A COST-EFFECTIVENESS ANALYSIS

OF

THE ALTERNATIVE APPROACHES TO

THE PROPHYLAXIS OF VENOUS THROMBOEMBOLISM

By

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ABSTRACT:

Up until the last decade, physicians were content to base management decisions in postoperative surgical patients on the clinical diagnosis of deep vein thrombosis (DVT). Subsequently, multiple studies have demonstrated the insensitivity of clinical diagnosis. Pulmonary embolism (PE) is the most common preventable cause of in-hospital death, which no doubt reflects the insensitivity of clinical diagnosis. Multiple randomized trials indicate that low-dose subcutaneous (sc) heparin and intravenous (IV) dextran are effective for preventing death due to pulmonary embolism in postoperative general surgical patients. Other approaches effective against venous thromboembolism are: intermittent pneumatic leg compression (IPLC) and screening with ^{125}I-fibrinogen leg scanning. We have performed a cost-effective analysis in 1,000 patients over the age of forty years undergoing major elective surgery comparing the prophylactic approaches described above with the "no-programme" situation (early ambulation but no other active prophylaxis). The total cost (Canadian dollars) and total effects (deaths from pulmonary embolism averted) are as follows: s.c. heparin $35,714 for 7 lives saved; IPLC $55,803 for 7 lives saved; IV dextran $137,235 for 6 lives saved; leg scanning $396,599 for 7 lives saved; and the "no-programme" situation $53,472 for 8 lives lost. The "no-programme" situation is clearly cost-ineffective. Incremental cost-effectiveness analysis indicates that s.c. heparin is the most cost-effective, followed by IPLC. Dextran and leg scanning, although effective, are both expensive; therefore s.c. heparin or IPLC prophylaxis are preferred.

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Chapter 1. INTRODUCTION

Pulmonary embolism is the most common preventable cause of death in hospitalized patients in North America. It is estimated that 0.1-0.8% of patients over the age of 40 years undergoing general surgery suffer fatal pulmonary embolism (1-3).

Primary Prevention:

Over the past two decades, a number of approaches for preventing pulmonary embolism have been evaluated in patients undergoing general surgery (1-3). Three approaches in particular have been shown to be both safe and effective in this patient group. These are:

a) low-dose subcutaneous heparin prophylaxis (1,4-14)

b) intravenous dextran (9,15-26) and

c) intermittent pneumatic compression of the legs (27-36).

These primary prophylactic agents act by preventing deep vein thrombosis which is the precursor of pulmonary embolism. Their safety and effectiveness in general surgical patients is well documented by the findings of multiple randomized clinical trials (1-36).

Secondary Prevention:

An alternative approach for preventing massive pulmonary embolism is the early detection (and treatment) of subclinical venous thrombosis by ^{125}I-fibrinogen leg scanning (37,38). The use of ^{125}I-fibrinogen leg scanning as a screening test provides the clinician with a method of early detection of deep vein thrombosis as, in the majority of general surgical patients, postoperative venous thrombosis is subclinical and therefore cannot be detected by clinical examination. The frequency of leg scan detected

postoperative venous thrombosis in general surgical patients over the age of 40 years, in the Hamilton region, ranges from 7% to 25% and is influenced by the risk factors of previous venous thromboembolism, advanced age, prolonged immobility, leg paralysis, obesity, varicose veins, heart failure and the presence of malignancy.

Screening with leg scanning will therefore, be considered in this analysis as an alternative to primary prophylaxis. It is probable that the application of routine primary prophylaxis would have a substantial impact in reducing the frequency of postoperative deep vein thrombosis and based on this, it is estimated that the routine use of effective prophylaxis in patients undergoing elective general surgery would prevent 4,000-8,000 postoperative deaths annually in the United States (39).

Objective of this Thesis:

The objective of this thesis is to perform a cost-effectiveness analysis comparing:

a) primary prophylaxis using subcutaneous heparin or intravenous dextran or intermittent pneumatic compression
b) secondary prophylaxis using ^{125}I-fibrinogen leg scanning for early detection of deep vein thrombosis, with
c) the "no-programme" situation, (in which patients undergo routine postoperative care including early ambulation but do not receive active prophylaxis).

Effectiveness will be measured in terms of the number of deaths due to pulmonary embolism prevented postoperatively in high-risk general surgical patients.

Clinical relevance of this cost-effectiveness analysis:

The use of cost-effectiveness analysis provides a practical economic tool which allows comparison of both the effects and costs of health care

approaches.

At present, there is no organized strategy for preventing venous thromboembolism in many hospitals throughout Canada and the United States and thus this disease and its complications continue unabated. The reasons for this are complex and include: 1) lack of concern as to the need for prophylaxis due largely to the unawareness that there is a significant problem which requires action (the reason for this is primarily the fact that each general surgeon would have to operate on approximately 300 patients to see one death from pulmonary embolism); 2) doubts as to the safety of anticoagulant prophylaxis have delayed acceptance of low-dose heparin prophylaxis. However, a recent randomized trial suggests that this fear is unfounded in the majority of general surgical patients; 3) there has been a failure to develop a cohesive approach to preventing thromboembolism in individual institutions, departments and hospitals. Furthermore, there has been a reluctance to develop new programmes which may increase health costs when the cost-effectiveness of such new programmes has not been adequately evaluated. There is an extensive and comprehensive body of literature dealing with the efficacy and safety of the various prophylactic measures, some of which is derived from clinical studies performed by members of the Hamilton Regional Thromboembolism Programme. Little or no attention, however, has been addressed to the economic implications of prophylaxis.

Chapter 2. PRIMARY AND SECONDARY PREVENTION - THE EVIDENCE SUPPORTING THE CURRENT ALTERNATIVE APPROACHES

Venous thrombi usually develop at sites of slow or disturbed flow and begin as small deposits of platelets, fibrin and red cells in valve cusp pockets or in the intramuscular sinuses of leg veins (40,41). As the thrombus grows it occludes the lumen of the vein producing stasis and then extends both proximally and distally as a coagulation thrombus composed of red cells with interspersed fibrin.

The mechanisms which are recognized to be important in the pathogenesis of venous thromboembolism are venous stasis, activation of blood coagulation and endothelial damage.

Two active approaches can be taken to prevent fatal pulmonary embolism. These are early detection of subclinical venous thrombosis by screening high-risk patients postoperatively with ^{125}I-fibrinogen leg scanning (37,38) and primary prophylaxis using drugs or physical methods (1-36). (see appendix 1 and 2).

The prophylactic methods which have been evaluated clinically have been directed at one or more of these pathogenic factors and include intermittent pneumatic compression of the legs which prevents stasis; low-dose subcutaneous heparin which counteracts the activation of blood coagulation; and dextran which suppresses platelet function and their interaction with the damaged vessel wall as well as altering the stability of the formed clot encouraging rapid lysis.

An alternative approach as mentioned previously is to screen high-risk patients with ^{125}I-fibrinogen leg scanning to detect venous thrombi in the

early stage thus preventing massive pulmonary embolism by the initiation of treatment before massive embolism can ensue.

Randomized clinical trials evaluating prophylactic agents provide the backbone for the current understanding of prophylaxis for venous thromboembolism. The clinician should consider a number of important study criteria when assessing the validity of the results of these clinical trials. These essential criteria are described in greater detail in Appendix 3.

a) The study should incorporate a concurrent control group with patients randomly allocated, thus avoiding the danger of conscious or unconscious bias.

b) To avoid diagnostic suspicion bias, the study should be "blinded" ideally by a double-blind design or, if the nature of the intervention does not allow this, interpretation of the endpoints must be carried out by an observer who does not have knowledge of the patient's treatment category

c) the use of clearly defined endpoints is mandatory

d) on analysis of the study, comparability of the groups for important prognostic factors should be demonstrated

e) appropriate statistical methods must be used for analysing the data

f) because of the inaccuracy of clinical diagnosis, it is essential that reliable, objective diagnostic methods are used to determine the endpoint.

The objective methods include ^{125}I-fibrinogen leg scanning, impedance plethysmography and ascending venography for the diagnosis of venous thrombosis; and pulmonary angiography (or pulmonary emboli demonstrated at

autopsy) for the diagnosis of pulmonary embolism. The most important endpoint is fatal pulmonary embolism but because the frequency is relatively low, large numbers of patients have to be studied before this endpoint is used. For this reason, the majority of studies have used venous thrombosis detected by either ^{125}I-fibrinogen leg scanning or by venography as the endpoint for evaluation of prophylaxis.

A number of prophylactic approaches including low-dose subcutaneous heparin, dextran and intermittent pneumatic compression have been evaluated in a large number of adequately designed studies following the above criteria (42,43) (see appendix 1 and 2). Because of the consistent findings obtained by these multiple studies, these three approaches are now accepted as the objective methods of prophylaxis in selected high-risk patient groups.

Oral anticoagulant therapy has been extensively evaluated as well and appears to be an effective form of prophylaxis in very high-risk patients but at the price of an increased and clinically significant risk of bleeding (42,43).

A number of antiplatelet agents including aspirin have been evaluated and have been shown to be ineffective in patients undergoing general surgery (42).

Other methods of prophylaxis under evaluation include heparin combined with dihydro-ergotamine, ultra low-doses of intravenous heparin, ancrod, and xylocaine; however, at present their effectiveness is uncertain (42).

Subcutaneous Heparin Prophylaxis:

The efficacy of low-dose heparin has been extensively evaluated in patients undergoing elective general surgery in more than fifteen randomized studies (1,4-14) satisfying the criteria outlined on page 5 and in appendix 3. The heparin was administered subcutaneously in a dose of 5,000 units. The

first dose was given preoperatively two hours before surgery and a postoperative dose was administered 12 hourly in nine studies and 6 hourly in six studies. All but two of these studies showed a significant reduction in venous thromboembolism in the heparin prophylaxis group. The majority of the studies used leg scan detected venous thrombosis as the endpoint and a marked reduction in venous thrombosis was demonstrated in the heparin versus control group. In two studies (10,11) however, the frequency of venous thrombosis was very low in the control group (5-10%) and a reduction with heparin was not demonstrated. In four of the above studies (1,6,12,14), the number of general surgical patients entered was large enough to assess the effects of prophylaxis on the frequency of popliteal or femoral vein thrombosis and in all four there was a significant reduction in the frequency of proximal vein thrombi in patients receiving subcutaneous heparin.

The effect of low-dose heparin on the frequency of venous thromboembolism was evaluated in six of the above studies. Two of these (8,10) used perfusion lung scanning as an endpoint and four used fatal pulmonary embolism (1, 44-46) at autopsy as the endpoint. In five (1,8,10,45,46) there was reduction in the frequency of postoperative pulmonary embolism. The most important of these studies was the International Multicentre Trial (1). Four thousand patients were randomly allocated to either a low-dose heparin or control group and the major endpoint was pulmonary embolism found at autopsy. There were 100 deaths in the control group and 80 in the heparin group; this difference was not statistically significant. Pulmonary embolism was found in 22 of the 72 autopsies in the control group and 5 of the 52 autopsies in the treatment group; a statistically significant difference ($p<0.01$). Pulmonary embolism was classified as being fatal if it was present in the

pulmonary trunk, in a main pulmonary artery, or in at least two lobar arteries if no other cause of death was found. Using these criteria, fatal pulmonary embolism was found in 16 control patients and two treated patients. This difference was statistically significant.

An important observation made in several of the studies was that after heparin prophylaxis was discontinued in patients who remained at risk (14,44), the subsequent rate of thromboembolic complications was equal in both groups, suggesting that prophylaxis should be continued until the patient is fully ambulant.

A recent large multicentre study (45), using death due to pulmonary embolism as the endpoint, compared low-dose heparin with dextran 70. Over 4,000 patients were entered into the study. There were 38 deaths during the period of the study in the dextran group and 37 in the low-dose heparin group. The autopsy rate was high in each group; pulmonary embolism was considered the sole or contributory cause of death in six patients in the dextran group and six patients in the heparin group (five of the six cases in the dextran group received a full prescribed course of prophylaxis compared with only two of the six in the heparin group). It is of interest that the frequency of death due to pulmonary embolism in the heparin group was similar to that reported in the other large multicentre study (1). Thus, in conclusion it is evident that dextran prophylaxis is effective for preventing death due to pulmonary embolism in general surgical patients and may be comparable with low-dose subcutaneous heparin in this patient group.

The major potential complication limiting the widespread use of low-dose heparin is bleeding. Since bleeding is a complication of any surgical procedure, the effects of heparin on bleeding can only be assessed in ran-

domized studies in which the effects of heparin are compared with a control group in either a double-blind manner or with the observer unaware of which treatment group the patient is in.

A prospective evaluation of bleeding complications was carried out in eight trials (1,4-6,9,14,44,47) involving general surgical patients, but only one of these was double-blind and in the others, no assurance was made that the observer was unaware of the treatment group. There was no significant difference in surgical bleeding between control and heparin group patients in five of these eight trials (4-6,9,44). One of the eight (47) reported an increase in bleeding which was considered to be both clinically and statistically significant but in no instance was a fatal bleeding episode attributed to heparin treatment. In the International Multicentre Trial (1) comparing low-dose subcutaneous heparin with a no treatment group there was a slight but statistically significant increase in the proportion of patients with excessive perioperative bleeding. An increase in the proportion of patients with postoperative wound hematomas in the heparin group was also observed. Similar findings were also reported by another group (44) who studied a large number of patients. The findings of the double-blind study using s.c. heparin 5,000 units every 12 hours are particularly important. It is of interest that this study showed identical transfusion requirements for each group and increased bleeding was not observed in the heparin group.

Dextran:

Dextran is a glucose polymer which was introduced as a volume expander and was then subsequently evaluated as an antithrombotic agent (15-17). Two sizes of dextran polymers are in clinical use - dextran 70 with a mean

molecular weight of 70,000 and dextran 40 with a mean molecular weight of 40,000. Only dextran 40 is licenced for use in North America.

The antithrombotic properties of dextran have been attributed to a number of actions including (18-21):

1) decreased blood viscosity
2) reduced platelet interaction with damaged vessel wall
3) decreased platelet aggregation and
4) an increase in the susceptibility to fibrinolysis of the fibrin clot formed in the presence of dextran.

The results of studies evaluating dextran 70 for the prevention of deep vein thrombosis in patients undergoing general surgical and gynaecological surgical procedures are potentially confusing. In the six or more studies (9,22-26) that meet the essential criteria listed in appendix 3, dextran was given intravenously both preoperatively and for a varying period of time postoperatively. The endpoint used in these studies was ^{125}I-fibrinogen leg scanning. In three studies (23,25), the frequency of postoperative venous thrombosis was significantly reduced while in the others (9,22-26), no benefit was demonstrated. In contrast to the results of studies in general surgical patients, dextran has been reported to consistently reduce the frequency of postoperative thrombosis in patients undergoing hip surgery (48-51) in whom venography was the test used to detect deep vein thrombosis. Furthermore, dextran was infused peroperatively and then postoperatively for 5-10 days.

There are two possible relevant explanations for these observed differences. The first is that the dextran was given for a longer period of time postoperatively and the second is that a venographic endpoint was used to

detect the thrombosis. With regard to the latter point, it has been noted that fibrin clots formed in the presence of dextran are more susceptible to fibrinolysis (20,21). It is therefore possible that ^{125}I-fibrinogen detectable thrombi formed postoperatively in patients treated with dextran undergo lysis and therefore may not have been detected when venography was performed at a fixed time postoperatively.

Of major importance are the results of the large multicentred trial (45) comparing low-dose heparin prophylaxis with dextran therapy in patients undergoing general surgery which suggests that dextran is likely to be as effective for preventing death due to fatal embolism.

The most important side-effect of dextran is the anaphylactoid reaction. Recent data suggests that this potentially fatal reaction can be prevented by the use of the hapten inhibition principle. Another potentially serious side-effect associated with dextran use is the risk of volume overload which particularly in elderly patients, can result in cardiac failure. Excessive bruising has been reported but bleeding has not been a serious problem.

Intermittent Pneumatic Compression and Other Methods which Enhance Venous Blood Flow in the Legs:

It is well established that stasis occurs in leg veins preoperatively and postoperatively in patients who are immobilized. A number of techniques or approaches designed to increase blood flow have been evaluated for the prevention of postoperative venous thrombosis. These include elastic stockings, leg elevation, intensive physiotherapy, graduated pressure stockings, electrical calf muscle stimulation and intermittent calf compression.

The most effective of these approaches is intermittent calf compression

and it is of interest that this method not only enhances venous flow in the legs but also enhances blood fibrinolysis.

Simple Physical Methods: A number of studies have been performed using relatively simple physical methods. These include leg elevation (52,54), elastic stockings (52,55), a combination of elastic stockings, intensive physiotherapy and leg elevation (53), and the use of graduated compression stockings (56). Neither elastic stockings alone nor leg elevation alone appears to be effective in reducing the frequency of postoperative venous thrombosis. However, the combination of elastic stockings, leg elevation and intensive physiotherapy reduced the frequency of postoperative thrombosis more than three-fold although, because only small numbers of patients were included in the study, the difference was not significant. In a recent study (56), a significant reduction in leg scan detected postoperative venous thrombosis was reported in patients fitted with graduated pressure stockings. Graduated pressure stockings are hemodynamically superior to the standard elastic stockings so that the different results obtained using these two modalities are not necessarily contradictory. It appears, therefore, that the simple physical methods that have been traditionally used in postoperative patients are ineffective. There is a possibility that the more hemodynamically effective graduated pressure stockings may be effective; this approach warrants further study.

Electrical Calf Muscle Stimulation: Calf muscle movement induced by electrical stimulation can only be used peroperatively because it produces leg discomfort in the conscious patient. Five studies (12,22,57-59) have been carried out in postoperative patients using peroperative calf muscle

electrical stimulation. In three (22,57,58), there was a significant reduction in the frequency of leg scan detected venous thrombosis and in two (12,59) there was no effect. A possible criticism of these studies is that the patients were only followed with leg scanning for a relatively short period of time postoperatively so that the results obtained cannot be extrapolated to high-risk patients who remain in bed for long periods of time postoperatively. Indeed, there is good evidence that in such patients, prophylaxis should be continued postoperatively until the patient is fully mobile.

Intermittent Calf Compression:

Intermittent calf compression has been extensively investigated for the prevention of postoperative venous thrombosis. Pressure is applied to the calf by intermittent inflation of a cuff or boot. Two types of compression cycles have been used; a fast cycle and a slow cycle. With the fast cycle, a brief period of calf compression (5-20 seconds) at 50 mm of mercury is followed by a long rest period of 60-100 seconds. For the slow cycle, each leg is compressed for one minute at a pressure of 40-55 mm mercury and this is followed by a rest period of one minute.

Intermittent compression of the calf not only increases pulsatile femoral blood flow (27,28) by periodic emptying of the calf but also increases systemic fibrinolytic activity (29). It is of further interest that intermittent compression of the arm (30), which also enhances fibrinolytic activity, has been reported to decrease the frequency of leg scan detected venous thrombosis in general surgical patients. It is possible, therefore, that the protection obtained with this approach may be due to both an increase in fibrinolytic activity and a decrease in stasis.

Five studies (31-34,60) using a fast compression cycle have shown a significant reduction in leg scan detected venous thrombosis in postoperative

patients. Two studies (35,36) have used a slow cycle and in both there was a reduction in the frequency of venous thrombosis in patients without malignant disease (35).

In many of the reports, pneumatic compression boots were applied perioperatively and continued for a maximum of 24 hours postoperatively and the patients were screened with leg scanning for between 3 and 7 days postoperatively. We noted that pneumatic compression of the calf for five days significantly reduced the frequency of thrombosis while the pneumatic devices were worn but that this protection was lost, and negating its early benefit, after the devices were removed. Many of the pneumatic devices in current use are uncomfortable because they produce excessive sweating of the legs and inconvenient because they cannot be worn while the patient is ambulant. Consequently, they need to be removed frequently during the period between complete bedrest and full ambulation. The ideal pneumatic device is one which does not produce excessive sweating and which does not interfere with the patient's progression to full ambulation. We have recently evaluated an inflatable pulsatile stocking which does have these desirable qualities in patients undergoing major elective knee surgery. Patient compliance was excellent and the stockings did not have to be removed during ambulation. This approach appeared to be highly effective, reducing the frequency of thrombosis in this very high-risk group of patients from 66% to 6%.

The major advantage of intermittent calf compression is the lack of side-effects. It is an effective method for preventing postoperative deep vein thrombosis in patients undergoing general surgery.

The effectiveness of intermittent pneumatic compression for preventing fatal pulmonary embolism is uncertain, as this major complication of deep vein

thrombosis has not been evaluated in studies of intermittent compression. Thus, further studies are also required addressing this endpoint but may not be feasible for obvious ethical reasons.

Practical Approaches for Preventing Venous Thromboembolism in Patients Undergoing Elective General Surgery:

Subcutaneous low-dose heparin and dextran are both effective for preventing death due to pulmonary embolism. Low-dose heparin prophylaxis is more convenient than dextran prophylaxis and is therefore, perhaps the prophylaxis of choice.

Intermittent pneumatic compression offers an alternative approach in those patients who are at risk of bleeding (i.e. spinal anaesthetic). It should be kept in mind however, that the efficacy of this approach for pulmonary embolism has not yet been evaluated.

A point of practical importance is whether the individual patient at risk for venous thromboembolism can be identified or whether it is necessary to administer prophylaxis to all patients undergoing general surgery. From the age of 40 years, the risk of developing postoperative venous thrombosis increases; thus, any patient undergoing general surgery of more than 1/2 hour duration over the age of 40 years should be considered for prophylaxis. Additional clinical risk factors for venous thrombosis include previous venous thromboembolism, the presence of malignancy, cardiac failure, prolonged immobility, paralysis, obesity or varicose veins. The frequency of post-operative venous thrombosis in individual general surgical patients over the age of 40 years varies from 10% up to as high as 30% or more depending upon the actual age and the presence of additional risk factors. This frequency can be reduced four-fold or more by the application of prophylaxis.

The Secondary Prevention of Pulmonary Embolism by Early Detection of Venous Thrombosis:

An alternative approach for preventing massive pulmonary embolism is the early detection (and treatment) of subclinical venous thrombosis by the use of currently available screening tests. In the majority of hospitalized patients, venous thrombosis developing as a complication of surgery or a severe medical illness is subclinical and therefore, cannot be detected by even a careful clinical examination. The use of screening tests, however, in particular ^{125}I-fibrinogen leg scanning, provides the clinician with a means of early detection and thus treatment. Because the mass screening of high-risk patients with deep vein thrombosis is clinically less preferable by comparison with primary prophylaxis, the use of screening should be confined to selected patients in whom primary prophylaxis is either not applicable or ineffective.

The screening procedure most widely used for the detection of venous thrombosis is ^{125}I-fibrinogen leg scanning. A number of investigators have compared results of expectant scanning and venography in general surgical and medical patients and have shown agreement of the results of the two techniques in about 90% of patients (61-66). We have recently completed a study in which the results of expectant scanning and venography were compared in 205 legs. Most patients studied had abdominal or thoracic surgical procedures but some were studied after suspected myocardial infarction. The indication for venography was an abnormal leg scan and, as bilateral venography was usually done even if the scan was only unilaterally abnormal, venograms were obtained in a larger number of legs with normal scans. The leg scan was positive in the calf in 96 of the 104 instances of calf vein

thrombosis (92%) demonstrated by venography, 20 of the 28 popliteal vein thrombi (71%) and 17 of the 26 femoral vein thrombi (60%). It is evident from these results that the leg scan is highly sensitive to calf vein thrombosis but is less sensitive in the thigh. The venogram was normal in 24 of the 99 instances of positive leg scans. Of these, 11 were associated with obvious superficial phlebitis, hematoma or skin rash. All of these disorders are known to produce a positive leg scan result.

Screening with a Combination of ^{125}I-Fibrinogen Leg Scanning and Impedance Plethysmography:

^{125}I-fibrinogen leg scanning and impedance plethysmography are potentially complementary as screening tests in high-risk patients. This approach is particularly attractive in patients who have hip surgery because of the high frequency of proximal vein thrombosis and because the surgical wound in the leg renders the leg scan uninterpretable in the thigh.

We have recently performed a comparative study (67) between patients undergoing general surgery and hip surgery using the combined approach of fibrinogen leg scanning and impedance plethysmography (see appendix 2). The aim of the study was to determine the clinical value of adding impedance plethysmography to leg scanning for the detection of deep vein thrombosis in these two high-risk groups. Six hundred and thirty general surgery patients and 385 patients who had hip surgery were screened by both techniques. Venography was performed if either test was positive to determine the frequency with which proximal deep vein thrombosis, confirmed by venography, was detected by impedance plethysmography but not by leg scanning and to assess the positive predictive value of these tests (likelihood that patients with positive results by screening would have venous thrombosis demonstrated at venography). Either the impedance plethysmograph result or the leg scanning

result was abnormal in 67 of 630 general surgical patients (11%) and 158 of 385 hip surgery patients (41%). The positive predictive values of these tests in general surgical and hip surgery patients was 79% and 86% for leg scan alone, 33% and 90% for impedance plethysmography alone and 87% and 95% when both the leg scan and IPG result were positive. The addition of impedance plethysmography to leg scanning in general surgical patients identified only one additional patient with proximal vein thrombosis (0.2%) whereas in hip surgery patients, the addition of impedance plethysmography identified 25 additional patients with proximal vein thrombosis (6%).

The results of this study are consistent with previous findings that suggested that the majority of venous thrombi occurring in general surgical patients arise in the calf and so can be detected by leg scanning, whereas a considerable number of thrombi in hip surgery patients arise in the femoral vein and may occur as an isolated event.

This study also provides previously unavailable data on the positive predictive values of abnormal impedance plethysmography or leg scan results in these patients and so provides a rational basis for making management decisions in patients who are screened and have positive results. Thus, the likelihood that a patient would have venous thrombosis confirmed by venography if both impedance plethysmography and leg scan results were abnormal was 87% for general surgical patients and 95% in hip surgery patients. The positive predictive value of an abnormal leg scan alone was 79% in patients who had general surgery and 86% in patients who had hip surgery, whereas the positive predictive value of an abnormal impedance plethysmograph result alone was only 33% in patients who had general surgical procedures and 97% in patients who had hip surgery. The lower predictive value of an abnormal plethysmograph

result in the presence of a normal leg scan result in general surgical patients is likely related to the low prevalence of proximal vein thrombosis undetected by leg scanning in this group, since prevalence is an important variable that influences the positive predictive value.

The results indicate that the addition of impedance plethysmography to leg scanning is of limited clinical value in patients who have general surgical procedures but is of considerable value in patients who have hip surgery. Thus, the addition of impedance plethysmography to the leg scan resulted in the detection of thrombosis in only one additional patient (0.2%) in the general surgical group but it led to the detection of proximal deep vein thrombosis in 25 additional patients (6%) who underwent hip surgery, almost doubling the frequency of the addition of proximal vein thrombosis in this latter group.

Chapter 3. ECONOMIC MODEL

In many, if not the majority of hospitals at present, there is no organized strategy for preventing venous thromboembolism and thus this disease and its complications continue relatively unabated. As stated previously, the reasons for this are complex and include

1) doubts as to the safety of anticoagulant prophylaxis (see previous chapter) and
2) lack of awareness that there is a problem of significant proportion which requires action.

This latter situation has arisen because massive or fatal pulmonary embolism is a relatively rare event in any individual physician or surgeon's experience (i.e. a busy general surgeon may only see one death from pulmonary embolism every 3-4 years). This is compounded by the fact that any side-effects attributable to a prophylactic approach are highly visible, whereas any benefits pass unnoticed because of the nature of prophylaxis.

An extensive and comprehensive body of literature deals with the efficacy and safety of the various prophylactic measures (see previous chapter); however, little attention has been addressed to the economic implications of prophylaxis.

The use of cost-effectiveness analysis allows an objective comparison of the cost of the different prophylactic strategies in relation to deaths due to massive pulmonary embolism prevented.

Alternative Economic Models:

To familiarize the reader with options for economic evaluation, a brief summary of cost-effectiveness analysis and the alternative options, cost-

benefit analysis and cost-utility analysis is provided below.

Cost-Effectiveness Analysis:

Cost-effectiveness analysis allows comparison of several alternative programmes directed at the same health care problem (i.e. death due to pulmonary embolism). This technique is only applicable if the programmes being compared have effects which can be measured in the same physician unit (i.e. deaths averted). Using this model, the costs are expressed in dollar terms and the effects in physical terms. The application of this model permits the ranking of alternative programmes.

Cost-Benefit Analysis:

This economic model (124) allows not only comparison of alternative programmes with the same outcome, but also alternative programmes with different outcomes. Using this model, both the benefits and costs are expressed in dollar terms.

Cost-benefit analysis provides a rank ordering of those projects which yield the greatest surplus of benefits over cost of which present the highest ratio of benefits to costs.

Cost-Utility Analysis:

This technique is relatively new. In cost-utility analysis, the programme benefits are measured in patient outcomes converted to health units (i.e. healthy days or quality adjusted life years). Utility refers to the usefulness of a specific level of health status and can be measured by the preference of individuals or society for any particular set of health outcomes. Because cost-utility analysis incorporates quality of life concerns, it depends to a much greater extent on subjective values than do the other two models.

Rationale for Choosing Cost-Effectiveness Analysis to Evaluate the Alternative Strategies for Preventing Pulmonary Embolism in Postoperative General Surgical Patients:

The objective of this thesis is to compare a number of strategies (programmes) for preventing venous thromboembolism. The outcomes (i.e. effects) of each strategy will be measured in the same units (i.e. deaths prevented), thus allowing the application of the cost-effectiveness model. The use of cost-effectiveness analysis allows, an objective comparison of the costs of the different strategies expressed in terms of deaths prevented.

The number of deaths prevented by each strategy can be extrapolated from the literature because the effectiveness of the alternative prophylactic measures has been evaluated by randomized trials in the majority of instances. The costs can be readily measured, thus both the cost estimates and outcome estimates are based on objective data.

Cost-benefit analysis could also be applied but this approach has the disadvantage that the deaths averted would have to be converted into dollar terms (i.e. the dollar benefit of preventing a death). For this reason, this approach is less objective as it is difficult to estimate the dollar benefit in terms of deaths prevented. By comparison, the number of deaths prevented by primary prophylactic agents is well documented.

Viewpoint:

The viewpoint expressed in this project is that of the Thromboembolism Programme. The approaches compared in this economic analysis are currently available in the Hamilton Region. The Ontario Ministry of Health carries all costs under insured services for physicians and hospitals. The Hamilton

Regional Thromboembolism Programme involves five hospitals.

Chapter 4. ALTERNATIVE PROGRAMMES AND THEIR EFFECTS

"No-Programme" - The clinical consequences of failing to use prophylactic measures postoperatively in general surgical patients are readily derived from the control groups of multiple randomized trials reported in the literature (see appendix 2).

Failure to use effective prophylaxis in general surgical patients over the age of 40 years would result in:

a) clinically suspected deep vein thrombosis in 3.5% of patients

b) clinically evident pulmonary embolism in 1.8% of patients

c) Fatal Pulmonary Embolism in 0.8% of Patients.

Because these are estimates based from multiple studies, they will also be subject to sensitivity analysis (see sensitivity analyses).

Because the clinical findings suggestive of deep vein thrombosis or pulmonary embolism are non-specific, clinically suspected deep vein thrombosis or pulmonary embolism requires confirmation by objective testing (chapter 2 and appendix 4). Patients with objectively confirmed deep vein thrombosis or pulmonary embolism will require 10 days of intravenous heparin therapy followed by three months of long-term anticoagulant therapy. This therapeutic approach is associated with a very low recurrence rate of less than 3%. The rate of major bleeding complications due to full-dose anticoagulant therapy in the Hamilton Region is approximately 8%. Mortality from bleeding in patients who receive anticoagulant therapy is very infrequent (0.2-0.3% of patients receiving full-dose anticoagulant therapy).

Primary Prophylaxis:

The effectiveness of low-dose subcutaneous heparin, dextran and inter-

mittent pneumatic compression of the legs has been tested in a large number of randomized clinical trials fulfilling the design criteria outlined on page 5 and in appendix 3, and the evidence for the effectiveness of these approaches is summarized in chapter 2.

Low-dose subcutaneous heparin: Low-dose subcutaneous heparin prophylaxis is highly effective in preventing postoperative deep vein thrombosis in general surgical patients. The application of low-dose subcutaneous heparin prophylaxis to patients over the age of 40 years undergoing general surgery for more than 1/2 hour would reduce:

a) clinically suspected deep vein thrombosis to 1.8% (compared with the no-programme situation of 3.5%)
b) clinically suspected pulmonary embolism to 0.6% (compared with the no-programme situation of 1.8%)
c) fatal pulmonary embolism to 0.1% (compared with the no-programme situation of 0.8%).

The frequency of clinically suspected deep vein thrombosis and clinically suspected pulmonary embolism was estimated from multiple randomized studies. The frequency of fatal pulmonary embolism used here is derived directly from the frequencies observed in large multicentre randomized trials.

Low-dose subcutaneous heparin prophylaxis is associated with a slight increase in the frequency of postoperative wound hematomas but in this patient group, it is not associated with clinically significant bleeding (double-blind randomized studies indicated that the frequency of bleeding in both the control group and the subcutaneous heparin group are the same).

Dextran: Intravenous dextran therapy is effective in preventing deaths due

to massive pulmonary embolism but is less effective in preventing leg scan-detected venous thrombosis. The reason that it is effective for preventing deaths due to massive pulmonary embolism may be its favourable effect with respect to enhancing clot lysis.

The use of dextran prophylaxis in general surgical patients over the age of 40 years would result in:

a) a reduction of clinically suspected deep vein thrombosis to 3.0% (compared with no-programme situation of 3.5%).

b) a reduction in the frequency of clinically suspected pulmonary embolism to 1.2% (compared with a no-programme situation of 1.8%)

c) fatal pulmonary embolism, however, is reduced to a similar extent as observed with low-dose subcutaneous heparin prophylaxis (that is from 0.8% to 0.1%).

The estimates of clinically suspected DVT are based on multiple studies whereas the estimate for fatal pulmonary embolism is based on direct observation by a large multicentre randomized trial.

The major concern with respect to dextran use is the risk of anaphylactoid directions and fluid overload. Both of these side-effects are rare and can be minimized by the use of both dextran 40 as compared with dextran 70 and judicious administration.

Intermittent pneumatic calf compression: Multiple studies have demonstrated that pneumatic calf compression is effective in general surgical patients over the age of 40 undergoing general surgery for more than 1/2 hours duration.

It is estimated from these studies that intermittent pneumatic compression

results in:

a similar reduction in the frequency of clinically suspected DVT as that seen with low-dose subcutaneous heparin prophylaxis.

Although data is not available, it is likely on the basis of the above findings, that the frequency of non-fatal pulmonary embolism is similar to that observed with subcutaneous heparin.

The use of the modern intermittent pneumatic compression devices is highly attractive and these devices are not associated with significant morbidity and can be worn for long periods.

Secondary prevention using ^{125}I-fibrinogen leg scanning for early detection (and treatment) of deep vein thrombosis: ^{125}I-fibrinogen leg scanning is a simple, reliable diagnostic technique that can be used to screen large numbers of patients. The clinical significance of leg scan detected venous thrombosis is discussed in the appendix section under the heading "Natural History of Venous Thromboembolism - Using a Sensitive Objective Method for Detecting Venous Thrombosis".

In the Hamilton region, approximately 10-20% of general surgical patients over the age of 40 years undergoing general surgery for more than 1/2 hour duration develop leg scan-detected venous thrombosis.

On literature review this approach appears to be highly effective in preventing pulmonary embolism. The frequency of pulmonary embolism in high-risk patients monitored prospectively with ^{125}I-fibrinogen leg scanning is shown in App. 4. Thus in terms of preventing pulmonary embolism, this approach is as effective as primary prophylaxis. The one patient suffering

from pulmonary embolism in the leg-scan monitored group shown in Appendix 4 was not fatal. The most informative data, however, is that reported by Kakkar. Kakkar performed a retrospective analysis of the frequency of fatal pulmonary embolism, as proven by autopsy, in two groups of surgical patients undergoing major elective operations. These patients formed the control group of a multicentre trial designed to assess the efficacy of low-dose heparin in preventing postoperative fatal pulmonary embolism. In one group, the fibrinogen leg scan test was used as a screening procedure to detect early thrombi and their extension which presumably initiated anticoagulant therapy, while in the other groups, screening was not performed and treatment was based on the presence of clinical features suggestive of deep vein thrombosis. Two thousand and forty-six patients, over the age of 40 years, undergoing major elective surgical procedures were included in this analysis. Kakkar reports that in "667 of these patients, the fibrinogen uptake test was used to detect the development of deep vein thrombosis; these constituted the screen group. While in the remaining 1409 patients, no specific screening procedure was employed and these constituted the non-screened group. The incidence of fatal pulmonary embolism proven by autopsy was determined in both groups. One hundred patients died during the postoperative period 29 (4.3%) in the screened group and 71 (5%) in the non-screened group. Twenty-two patients who died were found at post-mortem to have pulmonary emboli, 19 in the non-screened group and three in the screened group. Only one patient with a negative leg scan in the screened group died from pulmonary embolism. Two additional patients in the screened group suffered pulmonary embolism, one fatal and one non-fatal; both had positive leg scans several days before death but did not receive treatment with anticoagulants. In contrast, 19 patients in the non-screened group were found at autopsy to have pulmonary

embolism, 14 fatal and 5 non-fatal".

Thus from these data, the evidence suggests that leg scanning is effective for preventing deaths due to pulmonary embolism and thus non-fatal pulmonary embolism.

Leg scanning per se is free of complications, but approximately 10% of patients receiving anticoagulant therapy for leg scan-detected deep vein thrombosis will suffer bleeding complications.

Chapter 5. MEASUREMENT OF COSTS AND EFFECTS

The key factor in determing the costs incurred by a programme is the identification of the various components which make up the cost of the programme (i.e. that is, input into the programme). In determining the cost of an item, it is important to consider the significance of the cost and it is crucial that major costs be identified. If the cost is very minor, however, and consequently has little bearing on the overall outcome, then there is little point in including such a minor cost, (i.e. the side-effects of treating patients with DVT, such as bleeding). Another important factor in calculating costs is the time spent in the programme. In comparing the various programmes in this analysis, the time span is in days and thus the costs are expressed in present values. If the time span extended to years, then the costs must be calculated using discounting to reduce future costs into present values. Clearly, this latter point is not relevant to this thesis as the time span is in days or at the most, weeks.

The costs incurred by the different prophylactic approaches are for practical purposes, direct. Indirect costs (i.e. earnings lost while in hospital) are not major (in terms of the proportional contribution) as prophylactic approaches are adjuncts to patient management and are never the reason for admitting the patient to hospital (the primary reason for admission is the need for general surgery).

Identification of Costs:

The costs incurred by a programme or approach for preventing pulmonary embolism can be categorized as follows:

a) the cost of the prophylactic agent or measure

b) the diagnostic costs of confirming the presence of clinically evident venous thrombosis or pulmonary embolism in patients who break through the prophylactic measure

c) the cost of treating deep vein thrombosis and non-fatal pulmonary embolism; and the cost of excess hospital days attributed to the treatment of venous thromboembolism

d) the cost of treating the side-effects produced by the prophylactic measures.

The costs used in this analysis arise from the third-party and operating costs incurred in an urban hospital in Ontario. All costs are expressed in 1980 Canadian dollars (to the nearest dollar).

Cost of Prophylactic Measure or Agent:

The costs of prophylaxis using subcutaneous heparin, dextran, intermittent compression and early detection using ^{125}I-fibrinogen leg scanning are listed below. These costs are the direct costs of ^{125}I-fibrinogen leg scanning, a professional and technical component.

Cost of Prophylactic Measure or Agent

Measure or Agent	Cost
Primary prophylaxis	
Subcutaneous heparin* 5,000 units Q8H for 7 days:	$ 14.00
Dextran 500 ml x 2 first day and then daily for 3 days	90.00
Intermittent pneumatic compression for 7 days++	30.00
Early Detection	
Leg Scanning for 7 days	74.00

LEGEND

Where:

* Subcutaneous heparin 15,000 U/day	=	0.80
syringes with 23 gauge needles x 3 days	=	1.20
Thus the cost for 1 day	=	2.00
Thus the cost for 7 days	=	14.00
+ Dextran 70 500 ml	=	10.00
first day - 500 ml x 3	=	30.00
thereafter - 500 ml daily for 6 days	=	60.00
Therefore the cost for 7 days	=	90.00
++ Intermittent Pneumatic Compression		
Compressor $1,000 and has a 5 year expected life;		
$50.00 annual maintence, 50 uses/year		
Thus the cost for 7 days	=	5.00
Pneumatic cuffs or stockings - 1 pr.		
required for 7 days (non-reusable)	=	25.00
Therefore the cost for 7 days	=	30.00
No Leg Scanning for 7 days		
Technical component	=	74.00
Professional component		

The costs shown for heparin, dextran, and intermittent pneumatic compression are the costs charged to the patient through the hospital pharmacy or central supply and are the total cost for these agents. The cost of ^{125}I-fibrinogen leg scanning is derived from the third party costs (OHIP costs).

The diagnostic costs of confirming the presence of venous thrombosis or pulmonary embolism in patients with clinically suspected venous thromboembolism is shown below.

Clinically Suspected Deep Vein Thrombosis - It is now accepted that the clinical diagnosis of venous thrombosis is highly non-specific, as more than half of the patients with clinically diagnosed deep vein thrombosis are negative by objective testing. Because of this, the management of venous thrombosis based solely on clinical diagnosis is no longer acceptable. In the Hamilton region, the following diagnostic algorithm is used in patients with clinically suspected deep vein thrombosis: Impedance plethysmography is performed at the time of referral - if negative, the patient is injected with ^{125}I-fibrinogen, and leg scanning is performed the next day and at 72 hours. If both of these non-invasive tests remain negative, then the diagnostic process is halted as deep vein thrombosis has been excluded. If either the IPG or leg scan results are positive, however, then venography is performed to confirm the presence and extent of deep vein thrombosis.

Clinically Suspected Pulmonary Embolism - The clinical diagnosis of pulmonary embolism is also inaccurate and thus the use of complementary tests is mandatory.

At the time of suspected pulmonary embolism, a chest x-ray is performed followed immediately by perfusion lung scanning. If the perfusion lung scan is negative, then the diagnosis of pulmonary embolism has been ruled out. If the perfusion lung scan is positive, however, then a ventilation lung scan is also performed to determine whether the defect on perfusion scanning is a primary defect or secondary to a regional ventilation

disturbance. In a subgroup of patients, pulmonary angiography may also be performed.

The cost of pulmonary angiography will not be included in the primary analysis but is incorporated in a sensitivity analysis. The reasons for this is that the indications for pulmonary angiography are currently highly controversial.

The Diagnostic Costs of Confirming the Presence of Venous Thrombosis or Pulmonary Embolism in Patients with Suspected Venous Thromboembolism

The diagnostic costs are derived from the third party OHIP costs.

Clinically Suspected Deep Vein Thrombosis:

Objective Tests:

Impedance plethysmography (IPG)	=	$ 10.00
Leg Scanning	=	$ 74.00
or IPG combined with leg scanning	=	$ 84.00

The impedance plethysmography and leg scanning results are negative in half or more of these patients (see appendix 4).

Venography	=	$ 77.00

Diagnostic Algorithm

If IPG and leg scan are negative, then DVT is excluded.

If either IPG or leg scan is positive, then venography is performed to confirm the presence of DVT (see appendix 4).

Clinically Suspected Pulmonary Embolism

Objective tests:

Perfusion Lung Scan	=	$ 69.00

Half or more of the patients will have an abnormal lung scan and in these, ventilation lung scanning is performed.

Ventilation Lung Scan	=	$ 34.00

Diagnostic Algorithm

If perfusion lung scan is normal, pulmonary embolism is excluded.

If perfusion lung scan is normal, then ventilation scan is performed

to determine whether defect on perfusion scan is a primary defect or secondary to regional ventilation disturbance.

Ancillary Diagnostic Tests

Obligatory:

Chest x-ray (PA and lateral)	= $ 17.00

Other:

Electrocardiogram	= $ 9.00
Blood Gases	= $ 7.00

The Cost of Treating Venous Thrombosis and Non-Fatal Pulmonary Embolism - The costs of treating established venous thromboembolism are shown below. These costs include the cost of the therapeutic agent as well as the cost of the hospital room, for those days spent in hospital beyond the period of time normally spent in hospital post-surgery. The excess hospital days may vary from 0-7 days and the effect of this variable is examined also by sensitivity analysis.

Following intravenous heparin therapy, each patient is treated with long-term oral anticoagulant therapy for 3 months.

Cost of Treating Venous Thrombosis and Non-Fatal Pulmonary Embolism

IV heparin 25,000 u/day for 10 days (plus 5,000 U initial bolus)	=$ 26.00
PTT for 10 days	=$ 39.00
Oral anticoagulants (warfarin) for 3 months	=$ 9.00
Daily PT for 5 days then once per week for 12 weeks	=$ 53.00
Physician's fee	=$ 30.00
7 hospital days * at $250.00 per day	=$ 1,750.00
THEREFORE TOTAL TREATMENT COSTS	=$ 1,907.00

LEGEND:

* Excess days in hospital (days in hospital beyond expected hospital stay) due to the post-surgical complication of deep vein thrombosis or non-fatal pulmonary embolism.

The cost of the hospital bed (room) and board ("hotel costs") was $250.00 per day for each patient. The daily cost of $250.00 was based on the operating costs of hospitals participating in the Regional Thromboembolism Programme and represents that portion of hospital costs (i.e. general nursing, maintenance, meals and housekeeping) which remains approximately unaffected by the special needs of patients with this particular diagnosis.

The Costs of Side-Effects of Prophylactic Measures and Treatment - These are insignificant cost factors and thus they will not be included in the analysis. These potential costs are costs associated with bleeding complications which are very infrequent.

Time Focus of the Study: The time span of this study will be short term focusing on the immediate impact of the programme or "no-programme" situation. For this reason, discounting is not applicable to the study. Similarly the post-phlebitic syndrome which is a long-term complication of deep vein thrombosis and which occurs late in the course of this disease will not be considered in this analysis. The potential effect of this late complication is, however, discussed in the appendix and its impact examined by sensitivity analysis.

Chapter 6. DATA ANALYSIS

The objective of this thesis is to perform a cost-effectiveness analysis comparing:

a) low-dose subcutaneous heparin prophylaxis

b) intravenous dextran prophylaxis

c) intermittent pneumatic compression of the legs

d) secondary prevention using ^{125}I-fibrinogen leg scanning and

e) the "no-programme" situation.

Calculation of Costs:

Total cost of Strategy	= CST
Cost of agent (or screening test)	= Ca
Cost of confirming the diagnosis of deep vein thrombosis/pulmonary embolism	= Cd
Cost of treating deep vein thrombosis/ pulmonary embolism.	= Crx

Cost of side-effects of agents or intervention, if any, and the cost of side-effects of treatment of deep vein thrombosis/pulmonary embolism are not included in the calculation of the costs as the contribution to costs is insignificant compared with the other costs (see sensitivity analysis).

$$CST = Ca + Cd + Crx$$

Calculation of Effectiveness: Effectiveness is calculated in terms of the number of deaths due to pulmonary embolism averted by the alternative approaches. This measure is obtained directly from the literature from

the results of multicentre International trials.

"No-programme situation".

The cost-effectiveness of the "no-programme" situation for 1,000 general surgical patients over the age of 40 years undergoing general surgery for more than 1/2 hour is shown in Table I.

The cost of the "no-programme" situation is made up of the sum of the cost of objective diagnosis in 18 patients with clinically suspected pulmonary embolism and 35 patients with clinically suspected deep vein thrombosis; the cost of treatment of 8 patients with objectively documented pulmonary embolism and 17 patients with objectively documented deep vein thrombosis. The sum of these costs per 1,000 patients is $53,472.00.

The effect of the "no-programme" situation is 8 deaths from pulmonary embolism. This death rate is calculated by direct observation from the International Multicentre trial comparing "no-programme" with prophylaxis (subcutaneous heparin).

Subcutaneous Heparin Prophylaxis:

The cost-effectiveness per 1,000 general surgical patients over the age of 40 years undergoing general surgery for more than 1/2 hour is shown in Table II.

The cost of this approach is made up of the sum of the cost incurred by this approach. These costs are:

The cost of subcutaneous heparin and the syringes and needles for 7 days;

The cost of objective diagnosis of 6 patients with clinically suspected pulmonary embolism and 18 patients with clinically suspected

deep vein thrombosis;

and the cost of treatment of 2 patients with objectively documented pulmonary embolism and 8 patients with objectively documented deep vein thrombosis.

The cost per 1,000 patients using subcutaneous heparin prophylaxis = $35,714.00

The application of subcutaneous heparin prophylaxis results in 7 deaths from pulmonary embolism averted. This is calculated by direct observation from the International Multicentre Trial comparing no prophylaxis (i.e. "no-programme") with subcutaneous heparin prophylaxis.

Dextran Prophylaxis:

The cost-effectiveness of dextran prophylaxis is shown in Table III. The cost of using dextran prophylaxis in 1,000 general surgical patients over the age of 40 years undergoing surgery for more than 1/2 hour is made up of the sum of the following costs:

The cost of the agent - dextran prophylaxis 500 mls. x 3 on the first day then 500 mls daily thereafter for 3 days.

The cost of objective diagnosis of clinically suspected venous thromboembolism in 12 patients with clinically suspected pulmonary embolism and 35 patients with clinically suspected deep vein thrombosis.

The cost of treatment of 5 patients with objectively documented pulmonary embolism and 17 patients with objectively documented deep vein thrombosis.

The total cost for 1,000 patients = $137,235.00.

The use of dextran prophylaxis would result in six deaths from pulmonary embolism averted. This estimate is based on the multicentre trial comparing subcutaneous heparin and dextran prophylaxis.

Intermittent Pneumatic Compression:

The cost-effectiveness of intermittent pneumatic compression in 1,000 general surgical patients over the age of 40 years undergoing surgery for more than 1/2 hour is shown in Table IV.

The cost of using intermittent pneumatic compression is the sum of the following costs:

The use of intermittent pneumatic compression for 7 days.

The use of objective diagnosis in 9 patients with clinically suspected pulmonary embolism and 18 patients with clinically suspected deep vein thrombosis.

The treatment of four patients with objectively documented pulmonary embolism and eight patients with objectively documented deep vein thrombosis.

The sum of these costs = $55,803.00

By extrapolating the observation that intermittent pneumatic compression is as effective for preventing deep vein thrombosis in patients undergoing general surgery as subcutaneous heparin, it can be inferred that the use of intermittent pneumatic compression would result in seven deaths from pulmonary embolism averted.

Secondary Prevention using Early Detection of Deep Vein Thrombosis by ^{125}I-Fibrinogen Leg Scanning:

The cost-effectiveness of secondary prevention using ^{125}I-fibrinogen

leg scanning in 1,000 general surgical patients over the age of 40 years undergoing general surgery for more than 1/2 hour is shown in Table V.

The cost of this approach is made up of the sum of the following costs:

^{125}I-fibrinogen leg scanning for 7 days

The cost of confirming the diagnosis of deep vein thrombosis in 200 patients with leg scan detected deep vein thrombosis.

The cost of confirming the diagnosis in 2 patients with clinically suspected pulmonary embolism.

The cost of treatment for 160 patients with deep vein thrombosis and 1 patient with pulmonary embolism.

The sum of these costs = $396,599.00

Based on the descriptive study by Kakkar, it can be inferred that 7 deaths from pulmonary embolism would be averted by this approach.

Comparison of the Alternative Approaches by Cost-Effectiveness Analysis:

The total costs and total effects of the alternative approaches applied to 1,000 general surgical patients is shown in Table VI.

Low-dose subcutaneous heparin prophylaxis is the most cost-effective approach. By comparison with the "no-programme" situation, this use of low-dose heparin prophylaxis prevents seven deaths from pulmonary embolism at a cost saving of $18,500.00

It is likely by extrapolation of the literature that the use of intermittent pneumatic compression would result in seven deaths averted from pulmonary embolism for an additional cost (compared with "no-programme" situation) of $2,331.00

The use of dextran prophylaxis would result in six deaths from pulmonary embolism averted with an additional cost (by comparison with the "no-programme" situation) of $83,763.00

The use of secondary prevention with ^{125}I-fibrinogen leg scanning would result in seven deaths averted from pulmonary embolism for an additional cost (by comparison with the "no-programme" situation) of $343,127.00.

Incremental Cost-Effectiveness Analysis:

Incremental cost-effectiveness analysis allows a comparison to be made of the additional costs and additional effects between two approaches. The incremental cost-effectiveness of the alternative active prophylactic approaches compared with "no-programme" situation is shown in Table VII.

The application of low-dose heparin prophylaxis in 1,000 high-risk general surgical patients would result in a net saving of $2,537.00 each life saved.

The application of intermittent pneumatic compression in 1,000 high-risk general surgical patients would result in the additional cost of $333.00 for each life saved.

The application of dextran prophylaxis would result in the additional cost of $13,961.00 for each life saved and secondary prevention using ^{125}I-fibrinogen leg scanning $49,018.00 for each life saved.

It is evident that although dextran prophylaxis and secondary prevention using ^{125}I-fibrinogen leg scanning are effective, these approaches in comparison with subcutaneous heparin prophylaxis or intermittent compression are much more costly. Low-dose heparin prophylaxis is effective and results in a net saving compared with the "no-programme" situation.

Sensitivity Analyses:

Multiple sensitivity analyses were performed. The variables examined were the prevalence of deep vein thrombosis, prevalence of fatal and non-fatal pulmonary embolism, the cost of the hospital bed, the cost of treatment, the cost of the diagnostic test used and the cost of the prophylactic agents. For prevalence of deep vein thrombosis, a range of 1%-10% for clearly suspected deep vein thrombosis and 5%-30% for leg scan detected venous thrombosis was used (this range exceeds the prevalence reported in the literature in high-risk surgical patients). For the prevalence of non-fatal pulmonary embolism a range of 1%-10% was used and for fatal pulmonary embolism a range of 0.1%-1% (these ranges exceed those reported in the literature). For the cost of the hospital bed and treatment, a range of 40-300% was used. For the cost of impedance plethysmography and leg scanning, a range of 80-300% was used. For venography, a range of 80-600%; for ventilation-perfusion lung scanning, a range of 80-300% and pulmonary angiography, a range of 80-600%.

These ranges of costs were based on variation in regional Canadian and U.S. costs. The cost of venography was incorporated in the sensitivity analyses by assuming that all patients with a positive perfusion scan would undergo pulmonary angiography.

For the cost of the prophylactic agents, a range of 40-300% was used based on variations in regional Canadian and U.S. costs.

Even though the costs and effects of these prophylactic approaches were varied over a wide range, by comparison with the "no-programme" situation, subcutaneous heparin prophylaxis and intermittent pneumatic compression were the most cost-effective approaches and intravenous dextran and secondary prevention with ^{125}I-fibrinogen leg scanning, although effective, remained the most costly.

Chapter 7. THE CLINICAL RELEVANCE OF THE OBSERVED COSTS AND EFFECTS OF THE ALTERNATIVE PROPHYLACTIC APPROACHES

An ideal prophylactic method should be effective, safe, easily administered, require minimal or no monitoring, and should be well accepted by the patients, nurses and physicians.

Furthermore, the ideal prophylactic method should be cost-effective.

None of the currently available methods of prophylaxis fulfill all of these criteria. The majority of these criteria are fulfilled however, by low-dose subcutaneous heparin. Low-dose subcutaneous heparin is effective in preventing deaths due to pulmonary embolism and has not been associated with an increased clinically significant risk of bleeding (other than for an increased risk of wound hematoma). Its method of administration is relatively simple, monitoring is not required and it is well accepted by patients. Subcutaneous heparin prophylaxis is also highly cost-effective in comparison with alternative prophylactic approaches and also in comparison with the "no-programme" situation where no active prophylaxis other than physiotherapy and early ambulation is applied. Low-dose heparin prophylaxis is inexpensive and results in a net saving in cost over the "no-programme" situation because of the reduction in clinically evident thromboembolic events.

Intermittent pneumatic compression also is an attractive alternative to low-dose subcutaneous heparin prophylaxis. Intermittent pneumatic compression is highly effective for preventing deep vein thrombosis in general surgical patients. Its use does not require monitoring and it is not associated with significant morbidity; in particular, it is free of any

risk of bleeding. The original devices were cumbersome and associated with poor compliance, but recent developments have resulted in devices which are well accepted by patients, nurses and medical staff. This approach is also highly cost-effective. To date, however, no trials have been performed using fatal pulmonary embolism as an endpoint. For this reason, the effectiveness of pneumatic compression for pulmonary embolism must be inferred from knowledge that it is highly effective for preventing deep vein thrombosis, the precursor of pulmonary embolism. Multiple studies evaluating intermittent pneumatic compression in general surgical patients indicate that it is as effective as low-dose subcutaneous heparin and thus suggest that this approach is as effective as low-dose subcutaneous heparin for preventing fatal pulmonary embolism.

Thus, in summary, this approach is inexpensive, and likely to be highly cost-effective.

Intravenous dextran therapy is an effective method for preventing venous thromboembolism in general surgical patients. Because its administration requires intravenous route, it is more cumbersome than subcutaneous heparin. Its use is also associated with the risk of fluid overload and rarely, the risk of a major anaphylactoid reaction. For these reasons, intravenous dextran use has not received widespread acceptance in North America for preventing venous thromboembolism in general surgical patients. Furthermore, on cost-effectiveness analysis, this approach although effective, is much more costly than low-dose subcutaneous heparin or intermittent pneumatic compression.

Secondary prevention by early detection of deep vein thrombosis by using ^{125}I-fibrinogen leg scanning is the least attractive of the alterna-

tive active prophylactic approaches. This is because this approach is technically time consuming because of the requirement for daily screening and necessitates the treatment of a large number of patients with leg scan-detected deep vein thrombosis in order to prevent pulmonary embolism. Because the venous thrombi are established, full doses of anticoagulants are required with an associated risk of major bleeding of 5-10%. This approach, based on extrapolation of data in the literature, is likely to be effective but it is evident from these cost-effective analyses, that this approach is the most expensive. For this reason, screening with ^{125}I-fibrinogen leg scanning should be reserved for those patients in whom the alternative methods of prophylaxis described above are either contra-indicated or unavailable.

TABLE I. "NO-PROGRAMME"

Cost effectiveness per 1,000 general surgical patients over the age of 40 years

Cost:

Clinically suspected venous thromboembolism*

Cost of objective diagnosis

18 patients with clinically suspected pulmonary embolism	$ 1,548.00
35 patients with clinically suspected deep vein thrombosis	$ 4,249.00

Cost of Treatment

8 patients with objectively documented pulmonary embolism	$ 15,256.00
17 patients with objectively documented deep vein thrombosis	$ 32,419.00
THEREFORE cost per 1,000 patients	$ 53,472.00

Effect:

8 deaths from pulmonary embolism**

LEGEND

* estimated from multiple randomized trials

** calculated by direct observation from the International Multicentre Trial comparing no prophylaxis (i.e. "no programme") ~~with~~ prophylaxis (s.c. heparin).

TABLE II. SUBCUTANEOUS HEPARIN PROPHYLAXIS

Cost-Effectiveness per 1,000 general surgical patients over the age of 40 years.

Cost:	
Agent	
s.c. heparin prophylaxis (15,000 u/day) for 7 days	= $ 14,000.00
Clinically suspected venous thromboembolism*	
Objective Diagnosis	
6 patients with clinically suspected pulmonary embolism	= $ 516.00
18 patients with clinically suspected deep vein thrombosis	= $ 2,128.00
Treatment	
2 patients with objectively documented pulmonary embolism	= $ 3,814.00
8 patients with objectively documented deep vein thrombosis	= $ 15,256.00
THEREFORE the cost per 1,000 patients	= $ 35,714.00
Effect:	
1 death from pulmonary embolism**	
Thus, 7 deaths from pulmonary embolism averted***	

LEGEND

* estimated from multiple randomized trials
** calculated by direct observation from the International Multicentre Trial, comparing (i.e. "no programme") with prophylaxis (s.c. heparin).
*** compared with 8 deaths in the "no programme" situation.

TABLE III. DEXTRAN PROPHYLAXIS

Cost-Effectiveness for 1,000 general surgical patients over the age of 40.

Cost:	
Agent	
Dextran prophylaxis 500 ml X 3 on first day and then 500 ml daily thereafter for 3 days	= $ 90,000.00
Clinically suspected venous thromboembolism*	
Objective Diagnosis	
12 patients with clinically suspected pulmonary embolism	= $ 1,032.00
35 patients with clinically suspected deep vein thrombosis	= $ 4,249.00
Treatment	
5 patients with objectively documented pulmonary embolism	= $ 9,535.00
17 patients with objectively documented deep vein thrombosis	= $ 32,419.00
THEREFORE the cost per 1,000 patients	= $ 137,235.00
Effect:	
2 deaths from pulmonary embolism**	
Thus, 6 deaths from pulmonary embolism averted***	

LEGEND: * Estimated from multiple randomized trials
** Calculated by direct observation from a large randomized multicentre trial comparing dextran with subcutaneous heparin prophylaxis
*** compared with 8 deaths from pulmonary embolism in "no-programme" situation.

TABLE IV.

INTERMITTENT PNEUMATIC COMPRESSION

Cost-Effectiveness per 1,000 general surgical patients over the age of 40 years

Cost:	
Agent	
Intermittent pneumatic compression for 7 days	= $ 30,000.00
Clinically suspected venous thromboembolism*	
9 patients with clinically suspected pulmonary embolism	= $ 791.00
18 patients with clinically suspected deep vein thrombosis	= $ 2,128.00
Treatment	
4 patients with objectively documented pulmonary embolism	= $ 7,628.00
8 patients with objectively documented deep vein thrombosis	= $ 15,256.00
THEREFORE the cost per 1,000 patients	= $ 55,803.00
Effect:	
1 death from pulmonary embolism**	
Thus, 7 deaths from pulmonary embolism averted***	

LEGEND:
* Estimated from multiple randomized trials
** Based on the observation that intermittent pneumatic compression is as effective as subcutaneous heparin for preventing deep vein thrombosis.
*** compared with 8 deaths from pulmonary embolism in "no-programme" situation.

TABLE V. EARLY DETECTION OF DEEP VEIN THROMBOSIS USING LEG SCANNING

SECONDARY PREVENTION

Per 1,000 general surgical patients over the age of 40 years

Cost:		
Approach		
^{125}I-fibrinogen leg scanning for 7 days	= $	74,000.00
Clinically suspected venous thromboembolism*		
Cost of confirmation by venography or lung scanning		
200 patients with leg scan detected deep vein thrombosis underwent venography	= $	15,400.00
2 patients with clinically suspected pulmonary embolism underwent lung scanning	= $	172.00
Cost of treatment of patients with venous thromboembolism		
160 patients with deep vein thrombosis	= $	305,120.00
1 patient with pulmonary embolism	= $	1,907.00
THEREFORE the cost per 1,000 patients	= $	396,599.00
Effect:		
1 death from pulmonary embolism**		
Thus, 7 deaths from pulmonary embolism averted***		

LEGEND:
* Estimated from multiple randomized trials
** based on direct observation - 1 patient with a negative lung scan died of pulmonary embolism in the International Multicentre Trial
*** compared with 8 deaths from pulmonary embolism in "no-programme" situation.

TABLE VI

SUMMARY

Cost-Effectiveness of Preventive Measures (per 1,000 general surgical patients

Prophylactic Measure		Total Effect* (Deaths from Pulmonary Embolism Prevented)	Side-Effects
Subcutaneous Heparin	$ 35,714.00	7 lives saved	+ (increased frequency of wound hematomas)
Intermittent Pneumatic Compression	$ 55,803.00	? 7 lives saved	0
Dextran	$ 137,235.00	6 lives saved	++ (increased risk of bleeding)
Secondary Prevention using 125 I-Fibrinogen Leg Scanning	$ 396,599.00	7 lives saved	+++ (due to both an increased hospital stay in patients with venous thrombo-embolism and increased risk of clinically significant bleeding, due to anticoagulant treatment).

\+ Compared with the "no-programme" situation - cost per 1,000 general surgical patients = $ 53,472.00

* Compared with the "no-programme" situation, where 8 lives lost due to massive pulmonary embolism per 1,000 general surgical patients.

TABLE VII INCREMENTAL COST-EFFECTIVENESS OF THE ALTERNATIVE ACTIVE PROPHYLACTIC APPROACHES COMPARED WITH "NO-PROGRAMME" SITUATION IN 1,000 HIGH RISK GENERAL SURGICAL PATIENTS

Prophylactic Method	Additional (Incremental) Costs	Additional (Incremental) Costs	Incremental Cost For Each Life Saved
Subcutaneous Heparin -	$ 17,758.00 (i.e. a saving of $17,758)	7 lives saved	A net saving of $2,537.00
Intermittent Pneumatic Compression	$ 2,331.00	? 7 lives saved	A net cost of $ 333.00
Dextran	$ 83,763.00	6 lives saved	A net cost of $ 13,961.00
Secondary Prevention using 125 I-fibrinogen Leg Scanning	$343,127.00	7 lives saved	A net cost of $ 49,018.00

COSTS PER 1000 PATIENTS

APPROACH	a	+	b	+	c	=	TOTAL
"No-Programme"	0	+	5,797	+	47,675	=	$ 53,472.00
IV Dextran	90,000	+	5,281	+	41,954	=	$ 137,235.00
S.C. Heparin	14,000	+	2,644	+	19,070	=	$ 35,714.00
Intermittent Pneumatic Compression	3,000	+	2,919	+	22,884	=	$ 55,803.00
^{125}I-fibrinogen leg scanning	74,000	+	15,572	+	307,027	=	$ 396,599.00

LEGEND: a - cost of prophylactic agent

b - diagnostic costs

c - treatment costs

EVENTS PER 1000 PATIENTS

APPROACH	DVT	NON-FATAL PE	FATAL PE
"No-Programme"	17	8	8
IV Dextran	17	5	2
S.C. Heparin	8	2	1
Intermittent Pneumatic Compression	8	4	1
^{125}I-Fibrinogen Leg Scanning	160	1	1

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APPENDIX 1.

PRACTICAL APPLICATION OF ^{125}I-FIBRINOGEN LEG SCANNING

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PRACTICAL APPLICATION OF ^{125}I-FIBRINOGEN LEG SCANNING

INTRODUCTION:

This paper provides a review of the literature pertaining to ^{125}I-fibrinogen leg scanning. The information derived from the literature and which also involves our own experience is presented in three sections. The first provides a brief background and describes the principles of leg scanning. The second section reviews the application of leg scanning to investigations of the natural history of venous thrombosis and its use in clinical trials. The final section reviews the current clinical application of leg scanning.

BACKGROUND AND PRINCIPLES OF USE

The diagnosis of venous thrombosis by radioiodine-labelled fibrinogen scanning depends upon incorporation of circulating labelled fibrinogen into a developing or existing thrombus which is then detected by measuring the increase of overlying surface radioactivity with an isotope detector. The feasibility of this technique was demonstrated in animals[1] and in man[2] in the early 1960's and the method has been extensively evaluated over the last decade.[3]

The equipment used initially for external scanning was cumbersome but in the last few years, portable, convenient and sensitive equipment[4] has become available so that the tests can be performed at the patient's bedside and in approximately 15 minutes.

The use of radioactive fibrinogen carries a theoretical risk of transmitting serum hepatitis, but this risk has been eliminated for practical purposes by preparing fibrinogen from a small number of carefully selected donors who have not transmitted hepatitis during years of frequent blood donation and who are ~~hepatatis~~ HEPATITIS-associated antigen free. ^{125}Iodine crosses the placenta and a small amount enters the fetal circulation.[4] The radioactivity also appears in the breast milk of lactating women.[4] For these reasons, ^{125}I-fibrinogen leg scanning is contraindicated during pregnancy and lactation and should not be used in young patients unless very definite indications exist because radioactive Iodine accumulates in the thyroid gland, even though this is minimized

by administering non-radioactive iodine. Following the injection of 100 microcuries of ^{125}I-fibrinogen,[4] approximately 200 mrem is delivered to the blood, 20 mrem to tissues and 5 mrem to the kidneys. This is less than the acceptable annual total absorbed radiation dose (500 ~~m~~ ~~rad~~ mrem. per year) recommended for the general population by the British National Council for Radiation Protection, ← (LESS THAN THE RADIATION RECEIVED FROM 2 CHEST X-RAYS).

Scanning Technique: Patients are scanned with a lightly shielded isotope detector probe with their legs elevated 15° above the horizontal to minimize venous pooling in the calf veins. Readings are taken over both legs and recorded as a percentage of the surface radioactivity measured over the heart. The surface radioactivity is measured over the femoral vein at 7 - 8 cm. intervals starting just below the inguinal ligament and then at similar intervals over the medial and posterior aspects of the popliteal region and the calf. The criteria for a positive leg scan has been established by a number of investigators.[4-5] Venous thrombosis is suspected if there is an increase in the radioactive reading of more than 20% at any point compared with readings over adjacent points of the same leg, over the same point on a previous day and at the corresponding point on the opposite leg. Venous thrombosis is diagnosed if the scan remains abnormal after repeated examination and the abnormality persists for more than 24 hours. The technique is simple and rapid so that up to 15-20 patients may be screened each day by one technologist. Scanning time is limited by in-vivo survival of fibrinogen so that after

a single injection of 100 microcuries, counting is possible for about seven days. The thyroid gland is blocked by a daily 100 mg. dose of potassium iodide given orally for 14 days in order to prevent excessive uptake of radioactive iodine. If the patient is still at risk for developing venous thrombosis after seven days, the injection can be repeated at intervals to extend the scanning time for the period of high risk. EACH INJECTION PROVIDES A USEFUL SCANNING PERIOD FOR UP TO 7 DAYS BUT THIS MAY BE CONSIDERABLY LESS IF THE RADIOFIBRINOGEN IS INJECTED PRE-OPERATIVELY, ~~LARGELY~~ DUE TO PERIOPERATIVE LOSS.

^{125}I-FIBRINOGEN LEG SCANNING AS A PRACTICAL RESEARCH TOOL FOR INVESTIGATING THE NATURAL HISTORY OF VENOUS THROMBOSIS, AND ITS USE IN CLINICAL TRIALS

^{125}I-fibrinogen leg scanning has been a valuable research tool which has provided important information about the natural history, epidemiology, pathogenesis and methods of prophylaxis of venous thrombosis (Table 1). Leg scanning is also a useful clinical tool which can aid the clinician in the practical management of patients with venous thrombosis and this latter application will be discussed in the final section of this paper.

It is important to recognize that leg scanning has certain limitations and these will be discussed in more detail in the final section. Its major limitation[6,7] is its inability to detect the presence of venous thrombi above the inguinal ligament, and its reduced sensitivity for detecting thrombi in the upper thigh. These limitations, although important, are of little clinical significance in the majority of patients because thrombi rarely occur in the thigh or pelvis without concurrent calf vein thrombosis (to which the leg scan is highly sensitive).

Natural History of Venous Thrombosis:

The application of leg scanning has greatly increased our knowledge of the natural history of venous thromboembolism. Clinical studies using ^{125}I-fibrinogen leg scanning have drawn attention to the high frequency of venous thrombosis in a number of patient groups. Prior to

the use of leg scanning, the diagnostic methods used to measure the frequency of venous thromboembolism were clinical diagnosis and autopsy. Clinical examination is unreliable[8,9] because it is both insensitive and non-specific. Autopsy studies, although objective, may be misleading because they may not be generalised to living patients since they reflect preterminal events.

General Surgical Patients:

In a report by Kakkar[10] 469 consecutive patients, 40 years of age or older admitted to hospital for elective surgery were studied with leg scanning which was used as a routine screening procedure. Patients who had a recent clinical history or clinical signs of recent deep vein thrombosis and those undergoing leg or thyroid operations were excluded. One hundred and thirty patients, (27.8%) developed deep vein thrombosis; older patients (60-80 years of age or older) undergoing major operations, had an incidence of over 50%. In 68 patients (52.3%) thrombi formed during operation or within the first 24 hours while in the remaining 62 (47.7%) the increased radioactive counts developed within 3 - 7 days after operation. In one third of the patients with thrombosis, the process affected both limbs.

The frequency of thrombosis in postoperative general surgical patients has been examined by many other groups with a frequency ranging from as low as 5%[11] to as high as 44%[12]. On reviewing the literature, it is of interest that the reported frequency of venous thrombosis in studies

performed in North America[5,11,19] is less than that observed in studies performed in the United Kingdom and Europe.[13-18] In a large study performed at McMaster University[5] the thrombosis rate was 16%. Possible explanations for the marked differences in these observed rates of venous thrombosis (Table 2) are inherent differences in the patient groups studied or differences in patient management. A number of predisposing factors[23] influence the frequency of venous thrombosis (detected by leg scanning) and these include advancing age, obesity, previous thromboembolism, varicose veins and malignancy. Other factors influencing the frequency of postoperative deep vein thrombosis are; the type of operation and the development of postoperative infection.[24]

Using fibrinogen leg scanning and phlebography, Kakkar reported that in general surgical patients the majority of thrombi form in the calf veins.[4] Of 667 surgical patients who were screened for the development of deep vein thrombosis, fibrinogen leg scanning detected thrombi in 164 (24.6%). The venous thrombi were bilateral in 47 of the 164 patients. Thirty-eight percent were detected within 48 hours of surgery, 51% developed between the 3rd and 6th post-operative days, and 9% after the 7th post-operative day. In 49 patients (30%) the thrombus extended into the major veins. This is similar to the finding of others. Nicolaides[15] reported that 31% of patients with a positive scan following elective general surgery were positive in the popliteal or thigh region, similarly, Hartsuck and Greenfield[25] observed a 21% rate, and Gallus et al.,[5] an ~~16%~~ 18% rate.

Patients Undergoing Hip Surgery:

Leg scanning has special limitations when used to detect venous thrombosis in patients undergoing elective or emergency hip surgery. This is because extravascular isotope accumulation in the haematoma and healing wound invariably leads to scan abnormalities at the site of surgery, so that thrombi near the wound cannot be detected.[26] This is a major limitation in patients having hip surgery since up to 20% of all thrombi (in about 10% of all patients) are isolated in the femoral vein close to the surgical wound. Therefore leg scanning is likely to underestimate the true frequency of thrombosis.

Nevertheless, leg scanning has provided an estimate of the frequency of venous thrombosis in this special group. The reported frequency of leg scan detected venous thrombosis in patients undergoing elective hip surgery[5,27,28] ranges from 45% to 58%, (Table 3). In patients undergoing emergency hip surgery,[29,30] a rate of 32% to 49% has been reported (Table 4).

Other Patient Groups:

A number of other patient groups have been evaluated by leg scanning; these include neurosurgery patients, "stroke" patients, patients undergoing elective gynecologic surgery (Table 5). A frequency of 18% to 25% has been reported in patients undergoing neurosurgery,[31,32] a rate of 60% has been reported in stroke patients[33] in the majority of whom thrombi develop in the paralyzed leg. Among medical patients, the frequency following myocardial infarction[34-37] has been reported to vary

between 19% and 37%.

A very low incidence of 3% has been reported in postpartum women.[38]

The Clinical Significance of Leg Scan Detected Venous Thrombi:

The use of leg scanning re-emphasizes the insensitivity of the clinical diagnosis of venous thrombosis.

Kakkar reported[23,10,23] a prospective study of 203 surgical patients in whom the radioactive fibrinogen test was used to assess the value of clinical signs in the diagnosis of venous thrombosis. Patients were examined every day and particular attention was paid to any tenderness in the calf, the presence or absence of ankle edema, and a rise in skin temperature, and the circumference of the lower limbs was measured at various levels. If clinical signs suggestive of pulmonary embolism developed, a chest x-ray and an electrocardiogram were performed and repeated on subsequent days. In some patients, lung scanning was also performed using macroaggregated ferric chloride labelled with Indium 113M. Despite this careful examination, only 30 of the 62 patients in whom deep vein thrombosis developed showed any clinical signs. Local tenderness or mild ankle edema, or both, was present in only 37 of the 86 limbs with positive leg scans. Tenderness in the calf was detected in 27 of the 36 legs and corresponded roughly with the area of increased radioactivity. Mild ankle edema alone was present in the other 10 limbs. Whenever clinical signs did appear, the radioactive test anticipated the onset of thrombosis by at least 24-36 hours. Symptoms and signs of pul-

monary embolism developed in 6 of the 62 patients with proven thrombosis, and in only 2 of these were clinical signs of deep vein thrombosis demonstrated. The calf was by far the commonest site of thrombosis.

Thus it is evident that clinical diagnosis is very insensitive. If clinical diagnosis alone is used, more than half the patients with venous thrombosis would not be detected. Thus a clinician using clinical diagnosis would not be impressed by the frequency of post-operative venous thrombosis.

A number of investigators have studied the relationship between fibrinogen leg scanning and pulmonary embolism in post-operative patients.

The relationship between leg scanning and post-operative pulmonary embolism was investigated by Kakkar[39] in 132 consecutive surgical patients. Kakkar reported that there was no evidence of pulmonary embolism in 92 patients with negative leg scans and in 31 patients with scan evidence of calf vein thrombosis. In contrast, 4 of the 9 patients with proximal extension of calf vein thrombosis (detected by leg scanning) developed pulmonary embolism. These findings are supported by the observation of Scottish investigators[40] who studied 386 surgical patients and found no pulmonary emboli among 292 patients with negative leg scans, but observed pulmonary embolism in 8 of 94 scan positive patients. Similar results are reported by a number of other workers[13,33,34,39,41-44] (Table 6). Of 219 patients who had positive scans, 16 developed clinical evidence of pulmonary embolism while 1 out of 723 patients with negative scans developed this complication.

Browse et al. studied the relationship between a positive leg scan

result and pulmonary embolism detected by objective methods.[45] Routine pre and post-operative ventilation and perfusion lung scans were performed in 40 surgical patients studied with ^{125}I-fibrinogen leg scanning. The diagnosis of pulmonary embolism was made without knowledge of the leg scan results. Pulmonary embolism was diagnosed in 6 of 11 patients with positive leg scans but in only 1 of 29 patients with negative leg scans.

Kakkar has reported further evidence regarding the clinical significance of "isotopic thrombi".[4] He performed a retrospective analysis of the incidence of fatal pulmonary embolism, as proven by autopsy in two groups of surgical patients undergoing major elective operations. These patients formed the control group of a multi-centre trial designed to assess the efficacy of low-dose heparin in preventing post-operative fatal pulmonary embolism. In one group, the fibrinogen leg scan test was used as a screening procedure to detect early thrombi and their extension, (WHICH PRESUMABLY INITIATED ANTICOAGULANT THERAPY), while in the other group screening was not performed and treatment was based on the presence of clinical features suggestive of deep vein thrombosis.

Two thousand and forty-six patients over the age of 40 years, undergoing only major elective surgical procedures were included in this analysis. Kakkar reports "in 667 of these patients, the fibrinogen uptake test was used to detect the development of deep vein thrombosis, these constituted the screened group, while in the remaining 1,409 patients no specific screening procedure was employed and these constituted the non-screened group. The incidence of fatal pulmonary embolism as proven

by autopsy was determined in both groups. One hundred patients died during the post-operative period, 29 (4.3%) in the screened group and 71 (5%) in the non-screened group. Twenty-two of the patients who died were found at postmortem to have had pulmonary emboli, 19 in the non-screened group and 3 in the screened group. Only 1 patient with a negative leg scan in the screened group died from pulmonary embolism. Two additional patients in the screened group suffered pulmonary embolism, 1 fatal and 1 non-fatal; both had positive leg scans several days before death but did not receive treatment with anticoagulants. In contrast, 19 patients in the non-screened group were found at autopsy to have pulmonary embolism, 14 fatal and 5 non-fatal.

The findings at these studies support the hypothesis that thrombi which give rise to pulmonary embolism originate in the peripheral veins of the lower limbs. The findings suggest that early detection and treatment of venous thrombosis may reduce the incidence of fatal pulmonary embolism.

The Application of ^{125}I-Fibrinogen Leg Scanning in Trials of Prophylaxis of Venous Thrombosis:

In addition to providing a new insight into the natural history of venous thromboembolism, ^{125}I-fibrinogen leg scanning has played a major role in the evaluation of a number of different approaches for the prevention of venous thromboembolism. Leg scanning provides a sensitive tool for detecting venous thrombosis in the calf and distal thigh.

The relatively high frequency of leg scan detected venous thrombi in high risk patients (in contradistinction to the relatively low frequency of massive or fatal pulmonary embolism) has made it possible to perform a large number of trials which would not otherwise have been possible due to the very large number of patients needed using the endpoint of fatal pulmonary embolism. In more than 15 studies of general surgical patients, low-dose subcutaneous heparin prophylaxis has produced a clinically and statistically significant reduction in leg scan detected venous thrombosis. These findings are supported by the observation in a large international multi-centre trial that death due to pulmonary embolism was markedly reduced by subcutaneous heparin prophylaxis. The findings of the study using leg scanning as the endpoint are open to the criticism that the leg scan would have failed to detect upper thigh and pelvic vein thrombi. Kakkar has suggested that this limitation is not a significant one in general surgical patients since upper thigh or pelvic vein thrombi unaccompanied by calf vein thrombosis are rare in this group of patients. A study performed by the Groote Schurr Hospital Thromboembolus Study Group[46] reported that 9 of 200 patients studied with leg scanning and routine venography had venous thrombosis involving a proximal venous segment and in 3 with isolated femoral vein thrombosis, 1.5% of the population studied, the leg scan was normal.

Methods of prophylaxis of venous thrombosis have also been extensively evaluated using leg scanning in patients undergoing elective and emergency hip surgery. However, patients undergoing hip surgery represent

a special group as there is a relatively high frequency of isolated proximal vein thrombosis in the region of the surgical wound. Because of the inability of the leg scan to detect these thrombi, trials in this patient group using leg scanning are difficult to interpret as the risk of fatal pulmonary embolism is much higher with venous thrombi involving the proximal venous segments than with thrombosis confined to the calf.

In a study by Harris[47] a comparison was made of ^{125}I-fibrinogen leg scanning and venography in 142 limbs of 83 patients who underwent total hip replacement. Harris reported: "a localized accumulation of fibrinogen located away from the hip wound represented a fresh thrombus in 25 of 29 cases (86%). However, of all the fresh thrombi demonstrated by phlebography, the fibrinogen scan detected only 50%. Major reasons for failure to detect thrombi were the presence of the wound and the small size of some thrombi. In defining whether or not fresh venous thrombosis was present in a given patient, the scan was accurate in 3/4 of the cases.

Thus although fibrinogen scanning is a useful examination in patients after elective hip surgery, it has definite limitations if used alone. Because of this, in patients undergoing elective hip surgery or emergency hip surgery, additional tests such as impedance plethysmography and/or venography at a fixed interval are necessary to detect the proximal thrombi in the region of the wound.

Additional information is provided by a comparative study of patients undergoing general surgery and hip surgery performed at McMaster University[48] in which impedance plethysmography (a test sensitive to proximal vein thrombosis) was added to ^{125}I-fibrinogen leg scanning. (Table 7).

The combined approach of impedance plethysmography and ^{125}I-fibrinogen leg scanning was evaluated and compared in 630 patients who had general surgical procedures and 385 patients who had hip surgery. The addition of impedance plethysmography to leg scanning resulted in the detection of proximal vein thrombosis in only 1 additional patient (0.2%) in the general surgical group but it led to the detection of proximal vein thrombosis in 25 additional patients (6%) with hip surgery. Therefore, the addition of impedance plethysmography to leg scanning in hip surgery almost doubled the frequency of detection of proximal vein thrombosis. The results of this study support the findings of others suggesting that the majority of venous thrombi which occur in general surgical patients are associated with thrombi in the calf and thus can be detected by leg scanning whereas a considerable number of thrombi in hip surgery patients are isolated to the femoral vein and pass undetected by leg scanning.

PLEASE NOTE CHANGE IN ORDER OF CLINICAL INDICATIONS - SEE BELOW AND ALSO TABLE 8.

CLINICAL APPLICATION OF ^{125}I-FIBRINOGEN LEG SCANNING

Clinical indications for using ^{125}I-fibrinogen leg scanning are listed in Table 8. These are 1) screening selected high risk patients in whom ~~prophylaxes~~ PROPHYLAXIS are contraindicated or ineffective, 3) as an adjunct to impedance plethysmography or Doppler ultrasound in the diagnosis of clinically suspected venous thrombosis, 4) as a diagnostic test when acute venous thrombosis is suspected in patients with chronic insufficiency and 2) to detect proximal extension in patients who develop calf vein thrombosis when there are short-term relative or absolute contraindications to anticoagulant therapy.

The Use of Leg Scanning for Screening High Risk Patients:

Screening with ^{125}I-fibrinogen leg scanning cannot be recommended as a routine method of prophylaxis since it is less cost-effective than primary prophylaxis. However, this approach provides an alternative method of prophylaxis in patients at high risk of venous thrombosis in whom primary prophylaxis is ineffective or contraindicated.

A number of investigators[10,29,39,41,44,49-52] have compared results of expectant scanning and venography in general surgical and medical patients and have reported agreement between the results of these two techniques in about 90%, (Table 9). We performed[53] a study in which the results of expectant scanning and venography were compared in 205 legs. The majority of patients studied had abdominal or thoracic surgical

procedures, but some were studied after suspected myocardial infarction. Indication for venography was an abnormal leg scan and, as bilateral venography was usually done even if the scan was only unilaterally abnormal, venograms were obtained in a large number of legs with normal scans. The leg scan was positive in the calf in 96 of 104 (92%) instances of calf vein thrombosis demonstrated by venography, 20 of 28 popliteal vein thrombi (71%) and 17 of 26 femoral vein thrombi (65%). These results therefore support previous suggestions that the leg scan is highly sensitive to calf vein thrombosis but is less sensitive in the thigh, particularly the upper thigh. The venogram was normal in 24 of 99 instances of positive leg scans. Of these, 11 were associated with obvious superficial phlebitis, hematoma or skin rash. All of these conditions are known to produce a falsely positive leg scan result.

As discussed in the second section, leg scanning has special limitations when it is used to screen patients for thrombosis after surgery to the legs. It is unreliable over the operated thigh in patients having hip surgery; a major limitation because up to 20% of all thrombi may develop as isolated thrombi in the femoral vein under the surgical wound. Harris and associates[47] found that ^{125}I-fibrinogen leg scanning had a sensitivity of only 50% in 83 patients who underwent elective hip surgery and who have been leg scanned prospectively. Our results are very similar;[53] thus, in 219 patients undergoing hip replacement who were screened prospectively, the leg scan detected 20 of 43 (47%) instances of popliteal or femoral vein thrombosis and 33 of 40 (83%)

instances of calf vein thrombosis for an overall sensitivity of 64%.

In patients undergoing elective knee surgery, the leg scan is uninterpretable in the lower thigh, popliteal and upper calf regions due to extravascular accumulation of isotope and furthermore, leg scanning is often performed through a plaster cast or bulky post-operative dressing which may further hinder the accuracy of the test. We have reported a study[54] in which the accuracy of leg scanning was evaluated in 29 consecutive patients who had elective knee surgery. Venography was performed in all patients between 7 and 14 days after surgery. Deep vein thrombosis was demonstrated in 19 patients and in 14 of these (74%) it was correctly identified by leg scanning. Only one patient had a positive leg scan which was not associated with thrombosis detected by venography.

Because of its reduced sensitivity in the upper thigh, and inability to detect pelvic thrombi, the relevance of leg scanning for early detection of deep vein thrombosis has been questioned by some investigators.[46,55] In an editorial, Blaisdell[55] comments that "the fibrinogen I^{-125} scan lacks sensitivity where it is needed most - in the upper 1/3 of the thigh and the pelvis." We have reported a study[48] in which leg scanning was combined with a test sensitive to thrombosis in the popliteal, femoral, external and common iliac veins. This test, impedance plethysmography allowed us to evaluate the frequency with which proximal vein thrombosis detected by impedance plethysmography (and confirmed by venography) was not detected by leg scanning, (see Section 2).

As reported in Section 2, the addition of impedance plethysmography to leg scanning in general surgical patients identified only one additional patient with proximal vein thrombosis (0.2%) whereas in hip surgery patients, the addition of IPG detected 25 additional patients with proximal vein thrombosis (6%). Thus the addition of impedance plethysmography to leg scanning was not useful among general surgical patients as a screening test, but was of substantial clinical value in hip surgery patients. The results of this study were consistent with previous findings which suggested that the majority of venous thrombi which occur in general surgical patients arise from the calf and so can be detected by leg scanning while a considerable number of thrombi in hip surgery patients arise in the femoral vein and make an isolated event. Thus the use of leg scanning alone while appropriate in general surgical patients is clearly inappropriate in patients undergoing hip surgery.

Clinical Approach to the Positive Leg Scan in General Surgical Patients:

The management of patients with a positive leg scan in the calf is controversial (Table 10). Three approaches for selecting patients who require anticoagulant therapy, have been suggested.

The first is to commence treatment only when the raised counts detected over the calf have extended to involve the lower thigh region. Kakkar[4] based this approach on earlier observations that isotopic thrombi confined to the calf region did not produce significant pulmonary embolism. In contrast, scan detected popliteal or femoral vein thrombosis carried

a high risk of embolism. Using this approach between 2% - 5% of non-orthopedic patients would be treated (this represents the number of proximal extensions) including 95% of patients with proximal thrombosis.

A second approach advocated by Adar and Salzman[56] is to treat all patients with leg scan detected venous thrombosis confirmed by venography irrespective of whether it is confined to the calf or not. The investigators argue that left untreated, a proportion of these calf thrombi may propagate into the popliteal and femoral veins at a later time when leg scanning has been discontinued placing the patient at high risk of major pulmonary embolism. A limitation of this approach is that many of these leg scan detected venous thrombi occur in the first week post-operatively at which time anticoagulant therapy places the patient at high risk of bleeding.

The third approach advocated by Gallus et al[57] is to perform venography on all patients with a positive fibrinogen leg scan to confirm the presence of venous thrombosis and to base the patient's management on the venographic result. Patients with thrombosis involving the major veins above the knee joint are treated with anticoagulant therapy but the decision to treat patients with calf vein thrombosis is based on the size, site and extent of the calf vein thrombosis and whether or not the patient is at high risk for bleeding. Since this report was published we have modified our approach, (see below).

The Use of ^{125}I-Fibrinogen Leg Scanning to Detect Extension of Calf Vein Thrombosis in Patients who are at Short-term High Risk of Bleeding on

Anticoagulant Therapy:

If contraindications to anticoagulant therapy exist in patients with venographically confirmed calf vein thrombosis, then leg scanning provides a valuable management tool by providing a method for detecting extension of calf vein thrombosis should anticoagulant therapy be witheld. Anticoagulant therapy can thus be delayed or witheld until the period of high risk for bleeding has passed (e.g. the early post-operative period). Should proximal extension occur, the benefit versus risk ratio is tipped in favour of active treatment in view of the high risk of massive pulmonary embolism. If extension does not occur, anticoagulant therapy can be initiated when the risk of bleeding is lower.

The Use of ^{125}I-Fibrinogen Leg Scanning as an Adjunct to Impedance Plethysmography in Patients with Clinically Suspected Venous Thrombosis:

The sensitivity of diagnostic leg scanning depends upon the deposition of radiofibrinogen into or around an established thrombus, or its incorporation into a new thrombus if extension occurs. Diagnostic leg scanning has not been as extensively investigated as expectant scanning but the results of a number of studies[57] suggest that the leg scan becomes abnormal in over 70% of patients with established acute thrombosis. In these patients, the test result is frequently positive in 24 hours, but may not become positive for up to 72 hours.

Leg scanning fails to detect approximately 30% of thrombi in symptomatic patients[53] (many of which involve the femoral or iliac veins). Furthermore, there may be a delay of hours or even days before a suffi-

cient amount of fibrinogen accumulates in a thrombus to make the test positive. Clearly, leg scanning should never be used alone as the only diagnostic test in patients with clinically suspected venous thrombosis. Fibrinogen leg scanning, however, is a useful diagnostic test in symptomatic patients when used to complement impedance plethysmography.

We have evaluated the combined use of ^{125}I-fibrinogen leg scanning and impedance plethysmography in patients with clinically suspected venous thrombosis.[58] In the study, the patients were injected with ^{125}I-fibrinogen and had impedance plethysmography performed on the day of referral. Patients had leg scanning and impedance plethysmography performed daily for the next three days. All patients underwent bilateral ascending venography which was scheduled to be performed on the third day if the tests were negative, or earlier if either of the tests became positive. Either leg scanning or impedance plethysmography was positive in 81 of 86 patients with positive venograms (sensitivity 94%) and both tests were negative in 104 of 114 patients who had negative venograms (specificity 91%). These two tests detected all 60 patients with proximal vein thrombosis and 21 of 26 patients with calf vein thrombosis.

Impedance plethysmography detected 59 of 60 patients with proximal vein thrombosis and 5 of the 26 patients with calf vein thrombosis. The addition of leg scanning resulted in the detection of all 60 patients with proximal vein thrombosis and 21 of the 26 patients with calf vein thrombosis. Twenty-one of the 26 patients with calf vein thrombosis had symptoms for less than one week and leg scanning was positive in 20 of

these, whereas leg scanning was negative in 4 of the 5 patients with calf vein thrombosis who had symptoms for 7 days of greater. This study has now been repeated in another 300 patients with essentially similar results.

Based on these results, our present approach is to inject ^{125}I-fibrinogen after the results of impedance plethysmography are shown to be negative and then to scan the patient the next day and then at 72 hours. This approach is safe because proximal vein thrombi and many large calf vein thrombi are excluded by the negative impedance plethysmograph result. We have now studied 300 symptomatic patients with negative results for impedance plethysmography in this way, and none have developed extension or clinical evidence of pulmonary embolism while awaiting the result of the ^{125}I-fibrinogen leg scan. The ^{125}I-fibrinogen leg scan becomes positive in patients with acute venous thrombosis even though the thrombus is not extending, since the radioactive fibrinogen perfuses into the thrombus and is incorporated into it as radioactive fibrin.

Management of the Positive Fibrinogen Leg Scan Result in Patients with Clinically Suspected Venous Thrombosis:

In our experience, 10% - 15% of patients with clinically suspected venous thrombosis have a negative impedance plethysmograph result and a positive leg scan result. If clinical conditions known to produce a false positive leg scan result are excluded then the patient may be

treated with anticoagulants on the basis of the leg scan result. If cellulitis, previous knee surgery or trauma, arthritis of the knee, superficial phlebitis or muscle injury are suspected and the leg scan is positive, then the presence or absence of venous thrombosis should be clarified by performing venography before initiating anticoagulant therapy.

The Use of ^{125}I-Fibrinogen Leg Scanning as a Diagnostic Test in Patients with Chronic Venous Insufficiency Who Present with Symptoms Suggestive of Acute Recurrent Venous Thrombosis:

Barnes suggests,[59] "a unique application of leg scanning is in the identification of active venous thrombosis in patients with suspected recurrent deep venous disease. Patients with renewed leg pain, swelling, or inflammation with proven prior deep vein thrombosis may have post-phlebitic seguelae due to incompetent venous valves or chronic venous obstruction, rather than recurrent active venous thrombosis. In the past, most patients with recurrent symptoms were treated with hospitalization and anticoagulation for recurrent disease". Barnes reports that in his experience, "only 20% of patients with proven prior deep vein thrombosis had abnormal fibrinogen scans indicative of active thrombosis. The remaining 80% of patients responded to symptomatic measures such as leg elevation and elastic support and did not require anticoagulation".

We agree that leg scanning is a clinically useful test distinguishing acute recurrent venous thrombosis from the non-thrombotic complications

of chronic venous insufficiency. Venography is of limited diagnostic value in these patients unless the results can be compared with a previous venogram and unless a new filling defect is demonstrated.

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TABLE 1.

APPLICATION OF ^{125}I-FIBRINOGEN LEG SCANNING AS A PRACTICAL RESEARCH TOOL

Natural history

Epidemiology

Pathogenesis

Methods of prophylaxis of venous thrombosis

TABLE 2. REPORTED FREQUENCY OF LEG SCAN DETECTED THROMBOSIS IN GENERAL SURGICAL PATIENTS

Authors	Frequency of Thrombosis *
Gordon-Smith et al., 1972 (13)	21/50 (42%)
Kakkar et al., 1972 (14)	17/39 (42%)
Nicolaides et al., 1972 (15)	29/122 (29%)
Ballard et al., 1973 (16)	16/55 (29%)
Lahnborg et al., 1974 (17)	11/54 (20%)
Scottish Study, 1974 (18)	47/128 (37%)
Abernethy & Hartsuck, 1975 (11)	3/62 (5%)
Covey et al., 1975 (19)	5/52 (10%)
Rosenberg et al., 1975 (12)	39/89 (44%)
Gallus et al., 1975 (5)	66/412 (16%)
Rem et al., 1975 (20)	74/95 (36%)
International Trial, 1975 (21)	164/667 (25%)
Gruber, 1977 (22)	36/100 (36%)

* The thrombosis rates shown in this table are derived from untreated control groups.

TABLE 3. FREQUENCY OF LEG SCAN DETECTED VENOUS THROMBOSIS IN PATIENTS UNDERGOING ELECTIVE HIP SURGERY

Authors	Frequency of Thrombosis *
Gallus et al., 1973 (5)	11/23 (48%)
DeChavanne et al., 1974 (27)	13/27 (48%)
Manucci et al., 1976 (28)	14/23 (58%)
Manucci et al., 1976 (28)	22/51 (45%)

* The rates of thrombosis depicted in this table are derived from untreated control groups.

TABLE 4. FREQUENCY OF LEG SCAN DETECTED VENOUS THROMBOSIS IN PATIENTS UNDERGOING EMERGENCY HIP SURGERY

Authors	Frequency of Thrombosis*
Pinto et al, 1970 (29)	8/25 (32%)
Hamilton et al, 1970 (30)	18/38 (49%)

* The thrombosis rates shown in this table are derived from untreated control groups.

TABLE 5. OTHER PATIENT GROUPS: LEG SCAN DETECTED VENOUS THROMBOSIS

	Reported frequency of DVT
Neurosurgery (31,32)	18 - 25 %
Stroke patients (33)	60 %
Myocardial infarction (34-37)	19 - 37 %
Post partum women	3 %

TABLE 6. PULMONARY EMBOLISM IN PATIENTS MONITORED EXPECTANTLY WITH ^{125}I-FIBRINOGEN LEG SCANNING

Authors	Negative	Positive
Kakkar, et al (39)	0/92	4/40
Lambie, et al (41)	0/62	0/49
Williams (42)	0/40	0/16
Hills et al (43)	0/116	2/35
Bonnar & Walsh (44)	0/246	1/16
Gordon-Smith et al (13)	1/118	1/32
Murray et al (34)	0/37	4/13
Warlow et al (33)	0/12	4/18
TOTALS.....	1/723	16/219

TABLE 7. THE VALUE OF ADDING IMPEDANCE PLETHYSMOGRAPHY TO ^{125}I-FIBRINOGEN LEG SCANNING FOR THE DETECTION OF DEEP VEIN THROMBOSIS IN GENERAL SURGICAL PATIENTS AND PATIENTS UNDERGOING HIP SURGERY

General Surgical Patients - Total 630 patients

	Isolated Proximal*	Proximal & Calf*	Calf Only*
Leg Scan	1	10	29
Addition of IPG to leg scan	1 (+0)	11 (+1)	29 (+0)

Hip Surgery Patients - Total 385 patients

Leg Scan	4	35	66
Addition of IPG to leg scan	12 (+8)	52 (+17)	68 (+2)

* Venous thrombosis by venography

TABLE 8. CLINICAL APPLICATION OF ^{125}I-FIBRINOGEN LEG SCANNING

1. Screening selected high risk patients in whom prophylaxes are contraindicated or ineffective
3 2. As an adjunct to impedance plethysmography or Doppler ultrasound in the diagnosis of clinically suspected venous thrombosis
4 3. As a diagnostic test when acute venous thrombosis is suspected in patients with chronic insufficiency
2 4. To detect proximal extension in patients who develop calf vein thrombosis when there are short-term relative or absolute contraindications to anticoagulant therapy.

TABLE 9. CORRELATION OF VENOGRAPHIC FINDINGS WITH THE 125 I-FIBRINOGEN TEST IN REPORTED SERIES

	Leg Scan Negative		Leg Scan Positive	
Authors	-ve Venogram	+ Venogram	-ve Venogram	+ Venogram
Flanc et al (49)	0	0	1	17
Negus et al (50)	3	0	2	24
Kakkar et al (39)	0	0	1*	39*
Lambie et al (41)	16	2	2	40
Pinto (29)	3	0	2	20
Milne et al (51)	12	0	5	18
Bonnar & Walsh (44)	0	0	0*	15*
Kakkar (10)	50*	2*	4*	32
Hume and Gurewich (52)	0	0	2	10
TOTAL LIMBS	34	2	12	119
TOTAL PATIENTS	50*	2*	7*	96*

* The numbers of patients rather than limbs

TABLE 10. CLINICAL APPROACH TO THE POSITIVE LEG SCAN IN GENERAL SURGICAL PATIENTS

Authors	Alternative approaches
Kakkar (4)	Commence treatment only when the raised counts detected over the calf have extended to involve the lower thigh region.
Adar & Salzman (56)	Treat all patients with leg scan detected venous thrombosis confirmed by venography irrespective of whether it is confined to the calf or not.
Gallus (57)	Perform venography on all patients with a positive fibrinogen leg scan to confirm the presence of venous thrombosis and to base the patient's management on the venographic result. Patients with thrombosis involving the major veins above the knee joint are treated with anticoagulant therapy but the decision to treat patients with calf vein thrombosis is based on the size, site and extent of the calf vein thrombosis and whether or not the patient is at high risk for bleeding.
Hull & Hirsh	The use of leg scanning to detect extension of calf vein thrombosis in patients who are at short-term high risk of bleeding on anticoagulant therapy.

Prevention of Venous Thrombosis and Pulmonary Embolism With Particular Reference To The Surgical Patient

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It has been estimated that 100,000 hospitalized patients in the United States die each year from massive pulmonary embolism.[1] The majority of these embolic deaths occur in terminally ill patients but a significant proportion occur in patients who would have otherwise led a normal life.[2,3]

A number of clinical risk factors for venous thrombosis have been identified.[4] These include advanced age, previous venous thromboembolism, the presence of malignancy, cardiac failure, prolonged immobility or paralysis, obesity and varicose veins. In addition, certain surgical procedures including orthopedic surgery to the lower limbs and operations involving extensive pelvic surgery carry a particularly high risk of postoperative venous thromboembolism.

The frequency of fatal pulmonary embolism ranges from 0.1-0.8% in patients undergoing eleotive general surgery,[4-6] to 0.3-1.7% in patients undergoing elective hip surgery,[7-9] to 4-7% in patients undergoing emergency hip surgery.[10,11] It has been suggested that the routine use of effective prophylaxis in patients undergoing elective general surgery, for example, could prevent 4,000-8,000 postoperative deaths annually.[12]

Two approaches can be taken to prevent fatal pulmonary embolism. These are early detection of subclinical venous thrombosis by screening high risk patients (e.g. screening postoperative high risk patients with ^{125}I-fibrinogen leg scanning), and primary prophylaxis using either drugs or physical methods which are effective against deep vein thrombosis. Primary prophylaxis is likely to be the

more effective approach and is less expensive. The ideal primary prophylactic method should be safe, effective, well accepted by patients, nurses and medical staff, and easily administered. It should also be inexpensive and require minimal monitoring.

Venous thrombi usually develop at sites of slow or disturbed flow and begin as small deposits of platelets, fibrin and red cells in valve cusp pockets or in the intramuscular sinuses of the leg veins.[13,14] As the thrombus grows, it occludes the lumen of the vein producing stasis and then extends both proximally and distally as a coagulation thrombus composed of red cells with interspersed fibrin. The mechanisms which are recognized to be important in the pathogenesis of venous thromboembolism are venous stasis, activation of blood coagulation, and endothelial damage. The prophylactic methods which have been evaluated clinically have been directed at one or more of these pathogenetic factors and include mechanical devices which prevent stasis; anticoagulants which counteract the activation of blood coagulation; and drugs which suppress platelet function and their interaction with the damaged vessel wall.

A number of important design criteria should be considered when assessing the validity of results of clinical trials evaluating prophylactic agents. The clinical trials should be prospective, with a concurrent control group and the patients should be randomly allocated to avoid the danger of conscious or unconscious bias in patient selection. Ideally, the study should be double blind but, if this is not possible, the interpretation of the endpoints should be carried out by an observer who does not have knowledge of the patient's treatment category. Comparability of the groups with respect to important prognostic factors should be demonstrated and properly defined endpoints should be used for evaluation. Appropriate statistical methods should be used to analyse the data. Because of the inaccuracy of clinical diagnosis, it is essential that reliable objective diagnostic methods are used to determine the endpoint. These techniques include ^{125}I-fibrinogen leg scanning, impedance plethysmography and ascending venography for the diagnosis of venous thrombosis; and ventilation/perfusion lung scanning, pulmonary angiography or pulmonary embo-

lism demonstrated at autopsy for pulmonary embolism. The most important endpoint is fatal pulmonary embolism but because the frequency of fatal embolism is relatively low, large numbers of patients have to be studied if this endpoint is used. For this reason, the majority of studies have used venous thrombosis detected by either ^{125}I-fibrinogen leg scanning or by venography as the endpoint to evaluate prophylaxis. The frequency of ^{125}I-fibrinogen leg scan-detected or venographically detected venous thrombosis ranges from approximately 10-30% in patients over the age of 40 who undergo elective general surgery to 50% in patients undergoing elective or emergency hip surgery, to 65% in patients undergoing major elective knee surgery.[15] A relatively high proportion of thrombi (about 10-20%) in patients having knee or hip surgery involves the popliteal or femoral venous segments whereas only 3-5% of patients who have elective general surgery develop popliteal or femoral vein thrombosis.[16]

In this review, only studies which have used an acceptable method of randomization, which have included concurrent control groups, and which have used objective reliable endpoints for assessment of venous thromboembolism will be included for review.

ORAL ANTICOAGULANTS

Over 20 studies have been performed to evaluate the effectiveness or oral anticoagulants for preventing venous thrombosis in high risk patients. Of these, only 7 have used a concurrent control group and objective endpoints to assess the presence of venous thromboembolism (Table 1). In three, fatal pulmonary embolism detected at autopsy was used as the principle endpoint;[10,11,17] in two, venous thrombosis demonstrated venographically was used as the endpoint;[18,19] and in two, venous thrombosis detected by ^{125}I-fibrinogen leg scanning was used as the endpoint.[20,21] All three studies which used pulmonary embolism as an endpoint demonstrated that treatment with oral anticoagulants reduced the frequency of fatal pulmonary embolism found at autopsy. In the study by Sevitt and Gallagher,[11] there was also a reduction in total mortality which was

TABLE 1

ORAL ANTICOAGULANT PROPHYLAXIS FOR THE PREVENTION OF VENOUS THROMBOEMBOLISM IN PATIENTS UNDERGOING ELECTIVE OR EMERGENCY HIP SURGERY

			PATIENTS					
			TREATED			UNTREATED		
AUTHORS	SURGERY	ENDPOINT	NO	VTE	"FATAL" PE's	NO	VTE	"FATAL" PE's
Sevitt & Gallagher	Fractured Hip	Autopsy	150 (25 died 21 autop)	14*	1.3	150 (42 died 35 autop)	33*	10
Eskeland et al, 1966	"	"	100 (19 died 14 autop)		1.0	100 (24 died 20 autop)		7.0
Borgstrom et al, 1965	"	Verography Fractured Leg	29	9.5		29	56.5	
Hamilton et al, 1970	"	"	38	26		38	49	
Pinto 1970	"	Leg Scan	25	36		25	32	
Hume et al 1973	Elective Hip Surgery	Leg Scan	17	59		19	42	
Morris et al, 1976	Fractured Hip	Autopsy	75 (16 died 16 autop)	31	0	74 (23 died 16 autop)	68	8

* = % of patients undergoing autopsy

statistically significant. The randomization used in the study by Sevitt and Gallagher would be considered to be suboptimal by present day standards because allocation into the treatment groups was made on the basis of admission date. Nevertheless, the results demonstrated a striking reduction in death from massive pulmonary embolism and the other two studies which were methodologically sound largely confirmed the results obtained by Sevitt and Gallagher. The studies which used venography to detect the endpoint both showed a significant reduction in the frequency of venous thrombosis in the treated group.[18,19] In contrast, however, the two studies which used ^{125}I-fibrinogen leg scanning as the endpoint failed to show a reduction in the frequency of venous thrombosis in the treated group.[18,19] This probably reflects an inabiltiy of oral anticoagulants, which are started at the time of or immediately after surgery, to prevent small ^{125}I-fibrinogen scan-detected thrombi from developing after surgery. Nevertheless, the autopsy and venographic results suggest that oral anticoagulants commenced at this time do prevent the formation of large clinically significant thrombi. This interpretation is supported by the results of a recent study[22] in which oral anticoagulants were commenced 5 days preoperatively and were found to be as effective as low dose heparin in preventing postoperative venous thrombosis.

BLEEDING COMPLICATIONS

The frequency of reported bleeding has varied but there was a trend towards an increase in the frequency of clinically significant major bleeding in four studies[23-25] and in two studies the frequency of bleeding in patients treated with oral anticoagulants was statistically significant.[11,23] To minimize the risk of bleeding, careful laboratory control is required to maintain the prothrombin time to about twice normal control since it has been demonstrated that when the prothrombin time is greater than three times normal the risk of bleeding is increased.[26]

CONCLUSION

Oral anticoagulants are effective in preventing postoperative venous thrombosis. Despite this, the routine use of oral anticoagulant prophylaxis has not gained general acceptance because of the slight increase in the frequency of bleeding complications and the need for frequent laboratory monitoring.[27]

HEPARIN PROPHYLAXIS

ELECTIVE GENERAL SURGERY

The efficacy of low dose heparin has been extensively evaluated in patients undergoing elective general surgery. Thirteen randomized studies which satisfied the listed criteria for inclusion into this review have been performed in patients undergoing elective general surgery. In all, ^{125}I-fibrinogen leg scanning was used as a primary endpoint. The first dose of heparin was given preoperatively, usually in a dose of 5,000 units subcutaneously 2 hours before surgery and the postoperative dose of heparin was 5,000 units given subcutaneously which was administered 12 hourly in seven studies[28-35] (Table 2) and 8 hourly in 5 studies[4,36-39] (Table 3). Six of the eight studies[28-33] using the 12 hourly postoperative regimen showed a significant reduction in the frequency of leg scan detected venous thrombosis and all five of the studies in which heparin was given 8 hourly postoperatively showed a significant reduction in the frequency of venous thrombosis. In the two studies referred to above which did not show a reduction with heparin, the frequency of venous thrombosis was very low in the control group.[34,35]

In four studies, the number of patients included was large enough to assess the effects of prophylaxis on the frequency of popliteal or femoral vein thrombosis and in all four there was a significant reduction in the frequency of proximal vein thrombi (Table 4). In five studies, the effect of low dose heparin on the frequency of pulmonary embolism was evaluated. Two of these used perfusion lung scanning as an endpoint[32,34] and three used fatal pulmonary embolism found at autopsy as the end-

TABLE 2

RESULTS OF LOW-DOSE HEPARIN PROPHYLAXIS IN ELECTIVE GENERAL SURGERY, USING HEPARIN DOSE OF 5,000 U 12 HOURLY SUBCUTANEOUSLY (LEG SCAN ENDPOINT)

AUTHORS	FREQUENCY OF THROMBOSIS	
	TREATED	UNTREATED
Gordon-Smith et al, 1972	4/48 (8%)	21, 50 (42%)
Kakkar et al, 1972	3/29 (8%)	17/39 (42%)
Nicolaides et al, 1972	1 122 (1%)	29, 122 (29%)
Ballard et al, 1973	2/55 (4%)	16/55 (29%)
Lahnborg et al, 1974	3, 56 (5%)	11, 54 (20%)
Scottish Study, 1974	15 128 (12%)	47/128 (37%)
Abernethy & Hartsuck, 1975	4/63 (6%)	3/62 (5%)
Covey et al, 1975	4 53 (7.5%)	5/52 (10%)

TABLE 3

RESULTS OF LOW-DOSE HEPARIN PROPHYLAXIS IN ELECTIVE GENERAL SURGERY, USING HEPARIN DOSE OF 5,000 U 8 HOURLY SUBCUTANEOUSLY (LEG SCAN ENDPOINT)

AUTHORS	FREQUENCY OF THROMBOSIS	
	TREATED	UNTREATED
Rosenberg et al, 1975	4/55 (7%)	39/89 (44%)
Gallus et al, 1975	13/362(4%)	66/412(16%)
Rem et al, 1975	11/83 (13%)	74/95 (36%)
International Trial, 1975	48/625(8%)	164/667(25%)
Gruber, 1977	12/94 (13%)	36/100(36%)

TABLE 4

EFFECT OF LOW-DOSE HEPARIN ON THE FREQUENCY OF THROMBOSIS OF THE POPLITEAL OR FEMORAL VEIN (POP/FEM VT) IN GENERAL SURGICAL PATIENTS

	FREQUENCY OF THROMBOSIS					
	TREATED			UNTREATED		
AUTHOR	NO	TOTAL VT	POP/FEM VT	NO.	TOTAL VT	POP/FEM VT
Nicolaides et al, 1972	122	1 (1%)	0 (0%)	122	29 (24%)	9 (7%)
Rosenberg et al, 1975	55	4 (7%)	0 (0%)	89	39 (44%)	18 (20%)
Gallus et al, 1975	362	13 (4%)	3 (1%)	412	66 (16%)	12 (3%)
International Trial, 1975	625	48 (8%)	5 (1%)	667	164 (25%)	49 (7%)

point.[4,37,40] In four, there was a reduction in the frequency of postoperative pulmonary embolism.[4,32,34,40]

The most important of these studies was the International Multicentre Trial.[4] Over 4,000 patients were randomly allocated to either a low dose heparin or control group and the major endpoint was pulmonary embolism found at autopsy. There were 100 deaths in the control group and 80 in the heparin group. This difference was not statistically significant. Pulmonary embolism was found in 22 of the 72 autopsies in the control group and in 5 of 53 autopsies in the treatment group; a statistically significant difference ($p<0.01$). Pulmonary embolism was classified as being fatal if it was present in the pulmonary trunk, in a main pulmonary artery or in at least two lobar arteries, and if no other cause of death was found. Using these criteria, fatal pulmonary embolism was found in 16 control patients and 2 treated patients. This difference was statistically significant.

PROSTATIC SURGERY

The results of studies of low dose heparin prophylaxis in patients undergoing prostatic surgery are conflicting. In two studies, low dose heparin was ineffective[41,42] and in one study a significant reduction in deep vein thrombosis was seen in the heparin treated group.[43]

Bleeding Complications

The major potential complication limiting the widespread use of low dose heparin is bleeding. Since bleeding is a complication of any surgical procedure, the effects of heparin on bleeding can only be assessed in randomized studies in which the effects of heparin are compared with a control group. Ideally, this should be carried out in a double blind manner but, if this is not possible, then the observer recording the bleeding complication should be unaware of the treatment category. A prospective evaluation of bleeding complications was carried out in seven trials[4,28-30,33,38,44] but in none was the study double blind and so these assessments could be criticized.

There was no significant difference in surgical bleeding between control and heparin treated patients in 4 of these 7 trials.[28-30,33] One of the 7 studies reported an increase in bleeding which was considered to be both clinically and statistically significant[44] but in no instance was a fatal bleeding episode attributed to heparin treatment. In the International Multicentre Trial[4] there was a slight but statistically significant increase in the proportion of patients to have excessive peroperative bleeding and in the proportion of patients with postoperative wound hematoma in the treatment group. Similar findings were also reported by Gallus and associates.[38] Recently, a number of anecdotal reports have appeared in which bleeding complications have been reported in patients treated with low dose heparin. Since there was no concurrent control group, these reports are impossible to evaluate.

HIP SURGERY

Seven randomized clinical studies have evaluated low dose heparin in patients who had elective hip surgery.[21,38,45-48] The results summarized in Tables 5 and 6 are inconsistent, some reporting benefit and others reporting a lack of effectiveness of heparin. One of the difficulties in interpreting the results of these studies is that venography was not performed routinely on all patients and so the frequency of isolated femoral vein thrombosis, which is not uncommon in this group of patients, may have been underestimated in both groups. Because of this, definite conclusions cannot be drawn from the published reports but it is likely that any protection provided by low dose heparin is incomplete in this patient group.

A randomized clinical trial in patients undergoing fractured hip surgery showed that heparin reduced the total number of thrombi but not the frequency of large thrombi in the popliteal or femoral veins.[38]

Bleeding Complications

No excessive bleeding in heparin treated patients was reported in 2 studies[46,48] but, in the 3 less well documented studies, an increase in postoperat-

TABLE 5

LOW DOSE HEPARIN PROPHYLAXIS IN ELECTIVE HIP SURGERY

AUTHORS	DIAGNOSTIC ENDPOINT	FREQUENCY OF THROMBOSIS	
		TREATED	UNTREATED
Morris et al, 1974	Leg Scan + Venogram	3 [illegible] 11)	16, 32(50)
Hampson et al, 1974	Leg Scan Doppler + Venogram	22 48(46)	28, 52 54)
DeChavarne et al, 1974	Leg Scan	2/27( )	13/27(48)
Hume et al, 1973	Leg Scan Doppler + Venogram	6/18(33)	8, 19,42)
VT Study Group, 1975	Leg Scan Doppler + Venogram	2/38(5)	11/30(37)
Gallus et al, 1973	Leg Scan	3/23(13)	11/23(48)
Manucci et al, 1976	Leg Scan	9/45 20)	22, 51(45)
Manucci et al, 1976	Leg Scan	5/24(20)	14/23(58)

TABLE 6

EFFECT OF LOW-DOSE HEPARIN PROPHYLAXIS ON THE FREQUENCY OF THROMBOSIS OF THE POPLITEAL OR FEMORAL VEIN (POP/FEM VT) IN PATIENTS UNDERGOING ELECTIVE HIP REPLACEMENT

AUTHOR	FREQUENCY OF THROMBOSIS					
	TREATED			UNTREATED		
	NO	TOTAL VT	POP/FEM VT	NO	TOTAL VT	POP/FEM VT
Morris et al, 1974	27	3(11%)	0(0%)	32	16(50%)	5(16%)
Hampson et al, 1974	48	22(46%)	11(23%)	52	28(54%)	11(21%)
VT Study Group, 1975	34	2(6%)	0(0%)	30	11(37%)	3(10%)
Manucci et al, 1976	45	9(20%)	5(11%)	51	22(45%)	7(15%)

ive wound hematomas was reported in the heparin treated patients.[21,47.49]

CONCLUSIONS

Low dose subcutaneous heparin is effective in preventing postoperative venous thrombosis and pulmonary embolism in patients who have elective abdominothoracic surgery. In this patient group, the use of low dose heparin appears to be associated with a slight but statistically significant risk of bleeding. Nevertheless; in high risk patients undergoing elective surgery, the benefits of using low dose heparin outweigh the potential risk. In patients undergoing hip surgery and prostatic surgery, the role of low dose heparin is uncertain since reduction in venous thrombosis is incomplete and is not without risk.

PHYSICAN METHODS WHICH ENHANCE VENOUS BLOOD FLOW IN THE LEGS

It is well established that stasis occurs in leg veins peroperatively and postoperatively in patients who are immobilized.[50-54] A number of modalities designed to increase blood flow have been evaluated for the prevention of postoperative venous thrombosis. These include elastic stockings, leg elevation, intensive physiotherapy, a combination of elastic stockings, leg elevation and physiotherapy, graduated pressure stockings, electrical calf muscle stimulation, and intermittent calf compression.

SIMPLE PHYSICAL METHODS.

Six studies[55-59] have been performed using relatively simple physical methods (Table 7). In two, leg elevation was used;[56,58] in two, elastic stockings were used;[55,58] in one, a combination of elastic stockings and intensive physiotherapy and leg elevation was used;[57] and in one, graduated pressure stockings were used.[59] Neither elastic stockings alone or leg elevation alone reduced the frequency of postoperative venous thrombosis. However, the combination of elastic stockings, leg

TABLE 7

THE EFFECT OF SIMPLE PHYSICAL METHODS FOR BLOOD FLOW IN THE LEGS IN THE PREVENTION OF VENOUS THROMBOSIS

AUTHOR	METHOD OF PROPHYLAXIS	DIAGNOSIS	VENOUS THROMBOSIS TREATED	VENOUS THROMBOSIS CONTROL
Rosengarten et al 1970	Elastic Stockings	Leg Scan	8/25(32%)	8/25(32%)
Rosengarten & Laird, 1971	Leg Elevation	" "	4/12(33%)	4/13(31%)
Tsapogas et al, 1971	Elastic Stocking Leg Elevation Intensive Physiotherapy	Venogram	2/51(4%)	6/44(14%)
Browse et al, 1974	Leg Elevation (Peroperative only)	Leg Scan	19/97(20%)	16/97(16%)
Browse et al, 1974	Elastic Stockings	" "	22/90(24%)	20/90(29%)
Scurr et al, 1977	Graduate Pressure Stockings	" "	1/70(1.5%)	19/70(27%)

elevation and intensive physiotherapy reduced the frequency of postoperative venous thrombosis more than three-fold although, because only small numbers of patients were included in the study, the difference was not statistically significant. In a recent study,[59] a significant reduction in postoperative leg scan-detected venous thrombosis was reported with graduated pressure stockings. Graduated pressure stockings are hemodynamically superior to elastic stockings so that the different results obtained using these two modalities are not necessarily contradictory. It can be concluded, therefore, that simple measures do not usually provide benefit but may do so if hemodynamically effective and that this approach warrants further study.

ELECTRICAL CALF MUSCLE STIMULATION

Calf muscle movement induced by electrical stimulation can only be used peroperatively because it produces leg discomfort in the conscious patient. Five randomized studies[36,60-63] have been carried out in postoperative patients using peroperative calf muscle electrical stimulation (Table 8). In three,[60,61,63] there was a significant reduction in the frequency of leg scan-detected venous thrombosis and in two[36,62] there was no effect. Notably, in one of these three studies there was a very high frequency of thrombosis in both groups. A possible criticism of these studies is that the patients were only followed with leg scanning for a relatively short period of time postoperatively so that the results obtained cannot be extrapolated to high risk patients who remain in bed for long periods of time postoperatively. Indeed, there is good evidence (see below) that in such patients, prophylaxis should be continued postoperatively until the patient is fully mobile.

INTERMITTENT CALF COMPRESSION

Intermittent calf compression has been extensively investigated for the prevention of postoperative venous thrombosis. Pressure is applied to the calf by intermittent inflation of a cuff or boot. Two types of compression cycles have been used, a fast

TABLE 8

EFFECT OF PEROPERATIVE ELECTRICAL CALF MUSCLE STIMULATION FOR THE PREVENTION OF VENOUS THROMBOSIS IN PATIENT UNDERGOING GENERAL SURGERY (LEG SCAN ENDPOINT)

AUTHORS	NO. OF PATIENTS	FREQUENCY OF VENOUS THROMBOSIS	
		TREATED	CONTROL
Browse & Negus, 1970	110	9/110 (8%)	23/110 (21%)
Nicolaides et al, 1972	60	1/60 (2%)	9/60 (15%)
DeJode et al, 1973	64	16/64 (13%)	19/64 (15%)
Becker & Schampi, 1973	74	2/39 (5%)	11/35 (35%)
Rosenberg et al, 1975	194	22/73 (30%)	50/121 (41%)

cycle and a slow cycle. With the fast cycle, a brief period (5 seconds) of calf compression at 50 mm Hg is followed with a long rest period of 60-100 seconds. With the slow cycle, each leg is compressed for 1 minute at a pressure of 40-50 mm Hg and this is followed by a rest period of 1 minute.

Intermittent compression of the calf not only increases femoral blood flow[64,65] by emptying the calf but also increases systemic fibrinolytic activity[66] and it is of interest that intermittent compression of the arm, which also enhances fibrinolytic activity,[67] has been reported to increase the frequency of leg scan-detected deep vein thrombosis in general surgical patients. It is possible, therefore, that the protection obtained with this approach may be contributed to both by decreasing stasis and increasing fibrinolytic activity.

Five studies[42,68-71] using a fast compression cycle have shown a significant reduction in leg scan-detected venous thrombosis in postoperative patients. Two studies[72,73] have used a slow cycle and in both there was a reduction in the frequency of venous thrombosis in patients without malignant disease but in one it was relatively ineffective in patients with malignant disease[72] (Table 9). Although the results of these studies are promising, only limited conclusions can be made about the potential effectiveness of these approaches in high risk patients. In many of the reports, the pneumatic compression boots were applied peroperatively and continued for a maximum of 24 hours postoperatively and the patients were screened with leg scanning for between 3 and 7 days postoperatively. We noted that pneumatic compression of the calf for 5 days significantly reduced the frequency of thrombosis while the pneumatic devices were worn but that this protection was lost, negating its early benefit, after the devices were removed. Many of the new pneumatic devices in current use are uncomfotable because they produce excessive sweating of the legs and are inconvenient because they cannot be worn while the patient is ambulant and so they need to be removed frequently during the period between complete bed rest and full ambulation. The ideal pneumatic device is one which does not produce excessive sweating and which does not have

TABLE 9

EFFECT OF INTERMITTENT CALF-COMPRESSION ON THE FREQUENCY OF POST-OPERATIVE VENOUS THROMBOSIS (LEG SCAN ENDPOINT)

AUTHORS	TYPE OF SURGERY	VENOUS THROMBOSIS	
		TREATED	UNTREATED
Sabri et al, 1972	General	2/39 (5%)	12/39(31%)
Hills et al, 1973	"	7/70(10%)	23/70(33%)
Roberts & Cotton, 1974	"	6/94 (6%)	27/104(2%)
Clark et al, 1974	"	0/36 (0%)	7/36(19%)
Turpie et al, 1976	Neurosurgery	1/53 (2%)	9/69(18%)
Coe et al, 1978	Urological	2/29 (7%)	6/24(25%)
Skillman et al, 1978	Neurosurgery	4/47(8.5%)	12/48(25%)

to be removed while the patient is being ambulated. We have recently evaluated an inflatable pneumatic graduated pressure stocking which does have these desirable qualities. Patient compliance was excellent and the stockings did not have to be removed during ambulation. This approach proved to be highly effective, reducing the frequency of thrombosis in this very high risk group of patients (66% to 6%).

The major advantage of intermittent calf compression is the lack of side effects. It is effective and therefore may offer an alternative to low dose heparin in selected patient groups.

DEXTRAN

Dextran is a glucose polymer which was introduced as a volume expander and was then subsequently evaluated as an antithrombotic agent.[74-76] Two sizes of dextran polymer have been used clinically; dextran 70 with a mean molecular weight of 70,000 and dextran 40 with a mean molecular weight of 40,000. The antithrombotic properties of dextran have been attributed to a number of actions[77-80] including 1) decreased blood viscocity, 2) reduced platelet reactivity with the damaged vessel wall, 3) decreased platelet aggregation and 4) an increased susceptibility for the fibrin clot which is formed in the presence of dextran to fibrinolysis. The results of studies evaluating dextran 70 for the prevention of deep vein thrombosis in patients undergoing general surgical and gynecological procedures are conflicting (Table 10). In all of the six studies[33,63,81-84] that met the methodological criteria listed above, dextran was given intravenously both preoperatively and for a varying period of time postoperatively. The endpoint used in these studies was ^{125}I-fibrinogen leg scanning. In three studies[81-83] the frequency of postoperative venous thrombosis was significantly reduced while in the other three[33,63,84] no benefit was demonstrated. In contrast to the results of studies in general surgical patients, dextran has been reported to consistently reduce the frequency of postoperative thrombosis in patients following hip surgery.[85-88] In these studies, the test used to detect the end-

TABLE 10

DEXTRAN PROPHYLAXIS USING ^{125}I FIBRINOGEN LEG SCANNING TO DETECT VENOUS THROMBOSIS IN NON-ORTHOPEDIC PATIENTS

AUTHORS	SURGERY	PATIENTS	
		TREATED VT	UNTREATED VT
*Bonnar & Walsh, 1972	Elective Gynecologic	1/120(0.8%)	15/140(11%)
Bonnar et al, 1973	" "	2/45(4%)	10/45(36%)
*Carter & Eban, 1973	Elective General	1/106(0.9%)	10/101(10%)
Becker & Schampi, 1973	Elective Cholecystechomy & Prostate	13/42(31%)	11/35(31%)
Scottish Study, 1974	Elective General Gynecologic	32/128(25%)	47/128(37%)
*Kline et al, 1975	Elective General	20/94(21%)	32/121(26%)

* Control Infusion

point was venography (Table 11). Dextran was infused peroperatively and then postoperatively for 5-10 days.

There are two possible reasons for the more impressive results with dextran in hip surgery. The first is that the dextran was given for a longer period of time postoperatively and the second is that a venographic endpoint was used to detect venous thrombosis. With regard to the latter point, it has been noted that fibrin clots formed in the presence of dextran are more susceptible to fibrinolysis.[79,80] It is possible, therefore, that ^{125}I-fibrinogen detectable thrombi may have undergone lysis and therefore not been detected when venography was performed at a fixed time postoperatively.

SIDE EFFECTS

The major side effect of dextran is volume overload which can result in cardiac failure, particularly in the elderly patient with reduced cardiac reserve. Allergic reactions have been described but these are relatively uncommon. Excessive oozing has been reported in some patients but bleeding has not been a serious problem.

CONCLUSION

The major drawback with dextran is that it is relatively expensive and it has to be given by intravenous infusion. For these reasons, it is not an ideal prophylactic agent.

DRUGS WHICH SUPPRESS PLATELET FUNCTION

Histological studies have demonstrated that platelet aggregates occur at the site of origin of some venous thrombi, suggesting that platelets may sometimes be involved in the initiation of venous thrombosis. Aspirin, dipyridamole, hydroxychloroquine and sulphinpyrazone, drugs which suppress platelet function, have been evaluated as prophylactic agents against postoperative venous thrombosis. The results of these studies are described in detail in Chapter .

TABLE 11

DEXTRAN PROPHYLAXIS FOR THE PREVENTION OF VENOUS THROMBOSIS IN PATIENTS UNDERGOING HIP SURGERY (VENOGRAPHIC ENDPOINT)

AUTHORS	TYPE OF SURGERY	VENOUS THROMBOSIS	
		TREATED	UNTREATED
Ahlberg et al, 1968	Hip Fracture	5/39(13%)	16/45(36%)
Johnsson et al, 1968	" "	1/27(4%)	13/25(52%)
Myhre & Holen	" "	11/55(20%)	22/55(40%)
Evart & Fells, 1971	Elective Hip	5/29(26%)	10/20(50%)

Author Joist and Sherman

Title VENOUS AND ARTERIAL THROMBOSIS

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TABLE 12

A COMPARISON OF DIFFERENT APPROACHES TO PROPHYLAXIS FOR DEEP VEIN THROMBOSIS, RANDOMIZED TRIALS WITH AN UNTREATED CONTROL GROUP

AUTHOR	TYPE OF SURGERY	ENDPOINT	CONTROL	LOW-DOSE HEPARIN	DEXTRAN 70	COUMARIN	ELECTRICAL CALF STIMULATION	PNEUMATIC LEG COMPRESSION
Myre & Holen, 1969	Fracture	Venography	22/55(40%)	-	11/40(20%)	9/50(18%)	-	-
Hume et al, 1973	Elective Hip	Leg Scan	8/19(42%)	6/18(33%)	-	10/17(59%)	-	-
Becker & Schampi, 1973	General Surgery & Urology	"	11/35(31%)	-	13/42(31%)	-	2/39(5%)	-
Scottish Study, 1974	General Surgery	"	47/128(39%)	15/125(12%)	32/128(25%)	-	-	-
Rosenberg et al, 1975	General Surgery & Urology	"	50/121(41%)	12/79(15%)	-	-	22/73(30%)	-
Gruber et al, 1977	General Surgery	"	36/100(36%)	12/94(13%)	20/92(22%)	-	-	-
Taberner et al, 1978	Gynecology	"	11/48(23%)	3/49(6%)	-	3/48(6%)	-	-
Coe et al 1978	Urological	"	6/24(25%)	6/28(21%)	-	-	-	2/29(7%)

TABLE 12

A COMPARISON OF DIFFERENT APPROACHES TO PROPHYLAXIS FOR DEEP VEIN

AUTHOR	TYPE OF SURGERY	ENDPOINT	CONTROL
Myre & Holen, 1969	Fracture	Venography	22/55(40%)
Hume et al, 1973	Elective Hip	Leg Scan	8/19(42%)
Becker & Schampi, 1973	General Surgery & Urology	"	11/35(31%)
Scottish Study, 1974	General Surgery	"	47/128(39%)
Rosenberg et al, 1975	General Surgery & Urology	"	50/121(41%)
Gruber et al, 1977	General Surgery	"	36/100(36%)
Taberner et al, 1978	Gynecology	"	11/48(23%)
Coe et al 1978	Urology	"	6/24(25%)

THROMBOSIS, RANDOMIZED TRIALS WITH AN UNTREATED CONTROL GROUP

LOW-DOSE HEPARIN	DEXTRAN 70	COUMARIN	ELECTRICAL CALF STIMULATION	PNEUMATIC LEG COMPRESSION
-	11/40(20%)	9/50(18%)	-	-
6/18(33%)	-	10/17(59%)	-	-
-	13/42(31%)	-	2/39(5%)	-
15/125(12%)	32/128(25%)	-	-	-
12/79(15%)	-	-	22/73(30%)	-
12/94(13%)	20/92(22%)	-	-	-
3/49(6%)	-	3/48(6%)	-	-
6/28(21%)	-	-	-	2/29(7%)

Author Joist and Sherman

Title VENOUS AND ARTERIAL THROMBOSIS

Chapter Hirsch

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TABLE 13

COMPARISON OF DIFFERENT APPROACHES TO PROPHYLAXIS*FOR DEEP VEIN THROMBOSIS RANDOMIZED STUDY WITHOUT AN UNTREATED CONTROL GROUP

AUTHOR	TYPE OF SURGERY	ENDPOINT	LOW DOSE HEPARIN	DEXTRAN 40/70	COUMARIN	ASPIRIN
Lambie et al, 1970	Gynecological Surgery	Leg Scan	-	4/40(10%)	12/40(30%)	-
Davidson et al, 1972	"	" "	-	3/30(10%)	4/30(13%)	-
Vroonhaven et al, 1974	General Surgery	" "	1/50(2%)	-	9/50(18%)	-
Bronge et al, 1971	Hip Fracture	Venogram	-	31/74(42%)	21/61(34%)	
Lindquist et al, 1970	"	"	-	28/67(42%)	23/67(34%)	-
Berquist et al, 1972	"	"	-	25/75(33%)	19/63(30%)	-
Berquist & Dahlgrand 1973	"	Leg Scan	-	19/43(44%)	16/32(50%)	-
Myrvold et al, 1973	"	"	16/39(41%)	20/55(36%)	-	-
Harris et al, 1974	Elective Hip	Venogram	11/15(73%)	14/56(18%)	10/51(20%)	18/50(36%)
Barber et al, 1977	"	Leg Scan	10/19(52%)	26/51(51%)	34/58(58%)	-
Van Geloven et al, 1977	General Surgery Elective Hip	" "	-	9/70(11%)	20/80(25%)	15/65(18%)

TABLE 13

COMPARISON OF DIFFERENT APPROACHES TO PROPHYLAXIS FOR DEEP VEIN THROMBOSIS RANDOMIZED STUDY WITHOUT AN UNTREATED CONTROL GROUP

AUTHOR	TYPE OF SURGERY	ENDPOINT	LOW DOSE HEPARIN	DEXTRAN 40/70	COUMARIN	ASPIRIN
Lambie et al, 1970	Gynecological Surgery	Leg Scan	-	4/40(10%)	12/40(30%)	-
Davidson et al, 1972	"	" "	-	3/30(10%)	4/30(13%)	-
Vroonhaven et al,1974	General Surgery	" "	1/50(2%)	-	9/50(18%)	-
Bronge et al, 1971	Hip Fracture	Venogram	-	31/74(42%)	21/61(34%)	-
Lindquist et al, 1970	"	"	-	28/67(42%)	23/67(34%)	-

Berquist et al, 1972	"	"	-	25/75(33%)	19/63(30%)	-
Berquist & Dahlgrand 1973	"	Leg Scan	-	19/43(44%)	16/32(50%)	-
Myrvold et al, 1973	"	"	16/39(41%)	20/55(36%)	-	-
Harris et al, 1974	Elective Hip	Venogram	11/15(73%)	14/56(18%)	10/51(20%)	18/50(36%)
Barber et al, 1977	"	Leg Scan	10/19(52%)	26/51(51%)	34/58(58%)	
Van Geloven et al, 1977	General Surgery Elective Hip	"	-	9/70(11%)	20/80(25%)	15/65(18%)

COMPARISON OF DIFFERENT PROPHYLACTIC APPROACHES

A number of studies have been carried out comparing the effectiveness of a number of prophylactic agents. In those listed in Table 12, there was an untreated control group[21,22,33,36,37,63,87] while in those listed in Table 13 there was no control group.[7,89-98] The number of patients in each of the comparative groups was relatively small and it is difficult to draw definitive conclusions from these studies. However, the recent report by Coe and associates provides convincing evidence that low dose heparin is less effective in patients undergoing prostatic and genito-urinary surgery than intermittent calf compression.[42]

SUMMARY AND CONCLUSIONS

GENERAL SURGICAL PATIENTS

Two acceptable and practical forms of prophylaxis have been shown to be highly effective in high risk patients undergoing general surgical procedures. These are low dose heparin and inflatable mechanical devices. Of these, only low dose heparin has been shown to reduce the frequency of fatal pulmonary embolism but it is likely that this would also be reduced by hemodynamically effective physical methods such as intermittent calf compression.

The evidence that these two modalities are effective is sufficiently persuasive to recommend one of these two forms of prophylaxis in high risk general surgical patients.

SPECIAL SUB GROUPS

Prostatic Surgery

Results in patients undergoing prostatic surgery with low dose heparin prophylaxis have been inconclusive but in the one study evaluating intermittent calf compression this approach was found to be effective. Until more information is available in this patient group, it is recommended that they be treated prophylactically with a hemodynamically effective intermittent compression device.

Neurosurgical Patients

Low dose heparin and mechanical devices have both been shown to be effective in patients undergoing neurosurgery. Although in the one study using low dose heparin there was not an increased frequency of serious bleeding, this potential exists and therefore the mechanical device approach would be favoured in this patient group.

Orthopedic Patients

Hip Surgery

Three forms of prophylaxis have been shown to be effective in patients undergoing elective hip replacement. These are oral anticoagulants, dextran and aspirin. Of these, the effectiveness of oral anticoagulants has been most conclusively demonstrated. Dextran is effective but is associated with the same frequency of bleeding as oral anticoagulants and has the disadvantage of requiring intravenous infusion. Aspirin has been shown to be effective in some studies but this has not been consistent. Aspirin is the safest, least expensive and most convenient of the three methods but protection is incomplete so, at present, there is no very effective method of prophylaxis in patients undergoing elective hip surgery. It is possible that a combination of aspirin and mechanical devices will prove to be effective but this needs to be demonstrated. Until more information is available, it would be reasonable to treat these patients with aspirin.

Elective Knee Surgery

Mechanical devices which increase blood flow have been shown to be highly effective in this group and should be recommended.

Hip Surgery for Fractured Hip

Although oral anticoagulants have been shown to be effective in this group, this has not been accepted because of the potential risk of bleeding and the need for laboratory control. At present, no

safe, acceptable, proven form of prophylaxis is available in this group. If screening with ^{125}I-fibrinogen leg scanning and impedance plethysmography is available, it should be used in this group. If these screening tests are not available, it would be reasonable to treat these patients with oral anticoagulants starting 3 or 4 days post-operatively. Although this approach is unlikely to prevent fatal thrombosis, it might decrease their growth and therefore the frequency of pulmonary embolism.

FUTURE DEVELOPMENTS

The recommendation has been made that all high risk general surgical patients should be placed on low dose heparin prophylaxis. This recommendation has had mixed acceptance due to the continuing concern of many surgeons that the hazards of venous thromboembolism will be replaced by the hazards of bleeding. On review of the literature, it is evident that the magnitude of the risk of bleeding due to low dose heparin has not been convincingly defined. Recent reports document clinically significant bleeding but the design of these studies was deficient and the findings are therefore uninterpretable. To clarify this issue beyond doubt, additional double blind studies will be required with well defined endpoints addressing the problem of bleeding.

Of the other prophylactic agents currently under evaluation, intermittent compression of the legs appears to be the most promising. Design improvements have resulted in the development of devices which are much more acceptable than those which were previously available.

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POSTSCRIPT

The prophylactic effect of low dose heparin 5,000 units 12 hourly on postoperative fatal and on clinically apparent but non-fatal thromboembolic events was studied in a double-blind, prospective, randomized study of 1,296 patients who underwent elective surgery of the thorax, abdomen or lower extremities. Sixteen out of 653 patients in the placebo group developed thromboembolic complications during the first postoperative week compared

with 4 of 643 in the heparin group ($p<.05$) of which 4 cases in the placebo group and 1 in the heparin group were fatal. Each group had identical transfusion requirements and increased bleeding was not observed in the heparin group. The important observation was also made that after heparin prophylaxis was discontinued at the end of the first postoperative week, the subsequent rate of thromboembolic complications was equal for both groups suggesting that prophylaxis should be continued until the patient is fully ambulant.

In conclusion, this study supports and extends the findings of previous studies that low dose heparin is effective and associated with an acceptable risk of bleeding in general surgical patients.

Kiil J, Axelsen F, Kiil J, et al: Prophylaxis against postoperative pulmonary embolism and deep-vein thrombosis by low-dose heparin. *Lancet 1:* 1115-1116, 1978

APPENDIX 3

Venous thromboembolism

Applying epidemiology to controversies

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Instructions to CME Enrollees

The multiple-choice examination that appears on page 32 is designed to test your understanding of the following article according to the educational objectives listed below. If you have not registered for this 18-unit Category I course and wish to enroll, refer to the announcement on page 40.

Educational Objectives

Given a closed-book, multiple-choice examination, the enrollee should be able to apply the information learned in the journal article in answering all the test items that require him/her to: 1. Recognize objective risk factors associated with venous thromboembolism. 2. Identify various criteria used to determine the efficacy of a diagnostic test. 3. Assess the relationship between objective criteria and diagnostic tests used for venous thrombosis and pulmonary embolism. 4. Assess objective criteria used to determine efficacy of prophylactic agents. 5. Recognize the need for objective assessment of treatment for venous thrombosis and pulmonary embolism.

The application of the fundamentals of clinical epidemiology to studies of venous thromboembolism should enhance the capability of clinical trials to resolve controversial issues. Essential study criteria for appropriate clinical trials are illustrated by specific examples bearing on pathogenesis, diagnosis, prevention, and treatment.

The findings of adequately designed and appropriately executed clinical trials relating to the diagnosis, treatment, and prevention of venous thromboembolism have profoundly influenced the clinician's perception of this common problem. However, many specific clinical issues remain unresolved owing to a lack of adequate trials, resulting in uncertainty and confusion as to the most appropriate management for individual patients.

The development and refinement of readily repeated objective noninvasive tests that are sensitive to and specific for deep vein thrombosis have greatly enhanced the ability of clinical trials to resolve controversies concerning venous thromboembolism. The use of these tests has provided important information about pathogenesis, natural history, diagnosis, treatment, and prevention. The tests include leg scanning with use of fibrinogen labeled with iodine I 125, impedance plethysmography, and Doppler ultrasonography.[1-9]

The application of the fundamentals of clinical epidemiology to clinical trials is considered here under the headings pathogenesis, diagnosis, prevention, and treatment.

Pathogenesis

The clinical application of leg scanning has greatly increased our knowledge of the natural history of venous thromboembolism. Studies using ^{125}I-fibrinogen leg scanning have drawn attention to the high frequency of occurrence of venous thrombosis in hospitalized patients.[10] Other objective tests, including impedance plethysmography,[1-6] Doppler ultrasonography,[7-9] and ascending venography,[11,12] have provided insight into the location and distribution of venous thrombi in both symptomatic and high-risk asymptomatic patients.

Clinical diagnosis and autopsy—traditional measures of the frequency of occurrence of thromboembolism—are prone to error. Clinical examination is unreliable because it is both insensitive and nonspecific.[1] Autopsy studies, although objective and potentially highly accurate, may be misleading (see below).

By means of objective testing, a number of clinical risk factors for venous thromboembolism have been identified in medical and surgical patients.[10] These include advanced age, previous venous thromboembolism, malignant disease, cardiac failure, prolonged immobility or paralysis, obesity, and varicose veins. In addition, certain surgical procedures including orthopedic surgery of the lower limbs and extensive pelvic

Clinical diagnosis and autopsy studies of thromboembolism have been shown to be prone to error

surgery carry a particularly high risk of postoperative venous thromboembolism.

In addition, it is accepted—rightly or wrongly—that the use of oral contraceptive may be associated with an increased risk of venous thromboembolism. An examination of trials evaluating this purported association illustrates the importance of including essential criteria in the evaluation of a potential risk factor.

The dictum that women who use an estrogen-containing oral contraceptive have an increased risk of venous thrombosis and pulmonary embolism[13,14] is based on the results of multiple studies. However, on careful scrutiny the majority of these studies are seen to be flawed by (1) failure to use objective tests to diagnose venous thrombosis and (2) failure to ensure that the diagnosis of venous thrombosis or pulmonary embolism was made independently, without knowledge of the patient's use of oral contraceptive.

The clinical diagnosis of venous thrombosis is highly nonspecific. More than half the patients who are given a clinical diagnosis of deep vein thrombosis are found on objective testing not to have the disorder. Thus, any study of the relationship between use of oral contraceptive and deep vein thrombosis that relied on clinical diagnosis of the latter would be highly inaccurate. This inherent inaccuracy is compounded by the likelihood that the investigators in the majority of studies were aware of the patients' use of the agent. Thus, patients using it were more likely to be scrutinized more closely for venous thrombosis and given this clinical diagnosis more readily than patients not using oral contraceptive. This bias is referred to as the diagnostic suspicion bias.[15,16]

The majority of studies demonstrating a positive association between oral contraceptive and thromboembolism were carried out after a number of case reports suggesting such an association appeared in the literature. It is possible if not likely that knowledge of these case reports resulted in the more frequent clinical diagnosis of deep vein thrombosis in patients taking oral contraceptive, thus giving rise to a spurious association.

The diagnostic suspicion bias also applies to studies in which the autopsy diagnosis of fatal thromboembolism is used as an end point. The autopsy diagnosis of fatal thromboembolism is perhaps surprisingly subjective, because the frequency with which pulmonary emboli are found depends on the scope of the dissection. For example, with careful dissection down to the third- and fourth-order pulmonary vessels, the observed frequency of occurrence of pulmonary embolism is as high as 50% among subjects who died suddenly. However, if dissection is limited to major pulmonary vessels, the observed frequency is much less, 10% or so. Therefore, failure of investigators to ensure that the pathologist was unaware that the autopsy subjects took oral contraceptive leaves the possibility that an increased incidence of fatal pulmonary embolism in these subjects is attributable to a more intensive search for pulmonary emboli. Thus, a strong case can be made for retesting the association between oral contraceptive and venous thromboembolism by studies using objective diagnosis and interpretation of the results without knowledge of whether the subjects used oral contraceptive.

Table 1. Determination of the Efficacy of a Diagnostic Test

1. Test should be evaluated in consecutive patients, all of whom undergo reference test. This allows determination of the four indexes of efficacy: sensitivity, specificity, and positive and negative predictive values
2. Evaluation should be performed in a wide spectrum of patients with and without the disease in question, or efficacy may be judged falsely high
3. Diagnostic suspicion bias should be avoided by studying consecutive patients and interpreting results of diagnostic and reference tests independently and without knowledge of each other or of clinical findings
4. To determine the safety of withholding treatment from patients with negative tests, the validity of negative results should be evaluated by long-term follow-up observation

Diagnosis

After a promising introduction, many diagnostic tests prove with further experience to be either limited in clinical application or valueless. An example that is relevant to venous thromboembolism is the triad of increased lactic dehydrogenase, normal SGOT, and increased bilirubin to diagnose pulmonary embolism. This triad has fallen into disrepute because of a demonstrated lack of sensitivity and specificity.[17] Similarly, falsely high sensitivity and specificity were attributed to the measurement of arterial blood gases.[18]

There are two major reasons for inappropriate application of diagnostic tests. First, the clinical assumption of their value is based on incorrect equation of physiologic or pathophysiologic evaluations with hard evidence for clinical efficacy. Second, studies of diagnostic efficacy have frequently failed to include the essential design features for adequate assessment of the sensitivity, specificity, and predictive values of the tests. These essential design features are summarized in table 1.

The efficacy of a diagnostic test—its ability to indicate the presence or absence of disease[19]—is measured by four indexes: sensitivity, the proportion of positive test results among patients with the disease, specificity, the proportion of negative results among patients without the disease, positive predictive values, the likelihood that patients with positive tests have the disease, and negative predictive values, the likelihood that patients with negative tests do not have the disease.[19]

Essential to an accurate determination of the efficacy of a diagnostic test is evaluation of the test in a wide spectrum of patients with and without the disease in question.[19] In this way it is possible to assess the effect on the four indexes of efficacy of three important types of variables: pathologic (eg, extent of disease as characterized by presence of proximal deep vein thrombosis versus calf vein thrombosis), clinical (symptomatic deep vein thrombosis versus asymptomatic deep vein thrombosis), and comorbid (effect of coexisting conditions such as peripheral vascular disease or cardiac failure). Failure to assess the effect of these variables in a wide spectrum of patients may result in falsely high indexes of efficacy.

It is also crucial to avoid bias when performing the study and evaluating the test results. Bias—defined as a systematic error which deviates from the truth—can be caused by failure to perform both the diagnostic test and the reference test in *all* eligible patients and also operates if the tests are not assessed without knowledge of certain facts, ie, blindly (see table 1).

The final step in the process of evaluating a new diagnostic test is to confirm the clinical validity of a negative result. Clinical validity should be determined by long-term follow-up observation of consecutive patients in whom treatment has been

More than half of the patients given a diagnosis of deep vein thrombosis do not have the disorder

Table 2. Determination of Efficacy of an Agent for Prophylaxis or Treatment

1. Study should incorporate a control group, and allocation of patients should be random
2. To avoid diagnostic suspicion bias, study should be blind or, ideally, double-blind
3. Use of clearly defined end points is mandatory
4. Comparability of groups for important prognostic factors should be demonstrated
5. Appropriate statistical methods must be used for data analysis
6. Reliable, objective diagnostic methods to determine the end point are essential

withheld on the basis of the negative tests.

Noninvasive testing for the diagnosis of venous thrombosis is gaining increasing acceptance owing to the availability of techniques which satisfy the majority of the criteria in table 1. Noninvasive approaches gaining increasing acceptance are impedance plethysmography (with or without leg scanning) and Doppler ultrasonography. One approach in particular, the combined approach of impedance plethysmography and leg scanning, has been evaluated by multiple studies incorporating the criteria (see table 1) for determining the efficacy of a diagnostic test.[7-10] In comparison with venography (the diagnostic reference test), this combined approach is highly sensitive and specific for deep vein thrombosis and in the majority of patients provides a replacement for the more invasive ascending venography. The other noninvasive approaches have been less extensively evaluated.

In the diagnosis of pulmonary embolism, surprisingly the predictive values of abnormal ventilation-perfusion lung scans are uncertain. This is because an adequately designed prospective study of a large number of consecutive patients in whom the presence of pulmonary embolism is suspected has not been performed. The data that would allow the clinician to determine with confidence the predictive values of abnormal ventilation-perfusion lung scans are not available. None of the published studies evaluating ventilation-perfusion lung scanning fulfill the criteria in table 1. Unfortunately, ventilation-perfusion lung scanning has had an initial uncritical clinical acceptance which has made the performance of adequate studies difficult.

Initial studies comparing ventilation-perfusion lung scanning and pulmonary angiography suggested that the scans distinguished pulmonary emboli from other lung disorders with a high degree of efficacy.[11-13] Subsequent larger studies cast doubt on the specificity of a ventilation-perfusion mismatch for diagnosing pulmonary embolism.[11-14] In the most recent retrospective studies, the incidence of false-positive results was observed to be 20% to 48% if ventilation-perfusion mismatches per se were used to diagnose pulmonary embolism.

The concept of size and number of perfusion defects is currently in clinical use in an attempt to increase the positive predictive value of ventilation-perfusion lung scans. Multiple large defects which ventilate normally are generally accepted as indicating a high probability of pulmonary embolism. This may be true, but the subjects of the studies demonstrating this finding were nonconsecutive, highly selected patients, and no assurance was made that the results of lung scanning were interpreted independently and without knowledge of the pulmonary angiographic findings and the patients' condition.[11-14]

For this reason, there remains considerable uncertainty as to the predictive ability of lung scanning, the exception, as noted, being multiple large defects which ventilate normally. Unfortunately, this pattern is seen in the minority of patients with a ventilation-perfusion mismatch.

Resolution of this diagnostic dilemma requires prospective studies of consecutive patients with abnormal ventilation-perfusion findings, all of whom undergo pulmonary angiography and whose test results are interpreted blindly. Further, the clinical validity of negative (low probability) tests should be confirmed by withholding treatment and observing the patients over a long follow-up period.

Prevention

The results of randomized clinical trials form the basis of current understanding of prophylaxis for venous thromboembolism.[10]

The clinician should consider a number of study criteria when assessing the validity of the results of clinical trials evaluating prophylactic agents.[10] These essential criteria are listed in table 2.

Objective diagnostic methods for determination of the end point include ^{125}I-fibrinogen leg scanning, impedance plethysmography, and ascending venography for the diagnosis of venous thrombosis, and angiographic or autopsy demonstration of pulmonary embolism. The majority of studies have used venous thrombosis detected by either ^{125}I-fibrinogen leg scanning or venography as the end point for evaluating prophylaxis.

A number of prophylactic approaches including low-dose subcutaneous heparin, dextran, and intermittent pneumatic

The positive association reported between oral contraceptives and thromboembolism may be partly due to diagnostic suspicion bias

compression have been evaluated in a large number of adequately designed studies fulfilling the essential criteria.[10] Because of the consistent findings obtained, these three approaches are now accepted as effective methods of prophylaxis in selected high-risk patient groups.

Treatment

The availability of accurate, objective, noninvasive testing which is readily repeated together with modern clinical trial designs has made possible the evaluation of long-term treatment of venous thrombosis.[15] The fundamentals of a clinical trial of long-term treatment are identical to those outlined in table 2. In addition, special precautions must be taken to prevent the confounding influence of diagnostic suspicion bias. An approach for avoiding this confounder is as follows:

In view of the nature of the long-term treatment, a double-blind study design (eg, subcutaneous heparin versus sodium warfarin) frequently is not feasible. To avoid bias, the search for recurrent deep vein thrombosis (or pulmonary embolism) should be equal in both groups, with use of objective end points.[15] This can be achieved by (1) repeating objective testing at predetermined intervals, (2) performing objective testing of all patients who present on an emergency basis with symptoms suggesting recurrent venous thrombosis (or pulmonary embolism), and (3) interpreting the results of the diagnostic tests without knowledge of the treatment group to which the patients were randomized. For example, each patient could undergo repeated impedance plethysmography and leg scanning at three- or six-week intervals and serial lung scanning (at the beginning and end of active treatment) as well as on emergency presentations. With use of a study design incorporating the features in table 2 plus the added precautions discussed in this section, sodium warfarin has been shown to be effective in preventing venous thromboembolism.[15]

Conclusion

The essential criteria for clinical studies of venous thromboembolism have been illustrated by specific examples in the areas of pathogenesis, diagnosis, prevention, and treatment. These criteria are not all-encompassing, but their application in appropriate clinical trials should enhance the capability of trials to resolve unknown, uncertain, or controversial issues.

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Test Instructions

The following questions make up the CME examination based on the article "Venous thromboembolism. Applying epidemiology to controversies" by Hull. The intent of this test and its educational objectives are explained at the beginning of the article (page 28). There is one and only one correct answer to each test item. Please complete the test without referring back to the article. Answers must be submitted on authorized computer cards provided in the registration packet, and all cards must be postmarked no later than six weeks after receipt of issue. This article and examination have been reviewed and approved by Russell Hull, MD, FRACP, FRCP(C), author of the article. **If you have not already registered for this CME program and wish to enroll, refer to the announcement on page 40.**

Test Items

1. Which one of the following epidemiologic terms is matched *incorrectly*?
   a) Specificity—proportion of negative tests in patients without the disease.
   b) Sensitivity—proportion of positive tests in total population.
   c) Positive predictive value—likelihood that patient with positive tests will have disease.
   d) Negative predictive value—likelihood that patient with negative tests won't have disease.
   e) None of the above.
2. Which one of the following steps is *least* consistent with proper design for study of the effect of an antiplatelet agent in the

long-term treatment of deep venous thrombosis?
a) Identification of objective end points in determining deep venous thrombosis or pulmonary embolism
b) Randomization of patients into test and control groups
c) Repeated objective testing of both groups at random intervals
d) Interpreting results of diagnostic tests without knowledge of which treatment group the patient is in
e) Objective testing of all patients who appear on an emergency basis

3 Which one of the following reference tests is most indicated for determining the efficacy of a diagnostic test for venous thrombosis?
a) ^{125}I fibrinogen test
b) Doppler ultrasonography
c) Impedance plethysmography.
d) Ascending contrast venography
e) Lactic dehydrogenase, SGOT, and bilirubin levels

4 What is the significance of the imprecise nature of clinical diagnosis in the objective determination of the efficacy of a prophylactic treatment?
a) Only retrospective studies can determine efficacy of a prophylactic agent
b) All end-point findings must be diagnosed independently by at least two researchers.
c) Reliable objective diagnostic methods must be used to determine end points
d) Statistical methodology will account for clinical inaccuracy.
e) None of the above.

5. Which one of the following is *not* considered a contributing factor to the lack of objectivity in clinical studies which evaluate the relation among estrogen-containing contraceptives, venous thrombosis, and pulmonary embolism?
a) Knowledge of contraceptive use before autopsy diagnosis of thromboembolism is determined.
b) Failure to use objective criteria for diagnosing venous thrombosis.
c) Low physician suspicion for diagnosis of venous thrombosis if patient is not using contraceptives.
d) Diagnosis of venous thrombosis with previous knowledge of patient's use of contraceptives
e) None of the above.

6. What is the significance of a high false-positive rate when retrospective studies of ventilation-perfusion are used to diagnose pulmonary embolism?
a) It increases the sensitivity of ventilation-perfusion mismatch for diagnosing pulmonary embolism.
b) It eliminates the use of ventilation-perfusion mismatch as a diagnostic test for pulmonary embolism.
c) It decreases the specificity of ventilation-perfusion mismatch for diagnosing pulmonary embolism.
d) It increases the negative predictive value of ventilation-perfusion mismatch.
e) None of the above.

7. Which one of the following has been *least* objectively evaluated as a prophylactic agent for the treatment of deep venous thrombosis?
a) Sulfinpyrazone
b) Dextran.
c) Intermittent pneumatic compression.
d) Low-dose subcutaneous heparin.
e) Sodium warfarin.

8. Which one of the following is *not* consistent with an objective randomized clinical trial of a possible prophylactic treatment?
a) Concurrent random allocation of patients to test and control groups.
b) Double-blind design, if possible.
c) Appropriate statistical methodology
d) Varying independent clinical end points.
e) Reliable diagnostic tests used to establish clinical values.

9 If objective criteria are used, which one of the following is *least* established as a high-risk factor for venous thromboembolism?
a) Malignancy.
b) Paralysis.
c) Estrogen-containing oral contraceptives.
d) Previous venous thromboembolism.
e) Orthopedic surgery to lower extremities

10 Which one of the following is *not* consistent with an objective clinical trial demonstrating efficacy of a diagnostic test?
a) Long-term follow-up of patients with negative tests.
b) A patient population including those with and without the disease.
c) Interpreting results of a diagnostic test with prior knowledge of reference test results
d) All patients undergoing reference tests
e) None of the above

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APPENDIX 4

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THE VALUE OF ADDING IMPEDANCE PLETHYSMOGRAPHY TO ^{125}I-FIBRINOGEN LEG SCANNING FOR THE DETECTION OF DEEP VEIN THROMBOSIS IN HIGH RISK SURGICAL PATIENTS: A COMPARATIVE STUDY BETWEEN PATIENTS UNDERGOING GENERAL SURGERY AND HIP SURGERY

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ABSTRACT

The clinical value of adding impedance plethysmography (IPG) to 125 I-fibrinogen leg scanning was evaluated and compared in 630 patients who had general surgical procedures and 385 patients who had hip surgery. Patients were screened by both tests and venography was performed if either test was positive to determine a) the frequency with which proximal VT, confirmed by venography, was detected by IPG but not by leg scanning, and b) the positive predictive value of these tests used either alone or in combination. Either the IPG or leg scan result was abnormal in 67 of 630 general surgical patients (11%) and in 158 of 385 hip surgery patients (41%). The positive predictive values of the tests in general surgical and hip surgery patients was 79% and 86% respectively for the leg scan alone, 33% and 90% for IPG alone and 87% and 95% when both the leg scan and IPG were positive. The addition of IPG to leg scanning in general surgical patients identified only 1 addition patient with proximal vein thrombosis (0.2%) whereas in hip surgery patients the addition of IPG identified 25 additional patients with proximal vein thrombosis (6%). It is concluded that the addition of IPG to leg scanning is not useful among general surgical patients but is of substantial clinical value in hip surgery patients.

INTRODUCTION

The screening procedure most widely used for the detection of venous thrombosis is 125 I-fibrinogen leg scanning (1-6). This is highly accurate in detecting calf vein thrombosis but is limited by its inability to detect iliac vein thrombosis and its relative insensitivity to high femoral vein thrombosis.

Recently, another diagnostic test, impedance plethysmog-

raphy (IPG) has been introduced and shown to be sensitive to proximal vein thrombosis (thrombosis involving the popliteal, femoral or iliac veins) in symptomatic patients (7-10). The addition of IPG to leg scanning, therefore, has the potential of increasing the frequency of detection of deep vein thrombosis in high risk patients, particularly when thrombosis is confined to proximal veins.

We have used a combination of leg scanning and IPG to screen a large number of general surgical patients (in whom isolated proximal deep vein thrombosis is thought to be uncommon) (5,6) and a large number of patients who have undergone hip surgery (in whom isolated proximal vein thrombosis is thought to be a relatively common event) (11-13). Venography was performed when either the leg scan or IPG result became positive, making it possible to determine the positive predictive value of these two tests.

The aim of the study was to test the clinical value of adding IPG to leg scanning in each group by determining the frequency with which proximal vein thrombosis detected by IPG was undetected by leg scanning.

PATIENTS AND METHODS

1. Patients

Between August 1975 and January 1977, 630 high risk general surgical patients and 385 patients undergoing hip surgery admitted to five hospitals participating in the Hamilton District Thromboembolism Program were screened with both impedance plethysmography and leg scanning. All of the patients were over the age of 40 and had operations which lasted at least 30 minutes performed under general anesthesia. Of the 385 hip surgery patients, 176 (46%) had elective hip replacement and 209 (54%) had emergency surgery for fractured hips.

2. ^{125}I-fibrinogen leg scanning

Each patient was injected postoperatively with 125 I-fibrinogen within either 24 hours of surgery or 48 hours of admission to hospital and the fibrinogen injection was repeated at 7 day intervals as necessary. Leg scanning was carried out daily for the first three days and then every second day until the 28th day or discharge. The method for preparing the 125 I-fibrinogen and for performing and interpreting the fibrinogen leg scans have been described previously (14). In hip surgery patients, the scan results were considered to be uninterpretable over points on the operated thigh due to extravascular diffusion of radio fibrinogen into and around the site of surgery.

3. Impedance plethysmography

Occlusive cuff impedance plethysmography was performed between the 3rd and 5th day after surgery or admission and then on days 7, 10 and 14 and then twice weekly up to 28 days or discharge. In addition, impedance plethysmography was performed daily up to 7 days in all patients who developed positive leg

scans. The methods for performing and interpreting this procedure have been described previously (8).

4. Ascending venography

Bilateral ascending venography was performed in all patients with positive leg scan and/or IPG results. Venography was performed immediately in patients with a positive IPG result. Venography was also performed immediately if the leg scan was positive in the thigh in general surgical patients or in the non-operated thigh in hip surgery patients but was delayed between 72 hours and 7 days in patients with a positive leg scan result confined to the calf. Venography was performed by the method of Rabinov and Paulin (15) at two hospitals and by a previously described method at the other three hospitals (14). Two experienced observers independently interpreted the venograms and any disputes were resolved by adjudication by a third observer. The radiographic criteria used for venous thrombosis was the presence of a constant intraluminal filling defect. If non-filling of a venous segment occurred, venography was repeated and if, despite repeated examinations, poor visualization persisted the venogram was judged inadequate. Venograms were reported as negative, positive for proximal vein thrombosis (popliteal, femoral or iliac vein thrombosis), positive for calf vein thrombosis or inadequate for interpretation. Patients were treated with intravenous heparin when the presence of venous thrombosis was confirmed by venography.

5. Comparison between leg scanning, impedance plethysmography and venography

The results of leg scanning, IPG and venography were interpreted independently of each other and without knowledge of the patient's condition. The IPG and leg scan results were then compared with the venographic results and the results expressed in terms of the positive predictive value (likelihood that patients with positive results of leg scanning and/or IPG would have venous thrombosis demonstrated by venography) (16).

RESULTS

Either the leg scan or IPG result was abnormal in 67 of 630 general surgical patients (11%) and in 158 of the 385 hip surgery patients (41%). Venography was judged as being adequate in 52 of the general surgical patients who had a positive screening test, was unsuccessful or inadequate in 5 patients, and was not done in 10 patients all of whom had a positive leg scan result in the calf only. Venography was considered adequate in 148 of the 158 hip surgery patients in whom either the leg scan or the IPG was positive, was unsuccessful or inadequate in 4 patients and was not performed in 6 patients. Four of the ten patients who either had inadequate venography or had no venography had a positive IPG result and 6 had a positive leg scan result. The reasons for failure to perform venography were refusal by the patient or the attending physician, technical difficulties, or contraindication to venography due to allergy to the radio-opaque dye.

Positive Predictive Value of the Screening Tests

Positive predictive values were calculated for the 52 of 630 general surgical patients who had adequate venography and 148 of 158 hip surgery patients who had adequate venography.

Positive leg scan result only: The leg scan result alone was positive in 34 general surgical patients and in 79 patients who underwent hip surgery. Venography confirmed the presence of deep vein thrombosis in 27 of the 34 general surgical patients for a positive predictive value of 79% and in 68 of the 79 hip surgery patients, a positive predictive value of 86%.

Positive IPG result only: The IPG result was positive in the presence of a negative leg scan in an additional 3 of 630 general surgical patients and in an additional 30 of the 385 hip surgery patients. Venography confirmed the presence of deep vein thrombosis in only one of the 3 additional general surgery patients, a positive predictive value of 33% and in 27 of the 30 addition hip surgery patients, a positive predictive value of 90%.

Both IPG and leg scan results positive: Both the IPG and the leg scan results were positive in 15 patients who had general surgical procedures and in 39 patients who had hip surgery. Venography confirmed the presence of deep vein thrombosis in 13 of the 15 general surgical patients, a positive predictive value of 87% and in 37 of the 39 hip surgery patients, a positive predictive value of 95%.

Either a positive leg scan and/or positive IPG result: Venography confirmed the presence of deep vein thrombosis in 41 of 52 general surgical patients who were positive either by IPG and/or leg scanning (positive predictive value 79%) and in 132 of 148 patients who had hip surgery and who were positive by either leg scan or IPG (positive predictive value 89%).

Clinical Value of Combining IPG and Leg Scanning

The clinical value of combining IPG with leg scanning in the two patient groups is shown in Tables I and II.

Forty-one of the 630 general surgical patients had deep vein thrombosis confirmed by venography. The addition of IPG to leg scanning resulted in the detection of only one additional patient, an improved detection rate of 0.2% for all patients and 2.5% for patients with thrombosis (Table I). One hundred and thirty-two of the 385 hip surgery patients had deep vein thrombosis confirmed by venography. The addition of IPG to leg scanning resulted in the detection of thrombosis in 27 additional patients, an improved detection rate of 7% for all patients and 20% for those with venous thrombosis (Table II, next page). Twenty-five of the 27 thrombi detected by IPG in hip surgery patients were proximal vein thrombi so that the addition of IPG to

leg scanning resulted in an improved detection rate of 39% for proximal vein thrombi.

TABLE I

The Addition of IPG to Leg Scanning in General Surgical Patients Resulted in the Detection of One Additional Patient With Deep Vein Thrombosis (0.2%)

GENERAL SURGICAL PATIENTS

TOTAL = 630 PATIENTS

	DETECTED BY		
	LEG SCAN	ADDITION OF IPG TO LEG SCAN	
ISOLATED PROXIMAL *	1	1	+0
PROXIMAL + CALF *	10	11	+1
CALF ONLY *	29	29	+0

* venous thrombosis by venography

TABLE II

The Addition of IPG to Leg Scanning in Hip Surgery Patients Resulted in the Detection of 27 Additional Patients (7%)

HIP SURGERY PATIENTS

TOTAL = 385 PATIENTS

	DETECTED BY		
	LEG SCAN	ADDITION OF IPG TO LEG SCAN	
ISOLATED PROXIMAL *	4	12	+8
PROXIMAL + CALF *	35	52	+17
CALF ONLY *	63	63	+2

* venous thrombosis by venography

DISCUSSION

The results of this study are consistent with previous findings which suggested that the majority of venous thrombi which occur in general surgical patients arise in the calf (1,6) and so can be detected by leg scanning while a considerable number of thrombi in hip surgery patients arise in the femoral vein and may occur as an isolated event (12,13).

This study also provides previously unavailable data on the positive predictive values of an abnormal IPG or leg scan result in these patients and so provides a rational basis for making management decisions in patients who are screened and have positive results. Thus, the likelihood that a patient would have venous thrombosis confirmed by venography if both the IPG and leg scan results were abnormal was 87% in general surgical patients and 95% in hip surgery patients. The positive predictive value of an abnormal leg scan alone was 79% in patients who had general surgery and 86% in patients who had hip surgery, while the positive predictive value of an abnormal IPG result alone was only 33% in patients who had general surgical procedures and 90% in patients who had hip surgery. The poor positive predictive value of an abnormal IPG result in general surgical patients is likely to be related to the low prevalence of proximal vein thrombosis in this group since prevalence is an important variable which influences the positive predictive value (17).

It is likely that the true frequency of proximal vein thrombosis was higher than the recorded frequency since it is known that the IPG fails to detect non-obstructive proximal vein thrombosis (8). Nevertheless, this study does provide clinically important information about the value of adding IPG to leg scanning as a screening procedure in patients who undergo general surgery or hip surgery. The results indicate that the addition of IPG to leg scanning is of limited clinical value in patients who have general surgical procedures but is of considerable value in patients who have hip surgery. Thus, the addition of the IPG to the leg scan resulted in the detection of thrombosis in only one additional patient (0.2%) in the general surgical group but it led to the detection of thrombosis in 27 additional patients (7%) for hip surgery. Twenty-five of these 27 patients had proximal vein thrombosis, therefore, the addition of the IPG to the leg scan in this patient group almost doubled the frequency of detection of proximal vein thrombosis.

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