Regular Review

Risk of and prophylaxis for venous thromboembolism in hospital patients

Thromboembolic Risk Factors (THRIFT) Consensus Group

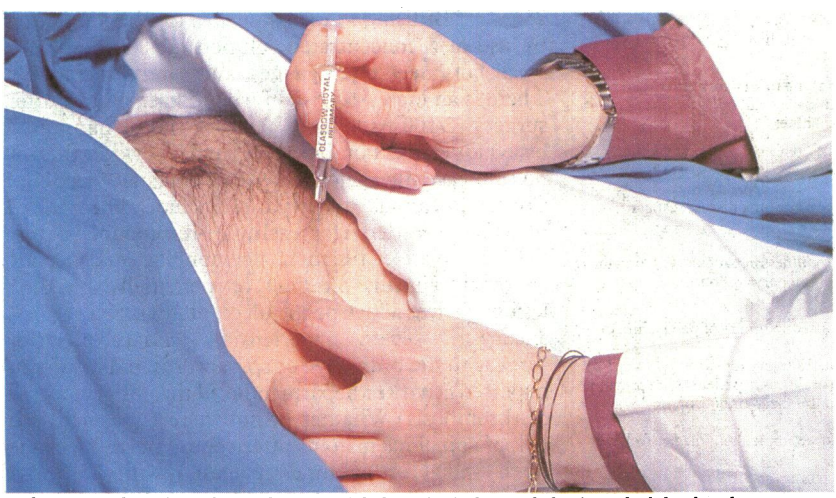
Members of the group: G D O Lowe (chairman); I A Greer, T G Cooke (Glasgow); E P Dewar (Plymouth); M J Evans (London); C D Forbes (Dundee); R A B Mollan (Belfast); J H Scurr, M de Swiet (London)

Correspondence to:
Dr G D O Lowe, University Department of Medicine, Royal Infirmary, 10 Alexandra Parade, Glasgow G31 2ER.

BMJ 1992;305:567-74

Necropsy studies have shown that pulmonary embolism has continued to be a major cause of death in hospital patients in developed countries during the 1980s.[1,2] A recent study in the United Kingdom found that 9% of patients admitted to a general hospital died and that 10% of these deaths (0·9% of all admissions) were due to pulmonary embolism.[2] Most fatal emboli arise from deep vein thrombosis in the lower limb[2] which can also cause both acute and chronic symptoms in the limb (pain, swelling, chronic dermatitis, and ulceration). However, in most patients with fatal embolism, preceding non-fatal thromboembolism was not recognised by clinicians.[1,2] Screening for asymptomatic thrombosis has been advocated[2] but is not cost effective in most patients.[3] The most efficient way to prevent both fatal and non-fatal venous thromboembolism is to use routine prophylaxis for moderate to high risk hospital patients. There is increasing evidence that such prophylaxis is not only life saving[4] but also cost effective in preventing non-fatal symptomatic thromboembolism, which requires investigation and treatment.[3,5-7]

Despite the recommendations of North American consensus conferences[8,9] that prophylaxis be used more widely recent surveys in the United Kingdom suggested that effective prophylaxis is used routinely by only a minority of surgeons,[4,10,11] although its use may be increasing.[12] We therefore thought it appropriate to review the incidence of venous thromboembolism in various groups of hospital patients; the effects of individual risk factors as well as of diagnostic groups on the risk of thromboembolism; and the efficacy of various prophylactic methods. We hope that our recommendations will stimulate practice and debate about a problem which we think has been insufficiently recognised by clinicians in the United Kingdom.



Subcutaneous heparin (or low molecular weight heparin) is the prophylactic method that has the greatest efficacy in preventing deep vein thrombosis and pulmonary embolism

Risk groups for venous thromboembolism

In the past 20 years many studies of the incidence of deep vein thrombosis have been performed in various groups of hospital patients, with leg scanning with fibrinogen labelled with iodine-125 (which has been validated at necropsy[13]) or venography (which is regarded as the standard diagnostic method in life), or both. These studies have disclosed the high incidence of thrombosis in hospital patients (only a few are symptomatic in the acute stage); compared the incidence in various patient groups; shown associations with certain risk markers; and, finally, established the efficacy of prophylaxis for several agents in randomised controlled trials. Several pooled analyses, or meta-analyses, have combined the available data to give more reliable estimates of the incidence in various groups and of the efficacy of prophylactic agents than are available from single studies.[4,14-20] Most studies have been performed in patients undergoing general surgery, followed by orthopaedic, urological, gynaecological, and neurological surgery. There are few studies in cardiovascular or emergency surgery, multiple trauma, pregnancy, or in medical patients; although medical patients have the highest risk.[2]

The risk of thromboembolism in a hospital patient depends not only on the illness, trauma, or planned surgical procedure which was the reason for admission but also on pre-existing patient-related variables which also increase the risk in the general population (table I). Epidemiological, necroscopic, and screening (^{125}I fibrinogen leg scanning) studies have each shown that the risk of venous thromboembolism increases exponentially with age. This risk becomes appreciable after the age of about 40 years in the presence of major illness, trauma, or surgery: hence this age is often used to define a higher risk group which merits prophylaxis. However, many other variables also increase risk (table I); hence high risk groups of patients aged under 40 should also be recognised as meriting prophylaxis. In this context it should be recognised that the younger the patient who dies of pulmonary embolism, the greater the life years lost.

An important (but neglected) part of history taking on admission is inquiry about previous episodes of venous thromboembolism. Patients with previous episodes form a high risk group, with a risk of postoperative deep vein thrombosis of over 50%,[21,22]

TABLE I—*Risk factors for venous thromboembolism in inpatients*

Patient factors	Disease or surgical procedure
Age	Trauma or surgery, especially of pelvis, hip, lower limb
Obesity	Malignancy, especially pelvic, abdominal, metastatic
Varicose veins	Heart failure
Immobility (bed rest over 4 days)	Recent myocardial infarction
Pregnancy	Paralysis of lower limb(s)
Puerperium	Infection
High dose oestrogen therapy	Inflammatory bowel disease
Previous deep vein thrombosis or pulmonary embolism	Nephrotic syndrome
Thrombophilia	Polycythaemia
Deficiency of antithrombin III, protein C, or protein S	Paraproteinaemia
Antiphospholipid antibody or lupus anticoagulant	Paroxysmal nocturnal haemoglobinuria
	Behçet's disease
	Homocystinaemia

and should therefore receive prophylaxis after surgery, trauma, or illness. Patients with venous thromboembolism which is premature (those aged under 45), recurrent, or familial merit screening for thrombophilias (table I). Such patients have a high risk of thromboembolism after surgery, trauma, or medical illness and also merit prophylaxis.[23] Women with thrombophilia should not receive oral contraceptives containing oestrogen and should be assessed for prophylaxis during pregnancy and the puerperium.[23 24]

A widely quoted classification of degree of risk in hospital patients is that of Salzman and Hirsh[25]; table II gives a modified version. Low risk patients have a risk of deep vein thrombosis of under 10%, with proportionally low risks of proximal extension (from calf veins to popliteal, femoral, or iliac veins) and of embolism (which usually arises from proximal thrombi). Routine prophylaxis in such low risk patients probably does not justify the costs and risks of prophylaxis.[3] Moderate risk patients have an incidence of thrombosis of 10-40%, with a risk of fatal pulmonary embolism up to the average risk in a hospital patient—that is, 1%.[2] High risk patients have an incidence of deep vein thrombosis of 40-80%, with proportionally high risks of proximal thrombi and of fatal embolism (the risk of the latter being up to 10%). Routine prophylaxis in moderate and high risk patients is advisable (particularly in high risk patients) and cost effective.[3 5-7] There may still be a significant incidence of venous thrombosis despite routine prophylaxis in high risk patients; hence screening tests for asymptomatic thrombi may be useful, but this requires further study.

TABLE II—*Incidence of venous thromboembolism in hospital patients according to risk group (modified from Salzman and Hirsh[25])*

		Deep vein thrombosis	Proximal vein thrombosis	Fatal pulmonary embolism
Low risk groups		<10%	<1%	0·01%
Moderate risk groups		10-40%	1-10%	0·1-1%
High risk groups		40-80%	10-30%	1-10%
Low risk groups	Minor surgery (<30 min); no risk factors other than age			
	Major surgery (>30 min); age <40; no other risk factors*			
	Minor trauma or medical illness			
Moderate risk groups	Major general, urological, gynaecological, cardiothoracic, vascular, or neurological surgery; age ≥40 y or other risk factor*			
	Major medical illness: heart or lung disease, cancer, inflammatory bowel disease			
	Major trauma or burns			
	Minor surgery, trauma, or illness in patients with previous deep vein thrombosis, pulmonary embolism, or thrombophilia			
High risk groups	Fracture or major orthopaedic surgery of pelvis, hip, or lower limb			
	Major pelvic or abdominal surgery for cancer			
	Major surgery, trauma, or illness in patients with previous deep vein thrombosis, pulmonary embolism, or thrombophilia			
	Lower limb paralysis (for example, hemiplegic stroke, paraplegia)			
	Major lower limb amputation			

*Table I.

Prophylaxis

Prophylaxis includes mechanical and pharmacological methods.

MECHANICAL METHODS

Mechanical methods of prophylaxis include graduated elastic compression stockings and intermittent pneumatic compression devices, which increase emptying of blood from venous valve pockets and increase the rate of blood flow in leg veins. Their advantage is that they do not increase the risk of bleeding; hence they may be preferred in patients at increased risk of bleeding with anticoagulant prophylaxis. They are effective in moderate risk surgical patients[17] (table III) and may also be combined with anticoagulant prophylaxis to increase efficacy of prophylaxis in high risk patients.[20] The limitations of mechanical methods are that: (1) unlike anticoagulant or dextran prophylaxis they have not been shown to reduce the risk of fatal pulmonary embolism; (2) there is little experience in medical patients; (3) compliance may be reduced in some patients who find them uncomfortable; and (4) stockings are contraindicated in overt leg ischaemia. In view of their ease of use, stockings might also be considered in low risk patients, but further studies are required in this group.

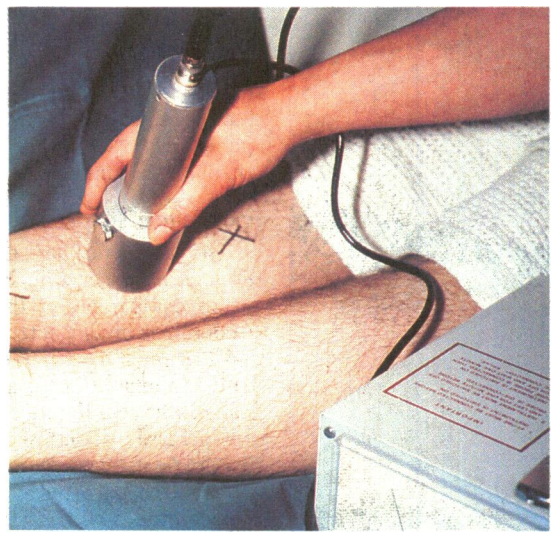
TABLE III—*Meta-analysis of incidence of deep vein thrombosis after major general surgery (defined by ^{125}I fibrinogen scanning)*[17]

	Mean incidence (%) (95% confidence interval)
No prophylaxis	25·1 (23·9 to 26·5)
Low dose heparin	8·7 (7·8 to 9·7)
Graduated elastic compression stockings	9·3 (6·4 to 13·3)
Intermittent pneumatic compression	9·9 (6·9 to 13·9)
Dextran	16·6 (13·1 to 18·4)
Aspirin	20·4 (16·5 to 25·0)

PHARMACOLOGICAL METHODS

Anticoagulant drugs reduce thrombin formation and hence reduce the initiation and extension of fibrin-rich venous thrombi.

Low dose subcutaneous heparin (5000 units 8-12 hourly; laboratory monitoring not usually required) is most widely used for prophylaxis of venous thromboembolism in moderate risk and high risk patients and is effective and generally safe in both medical and surgical patients, reducing not only the incidence of deep vein thrombosis but also fatal embolism and consequently total hospital mortality.[4 9 26-28] About two thirds of deep vein thrombi (table III) and two thirds of fatal pulmonary emboli are prevented by low dose heparin,[4 26] and hospital mortality is reduced by about 25%.[4 26-28] Bruising at injection sites can be minimised by use of a concentrated solution (25 000 units/ml), small bore needle (25 gauge), and careful technique. There is an increased risk of wound haematomas after surgery (2/100 patients),[4 17 26] which can be minimised by avoiding injection close to wounds: however there is no increase in major bleeding or fatal bleeding.[4] Contraindications to heparin include uncorrected bleeding disorders (for example, thrombocytopenia, defective platelet function, haemophilia, and hepatic or renal failure); bleeding or potentially bleeding lesions such as active peptic ulcer, oesophageal varices, aneurysm, severe hypertension, endocarditis, or surgery to the brain, eye or spinal cord; and history of hypersensitivity or heparin induced thrombocytopenia or thrombosis. Whether or not there is an increased risk of spinal haematoma after central nerve blockade (with spinal or epidural analgesia) with low dose heparin is controversial[29 30]; some anaesthetists recommend caution (avoiding instituting blockade within



Leg scanning with ^{125}I fibrinogen: a sensitive method of detecting deep vein thrombosis (asymptomatic or symptomatic) for studies of incidence, risk factors, and prophylaxis

four to six hours of heparin administration by omitting the preoperative dose or by giving the first dose after the block has been instituted).[30] Thrombocytopenia occurs in about 0·3% of patients given prophylactic porcine heparin[31]: the Committee on Safety of Medicines advises that the platelet count is monitored in patients receiving heparin for more than five days and that treatment is stopped immediately if thrombocytopenia occurs.[32] Arterial or venous thrombosis occurs in 0·4% of patients with heparin induced thrombocytopenia.[31] Other allergic reactions (including skin necrosis) and raised serum concentrations of transaminases may occur, as well as osteoporosis with long term heparin, especially in pregnancy.[31]

Adjusted low dose subcutaneous heparin (for example, 3500 units eight hourly, starting two days before surgery and adjusted to maintain the activated partial thromboplastin time in the upper normal range[31]) is more effective than fixed low dose heparin in preventing deep vein thrombosis in high risk patients (for example, those undergoing hip surgery[33-35]) but is more complicated to manage.

Low molecular weight heparins—Two low molecular weight heparins have recently been licensed in the United Kingdom for prophylaxis of deep vein thrombosis (enoxaparin and dalteparin). At doses recommended for prophylaxis low molecular weight heparins and heparinoids have little effect on the activated partial thromboplastin time compared with anti-factor Xa assays. They have the logistic advantage over standard heparin that their longer biological half life allows once daily injection instead of injections every eight to 12 hours. To date, controlled trials have shown that several low molecular weight heparins or heparinoids are at least as effective in preventing deep vein thrombosis as standard heparin in moderate and high risk patients and may have a greater efficacy in high risk patients, such as those undergoing hip surgery, without increased risk of bleeding.[18-20 36-38 38a] Different low molecular weight heparins are not necessarily equivalent, and published reports on individual products should be consulted. Higher doses of low molecular weight heparin are recommended for high risk patients compared with moderate risk patients. At present, the same contraindications (and monitoring of platelet count) are recommended for low molecular weight heparin as for standard heparin.

Oral anticoagulants such as warfarin are also effective in preventing deep vein thrombosis after major gynaecological surgery,[39 40] elective hip replacement,[41] and hip fractures,[42-44] whether started preoperatively or postoperatively.[18 19 45] Starting with a low dose before surgery[41] or starting after surgery[45] may reduce the risk of bleeding compared with full anticoagulation at the time of surgery. The recommended postoperative international normalised ratio of the prothrombin time is 2·0-2·5 (2·0-3·0 for hip surgery).[45] Because of the increased risk of bleeding and need for daily laboratory control anticoagulation is usually reserved for high risk patients such as those with previous thromboembolism, or those undergoing major orthopaedic surgery.[18-20 45] Contraindications to full dose oral anticoagulation include bleeding disorders and bleeding or potentially bleeding lesions as for heparin (see above); and pregnancy (see below) in which fetal complications may occur. Caution is required with spinal or epidural analgesia because spinal haematomas have been reported in patients receiving full anticoagulation treatment.[29 30] Perioperative minidose warfarin (1 mg daily) may be effective in major gynaecological surgery,[40] but further studies are required; it has shown little effect in elective hip replacement.[46 47]

Dextran 70, given as perioperative intravenous infusions, may have several antithrombotic effects including effects on blood flow, platelets, endothelium, and lysability of fibrin.[14 15] Dextran has not been evaluated in medical patients; shows limited efficacy in prevention of deep vein thrombi in general surgery (table III)[17]; but seems more effective in preventing thrombosis after hip fractures.[18-20] In controlled trials dextran also seems more effective in preventing pulmonary embolism than venous thrombosis, possibly by increasing the lysability of venous thrombi[14 15 17 20]; in a large multicentre study of dextran versus heparin the mortality was similar in both groups.[48] Limitations of dextran include the need for intravenous infusions, increased risk of bleeding (contraindications are similar to those for heparin), risk of fluid overload (hence caution is required in heart failure), and allergic (including anaphylactic) reactions. The risk of allergic reactions can be reduced by pretreatment with a hapten; however, this is not licensed for use in the United Kingdom.

Antiplatelet agents such as aspirin or hydroxychloroquine show limited efficacy in preventing deep vein thrombosis (table III)[15 17 19]; their effects on pulmonary embolism and mortality are not yet published.

Drugs stimulating endogenous fibrinolysis such as anabolic steroids also seem of limited efficacy in preventing deep vein thrombi.[49]

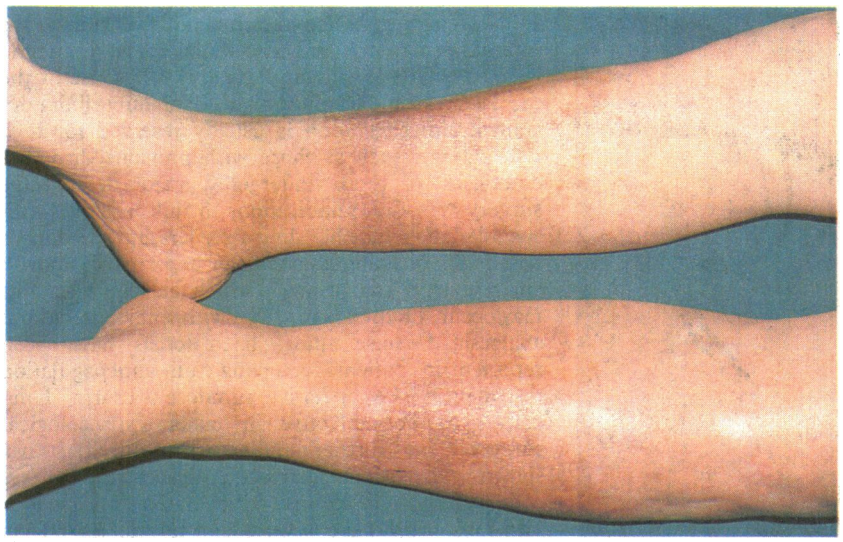
Recommendations for prophylaxis in surgical and medical patients

We recommend that all medical and surgical patients admitted to hospital should be assessed for clinical risk factors (table I) and for overall risk of venous thromboembolism (table II). All patients should receive prophylaxis, the intensity of which is related to the risk. Low risk patients should be encouraged to mobilise early after immobilisation. Patients at moderate and high risk (especially) should receive specific prophylaxis in addition to early mobilisation.

Individual clinicians, units, and hospitals in the United Kingdom should develop written policies for prophylaxis, and the use of prophylaxis should be included in clinical audit and plans for patient care.

Prophylaxis should continue at least until discharge, rather than for any predetermined time. Continued prophylaxis after discharge should be considered in individual patients at continued high risk.[50] Further studies are required to establish the efficacy of different prophylactic methods in outpatients, but graduated stockings, low dose heparin, low molecular weight heparins, and oral anticoagulants have each been used.

Selection of particular methods of prophylaxis in moderate and high risk patients is influenced by many factors and varies widely between clinicians and



Acute leg swelling in a patient with acute deep vein thrombosis: only a minority of patients with thrombosis have symptoms or signs

between specialties. Our recommendations are based on the following preconceptions.

(1) To minimise the risks of acute and chronic symptoms in the leg the preferred methods are those which have been shown in randomised controlled trials with objective diagnostic methods, to reduce the risk of deep vein thrombosis to less than 10% (that is, to the risk of "low risk" patients). (2) To minimise the risks of pulmonary embolism and death the preferred methods should ideally have been shown in randomised controlled trials to reduce these risks significantly, as well as the risk of deep vein thrombosis. (3) Preferred methods should be simple to use, acceptable to patients, and have minimal adverse effects. The choice between antithrombotic drugs and mechanical methods of prophylaxis often depends on the balance of risks of thromboembolism and bleeding in the individual patient.

GENERAL SURGERY

Meta-analyses of the many controlled trials in patients undergoing major general surgery (usually patients aged over 40 years) have shown that the incidence of deep vein thrombosis on screening was about 25% in patients who did not receive specific prophylaxis (table III).[4 17] In such patients we recommend either low dose subcutaneous heparin or a low molecular weight heparin of proved efficacy. Subcutaneous heparin reduces the risk of deep vein thrombosis by 60-70% (to about 9%; table III), reduces the incidence of fatal pulmonary embolism by 60-70% (from 0·7% to 0·2%), and reduces mortality in hospital.[4 17 26] Eight hourly heparin may be more effective than 12 hourly heparin[17] and hence may be preferred in high risk patients (for example, those with malignancy). Low molecular weight heparins seem equally effective in preventing deep vein thrombosis,[20 36 38 38b] and one placebo controlled trial reported reduction in mortality in hospital.[51] Graduated compression stockings may be added to treatment with low dose heparin or low molecular weight heparin because this combined approach increases efficacy.[20] This may be particularly appropriate in high risk patients and in acute abdominal surgery, in which few studies have been performed: one trial showed an incidence of thromboembolism of 15% in the low dose heparin group and 3% in the heparin and stockings group.[52]

In moderate and high risk patients in whom heparins are contraindicated (for example, owing to general or local high risk of bleeding) we recommend intermittent pneumatic compression, graduated compression stockings, or both (table III).[17] The confidence intervals for reduction in risk of deep vein thrombosis are wider for these methods than for low dose heparin[17] or low molecular weight heparins (table III), and their effect on pulmonary embolism is unknown. Dextran reduces the risk of pulmonary embolism but has limited efficacy in preventing deep vein thrombosis (table III)[17 20] as well as risks of fluid overload, anaphylaxis, and bleeding.

UROLOGICAL SURGERY

The incidence of deep vein thrombosis after urological surgery (including renal transplantation) seems comparable to that after general surgery.[4 15 19] Abdominal prostatectomy carries a moderate risk (40%) compared with transurethral resection (10%).[15 19] The administration of antifibrinolytic drugs such as tranexamic acid to reduce postoperative bleeding does not increase risk of thrombosis.[15] In moderate and high risk patients we recommend either low dose subcutaneous heparin or intermittent pneumatic compression combined with graduated compression stockings. Both methods are effective in reducing the risk of deep vein thrombosis; there is more evidence that subcutaneous heparin reduces the risk of pulmonary embolism,[4] but heparin, low molecular weight heparins, and heparinoids carry a higher risk of bleeding from the raw prostatic surface after prostatectomy than of bleeding in general surgery.[4 15 19]

GYNAECOLOGICAL SURGERY

The incidence of deep vein thrombosis after gynaecological surgery seems comparable to, or less than, that in general surgery.[15] The risk is highest in operations for malignancy (35%), less in abdominal hysterectomy (12%), and lowest for vaginal hysterectomy.[53] In moderate and high risk patients we recommend either low dose heparin or intermittent pneumatic compression combined with graduated compression stockings.[15] The recommended dose of subcutaneous heparin is 5000 units eight hourly in high risk patients (for example, those with malignancy)[54] and 5000 units 12 hourly in moderate risk patients.

CARDIOVASCULAR SURGERY

Few studies of the incidence of venous thrombosis have been performed after cardiothoracic or peripheral arterial surgery; however, the incidence seems similar to that in general abdominal surgery—that is, the risk is moderate.[15] Antiplatelet agents such as aspirin are increasingly used to maintain graft patency postoperatively: their effects on risk of postoperative

General recommendations for prophylaxis for thromboembolism

All hospital inpatients:

- 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

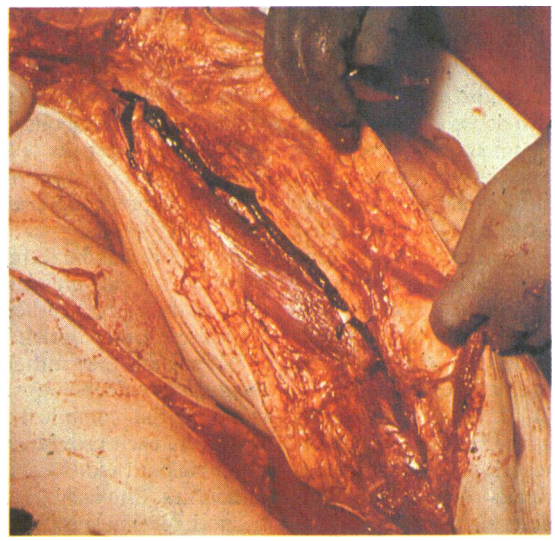
Moderate risk and high risk patients:

- 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



Proximal vein thrombosis in a patient who died of pulmonary embolism: most emboli arise from proximal veins

venous thromboembolism have not been established. Subcutaneous low dose heparin seems effective in the few studies of arterial surgery which have been performed.[15] Guidelines for central nerve blockade in such patients who receive preoperative heparin have been suggested.[30] Leg amputation for critical ischaemia carries a high risk of pulmonary embolism, and subcutaneous heparin is recommended in patients with critical leg ischaemia to reduce this risk.[55] No systematic studies have been performed after surgery to lower limb veins,[15] perhaps because of the limitations of ^{125}I fibrinogen scanning, but there is a risk of venous thromboembolism.

NEUROSURGERY

Few studies of the incidence of thrombosis after neurosurgery have been reported, but it seems similar to the incidence after general surgery.[15 19] Because of the dangers of bleeding to the brain or spinal cord few studies of anticoagulant prophylaxis have been performed; however, heparin seemed effective.[19] Intermittent pneumatic compression or graduated compression stockings, or both, seemed effective without increasing the risk of bleeding and are therefore recommended.[19 56]

ACCIDENT AND ORTHOPAEDIC SURGERY

In patients with major trauma subcutaneous heparin and intermittent pneumatic compression each seem effective in reducing the risk of deep vein thrombosis[57]: intermittent pneumatic compression may be preferred in patients at high risk of bleeding but is not always practical. The balance of risk of thromboembolism and bleeding should be considered in each patient.

In studies of major orthopaedic surgery on the hip or knee without specific prophylaxis the incidence of deep vein thrombosis was 40-80%; the incidence of proximal thrombi was 20%; the risk of fatal pulmonary embolism in hip surgery was 1-10%; and the risk of the post-thrombotic syndrome also seemed high.[4 5 13 15 18-20 25 42 43 58] The high risk of proximal thrombi (and hence pulmonary embolism and the post-thrombotic syndrome) may reflect local mechanical damage to the femoral vein in hip surgery[59] (or to the popliteal vein in knee arthroplasty) and local activation of blood coagulation.[60] Routine venography is required for diagnosis of non-occlusive proximal venous thrombi.[13 18-20 61 62]

Despite this high thromboembolic risk prophylaxis in such patients has been controversial, perhaps for two reasons. Firstly, because use of standard methods of prophylaxis which are effective in other types of surgery, such as low dose heparin[4 18-20] or intermittent pneumatic compression,[62] still leaves a substantial residual risk of deep vein thrombosis (typically, a reduction in incidence from 50% to 20-25%), possibly owing to the limited effect of such prophylactic methods on proximal venous damage and hence on proximal thrombi. Secondly, because some surgeons fear the risk of bleeding with anticoagulant prophylaxis, which may occasionally result in deep joint infection and failure of the implant.[12 63] In recent years the reductions in risk with low dose heparin (60-70%)[4] and intermittent pneumatic compression (50%)[62] have been established as similar in orthopaedic surgery and in general surgery; moreover, because of the higher risk of deep vein thrombosis without specific prophylaxis the *absolute* benefit of such prophylaxis in orthopaedic patients is greater than in general surgery.[4] Furthermore, the use of anticoagulant prophylaxis with heparin or warfarin by orthopaedic surgeons seems to be increasing in the United Kingdom,[10-12] perhaps because of the lesser risk of bleeding with heparin or delayed dose or low dose warfarin compared with earlier use of full dose oral anticoagulants.[18 19 42 43]

Elective hip surgery—For elective hip surgery we recommend high efficacy regimens: either a regimen of a low molecular weight heparin shown to reduce the risk of total deep vein thrombosis towards that in low risk hospital groups (5-15%) as well as the risk of proximal thrombosis towards that in moderate risk groups (2-8%)[18-20 36-38 38a 64-69] or an adjusted dose regimen of subcutaneous heparin,[9 34 37] which is similarly effective in reducing the risk of total deep vein thrombosis but may be less effective in preventing more proximal thrombi and is more complicated to manage. Alternative regimens which show only moderate efficacy in preventing deep vein thrombosis (residual incidence 15-30%) include fixed low dose subcutaneous heparin (which reduces the risk of fatal pulmonary embolism[4 20]), adjusted dose warfarin,[18 19 41] intermittent pneumatic compression,[18 62] or dextran.[18]

Hip fractures—We recommend either adjusted dose warfarin[9 18 42-45] or dextran 70.[9 14 15 18-20] Each of these methods prevents 40-50% of deep vein thrombi and reduces the risk of pulmonary embolism. Warfarin may be preferred in patients with heart disease because of its efficacy in prophylaxis of cardiogenic and arterial thromboembolism in such patients,[45] as well as the patients' risk of fluid overload with dextran. Fixed low dose heparin may be similarly effective in preventing deep vein thrombosis, but its efficacy in prevention of pulmonary embolism has not been shown in this group.[4 20] There are encouraging preliminary results from trials of low molecular weight heparins and heparinoids,[18-20 36 38 38b] some of which may prove to be the best agents in such patients if they are effective and safe in fixed doses.

Knee replacement surgery—There are few studies of prophylaxis in knee replacement surgery; however, intermittent pneumatic compression[70] or low dose warfarin[41] may be effective.

MEDICAL PATIENTS

Only one in four patients dying of pulmonary embolism in hospital has had recent surgery,[2] which emphasises the importance of prophylaxis in medical patients. Low dose subcutaneous heparin seems equally effective in preventing deep vein thrombosis and fatal pulmonary embolism in general medical and in surgical patients, reducing mortality in hospital from 4·2% to 3·3% in surgical patients,[4] but from 10·9% to 7·8% in medical patients,[27] consistent with their threefold greater risk of fatal embolism.[2]

Acute myocardial infarction—We recommend low dose subcutaneous heparin as prophylaxis for venous thromboembolism[71] in patients who are not already

receiving higher doses of heparin (25 000 units/day intravenously or subcutaneously) for maintaining patency after thrombolytic therapy or for prophylaxis for mural thrombosis and reinfarction, or both.[19 31]

Acute stroke—In patients with acute stroke causing lower limb weakness we recommend low dose subcutaneous heparin as prophylaxis for venous thromboembolism,[28 72] provided that intracranial haemorrhage and intracranial neoplasia have been excluded by computed tomographic brain scanning.[73] Though low dose heparin and some low molecular weight heparins or heparinoids are effective in preventing deep vein thrombosis after stroke,[72 74 75] their effects on intracranial bleeding, functional outcome, and mortality remain to be established by larger studies.[72] In patients in whom computed tomography is not performed, or who have intracranial haemorrhage or neoplasia or other contraindications to heparin, we recommend graduated compression stockings with or without intermittent pneumatic compression, extrapolating from controlled trials in neurosurgical patients.[19 56]

Other groups at moderate or high risk—In other groups (for example, those immobilised with chest infection, heart failure, respiratory failure, malignancy, inflammatory bowel disease and other conditions in table I) we recommend prophylaxis with low dose subcutaneous heparin[19 27]; warfarin (in high risk patients—for example, those with previous thromboembolism); or in patients with contraindications to heparin and warfarin graduated compression stockings with or without intermittent pneumatic compression (extrapolating from trials in surgical patients[18-20 56]).

Recommendations for prophylaxis: use of oral contraceptives, hormone replacement therapy, and during pregnancy and puerperium

SURGERY AND CONTRACEPTIVE PILL

Whether or not to stop the combined contraceptive pill before major surgery is a controversial issue.[76-79] The combined pill is associated with changes in the coagulation system which can be regarded as prothrombotic.[80] These changes correlate directly with its oestrogen content[80]; however, even the low dose (30-35 μg ethinyloestradiol) preparations are associated with significant changes in coagulation.[80 81] Epidemiologically, use of the high dose combined pill was associated with idiopathic[82] and postoperative venous thromboembolic complications.[79 82 83] There is more recent evidence to suggest that the risk of thromboembolic complications is lower with low dose (<50 μg ethinyloestradiol) preparations, although this is not conclusive.[83-86] The most recent study puts the risk of postoperative thromboembolism at 0·96% for pill users and 0·5% for non-users.[83] Hence young women taking the combined pill are at low risk presumably because they are young and fit and mobilise early.

Against this small absolute risk of postoperative venous thromboembolism in combined pill users must be balanced the risks of stopping the pill four to six weeks before major surgery.[77 87] These include unwanted pregnancy, the effects of surgery and anaesthesia on the pregnancy, and possibly also the risks of a subsequent termination. Those who advocate stopping the pill must therefore communicate these risks to the patient and ensure adequate and effective alternative contraception.[79]

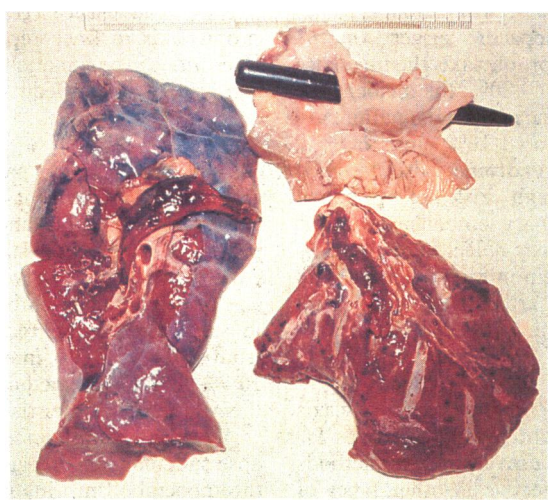
We suggest that without other risk factors there is insufficient evidence to support a policy of routinely stopping the combined pill before major surgery. However, each case should be judged on its merits, weighing both additional risk factors and contraceptive difficulties. Similarly, there is insufficient evidence to support routine specific thromboembolic prophylaxis in women without additional risk factors who are taking the combined pill, although prophylaxis may be a prudent measure when additional risk factors are present (table I). Again, this is best judged in the individual patient. In emergency surgery, when the risk of venous thromboembolism is greater, thromboprophylaxis should be employed.[52] There is no need to stop the combined pill or to use thromboprophylaxis for uncomplicated minor procedures such as diagnostic curettage or laparoscopy when there are no other risk factors. Finally, there is no evidence to suggest that progesterone only preparations are associated with any excess risk of venous thromboembolism.[88]

HORMONE REPLACEMENT THERAPY

In contrast to the findings for contraceptive pills containing oestrogen, there are no reliable data to suggest that postmenopausal oestrogen replacement therapy increases the risk of venous thromboembolism.[89 90] This lack of effect may be related to the lower oestrogen content of such preparations compared with the combined contraceptive pill. There is no information to suggest that hormone replacement therapy should be stopped before surgery, although many patients in the age group likely to receive such therapy will receive specific thromboprophylaxis after surgery because of their age or other risk factors.

PREGNANCY

Pregnancy is a risk factor for venous thromboembolism, and it seems to increase the risk sixfold compared with the non-pregnant state,[91] although the *absolute* risk is still low and does not merit routine thromboprophylaxis. However, until recently, long term administration of anticoagulants was often employed in the antenatal period as prophylaxis in women with a past history of thromboembolism or thrombophilia occurring during pregnancy or otherwise. This was because the incidence of recurrence of this potentially lethal complication was thought to be around 12%,[92] whereas the risks of long term anticoagulants in pregnancy were not appreciated. More recent studies, however, suggest that the risk of recurrence during pregnancy in patients who have had a single episode of thromboembolism in the past and who do not receive prophylaxis antenatally is much lower[93-95] and is probably between 1-5% whatever the original circumstances. When this is balanced against the hazards of anticoagulation in pregnancy prophylactic therapy is questionable[94] and perhaps is best reserved for those with recurrent thrombosis, certain congenital thrombophilias,[23 24] or post-thrombotic venous insufficiency. Additionally, pregnancy is not contraindicated in women with such a history. Some authorities, however, still advise prophylactic anti-



Pulmonary emboli in a patient who died of pulmonary embolism. Left: major pulmonary embolism causing death. Lower right: minor pulmonary embolism causing pulmonary infarction. Upper right: patent foramen ovale through which emboli may cause systemic arterial embolism

coagulant therapy if previous thrombosis occurred during pregnancy, starting four to six weeks before the gestation time when the previous thromboembolic problem occurred.[96 97] As thromboembolism is a potentially fatal condition and prophylaxis is not without hazard it seems prudent to discuss with the patient the various risks of these problems before pregnancy (or at least in early pregnancy), no matter which prophylactic strategy is taken, especially as neither approach has been fully evaluated in a large controlled clinical study. All authorities do agree, however, on *postnatal* prophylactic therapy in patients with a history of thromboembolism or thrombophilia.

The adverse effects of anticoagulants during pregnancy include osteoporosis and thrombocytopenia with heparin; and teratogenesis, nervous system malformations, and fetal and maternal bleeding with oral anticoagulants.[98-103] Because most cases of thromboembolism occur postnatally and because of the risks of adverse effects of heparin and oral anticoagulants, a compromise has been adopted[104] of no antenatal prophylaxis in patients with a single previous episode of thromboembolism; explanation to the patient of the relative risks and instruction that she should report any symptoms suggesting deep vein thrombosis or pulmonary embolism immediately; and subcutaneous heparin 5000 units eight hourly (or 7500 units 12 hourly), starting at the onset of labour and continuing for at least one week post partum. If the activated partial thromboplastin time is not significantly prolonged, instrumental delivery, caesarean section, and epidural block do not seem to carry any increased risk of bleeding.[15 105] Prophylaxis should continue until six weeks post partum. One week after delivery the risk of secondary postpartum haemorrhage associated with warfarin therapy is much less, and it is reasonable to change from heparin to warfarin should the patient wish to do so. If the patient does take warfarin, breast feeding is not hazardous for the neonate.[106] This regimen is not universally accepted, and some authorities still advise prophylactic heparin if the previous thromboembolism occurred during pregnancy, starting four to six weeks before the gestation time when the previous problem occurred.[96 97]

Patients who have had more than one episode of thromboembolism or who have had thromboembolism in association with thrombophilia may be at higher risk than those who have had an isolated single episode, and antenatal prophylaxis should be considered.[23 24 107]

PUERPERIUM

In addition to the conditions discussed above, caesarean section increases the risk of puerperal thromboembolism by fivefold to 10-fold, especially when performed as an emergency; elective caesarean section probably only doubles the risk. There have been no controlled trials of prophylaxis at the time of delivery, largely because of the difficulty of screening for deep vein thrombosis with radioactive isotopes in puerperal women who may be breast feeding. The risk of dying of pulmonary embolism is much greater in older, multiparous women,[108] and bed rest and obesity are additional risk factors. Therefore it would seem reasonable to use specific prophylaxis against venous thromboembolism for women who have: (*a*) had bed rest for at least one week immediately before delivery, or (*b*) are obese, or (*c*) are aged more than 35 years, or (*d*) are in their 3rd pregnancy or more (excluding abortions).

Because of the efficacy of low dose subcutaneous heparin in other surgical procedures we recommend it in a dose of 5000 units eight hourly (or 7500 units 12 hourly), starting at the onset of the procedure and continuing until the patient is fully mobile. This may require prophylaxis to be continued after discharge (most women who die of postnatal thromboembolism do so after discharge). This practice should be evaluated by future clinical trials.

Meetings of the Consensus Group were supported by an educational grant from Rhone-Poulenc-Rorer (UK). However, the views expressed are those of the group alone.

1 Karwinski B, Svendsen E. Comparison of clinical and postmortem diagnosis of pulmonary embolism. *J Clin Pathol* 1989;**42**:135-9.
2 Sandler DA, Martin JF. Autopsy proven pulmonary embolism in hospital patients: are we detecting enough deep vein thrombosis? *J R Soc Med* 1989;**82**:203-5.
3 Bergqvist D, Jendteg S, Lindgren B, Matzsch T, Persson U. The economics of general thromboembolic prophylaxis. *World J Surg* 1988;**12**:349-55.
4 Collins R, Scrimgeour A, Yusuf S, Peto R. Reduction in fatal pulmonary embolism and venous thrombosis by perioperative administration of subcutaneous heparin. Overview of results of randomized trials in general, orthopedic, and urologic surgery. *N Engl J Med* 1988;**318**:1162-73.
5 Salzman E, Davies GC. Prophylaxis of venous thromboembolism. Analysis of cost effectiveness. *Ann Surg* 1980;**191**:207-18.
6 Hull RD, Hirsh J, Sackett DL, Stoddart GL. Cost-effectiveness of primary and secondary prevention of fatal pulmonary embolism in high-risk surgical patients. *Can Med Assoc J* 1982;**127**:990-5.
7 Oster G, Tuden RL, Colditz GA. A cost-effectiveness analysis of prophylaxis against deep-vein thrombosis in major orthopedic surgery. *JAMA* 1987;**257**:203-8.
8 National Institutes of Health Consensus Conference. Prevention of venous thrombosis and pulmonary embolism. *JAMA* 1986;**256**:744-9.
9 Hyers TM, Hull RM, Weg JG. Antithrombotic therapy for venous thromboembolic disease. *Chest* 1989;**95**(suppl):37-51S.
10 Morris GK. Prevention of venous thromboembolism. A survey of methods used by orthopaedic and general surgeons. *Lancet* 1980;ii:572-4.
11 Brenkel IJ, Clancy MJ. Total hip replacement and antithrombotic prophylaxis. *Br J Hosp Med* 1989;**42**:282-4.
12 Laverick MD, Croal SA, Mollan RB. Orthopaedic surgeons and thromboprophylaxis. *BMJ* 1991;**303**:549-50.
13 Morris GK, Mitchell JRA. Evaluation of ^{125}I fibrinogen test for venous thrombosis in patients with hip fractures: comparison between isotope scanning and necropsy findings. *BMJ* 1977;i:264-7.
14 Bergentz S-E. Dextran in the prophylaxis of pulmonary embolism. *World J Surg* 1978;2:19-25.
15 Bergqvist D. *Postoperative thromboembolism. Frequency, etiology, prophylaxis.* Berlin: Springer Verlag, 1983.
16 Colditz GA, Tuden RL, Oster G. Rates of venous thrombosis after general surgery: combined results of randomised clinical trials. *Lancet* 1986;ii: 143-6.
17 Clagett GP, Reisch JS. Prevention of venous thromboembolism in general surgical patients. Results of meta-analysis. *Ann Surg* 1988;**208**:227-40.
18 Hirsh J. Prevention of venous thrombosis in patients undergoing major orthopaedic surgical procedures. *Acta Chir Scand* 1990;suppl 556:30-5.
19 Gallus AS. Anticoagulants in the prevention of venous thromboembolism. *Baillieres Clin Haematol* 1990;**3**:651-84.
20 Wille-Jorgensen P. *Prophylaxis of postoperative thromboembolism.* Copenhagen: Laegeforeningens Forlag, 1991.
21 Kakkar VV, Howe CT, Nicolaides AN, Renney JTG, Clarke MB. Deep vein thrombosis of the leg. Is there a high risk group? *Am J Surg* 1970;**120**: 527-30.
22 Nicolaides AN, Irving D. Clinical factors and the risk of deep venous thrombosis. In: Nicolaides AN, ed. *Thromboembolism.* Lancaster: MTP, 1975: 193-204.
23 British Committee for Standards in Haematology. Guidelines on the investigation and management of thrombophilia. *J Clin Pathol* 1990;**43**: 703-9.
24 Conard J, Horellou MH, Van Dreden P, Lecompte T, Samama M. Thrombosis and pregnancy in congenital deficiencies in ATIII, Protein C or Protein S: study of 78 women. *Thromb Haemostas* 1990;**63**:319-20.
25 Salzman EW, Hirsh J. Prevention of venous thromboembolism. In: Colman RW, Hirsh J, Marder V, Salzman EW, eds. *Hemostasis and thrombosis: basic principles and clinical practice.* New York: Lippincott, 1982:986.
26 International Multicentre Trial. Prevention of fatal postoperative pulmonary embolism by low doses of heparin. *Lancet* 1975;ii:45-51.
27 Halkin H, Goldberg J, Modan M, Modan B. Reduction of mortality in general medical inpatients by low-dose heparin prophylaxis. *Ann Intern Med* 1982;**96**:561-5.
28 McCarthy ST, Turner J. Low-dose subcutaneous heparin in the prevention of deep-vein thrombosis and pulmonary emboli following acute stroke. *Age Ageing* 1986;**15**:84-8.
29 Wille-Jorgensen P, Jorgensen LN, Rasmussen LS. Lumbar regional anaesthesia and prophylactic anticoagulant therapy. Is the combination safe? *Anaesthesia* 1991;**46**:624-8.
30 Wildsmith JAW, McClure JH. Anticoagulant drugs and central nerve blockade. *Anaesthesia* 1991;**46**:613-4.
31 Hirsh J. Heparin. *N Engl J Med* 1991;**324**:1565-74.
32 British Medical Association and Royal Pharmaceutical Society of Great Britain. *British national formulary.* No 21. BMA, RPS, 1991:89-91.
33 Poller L, Taberner DA, Sandilands DG, Galasko CSB. An evaluation of APTT monitoring of low-dose heparin dosage in hip surgery. *Thromb Haemostas* 1982;**47**:50-3.
34 Leyvraz PF, Richard J, Bachman F, van Melle G, Treyvaud J-M, Livio J-J, *et al.* Adjusted versus fixed-dose subcutaneous heparin in the prevention of deep-vein thrombosis after total hip replacement. *N Engl J Med* 1983;**309**: 954-8.
35 Taberner DA, Poller L, Thomson JM, Lemon G, Weighill FJ. Randomized study of adjusted versus fixed low dose heparin prophylaxis of deep vein thrombosis in hip surgery. *Br J Surg* 1989;**76**:933-5.
36 Levine MN, Hirsh J. Clinical potential of low molecular weight heparins. *Baillière's Clin Haematol* 1990;**3**:545-54.
37 Leyvraz PF, Bachmann F, Hoek J, Büller HR, Postel M, Samama M, *et al.* Prevention of deep vein thrombosis after hip replacement: randomised comparison between unfractionated heparin and low molecular weight heparin. *BMJ* 1991;**303**:543-8.

38 Samama MM, Desnoyers P. Low molecular weight heparins and related glycosaminoglycans in the prophylaxis and treatment of venous thromboembolism. In: Poller L, ed. *Recent advances in blood coagulation 5*. Edinburgh: Churchill Livingstone, 1991:177-222.

38a Thomas DP. Prevention of postoperative thrombosis by low molecular weight heparin in patients undergoing hip replacements. *Thromb Haemostas* 1992;**67**:491-3.

38b Nurmohamed MT, Rosendaál FT, Büller HR, Dekker E, Hommes DW, Vandenbroucke JP, *et al*. Low molecular-weight heparin versus standard heparin in general and orthopaedic surgery: a meta-analysis. *Lancet* 1992;**340**:152-6.

39 Taberner DA, Poller L, Burslem RW, Jones JB. Oral anticoagulants controlled by the British comparative thromboplastin versus low-dose heparin in prophylaxis of deep vein thrombosis. *BMJ* 1978;i:272-4.

40 Poller L, McKernan A, Thomson JM, Elstein M, Hirsch PJ, Jones JB. Fixed minidose warfarin: a new approach to prophylaxis against venous thrombosis after major surgery. *BMJ* 1987;**295**:1309-12.

41 Francis CW, Marder VJ, Evarts CM, Yaukoolbodi S. Two-step warfarin therapy: prevention of postoperative venous thrombosis without excessive bleeding. *JAMA* 1983;**249**:374-8.

42 Sevitt S, Gallagher NG. Prevention of venous thrombosis and pulmonary embolism in injured patients. A trial of anticoagulant prophylaxis with phenindione in middle-aged and elderly patients with fractured necks of femur. *Lancet* 1959;ii:981-9.

43 Morris GK, Mitchell JRA. Warfarin sodium in prevention of deep venous thrombosis and pulmonary embolism in patients with fractured neck of femur. *Lancet* 1976;ii:869-72.

44 Powers PJ, Gent M, Jay RM, Julian DH, Turpie AGG, Levine M, *et al*. A randomized trial of less intense postoperative warfarin or aspirin therapy in the prevention of venous thromboembolism after surgery for fractured hip. *Arch Intern Med* 1989;**149**:771-4.

45 Hirsh J. Oral anticoagulant drugs. *N Engl J Med* 1991;**324**:1865-75.

46 Fordyce MJF, Baker AS, Staddon GE. Efficacy of fixed minidose warfarin prophylaxis in total hip replacement. *BMJ* 1991;**303**:219-20.

47 Dale C, Gallus A, Wycherley A, Langlois S, Howie D. Prevention of venous thrombosis by minidose warfarin after joint replacement. *BMJ* 1991;**303**: 224.

48 Gruber UF, Saldeen T, Brokop T, Eklöf B, Eriksson I, Goldie I, *et al*. Incidences of fatal postoperative pulmonary embolism after prophylaxis with dextran 70 and low-dose heparin: an international multicentre trial. *BMJ* 1980;**280**:69-72.

49 Lowe GDO, Small M. Stimulation of endogenous fibrinolysis. In: Kluft C, ed. *Tissue-type plasminogen activator (t-PA): physiological and clinical aspects*. Vol II. Boca Raton, Florida: CRC Press, 1988:129-69.

50 Scurr JH, Coleridge-Smith PD, Hasty JH. Deep venous thrombosis: a continuing problem. *BMJ* 1988;**297**:28-9.

51 Pezzuoli G, Neri Serneri GG, Settembrini P, Coggi G, Olivari N, Buzzetti G, *et al*. Prophylaxis of fatal pulmonary embolism in general surgery using low-molecular weight heparin CY 216: a multicentre, double-blind, randomized, controlled clinical trial versus placebo (STEP). *Int Surg* 1989;**74**:205-10.

52 Wille-Jorgensen P, Hauch O, Dimo B, Christensen SW, Hansen B, Jensen R. Prophylaxis of deep venous thrombosis following acute abdominal surgery. An evaluation of three protocols. *Surg Gynecol Obstet* 1991;**172**:44-9.

53 Walsh JJ, Bonnar J, Wright FM. A study of pulmonary embolism and deep leg vein thrombosis after major gynaecological surgery using labelled fibrinogen, phlebography and lung scanning. *Journal of Obstetrics and Gynaecology of the British Commonwealth* 1974;**81**:311-5.

54 Clarke-Pearson DL, DeLong E, Synan IS, Soper JT, Creasman WT. Coleman RE. A controlled trial of two low-dose heparin regimens for the prevention of postoperative deep vein thrombosis. *Obstet Gynecol* 1990;**75**: 684-9.

55 European Working Group on Critical Leg Ischemia. European consensus document on critical leg ischemia. *Circulation* 1991;**84**(suppl).

56 Turpie AGG, Hirsh J, Gent M, Julian D, Johnson J. Prevention of deep vein thrombosis in potential neurosurgical patients: a randomized trial comparing graduated compression stockings plus intermittent pneumatic compression with control. *Arch Intern Med* 1989;**149**:679-81.

57 Shackford SR, Davis JW, Hollingworth-Fridlund P, Brewer NS, Hoyt DB, Mackersie RC. Venous thromboembolism in patients with major trauma. *Am J Surg* 1990;**159**:363-9.

58 Salzman EW, Harris WH. Prevention of venous thromboembolism in orthopedic patients. *J Bone Joint Surg [Am]* 1976;**58**:903-12.

59 Stamatakis JD, Kakkar VV, Sagar S, Lawrence D, Nairn D, Bentley PG. Femoral vein thrombosis and total hip replacement. *BMJ* 1977;ii:223-5.

60 Houghton GR, Papadekis EG, Rizza CR. Changes in blood coagulation during total hip replacement. *Lancet* 1977;i:1336.

61 Cruickshank MK, Levine MH, Hirsh J, Turpie AGG, Powers P, Jay R, *et al*. An evaluation of impedance plethysmography and ^{125}I-fibrinogen scanning in patients following hip surgery. *Thromb Haemostas* 1989;**62**:830-4.

62 Hull RD, Raskob GE, Gent M. Effectiveness of intermittent pneumatic leg compression for preventing deep vein thrombosis after total hip replacement. *JAMA* 1990;**263**:2313-7.

63 Parker-Williams J, Vickers R. Major orthopaedic surgery on the leg and thromboembolism. *BMJ* 1991;**303**:531-2.

64 Turpie AG, Levine MN, Hirsh J, Carter CJ, Jay RM, Powers PJ, *et al*. A randomized controlled trial of a low-molecular-weight heparin (enoxaparin) to prevent deep-vein thrombosis in patients undergoing elective hip surgery. *N Engl J Med* 1986;**315**:925-9.

65 Planes A, Vochelle N, Mazas F, Mansat CH, Zucman J, Landais A, *et al*. Prevention of postoperative venous thrombosis: a randomized trial comparing unfractionated heparin with low molecular weight heparin in patients undergoing total hip replacement. *Thromb Haemostas* 1988;**60**: 407-10.

66 Dechavenne M, Ville D, Berruyer M, Trepo F, Dalery F, Clermont N, *et al*. Randomised trial of a low-molecular-weight heparin (Kabi 2165) versus adjusted-dose subcutaneous standard heparin in the prophylaxis of deep-vein thrombosis after elective hip surgery. *Haemostasis* 1989;**19**:5-12.

67 Levine MN, Hirsh J, Gent M, Turpie AGG, Leclerc J, Powers PJ, *et al*. Prevention of deep-vein thrombosis after elective hip surgery. A randomized trial comparing low-molecular weight heparin with standard unfractionated heparin. *Ann Intern Med* 1991;**114**:545-51.

68 Planes A, Vochelle N, Fagola M, Feret J, Belland M. Prevention of deep-vein thrombosis after total hip replacement. The effect of low-molecular-weight heparin with spinal and general anaesthesia. *J Bone Joint Surg [Br]* 1991;**73**:418-22.

69 Torholm C, Broeng L, Jorgensen PS, Bjerregaard P, Josephsen L, Jorgensen PK, *et al*. Thromboprophylaxis by low-molecular-weight heparin in elective hip surgery. A placebo-controlled study. *J Bone Joint Surg [Br]* 1991;**73**:434-8.

70 Hull RD, Delmore TJ, Hirsh J, Gent M, Armstrong P, Lofthouse F, *et al*. Effectiveness of intermittent pulsatile elastic stockings for the prevention of calf and thigh vein thrombosis in patients undergoing elective knee surgery. *Thromb Res* 1979;**16**:37-45.

71 Kakkar VV. Prevention of venous thromboembolism. In: Bloom AL, Thomas DP, eds. *Haemostasis and thrombosis*. 2nd ed. Edinburgh: Churchill Livingstone, 1987:802-19.

72 Sandercock PAG, van den Belt AGM, Lindley RI, Slattery J. Anticoagulant and antiplatelet therapy in acute stroke: an overview of the completed randomized trials. Submitted for publication.

73 Royal College of Physicians of London. *Stroke: towards better management*. London: RCP, 1989.

74 Turpie AGG, Levine MN, Hirsh J, Carter CJ, Jay RM, Powers PJ, *et al*. Double-blind randomised trial of ORG 10172 low-molecular-weight heparinoid in prevention of deep-vein thrombosis in thrombotic stroke. *Lancet* 1987;i:523-6.

75 Prins MH, Gelsema R, Sing AK, van Heerala LR, den Ottolander GJH. Prophylaxis of deep venous thrombosis with a low-molecular-weight heparin (Kabi 2165/Fragmin) in stroke patients. *Haemostasis* 1989;**19**: 245-50.

76 Guillebaud J. Surgery and the pill. *BMJ* 1985;**291**:498-9.

77 Sue-Ling H, Hughes LE. Should the pill be stopped pre-operatively? *BMJ* 1988;**296**:447-8.

78 Guillebaud J. Should the pill be stopped pre-operatively? *BMJ* 1988;**296**: 786-7.

79 Hutchison GL. Oral contraception and post-operative thromboembolism: an epidemiological review. *Scott Med J* 1989;**34**:547-9.

80 Bonnar J. Coagulation effects of oral contraception. *Am J Obstet Gynecol* 1987;**157**:1042-8.

81 Robinson G, Mackie IJ, Cohen H, Machin SJ. Should the pill be stopped pre-operatively? *BMJ* 1988;**296**:787.

82 Vessey MP. Female hormones and vascular disease—an epidemiological overview. *British Journal of Family Planning* 1980;**suppl 6**:1-12.

83 Vessey MP, Mant D, Smith A, Yeate SD. Oral contraceptives and venous thromboembolism: findings in a large prospective study. *BMJ* 1986;**292**: 526-8.

84 Helmrich SP, Rosenberg L, Kaufman DW, Strom B, Shapiro S. Venous thromboembolism in relation to oral contraceptive use. *Obstet Gynecol* 1987;**69**:91-5.

85 Stolley PD, Tonascia JA, Tockman MS, Sartwell PE, Rutledge AH, Jacobs MP. Thrombosis with low estrogen oral contraceptives. *Am J Epidemiol* 1975;**102**:197-208.

86 Meade TW, Greenberg G, Thompson SG. Progestogens and cardiovascular reactions associated with oral contraceptives and a comparison of safety of 50 and 30 μg oestrogen preparations. *BMJ* 1980;**280**:1157-61.

87 Canter RJ, Pryce J. Risk of pregnancy while waiting for an operation. *BMJ* 1985;**291**:516.

88 Fotherby K. The progesterone only pill and thrombosis. *British Journal of Family Planning* 1989;**15**:83-5.

89 Notelowitz M, Ware M. Coagulation risks with postmenopausal oestrogen therapy. In: Studd JWW, ed. *Progress in obstetrics and gynaecology*. Edinburgh: Churchill Livingstone, 1982:228-40.

90 Carter CJ. Thrombosis in relation to oral contraceptives and hormone replacement therapy. In: Greer IA, Turpie AGG, Forbes CD, eds. *Haemostasis and thrombosis in obstetrics and gynaecology*. London: Chapman and Hall, 1992:371-88.

91 Royal College of General Practitioners. Oral contraception and thromboembolic disease. *J R Coll Gen Pract* 1967;**13**:719-39.

92 Badaracco MA, Vessey M. Recurrence of venous thromboembolic disease and use of oral contraceptives. *BMJ* 1974;i:215-7.

93 Howell R, Fidler J, Letsky E, de Swiet M. The risks of antenatal subcutaneous heparin prophylaxis: a controlled trial. *Br J Obstet Gynaecol* 1983;**90**:1124-8.

94 Lao TT, de Swiet M, Letsky E, Walters BNJ. Prophylaxis of thromboembolism in pregnancy: an alternative. *Br J Obstet Gynaecol* 1985;**92**: 202-6.

95 de Swiet M, Floyd E, Letsky E. Low risk of recurrent thromboembolism in pregnancy. *Br J Hosp Med* 1987;**38**:264.

96 Rutherford SE, Phelan JP. Thromboembolic disease in pregnancy. *Clin Perinatol* 1986;**13**:719-39.

97 Hathaway WE, Bonnar J. *Haemostatic disorders of the pregnant woman and newborn infant*. New York: Elsevier, 1987.

98 Ginsberg JS, Hirsh J. Use of anticoagulants during pregnancy. *Chest* 1989;**95**(suppl):156-160S.

99 de Swiet M, Letsky E, Mellows H. Drug treatment and prophylaxis of thromboembolism in pregnancy. In: Lewis PJ, ed. *Therapeutic problems in pregnancy*. Lancaster: MTP, 1977.

100 Hall JG, Pauli RM, Wilson KM. Maternal and fetal sequelae of anticoagulation during pregnancy. *Am J Med* 1989;**68**:122-40.

101 Stevenson RE, Burton M, Ferlauto GJ, Taylor HA. Hazards of oral anticoagulants during pregnancy. *JAMA* 1989;**243**:1549-51.

102 Gallus AS. Anticoagulants in the prevention and treatment of thromboembolic problems in pregnancy including cardiac problems. In: Greer IA, Turpie AGG, Forbes CD, eds. *Haemostasis and thrombosis in obstetrics and gynaecology*. London: Chapman and Hall, 1992:319-47.

103 Ginsberg JS. Fetal abnormalities and anticoagulants. In: Greer IA, Turpie AGG, Forbes CD, eds. *Haemostasis and thrombosis in obstetrics and gynaecology*. London: Chapman and Hall, 1992:361-9.

104 de Swiet M. Thromboembolism. In: de Swiet M, ed. *Medical disorders in obstetric practice*. London: Blackwell Scientific, 1989:116-97.

105 Hill NCW, Hill JG, Sargent JM, Taylor CG, Bush PV. Effect of low dose heparin on blood loss of caesarean section. *BMJ* 1988;**296**:1505-6.

106 Orme ML'E, Lewis PJ, de Swiet M. May mothers given warfarin breast feed their infants? *BMJ* 1977;i:1564-5.

107 Winter JH, Douglas AS. Congenital thrombotic problems in obstetrics and gynaecology. In: Greer IA, Turpie AGG, Forbes CD, eds. *Haemostasis and thrombosis in obstetrics and gynaecology*. London: Chapman and Hall, 1992:431-57.

108 Department of Health. *Confidential enquiries into maternal deaths in England and Wales 1982-1984*. London: HMSO, 1989.

(Accepted 29 May 1992)