombolytic therapy
- vena caval interruption
- surgical embolectomy

### Anticoagulant therapy

After more than fifty years of clinical use, anticoagulants are still the standard treatment for venous thrombosis. Early evidence that anticoagulants are of benefit to patients with PE come from a controlled trial carried out in 1960 by Barritt and Jordan. Since then, several randomised control trials have confirmed the effectiveness of anticoagulants in the treatment of thromboembolism. But direct evidence supporting the early use of heparin, an anticoagulant, was not available until 1992. In a study conducted in the Netherlands (Brandjes et al, 1992), patients with proximal vein thrombosis were randomly allocated to receive heparin and/or anticoagulants or saline placebo and an oral anticoagulant. The outcome measures used were: clinically detected recurrence of venous thrombosis in the following three months; extension of thrombosis detected at one week by a second venogram; and the development of a new high-probability lung scan defect by pulmonary scanning after one week. It was found that in the patients treated with heparin there was a 50 per cent reduction in the incidence of symptomatic and asymptomatic recurrence or extension. Other recent studies have indicated that when heparin is given in an adequate dose to patients with venous thrombosis, symptomatic pulmonary embolism occurs

2. Anticoagulants can also be used to prevent deep vein thrombosis (see page 39).

in only 5 per cent of patients and fatal PE in less than 0.5 per cent (Hull et al 1990; Pini et al 1990). Hull et al (1986), in a study of 115 patients with proximal vein thrombosis demonstrated that there is a high rate of recurrence where there is a failure to obtain an adequate anticoagulant effect.

Other prospectus studies have confirmed that the risk of clinically important recurrence is low if heparin is given in an adequate dose. In a study of 180 patients with venographically proven DVT who were treated with heparin by continuous infusion for at least five days and then with warfarin, symptomatic PE was reported in 5 per cent and fatal PE in one patient (0.3 per cent) (Holm et al, 1984).

Studies examining the length of time treatment must be continued suggest that the duration of initial heparin therapy can be shortened from the traditionally accepted 10 to 14 days in the USA to 5 days, which clearly offers a considerable financial benefit (Hull et al, 1990). In the UK, the traditional view is that heparin is given until the INR<sup>3</sup> has reached a therapeutic level and this is often for three days.

### **Low Molecular Weight Heparin (LMWH)**

The therapeutic use of heparin carries with it the risk of bleeding which ranges from 1 to 12 per cent (Hull et al, 1996). The theory is that the antithrombotic effect of heparin (ie. inhibition of thrombus formation) is a consequence of Factor Xa inhibition whereas its anticoagulant effect (viz prolongation of coagulation times) is due to inhibition of prothrombin activation. The theory is that, if Factor Xa could be selectively inhibited, it should be possible to reduce the risk of bleeding while at the same time maintaining antithrombotic activity. LMWHs were developed to explore this possibility.

Recent studies have indicated that LMWHs are both safe and effective for the treatment of thrombosis and that, in addition to the lower risk of bleeding, they have several other advantages over standard heparin. Most important are their more predictable dose response and their longer half-life – which means that LMWH can be administered by subcutaneous injection without laboratory monitoring. Initially, large pilot studies compared LMWH and standard heparin in the treatment of established thrombosis, looking at the size of the thrombus before therapy commenced and 5-10 days afterwards (Hirsh and Levine, 1992). However, other studies have looked at the more clinically relevant end point of confirmed



symptomatic recurrent thromboembolism (Prandoni et al, 1992; Hull et al, 1992).

In the study by Prandoni et al, 170 patients with confirmed DVT were randomised to either LMWH or standard heparin. The outcome measures were symptomatic recurrence at 10 days and six months. After ten days, four of the 85 (4.7 per cent) receiving standard heparin had developed a recurrence compared to one of the 85 (1.2 per cent) receiving LMWH. At six months, 11 of the 85 (12.9 per cent) receiving a standard heparin had developed recurrent thromboembolism compared with six of the 85 (7.1 per cent) patients receiving LMWH. However, while results of such studies indicate that for patients with proximal vein thrombosis the use of LMWH appears to be a promising approach, further studies involving more patients (and thus more statistical power) are needed before it can be definitely stated that there are differences of around 50 per cent.

### **Thrombolytic therapy**

Between 60 and 70 per cent of patients with symptomatic proximal vein thrombosis who are treated with heparin followed by oral anticoagulants have developed post-thrombotic syndrome at five years (Hirsh et al, 1994). This is not altogether surprising given that heparin though it prevents thromboembolism, does not produce substantial lysis (dissolution) of most proximal vein thrombi. In studies comparing thrombus size on venography before and after heparin treatment, in patients with symptomatic proximal vein thrombosis, complete lysis occurred in under 10 per cent and partial lysis in only 20-25 per cent (Elliot et al, 1979; Turpie et al, 1990). Whereas thrombolytic therapy produces complete or substantial thrombolysis at venography in up to 70 per cent of patients (Elliot et al, 1979; Turpie et al, 1990).

The major limitation of thrombolytic therapy is its increased potential for severe bleeding (Mercer et al, 1988). Because the haemorrhagic effects of thrombolytic agents can be life-threatening, the risks and benefits of thrombolytic therapy must be carefully considered when completing this therapy in patients with acute DVT (The UKEP Study Research Group, 1974).

### **Comparisons between various thrombolytic agents**

Four randomised studies have compared different thrombolytic regimens for the treatment of pulmonary embolism. The first and largest was the multicentre USPET trial (1974). One hundred and sixty seven patients were randomised to either receive Streptokinase (SK) or Urokinase (UK). Both groups of patients then received

heparin treatment. No differences in thrombolytic efficacy, bleeding or mortality was detected.

The UKEP (1987) trial was a multicentre European study that randomised 137 patients to either UK for 24 hours with simultaneous heparin or UK for 12 hours followed by 12 hours of heparin. Once again the thrombolytic efficacy, bleeding and mortality rate was similar with each of the regimens.

Verstraete et al (1988), in a multicentre study (34 patients), compared intrapulmonary t-PA with intravenous t-PA for the treatment of pulmonary embolism. There was found to be no difference between the two regimens in terms of the resolution of angiographic abnormalities or in the reduction of PAP (pulmonary artery pressure). There were two deaths and 5 major bleeding events in the trial but the authors did not indicate to which groups these were applicable.

In a multicentre study (Goldhaber et al, 1988), 45 patients were randomised to either receive t-PA or Urokinase. After 2 hours of therapy (completion of t-PA, eighth of course of UK) repeat pulmonary angiographic and haemodynamic evaluations were performed. The results showed that t-PA produced significantly greater resolution of angiographic abnormalities and reduction of the PAP compared to UK. However, when lung scans were conducted 24 hours after therapy began differences between the two groups were negligible.

It can be concluded that thrombolytic therapy leads to more rapid resolution of both radiographic (pulmonary angiography and perfusion lung scan) and haemodynamic (PAP) abnormalities caused by acute PE from heparin alone (Hirsh et al, 1994). However, these benefits are short-lived. After 5-7 days the degree of resolution of perfusion defects in patients who received thrombolytic therapy is similar to that accrued by patients treated with heparin alone (Hirsh et al, 1994).

On a cautionary note, the early haemodynamic and radiographic improvement in thrombolytic therapy groups were not associated with an observed reduction in mortality or improvement in symptoms. Bleeding complications were also more frequent and more serious in patients receiving this therapy although these events were often related to the use of invasive procedures (Goldhaber et al, 1988).

### **Surgical management of venous thromboembolism**

Although anticoagulation therapy is generally accepted to be the standard treatment for acute venous thrombosis and PE, surgery is occasionally indicated where either anticoagulation therapy has

proved to be ineffective or for those patients where it is considered unsafe.

### **Vena caval interruption**

Vena caval interruption by a filter device may be used to intercept emboli arising from venous thrombi in the leg or pelvic veins. This has to be large enough to ensure that the embolism cannot move on but small enough to ensure that the blood can continue to flow smoothly.

There is a small risk of mortality with this procedure but it largely appears to be associated with the cardiovascular instability of patients with PE, many of whom have an underlying cardiac disease. In a study of 119 patients undergoing vena caval ligation, Amador et al (1968) reported 16 deaths among the 85 who exhibited heart failure (19 per cent) compared to two deaths among the 34 patients without overt cardiac failure (6 per cent). Among 20 patients with severe heart failure, mortality related to surgery was 55 per cent.

### **Surgical embolectomy**

The theory behind venous thrombectomy as a procedure is that removing the thrombus should give the greatest chance of restoring normal venous valvular function and consequently the greatest prospect of avoiding post-phlebotic stasis complications. The procedure has not fulfilled expectations (Hirsh et al, 1994). Phlebographic studies have shown that rethrombosis occurs more often than not (Karp and Wylie, 1966). Nevertheless, venous thrombectomy can provide relief from acute symptoms and, when performed in conjunction with heparin therapy, a low rate of pulmonary embolism has been reported (Kistner and Sparkuhl, 1979).

Pulmonary embolectomy is an older surgical approach and was first successfully performed in 1924 by Kirscher (1924). In this procedure the pulmonary artery is opened and the embolus removed. Unfortunately, more patients died in such attempts than survived and the method was virtually abandoned until recently. Surgical access to extracorporeal cardiopulmonary bypass techniques has made the surgical management of massive PE a practical procedure, but the mortality remains high. A further major difficulty with this procedure is that time is needed to prepare a patient for surgery and in most instances death occurs too rapidly for embolectomy. It is usually agreed that if the patient survives while the surgical system is activated that they will survive in any case! Embolectomy is therefore not routinely advised.



## 6 Prevention of deep vein thrombosis and pulmonary embolism

Given the levels of morbidity and mortality caused by deep vein thrombosis and pulmonary embolism, described in an earlier chapter, particularly in the hospital population, consideration should be given to prevention. The most effective way to prevent the major consequences of venous thrombosis is through the use of effective prophylactic measures in high risk patients (Gallus et al, 1994).

This type of approach to prophylaxis is possible since the majority of cases of venous thromboembolism occur in hospital patients. It should therefore be feasible to identify patients at risk in order that preventive measures can be applied before, during or after thrombogenic episodes. As outlined in the chapter on risk factors, there are strong associations between venous thromboembolism and increasing age over 40 years, bed rest of more than four days duration, major surgery or trauma (especially hip fracture), malignancy, recent myocardial infarction, recent stroke, oral contraceptives and previous venous thromboembolism. The effects of these risk factors are shown in Table 2.

Risk factors may combine to increase the incidence of venous thromboembolism in various circumstances. For example, at one extreme, the risk of deep vein thrombosis in the course of daily activity may be so low that no specific preventive measures are necessary. A patient at low risk needs only minimal prophylactic

Table 2 Classification of disease or risk (based on published data)

Nature of thromboembolic event	Low risk*	Moderate/High risk#	Very high risk+
Calf vein thrombosis (%)	2	10-40	40-80
Proximal vein thrombosis (%)	0.4	2-8	10-20
Clinical pulmonary embolism (%)	0.2	1-8	5-10
Fatal pulmonary embolism (%)	0.002	0.1-0.4	1-5

Source: Gallus et al, 1994.

\* Uncomplicated surgery in patients under 40 years with no other risk factor.

# Surgery in patients over 40 years lasting more than 30 minutes, or myocardial infarction or heart failure. Risk is increased by obesity, age, malignancy, varicose veins, or prolonged bed rest.

+ Surgery in patients over 40 years, plus previous deep vein thrombosis or pulmonary embolism or extensive malignant disease or major orthopaedic surgery or stroke.

measures, such as early ambulation after surgery and the use of elastic stockings, increasing the flow of blood from the ankle to the knee. However, at the other extreme, for a patient older than 40 years of age, undergoing an operation lasting more than half an hour, who has had congestive heart failure, who has been taking oral contraceptives, or who has had multiple traumatic injuries the risk is likely to be very high. Unless prophylactic measures are used, the incidence of deep vein thrombosis could exceed 60 per cent (Kudsk et al, 1989).

There is a range of prophylactic measures currently in use. They prevent thrombosis occurring during and soon after surgery (eg. low-dose heparin), prevent the extension of small thrombi to clinical significance (eg. post-operative warfarin or post-operative low molecular weight heparin), or aim to achieve both (eg. two-step warfarin or adjusted dose heparin therapy). They act by interfering with blood coagulation (heparin, warfarin), fibrin stability (dextrans), and by accelerating venous return (eg. graded-pressure elastic stockings and external pneumatic compression of the lower limb). Each of these prophylactic measures will be examined briefly in turn.

## **Prophylactic methods**

### **Preventing venous stasis**

In the past, it was believed that the slowing of the blood flow in the leg veins was the chief cause of deep vein thrombosis. Consequently, the oldest prophylactic approach was early mobilization and ambulation after surgery. These were later supplemented by the use of elastic stockings to minimize venous stasis at rest, massage of the lower limbs, perioperative electric stimulation to induce intermittent calf muscle contractions during anaesthesia, and external leg compression devices (intermittent pneumatic compression – IPC) that cause the blood flow to speed up and pulsate. These methods seem to have some beneficial, if modest, effects by reducing the incidence of deep vein thrombosis (Sharnoff, 1980), although they have not been proven to reduce mortality from PE (SIGN, 1995). Interest in the general approach of preventing venous stasis has been ensured by its safety and by improved understanding of haemodynamics in recent years.

### **Anticoagulants**

#### *Heparin*

Prophylactic heparin came into widespread use after it was found that 'low-dose' or 'mini-dose' heparin was effective. This method

has now become the standard by which the effectiveness of all other prophylactic methods are measured. It is believed to work because heparin concentrations too small to block the extension of preformed thrombi can still prevent the activation of clotting factors from leading to thrombin generation and thrombus formation (Gallus et al, 1994).

The most direct evidence that low dose heparin prevents pulmonary embolism in general surgical patients comes from a large multicentre study of over 4000 patients, which found a significant reduction in two findings at post-mortem examination: pulmonary embolism of any size, and 'fatal' embolism (that is major pulmonary embolism thought to have been the cause of death) (Kakkar et al, 1975). These findings were confirmed by Sagar et al (1975) in a smaller single-centre trial of 500 patients. It would therefore seem reasonable to conclude that low dose heparin does prevent fatal embolism after general surgery.

Meta-analyses have confirmed the results of these studies. In one meta-analysis (Claggett and Reisch, 1988) the results of 24 randomized clinical trials enrolling nearly 9500 elective abdominal, urological or gynaecological patients were analysed. It was found that heparin reduced the incidence of fatal pulmonary embolism from 0.7 per cent in controls to 0.2 per cent. A larger meta-analysis of 74 trials and 14,000 patients, including studies in orthopaedic surgery (Collins et al, 1988), found fatal pulmonary embolism in 0.8 per cent of controls compared with 0.26 per cent in treated patients.

Although it is very safe, low-dose heparin prophylaxis does lead to an increase in clinically minor but still excessive surgical bleeding which has led many anaesthesiologists to avoid the use of spinal and epidural analgesia in treated patients. There is also a potential risk of heparin induced thrombocytopenia (HIT), an immune mediated drug related reduction in platelet count associated with thrombosis rather than bleeding. HIT occurs in up to 5 per cent of patients given therapeutic heparin but it is rare during heparin prophylaxis.

#### *Low-Molecular Weight Heparins (LMWH)*

Considerable interest has recently focused on the evidence that LMWHs may have a therapeutic advantage over standard low-dose heparin (Hirsh, 1986; Salzman, 1986). Some research also claims that LMWHs may cause less bleeding than standard heparins for an equivalent antithrombotic effect (Levine et al, 1991; Kakkar et al, 1993) but there is doubt about this.

Not all reports on LMWHs have been entirely favourable, however. In elective surgery of the hip and knee, a once-daily dose



of LMWH was more effective than less intense warfarin prophylaxis, with an incidence of deep vein thrombosis of 31 per cent versus 37 per cent ( $P=0.03$ ). It was associated with a higher incidence of serious bleeding complication (2.8 per cent versus 1.2 per cent ( $P=0.04$ )) (Hull et al, 1993). In addition, an unexpectedly high rate of deep vein thrombosis (24 per cent, proved by phlebography) followed abdominal surgery, despite daily doses of LMWH at recommended levels (Bounameaux et al, 1993). The explanation for these events is unknown.

Overall, the results suggest a small therapeutic advantage for LMWHs (Prandoni et al, 1993; Bratt et al, 1990; European Collaborative Group, 1991). The long biologic half life and predictable plasma concentrations of low molecular weight heparin allows it to be administered once or twice daily in a fixed dose without the need for laboratory tests which would not only lead to easier patient management but could also result in considerable cost savings (see chapter 7).

#### *Oral vitamin K antagonists*

Oral anticoagulants decreased in popularity as preventive agents after their widespread use in the 1950s and 1960s because most surgeons were unwilling to accept the additional bleeding risk and the inconvenience of frequent monitoring for both patients and hospital staff (Aggeler & Kosmin, 1969). However, when less hazardous methods are relatively ineffective, as in orthopaedics, and in general surgical patients with a very high thrombosis risk, they remain valuable. Among these drugs only warfarin is available as a water soluble salt that can be given parenterally, a consideration in postoperative patients.

Prophylactic oral anticoagulants are probably most effective when given for several days prior to surgery to accommodate their delayed onset of action. In practice, however, they are usually started on the evening prior to or just after surgery. The compromise of beginning with a modest warfarin dose followed by more intense therapy once the risk of bleeding has waned appears to reduce the risk of bleeding without sacrificing much of the prophylactic effect (Gallus et al, 1994; Francis et al, 1983).

#### *Dextran and Aspirin*

Dextrans are branched chain polysaccharides of bacterial origin which by various mechanisms improve blood flow. In clinical trials they have been found to reduce the incidence of deep vein thrombosis (Bonnar & Walsh, 1972). In a study by Clagett and Reisch

(1988) it was found that dextrans' ability to protect against pulmonary emboli appears to be approximately the same as low dose heparin. This study also found that bleeding complications were dose-related and were uncommon at dosages customarily given to prevent deep vein thrombosis.

However, other studies have shown that dextran may impair platelet aggregation and adhesiveness, an important cause of intravascular thrombosis (Browse et al, 1977; Gruber et al, 1977). Allergic reactions, including anaphylaxis, adverse reactions such as the overloading of the circulation, the necessity of repeated venous injections and high cost, have limited the use of dextrans as a method of prophylaxis.

Whereas aspirin is effective in the prevention and treatment of arterial disorders, it remains open to debate as to whether or not it also prevents venous thromboembolism. Aspirin has been studied extensively as prophylaxis against deep vein thrombosis and its use for this purpose has caused considerable controversy (Clagett et al, 1992; Patrona, 1994). In a recent large meta-analysis (Anti-platelets Trialists Collaboration, 1994), prophylactic aspirin reduced both proximal and distal deep vein thrombosis by 30 to 40 per cent and pulmonary embolism by 60 per cent in patients undergoing general surgical, orthopaedic and medical procedures. On balance though, aspirin appears to provide less protection than can be safely achieved with more modern regimens of anticoagulants.

### *Danaparoid sodium*

Danaparoid is a new antithrombotic agent currently undergoing clinical trials in the Netherlands for the prophylaxis of DVT after general and orthopaedic surgery. It is a mixture of low molecular weight glycosaminoglycans, comprising mainly heparin sulphate, some dermatan sulphate and a small amount of chondroitin sulphate. It is chemically distinct from heparin and low molecular weight heparins. Pharmacological studies have shown that danaparoid inhibits the formation of thrombi, is more effective than heparin and LMWH in preventing extension of established thrombi, has less bleeding enhancing effects than heparin and does not effect normal platelet function. The experimental data suggest that it has a better antithrombotic and fewer haemorrhagic side effects than heparin (Nicolaidis and Ramaswami, 1993). In a study of danaparoid versus a placebo, danaparoid produced a 74 per cent reduction in the incidence of DVT (Hoek et al, 1992).

## Indications for prophylaxis

Prophylaxis is used when the risk of thrombosis is considered to be greater than the risks, inconvenience and cost of preventive therapy. Consequently, because prediction of who is at risk is imperfect, many more individuals are treated than the number that could be expected to develop venous thromboembolism. Preventive treatments must be free from serious side effects that might dilute their overall expected benefit, and medicines such as heparin and warfarin that may cause excessive bleeding should not be used when they could induce major morbidity (such as after neurosurgery) or in the presence of underlying bleeding disorders.

Since the value of prophylactic methods varies in different patient populations it is important to select the form of prophylaxis most appropriate for each clinical setting (see Table 3). This table summarises the current state of knowledge gathered from published

Table 3 Graded recommendations for effectiveness based on levels of evidence

Category	Recommended preventive method				
	Low dose heparin	LMW heparin	Warfarin	Dextran 70	IPC+ / GECS#
Hip fracture or lower limb fracture		A	A	A	
Spinal cord injury	B*	C			C
Other major trauma	C	C	C		C
Intracranial neurosurgery					A
Hip replacement	A*	A	A	A	A
Knee replacement		A	A		A
Other major surgery	A	A	A	A	A
Myocardial infarction	A		A		C
Stroke	A~				C
Other medical illness	C		C		C
Puerperium	C	C	C		C

Source: Scottish Intercollegiate Guidelines Network, 1995.

+ IPC = Intermittent pneumatic compression.

# GECS = graduated elastic compression stockings.

\* adjusted dose.

~ selected high risk cases.

### Notes

A = at least one RCT as part of literature

B = availability of well-conducted clinical trials but no RCT

C = evidence obtained from expert committee reports or opinions



rules of evidence, consensus statements and meta-analyses or pooled analyses. For each option the grade of recommendation (A, B or C), based on the definitions of level of evidence used by the US Agency for Health Care Policy, is indicated.

The graded recommendations (A, B and C) given in Table 3 relate to the the levels of evidence available. Grade A requires at least one randomised controlled trial as part of the body of literature of overall good quality and consistency addressing the specific recommendations. Grade B requires the availability of well-conducted clinical studies but no randomised clinical trials on the topic of recommendation. Grade C requires evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities. Where no grading has been given this indicates the absence of directly applicable clinical studies of good quality. It should be recognised that clinical trials are still being carried out in this area, particularly with low molecular weight heparins, and that over time it is possible that the recommendations given in Table 3 will change.

Prophylaxis should cover the entire period of risk. After general surgery this means continuing until the patient is mobile rather than for any predetermined time. In hip surgery, where the onset of venous thrombosis may be delayed for some weeks, there is a good case for persisting with preventive therapy after discharge from hospital if the patient is not yet fully mobile at the time of discharge (Gallus et al, 1994).

## 7 Economic evaluations of thrombolytic prophylaxis and treatment

Knowledge of thromboembolic complications has increased substantially in recent years, both in regard to prevention and identification of risk factors (see chapters 4 and 6). It is now generally recognised that the patient's age and the type of surgery involved are the two most important risk factors. There are several pharmacological and non-pharmacological methods of reducing the incidence of deep vein thrombosis and pulmonary embolism and these are outlined in an earlier chapter. However, because deaths due to PE are relatively rare following general surgery, many question the need for general prophylaxis. Other concerns have been expressed about the value of thrombosis prophylaxis with regard to associated complications such as haemorrhage and allergic reactions. Screening of operated patients to detect thrombosis has been suggested as an alternative to general thromboembolic prophylaxis. This would mean that only those patients developing thromboembolism (assuming no false positives or false negatives) would be treated. Thus the demand for prophylaxis and consequently the complications would be reduced. Although it should be remembered that there would be some complications from treatment. Perhaps as important, there has been a reluctance to apply interventions whose cost-effectiveness has not been adequately evaluated. In recent years economic evaluations have been conducted and a discussion of the results of some of these studies follows.

In a study by Bergqvist et al (1988) the clinical and economic effects of three alternatives, no prophylaxis, general prophylaxis (low dose heparin) and selective treatment, were assessed in conjunction with three types of surgery: general surgery; a subset of that group, surgery for cholecystectomy; and elective hip replacement. Their analysis was based on a 'synthesis' of approximately 100 international studies and covering 1000 patients in each of the three surgical treatments considered.

Costs were based on figures available for general surgery patients at Malmo General Hospital, Sweden: 28 patients hospitalised with thrombosis, pulmonary embolism and/or haemorrhagic complications.

In the general surgery group it was found that in the no prophylaxis alternative, the frequency of thromboembolism was 115 in 1000 patients, composed of 70 distal thromboses, 30 proximal vein thromboses and 15 pulmonary embolisms (10 fatal). Thirteen

patients developed haemorrhagic complications due to heparin therapy for confirmed thrombosis or PE (0.11 x 115) (see Table 4).

In the general prophylaxis alternative, the authors found that the frequency of thromboembolism fell by 70 per cent, leaving 35 affected patients accounting for 20 distal thromboses, 10 proximal thromboses and 5 PEs (three fatal). The use of general prophylaxis was accompanied by an increase in the frequency of haemorrhagic complications; in addition to the four cases of complications due to heparin treatment for confirmed diagnosis of thrombosis or PE (0.11 x 35), there were 87 (0.09 x 965) due to prophylaxis in the 965 unaffected patients. Complications with general prophylaxis would therefore have been seen in 91 patients.

In the third alternative, using the <sup>125</sup>I-fibrinogen test (see Box 1) for selective treatment, 290 patients were affected, accounting for 188 distal thromboses, 92 proximal thromboses and 10 PEs, plus 32 cases of haemorrhagic complications. By using phlebography to verify the presence of thrombosis according to the fibrinogen test in the 290 affected patients, the number of true positives was reduced to 196, accounting for 94 distal thromboses, 92 proximal thromboses and 10 PEs, plus 22 cases of haemorrhagic complications.

In the general surgery group the lowest frequency of thromboembolism was achieved with general prophylaxis, the lowest frequency of complications with no prophylaxis and the lowest mortality with general prophylaxis.

The expected clinical outcomes were similarly calculated for the other two types of surgery, cholecystectomy and elective hip surgery and the overall findings were the same: general prophylaxis

Table 4 Basic data for three different categories of surgery

Variable	General abdominal surgery	Cholecystectomy	Elective hip surgery
<b>Frequency of thromboembolism</b>			
Clinically detected	0.115	0.050	0.232
Fibrinogen diagnosis	0.290	0.100	0.590
Phlebographic diagnosis	0.196	0.068	0.400
<b>Frequency of haemorrhagic complications</b>			
Prophylaxis	0.09	0.09	0.09
Therapy	0.11	0.11	0.11
Prophylactic effect	0.7	0.5	0.7



**Table 5 Expected costs per patient for three alternatives in three different categories of surgery**

	General abdominal surgery		Cholecystectomy		Elective hip surgery	
	SEK	£	SEK	£	SEK	£
No prophylaxis	2259	213.11	989	93.30	4402	415.28
General prophylaxis	<b>1793</b>	<b>169.15</b>	1604	151.32	<b>2392</b>	<b>225.66</b>
Selective treatment following						
Fibrinogen test	6790	640.57	3173	299.34	12531	1182.17
Fibrinogen test and phlebography	5987	564.81	2887	272.35	10847	1023.30
Costs for the general prophylaxis and selective treatment alternatives include those both for the prophylaxis itself and the test (costs per patient are expressed in 1990 prices). Based on an exchange rate of 10.6 SEK to £1.00.						

Source: Bergqvist, 1994.

minimized the frequency of thromboembolism and fatal pulmonary embolism but the lowest frequency of complications was obtained with no prophylaxis. The authors concluded that the higher the initial frequency of thromboembolism the more clinically effective the alternative of general prophylaxis.

Basic cost estimates from the 28 general surgical patients hospitalised with thrombosis, PE or haemorrhagic complications were used together with the information presented in Table 4 to form the basis for calculating the expected costs for each of the three alternatives for each type of surgery (see Table 5). The authors found, in both elective hip surgery and general abdominal surgery, that the most cost-effective alternative was general prophylaxis, followed by no prophylaxis and then selective treatment. In cholecystectomy, no prophylaxis was the most cost effective, followed by general prophylaxis.

Throughout this study low dose heparin was used for prophylaxis. Other prophylactic agents, such as dextran and low molecular weight heparins (LMWH) have been shown to incur fewer haemorrhagic complications and improved prophylactic effect in elective hip surgery (see chapter 6). The findings of Bergqvist et al's analysis have been confirmed by the preliminary results of an economic evaluation of low dose heparin, LMWH in low doses and dextran in general surgery and elective hip surgery (Lindgren, 1989).

Bergqvist et al, suggest that the costs of prophylaxis might be further reduced if LMWH was used since it has been found to be less complicated to administer. Further evidence has also pointed to higher efficacy rates for LMWH as compared to standard unfractionated heparin (see page 39). Consequently, in the study discussed above, the choice of low dose heparin means that the relative cost-effectiveness of general prophylaxis was not overestimated.

A study from McMaster University (Anderson et al, 1993) appears to confirm the suggestion that costs of prophylaxis might be reduced by using LMWH. In a systematic review, six randomised controlled trials which compared LMWH directly with standard heparins in total hip replacement were identified. The six studies involved over 1,400 patients all more than 40 years of age. The principal outcome measure was total incidence of DVT, subdivided into proximal and distal vein events. The principal safety outcome was haemorrhage, major and minor, as determined by the studies.

The only statistically significant differences in outcome found between the two therapies were for total DVT and proximal DVT. There were no differences for distal DVT or for haemorrhagic events. Low molecular weight heparin resulted in a reduction of total DVT from 149 of 685 patients (22 per cent) to 117 of 735 patients (16 per cent) and of proximal DVT from 86 of 685 patients (13 per cent) to 40 of 735 patients (five per cent).

The authors found that the development of a proximal vein thrombosis increased the length of hospital stay by five days. A cost analysis demonstrated that this would add approximately US \$1,400 to the cost per case. The relative cost of LMWH to standard heparin was found to be an important factor in the cost analysis. If the relative cost of LMWH was less than 3.7 times that of the standard heparin, the cost analysis favoured LMWH. However, based on the cost of managing 1,000 patients, the authors found that when the ratio was between 2.6 and 5.0, the balance of costs was only about US \$50,000, that is \$50 per patient. Only when the cost of LMWH was 10 times that of standard heparin was there a significant balance of cost in favour of standard heparin. In the UK, LMWH costs around ten times more than standard heparin (BNF, 1995).

In a retrospective analysis of controlled clinical trials (Bergqvist 1988, 1983; Bergqvist et al, 1991; Lindblad, 1988; Wille-Jorgensen, 1991; Gerhart et al, 1991; Roise et al, 1993; Jorgensen et al, 1989; Monreal et al, 1989), examining the total cost of prevention and treatment for venous thromboembolism in patients undergoing hip fracture surgery, the cost-effectiveness in terms of lives saved of five prophylactic regimens, oral anticoagulants, dextran, low dose

**Table 6 Estimated total costs and savings compared with no prophylaxis for various prophylactic regimens for 100 patients undergoing hip fracture surgery**

Intervention	Total costs		Cost savings <sup>1</sup>		Potential number <sup>2</sup>	Cost effectiveness ratio (per life saved)	
	NLG	£ <sup>3</sup>	NLG	£		NLG	£
No prophylaxis	133,177	47,905					
Dextran	78,959	28,402	54,218	19,502	2.6	30,369	10,924
Heparin	74,399	26,762	58,778	21,143	2.7	27,533	9,903
Oral anticoagulants	62,775	22,581	70,402	25,324	3.2	19,617	7,056
LMWH							
list price	61,269	22,039	71,908	25,866	3.5	17,505	6,296
discounted price	55,689	20,032	77,508	27,880	3.5	15,905	5,721
Danaparoid sodium	38,214	13,746	94,963	34,159	4.8	7,961	2,864

Source: Mol & Egberts, 1994.

Notes: 1 Compared with no prophylaxis

2 Based on the difference in fatal embolism in patients who were not receiving prophylaxis versus those who were

3 Based on an exchange rate of 2.78 NLG to £1.00 Sterling

heparin, LMWH and danaparoid sodium was calculated and compared with clinical diagnosis and conventional treatment of DVT only (Mol & Egberts, 1994). The results of this study show (see Table 6) that the total cost, including the savings in treatment of the complications of DVT, of each prophylactic regimen was less than the total cost of no prophylaxis. The total cost of the new antithrombotic, danaparoid sodium (see chapter 6) is less than that of the other forms of prophylaxis considered and in this study appears to be the most cost-effective modality. The authors concluded that not only would prophylaxis save lives but might also lead to lower costs of care.

In a study comparing the cost of using a LMWH (tinzaparin) to that of using intravenous conventional unfractionated heparin in the treatment of DVT, data collected from a large clinical trial were used to construct a simple decision tree (Valette, Hoffmeyer & Lloyd, 1995). This was used to represent the choice between the two treatments and the clinical consequences (full, recovery, recurrence of thromboembolism and bleeding) which are likely to ensue. UK cost data was entered into this model to determine the expected cost per patient for both treatments.

The expected cost per patient including initial treatment costs and the cost of managing adverse events was found to be £197.50 for



conventional unfractionated heparin and £144.71 for LMWH at 1994 prices. When adverse events which were not directly attributable to the heparin therapies were excluded, expected costs per patient for the LMWH fell to £132.91 and the unfractionated heparin to £197.07. The conclusion that can be drawn from this study is that LMWHs reduce the cost of treatment.

The authors found that there were two key economic advantages of LMWH over the standard heparin: greater ease of administration, since it removes the need for extensive laboratory monitoring and infusion equipment and saves staff time; and, reduced incidence of adverse outcomes. It was found that these results were robust to variations in key factors such as frequency of laboratory monitoring, length of treatment and dosage used.

To summarise, the studies discussed in this section clearly show that general prophylaxis for patients undergoing most forms of surgery is cost effective. Other published studies support the finding that general prophylaxis is more cost-effective than no prophylaxis (Salzman & Davies, 1980; Hull et al, 1982). General prophylaxis in most of these studies has meant prophylaxis to all patients above a critical certain age, usually 40 to 45 years, a more targeted approach might make general prophylaxis even more cost-effective. Furthermore, the cost effectiveness of LMWH, compared to other forms of prophylaxis, appears to be sensitive to price and costing assumptions. However, all the studies show that there are monetary savings to be made through general prophylaxis, to this effect must be added the reduction in frequency of fatal pulmonary embolism. Although the frequency of post-thrombotic syndrome is probably low, the inclusion of costs related to this disease would make general prophylaxis a still more cost-effective alternative (Bergqvist, 1994).

## 8 Cost to the NHS of deep vein thrombosis

It is difficult to obtain precise UK figures for the total number of people developing a deep vein thrombosis and/or a pulmonary embolism in any given year. Whilst figures are available for the number of patients consulting their GP (see Table 7) and also for those admitted to hospital (see Table 8) there are very limited data available about the number of patients admitted to hospital for surgery who subsequently develop a deep vein thrombosis.

It is estimated that in 1993 there were 0.21 million GP consultations for DVT and 0.056 million consultations for pulmonary embolism in England and Wales. With an average GP consultation being £11.90 this gives a cost to the NHS of £2.5 million and £666,000 respectively. Figures for the number of prescriptions written by GPs are not available but if it were assumed that for each consultation for DVT one prescription was written, with an average net ingredient cost of £7.45 for this therapeutic group this would give a cost of £1.6 million (prescriptions for pulmonary embolism have not been estimated since it is almost certain that cases would be

Table 7 Costs of thromboembolic disease in general practice (1993)

Diagnosis	Cost of consultation	Cost of Rx	Cost to NHS (£ million)
Deep vein thrombosis	2.5	1.6	4.1
Pulmonary embolism	0.6	–	0.6
Total	3.1	1.6	4.7

Source: RCGP Morbidity Data, 1993; OHE Compendium, 1995.

Table 8 In-patient cases by main diagnosis – ordinary admissions and day cases combined, 1993 Hospital Episode Statistics

Diagnosis	All	Age					
		0-14	15-44	45-64	65-74	75-84	85+
Pulmonary embolism	16,698	8	2,463	4,597	4,240	4,066	1,303
DVT	25,490	74	4,260	7,893	6,553	5,077	1,600

Source: OPCS, 1993.

immediately referred to hospital and would therefore be minimal). Thus the total cost of thromboembolic disease in general practice in 1993 is estimated to be £4.7 million.

Table 8 shows that there are nearly 17,000 admissions for pulmonary embolism and over 25,000 for deep vein thrombosis. Most cases of DVT and pulmonary embolism are admitted under the specialty of general medicine (CHKS, 1993-94) and the mean duration of stay for this specialty is 7.2 days. For 1993, the average cost of an acute bed day in this specialty was £162.00 (OHE Compendium, 1995). This gives an overall cost of £4.1 million for DVT and £2.7 million for pulmonary embolism (see Table 9).

However, these are only a fraction of the total costs to the NHS of thromboembolic disease since most cases develop in patients who have been admitted to hospital for other conditions or surgery. Using the incidence figures given for DVT in association with different types of surgery (see Table 1, page 22) and the number of these operations carried out in England in 1993/94 as given in the Hospital Episode Statistics, an attempt has been made to calculate the number of people at risk of developing a DVT.

In 1993/94 a total of 5.2 million operations were carried out in England. Incidence figures for DVT are available for 1.5 million (29 per cent) of these operations. Since DVT principally affects those over the age of 40, only those operations occurring in these age groups were included in the analysis. Due to the way in which the Hospital Episode Statistics composes its age bands only those operations performed on patients aged over 45 years of age are actually included in the analysis. Thus the total number of patients having an operation included in the analysis is 1,115,757 (21 per cent of all operations undertaken in England). Of these patients we estimate, based on the incidence figures given that approximately 27 per cent can be expected to develop a DVT if they do not receive prophylactic treatment (see page 22).

Table 9 Costs of hospital admissions for thromboembolic disease, 1993

Diagnosis	Number of admissions	Cost of admissions (£ million)
Pulmonary embolism	16,698	2.7
DVT	25,490	4.1



Figure 2 shows an assumption whereby no patients in England over the age of 45 undergoing one of the surgical treatments included in the analysis received prophylaxis. The cost of treating those patients who develop a DVT would, it is calculated, be in the region of £256-264 million. The treatment costs are composed of an additional five days<sup>4</sup> in hospital, that is on top of the days in hospital they would have had for the operation, (Mol & Egberts, 1994) plus seven days of medication (standard heparin or LMW heparin<sup>5</sup>).

The opposite assumption is shown in the flow diagram given in Figure 3, that is that all patients at risk (1,115,757 patients aged over 45 having one of the selected operations) receive prophylaxis at a cost of between £6.7 million (standard heparin) and £33 million (LMW heparin<sup>6</sup>). At their least recorded efficiency, both standard heparin and LMW heparin have been shown to reduce the risk of the development of DVT by 50 per cent (Brandjes et al, 1992), although it has been reported to be as high as 72 per cent for low dose heparin and 79 per cent for LMWH (Bergqvist, 1994). Consequently, the assumption for the purposes of this analysis that 14 per cent (ie. 50 per cent of 27 per cent) of patients receiving prophylaxis will still develop a DVT is likely to be higher than what might be expected. It is estimated that the cost of treating this group will be in the region of £133-137 million, due to an additional five days in hospital and medication costs. The costs of treatment and the cost of prophylaxis added together gives a total expected cost for giving everyone at risk prophylactic therapy of between £140-170 million. A saving of around £100 million over no prophylaxis in addition to over 700 fewer deaths due to pulmonary embolism.

The percentage of patients at risk of DVT actually receiving prophylaxis in English hospitals is going to be somewhere between these two extremes. Limited data collection means that it is not known precisely how many patients undergoing surgery receive prophylaxis. However, using *The Report of the National Confidential*

4 These additional 5 days in hospital are calculated on the basis of an average cost per patient per acute hospital in-patient day, this being approximately £170 in 1992 (OHE, 1995).

5 Standard Heparin and LMWH have been used for the purpose of these calculations as these are considered to be the 'gold-standard' in preventative treatment. Warfarin is considerably cheaper than either of the alternatives used but unlike the heparins which can be literally given hours before surgery, warfarin therapy must be started up to four or five days prior to surgery which obviously has implications for administration.

6 Although the actual cost of LMWH heparin is higher than standard heparin the costs of administration and monitoring are considerably lower and the number of adverse events are fewer. However, due to difficulties in getting information about these costs an allowance has not been made for these differences in the calculations.

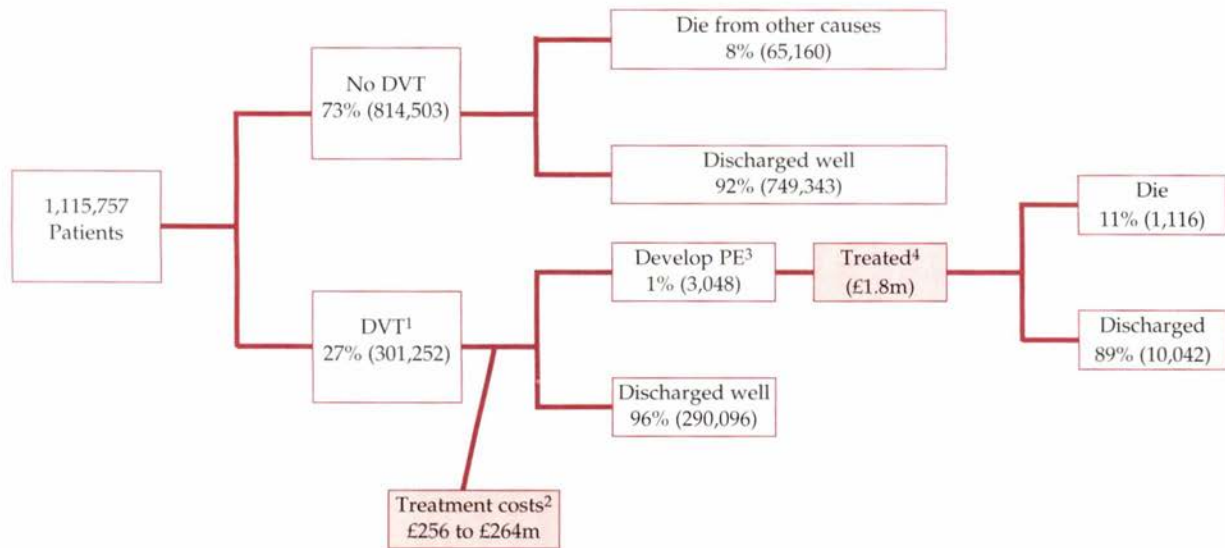


Figure 2 No prophylaxis

**Notes**

1 Incidence figures taken from Table 1 (page 22) (Becker, 1986)

2 Treatment costs are based on an additional five days in hospital (Anderson et al, 1993) plus medication costs (OHE, 1995). With an average cost per day in an acute hospital bed being approximately £170 the treatment costs are highly sensitive to the number of days spent in hospital. The treatment costs if four days in hospital were used instead of five would be approximately £205 to £213 million or approximately £307 to £315 million if six days were required

3 Figures for fatal pulmonary embolism and clinical pulmonary embolism taken from Table 2 (page 37) (Gallus et al, 1994).

4 Treatment costs for pulmonary embolism are not available, but it is not unreasonable to assume one further additional day in hospital per person.

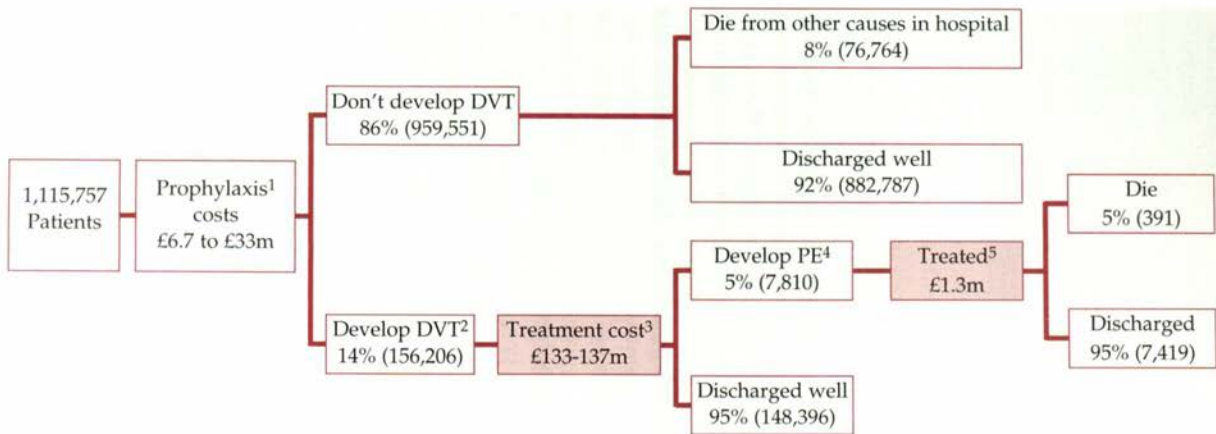


Figure 3 Prophylaxis

Notes

- 1 Prophylaxis costs are based on the average cost of standard Heparin and LMWH
- 2 Prophylaxis is taken to reduce the incidence of DVT by 50 per cent (Brandjes et al, 1992)
- 3 See Note 2, Figure 2
- 4 Figures for development of pulmonary embolism and fatal pulmonary embolism following prophylaxis for DVT are taken from Hill et al, 1990
- 5 See Note 4, Figure 2



Table 10 The number of patients undergoing different forms of surgery receiving prophylaxis, England 1993/94

Type of surgery	Number having surgery	Prophylaxis		No prophylaxis	
		%	Number	%	Number
Orthopaedic	140,711	46	64,727	54	75,984
Gynaecology	37,645	39	14,682	61	22,963
General Surgery	555,061	52	288,632	48	266,429
Neurosurgery	30,915	21	6,492	79	24,423
Urology	351,425	39	137,056	61	214,369
Total	1,115,757	46	511,589	54	604,168

Source: CEPOD, 1995; Hospital Episode Statistics 1993/4.

*Enquiry into Perioperative Deaths 1992/93* (CEPOD, 1995)<sup>7</sup> it is possible to gain some insight into current practice. CEPOD records the percentage of patients who received thrombolytic prophylaxis. Of the patients who died following/during one of the operations listed in CEPOD and included in our analysis between 48 and 79<sup>8</sup> per cent did not receive any form of prophylaxis for DVT. Although it is possible that a higher percentage of patients who survived did receive prophylaxis, given that each patient that died in the CEPOD sample was compared with a patient who survived (matched for age, sex, operation and mode of admission) it appears probable that they are reflective of both a wider population and current policies and practices with regard to thrombolytic prophylaxis.

Using the CEPOD figures for the percentage of patients receiving prophylaxis in different surgical areas and the number of patient over the age of 45 having these forms of surgery in 1993/94 according to the Hospital Episode Statistics (see Table 10), the flow diagram has been recalculated (Figure 4). This shows that in 1993 only 46 per cent of patients at risk received routine prophylaxis at a cost in England of between £3.1 and 15.2 million. Again it is

7 CEPOD investigates deaths which occur in hospital within 30 days of any surgical or gynaecological operation. All NHS hospitals within England, Wales and Northern Ireland as well as hospitals managed by the Ministry of Defence and BUPA are included in the survey. A sample of all deaths reported are investigated each year, this sample is between 0.5 and 1 per cent of all deaths occurring in hospital (which includes non-surgical). In the 1992/93 survey over 1,500 consultant surgeons completed questionnaires about their patients.

8 This figure may be explained by the fact that it was for neurosurgery. Patients who are undergoing surgery for the removal of a brain tumour are at a risk of a bleed and this risk would be further increased by the use of thrombolytics and would be considered inappropriate by many surgeons. It is therefore possible that this figure gives a overly pessimistic impression of the use of thrombolytics in neurosurgery as a whole.

assumed, that of these patients, approximately 14 per cent will develop a DVT, thus incurring treatment costs of approximately £61-63 million. No data are available on the costs of treating pulmonary embolism but for the purposes of this evaluation it has been assumed that a minimum of one additional day in hospital will be incurred at a cost of £0.6 million giving total expected treatment costs for this group of patients of between £61.6 and £63.6 million.

Also shown in the flow diagram are the 54 per cent of patients who received no prophylaxis. Since, as previously mentioned, 27 per cent of patients who receive no prophylaxis will develop a DVT, the cost of treating them was between £139 and £143 million in 1993, with an additional cost of around £1 million for the cost of treating pulmonary embolism. Consequently it can be said that the total expected cost to the NHS in 1993 of treating post surgical DVT was between £201.6 and £207.6 million.

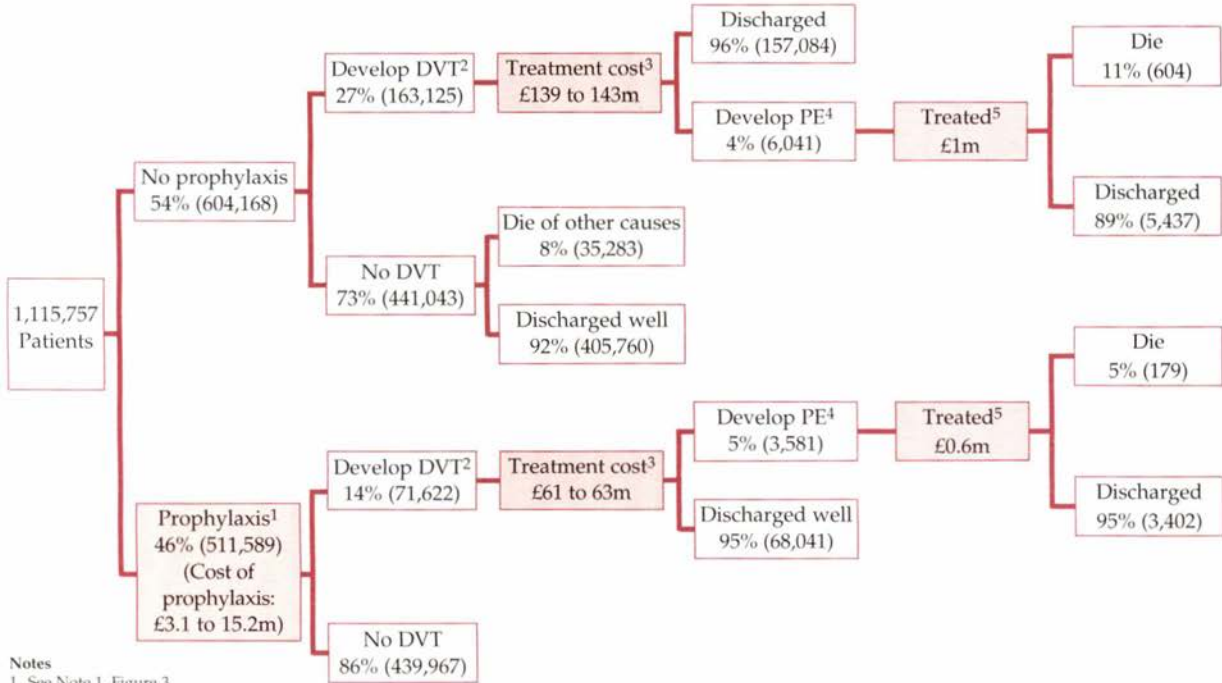
This analysis suggests that if all patients at risk had received routine prophylaxis in 1993 (Figure 3) the costs of post surgical DVT could have been reduced by between £33.4 and £81.8 million<sup>9</sup>. More importantly, nearly 3,000 cases of pulmonary embolism and around 400 deaths would have been prevented.

Other conditions for which patients are admitted to hospital for and which are associated with a high incidence of DVT include malignant neoplasm (35 per cent incidence) and myocardial infarction (20 to 40 per cent incidence). In 1993, there were 565,619 cases of malignant neoplasm and 112,385 cases of myocardial infarction in patients aged 45 and over. The usage of prophylaxis for these patients is unknown but if it was taken to be similar to that in surgery, that is approximately 50 per cent, and we assume that the development of a thrombosis will result in a minimum of one additional day in hospital plus thrombolytic treatment, then the cost of DVT in patients with malignant neoplasm is likely to have been in the region of £17 to £20 million in 1993, and for patients with myocardial infarction between £2 and £3 million.

As stated in chapter 4, any condition which requires prolonged bed rest or results in immobility will carry some risk of DVT, it is therefore probable that these estimates are on the low side.

Table 11 shows the estimated total costs to the NHS of deep vein thrombosis and pulmonary embolism in 1993 as being between £235 and £259 million. As can be seen, the substantial majority of these costs are due to post surgical development of DVT and the need to treat.

<sup>9</sup> Total costs given in Figure 3 less the total costs given in Figure 4.



## Notes

- 1 See Note 1, Figure 3
- 2 See Note 2, Figure 3
- 3 See Note 2, Figure 2
- 4 See Note 4, Figure 3
- 5 See Note 4, Figure 2

Figure 4 Use of thrombolytic prophylaxis, England 1993



**Table 11 Estimated total costs to the NHS of Deep Vein Thrombosis and Pulmonary Embolism, England 1993 (£ millions)**

	DVT	PE	Total
Cost of GP consultations	2.5	0.6	3.1
Cost of GP prescriptions	1.6	–	1.6
Cost of hospital admissions	4.1	2.7	6.8
Cost of pre-surgical prophylaxis	3.1-15.2	–	3.1-15.2
Cost of post-surgical treatment	200-206	1.6	201.6-207.6
Cost of dvt in malignant neoplasms and myocardial infarction	19 -23	–	19-23
<b>Total</b>	<b>230.3-252.4</b>	<b>4.9</b>	<b>235.2-257.3</b>

**BOX 3 General recommendations for the use of thromboembolic prophylaxis in hospital patients**

**All hospital patients:**

- should be assessed for clinical risk factors and overall risk of thromboembolism
- should receive prophylaxis, according to degree of risk, at least until discharge

**Low risk patients:**

- should be mobilised early

**Moderate risk and high risk patients:**

- should receive specific prophylaxis
- should be mobilised early

**Clinicians, units and hospitals:**

- should develop written policies for prophylaxis
- should include prophylaxis in clinical audit and in patient care plans

Efficacy of prophylactic methods should be assessed in outpatients

Source: THRIFT, 1992

The analysis given in this section clearly draws on figures that suggest that around half the people at risk of developing DVT are not receiving prophylactic therapy prior to surgery. Evidence supporting the use of prophylaxis is well-documented and readily available in medical journals. In 1992, three separate consensus studies in the United Kingdom (THRIFT, 1992), Europe (European Consensus Statement, 1992) and North America (Clagett et al, 1992) each published recommendations for prophylaxis of venous thromboembolism. While differing in some details, their general recommendations are very similar (see Box 3), and these have not been disputed either in subsequent correspondence in medical journals or published reviews. Yet given that prophylaxis against thromboembolism belongs to a particularly valuable medical technology, in that it saves lives at the same time as it saves health care money it must be questioned why so many surgeons are failing to ensure that their patients have appropriate prophylaxis.

## 9 Conclusion

We estimate that post-surgical deep vein thrombosis (DVT) and pulmonary embolism (PE) cost the National Health Service between £204.7 and £222.8 million in 1993. This estimate ignores the costs incurred by the patients and their families. If all the patients at high risk of developing a post-surgical DVT (ie. those aged over 45 years and undergoing an operation associated with a high incidence of thrombosis) had received adequate prophylaxis we estimate that the NHS would have made a cost saving of between £33.4 and £81.8 million and the number of deaths due to post surgical pulmonary embolism would have been reduced by more than 400.

Yet, despite the fact that the major risk factors for DVT of age, immobility and certain forms of surgery are well known among the medical profession and have been recognised for many years, less than half (46 per cent) of high risk surgical patients appear to be receiving any form of prophylaxis. It can be argued that for some patients, particularly those undergoing brain surgery, the risks of using thrombolytic prophylaxis, such as excessive bleeding, outweigh the benefits of preventing deep vein thrombosis. However, there are other non-pharmaceutical methods of prophylaxis such as elasticated stockings. According to the sample quoted in the National Confidential Enquiry into Perioperative Deaths (CEPOD, 1995), only 17 per cent of patients of neurosurgery patients were given these.

The use of thrombolytic prophylaxis for the prevention of DVT is a classic example of clinical and cost-effectiveness evidence about a therapy not being put into practice. At a time when evidence-based medicine is receiving considerable emphasis in the NHS, it would appear from this research, that much could be achieved in terms of cost savings and health gain if prophylactic measures were implemented for surgical patients at high risk of developing a DVT.



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the 1990s, the number of people in the world who are illiterate has increased from 1.1 billion to 1.2 billion (UNESCO, 2003).

There are many reasons for the increase in illiteracy. One of the reasons is that the population of the world is growing rapidly. In 1990, the world population was 5.3 billion. In 2000, it was 6.1 billion. In 2010, it is expected to be 7.1 billion. This means that there are more people in the world who are illiterate than in 1990. Another reason is that the quality of education is poor in many developing countries. Many children do not attend school, and those who do attend often do not learn to read and write.

There are many ways to reduce illiteracy. One way is to improve the quality of education. This can be done by training teachers, improving school facilities, and providing textbooks. Another way is to encourage parents to send their children to school. This can be done by providing financial incentives and by making schools more accessible. A third way is to provide literacy training for adults. This can be done through community-based programs and through mass media.

Reducing illiteracy is important for many reasons. First, it is important for economic development. Literate people are more productive and can earn higher wages. Second, it is important for social development. Literate people are more active in their communities and can help to improve the lives of others. Third, it is important for personal development. Literate people are more confident and can make better decisions for themselves.

There are many challenges to reducing illiteracy. One challenge is that there are not enough resources to improve the quality of education in many developing countries. Another challenge is that there are not enough people who are trained to teach literacy to adults. A third challenge is that there are not enough people who are interested in learning to read and write. However, there are many ways to overcome these challenges. One way is to increase international aid for education. Another way is to train more people to teach literacy to adults. A third way is to make learning to read and write more interesting and relevant to people's lives.

Reducing illiteracy is a goal that should be pursued by all countries. It is a goal that can be achieved through the efforts of governments, educators, and the public. By working together, we can reduce the number of people in the world who are illiterate and improve the lives of millions of people.